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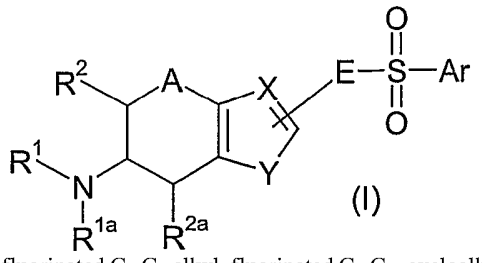
(54) Title: ARYLSULFONYLMETHYL OR ARYLSULFONAMIDE SUBSTITUTED AROMATIC COMPOUNDS SUITABLE FOR TREATING DISORDERS THAT RESPOND TO MADULATION OF THE DOPAMINE D_3 RECEPTOR



(I)

(57) Abstract: The present invention relates to aromatic compounds of the formula (I), wherein Ar is phenyl or an aromatic 5- or 6-membered C-bound heteroaromatic radical, wherein Ar may carry 1 radical R^a and wherein Ar may also carry 1 or 2 radicals R^b; X is N or CH; Y is O, S, -CH=N-, -CH=CH- or -N=CH-; A is CH_{2i} O or S; E is CR^6R^7 or NR^3; R^1 is C_1-C_4-alkyl, C_3-C_4-cycloalkyl, C_3-C4-cycloalkylmethyl, C_3-C_4-alkenyl, fluorinated C_1-C_4-alkyl, fluorinated C_3-C_4-cycloalkyl, fluorinated C_3-C_4-cycloalkylmethyl, fluorinated C_3-C_4-alkenyl, formyl or C,-C_3-alkylcarbonyl; R^{1a} is H, C_2-C_4-alkyl, C_3-C_4-cycloalkyl, C_3-C_4-alkenyl, fluorinated C_1-C_4-alkyl, fluorinated C_3-C_4 -cycloalkyl, or R^{1a} and R^2 together are $(CH_2)_n$ with n being 2 or 3, or R_1^a and R^{2a} together are $(CH_2)_n$ with n being 2 or 3; R^2 and R^{2a} are independently of each other H, CH_3, CH_2F, CHF_2 or CF_3; R^3 is H or C_1-C_4-alkyl; R^6, R^7 independently of each other are selected from H, C_1-C_2-alkyl and fluorinated C_1-C_2-alkyl; and the physiologically tolerated acid addition salts thereof. The invention also relates to the use of a compound of the formula I or a pharmaceutically acceptable salt thereof for preparing a pharmaceutical composition for the treatment of a medical disorder susceptible to treatment with a dopamine D3 receptor ligand.

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ARYLSULFONYLMETHYL OR ARYLSULFONAMIDE SUBSTITUTED AROMATIC COMPOUNDS SUITABLE FOR TREATING DISORDERS THAT RESPOND TO MODULATION OF THE DOPAMINE D_3 RECEPTOR

Background Of The Invention

The present invention relates to novel arylsulfonylmethyl- and arylsulfonamide substituted aromatic compounds. The compounds possess valuable therapeutic properties and are suitable, in particular, for treating diseases that respond to modulation of the dopamine D_3 receptor.

Neurons obtain their information by way of G protein-coupled receptors, inter alia. A large number of substances exert their effect by way of these receptors. One of them is dopamine. Confirmed findings exist with regard to the presence of dopamine and its physiological function as a neurotransmitter. Disorders in the dopaminergic transmitter system result in diseases of the central nervous system which include, for example, schizophrenia, depression and Parkinson's disease. These diseases, and others, are treated with drugs which interact with the dopamine receptors.

Up until 1990, two subtypes of dopamine receptor had been clearly defined pharmacologically, namely the D_1 and D_2 receptors. More recently, a third subtype was found, namely the D_3 receptor which appears to mediate some effects of antipsychotics and antiparkinsonians (J.C. Schwartz et al., The Dopamine D_3 Receptor as a Target for Antipsychotics, in Novel Antipsychotic Drugs, H.Y. Meltzer, Ed. Raven Press, New York 1992, pages 135-144; M. Dooley et al., Drugs and Aging 1998, 12, 495-514, J.N. Joyce, Pharmacology and Therapeutics 2001, 90, pp. 231-59 "The Dopamine D_3 Receptor as a Therapeutic Target for Antipsychotic and Antiparkinsonian Drugs").

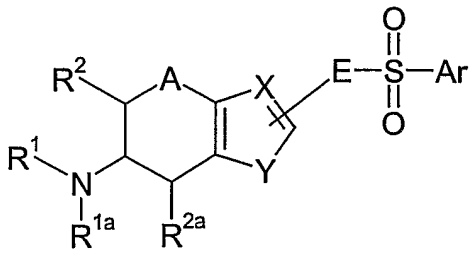
Since then, the dopamine receptors have been divided into two families. On the one hand, there is the D_2 group, consisting of D_2, D_3 and D_4 receptors, and, on the other hand, the D_1 group, consisting of D_1 and D_5 receptors. Whereas D_1 and D_2 receptors are widely distributed, D_3 receptors appear to be expressed regioselectively. Thus, these receptors are preferentially to be found in the limbic system and the projection regions of the mesolimbic dopamine system, especially in the nucleus accumbens, but also in other regions, such as the amygdala. Because of this comparatively regioselective expression, D_3 receptors are regarded as being a target having few side-effects and it is assumed that while a selective D_3 ligand would have the properties of known antipsychotics, it would not have their dopamine D_2 receptor-mediated neurological side-effects (P. Sokoloff et al., Localization and Function of the D_3 Dopamine Receptor,

Arzneim. Forsch./Drug Res. 42(1), 224 (1992); P. Sokoloff et al. Molecular Cloning and Characterization of a Novel Dopamine Receptor (D_3) as a Target for Neuroleptics, Nature, 347, 146 (1990)).

WO 97/45403 discloses inter alia 6-aminotetraline compounds having an affinity for the dopamine D_3 receptor. Some of these compounds possess a certain selectivity for the dopamine D_3 receptor in comparison with their affinity for the D_2 receptor. They have therefore been proposed as being suitable for treating diseases of the central nervous system. Unfortunately their affinity and selectivity towards the D_3 receptor is only moderate or their pharmacological profile are not satisfactory. Consequently there is an ongoing need to provide new compounds, which either have an high affinity and an improved selectivity. The compounds should also have good pharmacological profile, e.g. a high brain plasma ratio, a high bioavailability, good metabolic stability or a decreased inhibition of the mitochondrial respiration.

Summary Of The Invention

The invention is based on the object of providing compounds which act as highly selective dopamine D_3 receptor ligands. This object is surprisingly achieved by means of arylsulfonylmethyl substituted aromatic compounds and by arylsulfonamide substituted aromatic compounds of the formula I



(I)

wherein

Ar is phenyl or an aromatic 5- or 6-membered C-bound heteroaromatic radical, wherein Ar may carry 1 radical R^a and wherein Ar may carry 1 or 2 further radicals R^b;

R^a being selected from the group consisting of C_1-C_6-alkyl, C_2-C_6-alkenyl, fluorinated C_2-C_6-alkenyl, C_3-C_6-cycloalkyl, C_1-C_6-alkoxy, fluorinated C_1-C_6-alkyl, fluorinated C_3-C_6-cycloalkyl, fluorinated C_1-C_6-alkoxy, C_1-C_6-hydroxyalkyl, C_1-C_6-alkoxy-C_1-C_4-alkyl, C_1-C_6-hydroxyalkoxy, C_1-C_6-alkoxy-C_1-C_4-alkoxy, COOH, NR^4R^5, $CH_2NR^4R^5$, ONR^4R^5, $NHC(O)NR^4R^5$, $C(O)NR^4R^5$, $SO_2NR^4R^5$, C_1-C_6-alkylcarbonyl, fluorinated C_1-C_6-

alkylcarbonyl, C_1-C_6-alkylcarbonylamino, fluorinated C_1-C_6-alkylcarbonylamino, C_1-C_6-alkylcarbonyloxy, fluorinated C_1-C_6-alkylcarbonyloxy, C_1-C_6-alkoxycarbonyl, C_1-C_6-alkylthio, fluorinated C_1-C_6-alkylthio, C_1-C_6-alkylsulfinyl, C_1-C_6-alkylsulfonyl, fluorinated C_1-C_6-alkylsulfinyl, fluorinated C_1-C_6-alkylsulfonyl, phenylsulfonyl, phenyl, phenoxy, benzyloxy and a 3- to 7-membered heterocyclic radical, wherein the five last mentioned radicals may carry 1, 2, 3 or 4 radicals selected from halogen, cyano, OH, oxo, CN, and the radicals R^a,

R^b being, independently from each other, selected from halogen, cyano, nitro, OH, methyl, methoxy, fluoromethyl, difluoromethyl, trifluoromethyl, fluormethoxy, difluoromethoxy and trifluoromethoxy,

the radical R^a and one radical R^b, if present and bound to two adjacent carbon atoms of phenyl, may form a 5-or 6-memberd heterocyclic or carbocylic ring which is fused to the phenyl ring and which is unsubstituted or which may carry 1, 2 or 3 radicals selected from halogen, NO_2, NH_2, OH, CN, C_1-C_6-alkyl, C_3-C_6-cycloalkyl, C_1-C_6-alkoxy, fluorinated C_1-C_6-alkyl, fluorinated C_3-C_6-cycloalkyl, fluorinated C_1-C_6-alkoxy, C_1-C_6-hydroxyalkyl, C_1-C_4-alkoxy-C_2-C_4-alkyl, C_1-C_6-hydroxyalkoxy, C_1-C_4-alkoxy-C_2-C_4-alkoxy, C_1-C_6-alkylcarbonyl, C_1-C_6-alkylamino, di-C_1-C_6-alkylamino, C_1-C_6-alkylaminocarbonyl, di-C_1-C_6-alkylaminocarbonyl, fluorinated C_1-C_6-alkylcarbonyl, C_1-C_6-alkylcarbonylamino, fluorinated C_1-C_6-alkylcarbonylamino, C_1-C_6-alkylcarbonyloxy, fluorinated C_1-C_6-alkylcarbonyloxy, C_1-C_6-alkoxycarbonyl, C_1-C_6-alkylthio, fluorinated C_1-C_6-alkylthio, C_1-C_6-alkylsulfinyl, C_1-C_6-alkylsulfonyl, fluorinated C_1-C_6-alkylsulfinyl and fluorinated C_1-C_6-alkylsulfonyl;

provided that if Ar is phenyl, R^{2a} is hydrogen and R^{2b} is hydrogen and A is CH_2, Ar carries 1 radical R^a which is different from methyl, methoxy, trifluormethyl and trifluoromethoxy, and optionally 1 or 2 radicals R^b;

X is N or CH;

Y is O, S, -CH=N-, -CH=CH- or -N=CH-;

A is CH_2, O or S;

E is CR^6R^7 or NR^3;

R^1 is C_1-C_4-alkyl, C_3-C_4-cycloalkyl, C_3-C_4-cycloalkylmethyl, C_3-C_4-alkenyl, fluorinated C_1-C_4-alkyl, fluorinated C_3-C_4-cycloalkyl, fluorinated C_3-C_4-cycloalkylmethyl, fluorinated C_3-C_4-alkenyl, formyl or C_1-C_3-alkylcarbonyl;

R^{1a} is H, C_2-C_4-alkyl, C_3-C_4-cycloalkyl, C_3-C_4-alkenyl, fluorinated C_1-C_4-alkyl, fluorinated C_3-C_4-cycloalkyl, or R^{1a} and R^2 together are $(CH_2)_n$ with n being 2 or 3, or R^{1a} and R^{2a} together are $(CH_2)_n$ with n being 2 or 3;

R^2 and R^{2a} each independently are H, CH_3, CH_2F, CHF_2 or CF_3

R^3 is H or C_1-C_4-alkyl;

R^4, R^5 independently of each other are selected from H, C_1-C_2-alkyl, C_1-C_2-alkoxy and fluorinated C_1-C_2-alkyl; and

R^6, R^7 independently of each other are selected from H, C_1-C_2-alkyl and fluorinated C_1-C_2-alkyl, in particular hydrogen;

and the physiologically tolerated acid addition salts of these compounds.

The present invention therefore relates to bicyclic aromatic compounds of the general formula I and to their physiologically tolerated acid addition salts.

The present invention also relates to a pharmaceutical composition which comprises at least one aromatic of the formula I and/or at least one physiologically tolerated acid addition salt of I, where appropriate together with physiologically acceptable carriers and/or auxiliary substances.

The present invention also relates to a method for treating disorders which respond to influencing by dopamine D_3 receptor antagonists or dopamine D_3 agonists, said method comprising administering an effective amount of at least one aromatic compound of the formula I and/or at least one physiologically tolerated acid addition salt of I to a subject in need thereof.

Detailed Description Of The Invention

The diseases which respond to the influence of dopamine D_3 receptor antagonists or agonists include, in particular, disorders and diseases of the central nervous system, in particular affective disturbances, neurotic disturbances, stress disturbances and somatoform disturbances and psychoses, especially schizophrenia and depression and, in addition, disturbances of kidney function, in particular kidney function disturbances which are caused by diabetes mellitus (see WO 00/67847).

According to the invention, at least one compound of the general formula I having the meanings mentioned at the outset is used for treating the above mentioned indications. Provided the compounds of the formula I of a given constitution may exist in different spatial arrangements, for example if they possess one or more centers of asymmetry, polysubstituted rings or double bonds, or as different tautomers, it is also possible to use enantiomeric mixtures, in particular racemates, diastereomeric mixtures and tautomeric mixtures, preferably, however, the respective essentially pure enantiomers, diastereomers and tautomers of the compounds of formula I and/or of their salts.

It is likewise possible to use physiologically tolerated salts of the compounds of the formula I, especially acid addition salts with physiologically tolerated acids. Examples of suitable physiologically tolerated organic and inorganic acids are hydrochloric acid, hydrobromic acid, phosphoric acid, sulfuric acid, C_1-C_4-alkylsulfonic acids, such as methanesulfonic acid, aromatic sulfonic acids, such as benzenesulfonic acid and toluenesulfonic acid, oxalic acid, maleic acid, fumaric acid, lactic acid, tartaric acid, adipic acid and benzoic acid. Other utilizable acids are described in Fortschritte der Arzneimittelforschung [Advances in drug research], Volume 10, pages 224 ff., Birkhäuser Verlag, Basel and Stuttgart, 1966.

The organic moieties mentioned in the above definitions of the variables are - like the term halogen – collective terms for individual listings of the individual group members. The prefix C_n-C_m indicates in each case the possible number of carbon atoms in the group.

The term halogen denotes in each case fluorine, bromine, chlorine or iodine, in particular fluorine or chlorine.

C_1-C_4 Alkyl (and likeweise in C_1-C_4 hydroxyalkyl, C_1-C_6 alkoxy-C_1-C_4-alkyl, C_1-C_4 alkylcarbonyl, C_1-C_4 alkylcarbonylamino, C_1-C_4 alkylcarbonyloxy, C_1-C_4 alkylthio, C_1-C_4 alkylsulfinyl, C_1-C_4 alkylsulfonyl etc.) is a straight-chain or branched alkyl group having from 1 to 4 carbon atoms. Examples of an alkyl group are methyl, ethyl, n-propyl, iso-propyl, n-butyl, 2-butyl, iso-butyl or tert-butyl

C_1-C_6 Alkyl (and likeweise in C_1-C_6 hydroxyalkyl, C_1-C_6 alkoxy-C_1-C_4-alkyl, C_1-C_6 alkylcarbonyl, C_1-C_6 alkylcarbonylamino, C_1-C_6 alkylcarbonyloxy, C_1-C_6 alkylthio, C_1-C_6 alkylsulfinyl, C_1-C_6 alkylsulfonyl etc.) is a straight-chain or branched alkyl group having from 1 to 6 carbon atoms. Examples include C_1-C_4 alkyl as mentioned above and also pentyl, 1-methylbutyl, 2-methylbutyl, 3-methylbutyl, 2,2-dimethylpropyl, 1-ethylpropyl, hexyl, 1,1-dimethylpropyl, 1,2-dimethylpropyl, 1-methylpentyl, 2-methylpentyl, 3-methylpentyl, 4-methylpentyl, 1,1-dimethylbutyl, 1,2-dimethylbutyl, 1,3-dimethylbutyl, 2,2-dimethylbutyl, 2,3-dimethylbutyl, 3,3-dimethylbutyl, 1-ethylbutyl, 2-ethylbutyl, 1,1,2-trimethylpropyl, 1,2,2-trimethylpropyl, 1-ethyl-1-methylpropyl and 1-ethyl-2-methylpropyl;

Fluorinated C_1-C_6 alkyl (and likeweise in fluorinated C_1-C_6 alkylcarbonyl, fluorinated C_1-C_6 alkylcarbonylamino, fluorinated C_1-C_6 alkylcarbonyloxy, fluorinated C_1-C_6 alkylthio, fluorinated C_1-C_6 alkylsulfinyl, fluorinated C_1-C_6 alkylsulfonyl etc.)is a straight-chain or branched alkyl group having from 1 to 6, in particular 1 to 4 carbon atoms, more preferably 1 to 3 carbon atoms, wherein at least one, e.g. 1, 2, 3, 4 or all of the hydrogen atoms are replaced by a fluorine atoms such as in fluoromethyl, difluoromethyl, trifluoromethyl, (R)-1-fluoroethyl, (S)-1-fluoroethyl, 2-fluoroethyl, 1,1-difluoroethyl, 2,2-difluoroethyl, 2,2,2-trifluoroethyl, (R)-1-fluoropropyl, (S)-1-fluoropropyl, 2-fluoropropyl, 3-fluoropropyl, 1,1-difluoropropyl, 2,2-difluoropropyl, 3,3-difluoropropyl, 3,3,3-trifluoropropyl, (R)-2-fluoro-1-methylethyl, (S)-2-fluoro-1-methylethyl, (R)-2,2-difluoro-1-methylethyl, (S)-2,2-difluoro-1-methylethyl, (R)-1,2-difluoro-1-methylethyl, (S)-1,2-difluoro-1-methylethyl, (R)-2,2,2-trifluoro-1-methylethyl, (S)-2,2,2-trifluoro-1-methylethyl, 2-fluoro-1-(fluoromethyl)ethyl, 1-(difluoromethyl)-2,2-difluoroethyl, (R)-1-fluorobutyl, (S)-1-fluorobutyl, 2-fluorobutyl, 3-fluorobutyl, 4-fluorobutyl, 1,1-difluorobutyl, 2,2-difluorobutyl, 3,3-difluorobutyl, 4,4-difluorobutyl, 4,4,4-trifluorobutyl, etc.;

Branched C_3-C_6 alkyl is alkyl having 3 to 6 carbon atoms at least one being a secondary or tertiary carbon atom. Examples are isopropyl, tert.-butyl, 2- butyl, isobutyl, 2-pentyl, 2-hexyl, 3-methylpentyl, 1,1-dimethylbutyl, 1,2-dimethylbutyl 1-methyl-1-ethylpropyl.

C_1-C_6 Alkoxy (and likewise in C_1-C_6 alkoxycarbonyl, C_1-C_6 alkoxy-C_1-C_4 alkyl, C_1-C_6 alkoxy-C_1-C_4 alkoxy and C_1-C_6 hydroxyalkoxy) is a straight-chain or branched alkyl group having from 1 to 6, in particular 1 to 4 carbon atoms, which is bound to the remainder of the molecule via an oxygen atom. Examples include methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, 2-butoxy, iso-butoxy, tert.-butoxy pentyloxy, 1-methylbutoxy, 2-methylbutoxy, 3-methylbutoxy, 2,2-dimethylpropoxy, 1-ethylpropoxy,

hexyloxy, 1,1-dimethylpropoxy, 1,2-dimethylpropoxy, 1-methylpentyloxy, 2-methylpentyloxy, 3-methylpentyloxy, 4-methylpentyloxy, 1,1-dimethylbutyloxy, 1,2-dimethylbutyloxy, 1,3-dimethylbutyloxy, 2,2-dimethylbutyloxy, 2,3-dimethylbutyloxy, 3,3-dimethylbutyloxy, 1-ethylbutyloxy, 2-ethylbutyloxy, 1,1,2-trimethylpropoxy, 1,2,2-trimethylpropoxy, 1-ethyl-1-methylpropoxy and 1-ethyl-2-methylpropoxy;

Fluorinated C_1-C_6 alkoxy (and likewise in fluorinated C_1-C_6 alkoxycarbonyl) is a straight-chain or branched alkoxy group having from 1 to 6, in particular 1 to 4 carbon atoms, wherein at least one, e.g. 1, 2, 3, 4 or all of the hydrogen atoms are replaced by a fluorine atoms such as in fluoromethoxy, difluoromethoxy, trifluoromethoxy, (R)-1-fluoroethoxy, (S)-1-fluoroethoxy, 2-fluoroethoxy, 1,1-difluoroethoxy, 2,2-difluoroethoxy, 2,2,2-trifluoroethoxy, (R)-1-fluoropropoxy, (S)-1-fluoropropoxy, 2-fluoropropoxy, 3-fluoropropoxy, 1,1-difluoropropoxy, 2,2-difluoropropoxy, 3,3-difluoropropoxy, 3,3,3-trifluoropropoxy, (R)-2-fluoro-1-methylethoxy, (S)-2-fluoro-1-methylethoxy, (R)-2,2-difluoro-1-methylethoxy, (S)-2,2-difluoro-1-methylethoxy, (R)-1,2-difluoro-1-methylethoxy, (S)-1,2-difluoro-1-methylethoxy, (R)-2,2,2-trifluoro-1-methylethoxy, (S)-2,2,2-trifluoro-1-methylethoxy, 2-fluoro-1-(fluoromethyl)ethoxy, 1-(difluoromethyl)-2,2-difluoroethoxy, (R)-1-fluorobutoxy, (S)-1-fluorobutoxy, 2-fluorobutoxy, 3-fluorobutoxy, 4-fluorobutoxy, 1,1-difluorobutoxy, 2,2-difluorobutoxy, 3,3-difluorobutoxy, 4,4-difluorobutoxy, 4,4,4-trifluorobutoxy, etc.;

C_3-C_6 Cycloalkyl is a cycloaliphatic radical having from 3 to 6 C atoms, such as cyclopropyl, cyclobutyl and cyclopentyl. The cycloalkyl radical may be unsubstituted or may carry 1, 2, 3 or 4 C_1-C_4 alkyl radicals, preferably a methyl radical. One alkyl radical is preferably located in the 1-position of the cycloalkyl radical, such as in 1-methylcyclopropyl or 1-methylcyclobutyl.

Fluorinated C_3-C_6 cycloalkyl is a cycloaliphatic radical having from 3 to 6 C atoms, such as cyclopropyl, cyclobutyl and cyclopentyl, wherein at least one, e.g. 1, 2, 3, 4 or all of the hydrogen atoms are replaced by a fluorine atoms such as in 1-fluorocyclopropyl, 2-fluorocyclopropyl, 2,2-difluorocyclopropyl, 1,2-difluorocyclopropyl, 2,3-difluorocyclopropyl, pentafluorocyclopropyl, 1-fluorocyclobutyl, 2-fluorocyclobutyl, 3-fluorocyclobutyl, 2,2-difluorocyclobutyl, 3,3-difluorocyclobutyl, 1,2-difluorocyclobutyl, 1,3-difluorocyclobutyl, 2,3-difluorocyclobutyl, 2,4-difluorocyclobutyl, or 1,2,2-trifluorocyclobutyl.

C_2-C_6-Alkenyl is a singly unsaturated hydrocarbon radical having 2, 3, 4, 5 or 6 C-atoms, e.g. vinyl, allyl (2-propen-1-yl), 1-propen-1-yl, 2-propen-2-yl, methallyl(2-methylprop-2-en-1-yl) and the like. C_3-C_4-Alkenyl is, in particular, allyl, 1-methylprop-2-

en-1-yl, 2-buten-1-yl, 3-buten-1-yl, methallyl, 2-penten-1-yl, 3-penten-1-yl, 4-penten-1-yl, 1-methylbut-2-en-1-yl or 2-ethylprop-2-en-1-yl.

Fluorinated C_2-C_6-alkenyl is a singly unsaturated hydrocarbon radical having 2, 3, 4, 5 or 6 C-atoms, wherein at least one, e.g. 1, 2, 3, 4 or all of the hydrogen atoms are replaced by a fluorine atoms such as in 1-fluorovinyl, 2-fluorovinyl, 2,2-fluorovinyl, 3,3,3-fluoropropenyl, 1,1-difluoro-2-propenyl 1-fluoro-2-propenyl and the like

C_1-C_6 hydroxyalkyl is an alkyl radical having from 1 to 6 carbon atoms as defined above, wherein one hydrogen atom is replaced by hydroxy. Examples comprise hydroxymethyl, 2-hydroxyethyl, 1-hydroxyethyl, 3-hydroxypropyl, 2-hydroxypropyl, 1-methyl-1-hydroxyethyl and the like.

C_1-C_6 hydroxyalkoxy is an alkoxy radical having from 1 to 6, preferably from 2 to 4 carbon atoms as defined above, wherein one hydrogen atom is replaced by hydroxy. Examples comprise 2-hydroxyethyl, 3-hydroxypropyl, 2-hydroxypropyl, 1-methyl-2-hydroxyethyl and the like.

C_1-C_6 alkoxy-C_1-C_4-alkyl is an alkyl radical having from 1 to 4 carbon atoms as defined above, wherein one hydrogen atom is replaced by C_1-C_6 alkoxy. Examples comprise methoxymethyl, 2-methoxyethyl, 1-methoxyethyl, 3-methoxypropyl, 2-methoxypropyl, 1-methyl-1-methoxyethyl, ethoxymethyl, 2-ethoxyethyl, 1-ethoxyethyl, 3-ethoxypropyl, 2-ethoxypropyl, 1-methyl-1-ethoxyethyl and the like.

C_1-C_6 alkoxy-C_1-C_4-alkoxy is an alkoxy radical having from 1 to 4 carbon atoms as defined above, wherein one hydrogen atom is replaced by C_1-C_6 alkoxy. Examples comprise methoxymethoxy, 2-methoxyethoxy, 1-methoxyethoxy, 3-methoxypropoxy, 2-methoxypropoxy, 1-methyl-1-methoxyethoxy, ethoxymethoxy, 2-ethoxyethoxy, 1-ethoxyethoxy, 3-ethoxypropoxy, 2-ethoxypropoxy, 1-methyl-1-ethoxyethoxy and the like.

C_1-C_6 alkylcarbonyl is a radical of the formula R-C(O)-, wherein R is an alkyl radical having from 1 to 6 carbon atoms as defined above. Examples comprise acetyl, propionyl, n-butylryl, 2-methylpropionyl, pivalyl and the like.

C_1-C_6 alkylcarbonylamino is a radical of the formula R-C(O)-NH-, wherein R is an alkyl radical having from 1 to 6 carbon atoms as defined above. Examples comprise acetamido, propionamido, n-butyramido, 2-methylpropionamido, 2,2-

C_1-C_6 alkylcarbonyloxy is a radical of the formula R-C(O)-O-, wherein R is an alkyl radical having from 1 to 6 carbon atoms as defined above. Examples comprise acetyloxy, propionyloxy, n-butyryloxy, 2-methylpropionyloxy, 2,2-dimethylpropionyloxy and the like.

C_1-C_6 alkylthio is a radical of the formula R-S-, wherein R is an alkyl radical having from 1 to 6 carbon atoms as defined above. Examples comprise methylthio, ethylthio, propylthio, butylthio, pentylthio, 1-methylbutylthio, 2-methylbutylthio, 3-methylbutylthio, 2,2-dimethylpropylthio, 1-ethylpropylthio, hexylthio, 1,1-dimethylpropylthio, 1,2-dimethylpropylthio, 1-methylpentylthio, 2-methylpentylthio, 3-methylpentylthio, 4-methylpentylthio, 1,1-dimethylbutylthio, 1,2-dimethylbutylthio, 1,3-dimethylbutylthio, 2,2-dimethylbutylthio, 2,3-dimethylbutylthio, 3,3-dimethylbutylthio, 1-ethylbutylthio, 2-ethylbutylthio, 1,1,2-trimethylpropylthio, 1,2,2-trimethylpropylthio, 1-ethyl-1-methylpropyl and 1-ethyl-2-methylpropyl;

C_1-C_6 alkylsulfinyl is a radical of the formula R-S(O)-, wherein R is an alkyl radical having from 1 to 6 carbon atoms as defined above. Examples comprise methylsulfinyl, ethylsulfinyl, propylsulfinyl, butylsulfinyl, pentylsulfinyl, 1-methylbutylsulfinyl, 2-methylbutylsulfinyl, 3-methylbutylsulfinyl, 2,2-dimethylpropylsulfinyl, 1-ethylpropylsulfinyl, hexylsulfinyl, 1,1-dimethylpropylsulfinyl, 1,2-dimethylpropylsulfinyl, 1-methylpentylsulfinyl, 2-methylpentylsulfinyl, 3-methylpentylsulfinyl, 4-methylpentylsulfinyl, 1,1-dimethylbutylsulfinyl, 1,2-dimethylbutylsulfinyl, 1,3-dimethylbutylsulfinyl, 2,2-dimethylbutylsulfinyl, 2,3-dimethylbutylsulfinyl, 3,3-dimethylbutylsulfinyl, 1-ethylbutylsulfinyl, 2-ethylbutylsulfinyl, 1,1,2-trimethylpropylsulfinyl, 1,2,2-trimethylpropylsulfinyl, 1-ethyl-1-methylpropyl and 1-ethyl-2-methylpropyl;

C_1-C_6 alkylsulfonyl is a radical of the formula R-S$(O)_2$-, wherein R is an alkyl radical having from 1 to 6 carbon atoms as defined above. Examples comprise methylsulfonyl, ethylsulfonyl, propylsulfonyl, butylsulfonyl, pentylsulfonyl, 1-methylbutylsulfonyl, 2-methylbutylsulfonyl, 3-methylbutylsulfonyl, 2,2-dimethylpropylsulfonyl, 1-ethylpropylsulfonyl, hexylsulfonyl, 1,1-dimethylpropylsulfonyl, 1,2-dimethylpropylsulfonyl, 1-methylpentylsulfonyl, 2-methylpentylsulfonyl, 3-methylpentylsulfonyl, 4-methylpentylsulfonyl, 1,1-dimethylbutylsulfonyl, 1,2-dimethylbutylsulfonyl, 1,3-dimethylbutylsulfonyl, 2,2-dimethylbutylsulfonyl, 2,3-dimethylbutylsulfonyl, 3,3-dimethylbutylsulfonyl, 1-ethylbutylsulfonyl, 2-ethylbutylsulfonyl, 1,1,2-trimethylpropylsulfonyl, 1,2,2-trimethylpropylsulfonyl, 1-ethyl-1-methylpropyl and 1-ethyl-2-methylpropyl;

fluorinated C_1-C_6 alkylcarbonyl is a radical of the formula R-C(O)-, wherein R is a fluorinated alkyl radical having from 1 to 6 carbon atoms as defined above. Examples comprise fluoroacetyl, difluoroacetyl, trifluoroacetyl, (R)-1-fluoroethylcarbonyl, (S)-1-fluoroethylcarbonyl, 2-fluoroethylcarbonyl, 1,1-difluoroethylcarbonyl, 2,2-difluoroethylcarbonyl, 2,2,2-trifluoroethylcarbonyl, (R)-1-fluoropropylcarbonyl, (S)-1-fluoropropylcarbonyl, 2-fluoropropylcarbonyl, 3-fluoropropylcarbonyl, 1,1-difluoropropylcarbonyl, 2,2-difluoropropylcarbonyl, 3,3-difluoropropylcarbonyl, 3,3,3-trifluoropropylcarbonyl, (R)-2-fluoro-1-methylethylcarbonyl, (S)-2-fluoro-1-methylethylcarbonyl, (R)-2,2-difluoro-1-methylethylcarbonyl, (S)-2,2-difluoro-1-methylethylcarbonyl, (R)-1,2-difluoro-1-methylethylcarbonyl, (S)-1,2-difluoro-1-methylethylcarbonyl, (R)-2,2,2-trifluoro-1-methylethylcarbonyl, (S)-2,2,2-trifluoro-1-methylethylcarbonyl, 2-fluoro-1-(fluoromethyl)ethylcarbonyl, 1-(difluoromethyl)-2,2-difluoroethylcarbonyl, (R)-1-fluorobutylcarbonyl, (S)-1-fluorobutylcarbonyl, 2-fluorobutylcarbonyl, 3-fluorobutylcarbonyl, 4-fluorobutylcarbonyl, 1,1-difluorobutylcarbonyl, 2,2-difluorobutylcarbonyl, 3,3-difluorobutylcarbonyl, 4,4-difluorobutylcarbonyl, 4,4,4-trifluorobutylcarbonyl, etc.;

fluorinated C_1-C_6 alkylcarbonylamino is a radical of the formula R-C(O)-NH-, wherein R is a fluorinated alkyl radical having from 1 to 6 carbon atoms as defined above. Examples comprise fluoroacetamido, difluoroacetamido, trifluoroacetamido, (R)-1-fluoroethylcarbonylamino, (S)-1-fluoroethylcarbonylamino, 2-fluoroethylcarbonylamino, 1,1-difluoroethylcarbonylamino, 2,2-difluoroethylcarbonylamino, 2,2,2-trifluoroethylcarbonylamino, (R)-1-fluoropropylcarbonylamino, (S)-1-fluoropropylcarbonylamino, 2-fluoropropylcarbonylamino, 3-fluoropropylcarbonylamino, 1,1-difluoropropylcarbonylamino, 2,2-difluoropropylcarbonylamino, 3,3-difluoropropylcarbonylamino, 3,3,3-trifluoropropylcarbonylamino, (R)-2-fluoro-1-methylethylcarbonylamino, (S)-2-fluoro-1-methylethylcarbonylamino, (R)-2,2-difluoro-1-methylethylcarbonylamino, (S)-2,2-difluoro-1-methylethylcarbonylamino, (R)-1,2-difluoro-1-methylethylcarbonylamino, (S)-1,2-difluoro-1-methylethylcarbonylamino, (R)-2,2,2-trifluoro-1-methylethylcarbonylamino, (S)-2,2,2-trifluoro-1-methylethylcarbonylamino, 2-fluoro-1-(fluoromethyl)ethylcarbonylamino, 1-(difluoromethyl)-2,2-difluoroethylcarbonylamino, (R)-1-fluorobutylcarbonylamino, (S)-1-fluorobutylcarbonylamino, 2-fluorobutylcarbonylamino, 3-fluorobutylcarbonylamino, 4-fluorobutylcarbonylamino, 1,1-difluorobutylcarbonylamino, 2,2-difluorobutylcarbonylamino, 3,3-difluorobutylcarbonylamino, 4,4-difluorobutylcarbonylamino, 4,4,4-trifluorobutylcarbonylamino, etc.,

fluorinated C_1-C_6 alkylcarbonyloxy is a radical of the formula R-C(O)-O-, wherein R is a fluorinated alkyl radical having from 1 to 6 carbon atoms as defined above fluoroacetyl

difluoroacetyl, trifluoroacetyl, (R)-1-fluoroethylcarbonyloxy, (S)-1-fluoroethylcarbonyloxy, 2-fluoroethylcarbonyloxy, 1,1-difluoroethylcarbonyloxy, 2,2-difluoroethylcarbonyloxy, 2,2,2-trifluoroethylcarbonyloxy, (R)-1-fluoropropylcarbonyloxy, (S)-1-fluoropropylcarbonyloxy, 2-fluoropropylcarbonyloxy, 3-fluoropropylcarbonyloxy, 1,1-difluoropropylcarbonyloxy, 2,2-difluoropropylcarbonyloxy, 3,3-difluoropropylcarbonyloxy, 3,3,3-trifluoropropylcarbonyloxy, (R)-2-fluoro-1-methylethylcarbonyloxy, (S)-2-fluoro-1-methylethylcarbonyloxy, (R)-2,2-difluoro-1-methylethylcarbonyloxy, (S)-2,2-difluoro-1-methylethylcarbonyloxy, (R)-1,2-difluoro-1-methylethylcarbonyloxy, (S)-1,2-difluoro-1-methylethylcarbonyloxy, (R)-2,2,2-trifluoro-1-methylethylcarbonyloxy, (S)-2,2,2-trifluoro-1-methylethylcarbonyloxy, 2-fluoro-1-(fluoromethyl)ethylcarbonyloxy, 1-(difluoromethyl)-2,2-difluoroethylcarbonyloxy, (R)-1-fluorobutylcarbonyloxy, (S)-1-fluorobutylcarbonyloxy, 2-fluorobutylcarbonyloxy, 3-fluorobutylcarbonyloxy, 4-fluorobutylcarbonyloxy, 1,1-difluorobutylcarbonyloxy, 2,2-difluorobutylcarbonyloxy, 3,3-difluorobutylcarbonyloxy, 4,4-difluorobutylcarbonyloxy, 4,4,4-trifluorobutylcarbonyloxy, etc.;

fluorinated C_1-C_6 alkylthio is a radical of the formula R-S-, wherein R is a fluorinated alkyl radical having from 1 to 6 carbon atoms as defined above. Examples comprise fluoromethylthio, difluoromethylthio, trifluoromethylthio, (R)-1-fluoroethylthio, (S)-1-fluoroethylthio, 2-fluoroethylthio, 1,1-difluoroethylthio, 2,2-difluoroethylthio, 2,2,2-trifluoroethylthio, (R)-1-fluoropropylthio, (S)-1-fluoropropylthio, 2-fluoropropylthio, 3-fluoropropylthio, 1,1-difluoropropylthio, 2,2-difluoropropylthio, 3,3-difluoropropylthio, 3,3,3-trifluoropropylthio, (R)-2-fluoro-1-methylethylthio, (S)-2-fluoro-1-methylethylthio, (R)-2,2-difluoro-1-methylethylthio, (S)-2,2-difluoro-1-methylethylthio, (R)-1,2-difluoro-1-methylethylthio, (S)-1,2-difluoro-1-methylethylthio, (R)-2,2,2-trifluoro-1-methylethylthio, (S)-2,2,2-trifluoro-1-methylethylthio, 2-fluoro-1-(fluoromethyl)ethylthio, 1-(difluoromethyl)-2,2-difluoroethylthio, (R)-1-fluorobutylthio, (S)-1-fluorobutylthio, 2-fluorobutylthio, 3-fluorobutylthio, 4-fluorobutylthio, 1,1-difluorobutylthio, 2,2-difluorobutylthio, 3,3-difluorobutylthio, 4,4-difluorobutylthio, 4,4,4-trifluorobutylthio, etc.;

fluorinated C_1-C_6 alkylsulfinyl is a radical of the formula R-S(O)-, wherein R is a fluorinated alkyl radical having from 1 to 6 carbon atoms as defined above. Examples comprise fluoromethylsulfinyl, difluoromethylsulfinyl, trifluoromethylsulfinyl, (R)-1-fluoroethylsulfinyl, (S)-1-fluoroethylsulfinyl, 2-fluoroethylsulfinyl, 1,1-difluoroethylsulfinyl, 2,2-difluoroethylsulfinyl, 2,2,2-trifluoroethylsulfinyl, (R)-1-fluoropropylsulfinyl, (S)-1-fluoropropylsulfinyl, 2-fluoropropylsulfinyl, 3-fluoropropylsulfinyl, 1,1-difluoropropylsulfinyl, 2,2-difluoropropylsulfinyl, 3,3-difluoropropylsulfinyl, 3,3,3-trifluoropropylsulfinyl, (R)-2-fluoro-1-methylethylsulfinyl, (S)-2-fluoro-1-

methylethylsulfinyl, (R)-1,2-difluoro-1-methylethylsulfinyl, (S)-1,2-difluoro-1-methylethylsulfinyl, (R)-2,2,2-trifluoro-1-methylethylsulfinyl, (S)-2,2,2-trifluoro-1-methylethylsulfinyl, 2-fluoro-1-(fluoromethyl)ethylsulfinyl, 1-(difluoromethyl)-2,2-difluoroethylsulfinyl, (R)-1-fluorobutylsulfinyl, (S)-1-fluorobutylsulfinyl, 2-fluorobutylsulfinyl, 3-fluorobutylsulfinyl, 4-fluorobutylsulfinyl, 1,1-difluorobutylsulfinyl, 2,2-difluorobutylsulfinyl, 3,3-difluorobutylsulfinyl, 4,4-difluorobutylsulfinyl, 4,4,4-trifluorobutylsulfinyl, etc.;

fluorinated C_1-C_6 alkylsulfonyl is a radical of the formula R-S(O)$_2$-, wherein R is a fluorinated alkyl radical having from 1 to 6 carbon atoms as defined above. Examples comprise fluoromethylsulfonyl, difluoromethylsulfonyl, trifluoromethylsulfonyl, (R)-1-fluoroethylsulfonyl, (S)-1-fluoroethylsulfonyl, 2-fluoroethylsulfonyl, 1,1-difluoroethylsulfonyl, 2,2-difluoroethylsulfonyl, 2,2,2-trifluoroethylsulfonyl, (R)-1-fluoropropylsulfonyl, (S)-1-fluoropropylsulfonyl, 2-fluoropropylsulfonyl, 3-fluoropropylsulfonyl, 1,1-difluoropropylsulfonyl, 2,2-difluoropropylsulfonyl, 3,3-difluoropropylsulfonyl, 3,3,3-trifluoropropylsulfonyl, (R)-2-fluoro-1-methylethylsulfonyl, (S)-2-fluoro-1-methylethylsulfonyl, (R)-2,2-difluoro-1-methylethylsulfonyl, (S)-2,2-difluoro-1-methylethylsulfonyl, (R)-1,2-difluoro-1-methylethylsulfonyl, (S)-1,2-difluoro-1-methylethylsulfonyl, (R)-2,2,2-trifluoro-1-methylethylsulfonyl, (S)-2,2,2-trifluoro-1-methylethylsulfonyl, 2-fluoro-1-(fluoromethyl)ethylsulfonyl, 1-(difluoromethyl)-2,2-difluoroethylsulfonyl, (R)-1-fluorobutylsulfonyl, (S)-1-fluorobutylsulfonyl, 2-fluorobutylsulfonyl, 3-fluorobutylsulfonyl, 4-fluorobutylsulfonyl, 1,1-difluorobutylsulfonyl, 2,2-difluorobutylsulfonyl, 3,3-difluorobutylsulfonyl, 4,4-difluorobutylsulfonyl, 4,4,4-trifluorobutylsulfonyl, etc.

3- to 7-membered heterocyclic radicals comprise saturated heterocyclic radicals, which generally have 3-, 4-, 5-, 6- or 7 ring forming atoms (ring members), unsaturated non-aromatic heterocyclic radicals, which generally have 5-, 6- or 7 ring forming atoms, and heteroaromatic radicals, which generally have 5-, 6- or 7 ring forming atoms. The heterocylcic radicals may be bound via a carbon atom (C-bound) or an nitrogen atom (N-bound). Preferred heterocyclic radicals comprise 1 nitrogen atom as ring member atom and optionally 1, 2 or 3 further heteroatoms as ring members, which are selected, independently of each other from O, S and N. Likewise preferred heterocyclic radicals comprise 1 heteroatom as ring member, which is selected from O, S and N, and optionally 1, 2 or 3 further nitrogen atoms as ring members.

Examples of 3- to 7-membered, saturated heterocyclic radicals comprise 1- or 2-aziridinyl, 1-, 2- or 3-azetidinyl, 1-, 2- or 3-pyrrolidinyl, 1-, 2-, 3- or 4-piperidinyl, 1-, 2- or 3-morpholinyl, 1-, 2- or 3-thiomorpholinyl, 1-, 2- or 3-piperazinyl, 1-, 2- or 4-oxazolidinyl

1-, 3- or 4-isoxazolidinyl, 2-oxiranyl, 2- or 3-oxetanyl, 2- or 3-oxolanyl, 2-, 3- or 4-oxanyl, 1,3-dioxolan-2- or 4-yl and the like, which may be unsubstituted or which may carry 1, 2 or 3 of the aforementioned radicals R^a and/or R^b.

Unsaturated non-aromatic heterocyclic radicals, are heterocyclic radicals which generally have 5-, 6- or 7 ring forming atoms and which have 1 or 2 doublebonds that do not form an aromatic p-electron system. Examples are 2,3-dihydropyrrolyl, 3,4-dihydropyrrolyl, 2,3-dihydrofuranyl, 3,4-dihydrofuranyl, 2,3-dihydrothiophenyl, 3,4-dihydrothiophenyl, 1,2-dihydropyridinyl, 2,3-Dihydropyridiynl, 3,4-dihydropyridinyl, 1,2,3,4-tetrahydropyridinyl, 2,3,4,5-tetrahydropyridinyl, and the like.

5- or 6-membered heteroaromatic radicals are heteroaromatic cyclic radicals, wherein the cyclic radical has 5 or 6 atoms which form the ring (ring members) and wherein generally 1, 2, 3 or 4 ring member atoms are selected from O, S and N, the other ring member atoms being carbon atoms. The heteroaromatic radicals may be bound via a carbon atom (C-bound) or an nitrogen atom (N-bound). Preferred heteroaromatic radicals comprise 1 nitrogen atom as ring member atom and optionally 1, 2 or 3 further heteroatoms as ring members, which are selected, independently of each other from O, S and N. Likewise preferred heteroaromatic radicals comprise 1 heteroatom as ring member, which is selected from O, S and N, and optionally 1, 2 or 3 further nitrogen atoms as ring members. Examples of 5- or 6-membered heteroaromatic radicals comprise 2-, 3-, or 4-pyridyl, 2-, 4- or 5-pyrimidinyl, pyrazinyl, 3- or 4-pyridazinyl, 2- or 3-thienyl, 2- or 3-furyl, 1-, 2- or 3-pyrrolyl, 1-, 2- or 4-imidazolyl, 1-, 3- or 4-pyrazolyl, 1- or 3-[1,2,4]-triazolyl, 1- or 4-[1,2,3]-triazolyl, 1-, 2- or 5-tetrazolyl, 2-, 3- or 5-oxazolyl, 3-, 4- or 5-isoxazolyl, 2-, 3- or 5-thiazolyl, 3-, 4- or 5-isothiazolyl, 4- or 5-[1,2,3]-oxadiazolyl, [1,2,5]-oxadiazolyl (= furazanyl), 3- or 5-[1,2,4]-oxadizolyl, [1,3,4]-oxadizolyl, 4- or 5-[1,2,3]-thiadiazolyl, [1,2,5]-thiadiazolyl, 3- or 5-[1,2,4]-thiadizolyl or [1,3,4]-thiadiazolyl, which may be unsubstituted or which may carry 1, 2 or 3 of the aforementioned radicals R^a and/or R^b.

A skilled person will appreciate that the radical -E-SO_2-Ar is bound to one of those carbon atoms of the aromatic part of the bicyclic moiety in formula I which carry a hydrogen atom, thereby substituting said hydrogen atom. Preferably the radical -E-SO_2-Ar is not bound to a carbon atom, which is adjacent to a bridgehead carbon atom. A skilled person will further appreciate that for Y being -CH=N- the carbon atom is attached to the bridgehead carbon atom while for Y being -N=CH- the nitrogen atom is attached to the carbon atom.

Preferably, Ar is phenyl or an aromatic 5- or 6-membered C-bound heteroaromatic radical, comprising 1 nitrogen atom as ring member and 0, 1, 2 or 3 further heteroatoms, independently of each other, selected from O, S and N, as ring members which may be unsubstituted or which may carry 1, 2 or 3 of the aforementioned radicals R^a and/or R^b. Amongst these heteroaromatic radicals those are preferred, which comprise 1, 2 or 3 nitrogen atoms and no further heteroatom as ring members, or 1 or 2 nitrogen atoms and 1 atom, selected from O and S, as ring members. However, thienyl and furyl are likewise preferred. Particularly preferred radicals Ar are 2- or 3-thienyl, 2-, 3- or 4-pyridyl, 2-, 4- or 5-pyrimidinyl, 2-, 3-or 5-thiazolyl, 1,2,4-triazol-3-yl, 1,2,3-triazol-4-yl, 1,3,4-thiadiazol-2-yl, in particular 2-thienyl, 2-pyrimidinyl, 5-pyrimidinyl, 2-pyridinyl and more particularly phenyl which may be unsubstituted or which may carry 1, 2 or 3 of the aforementioned radicals R^a and/or R^b.

Preferably the aromatic radical Ar carries one radical R^a and optionally one or two further radicals R^b as mentioned above, R^b being particularly selected from methyl, fluorinated methyl, halogen, more preferably from fluorine or chlorine.

The aforementioned 5-membered heteroaromatic radicals Ar preferably one radical R^a in the 3-position (related to the position of the SO_2-radical) and optionally one or two further radicals R^b, which are preferably selected from halogen, in particular fluorine or chlorine.

Phenyl and the aforementioned 6-membered heteroaromatic radicals Ar preferably carry one radical R^a in the 4-position (related to the position of the SO_2-radical) and optionally one or two further radicals R^b, which are preferably selected from halogen, in particular fluorine or chlorine.

In a very preferred embodiment of the invention Ar is phenyl that carries a radical R^a in the 4-position of the phenyl ring and optionally 1 or 2 further radicals R^b, which are preferably selected from halogen, in particular from fluorine or chlorine.

In another preferred embodiment of the invention Ar is 2-pyrimidinyl that carries a radical R^a in the 5-position of the pyrimidine ring and optionally 1 or 2 further radicals R^b, which are preferably selected from halogen, in particular from fluorine or chlorine.

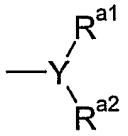
In a further preferred embodiment of the invention Ar is 5-pyrimidinyl that carries a radical R^a in the 2-position of the pyrimidine ring and optionally 1 or 2 further radicals R^b, which are preferably selected from halogen, in particular from fluorine or chlorine.

In a further preferred embodiment of the invention Ar is 2-thienyl that carries a radical R^a in the 3-position of the thiophene ring and optionally 1 or 2 further radicals R^b, which are preferably selected from halogen, in particular from fluorine or chlorine.

Preferably Ar carries 1 radical R^a which is different from CH_3, OCH_3, CF_3, OCF_3, NH_2, SO_2NH_2, acetamido, C_2-C_6-alkoxy or acetyl.

In a preferred embodiment Ar carries 1 radical R^a which selected from the group consisting of C_2-C_6-alkyl, C_3-C_6-cycloalkyl, C_2-C_6-alkoxy, fluorinated C_2-C_6-alkyl, fluorinated C_3-C_6-cycloalkyl, fluorinated C_2-C_6-alkoxy, NR^4R^5, 1-aziridinyl, azetidin-1-yl, pyrrolidin-1-yl or piperidin-1-yl, wherein the last four mentioned radicals may be fluorinated, a phenyl group and an aromatic 5- or 6-membered C-bound heteroaromatic radical, comprising 1 nitrogen atom as ring member and 0, 1, 2 or 3 further heteroatoms, independently of each other, selected from O, S and N, wherein the last two mentioned radicals may carry 1, 2, 3 or 4 radicals selected from Halogen and the radicals R^a, and wherein Ar may carry 1 or 2 further radicals R^b, which are independently from each other selected from halogen, cyano, methyl, fluoromethyl, difluoromethyl, trifluoromethyl, difluoromethoxy and trifluoromethoxy. In this embodiment R^4, R^5 are, independently of each other, preferably selected from H, C_1-C_2-alkyl and fluorinated C_1-C_2-alkyl. Preferably one of the radicals R^4 or R^5 is different from hydrogen. One of the radicals R^4 or R^5 may also be C_1-C_2-alkoxy.

In a very preferred embodiment, the radical Ar preferably carries one radical R^a, which has the formula $R^{a'}$



$R^{a'}$

wherein

Y is N, CH or CF,

R^{a1} and R^{a2} are independently of each other selected from C_1-C_2-alkyl, C_1-C_2-alkoxy, fluorinanted C_1-C_2-alkyl, provided for Y being CH or CF one of the radicals R^{a1} or R^{a2} may also be hydrogen or fluorine, or

R^{a1} and R^{a2} together form a radical $(CH_2)_m$ wherein 1 or 2 of the hydrogen atoms may be replaced by fluorine, hydroxy, oxo, C_1-C_2-alkyl or C_1-C_2-alkoxy, wherein one CH_2 moiety may be replaced by O, S, S=O, SO_2 or N-R^c, R^c being hydrogen or C_1-C_2-alkyl and wherein m is 2, 3, 4, 5 or 6;

In particular

R^{a1} and R^{a2} are independently of each other selected from C_1-C_2-alkyl, in particular methyl, fluorinated C_1-C_2-alkyl, in particular fluoromethyl, difluoromethyl or trifluoromethyl, provided for Y being CH or CF one of the radicals R^{a1} or R^{a2} may also be hydrogen or fluorine, or

R^{a1} and R^{a2} form a radical $(CH_2)_m$ wherein 1 or 2 of the hydrogen atoms may be replaced by fluorine and wherein m is 2, 3 or 4, in particular CH_2-CH_2, CHF-CH_2 CF_2-CH_2, CH_2-CH_2-CH_2, CHF-CH_2-CH_2, CF_2-CH_2-CH_2, CH_2-CHF-CH_2, CH_2-CF_2-CH_2.

In case R^{a1} and R^{a2} are different from each other, the radical of the aforementioned formula $R^{a'}$ may have either (R)- or (S)-configuration with regard to the Y-moiety.

Examples for preferred radicals of the formula $R^{a'}$ comprise isopropyl, (R)-1-fluoroethyl, (S)-1-fluoroethyl, 2-fluoroethyl, 1,1-difluoroethyl, 2,2-difluoroethyl, 2,2,2-trifluoroethyl, (R)-1-fluoropropyl, (S)-1-fluoropropyl, 2-fluoropropyl, 3-fluoropropyl, 1,1-difluoropropyl, 2,2-difluoropropyl, 3,3-difluoropropyl, 3,3,3-trifluoropropyl, (R)-2-fluoro-1-methylethyl, (S)-2-fluoro-1-methylethyl, (R)-2,2-difluoro-1-methylethyl, (S)-2,2-difluoro-1-methylethyl, (R)-1,2-difluoro-1-methylethyl, (S)-1,2-difluoro-1-methylethyl, (R)-2,2,2-trifluoro-1-methylethyl, (S)-2,2,2-trifluoro-1-methylethyl, 2-fluoro-1-(fluoromethyl)ethyl, 1-(difluoromethyl)-2,2-difluoroethyl, 1-fluoro-1-methylethyl cyclopropyl, cyclobutyl, 1-fluorocyclopropyl, (R)- and (S)-2,2-difluorocyclopropyl, (R)- and (S)-2-fluorocyclopropyl.

Also preferred are radicals $R^{a'}$ wherein one of R^{a1} or R^{a2} is C_1-C_2-alkoxy and the other other of R^{a1} or R^{a2} is selected from H, C_1-C_2-alkyl, in particular methyl, fluorinated C_1-C_2-alkyl, in particular fluoromethyl, difluoromethyl or trifluoromethyl. Examples comprise N-methoxy-N-methylamino, N-methoxyamino and N-ethoxyamino.

Preferred radicals of the formula $R^{a'}$ also comprise those wherein Y is nitrogen and wherein R^{a1} and R^{a2} form a radical $(CH_2)_m$ wherein 1 or 2 of the hydrogen atoms may be replaced by fluorine, methyl, trifluoromethyl, methoxy or oxo and wherein m is 2, 3, 4 or 5. Examples comprise azetidin-1-yl, 2-methylazetidin-1-yl, (S)-2-methylazetidin-1-yl, (R)-2-methylazetidin-1-yl, 3-fluoroazetidin-1-yl, 3-methoxyazetidin-1-yl, 3-hydroxyazetidin-1-yl, pyrrolidin-1-yl, (S)-2-fluoropyrrolidin-1-yl, (R)-2-fluoropyrrolidin-1-yl, 3-fluoropyrrolidin-1-yl, (S)-3-fluoropyrrolidin-1-yl, (R)-3-fluoropyrrolidin-1-yl, 2,2-difluoropyrrolidin-1-yl, 3,3-difluoropyrrolidin-1-yl, 2-methylpyrrolidin-1-yl, (S)-2-methylpyrrolidin-1-yl, (R)-2-methylpyrrolidin-1-yl, 3-methylpyrrolidin-1-yl, (S)-3-methylpyrrolidin-1-yl, (R)-3-methylpyrrolidin-1-yl, 2,2-dimethylpyrrolidin-1-yl, 3,3-dimethylpyrrolidin-1-yl, 2-trifluoromethylpyrrolidin-1-yl, (S)-2-trifluoromethylpyrrolidin-1-

yl, (R)-2-trifluoromethylpyrrolidin-1-yl, 3-trifluoromethylpyrrolidin-1-yl, (S)-3-trifluoromethylpyrrolidin-1-yl, (R)-3-trifluoromethylpyrrolidin-1-yl, 2-oxopyrrolidin-1-yl, piperidin-1-yl, 2-methylpiperidin-1-yl, (S)-2-methylpiperidin-1-yl and (R)-2-methylpiperidin-1-yl.

Likewise preferred are radicals $R^{a'}$, wherein R^{a1} and R^{a2} together form a radical $(CH_2)_m$ wherein 1 or 2 of the hydrogen atoms may be replaced by fluorine, hydroxy, oxo, C_1-C_2-alkyl or C_1-C_2-alkoxy, wherein one CH_2 moiety is replaced by O, S, S=O, SO_2 or N-R^c, R^c being hydrogen or C_1-C_2-alkyl and wherein m is 2, 3, 4, 5 or 6. Examples for preferred radicals of the formula $R^{a'}$ also comprise 4-morpholinyl, 4-thiomorpholinyl, 4-(1,1-dioxo)thiomorpholinyl, piperazin-1-yl, 4-methylpiperazin-1-yl, 2-oxo-oxazolidin-3-yl, pyrrolidin-2-yl, (S)-pyrrolidin-2-yl, (R)-pyrrolidin-2-yl, pyrrolidin-3-yl, (S)-pyrrolidin-3-yl, (R)-pyrrolidin-3-yl, 2-fluoropyrrolidin-1-yl, 1-methylpyrrolidin-2-yl, (S)-1-methylpyrrolidin-2-yl, (R)-1-methylpyrrolidin-2-yl, 1-methylpyrrolidin-3-yl, (S)-1-methylpyrrolidin-3-yl and (R)-1-methylpyrrolidin-3-yl.

Amongst the radicals of the formula $R^{a'}$ those are preferred which carry 1, 2, 3 or 4, in particular 1, 2 or 3 fluorine atoms.

In a further preferred embodiment Ar carries one radical R^a, which is selected from 5- or 6-membered heteroaromatic radicals having as ring members 1 heteroatom selected from O, S and N and which may further have 1, 2 or 3 nitrogen atoms as ring members, and wherein the 5- or 6-membered heteroaromatic radical may carry 1, 2 or 3 substituents selected from halogen, NO_2, NH_2, OH, CN, C_1-C_6-alkyl, C_3-C_6-cycloalkyl, C_1-C_6-alkoxy, fluorinated C_1-C_6-alkyl, fluorinated C_3-C_6-cycloalkyl, fluorinated C_1-C_6-alkoxy, C_1-C_6-hydroxyalkyl, C_1-C_4-alkoxy-C_2-C_4-alkyl, C_1-C_6-hydroxyalkoxy, C_1-C_4-alkoxy-C_2-C_4-alkoxy, C_1-C_6-alkylcarbonyl, C_1-C_6-alkylamino, di-C_1-C_6-alkylamino, C_1-C_6-alkylaminocarbonyl, di-C_1-C_6-alkylaminocarbonyl, fluorinated C_1-C_6-alkylcarbonyl, C_1-C_6-alkylcarbonylamino, fluorinated C_1-C_6-alkylcarbonylamino, C_1-C_6-alkylcarbonyloxy, fluorinated C_1-C_6-alkylcarbonyloxy, C_1-C_6-alkoxycarbonyl, C_1-C_6-alkylthio, fluorinated C_1-C_6-alkylthio, C_1-C_6-alkylsulfinyl, C_1-C_6-alkylsulfonyl, fluorinated C_1-C_6-alkylsulfinyl and fluorinated C_1-C_6-alkylsulfonyl. Amongst these radicals R^a, preference is given to radicals selected from 2-, 3-, or 4-pyridyl, 2-, 4- or 5-pyrimidinyl, pyrazinyl, 3- or 4-pyridazinyl, 2- or 3-thienyl, 2- or 3-furyl, 1-, 2- or 3-pyrrolyl, 1-, 2- or 4-imidazolyl, 1-, 3- or 4-pyrazolyl, 1- or 3-[1,2,4]-triazolyl, 1- or 4-[1,2,3]-triazolyl, 1-, 2- or 5-tetrazolyl, 2-, 3- or 5-oxazolyl, 3-, 4- or 5-isoxazolyl, 2-, 3- or 5-thiazolyl, 3-, 4- or 5-isothiazolyl, 4- or 5-[1,2,3]-oxadiazolyl, [1,2,5]-oxadiazolyl (= furazanyl), 3- or 5-[1,2,4]-oxadizolyl, [1,3,4]-oxadizolyl, 4- or 5-[1,2,3]-thiadiazolyl, [1,2,5]-thiadiazolyl, 3- or 5-[1,2,4]-thiadizolyl or

pyrazolyl, imidazolyl, oxazolyl, isoxazolyl, 1,3,4-thiadiazolyl, 1,2,4-triazolyl, 1,2,3-triazolyl and tetrazolyl, where the heteroaromatic radical may be unsubstituted or may carry 1 to 3 substituents as given above. Preferred substituents on heteroaromatic R^a are selected from halogen, C_1-C_4-alkyl, C_1-C_4-alkoxy, fluorinated C_1-C_4-alkyl and fluorinated C_1-C_4-alkoxy.

In a further preferred embodiment Ar carries 1 radical R^a which selected from the group consisting of CHF_2, CH_2F, $OCHF_2$ and OCH_2F, with $OCHF_2$ being preferred. In this embodiment Ar may also carry 1 or 2 further radicals R^b, which are independently from each other selected from halogen, cyano, methyl, fluoromethyl, difluoromethyl, trifluoromethyl, difluoromethoxy and trifluoromethoxy. Preferably Ar carries no further radicla R^b. In this embodiment Ar is preferably phenyl which carries 1 radical R^a which selected from the group consisting of CHF_2, CH_2F, $OCHF_2$ and OCH_2F, with $OCHF_2$ being preferred. In this embodiment Ar is preferably phenyl, which carries R^a in the 4 position with respect to the SO_2-group.

In another embodiment of the invention, Ar carries 1 radical R^a which selected from the group consisting of C_2-C_6-alkenyl, fluorinated C_2-C_6-alkenyl, C_1-C_6-hydroxyalkyl, C_1-C_6-alkoxy-C_1-C_4-alkyl, C_1-C_6-hydroxyalkoxy, C_1-C_6-alkoxy-C_1-C_4-alkoxy, COOH, $CH_2NR^4R^5$, ONR^4R^5, $NHC(O)NR^4R^5$, $C(O)NR^4R^5$, $SO_2NR^4R^5$, C_1-C_6-alkylcarbonyl, fluorinated C_2-C_6-alkylcarbonyl, C_1-C_6-alkylcarbonylamino, fluorinated C_1-C_6-alkylcarbonylamino, C_1-C_6-alkylcarbonyloxy, fluorinated C_1-C_6-alkylcarbonyloxy, C_1-C_6-alkoxycarbonyl, C_1-C_6-alkylthio, fluorinated C_1-C_6-alkylthio, C_1-C_6-alkylsulfinyl, C_1-C_6-alkylsulfonyl, fluorinated C_1-C_6-alkylsulfinyl, fluorinated C_1-C_6-alkylsulfonyl, phenylsulfonyl, phenoxy, benzyloxy and a 5-or 6-membered N-bound heteroaromatic radical, wherein the four last mentioned radicals may carry 1, 2, 3 or 4 radicals selected from halogen, NO_2, NH_2, OH, CN, C_1-C_6-alkyl, C_3-C_6-cycloalkyl, C_1-C_6-alkoxy, fluorinated C_1-C_6-alkyl, fluorinated C_3-C_6-cycloalkyl, fluorinated C_1-C_6-alkoxy, C_1-C_6-hydroxyalkyl, C_1-C_4-alkoxy-C_2-C_4-alkyl, C_1-C_6-hydroxyalkoxy, C_1-C_4-alkoxy-C_2-C_4-alkoxy, C_1-C_6-alkylcarbonyl, C_1-C_6-alkylamino, di-C_1-C_6-alkylamino, C_1-C_6-alkylaminocarbonyl, di-C_1-C_6-alkylaminocarbonyl, fluorinated C_1-C_6-alkylcarbonyl, C_1-C_6-alkylcarbonylamino, fluorinated C_1-C_6-alkylcarbonylamino, C_1-C_6-alkylcarbonyloxy, fluorinated C_1-C_6-alkylcarbonyloxy, C_1-C_6-alkoxycarbonyl, C_1-C_6-alkylthio, fluorinated C_1-C_6-alkylthio, C_1-C_6-alkylsulfinyl, C_1-C_6-alkylsulfonyl, fluorinated C_1-C_6-alkylsulfinyl and fluorinated C_1-C_6-alkylsulfonyl.

In another embodiment of the invention, Ar is phenyl, which carries 1 radical R^a and at least one radical R^b and wherein R^a and one radical R^b are bound to two adjacent car-

is fused to the phenyl ring and which is unsubstituted or which may carry 1, 2 or 3 radicals as given above. Examples of a phenyl ring fused to a saturated or unsaturated 5- or 6-membered carbocyclic or heterocyclic ring comprise indenyl, indanyl, naphthyl, tetralin, benzofuranyl, 2,3-dihydrobenzofuranyl, benzothienyl, indolyl, indazolyl, benzimidazolyl, benzoxathiazolyl, benzoxadiazolyl, benzothiadiazolyl, benzoxazinyl, dihydrobenzoxazinyl, chinolinyl, isochinolinyl, tetrahydroisochinolinyl, chromenyl, chromanyl and the like, which may be unsubstituted or which may carry 1, 2 or 3 of the aforementioned radicals. Preferred substituents for the saturated or unsaturated 5- or 6-membered carbocyclic or heterocyclic ring fused to the phenyl ring are selected from halogen, C_1-C_4-alkyl, C_1-C_4-alkoxy, fluorinated C_1-C_4-alkyl and fluorinated C_1-C_4-alkoxy.

The radical R^1 is preferably C_2-C_4-alkyl, C_3-C_4-cycloalkyl, C_3-C_4-cycloalkylmethyl, C_3-C_4-alkenyl, fluorinated C_1-C_4-alkyl, fluorinated C_3-C_4-cycloalkyl, fluorinated C_3-C_4-cycloalkylmethyl, fluorinated C_3-C_4-alkenyl, formyl or C_1-C_3-alkylcarbonyl, in particular C_2-C_4-alkyl, C_3-C_4-cycloalkyl, C_3-C_4-alkenyl, fluorinated C_1-C_4-alkyl, fluorinated C_3-C_4-cycloalkyl, more preferably n-propyl, fluorinated linear C_2-C_3-alkyl or 1-propen-3-yl, in particular n-propyl or 1-propen-3-yl.

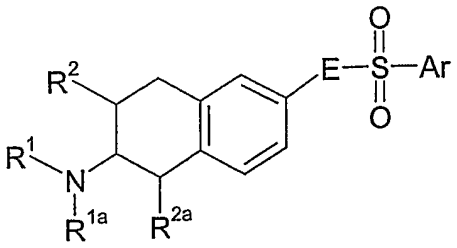
Preferably, the moiety E is N-R^3, wherein R^3 is as defined above. R^3 is in particular H or methyl and most preferred H.

One preferred embodiment of the invention relates to compounds, wherein R^{1a} is hydrogen and R^2 and R^{2a} have the meanings given above. In particular R^2 and/or R^{2a} is (are) also hydrogen. For R^2 or R^{2a} being different from hydrogen the radicals R^2 (or R^{2a}) and NR^1R^{1a} may be located cis- or trans.

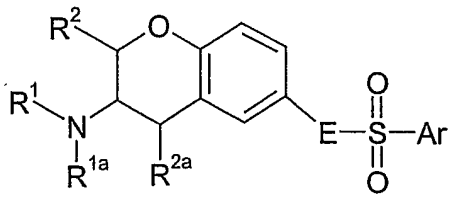
Another preferred embodiment of the invention relates to compounds, wherein R^{1a} and R^2 or R^{1a} and R^{2a} together form a moiety $(CH_2)_n$, wherein n is as defined above and in particular 2 or 3. Thereby a fused ring is formed, which may be trans-fused or cis-fused.

A further preferred embodiment of the invention relates to compounds, wherein R^{1a} is C_2-C_4-alkyl, C_3-C_4-cycloalkyl, C_3-C_4-alkenyl, fluorinated C_1-C_4-alkyl, fluorinated C_3-C_4-cycloalkyl, in particular n-propyl, fluorinated linear C_2-C_3-alkyl or 1-propen-3-yl, more particularly propyl or 1-propen-3-yl. In this embodiment R^2 and R^{2a} have the meanings given above. In particular R^2 and/or R^{2a} is (are) also hydrogen. For R^2 or R^{2a} being different from hydrogen the radicals R^2 (or R^{2a}) and NR^1R^{1a} may be located cis- or trans. The carbon atom of the bicylic core that carries the radical NR^1R^{1a} may have (R) or (S) configuration

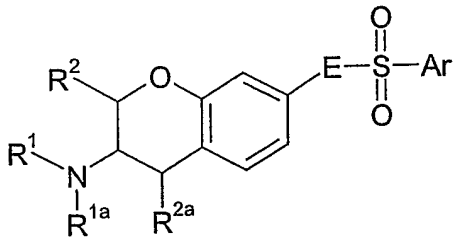
One embodiment of the invention relates to compounds of the formula I, wherein X is CH. In this embodiment Y is preferably -CH=N-, -CH=CH- or -N=CH- and in particular -CH=CH-. In particular this embodiment relates to compounds of the general formulae Ia, Ib and Ic,



(Ia)



(Ib)



(Ic)

wherein R^1, R^{1a}, R^2, R^{2a}, R^3, E and Ar have the meanings given above and to the physiologically tolerated acid addition salts of these compounds. The preferences given above for R^1, R^{1a}, R^2, R^{2a}, R^3, E and Ar naturally apply to formulae Ia, Ib and Ic.

Preferred embodiments of compounds Ia, Ib and Ic are compounds wherein R^2 and R^{2a} are hydrogen. These compounds are also referred to as compouns Iaa, Iba and Ica.

Other preferred embodiments of compopunds Ia are those, wherein R^{2a} is hydrogen and R^{1a} together with R^2 is 1,3-propandiyl. These compounds are also referred to as compouns Iab.

Further preferred embodiments of compopunds Ia are those, wherein R^2 is hydrogen and R^{1a} together with R^{2a} is 1,3-propandiyl. These compounds are also referred to as compouns Iac.

Most preferred are compounds Iaa and the physiologically tolerated acid addition salts of Iaa. In formula Iaa, Ar is preferably phenyl which carries a radical R^a in the 4-position of the phenyl ring. Amongst these, compounds Iaa are preferred, wherein R^a is a radi-

which carries a radical R^a in the 4-position, the radical R^a being selected from CHF_2, CH_2F, $OCHF_2$ and OCH_2F, with $OCHF_2$ being preferred. In compounds Iaa, R^1 is preferably C_2-C_4-alkyl, C_3-C_4-cycloalkyl, C_3-C_4-cycloalkylmethyl, C_3-C_4-alkenyl, fluorinated C_1-C_4-alkyl, fluorinated C_3-C_4-cycloalkyl, fluorinated C_3-C_4-cycloalkylmethyl, fluorinated C_3-C_4-alkenyl, formyl or C_1-C_3-alkylcarbonyl, in particular C_2-C_4-alkyl, C_3-C_4-cycloalkyl, C_3-C_4-alkenyl, fluorinated C_1-C_4-alkyl, fluorinated C_3-C_4-cycloalkyl, more preferably n-propyl, fluorinated linear C_2-C_3-alkyl or 1-propen-3-yl, in particular n-propyl or 1-propen-3-yl. A very preferred example of compounds Iaa is the compound Iaa, wherein R^1 is n-propyl and Ar is 4-difluoromethoxyphenyl. Therefore, a very preferred embodiment of the invention relates to compounds of the formula Iaa, wherein R^1 is n-propyl and Ar is 4-difluoromethoxyphenyl and to the physiologically tolerated acid addition salts thereof, includes the pure S- and R-stereoisomers and mixtures of S- and R-stereoisomers thereof.

In compounds Ia, Ib and Ic and likewise in compounds Iaa, Iba and Ica, the carbon atom to which the radical $R^1R^{1a}N$ is bound, may have S- or R configuration. The invention includes the pure S- and R-stereoisomers and mixtures of S- and R-stereoisomers.

Examples for preferred compounds Iaa, Iab, Iac, Iba and Ica are given in the following tables A-1, A-2, A-3, A-4 and A-5.

Table A-1: Compounds of the formula Iaa, including the pure S-isomers, the pure R-isomers and the racemic mixtures, wherein R^{1a} is H and Ar and R^1 have the meaning given in one row of table A.

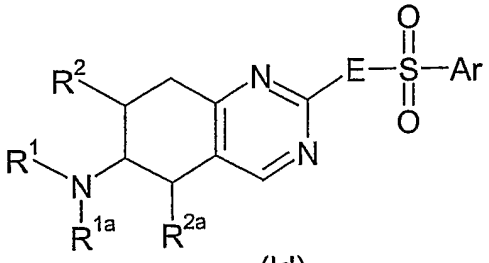
Table A-2: Compounds of the formula Iba, including the pure S-isomers, the pure R-isomers and the racemic mixtures, wherein R^{1a} is H and Ar and R^1 have the meaning given in one row of table A.

Table A-3: Compounds of the formula Ica, including the pure S-isomers, the pure R-isomers and the racemic mixtures, wherein R^{1a} is H and Ar and R^1 have the meaning given in one row of table A.

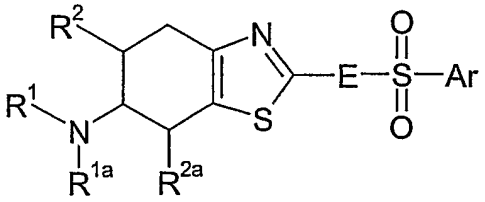
Table A-4:
Compounds of the formula Iab, wherein Ar and R^1 have the meaning given in one row of table A, wherein R^2 and NR^1R^2 are mutually trans, including the pure S/R-isomers, the pure R/S-isomers and the racemic mixtures.

Compounds of the formula Iab, wherein Ar and R^1 have the meaning given in one row of table A, wherein R^{2a} and NR^1R^2 are mutually trans, including the pure S/R-isomers, the pure R/S-isomers and the racemic mixtures.

Another embodiment of the invention, relates to compounds of the formula I, wherein X is N. In this embodiment Y is preferably S, -CH=N- or -CH=CH- and in particular S or -CH=N-. In particular this embodiment relates to compounds of the general formulae Ic and Id,



(Id)



(Ie)

wherein R^1, R^{1a}, R^2, R^{2a}, R^3, E and Ar have the meanings given above. The preferences given above for R^1, R^{1a}, R^2, R^{2a}, R^3, E and Ar naturally apply to formulae Id and Ie. Preferred embodiments of compounds Id and Ie are compounds wherein R^2 and R^{2a} are hydrogen. These compounds are also referred to as compouns Ida and Iea.

Examples for preferred compounds Ida and Iea are given in the following tables A-6 and A-7.

Table A-6:
Compounds of the formula Iaa, wherein Ar and R^1 have the meaning given in one row of table A, including the pure S-isomers, the pure R-isomers and the racemic mixtures.

Table A-7:
Compounds of the formula Iba, wherein Ar and R^1 have the meaning given in one row of table A, including the pure S-isomers, the pure R-isomers and the racemic mixtures.

Table A:

No.	R^1	Ar
1.	propyl	4-ethylphenyl
2.	propyl	4-propylphenyl
3.	propyl	4-isopropylphenyl
4	propyl	4-sec-butylphenyl

No.	R^1	Ar
5.	propyl	4-isobutylphenyl
6.	propyl	4-(1,1-dimethylpropyl)-phenyl
7.	propyl	4-vinylphenyl
8.	propyl	4-isopropenylphenyl
9.	propyl	4-(fluoromethyl)phenyl
10.	propyl	3-(fluoromethyl)phenyl
11.	propyl	2-(fluoromethyl)phenyl
12.	propyl	4-(difluoromethyl)phenyl
13.	propyl	3-(difluoromethyl)phenyl
14.	propyl	2-(difluoromethyl)phenyl
15.	propyl	4-(trifluoromethyl)phenyl
16.	propyl	3-(trifluoromethyl)phenyl
17.	propyl	2-(trifluoromethyl)phenyl
18.	propyl	4-(1-fluoroethyl)-phenyl
19.	propyl	4-((S)-1-fluoroethyl)-phenyl
20.	propyl	4-((R)-1-fluoroethyl)-phenyl
21.	propyl	4-(2-fluoroethyl)-phenyl
22.	propyl	4-(1,1-difluoroethyl)-phenyl
23.	propyl	4-(2,2-difluoroethyl)-phenyl
24.	propyl	4-(2,2,2-trifluoroethyl)-phenyl
25.	propyl	4-(3-fluoropropyl)-phenyl
26.	propyl	4-(2-fluoropropyl)-phenyl
27.	propyl	4-((S)-2-fluoropropyl)-phenyl
28.	propyl	4-((R)-2-fluoropropyl)-phenyl
29.	propyl	4-(3,3-difluoropropyl)-phenyl
30.	propyl	4-(3,3,3-trifluoropropyl)-phenyl
31.	propyl	4-(1-fluoro-1-methylethyl)-phenyl
32.	propyl	4-(2-fluoro-1-methylethyl)-phenyl
33.	propyl	4-((S)-2-fluoro-1-methylethyl)-phenyl
34.	propyl	4-((R)-2-fluoro-1-methylethyl)-phenyl
35.	propyl	4-(2,2-difluoro-1-methylethyl)-phenyl
36.	propyl	4-((S)-2,2-difluoro-1-methylethyl)-phenyl
37.	propyl	4-((R)-2,2-difluoro-1-methylethyl)-phenyl
38.	propyl	4-(2,2,2-trifluoro-1-methylethyl)-phenyl
39.	propyl	4-((S)-2,2,2-trifluoro-1-methylethyl)-phenyl
40.	propyl	4-((R)-2,2,2-trifluoro-1-methylethyl)-phenyl
41.	propyl	4-(2-fluoro-1-fluoromethylethyl)-phenyl
42.	propyl	4-(1-difluoromethyl-2,2-difluoroethyl)-phenyl
43.	propyl	4-(1,1-dimethyl-2-fluoroethyl)-phenyl
44.	propyl	4-ethoxyphenyl
45.	propyl	4-propoxyphenyl
46.	propyl	4-isopropoxyphenyl
47.	propyl	4-butoxyphenyl

No.	R^1	Ar
48.	propyl	4-(fluoromethoxy)-phenyl
49.	propyl	4-(difluoromethoxy)-phenyl
50.	propyl	4-(2-fluoroethoxy)-phenyl
51.	propyl	4-(2,2-difluoroethoxy)-phenyl
52.	propyl	4-(2,2,2-trifluoroethoxy)-phenyl
53.	propyl	4-(1,1,2,2-tetrafluoroethoxy)-phenyl
54.	propyl	4-cyclopropylphenyl
55.	propyl	4-cyclobutylphenyl
56.	propyl	4-cyclopentylphenyl
57.	propyl	4-(2,2-difluorocyclopropyl)-phenyl
58.	propyl	2-fluoro-4-isopropylphenyl
59.	propyl	3-fluoro-4-isopropylphenyl
60.	propyl	4-(1-hydroxy-1-methylethyl)-phenyl
61.	propyl	4-(2-hydroxy-2-methylpropyl)-phenyl
62.	propyl	4-acetylphenyl
63.	propyl	4-carboxyphenyl
64.	propyl	4-(O-benzyl)-phenyl
65.	propyl	4-(2-methoxyethoxy)-phenyl
66.	propyl	4-(CH_2-$N(CH_3)_2$)-phenyl
67.	propyl	4-(NH-CO-NH_2)-phenyl
68.	propyl	4-(methylsulfanyl)-phenyl
69.	propyl	4-(fluoromethylsulfanyl)-phenyl
70.	propyl	4-(difluoromethylsulfanyl)-phenyl
71.	propyl	4-(trifluoromethylsulfanyl)-phenyl
72.	propyl	4-(methylsulfonyl)-phenyl
73.	propyl	4-(N-methoxy-N-methyl-amino)-phenyl
74.	propyl	4-(methoxyamino)-phenyl
75.	propyl	4-(ethoxyamino)-phenyl
76.	propyl	4-(N-methylaminooxy)-phenyl
77.	propyl	4-(N,N-dimethylaminooxy)-phenyl
78.	propyl	4-(azetidin-1-yl)-phenyl
79.	propyl	4-(2-methylazetidin-1-yl)-phenyl
80.	propyl	4-((S)-2-methylazetidin-1-yl)-phenyl
81.	propyl	4-((R)-2-methylazetidin-1-yl)-phenyl
82.	propyl	4-(3-fluoroazetidin-1-yl)-phenyl
83.	propyl	4-(3-methoxyazetidin-1-yl)-phenyl
84.	propyl	4-(3-hydroxyazetidin-1-yl)-phenyl
85.	propyl	4-(pyrrolidin-1-yl)-phenyl
86.	propyl	4-(pyrrolidin-2-yl)-phenyl
87.	propyl	4-((S)-pyrrolidin-2-yl)-phenyl
88.	propyl	4-((R)-pyrrolidin-2-yl)-phenyl
89.	propyl	4-(pyrrolidin-3-yl)-phenyl
90.	propyl	4-((S)-pyrrolidin-3-yl)-phenyl

No.	R^1	Ar
91.	propyl	4-((R)-pyrrolidin-3-yl)-phenyl
92.	propyl	4-(2-fluoropyrrolidin-1-yl)-phenyl
93.	propyl	4-((S)-2-fluoropyrrolidin-1-yl)-phenyl
94.	propyl	4-((R)-2-fluoropyrrolidin-1-yl)-phenyl
95.	propyl	4-(3-fluoropyrrolidin-1-yl)-phenyl
96.	propyl	4-((S)-3-fluoropyrrolidin-1-yl)-phenyl
97.	propyl	4-((R)-3-fluoropyrrolidin-1-yl)-phenyl
98.	propyl	4-(2,2-difluoropyrrolidin-1-yl)-phenyl
99.	propyl	4-(3,3-difluoropyrrolidin-1-yl)-phenyl
100.	propyl	4-(2-methylpyrrolidin-1-yl)-phenyl
101.	propyl	4-((S)-2-methylpyrrolidin-1-yl)-phenyl
102.	propyl	4-((R)-2-methylpyrrolidin-1-yl)-phenyl
103.	propyl	4-(3-methylpyrrolidin-1-yl)-phenyl
104.	propyl	4-((S)-3-methylpyrrolidin-1-yl)-phenyl
105.	propyl	4-((R)-3-methylpyrrolidin-1-yl)-phenyl
106.	propyl	4-(1-methylpyrrolidin-2-yl)-phenyl
107.	propyl	4-((S)-1-methylpyrrolidin-2-yl)-phenyl
108.	propyl	4-((R)-1-methylpyrrolidin-2-yl)-phenyl
109.	propyl	4-(1-methylpyrrolidin-3-yl)-phenyl
110.	propyl	4-((S)-1-methylpyrrolidin-3-yl)-phenyl
111.	propyl	4-((R)-1-methylpyrrolidin-3-yl)-phenyl
112.	propyl	4-(2,2-dimethylpyrrolidin-1-yl)-phenyl
113.	propyl	4-(3,3-dimethylpyrrolidin-1-yl)-phenyl
114.	propyl	4-(2-trifluoromethylpyrrolidin-1-yl)-phenyl
115.	propyl	4-((S)-2-trifluoromethylpyrrolidin-1-yl)-phenyl
116.	propyl	4-((R)-2-trifluoromethylpyrrolidin-1-yl)-phenyl
117.	propyl	4-(3-trifluoromethylpyrrolidin-1-yl)-phenyl
118.	propyl	4-((S)-3-trifluoromethylpyrrolidin-1-yl)-phenyl
119.	propyl	4-((R)-3-trifluoromethylpyrrolidin-1-yl)-phenyl
120.	propyl	4-(2-oxopyrrolidin-1-yl)-phenyl
121.	propyl	4-(2-oxo-oxazolidin-3-yl)-phenyl
122.	propyl	4-(piperidin-1-yl)-phenyl
123.	propyl	4-(2-methylpiperidin-1-yl)-phenyl
124.	propyl	4-((S)-2-methylpiperidin-1-yl)-phenyl
125.	propyl	4-((R)-2-methylpiperidin-1-yl)-phenyl
126.	propyl	4-(piperazin-1-yl)-phenyl
127.	propyl	4-(4-methylpiperazin-1-yl)-phenyl
128.	propyl	4-(morpholin-4-yl)-phenyl
129.	propyl	4-(thiomorpholin-4-yl)-phenyl
130.	propyl	4-(1-oxo-thiomorpholin-4-yl)-phenyl
131.	propyl	4-(1,1-dioxo-thiomorpholin-4-yl)-phenyl
132.	propyl	4-(pyrrol-1-yl)-phenyl
133.	propyl	4-(pyrrol-2-yl)-phenyl

No.	R^1	Ar
134.	propyl	4-(pyrrol-3-yl)-phenyl
135.	propyl	4-(1-methylpyrrol-2-yl)-phenyl
136.	propyl	4-(1-methylpyrrol-3-yl)-phenyl
137.	propyl	4-(furan-2-yl)-phenyl
138.	propyl	4-(furan-3-yl)–phenyl
139.	propyl	4-(thiophen-2-yl)–phenyl
140.	propyl	4-(thiophen-3-yl)–phenyl
141.	propyl	4-(5-propylthien-2-yl)–phenyl
142.	propyl	4-(pyrazol-1-yl)–phenyl
143.	propyl	4-(pyrazol-3-yl)–phenyl
144.	propyl	4-(pyrazol-4-yl)–phenyl
145.	propyl	4-(1-methyl-1H-pyrazol-4-yl)-phenyl
146.	propyl	4-(1-ethyl-1H-pyrazol-4-yl)-phenyl
147.	propyl	4-(1-methyl-1H-pyrazol-5-yl)-phenyl
148.	propyl	4-(1H-imidazol-2-yl)-phenyl
149.	propyl	4-(imidazol-1-yl)-phenyl
150.	propyl	4-(1-methylimidazol-2-yl)-phenyl
151.	propyl	4-(oxazol-2-yl)-phenyl
152.	propyl	4-(oxazol-4-yl)-phenyl
153.	propyl	4-(oxazol-5-yl)-phenyl
154.	propyl	4-(isoxazol-3-yl)-phenyl
155.	propyl	4-(isoxazol-4-yl)-phenyl
156.	propyl	4-(isoxazol-5-yl)-phenyl
157.	propyl	4-([1,2,3]-triazol-1-yl)-phenyl
158.	propyl	4-([1,2,4]-triazol-1-yl)-phenyl
159.	propyl	4-([1,2,3]-triazol-2-yl)-phenyl
160.	propyl	4-(4H-[1,2,4]-triazol-3-yl)-phenyl
161.	propyl	4-([1,2,4]-triazol-4-yl)-phenyl
162.	propyl	4-(2H-[1,2,3]-triazol-4-yl)-phenyl
163.	propyl	4-(4-methyl-4H-[1,2,4]-triazol-3-yl)-phenyl
164.	propyl	4-(2-methyl-2H-[1,2,3]-triazol-4-yl)-phenyl
165.	propyl	4-([1,3,4]-oxadiazol-2-yl)-phenyl
166.	propyl	4-([1,2,4]-oxadiazol-3-yl)-phenyl
167.	propyl	4-([1,2,4]-oxadiazol-5-yl)-phenyl
168.	propyl	4-([1,2,3]-oxadiazol-4-yl)-phenyl
169.	propyl	4-([1,2,3]-oxadiazol-5-yl)-phenyl
170.	propyl	4-([1,2,3]-thiadiazol-4-yl)-phenyl
171.	propyl	4-(1H-tetrazol-5-yl)-phenyl
172.	propyl	4-(tetrazol-1-yl)-phenyl
173.	propyl	4-(2-methyl-2H-tetrazol-5-yl)-phenyl
174.	propyl	4-(1-methyl-1H-tetrazol-5-yl)-phenyl
175.	propyl	4-furazan-3-yl-phenyl
176.	propyl	4-(pyrid-2-yl)-phenyl

No.	R^1	Ar
177.	propyl	4-(pyrid-3-yl)-phenyl
178.	propyl	4-(pyrid-4-yl)-phenyl
179.	propyl	4-(pyrimidin-2-yl)-phenyl
180.	propyl	4-(pyrimidin-4-yl)-phenyl
181.	propyl	4-(pyrimidin-5-yl)-phenyl
182.	propyl	5-isopropylthiophen-2-yl
183.	propyl	2-chlorothiophen-5-yl
184.	propyl	2,5-dichlorothiophen-4-yl
185.	propyl	2,3-dichlorothiophen-5-yl
186.	propyl	2-chloro-3-nitrothiophen-5-yl
187.	propyl	2-(phenylsulfonyl)-thiophen-5-yl
188.	propyl	2-(pyridin-2-yl)thiophen-5-yl
189.	propyl	2-(5-(trifluoromethyl)isoxazol-3-yl)-thiophen-5-yl
190.	propyl	2-(2-methylthiazol-4-yl)-thiophen-5-yl
191.	propyl	1-methyl-1H-imidazol-4-yl
192.	propyl	1,2-dimethyl-1H-imidazol-4-yl
193.	propyl	3,5-dimethylisoxazol-4-yl
194.	propyl	thiazol-2-yl
195.	propyl	4-methylthiazol-2-yl
196.	propyl	4-isopropylthiazol-2-yl
197.	propyl	4-trifluoromethylthiazol-2-yl
198.	propyl	5-methylthiazol-2-yl
199.	propyl	5-isopropylthiazol-2-yl
200.	propyl	5-trifluoromethylthiazol-2-yl
201.	propyl	2,4-dimethylthiazol-5-yl
202.	propyl	2-acetamido-4-methylthiazol-5-yl
203.	propyl	4H-[1,2,4]triazol-3-yl
204.	propyl	5-methyl-4H-[1,2,4]triazol-3-yl
205.	propyl	4-methyl-4H-[1,2,4]triazol-3-yl
206.	propyl	5-isopropyl-4H-[1,2,4]triazol-3-yl
207.	propyl	5-trifluoromethyl-4H-[1,2,4]triazol-3-yl
208.	propyl	4,5-dimethyl-4H-[1,2,4]triazol-3-yl
209.	propyl	5-isopropyl-4-methyl-4H-[1,2,4]triazol-3-yl
210.	propyl	5-trifluoromethyl-4-methyl-4H-[1,2,4]triazol-3-yl
211.	propyl	[1,3,4]thiadiazol-2-yl
212.	propyl	5-methyl-[1,3,4]thiadiazol-2-yl
213.	propyl	5-isopropyl-[1,3,4]thiadiazol-2-yl
214.	propyl	5-trifluoromethyl-[1,3,4]thiadiazol-2-yl
215.	propyl	3-bromo-2-chloropyrid-5-yl
216.	propyl	2-(4-morpholino)-pyrid-5-yl
217.	propyl	2-phenoxypyrid-5-yl
218.	propyl	(2-isopropyl)-pyrimidin-5-yl
219.	propyl	(5-isopropyl)-pyrimidin-2-yl

No.	R^1	Ar
220.	propyl	8-quinolyl
221.	propyl	5-isoquinolyl
222.	propyl	2-(2,2,2-trifluoroacetyl)-1,2,3,4-tetrahydroisoquinolin-7-yl
223.	propyl	5-chloro-3-methylbenzothiophen-2-yl
224.	propyl	3,4-dihydro-4-methyl-2H-benzo[b][1,4]oxazinyl
225.	propyl	benzothiazol-6-yl
226.	propyl	benzo[2,1,3]oxadiazol-4-yl
227.	propyl	5-chlorobenzo[1,2,5]oxadiazolyl
228.	propyl	7-chlorobenzo[2,1,3]oxadiazol-4-yl
229.	propyl	benzo[2,1,3]thiadiazol-4-yl
230.	ethyl	4-propylphenyl
231.	ethyl	4-ethylphenyl
232.	ethyl	4-isopropylphenyl
233.	ethyl	4-sec-butylphenyl
234.	ethyl	4-isobutylphenyl
235.	ethyl	4-(1,1-dimethylpropyl)-phenyl
236.	ethyl	4-vinylphenyl
237.	ethyl	4-isopropenylphenyl
238.	ethyl	4-(fluoromethyl)phenyl
239.	ethyl	3-(fluoromethyl)phenyl
240.	ethyl	2-(fluoromethyl)phenyl
241.	ethyl	4-(difluoromethyl)phenyl
242.	ethyl	3-(difluoromethyl)phenyl
243.	ethyl	2-(difluoromethyl)phenyl
244.	ethyl	4-(trifluoromethyl)phenyl
245.	ethyl	3-(trifluoromethyl)phenyl
246.	ethyl	2-(trifluoromethyl)phenyl
247.	ethyl	4-(1-fluoroethyl)-phenyl
248.	ethyl	4-((S)-1-fluoroethyl)-phenyl
249.	ethyl	4-((R)-1-fluoroethyl)-phenyl
250.	ethyl	4-(2-fluoroethyl)-phenyl
251.	ethyl	4-(1,1-difluoroethyl)-phenyl
252.	ethyl	4-(2,2-difluoroethyl)-phenyl
253.	ethyl	4-(2,2,2-trifluoroethyl)-phenyl
254.	ethyl	4-(3-fluoropropyl)-phenyl
255.	ethyl	4-(2-fluoropropyl)-phenyl
256.	ethyl	4-((S)-2-fluoropropyl)-phenyl

No.	R^1	Ar
257.	ethyl	4-((R)-2-fluoropropyl)-phenyl
258.	ethyl	4-(3,3-difluoropropyl)-phenyl
259.	ethyl	4-(3,3,3-trifluoropropyl)-phenyl
260.	ethyl	4-(1-fluoro-1-methylethyl)-phenyl
261.	ethyl	4-(2-fluoro-1-methylethyl)-phenyl
262.	ethyl	4-((S)-2-fluoro-1-methylethyl)-phenyl
263.	ethyl	4-((R)-2-fluoro-1-methylethyl)-phenyl
264.	ethyl	4-(2,2-difluoro-1-methylethyl)-phenyl
265.	ethyl	4-((S)-2,2-difluoro-1-methylethyl)-phenyl
266.	ethyl	4-((R)-2,2-difluoro-1-methylethyl)-phenyl
267.	ethyl	4-(2,2,2-trifluoro-1-methylethyl)-phenyl
268.	ethyl	4-((S)-2,2,2-trifluoro-1-methylethyl)-phenyl
269.	ethyl	4-((R)-2,2,2-trifluoro-1-methylethyl)-phenyl
270.	ethyl	4-(2-fluoro-1-fluoromethylethyl)-phenyl
271.	ethyl	4-(1-difluoromethyl-2,2-difluoroethyl)-phenyl
272.	ethyl	4-(1,1-dimethyl-2-fluoroethyl)-phenyl
273.	ethyl	4-ethoxyphenyl
274.	ethyl	4-propoxyphenyl
275.	ethyl	4-isopropoxyphenyl
276.	ethyl	4-butoxyphenyl
277.	ethyl	4-(fluoromethoxy)-phenyl
278.	ethyl	4-(difluoromethoxy)-phenyl
279.	ethyl	4-(2-fluoroethoxy)-phenyl
280.	ethyl	4-(2,2-difluoroethoxy)-phenyl
281.	ethyl	4-(2,2,2-trifluoroethoxy)-phenyl
282.	ethyl	4-(1,1,2,2-tetrafluoroethoxy)-phenyl
283.	ethyl	4-cyclopropylphenyl
284.	ethyl	4-cyclobutylphenyl
285.	ethyl	4-cyclopentylphenyl
286.	ethyl	4-(2,2-difluorocyclopropyl)-phenyl
287.	ethyl	2-fluoro-4-isopropylphenyl
288.	ethyl	3-fluoro-4-isopropylphenyl
289.	ethyl	4-(1-hydroxy-1-methylethyl)-phenyl
290.	ethyl	4-(2-hydroxy-2-methylpropyl)-phenyl
291.	ethyl	4-acetylphenyl
292.	ethyl	4-carboxyphenyl

No.	R^1	Ar
293.	ethyl	4-(O-benzyl)-phenyl
294.	ethyl	4-(2-methoxyethoxy)-phenyl
295.	ethyl	4-(CH_2-$N(CH_3)_2$)-phenyl
296.	ethyl	4-(NH-CO-NH_2)-phenyl
297.	ethyl	4-(methylsulfanyl)-phenyl
298.	ethyl	4-(fluoromethylsulfanyl)-phenyl
299.	ethyl	4-(difluoromethylsulfanyl)-phenyl
300.	ethyl	4-(trifluoromethylsulfanyl)-phenyl
301.	ethyl	4-(methylsulfonyl)-phenyl
302.	ethyl	4-(N-methoxy-N-methyl-amino)-phenyl
303.	ethyl	4-(methoxyamino)-phenyl
304.	ethyl	4-(ethoxyamino)-phenyl
305.	ethyl	4-(N-methylaminooxy)-phenyl
306.	ethyl	4-(N,N-dimethylaminooxy)-phenyl
307.	ethyl	4-(azetidin-1-yl)-phenyl
308.	ethyl	4-(2-methylazetidin-1-yl)-phenyl
309.	ethyl	4-((S)-2-methylazetidin-1-yl)-phenyl
310.	ethyl	4-((R)-2-methylazetidin-1-yl)-phenyl
311.	ethyl	4-(3-fluoroazetidin-1-yl)-phenyl
312.	ethyl	4-(3-methoxyazetidin-1-yl)-phenyl
313.	ethyl	4-(3-hydroxyazetidin-1-yl)-phenyl
314.	ethyl	4-(pyrrolidin-1-yl)-phenyl
315.	ethyl	4-(pyrrolidin-2-yl)-phenyl
316.	ethyl	4-((S)-pyrrolidin-2-yl)-phenyl
317.	ethyl	4-((R)-pyrrolidin-2-yl)-phenyl
318.	ethyl	4-(pyrrolidin-3-yl)-phenyl
319.	ethyl	4-((S)-pyrrolidin-3-yl)-phenyl
320.	ethyl	4-((R)-pyrrolidin-3-yl)-phenyl
321.	ethyl	4-(2-fluoropyrrolidin-1-yl)-phenyl
322.	ethyl	4-((S)-2-fluoropyrrolidin-1-yl)-phenyl
323.	ethyl	4-((R)-2-fluoropyrrolidin-1-yl)-phenyl
324.	ethyl	4-(3-fluoropyrrolidin-1-yl)-phenyl
325.	ethyl	4-((S)-3-fluoropyrrolidin-1-yl)-phenyl
326.	ethyl	4-((R)-3-fluoropyrrolidin-1-yl)-phenyl
327.	ethyl	4-(2,2-difluoropyrrolidin-1-yl)-phenyl
328.	ethyl	4-(3,3-difluoropyrrolidin-1-yl)-phenyl

No.	R^1	Ar
329.	ethyl	4-(2-methylpyrrolidin-1-yl)-phenyl
330.	ethyl	4-((S)-2-methylpyrrolidin-1-yl)-phenyl
331.	ethyl	4-((R)-2-methylpyrrolidin-1-yl)-phenyl
332.	ethyl	4-(3-methylpyrrolidin-1-yl)-phenyl
333.	ethyl	4-((S)-3-methylpyrrolidin-1-yl)-phenyl
334.	ethyl	4-((R)-3-methylpyrrolidin-1-yl)-phenyl
335.	ethyl	4-(1-methylpyrrolidin-2-yl)-phenyl
336.	ethyl	4-((S)-1-methylpyrrolidin-2-yl)-phenyl
337.	ethyl	4-((R)-1-methylpyrrolidin-2-yl)-phenyl
338.	ethyl	4-(1-methylpyrrolidin-3-yl)-phenyl
339.	ethyl	4-((S)-1-methylpyrrolidin-3-yl)-phenyl
340.	ethyl	4-((R)-1-methylpyrrolidin-3-yl)-phenyl
341.	ethyl	4-(2,2-dimethylpyrrolidin-1-yl)-phenyl
342.	ethyl	4-(3,3-dimethylpyrrolidin-1-yl)-phenyl
343.	ethyl	4-(2-trifluoromethylpyrrolidin-1-yl)-phenyl
344.	ethyl	4-((S)-2-trifluoromethylpyrrolidin-1-yl)-phenyl
345.	ethyl	4-((R)-2-trifluoromethylpyrrolidin-1-yl)-phenyl
346.	ethyl	4-(3-trifluoromethylpyrrolidin-1-yl)-phenyl
347.	ethyl	4-((S)-3-trifluoromethylpyrrolidin-1-yl)-phenyl
348.	ethyl	4-((R)-3-trifluoromethylpyrrolidin-1-yl)-phenyl
349.	ethyl	4-(2-oxopyrrolidin-1-yl)-phenyl
350.	ethyl	4-(2-oxo-oxazolidin-3-yl)-phenyl
351.	ethyl	4-(piperidin-1-yl)-phenyl
352.	ethyl	4-(2-methylpiperidin-1-yl)-phenyl
353.	ethyl	4-((S)-2-methylpiperidin-1-yl)-phenyl
354.	ethyl	4-((R)-2-methylpiperidin-1-yl)-phenyl
355.	ethyl	4-(piperazin-1-yl)-phenyl
356.	ethyl	4-(4-methylpiperazin-1-yl)-phenyl
357.	ethyl	4-(morpholin-4-yl)-phenyl
358.	ethyl	4-(thiomorpholin-4-yl)-phenyl
359.	ethyl	4-(1-oxo-thiomorpholin-4-yl)-phenyl
360.	ethyl	4-(1,1-dioxo-thiomorpholin-4-yl)-phenyl
361.	ethyl	4-(pyrrol-1-yl)-phenyl
362.	ethyl	4-(pyrrol-2-yl)-phenyl
363.	ethyl	4-(pyrrol-3-yl)-phenyl
364.	ethyl	4-(1-methylpyrrol-2-yl)-phenyl

No.	R^1	Ar
365.	ethyl	4-(1-methylpyrrol-3-yl)-phenyl
366.	ethyl	4-(furan-2-yl)-phenyl
367.	ethyl	4-(furan-3-yl)–phenyl
368.	ethyl	4-(thiophen-2-yl)–phenyl
369.	ethyl	4-(thiophen-3-yl)–phenyl
370.	ethyl	4-(5-propylthien-2-yl)–phenyl
371.	ethyl	4-(pyrazol-1-yl)–phenyl
372.	ethyl	4-(pyrazol-3-yl)–phenyl
373.	ethyl	4-(pyrazol-4-yl)–phenyl
374.	ethyl	4-(1-methyl-1H-pyrazol-4-yl)-phenyl
375.	ethyl	4-(1-ethyl-1H-pyrazol-4-yl)-phenyl
376.	ethyl	4-(1-methyl-1H-pyrazol-5-yl)-phenyl
377.	ethyl	4-(1H-imidazol-2-yl)-phenyl
378.	ethyl	4-(imidazol-1-yl)-phenyl
379.	ethyl	4-(1-methylimidazol-2-yl)-phenyl
380.	ethyl	4-(oxazol-2-yl)-phenyl
381.	ethyl	4-(oxazol-4-yl)-phenyl
382.	ethyl	4-(oxazol-5-yl)-phenyl
383.	ethyl	4-(isoxazol-3-yl)-phenyl
384.	ethyl	4-(isoxazol-4-yl)-phenyl
385.	ethyl	4-(isoxazol-5-yl)-phenyl
386.	ethyl	4-([1,2,3]-triazol-1-yl)-phenyl
387.	ethyl	4-([1,2,4]-triazol-1-yl)-phenyl
388.	ethyl	4-([1,2,3]-triazol-2-yl)-phenyl
389.	ethyl	4-(4H-[1,2,4]-triazol-3-yl)-phenyl
390.	ethyl	4-([1,2,4]-triazol-4-yl)-phenyl
391.	ethyl	4-(2H-[1,2,3]-triazol-4-yl)-phenyl
392.	ethyl	4-(4-methyl-4H-[1,2,4]-triazol-3-yl)-phenyl
393.	ethyl	4-(2-methyl-2H-[1,2,3]-triazol-4-yl)-phenyl
394.	ethyl	4-([1,3,4]-oxadiazol-2-yl)-phenyl
395.	ethyl	4-([1,2,4]-oxadiazol-3-yl)-phenyl
396.	ethyl	4-([1,2,4]-oxadiazol-5-yl)-phenyl
397.	ethyl	4-([1,2,3]-oxadiazol-4-yl)-phenyl
398.	ethyl	4-([1,2,3]-oxadiazol-5-yl)-phenyl
399.	ethyl	4-([1,2,3]-thiadiazol-4-yl)-phenyl
400.	ethyl	4-(1H-tetrazol-5-yl)-phenyl

No.	R^1	Ar
401.	ethyl	4-(tetrazol-1-yl)-phenyl
402.	ethyl	4-(2-methyl-2H-tetrazol-5-yl)-phenyl
403.	ethyl	4-(1-methyl-1H-tetrazol-5-yl)-phenyl
404.	ethyl	4-furazan-3-yl-phenyl
405.	ethyl	4-(pyrid-2-yl)-phenyl
406.	ethyl	4-(pyrid-3-yl)-phenyl
407.	ethyl	4-(pyrid-4-yl)-phenyl
408.	ethyl	4-(pyrimidin-2-yl)-phenyl
409.	ethyl	4-(pyrimidin-4-yl)-phenyl
410.	ethyl	4-(pyrimidin-5-yl)-phenyl
411.	ethyl	5-isopropylthiophen-2-yl
412.	ethyl	2-chlorothiophen-5-yl
413.	ethyl	2,5-dichlorothiophen-4-yl
414.	ethyl	2,3-dichlorothiophen-5-yl
415.	ethyl	2-chloro-3-nitrothiophen-5-yl
416.	ethyl	2-(phenylsulfonyl)-thiophen-5-yl
417.	ethyl	2-(pyridin-2-yl)thiophen-5-yl
418.	ethyl	2-(5-(trifluoromethyl)isoxazol-3-yl)-thiophen-5-yl
419.	ethyl	2-(2-methylthiazol-4-yl)-thiophen-5-yl
420.	ethyl	1-methyl-1H-imidazol-4-yl
421.	ethyl	1,2-dimethyl-1H-imidazol-4-yl
422.	ethyl	3,5-dimethylisoxazol-4-yl
423.	ethyl	thiazol-2-yl
424.	ethyl	4-methylthiazol-2-yl
425.	ethyl	4-isopropylthiazol-2-yl
426.	ethyl	4-trifluoromethylthiazol-2-yl
427.	ethyl	5-methylthiazol-2-yl
428.	ethyl	5-isopropylthiazol-2-yl
429.	ethyl	5-trifluoromethylthiazol-2-yl
430.	ethyl	2,4-dimethylthiazol-5-yl
431.	ethyl	2-acetamido-4-methylthiazol-5-yl
432.	ethyl	4H-[1,2,4]triazol-3-yl
433.	ethyl	5-methyl-4H-[1,2,4]triazol-3-yl
434.	ethyl	4-methyl-4H-[1,2,4]triazol-3-yl
435.	ethyl	5-isopropyl-4H-[1,2,4]triazol-3-yl
436.	ethyl	5-trifluoromethyl-4H-[1,2,4]triazol-3-yl

No.	R^1	Ar
437.	ethyl	4,5-dimethyl-4H-[1,2,4]triazol-3-yl
438.	ethyl	5-isopropyl-4-methyl-4H-[1,2,4]triazol-3-yl
439.	ethyl	5-trifluoromethyl-4-methyl-4H-[1,2,4]triazol-3-yl
440.	ethyl	[1,3,4]thiadiazol-2-yl
441.	ethyl	5-methyl-[1,3,4]thiadiazol-2-yl
442.	ethyl	5-isopropyl-[1,3,4]thiadiazol-2-yl
443.	ethyl	5-trifluoromethyl-[1,3,4]thiadiazol-2-yl
444.	ethyl	3-bromo-2-chloropyrid-5-yl
445.	ethyl	2-(4-morpholino)-pyrid-5-yl
446.	ethyl	2-phenoxypyrid-5-yl
447.	ethyl	(2-isopropyl)-pyrimidin-5-yl
448.	ethyl	(5-isopropyl)-pyrimidin-2-yl
449.	ethyl	8-quinolyl
450.	ethyl	5-isoquinolyl
451.	ethyl	2-(2,2,2-trifluoroacetyl)-1,2,3,4-tetrahydroisoquinolin-7-yl
452.	ethyl	5-chloro-3-methylbenzothiophen-2-yl
453.	ethyl	3,4-dihydro-4-methyl-2H-benzo[b][1,4]oxazinyl
454.	ethyl	benzothiazol-6-yl
455.	ethyl	benzo[2,1,3]oxadiazol-4-yl
456.	ethyl	5-chlorobenzo[1,2,5]oxadiazolyl
457.	ethyl	7-chlorobenzo[2,1,3]oxadiazol-4-yl
458.	ethyl	benzo[2,1,3]thiadiazol-4-yl
459.	methyl	4-ethylphenyl
460.	methyl	4-propylphenyl
461.	methyl	4-isopropylphenyl
462.	methyl	4-sec-butylphenyl
463.	methyl	4-isobutylphenyl
464.	methyl	4-(1,1-dimethylpropyl)-phenyl
465.	methyl	4-vinylphenyl
466.	methyl	4-isopropenylphenyl
467.	methyl	4-(fluoromethyl)phenyl
468.	methyl	3-(fluoromethyl)phenyl
469.	methyl	2-(fluoromethyl)phenyl
470.	methyl	4-(difluoromethyl)phenyl
471.	methyl	3-(difluoromethyl)phenyl
472.	methyl	2-(difluoromethyl)phenyl

No.	R^1	Ar
473.	methyl	4-(trifluoromethyl)phenyl
474.	methyl	3-(trifluoromethyl)phenyl
475.	methyl	2-(trifluoromethyl)phenyl
476.	methyl	4-(1-fluoroethyl)-phenyl
477.	methyl	4-((S)-1-fluoroethyl)-phenyl
478.	methyl	4-((R)-1-fluoroethyl)-phenyl
479.	methyl	4-(2-fluoroethyl)-phenyl
480.	methyl	4-(1,1-difluoroethyl)-phenyl
481.	methyl	4-(2,2-difluoroethyl)-phenyl
482.	methyl	4-(2,2,2-trifluoroethyl)-phenyl
483.	methyl	4-(3-fluoropropyl)-phenyl
484.	methyl	4-(2-fluoropropyl)-phenyl
485.	methyl	4-((S)-2-fluoropropyl)-phenyl
486.	methyl	4-((R)-2-fluoropropyl)-phenyl
487.	methyl	4-(3,3-difluoropropyl)-phenyl
488.	methyl	4-(3,3,3-trifluoropropyl)-phenyl
489.	methyl	4-(1-fluoro-1-methylethyl)-phenyl
490.	methyl	4-(2-fluoro-1-methylethyl)-phenyl
491.	methyl	4-((S)-2-fluoro-1-methylethyl)-phenyl
492.	methyl	4-((R)-2-fluoro-1-methylethyl)-phenyl
493.	methyl	4-(2,2-difluoro-1-methylethyl)-phenyl
494.	methyl	4-((S)-2,2-difluoro-1-methylethyl)-phenyl
495.	methyl	4-((R)-2,2-difluoro-1-methylethyl)-phenyl
496.	methyl	4-(2,2,2-trifluoro-1-methylethyl)-phenyl
497.	methyl	4-((S)-2,2,2-trifluoro-1-methylethyl)-phenyl
498.	methyl	4-((R)-2,2,2-trifluoro-1-methylethyl)-phenyl
499.	methyl	4-(2-fluoro-1-fluoromethylethyl)-phenyl
500.	methyl	4-(1-difluoromethyl-2,2-difluoroethyl)-phenyl
501.	methyl	4-(1,1-dimethyl-2-fluoroethyl)-phenyl
502.	methyl	4-ethoxyphenyl
503.	methyl	4-propoxyphenyl
504.	methyl	4-isopropoxyphenyl
505.	methyl	4-butoxyphenyl
506.	methyl	4-(fluoromethoxy)-phenyl
507.	methyl	4-(difluoromethoxy)-phenyl
508.	methyl	4-(2-fluoroethoxy)-phenyl

No.	R^1	Ar
509.	methyl	4-(2,2-difluoroethoxy)-phenyl
510.	methyl	4-(2,2,2-trifluoroethoxy)-phenyl
511.	methyl	4-(1,1,2,2-tetrafluoroethoxy)-phenyl
512.	methyl	4-cyclopropylphenyl
513.	methyl	4-cyclobutylphenyl
514.	methyl	4-cyclopentylphenyl
515.	methyl	4-(2,2-difluorocyclopropyl)-phenyl
516.	methyl	2-fluoro-4-isopropylphenyl
517.	methyl	3-fluoro-4-isopropylphenyl
518.	methyl	4-(1-hydroxy-1-methylethyl)-phenyl
519.	methyl	4-(2-hydroxy-2-methylpropyl)-phenyl
520.	methyl	4-acetylphenyl
521.	methyl	4-carboxyphenyl
522.	methyl	4-(O-benzyl)-phenyl
523.	methyl	4-(2-methoxyethoxy)-phenyl
524.	methyl	4-(CH_2-$N(CH_3)_2$)-phenyl
525.	methyl	4-(NH-CO-NH_2)-phenyl
526.	methyl	4-(methylsulfanyl)-phenyl
527.	methyl	4-(fluoromethylsulfanyl)-phenyl
528.	methyl	4-(difluoromethylsulfanyl)-phenyl
529.	methyl	4-(trifluoromethylsulfanyl)-phenyl
530.	methyl	4-(methylsulfonyl)-phenyl
531.	methyl	4-(N-methoxy-N-methyl-amino)-phenyl
532.	methyl	4-(methoxyamino)-phenyl
533.	methyl	4-(ethoxyamino)-phenyl
534.	methyl	4-(N-methylaminooxy)-phenyl
535.	methyl	4-(N,N-dimethylaminooxy)-phenyl
536.	methyl	4-(azetidin-1-yl)-phenyl
537.	methyl	4-(2-methylazetidin-1-yl)-phenyl
538.	methyl	4-((S)-2-methylazetidin-1-yl)-phenyl
539.	methyl	4-((R)-2-methylazetidin-1-yl)-phenyl
540.	methyl	4-(3-fluoroazetidin-1-yl)-phenyl
541.	methyl	4-(3-methoxyazetidin-1-yl)-phenyl
542.	methyl	4-(3-hydroxyazetidin-1-yl)-phenyl
543.	methyl	4-(pyrrolidin-1-yl)-phenyl
544.	methyl	4-(pyrrolidin-2-yl)-phenyl

No.	R^1	Ar
545.	methyl	4-((S)-pyrrolidin-2-yl)-phenyl
546.	methyl	4-((R)-pyrrolidin-2-yl)-phenyl
547.	methyl	4-(pyrrolidin-3-yl)-phenyl
548.	methyl	4-((S)-pyrrolidin-3-yl)-phenyl
549.	methyl	4-((R)-pyrrolidin-3-yl)-phenyl
550.	methyl	4-(2-fluoropyrrolidin-1-yl)-phenyl
551.	methyl	4-((S)-2-fluoropyrrolidin-1-yl)-phenyl
552.	methyl	4-((R)-2-fluoropyrrolidin-1-yl)-phenyl
553.	methyl	4-(3-fluoropyrrolidin-1-yl)-phenyl
554.	methyl	4-((S)-3-fluoropyrrolidin-1-yl)-phenyl
555.	methyl	4-((R)-3-fluoropyrrolidin-1-yl)-phenyl
556.	methyl	4-(2,2-difluoropyrrolidin-1-yl)-phenyl
557.	methyl	4-(3,3-difluoropyrrolidin-1-yl)-phenyl
558.	methyl	4-(2-methylpyrrolidin-1-yl)-phenyl
559.	methyl	4-((S)-2-methylpyrrolidin-1-yl)-phenyl
560.	methyl	4-((R)-2-methylpyrrolidin-1-yl)-phenyl
561.	methyl	4-(3-methylpyrrolidin-1-yl)-phenyl
562.	methyl	4-((S)-3-methylpyrrolidin-1-yl)-phenyl
563.	methyl	4-((R)-3-methylpyrrolidin-1-yl)-phenyl
564.	methyl	4-(1-methylpyrrolidin-2-yl)-phenyl
565.	methyl	4-((S)-1-methylpyrrolidin-2-yl)-phenyl
566.	methyl	4-((R)-1-methylpyrrolidin-2-yl)-phenyl
567.	methyl	4-(1-methylpyrrolidin-3-yl)-phenyl
568.	methyl	4-((S)-1-methylpyrrolidin-3-yl)-phenyl
569.	methyl	4-((R)-1-methylpyrrolidin-3-yl)-phenyl
570.	methyl	4-(2,2-dimethylpyrrolidin-1-yl)-phenyl
571.	methyl	4-(3,3-dimethylpyrrolidin-1-yl)-phenyl
572.	methyl	4-(2-trifluoromethylpyrrolidin-1-yl)-phenyl
573.	methyl	4-((S)-2-trifluoromethylpyrrolidin-1-yl)-phenyl
574.	methyl	4-((R)-2-trifluoromethylpyrrolidin-1-yl)-phenyl
575.	methyl	4-(3-trifluoromethylpyrrolidin-1-yl)-phenyl
576.	methyl	4-((S)-3-trifluoromethylpyrrolidin-1-yl)-phenyl
577.	methyl	4-((R)-3-trifluoromethylpyrrolidin-1-yl)-phenyl
578.	methyl	4-(2-oxopyrrolidin-1-yl)-phenyl
579.	methyl	4-(2-oxo-oxazolidin-3-yl)-phenyl
580.	methyl	4-(piperidin-1-yl)-phenyl

No.	R^1	Ar
581.	methyl	4-(2-methylpiperidin-1-yl)-phenyl
582.	methyl	4-((S)-2-methylpiperidin-1-yl)-phenyl
583.	methyl	4-((R)-2-methylpiperidin-1-yl)-phenyl
584.	methyl	4-(piperazin-1-yl)-phenyl
585.	methyl	4-(4-methylpiperazin-1-yl)-phenyl
586.	methyl	4-(morpholin-4-yl)-phenyl
587.	methyl	4-(thiomorpholin-4-yl)-phenyl
588.	methyl	4-(1-oxo-thiomorpholin-4-yl)-phenyl
589.	methyl	4-(1,1-dioxo-thiomorpholin-4-yl)-phenyl
590.	methyl	4-(pyrrol-1-yl)-phenyl
591.	methyl	4-(pyrrol-2-yl)-phenyl
592.	methyl	4-(pyrrol-3-yl)-phenyl
593.	methyl	4-(1-methylpyrrol-2-yl)-phenyl
594.	methyl	4-(1-methylpyrrol-3-yl)-phenyl
595.	methyl	4-(furan-2-yl)-phenyl
596.	methyl	4-(furan-3-yl)–phenyl
597.	methyl	4-(thiophen-2-yl)–phenyl
598.	methyl	4-(thiophen-3-yl)–phenyl
599.	methyl	4-(5-propylthien-2-yl)–phenyl
600.	methyl	4-(pyrazol-1-yl)–phenyl
601.	methyl	4-(pyrazol-3-yl)–phenyl
602.	methyl	4-(pyrazol-4-yl)–phenyl
603.	methyl	4-(1-methyl-1H-pyrazol-4-yl)-phenyl
604.	methyl	4-(1-ethyl-1H-pyrazol-4-yl)-phenyl
605.	methyl	4-(1-methyl-1H-pyrazol-5-yl)-phenyl
606.	methyl	4-(1H-imidazol-2-yl)-phenyl
607.	methyl	4-(imidazol-1-yl)-phenyl
608.	methyl	4-(1-methylimidazol-2-yl)-phenyl
609.	methyl	4-(oxazol-2-yl)-phenyl
610.	methyl	4-(oxazol-4-yl)-phenyl
611.	methyl	4-(oxazol-5-yl)-phenyl
612.	methyl	4-(isoxazol-3-yl)-phenyl
613.	methyl	4-(isoxazol-4-yl)-phenyl
614.	methyl	4-(isoxazol-5-yl)-phenyl
615.	methyl	4-([1,2,3]-triazol-1-yl)-phenyl
616.	methyl	4-([1,2,4]-triazol-1-yl)-phenyl

No.	R^1	Ar
617.	methyl	4-([1,2,3]-triazol-2-yl)-phenyl
618.	methyl	4-(4H-[1,2,4]-triazol-3-yl)-phenyl
619.	methyl	4-([1,2,4]-triazol-4-yl)-phenyl
620.	methyl	4-(2H-[1,2,3]-triazol-4-yl)-phenyl
621.	methyl	4-(4-methyl-4H-[1,2,4]-triazol-3-yl)-phenyl
622.	methyl	4-(2-methyl-2H-[1,2,3]-triazol-4-yl)-phenyl
623.	methyl	4-([1,3,4]-oxadiazol-2-yl)-phenyl
624.	methyl	4-([1,2,4]-oxadiazol-3-yl)-phenyl
625.	methyl	4-([1,2,4]-oxadiazol-5-yl)-phenyl
626.	methyl	4-([1,2,3]-oxadiazol-4-yl)-phenyl
627.	methyl	4-([1,2,3]-oxadiazol-5-yl)-phenyl
628.	methyl	4-([1,2,3]-thiadiazol-4-yl)-phenyl
629.	methyl	4-(1H-tetrazol-5-yl)-phenyl
630.	methyl	4-(tetrazol-1-yl)-phenyl
631.	methyl	4-(2-methyl-2H-tetrazol-5-yl)-phenyl
632.	methyl	4-(1-methyl-1H-tetrazol-5-yl)-phenyl
633.	methyl	4-furazan-3-yl-phenyl
634.	methyl	4-(pyrid-2-yl)-phenyl
635.	methyl	4-(pyrid-3-yl)-phenyl
636.	methyl	4-(pyrid-4-yl)-phenyl
637.	methyl	4-(pyrimidin-2-yl)-phenyl
638.	methyl	4-(pyrimidin-4-yl)-phenyl
639.	methyl	4-(pyrimidin-5-yl)-phenyl
640.	methyl	5-isopropylthiophen-2-yl
641.	methyl	2-chlorothiophen-5-yl
642.	methyl	2,5-dichlorothiophen-4-yl
643.	methyl	2,3-dichlorothiophen-5-yl
644.	methyl	2-chloro-3-nitrothiophen-5-yl
645.	methyl	2-(phenylsulfonyl)-thiophen-5-yl
646.	methyl	2-(pyridin-2-yl)thiophen-5-yl
647.	methyl	2-(5-(trifluoromethyl)isoxazol-3-yl)-thiophen-5-yl
648.	methyl	2-(2-methylthiazol-4-yl)-thiophen-5-yl
649.	methyl	1-methyl-1H-imidazol-4-yl
650.	methyl	1,2-dimethyl-1H-imidazol-4-yl
651.	methyl	3,5-dimethylisoxazol-4-yl
652.	methyl	thiazol-2-yl

No.	R^1	Ar
653.	methyl	4-methylthiazol-2-yl
654.	methyl	4-isopropylthiazol-2-yl
655.	methyl	4-trifluoromethylthiazol-2-yl
656.	methyl	5-methylthiazol-2-yl
657.	methyl	5-isopropylthiazol-2-yl
658.	methyl	5-trifluoromethylthiazol-2-yl
659.	methyl	2,4-dimethylthiazol-5-yl
660.	methyl	2-acetamido-4-methylthiazol-5-yl
661.	methyl	4H-[1,2,4]triazol-3-yl
662.	methyl	5-methyl-4H-[1,2,4]triazol-3-yl
663.	methyl	4-methyl-4H-[1,2,4]triazol-3-yl
664.	methyl	5-isopropyl-4H-[1,2,4]triazol-3-yl
665.	methyl	5-trifluoromethyl-4H-[1,2,4]triazol-3-yl
666.	methyl	4,5-dimethyl-4H-[1,2,4]triazol-3-yl
667.	methyl	5-isopropyl-4-methyl-4H-[1,2,4]triazol-3-yl
668.	methyl	5-trifluoromethyl-4-methyl-4H-[1,2,4]triazol-3-yl
669.	methyl	[1,3,4]thiadiazol-2-yl
670.	methyl	5-methyl-[1,3,4]thiadiazol-2-yl
671.	methyl	5-isopropyl-[1,3,4]thiadiazol-2-yl
672.	methyl	5-trifluoromethyl-[1,3,4]thiadiazol-2-yl
673.	methyl	3-bromo-2-chloropyrid-5-yl
674.	methyl	2-(4-morpholino)-pyrid-5-yl
675.	methyl	2-phenoxypyrid-5-yl
676.	methyl	(2-isopropyl)-pyrimidin-5-yl
677.	methyl	(5-isopropyl)-pyrimidin-2-yl
678.	methyl	8-quinolyl
679.	methyl	5-isoquinolyl
680.	methyl	2-(2,2,2-trifluoroacetyl)-1,2,3,4-tetrahydroisoquinolin-7-yl
681.	methyl	5-chloro-3-methylbenzothiophen-2-yl
682.	methyl	3,4-dihydro-4-methyl-2H-benzo[b][1,4]oxazinyl
683.	methyl	benzothiazol-6-yl
684.	methyl	benzo[2,1,3]oxadiazol-4-yl
685.	methyl	5-chlorobenzo[1,2,5]oxadiazolyl
686.	methyl	7-chlorobenzo[2,1,3]oxadiazol-4-yl
687.	methyl	benzo[2,1,3]thiadiazol-4-yl
688.	3-fluoropropyl	4-ethylphenyl

No.	R^1	Ar
689.	3-fluoropropyl	4-propylphenyl
690.	3-fluoropropyl	4-isopropylphenyl
691.	3-fluoropropyl	4-sec-butylphenyl
692.	3-fluoropropyl	4-isobutylphenyl
693.	3-fluoropropyl	4-(1,1-dimethylpropyl)-phenyl
694.	3-fluoropropyl	4-vinylphenyl
695.	3-fluoropropyl	4-isopropenylphenyl
696.	3-fluoropropyl	4-(fluoromethyl)phenyl
697.	3-fluoropropyl	3-(fluoromethyl)phenyl
698.	3-fluoropropyl	2-(fluoromethyl)phenyl
699.	3-fluoropropyl	4-(difluoromethyl)phenyl
700.	3-fluoropropyl	3-(difluoromethyl)phenyl
701.	3-fluoropropyl	2-(difluoromethyl)phenyl
702.	3-fluoropropyl	4-(trifluoromethyl)phenyl
703.	3-fluoropropyl	3-(trifluoromethyl)phenyl
704.	3-fluoropropyl	2-(trifluoromethyl)phenyl
705.	3-fluoropropyl	4-(1-fluoroethyl)-phenyl
706.	3-fluoropropyl	4-((S)-1-fluoroethyl)-phenyl
707.	3-fluoropropyl	4-((R)-1-fluoroethyl)-phenyl
708.	3-fluoropropyl	4-(2-fluoroethyl)-phenyl
709.	3-fluoropropyl	4-(1,1-difluoroethyl)-phenyl
710.	3-fluoropropyl	4-(2,2-difluoroethyl)-phenyl
711.	3-fluoropropyl	4-(2,2,2-trifluoroethyl)-phenyl
712.	3-fluoropropyl	4-(3-fluoropropyl)-phenyl
713.	3-fluoropropyl	4-(2-fluoropropyl)-phenyl
714.	3-fluoropropyl	4-((S)-2-fluoropropyl)-phenyl
715.	3-fluoropropyl	4-((R)-2-fluoropropyl)-phenyl
716.	3-fluoropropyl	4-(3,3-difluoropropyl)-phenyl
717.	3-fluoropropyl	4-(3,3,3-trifluoropropyl)-phenyl
718.	3-fluoropropyl	4-(1-fluoro-1-methylethyl)-phenyl
719.	3-fluoropropyl	4-(2-fluoro-1-methylethyl)-phenyl
720.	3-fluoropropyl	4-((S)-2-fluoro-1-methylethyl)-phenyl
721.	3-fluoropropyl	4-((R)-2-fluoro-1-methylethyl)-phenyl
722.	3-fluoropropyl	4-(2,2-difluoro-1-methylethyl)-phenyl
723.	3-fluoropropyl	4-((S)-2,2-difluoro-1-methylethyl)-phenyl
724.	3-fluoropropyl	4-((R)-2,2-difluoro-1-methylethyl)-phenyl

No.	R^1	Ar
725.	3-fluoropropyl	4-(2,2,2-trifluoro-1-methylethyl)-phenyl
726.	3-fluoropropyl	4-((S)-2,2,2-trifluoro-1-methylethyl)-phenyl
727.	3-fluoropropyl	4-((R)-2,2,2-trifluoro-1-methylethyl)-phenyl
728.	3-fluoropropyl	4-(2-fluoro-1-fluoromethylethyl)-phenyl
729.	3-fluoropropyl	4-(1-difluoromethyl-2,2-difluoroethyl)-phenyl
730.	3-fluoropropyl	4-(1,1-dimethyl-2-fluoroethyl)-phenyl
731.	3-fluoropropyl	4-ethoxyphenyl
732.	3-fluoropropyl	4-propoxyphenyl
733.	3-fluoropropyl	4-isopropoxyphenyl
734.	3-fluoropropyl	4-butoxyphenyl
735.	3-fluoropropyl	4-(fluoromethoxy)-phenyl
736.	3-fluoropropyl	4-(difluoromethoxy)-phenyl
737.	3-fluoropropyl	4-(2-fluoroethoxy)-phenyl
738.	3-fluoropropyl	4-(2,2-difluoroethoxy)-phenyl
739.	3-fluoropropyl	4-(2,2,2-trifluoroethoxy)-phenyl
740.	3-fluoropropyl	4-(1,1,2,2-tetrafluoroethoxy)-phenyl
741.	3-fluoropropyl	4-cyclopropylphenyl
742.	3-fluoropropyl	4-cyclobutylphenyl
743.	3-fluoropropyl	4-cyclopentylphenyl
744.	3-fluoropropyl	4-(2,2-difluorocyclopropyl)-phenyl
745.	3-fluoropropyl	2-fluoro-4-isopropylphenyl
746.	3-fluoropropyl	3-fluoro-4-isopropylphenyl
747.	3-fluoropropyl	4-(1-hydroxy-1-methylethyl)-phenyl
748.	3-fluoropropyl	4-(2-hydroxy-2-methylpropyl)-phenyl
749.	3-fluoropropyl	4-acetylphenyl
750.	3-fluoropropyl	4-carboxyphenyl
751.	3-fluoropropyl	4-(O-benzyl)-phenyl
752.	3-fluoropropyl	4-(2-methoxyethoxy)-phenyl
753.	3-fluoropropyl	4-(CH_2-$N(CH_3)_2$)-phenyl
754.	3-fluoropropyl	4-(NH-CO-NH_2)-phenyl
755.	3-fluoropropyl	4-(methylsulfanyl)-phenyl
756.	3-fluoropropyl	4-(fluoromethylsulfanyl)-phenyl
757.	3-fluoropropyl	4-(difluoromethylsulfanyl)-phenyl
758.	3-fluoropropyl	4-(trifluoromethylsulfanyl)-phenyl
759.	3-fluoropropyl	4-(methylsulfonyl)-phenyl
760.	3-fluoropropyl	4-(N-methoxy-N-methyl-amino)-phenyl

No.	R^1	Ar
761.	3-fluoropropyl	4-(methoxyamino)-phenyl
762.	3-fluoropropyl	4-(ethoxyamino)-phenyl
763.	3-fluoropropyl	4-(N-methylaminooxy)-phenyl
764.	3-fluoropropyl	4-(N,N-dimethylaminooxy)-phenyl
765.	3-fluoropropyl	4-(azetidin-1-yl)-phenyl
766.	3-fluoropropyl	4-(2-methylazetidin-1-yl)-phenyl
767.	3-fluoropropyl	4-((S)-2-methylazetidin-1-yl)-phenyl
768.	3-fluoropropyl	4-((R)-2-methylazetidin-1-yl)-phenyl
769.	3-fluoropropyl	4-(3-fluoroazetidin-1-yl)-phenyl
770.	3-fluoropropyl	4-(3-methoxyazetidin-1-yl)-phenyl
771.	3-fluoropropyl	4-(3-hydroxyazetidin-1-yl)-phenyl
772.	3-fluoropropyl	4-(pyrrolidin-1-yl)-phenyl
773.	3-fluoropropyl	4-(pyrrolidin-2-yl)-phenyl
774.	3-fluoropropyl	4-((S)-pyrrolidin-2-yl)-phenyl
775.	3-fluoropropyl	4-((R)-pyrrolidin-2-yl)-phenyl
776.	3-fluoropropyl	4-(pyrrolidin-3-yl)-phenyl
777.	3-fluoropropyl	4-((S)-pyrrolidin-3-yl)-phenyl
778.	3-fluoropropyl	4-((R)-pyrrolidin-3-yl)-phenyl
779.	3-fluoropropyl	4-(2-fluoropyrrolidin-1-yl)-phenyl
780.	3-fluoropropyl	4-((S)-2-fluoropyrrolidin-1-yl)-phenyl
781.	3-fluoropropyl	4-((R)-2-fluoropyrrolidin-1-yl)-phenyl
782.	3-fluoropropyl	4-(3-fluoropyrrolidin-1-yl)-phenyl
783.	3-fluoropropyl	4-((S)-3-fluoropyrrolidin-1-yl)-phenyl
784.	3-fluoropropyl	4-((R)-3-fluoropyrrolidin-1-yl)-phenyl
785.	3-fluoropropyl	4-(2,2-difluoropyrrolidin-1-yl)-phenyl
786.	3-fluoropropyl	4-(3,3-difluoropyrrolidin-1-yl)-phenyl
787.	3-fluoropropyl	4-(2-methylpyrrolidin-1-yl)-phenyl
788.	3-fluoropropyl	4-((S)-2-methylpyrrolidin-1-yl)-phenyl
789.	3-fluoropropyl	4-((R)-2-methylpyrrolidin-1-yl)-phenyl
790.	3-fluoropropyl	4-(3-methylpyrrolidin-1-yl)-phenyl
791.	3-fluoropropyl	4-((S)-3-methylpyrrolidin-1-yl)-phenyl
792.	3-fluoropropyl	4-((R)-3-methylpyrrolidin-1-yl)-phenyl
793.	3-fluoropropyl	4-(1-methylpyrrolidin-2-yl)-phenyl
794.	3-fluoropropyl	4-((S)-1-methylpyrrolidin-2-yl)-phenyl
795.	3-fluoropropyl	4-((R)-1-methylpyrrolidin-2-yl)-phenyl
796.	3-fluoropropyl	4-(1-methylpyrrolidin-3-yl)-phenyl

No.	R^1	Ar
797.	3-fluoropropyl	4-((S)-1-methylpyrrolidin-3-yl)-phenyl
798.	3-fluoropropyl	4-((R)-1-methylpyrrolidin-3-yl)-phenyl
799.	3-fluoropropyl	4-(2,2-dimethylpyrrolidin-1-yl)-phenyl
800.	3-fluoropropyl	4-(3,3-dimethylpyrrolidin-1-yl)-phenyl
801.	3-fluoropropyl	4-(2-trifluoromethylpyrrolidin-1-yl)-phenyl
802.	3-fluoropropyl	4-((S)-2-trifluoromethylpyrrolidin-1-yl)-phenyl
803.	3-fluoropropyl	4-((R)-2-trifluoromethylpyrrolidin-1-yl)-phenyl
804.	3-fluoropropyl	4-(3-trifluoromethylpyrrolidin-1-yl)-phenyl
805.	3-fluoropropyl	4-((S)-3-trifluoromethylpyrrolidin-1-yl)-phenyl
806.	3-fluoropropyl	4-((R)-3-trifluoromethylpyrrolidin-1-yl)-phenyl
807.	3-fluoropropyl	4-(2-oxopyrrolidin-1-yl)-phenyl
808.	3-fluoropropyl	4-(2-oxo-oxazolidin-3-yl)-phenyl
809.	3-fluoropropyl	4-(piperidin-1-yl)-phenyl
810.	3-fluoropropyl	4-(2-methylpiperidin-1-yl)-phenyl
811.	3-fluoropropyl	4-((S)-2-methylpiperidin-1-yl)-phenyl
812.	3-fluoropropyl	4-((R)-2-methylpiperidin-1-yl)-phenyl
813.	3-fluoropropyl	4-(piperazin-1-yl)-phenyl
814.	3-fluoropropyl	4-(4-methylpiperazin-1-yl)-phenyl
815.	3-fluoropropyl	4-(morpholin-4-yl)-phenyl
816.	3-fluoropropyl	4-(thiomorpholin-4-yl)-phenyl
817.	3-fluoropropyl	4-(1-oxo-thiomorpholin-4-yl)-phenyl
818.	3-fluoropropyl	4-(1,1-dioxo-thiomorpholin-4-yl)-phenyl
819.	3-fluoropropyl	4-(pyrrol-1-yl)-phenyl
820.	3-fluoropropyl	4-(pyrrol-2-yl)-phenyl
821.	3-fluoropropyl	4-(pyrrol-3-yl)-phenyl
822.	3-fluoropropyl	4-(1-methylpyrrol-2-yl)-phenyl
823.	3-fluoropropyl	4-(1-methylpyrrol-3-yl)-phenyl
824.	3-fluoropropyl	4-(furan-2-yl)-phenyl
825.	3-fluoropropyl	4-(furan-3-yl)–phenyl
826.	3-fluoropropyl	4-(thiophen-2-yl)–phenyl
827.	3-fluoropropyl	4-(thiophen-3-yl)–phenyl
828.	3-fluoropropyl	4-(5-propylthien-2-yl)–phenyl
829.	3-fluoropropyl	4-(pyrazol-1-yl)–phenyl
830.	3-fluoropropyl	4-(pyrazol-3-yl)–phenyl
831.	3-fluoropropyl	4-(pyrazol-4-yl)–phenyl
832.	3-fluoropropyl	4-(1-methyl-1H-pyrazol-4-yl)-phenyl

No.	R^1	Ar
833.	3-fluoropropyl	4-(1-ethyl-1H-pyrazol-4-yl)-phenyl
834.	3-fluoropropyl	4-(1-methyl-1H-pyrazol-5-yl)-phenyl
835.	3-fluoropropyl	4-(1H-imidazol-2-yl)-phenyl
836.	3-fluoropropyl	4-(imidazol-1-yl)-phenyl
837.	3-fluoropropyl	4-(1-methylimidazol-2-yl)-phenyl
838.	3-fluoropropyl	4-(oxazol-2-yl)-phenyl
839.	3-fluoropropyl	4-(oxazol-4-yl)-phenyl
840.	3-fluoropropyl	4-(oxazol-5-yl)-phenyl
841.	3-fluoropropyl	4-(isoxazol-3-yl)-phenyl
842.	3-fluoropropyl	4-(isoxazol-4-yl)-phenyl
843.	3-fluoropropyl	4-(isoxazol-5-yl)-phenyl
844.	3-fluoropropyl	4-([1,2,3]-triazol-1-yl)-phenyl
845.	3-fluoropropyl	4-([1,2,4]-triazol-1-yl)-phenyl
846.	3-fluoropropyl	4-([1,2,3]-triazol-2-yl)-phenyl
847.	3-fluoropropyl	4-(4H-[1,2,4]-triazol-3-yl)-phenyl
848.	3-fluoropropyl	4-([1,2,4]-triazol-4-yl)-phenyl
849.	3-fluoropropyl	4-(2H-[1,2,3]-triazol-4-yl)-phenyl
850.	3-fluoropropyl	4-(4-methyl-4H-[1,2,4]-triazol-3-yl)-phenyl
851.	3-fluoropropyl	4-(2-methyl-2H-[1,2,3]-triazol-4-yl)-phenyl
852.	3-fluoropropyl	4-([1,3,4]-oxadiazol-2-yl)-phenyl
853.	3-fluoropropyl	4-([1,2,4]-oxadiazol-3-yl)-phenyl
854.	3-fluoropropyl	4-([1,2,4]-oxadiazol-5-yl)-phenyl
855.	3-fluoropropyl	4-([1,2,3]-oxadiazol-4-yl)-phenyl
856.	3-fluoropropyl	4-([1,2,3]-oxadiazol-5-yl)-phenyl
857.	3-fluoropropyl	4-([1,2,3]-thiadiazol-4-yl)-phenyl
858.	3-fluoropropyl	4-(1H-tetrazol-5-yl)-phenyl
859.	3-fluoropropyl	4-(tetrazol-1-yl)-phenyl
860.	3-fluoropropyl	4-(2-methyl-2H-tetrazol-5-yl)-phenyl
861.	3-fluoropropyl	4-(1-methyl-1H-tetrazol-5-yl)-phenyl
862.	3-fluoropropyl	4-furazan-3-yl-phenyl
863.	3-fluoropropyl	4-(pyrid-2-yl)-phenyl
864.	3-fluoropropyl	4-(pyrid-3-yl)-phenyl
865.	3-fluoropropyl	4-(pyrid-4-yl)-phenyl
866.	3-fluoropropyl	4-(pyrimidin-2-yl)-phenyl
867.	3-fluoropropyl	4-(pyrimidin-4-yl)-phenyl
868.	3-fluoropropyl	4-(pyrimidin-5-yl)-phenyl

No.	R^1	Ar
869.	3-fluoropropyl	5-isopropylthiophen-2-yl
870.	3-fluoropropyl	2-chlorothiophen-5-yl
871.	3-fluoropropyl	2,5-dichlorothiophen-4-yl
872.	3-fluoropropyl	2,3-dichlorothiophen-5-yl
873.	3-fluoropropyl	2-chloro-3-nitrothiophen-5-yl
874.	3-fluoropropyl	2-(phenylsulfonyl)-thiophen-5-yl
875.	3-fluoropropyl	2-(pyridin-2-yl)thiophen-5-yl
876.	3-fluoropropyl	2-(5-(trifluoromethyl)isoxazol-3-yl)-thiophen-5-yl
877.	3-fluoropropyl	2-(2-methylthiazol-4-yl)-thiophen-5-yl
878.	3-fluoropropyl	1-methyl-1H-imidazol-4-yl
879.	3-fluoropropyl	1,2-dimethyl-1H-imidazol-4-yl
880.	3-fluoropropyl	3,5-dimethylisoxazol-4-yl
881.	3-fluoropropyl	thiazol-2-yl
882.	3-fluoropropyl	4-methylthiazol-2-yl
883.	3-fluoropropyl	4-isopropylthiazol-2-yl
884.	3-fluoropropyl	4-trifluoromethylthiazol-2-yl
885.	3-fluoropropyl	5-methylthiazol-2-yl
886.	3-fluoropropyl	5-isopropylthiazol-2-yl
887.	3-fluoropropyl	5-trifluoromethylthiazol-2-yl
888.	3-fluoropropyl	2,4-dimethylthiazol-5-yl
889.	3-fluoropropyl	2-acetamido-4-methylthiazol-5-yl
890.	3-fluoropropyl	4H-[1,2,4]triazol-3-yl
891.	3-fluoropropyl	5-methyl-4H-[1,2,4]triazol-3-yl
892.	3-fluoropropyl	4-methyl-4H-[1,2,4]triazol-3-yl
893.	3-fluoropropyl	5-isopropyl-4H-[1,2,4]triazol-3-yl
894.	3-fluoropropyl	5-trifluoromethyl-4H-[1,2,4]triazol-3-yl
895.	3-fluoropropyl	4,5-dimethyl-4H-[1,2,4]triazol-3-yl
896.	3-fluoropropyl	5-isopropyl-4-methyl-4H-[1,2,4]triazol-3-yl
897.	3-fluoropropyl	5-trifluoromethyl-4-methyl-4H-[1,2,4]triazol-3-yl
898.	3-fluoropropyl	[1,3,4]thiadiazol-2-yl
899.	3-fluoropropyl	5-methyl-[1,3,4]thiadiazol-2-yl
900.	3-fluoropropyl	5-isopropyl-[1,3,4]thiadiazol-2-yl
901.	3-fluoropropyl	5-trifluoromethyl-[1,3,4]thiadiazol-2-yl
902.	3-fluoropropyl	3-bromo-2-chloropyrid-5-yl
903.	3-fluoropropyl	2-(4-morpholino)-pyrid-5-yl
904.	3-fluoropropyl	2-phenoxypyrid-5-yl

No.	R^1	Ar
905.	3-fluoropropyl	(2-isopropyl)-pyrimidin-5-yl
906.	3-fluoropropyl	(5-isopropyl)-pyrimidin-2-yl
907.	3-fluoropropyl	8-quinolyl
908.	3-fluoropropyl	5-isoquinolyl
909.	3-fluoropropyl	2-(2,2,2-trifluoroacetyl)-1,2,3,4-tetrahydroisoquinolin-7-yl
910.	3-fluoropropyl	5-chloro-3-methylbenzothiophen-2-yl
911.	3-fluoropropyl	3,4-dihydro-4-methyl-2H-benzo[b][1,4]oxazinyl
912.	3-fluoropropyl	benzothiazol-6-yl
913.	3-fluoropropyl	benzo[2,1,3]oxadiazol-4-yl
914.	3-fluoropropyl	5-chlorobenzo[1,2,5]oxadiazolyl
915.	3-fluoropropyl	7-chlorobenzo[2,1,3]oxadiazol-4-yl
916.	3-fluoropropyl	benzo[2,1,3]thiadiazol-4-yl
917.	2-fluoroethyl	4-ethylphenyl
918.	2-fluoroethyl	4-propylphenyl
919.	2-fluoroethyl	4-isopropylphenyl
920.	2-fluoroethyl	4-sec-butylphenyl
921.	2-fluoroethyl	4-isobutylphenyl
922.	2-fluoroethyl	4-(1,1-dimethylpropyl)-phenyl
923.	2-fluoroethyl	4-vinylphenyl
924.	2-fluoroethyl	4-isopropenylphenyl
925.	2-fluoroethyl	4-(fluoromethyl)phenyl
926.	2-fluoroethyl	3-(fluoromethyl)phenyl
927.	2-fluoroethyl	2-(fluoromethyl)phenyl
928.	2-fluoroethyl	4-(difluoromethyl)phenyl
929.	2-fluoroethyl	3-(difluoromethyl)phenyl
930.	2-fluoroethyl	2-(difluoromethyl)phenyl
931.	2-fluoroethyl	4-(trifluoromethyl)phenyl
932.	2-fluoroethyl	3-(trifluoromethyl)phenyl
933.	2-fluoroethyl	2-(trifluoromethyl)phenyl
934.	2-fluoroethyl	4-(1-fluoroethyl)-phenyl
935.	2-fluoroethyl	4-((S)-1-fluoroethyl)-phenyl
936.	2-fluoroethyl	4-((R)-1-fluoroethyl)-phenyl
937.	2-fluoroethyl	4-(2-fluoroethyl)-phenyl
938.	2-fluoroethyl	4-(1,1-difluoroethyl)-phenyl
939.	2-fluoroethyl	4-(2,2-difluoroethyl)-phenyl
940.	2-fluoroethyl	4-(2,2,2-trifluoroethyl)-phenyl

No.	R^1	Ar
941.	2-fluoroethyl	4-(3-fluoropropyl)-phenyl
942.	2-fluoroethyl	4-(2-fluoropropyl)-phenyl
943.	2-fluoroethyl	4-((S)-2-fluoropropyl)-phenyl
944.	2-fluoroethyl	4-((R)-2-fluoropropyl)-phenyl
945.	2-fluoroethyl	4-(3,3-difluoropropyl)-phenyl
946.	2-fluoroethyl	4-(3,3,3-trifluoropropyl)-phenyl
947.	2-fluoroethyl	4-(1-fluoro-1-methylethyl)-phenyl
948.	2-fluoroethyl	4-(2-fluoro-1-methylethyl)-phenyl
949.	2-fluoroethyl	4-((S)-2-fluoro-1-methylethyl)-phenyl
950.	2-fluoroethyl	4-((R)-2-fluoro-1-methylethyl)-phenyl
951.	2-fluoroethyl	4-(2,2-difluoro-1-methylethyl)-phenyl
952.	2-fluoroethyl	4-((S)-2,2-difluoro-1-methylethyl)-phenyl
953.	2-fluoroethyl	4-((R)-2,2-difluoro-1-methylethyl)-phenyl
954.	2-fluoroethyl	4-(2,2,2-trifluoro-1-methylethyl)-phenyl
955.	2-fluoroethyl	4-((S)-2,2,2-trifluoro-1-methylethyl)-phenyl
956.	2-fluoroethyl	4-((R)-2,2,2-trifluoro-1-methylethyl)-phenyl
957.	2-fluoroethyl	4-(2-fluoro-1-fluoromethylethyl)-phenyl
958.	2-fluoroethyl	4-(1-difluoromethyl-2,2-difluoroethyl)-phenyl
959.	2-fluoroethyl	4-(1,1-dimethyl-2-fluoroethyl)-phenyl
960.	2-fluoroethyl	4-ethoxyphenyl
961.	2-fluoroethyl	4-propoxyphenyl
962.	2-fluoroethyl	4-isopropoxyphenyl
963.	2-fluoroethyl	4-butoxyphenyl
964.	2-fluoroethyl	4-(fluoromethoxy)-phenyl
965.	2-fluoroethyl	4-(difluoromethoxy)-phenyl
966.	2-fluoroethyl	4-(2-fluoroethoxy)-phenyl
967.	2-fluoroethyl	4-(2,2-difluoroethoxy)-phenyl
968.	2-fluoroethyl	4-(2,2,2-trifluoroethoxy)-phenyl
969.	2-fluoroethyl	4-(1,1,2,2-tetrafluoroethoxy)-phenyl
970.	2-fluoroethyl	4-cyclopropylphenyl
971.	2-fluoroethyl	4-cyclobutylphenyl
972.	2-fluoroethyl	4-cyclopentylphenyl
973.	2-fluoroethyl	4-(2,2-difluorocyclopropyl)-phenyl
974.	2-fluoroethyl	2-fluoro-4-isopropylphenyl
975.	2-fluoroethyl	3-fluoro-4-isopropylphenyl
976.	2-fluoroethyl	4-(1-hydroxy-1-methylethyl)-phenyl

No.	R^1	Ar
977.	2-fluoroethyl	4-(2-hydroxy-2-methylpropyl)-phenyl
978.	2-fluoroethyl	4-acetylphenyl
979.	2-fluoroethyl	4-carboxyphenyl
980.	2-fluoroethyl	4-(O-benzyl)-phenyl
981.	2-fluoroethyl	4-(2-methoxyethoxy)-phenyl
982.	2-fluoroethyl	4-(CH_2-N(CH_3)$_2$)-phenyl
983.	2-fluoroethyl	4-(NH-CO-NH_2)-phenyl
984.	2-fluoroethyl	4-(methylsulfanyl)-phenyl
985.	2-fluoroethyl	4-(fluoromethylsulfanyl)-phenyl
986.	2-fluoroethyl	4-(difluoromethylsulfanyl)-phenyl
987.	2-fluoroethyl	4-(trifluoromethylsulfanyl)-phenyl
988.	2-fluoroethyl	4-(methylsulfonyl)-phenyl
989.	2-fluoroethyl	4-(N-methoxy-N-methyl-amino)-phenyl
990.	2-fluoroethyl	4-(methoxyamino)-phenyl
991.	2-fluoroethyl	4-(ethoxyamino)-phenyl
992.	2-fluoroethyl	4-(N-methylaminooxy)-phenyl
993.	2-fluoroethyl	4-(N,N-dimethylaminooxy)-phenyl
994.	2-fluoroethyl	4-(azetidin-1-yl)-phenyl
995.	2-fluoroethyl	4-(2-methylazetidin-1-yl)-phenyl
996.	2-fluoroethyl	4-((S)-2-methylazetidin-1-yl)-phenyl
997.	2-fluoroethyl	4-((R)-2-methylazetidin-1-yl)-phenyl
998.	2-fluoroethyl	4-(3-fluoroazetidin-1-yl)-phenyl
999.	2-fluoroethyl	4-(3-methoxyazetidin-1-yl)-phenyl
1000.	2-fluoroethyl	4-(3-hydroxyazetidin-1-yl)-phenyl
1001.	2-fluoroethyl	4-(pyrrolidin-1-yl)-phenyl
1002.	2-fluoroethyl	4-(pyrrolidin-2-yl)-phenyl
1003.	2-fluoroethyl	4-((S)-pyrrolidin-2-yl)-phenyl
1004.	2-fluoroethyl	4-((R)-pyrrolidin-2-yl)-phenyl
1005.	2-fluoroethyl	4-(pyrrolidin-3-yl)-phenyl
1006.	2-fluoroethyl	4-((S)-pyrrolidin-3-yl)-phenyl
1007.	2-fluoroethyl	4-((R)-pyrrolidin-3-yl)-phenyl
1008.	2-fluoroethyl	4-(2-fluoropyrrolidin-1-yl)-phenyl
1009.	2-fluoroethyl	4-((S)-2-fluoropyrrolidin-1-yl)-phenyl
1010.	2-fluoroethyl	4-((R)-2-fluoropyrrolidin-1-yl)-phenyl
1011.	2-fluoroethyl	4-(3-fluoropyrrolidin-1-yl)-phenyl
1012.	2-fluoroethyl	4-((S)-3-fluoropyrrolidin-1-yl)-phenyl

No.	R^1	Ar
1013.	2-fluoroethyl	4-((R)-3-fluoropyrrolidin-1-yl)-phenyl
1014.	2-fluoroethyl	4-(2,2-difluoropyrrolidin-1-yl)-phenyl
1015.	2-fluoroethyl	4-(3,3-difluoropyrrolidin-1-yl)-phenyl
1016.	2-fluoroethyl	4-(2-methylpyrrolidin-1-yl)-phenyl
1017.	2-fluoroethyl	4-((S)-2-methylpyrrolidin-1-yl)-phenyl
1018.	2-fluoroethyl	4-((R)-2-methylpyrrolidin-1-yl)-phenyl
1019.	2-fluoroethyl	4-(3-methylpyrrolidin-1-yl)-phenyl
1020.	2-fluoroethyl	4-((S)-3-methylpyrrolidin-1-yl)-phenyl
1021.	2-fluoroethyl	4-((R)-3-methylpyrrolidin-1-yl)-phenyl
1022.	2-fluoroethyl	4-(1-methylpyrrolidin-2-yl)-phenyl
1023.	2-fluoroethyl	4-((S)-1-methylpyrrolidin-2-yl)-phenyl
1024.	2-fluoroethyl	4-((R)-1-methylpyrrolidin-2-yl)-phenyl
1025.	2-fluoroethyl	4-(1-methylpyrrolidin-3-yl)-phenyl
1026.	2-fluoroethyl	4-((S)-1-methylpyrrolidin-3-yl)-phenyl
1027.	2-fluoroethyl	4-((R)-1-methylpyrrolidin-3-yl)-phenyl
1028.	2-fluoroethyl	4-(2,2-dimethylpyrrolidin-1-yl)-phenyl
1029.	2-fluoroethyl	4-(3,3-dimethylpyrrolidin-1-yl)-phenyl
1030.	2-fluoroethyl	4-(2-trifluoromethylpyrrolidin-1-yl)-phenyl
1031.	2-fluoroethyl	4-((S)-2-trifluoromethylpyrrolidin-1-yl)-phenyl
1032.	2-fluoroethyl	4-((R)-2-trifluoromethylpyrrolidin-1-yl)-phenyl
1033.	2-fluoroethyl	4-(3-trifluoromethylpyrrolidin-1-yl)-phenyl
1034.	2-fluoroethyl	4-((S)-3-trifluoromethylpyrrolidin-1-yl)-phenyl
1035.	2-fluoroethyl	4-((R)-3-trifluoromethylpyrrolidin-1-yl)-phenyl
1036.	2-fluoroethyl	4-(2-oxopyrrolidin-1-yl)-phenyl
1037.	2-fluoroethyl	4-(2-oxo-oxazolidin-3-yl)-phenyl
1038.	2-fluoroethyl	4-(piperidin-1-yl)-phenyl
1039.	2-fluoroethyl	4-(2-methylpiperidin-1-yl)-phenyl
1040.	2-fluoroethyl	4-((S)-2-methylpiperidin-1-yl)-phenyl
1041.	2-fluoroethyl	4-((R)-2-methylpiperidin-1-yl)-phenyl
1042.	2-fluoroethyl	4-(piperazin-1-yl)-phenyl
1043.	2-fluoroethyl	4-(4-methylpiperazin-1-yl)-phenyl
1044.	2-fluoroethyl	4-(morpholin-4-yl)-phenyl
1045.	2-fluoroethyl	4-(thiomorpholin-4-yl)-phenyl
1046.	2-fluoroethyl	4-(1-oxo-thiomorpholin-4-yl)-phenyl
1047.	2-fluoroethyl	4-(1,1-dioxo-thiomorpholin-4-yl)-phenyl
1048.	2-fluoroethyl	4-(pyrrol-1-yl)-phenyl

No.	R^1	Ar
1049.	2-fluoroethyl	4-(pyrrol-2-yl)-phenyl
1050.	2-fluoroethyl	4-(pyrrol-3-yl)-phenyl
1051.	2-fluoroethyl	4-(1-methylpyrrol-2-yl)-phenyl
1052.	2-fluoroethyl	4-(1-methylpyrrol-3-yl)-phenyl
1053.	2-fluoroethyl	4-(furan-2-yl)-phenyl
1054.	2-fluoroethyl	4-(furan-3-yl)–phenyl
1055.	2-fluoroethyl	4-(thiophen-2-yl)–phenyl
1056.	2-fluoroethyl	4-(thiophen-3-yl)–phenyl
1057.	2-fluoroethyl	4-(5-propylthien-2-yl)–phenyl
1058.	2-fluoroethyl	4-(pyrazol-1-yl)–phenyl
1059.	2-fluoroethyl	4-(pyrazol-3-yl)–phenyl
1060.	2-fluoroethyl	4-(pyrazol-4-yl)–phenyl
1061.	2-fluoroethyl	4-(1-methyl-1H-pyrazol-4-yl)-phenyl
1062.	2-fluoroethyl	4-(1-ethyl-1H-pyrazol-4-yl)-phenyl
1063.	2-fluoroethyl	4-(1-methyl-1H-pyrazol-5-yl)-phenyl
1064.	2-fluoroethyl	4-(1H-imidazol-2-yl)-phenyl
1065.	2-fluoroethyl	4-(imidazol-1-yl)-phenyl
1066.	2-fluoroethyl	4-(1-methylimidazol-2-yl)-phenyl
1067.	2-fluoroethyl	4-(oxazol-2-yl)-phenyl
1068.	2-fluoroethyl	4-(oxazol-4-yl)-phenyl
1069.	2-fluoroethyl	4-(oxazol-5-yl)-phenyl
1070.	2-fluoroethyl	4-(isoxazol-3-yl)-phenyl
1071.	2-fluoroethyl	4-(isoxazol-4-yl)-phenyl
1072.	2-fluoroethyl	4-(isoxazol-5-yl)-phenyl
1073.	2-fluoroethyl	4-([1,2,3]-triazol-1-yl)-phenyl
1074.	2-fluoroethyl	4-([1,2,4]-triazol-1-yl)-phenyl
1075.	2-fluoroethyl	4-([1,2,3]-triazol-2-yl)-phenyl
1076.	2-fluoroethyl	4-(4H-[1,2,4]-triazol-3-yl)-phenyl
1077.	2-fluoroethyl	4-([1,2,4]-triazol-4-yl)-phenyl
1078.	2-fluoroethyl	4-(2H-[1,2,3]-triazol-4-yl)-phenyl
1079.	2-fluoroethyl	4-(4-methyl-4H-[1,2,4]-triazol-3-yl)-phenyl
1080.	2-fluoroethyl	4-(2-methyl-2H-[1,2,3]-triazol-4-yl)-phenyl
1081.	2-fluoroethyl	4-([1,3,4]-oxadiazol-2-yl)-phenyl
1082.	2-fluoroethyl	4-([1,2,4]-oxadiazol-3-yl)-phenyl
1083.	2-fluoroethyl	4-([1,2,4]-oxadiazol-5-yl)-phenyl
1084.	2-fluoroethyl	4-([1,2,3]-oxadiazol-4-yl)-phenyl

No.	R^1	Ar
1085.	2-fluoroethyl	4-([1,2,3]-oxadiazol-5-yl)-phenyl
1086.	2-fluoroethyl	4-([1,2,3]-thiadiazol-4-yl)-phenyl
1087.	2-fluoroethyl	4-(1H-tetrazol-5-yl)-phenyl
1088.	2-fluoroethyl	4-(tetrazol-1-yl)-phenyl
1089.	2-fluoroethyl	4-(2-methyl-2H-tetrazol-5-yl)-phenyl
1090.	2-fluoroethyl	4-(1-methyl-1H-tetrazol-5-yl)-phenyl
1091.	2-fluoroethyl	4-furazan-3-yl-phenyl
1092.	2-fluoroethyl	4-(pyrid-2-yl)-phenyl
1093.	2-fluoroethyl	4-(pyrid-3-yl)-phenyl
1094.	2-fluoroethyl	4-(pyrid-4-yl)-phenyl
1095.	2-fluoroethyl	4-(pyrimidin-2-yl)-phenyl
1096.	2-fluoroethyl	4-(pyrimidin-4-yl)-phenyl
1097.	2-fluoroethyl	4-(pyrimidin-5-yl)-phenyl
1098.	2-fluoroethyl	5-isopropylthiophen-2-yl
1099.	2-fluoroethyl	2-chlorothiophen-5-yl
1100.	2-fluoroethyl	2,5-dichlorothiophen-4-yl
1101.	2-fluoroethyl	2,3-dichlorothiophen-5-yl
1102.	2-fluoroethyl	2-chloro-3-nitrothiophen-5-yl
1103.	2-fluoroethyl	2-(phenylsulfonyl)-thiophen-5-yl
1104.	2-fluoroethyl	2-(pyridin-2-yl)thiophen-5-yl
1105.	2-fluoroethyl	2-(5-(trifluoromethyl)isoxazol-3-yl)-thiophen-5-yl
1106.	2-fluoroethyl	2-(2-methylthiazol-4-yl)-thiophen-5-yl
1107.	2-fluoroethyl	1-methyl-1H-imidazol-4-yl
1108.	2-fluoroethyl	1,2-dimethyl-1H-imidazol-4-yl
1109.	2-fluoroethyl	3,5-dimethylisoxazol-4-yl
1110.	2-fluoroethyl	thiazol-2-yl
1111.	2-fluoroethyl	4-methylthiazol-2-yl
1112.	2-fluoroethyl	4-isopropylthiazol-2-yl
1113.	2-fluoroethyl	4-trifluoromethylthiazol-2-yl
1114.	2-fluoroethyl	5-methylthiazol-2-yl
1115.	2-fluoroethyl	5-isopropylthiazol-2-yl
1116.	2-fluoroethyl	5-trifluoromethylthiazol-2-yl
1117.	2-fluoroethyl	2,4-dimethylthiazol-5-yl
1118.	2-fluoroethyl	2-acetamido-4-methylthiazol-5-yl
1119.	2-fluoroethyl	4H-[1,2,4]triazol-3-yl
1120.	2-fluoroethyl	5-methyl-4H-[1,2,4]triazol-3-yl

No.	R^1	Ar
1121.	2-fluoroethyl	4-methyl-4H-[1,2,4]triazol-3-yl
1122.	2-fluoroethyl	5-isopropyl-4H-[1,2,4]triazol-3-yl
1123.	2-fluoroethyl	5-trifluoromethyl-4H-[1,2,4]triazol-3-yl
1124.	2-fluoroethyl	4,5-dimethyl-4H-[1,2,4]triazol-3-yl
1125.	2-fluoroethyl	5-isopropyl-4-methyl-4H-[1,2,4]triazol-3-yl
1126.	2-fluoroethyl	5-trifluoromethyl-4-methyl-4H-[1,2,4]triazol-3-yl
1127.	2-fluoroethyl	[1,3,4]thiadiazol-2-yl
1128.	2-fluoroethyl	5-methyl-[1,3,4]thiadiazol-2-yl
1129.	2-fluoroethyl	5-isopropyl-[1,3,4]thiadiazol-2-yl
1130.	2-fluoroethyl	5-trifluoromethyl-[1,3,4]thiadiazol-2-yl
1131.	2-fluoroethyl	3-bromo-2-chloropyrid-5-yl
1132.	2-fluoroethyl	2-(4-morpholino)-pyrid-5-yl
1133.	2-fluoroethyl	2-phenoxypyrid-5-yl
1134.	2-fluoroethyl	(2-isopropyl)-pyrimidin-5-yl
1135.	2-fluoroethyl	(5-isopropyl)-pyrimidin-2-yl
1136.	2-fluoroethyl	8-quinolyl
1137.	2-fluoroethyl	5-isoquinolyl
1138.	2-fluoroethyl	2-(2,2,2-trifluoroacetyl)-1,2,3,4-tetrahydroisoquinolin-7-yl
1139.	2-fluoroethyl	5-chloro-3-methylbenzothiophen-2-yl
1140.	2-fluoroethyl	3,4-dihydro-4-methyl-2H-benzo[b][1,4]oxazinyl
1141.	2-fluoroethyl	benzothiazol-6-yl
1142.	2-fluoroethyl	benzo[2,1,3]oxadiazol-4-yl
1143.	2-fluoroethyl	5-chlorobenzo[1,2,5]oxadiazolyl
1144.	2-fluoroethyl	7-chlorobenzo[2,1,3]oxadiazol-4-yl
1145.	2-fluoroethyl	benzo[2,1,3]thiadiazol-4-yl
1146.	cyclopropylmethyl	4-ethylphenyl
1147.	cyclopropylmethyl	4-propylphenyl
1148.	cyclopropylmethyl	4-isopropylphenyl
1149.	cyclopropylmethyl	4-sec-butylphenyl
1150.	cyclopropylmethyl	4-isobutylphenyl
1151.	cyclopropylmethyl	4-(1,1-dimethylpropyl)-phenyl
1152.	cyclopropylmethyl	4-vinylphenyl
1153.	cyclopropylmethyl	4-isopropenylphenyl
1154.	cyclopropylmethyl	4-(fluoromethyl)phenyl
1155.	cyclopropylmethyl	3-(fluoromethyl)phenyl
1156.	cyclopropylmethyl	2-(fluoromethyl)phenyl

No.	R^1	Ar
1157.	cyclopropylmethyl	4-(difluoromethyl)phenyl
1158.	cyclopropylmethyl	3-(difluoromethyl)phenyl
1159.	cyclopropylmethyl	2-(difluoromethyl)phenyl
1160.	cyclopropylmethyl	4-(trifluoromethyl)phenyl
1161.	cyclopropylmethyl	3-(trifluoromethyl)phenyl
1162.	cyclopropylmethyl	2-(trifluoromethyl)phenyl
1163.	cyclopropylmethyl	4-(1-fluoroethyl)-phenyl
1164.	cyclopropylmethyl	4-((S)-1-fluoroethyl)-phenyl
1165.	cyclopropylmethyl	4-((R)-1-fluoroethyl)-phenyl
1166.	cyclopropylmethyl	4-(2-fluoroethyl)-phenyl
1167.	cyclopropylmethyl	4-(1,1-difluoroethyl)-phenyl
1168.	cyclopropylmethyl	4-(2,2-difluoroethyl)-phenyl
1169.	cyclopropylmethyl	4-(2,2,2-trifluoroethyl)-phenyl
1170.	cyclopropylmethyl	4-(3-fluoropropyl)-phenyl
1171.	cyclopropylmethyl	4-(2-fluoropropyl)-phenyl
1172.	cyclopropylmethyl	4-((S)-2-fluoropropyl)-phenyl
1173.	cyclopropylmethyl	4-((R)-2-fluoropropyl)-phenyl
1174.	cyclopropylmethyl	4-(3,3-difluoropropyl)-phenyl
1175.	cyclopropylmethyl	4-(3,3,3-trifluoropropyl)-phenyl
1176.	cyclopropylmethyl	4-(1-fluoro-1-methylethyl)-phenyl
1177.	cyclopropylmethyl	4-(2-fluoro-1-methylethyl)-phenyl
1178.	cyclopropylmethyl	4-((S)-2-fluoro-1-methylethyl)-phenyl
1179.	cyclopropylmethyl	4-((R)-2-fluoro-1-methylethyl)-phenyl
1180.	cyclopropylmethyl	4-(2,2-difluoro-1-methylethyl)-phenyl
1181.	cyclopropylmethyl	4-((S)-2,2-difluoro-1-methylethyl)-phenyl
1182.	cyclopropylmethyl	4-((R)-2,2-difluoro-1-methylethyl)-phenyl
1183.	cyclopropylmethyl	4-(2,2,2-trifluoro-1-methylethyl)-phenyl
1184.	cyclopropylmethyl	4-((S)-2,2,2-trifluoro-1-methylethyl)-phenyl
1185.	cyclopropylmethyl	4-((R)-2,2,2-trifluoro-1-methylethyl)-phenyl
1186.	cyclopropylmethyl	4-(2-fluoro-1-fluoromethylethyl)-phenyl
1187.	cyclopropylmethyl	4-(1-difluoromethyl-2,2-difluoroethyl)-phenyl
1188.	cyclopropylmethyl	4-(1,1-dimethyl-2-fluoroethyl)-phenyl
1189.	cyclopropylmethyl	4-ethoxyphenyl
1190.	cyclopropylmethyl	4-propoxyphenyl
1191.	cyclopropylmethyl	4-isopropoxyphenyl
1192.	cyclopropylmethyl	4-butoxyphenyl

No.	R^1	Ar
1193.	cyclopropylmethyl	4-(fluoromethoxy)-phenyl
1194.	cyclopropylmethyl	4-(difluoromethoxy)-phenyl
1195.	cyclopropylmethyl	4-(2-fluoroethoxy)-phenyl
1196.	cyclopropylmethyl	4-(2,2-difluoroethoxy)-phenyl
1197.	cyclopropylmethyl	4-(2,2,2-trifluoroethoxy)-phenyl
1198.	cyclopropylmethyl	4-(1,1,2,2-tetrafluoroethoxy)-phenyl
1199.	cyclopropylmethyl	4-cyclopropylphenyl
1200.	cyclopropylmethyl	4-cyclobutylphenyl
1201.	cyclopropylmethyl	4-cyclopentylphenyl
1202.	cyclopropylmethyl	4-(2,2-difluorocyclopropyl)-phenyl
1203.	cyclopropylmethyl	2-fluoro-4-isopropylphenyl
1204.	cyclopropylmethyl	3-fluoro-4-isopropylphenyl
1205.	cyclopropylmethyl	4-(1-hydroxy-1-methylethyl)-phenyl
1206.	cyclopropylmethyl	4-(2-hydroxy-2-methylpropyl)-phenyl
1207.	cyclopropylmethyl	4-acetylphenyl
1208.	cyclopropylmethyl	4-carboxyphenyl
1209.	cyclopropylmethyl	4-(O-benzyl)-phenyl
1210.	cyclopropylmethyl	4-(2-methoxyethoxy)-phenyl
1211.	cyclopropylmethyl	4-(CH_2-$N(CH_3)_2$)-phenyl
1212.	cyclopropylmethyl	4-(NH-CO-NH_2)-phenyl
1213.	cyclopropylmethyl	4-(methylsulfanyl)-phenyl
1214.	cyclopropylmethyl	4-(fluoromethylsulfanyl)-phenyl
1215.	cyclopropylmethyl	4-(difluoromethylsulfanyl)-phenyl
1216.	cyclopropylmethyl	4-(trifluoromethylsulfanyl)-phenyl
1217.	cyclopropylmethyl	4-(methylsulfonyl)-phenyl
1218.	cyclopropylmethyl	4-(N-methoxy-N-methyl-amino)-phenyl
1219.	cyclopropylmethyl	4-(methoxyamino)-phenyl
1220.	cyclopropylmethyl	4-(ethoxyamino)-phenyl
1221.	cyclopropylmethyl	4-(N-methylaminooxy)-phenyl
1222.	cyclopropylmethyl	4-(N,N-dimethylaminooxy)-phenyl
1223.	cyclopropylmethyl	4-(azetidin-1-yl)-phenyl
1224.	cyclopropylmethyl	4-(2-methylazetidin-1-yl)-phenyl
1225.	cyclopropylmethyl	4-((S)-2-methylazetidin-1-yl)-phenyl
1226.	cyclopropylmethyl	4-((R)-2-methylazetidin-1-yl)-phenyl
1227.	cyclopropylmethyl	4-(3-fluoroazetidin-1-yl)-phenyl
1228.	cyclopropylmethyl	4-(3-methoxyazetidin-1-yl)-phenyl

No.	R^1	Ar
1229.	cyclopropylmethyl	4-(3-hydroxyazetidin-1-yl)-phenyl
1230.	cyclopropylmethyl	4-(pyrrolidin-1-yl)-phenyl
1231.	cyclopropylmethyl	4-(pyrrolidin-2-yl)-phenyl
1232.	cyclopropylmethyl	4-((S)-pyrrolidin-2-yl)-phenyl
1233.	cyclopropylmethyl	4-((R)-pyrrolidin-2-yl)-phenyl
1234.	cyclopropylmethyl	4-(pyrrolidin-3-yl)-phenyl
1235.	cyclopropylmethyl	4-((S)-pyrrolidin-3-yl)-phenyl
1236.	cyclopropylmethyl	4-((R)-pyrrolidin-3-yl)-phenyl
1237.	cyclopropylmethyl	4-(2-fluoropyrrolidin-1-yl)-phenyl
1238.	cyclopropylmethyl	4-((S)-2-fluoropyrrolidin-1-yl)-phenyl
1239.	cyclopropylmethyl	4-((R)-2-fluoropyrrolidin-1-yl)-phenyl
1240.	cyclopropylmethyl	4-(3-fluoropyrrolidin-1-yl)-phenyl
1241.	cyclopropylmethyl	4-((S)-3-fluoropyrrolidin-1-yl)-phenyl
1242.	cyclopropylmethyl	4-((R)-3-fluoropyrrolidin-1-yl)-phenyl
1243.	cyclopropylmethyl	4-(2,2-difluoropyrrolidin-1-yl)-phenyl
1244.	cyclopropylmethyl	4-(3,3-difluoropyrrolidin-1-yl)-phenyl
1245.	cyclopropylmethyl	4-(2-methylpyrrolidin-1-yl)-phenyl
1246.	cyclopropylmethyl	4-((S)-2-methylpyrrolidin-1-yl)-phenyl
1247.	cyclopropylmethyl	4-((R)-2-methylpyrrolidin-1-yl)-phenyl
1248.	cyclopropylmethyl	4-(3-methylpyrrolidin-1-yl)-phenyl
1249.	cyclopropylmethyl	4-((S)-3-methylpyrrolidin-1-yl)-phenyl
1250.	cyclopropylmethyl	4-((R)-3-methylpyrrolidin-1-yl)-phenyl
1251.	cyclopropylmethyl	4-(1-methylpyrrolidin-2-yl)-phenyl
1252.	cyclopropylmethyl	4-((S)-1-methylpyrrolidin-2-yl)-phenyl
1253.	cyclopropylmethyl	4-((R)-1-methylpyrrolidin-2-yl)-phenyl
1254.	cyclopropylmethyl	4-(1-methylpyrrolidin-3-yl)-phenyl
1255.	cyclopropylmethyl	4-((S)-1-methylpyrrolidin-3-yl)-phenyl
1256.	cyclopropylmethyl	4-((R)-1-methylpyrrolidin-3-yl)-phenyl
1257.	cyclopropylmethyl	4-(2,2-dimethylpyrrolidin-1-yl)-phenyl
1258.	cyclopropylmethyl	4-(3,3-dimethylpyrrolidin-1-yl)-phenyl
1259.	cyclopropylmethyl	4-(2-trifluoromethylpyrrolidin-1-yl)-phenyl
1260.	cyclopropylmethyl	4-((S)-2-trifluoromethylpyrrolidin-1-yl)-phenyl
1261.	cyclopropylmethyl	4-((R)-2-trifluoromethylpyrrolidin-1-yl)-phenyl
1262.	cyclopropylmethyl	4-(3-trifluoromethylpyrrolidin-1-yl)-phenyl
1263.	cyclopropylmethyl	4-((S)-3-trifluoromethylpyrrolidin-1-yl)-phenyl
1264.	cyclopropylmethyl	4-((R)-3-trifluoromethylpyrrolidin-1-yl)-phenyl

No.	R^1	Ar
1265.	cyclopropylmethyl	4-(2-oxopyrrolidin-1-yl)-phenyl
1266.	cyclopropylmethyl	4-(2-oxo-oxazolidin-3-yl)-phenyl
1267.	cyclopropylmethyl	4-(piperidin-1-yl)-phenyl
1268.	cyclopropylmethyl	4-(2-methylpiperidin-1-yl)-phenyl
1269.	cyclopropylmethyl	4-((S)-2-methylpiperidin-1-yl)-phenyl
1270.	cyclopropylmethyl	4-((R)-2-methylpiperidin-1-yl)-phenyl
1271.	cyclopropylmethyl	4-(piperazin-1-yl)-phenyl
1272.	cyclopropylmethyl	4-(4-methylpiperazin-1-yl)-phenyl
1273.	cyclopropylmethyl	4-(morpholin-4-yl)-phenyl
1274.	cyclopropylmethyl	4-(thiomorpholin-4-yl)-phenyl
1275.	cyclopropylmethyl	4-(1-oxo-thiomorpholin-4-yl)-phenyl
1276.	cyclopropylmethyl	4-(1,1-dioxo-thiomorpholin-4-yl)-phenyl
1277.	cyclopropylmethyl	4-(pyrrol-1-yl)-phenyl
1278.	cyclopropylmethyl	4-(pyrrol-2-yl)-phenyl
1279.	cyclopropylmethyl	4-(pyrrol-3-yl)-phenyl
1280.	cyclopropylmethyl	4-(1-methylpyrrol-2-yl)-phenyl
1281.	cyclopropylmethyl	4-(1-methylpyrrol-3-yl)-phenyl
1282.	cyclopropylmethyl	4-(furan-2-yl)-phenyl
1283.	cyclopropylmethyl	4-(furan-3-yl)–phenyl
1284.	cyclopropylmethyl	4-(thiophen-2-yl)–phenyl
1285.	cyclopropylmethyl	4-(thiophen-3-yl)–phenyl
1286.	cyclopropylmethyl	4-(5-propylthien-2-yl)–phenyl
1287.	cyclopropylmethyl	4-(pyrazol-1-yl)–phenyl
1288.	cyclopropylmethyl	4-(pyrazol-3-yl)–phenyl
1289.	cyclopropylmethyl	4-(pyrazol-4-yl)–phenyl
1290.	cyclopropylmethyl	4-(1-methyl-1H-pyrazol-4-yl)-phenyl
1291.	cyclopropylmethyl	4-(1-ethyl-1H-pyrazol-4-yl)-phenyl
1292.	cyclopropylmethyl	4-(1-methyl-1H-pyrazol-5-yl)-phenyl
1293.	cyclopropylmethyl	4-(1H-imidazol-2-yl)-phenyl
1294.	cyclopropylmethyl	4-(imidazol-1-yl)-phenyl
1295.	cyclopropylmethyl	4-(1-methylimidazol-2-yl)-phenyl
1296.	cyclopropylmethyl	4-(oxazol-2-yl)-phenyl
1297.	cyclopropylmethyl	4-(oxazol-4-yl)-phenyl
1298.	cyclopropylmethyl	4-(oxazol-5-yl)-phenyl
1299.	cyclopropylmethyl	4-(isoxazol-3-yl)-phenyl
1300.	cyclopropylmethyl	4-(isoxazol-4-yl)-phenyl

No.	R^1	Ar
1301.	cyclopropylmethyl	4-(isoxazol-5-yl)-phenyl
1302.	cyclopropylmethyl	4-([1,2,3]-triazol-1-yl)-phenyl
1303.	cyclopropylmethyl	4-([1,2,4]-triazol-1-yl)-phenyl
1304.	cyclopropylmethyl	4-([1,2,3]-triazol-2-yl)-phenyl
1305.	cyclopropylmethyl	4-(4H-[1,2,4]-triazol-3-yl)-phenyl
1306.	cyclopropylmethyl	4-([1,2,4]-triazol-4-yl)-phenyl
1307.	cyclopropylmethyl	4-(2H-[1,2,3]-triazol-4-yl)-phenyl
1308.	cyclopropylmethyl	4-(4-methyl-4H-[1,2,4]-triazol-3-yl)-phenyl
1309.	cyclopropylmethyl	4-(2-methyl-2H-[1,2,3]-triazol-4-yl)-phenyl
1310.	cyclopropylmethyl	4-([1,3,4]-oxadiazol-2-yl)-phenyl
1311.	cyclopropylmethyl	4-([1,2,4]-oxadiazol-3-yl)-phenyl
1312.	cyclopropylmethyl	4-([1,2,4]-oxadiazol-5-yl)-phenyl
1313.	cyclopropylmethyl	4-([1,2,3]-oxadiazol-4-yl)-phenyl
1314.	cyclopropylmethyl	4-([1,2,3]-oxadiazol-5-yl)-phenyl
1315.	cyclopropylmethyl	4-([1,2,3]-thiadiazol-4-yl)-phenyl
1316.	cyclopropylmethyl	4-(1H-tetrazol-5-yl)-phenyl
1317.	cyclopropylmethyl	4-(tetrazol-1-yl)-phenyl
1318.	cyclopropylmethyl	4-(2-methyl-2H-tetrazol-5-yl)-phenyl
1319.	cyclopropylmethyl	4-(1-methyl-1H-tetrazol-5-yl)-phenyl
1320.	cyclopropylmethyl	4-furazan-3-yl-phenyl
1321.	cyclopropylmethyl	4-(pyrid-2-yl)-phenyl
1322.	cyclopropylmethyl	4-(pyrid-3-yl)-phenyl
1323.	cyclopropylmethyl	4-(pyrid-4-yl)-phenyl
1324.	cyclopropylmethyl	4-(pyrimidin-2-yl)-phenyl
1325.	cyclopropylmethyl	4-(pyrimidin-4-yl)-phenyl
1326.	cyclopropylmethyl	4-(pyrimidin-5-yl)-phenyl
1327.	cyclopropylmethyl	5-isopropylthiophen-2-yl
1328.	cyclopropylmethyl	2-chlorothiophen-5-yl
1329.	cyclopropylmethyl	2,5-dichlorothiophen-4-yl
1330.	cyclopropylmethyl	2,3-dichlorothiophen-5-yl
1331.	cyclopropylmethyl	2-chloro-3-nitrothiophen-5-yl
1332.	cyclopropylmethyl	2-(phenylsulfonyl)-thiophen-5-yl
1333.	cyclopropylmethyl	2-(pyridin-2-yl)thiophen-5-yl
1334.	cyclopropylmethyl	2-(5-(trifluoromethyl)isoxazol-3-yl)-thiophen-5-yl
1335.	cyclopropylmethyl	2-(2-methylthiazol-4-yl)-thiophen-5-yl
1336.	cyclopropylmethyl	1-methyl-1H-imidazol-4-yl

No.	R^1	Ar
1337.	cyclopropylmethyl	1,2-dimethyl-1H-imidazol-4-yl
1338.	cyclopropylmethyl	3,5-dimethylisoxazol-4-yl
1339.	cyclopropylmethyl	thiazol-2-yl
1340.	cyclopropylmethyl	4-methylthiazol-2-yl
1341.	cyclopropylmethyl	4-isopropylthiazol-2-yl
1342.	cyclopropylmethyl	4-trifluoromethylthiazol-2-yl
1343.	cyclopropylmethyl	5-methylthiazol-2-yl
1344.	cyclopropylmethyl	5-isopropylthiazol-2-yl
1345.	cyclopropylmethyl	5-trifluoromethylthiazol-2-yl
1346.	cyclopropylmethyl	2,4-dimethylthiazol-5-yl
1347.	cyclopropylmethyl	2-acetamido-4-methylthiazol-5-yl
1348.	cyclopropylmethyl	4H-[1,2,4]triazol-3-yl
1349.	cyclopropylmethyl	5-methyl-4H-[1,2,4]triazol-3-yl
1350.	cyclopropylmethyl	4-methyl-4H-[1,2,4]triazol-3-yl
1351.	cyclopropylmethyl	5-isopropyl-4H-[1,2,4]triazol-3-yl
1352.	cyclopropylmethyl	5-trifluoromethyl-4H-[1,2,4]triazol-3-yl
1353.	cyclopropylmethyl	4,5-dimethyl-4H-[1,2,4]triazol-3-yl
1354.	cyclopropylmethyl	5-isopropyl-4-methyl-4H-[1,2,4]triazol-3-yl
1355.	cyclopropylmethyl	5-trifluoromethyl-4-methyl-4H-[1,2,4]triazol-3-yl
1356.	cyclopropylmethyl	[1,3,4]thiadiazol-2-yl
1357.	cyclopropylmethyl	5-methyl-[1,3,4]thiadiazol-2-yl
1358.	cyclopropylmethyl	5-isopropyl-[1,3,4]thiadiazol-2-yl
1359.	cyclopropylmethyl	5-trifluoromethyl-[1,3,4]thiadiazol-2-yl
1360.	cyclopropylmethyl	3-bromo-2-chloropyrid-5-yl
1361.	cyclopropylmethyl	2-(4-morpholino)-pyrid-5-yl
1362.	cyclopropylmethyl	2-phenoxypyrid-5-yl
1363.	cyclopropylmethyl	(2-isopropyl)-pyrimidin-5-yl
1364.	cyclopropylmethyl	(5-isopropyl)-pyrimidin-2-yl
1365.	cyclopropylmethyl	8-quinolyl
1366.	cyclopropylmethyl	5-isoquinolyl
1367.	cyclopropylmethyl	2-(2,2,2-trifluoroacetyl)-1,2,3,4-tetrahydroisoquinolin-7-yl
1368.	cyclopropylmethyl	5-chloro-3-methylbenzothiophen-2-yl
1369.	cyclopropylmethyl	3,4-dihydro-4-methyl-2H-benzo[b][1,4]oxazinyl
1370.	cyclopropylmethyl	benzothiazol-6-yl
1371.	cyclopropylmethyl	benzo[2,1,3]oxadiazol-4-yl
1372.	cyclopropylmethyl	5-chlorobenzo[1,2,5]oxadiazolyl

No.	R^1	Ar
1373.	cyclopropylmethyl	7-chlorobenzo[2,1,3]oxadiazol-4-yl
1374.	cyclopropylmethyl	benzo[2,1,3]thiadiazol-4-yl
1375.	1-propen-3-yl	4-ethylphenyl
1376.	1-propen-3-yl	4-propylphenyl
1377.	1-propen-3-yl	4-isopropylphenyl
1378.	1-propen-3-yl	4-sec-butylphenyl
1379.	1-propen-3-yl	4-isobutylphenyl
1380.	1-propen-3-yl	4-(1,1-dimethylpropyl)-phenyl
1381.	1-propen-3-yl	4-vinylphenyl
1382.	1-propen-3-yl	4-isopropenylphenyl
1383.	1-propen-3-yl	4-(fluoromethyl)phenyl
1384.	1-propen-3-yl	3-(fluoromethyl)phenyl
1385.	1-propen-3-yl	2-(fluoromethyl)phenyl
1386.	1-propen-3-yl	4-(difluoromethyl)phenyl
1387.	1-propen-3-yl	3-(difluoromethyl)phenyl
1388.	1-propen-3-yl	2-(difluoromethyl)phenyl
1389.	1-propen-3-yl	4-(trifluoromethyl)phenyl
1390.	1-propen-3-yl	3-(trifluoromethyl)phenyl
1391.	1-propen-3-yl	2-(trifluoromethyl)phenyl
1392.	1-propen-3-yl	4-(1-fluoroethyl)-phenyl
1393.	1-propen-3-yl	4-((S)-1-fluoroethyl)-phenyl
1394.	1-propen-3-yl	4-((R)-1-fluoroethyl)-phenyl
1395.	1-propen-3-yl	4-(2-fluoroethyl)-phenyl
1396.	1-propen-3-yl	4-(1,1-difluoroethyl)-phenyl
1397.	1-propen-3-yl	4-(2,2-difluoroethyl)-phenyl
1398.	1-propen-3-yl	4-(2,2,2-trifluoroethyl)-phenyl
1399.	1-propen-3-yl	4-(3-fluoropropyl)-phenyl
1400.	1-propen-3-yl	4-(2-fluoropropyl)-phenyl
1401.	1-propen-3-yl	4-((S)-2-fluoropropyl)-phenyl
1402.	1-propen-3-yl	4-((R)-2-fluoropropyl)-phenyl
1403.	1-propen-3-yl	4-(3,3-difluoropropyl)-phenyl
1404.	1-propen-3-yl	4-(3,3,3-trifluoropropyl)-phenyl
1405.	1-propen-3-yl	4-(1-fluoro-1-methylethyl)-phenyl
1406.	1-propen-3-yl	4-(2-fluoro-1-methylethyl)-phenyl
1407.	1-propen-3-yl	4-((S)-2-fluoro-1-methylethyl)-phenyl
1408.	1-propen-3-yl	4-((R)-2-fluoro-1-methylethyl)-phenyl

No.	R^1	Ar
1409.	1-propen-3-yl	4-(2,2-difluoro-1-methylethyl)-phenyl
1410.	1-propen-3-yl	4-((S)-2,2-difluoro-1-methylethyl)-phenyl
1411.	1-propen-3-yl	4-((R)-2,2-difluoro-1-methylethyl)-phenyl
1412.	1-propen-3-yl	4-(2,2,2-trifluoro-1-methylethyl)-phenyl
1413.	1-propen-3-yl	4-((S)-2,2,2-trifluoro-1-methylethyl)-phenyl
1414.	1-propen-3-yl	4-((R)-2,2,2-trifluoro-1-methylethyl)-phenyl
1415.	1-propen-3-yl	4-(2-fluoro-1-fluoromethylethyl)-phenyl
1416.	1-propen-3-yl	4-(1-difluoromethyl-2,2-difluoroethyl)-phenyl
1417.	1-propen-3-yl	4-(1,1-dimethyl-2-fluoroethyl)-phenyl
1418.	1-propen-3-yl	4-ethoxyphenyl
1419.	1-propen-3-yl	4-propoxyphenyl
1420.	1-propen-3-yl	4-isopropoxyphenyl
1421.	1-propen-3-yl	4-butoxyphenyl
1422.	1-propen-3-yl	4-(fluoromethoxy)-phenyl
1423.	1-propen-3-yl	4-(difluoromethoxy)-phenyl
1424.	1-propen-3-yl	4-(2-fluoroethoxy)-phenyl
1425.	1-propen-3-yl	4-(2,2-difluoroethoxy)-phenyl
1426.	1-propen-3-yl	4-(2,2,2-trifluoroethoxy)-phenyl
1427.	1-propen-3-yl	4-(1,1,2,2-tetrafluoroethoxy)-phenyl
1428.	1-propen-3-yl	4-cyclopropylphenyl
1429.	1-propen-3-yl	4-cyclobutylphenyl
1430.	1-propen-3-yl	4-cyclopentylphenyl
1431.	1-propen-3-yl	4-(2,2-difluorocyclopropyl)-phenyl
1432.	1-propen-3-yl	2-fluoro-4-isopropylphenyl
1433.	1-propen-3-yl	3-fluoro-4-isopropylphenyl
1434.	1-propen-3-yl	4-(1-hydroxy-1-methylethyl)-phenyl
1435.	1-propen-3-yl	4-(2-hydroxy-2-methylpropyl)-phenyl
1436.	1-propen-3-yl	4-acetylphenyl
1437.	1-propen-3-yl	4-carboxyphenyl
1438.	1-propen-3-yl	4-(O-benzyl)-phenyl
1439.	1-propen-3-yl	4-(2-methoxyethoxy)-phenyl
1440.	1-propen-3-yl	4-(CH_2-N(CH_3)$_2$)-phenyl
1441.	1-propen-3-yl	4-(NH-CO-NH_2)-phenyl
1442.	1-propen-3-yl	4-(methylsulfanyl)-phenyl
1443.	1-propen-3-yl	4-(fluoromethylsulfanyl)-phenyl
1444.	1-propen-3-yl	4-(difluoromethylsulfanyl)-phenyl

No.	R^1	Ar
1445.	1-propen-3-yl	4-(trifluoromethylsulfanyl)-phenyl
1446.	1-propen-3-yl	4-(methylsulfonyl)-phenyl
1447.	1-propen-3-yl	4-(N-methoxy-N-methyl-amino)-phenyl
1448.	1-propen-3-yl	4-(methoxyamino)-phenyl
1449.	1-propen-3-yl	4-(ethoxyamino)-phenyl
1450.	1-propen-3-yl	4-(N-methylaminooxy)-phenyl
1451.	1-propen-3-yl	4-(N,N-dimethylaminooxy)-phenyl
1452.	1-propen-3-yl	4-(azetidin-1-yl)-phenyl
1453.	1-propen-3-yl	4-(2-methylazetidin-1-yl)-phenyl
1454.	1-propen-3-yl	4-((S)-2-methylazetidin-1-yl)-phenyl
1455.	1-propen-3-yl	4-((R)-2-methylazetidin-1-yl)-phenyl
1456.	1-propen-3-yl	4-(3-fluoroazetidin-1-yl)-phenyl
1457.	1-propen-3-yl	4-(3-methoxyazetidin-1-yl)-phenyl
1458.	1-propen-3-yl	4-(3-hydroxyazetidin-1-yl)-phenyl
1459.	1-propen-3-yl	4-(pyrrolidin-1-yl)-phenyl
1460.	1-propen-3-yl	4-(pyrrolidin-2-yl)-phenyl
1461.	1-propen-3-yl	4-((S)-pyrrolidin-2-yl)-phenyl
1462.	1-propen-3-yl	4-((R)-pyrrolidin-2-yl)-phenyl
1463.	1-propen-3-yl	4-(pyrrolidin-3-yl)-phenyl
1464.	1-propen-3-yl	4-((S)-pyrrolidin-3-yl)-phenyl
1465.	1-propen-3-yl	4-((R)-pyrrolidin-3-yl)-phenyl
1466.	1-propen-3-yl	4-(2-fluoropyrrolidin-1-yl)-phenyl
1467.	1-propen-3-yl	4-((S)-2-fluoropyrrolidin-1-yl)-phenyl
1468.	1-propen-3-yl	4-((R)-2-fluoropyrrolidin-1-yl)-phenyl
1469.	1-propen-3-yl	4-(3-fluoropyrrolidin-1-yl)-phenyl
1470.	1-propen-3-yl	4-((S)-3-fluoropyrrolidin-1-yl)-phenyl
1471.	1-propen-3-yl	4-((R)-3-fluoropyrrolidin-1-yl)-phenyl
1472.	1-propen-3-yl	4-(2,2-difluoropyrrolidin-1-yl)-phenyl
1473.	1-propen-3-yl	4-(3,3-difluoropyrrolidin-1-yl)-phenyl
1474.	1-propen-3-yl	4-(2-methylpyrrolidin-1-yl)-phenyl
1475.	1-propen-3-yl	4-((S)-2-methylpyrrolidin-1-yl)-phenyl
1476.	1-propen-3-yl	4-((R)-2-methylpyrrolidin-1-yl)-phenyl
1477.	1-propen-3-yl	4-(3-methylpyrrolidin-1-yl)-phenyl
1478.	1-propen-3-yl	4-((S)-3-methylpyrrolidin-1-yl)-phenyl
1479.	1-propen-3-yl	4-((R)-3-methylpyrrolidin-1-yl)-phenyl
1480.	1-propen-3-yl	4-(1-methylpyrrolidin-2-yl)-phenyl

No.	R^1	Ar
1481.	1-propen-3-yl	4-((S)-1-methylpyrrolidin-2-yl)-phenyl
1482.	1-propen-3-yl	4-((R)-1-methylpyrrolidin-2-yl)-phenyl
1483.	1-propen-3-yl	4-(1-methylpyrrolidin-3-yl)-phenyl
1484.	1-propen-3-yl	4-((S)-1-methylpyrrolidin-3-yl)-phenyl
1485.	1-propen-3-yl	4-((R)-1-methylpyrrolidin-3-yl)-phenyl
1486.	1-propen-3-yl	4-(2,2-dimethylpyrrolidin-1-yl)-phenyl
1487.	1-propen-3-yl	4-(3,3-dimethylpyrrolidin-1-yl)-phenyl
1488.	1-propen-3-yl	4-(2-trifluoromethylpyrrolidin-1-yl)-phenyl
1489.	1-propen-3-yl	4-((S)-2-trifluoromethylpyrrolidin-1-yl)-phenyl
1490.	1-propen-3-yl	4-((R)-2-trifluoromethylpyrrolidin-1-yl)-phenyl
1491.	1-propen-3-yl	4-(3-trifluoromethylpyrrolidin-1-yl)-phenyl
1492.	1-propen-3-yl	4-((S)-3-trifluoromethylpyrrolidin-1-yl)-phenyl
1493.	1-propen-3-yl	4-((R)-3-trifluoromethylpyrrolidin-1-yl)-phenyl
1494.	1-propen-3-yl	4-(2-oxopyrrolidin-1-yl)-phenyl
1495.	1-propen-3-yl	4-(2-oxo-oxazolidin-3-yl)-phenyl
1496.	1-propen-3-yl	4-(piperidin-1-yl)-phenyl
1497.	1-propen-3-yl	4-(2-methylpiperidin-1-yl)-phenyl
1498.	1-propen-3-yl	4-((S)-2-methylpiperidin-1-yl)-phenyl
1499.	1-propen-3-yl	4-((R)-2-methylpiperidin-1-yl)-phenyl
1500.	1-propen-3-yl	4-(piperazin-1-yl)-phenyl
1501.	1-propen-3-yl	4-(4-methylpiperazin-1-yl)-phenyl
1502.	1-propen-3-yl	4-(morpholin-4-yl)-phenyl
1503.	1-propen-3-yl	4-(thiomorpholin-4-yl)-phenyl
1504.	1-propen-3-yl	4-(1-oxo-thiomorpholin-4-yl)-phenyl
1505.	1-propen-3-yl	4-(1,1-dioxo-thiomorpholin-4-yl)-phenyl
1506.	1-propen-3-yl	4-(pyrrol-1-yl)-phenyl
1507.	1-propen-3-yl	4-(pyrrol-2-yl)-phenyl
1508.	1-propen-3-yl	4-(pyrrol-3-yl)-phenyl
1509.	1-propen-3-yl	4-(1-methylpyrrol-2-yl)-phenyl
1510.	1-propen-3-yl	4-(1-methylpyrrol-3-yl)-phenyl
1511.	1-propen-3-yl	4-(furan-2-yl)-phenyl
1512.	1-propen-3-yl	4-(furan-3-yl)–phenyl
1513.	1-propen-3-yl	4-(thiophen-2-yl)–phenyl
1514.	1-propen-3-yl	4-(thiophen-3-yl)–phenyl
1515.	1-propen-3-yl	4-(5-propylthien-2-yl)–phenyl
1516.	1-propen-3-yl	4-(pyrazol-1-yl)–phenyl

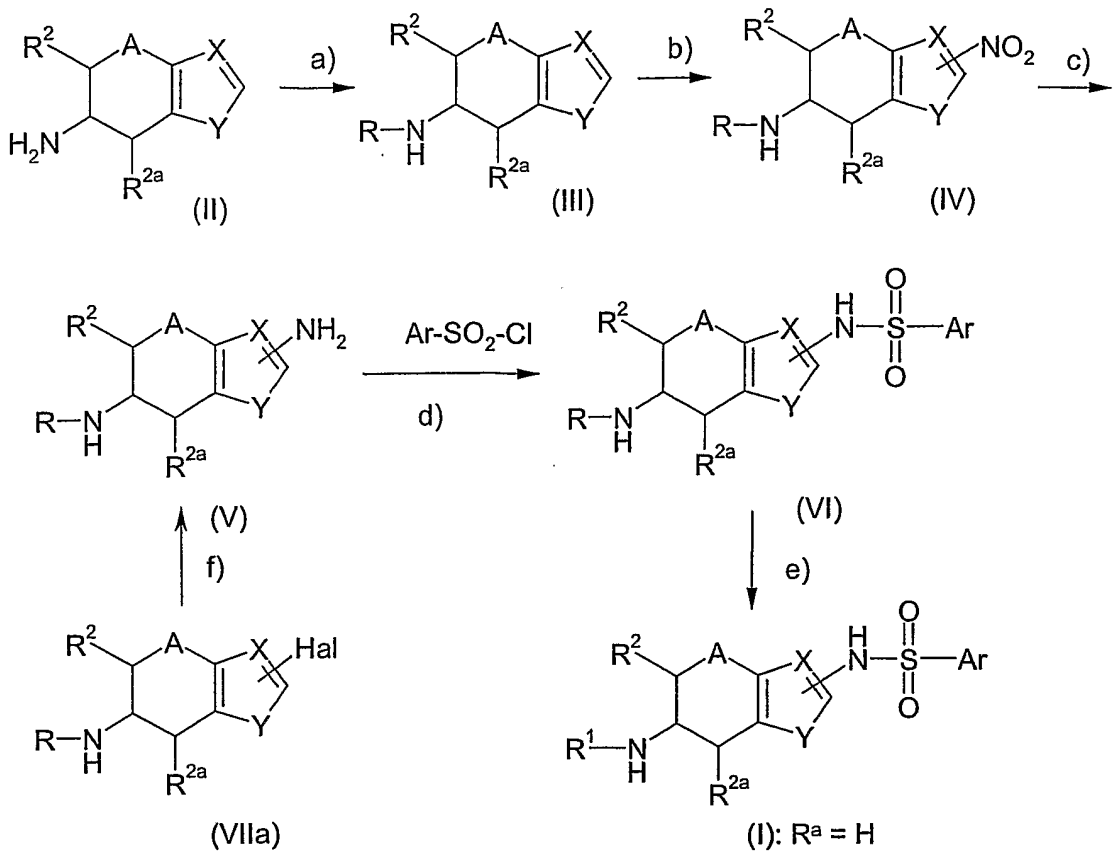
No.	R^1	Ar
1517.	1-propen-3-yl	4-(pyrazol-3-yl)–phenyl
1518.	1-propen-3-yl	4-(pyrazol-4-yl)–phenyl
1519.	1-propen-3-yl	4-(1-methyl-1H-pyrazol-4-yl)-phenyl
1520.	1-propen-3-yl	4-(1-ethyl-1H-pyrazol-4-yl)-phenyl
1521.	1-propen-3-yl	4-(1-methyl-1H-pyrazol-5-yl)-phenyl
1522.	1-propen-3-yl	4-(1H-imidazol-2-yl)-phenyl
1523.	1-propen-3-yl	4-(imidazol-1-yl)-phenyl
1524.	1-propen-3-yl	4-(1-methylimidazol-2-yl)-phenyl
1525.	1-propen-3-yl	4-(oxazol-2-yl)-phenyl
1526.	1-propen-3-yl	4-(oxazol-4-yl)-phenyl
1527.	1-propen-3-yl	4-(oxazol-5-yl)-phenyl
1528.	1-propen-3-yl	4-(isoxazol-3-yl)-phenyl
1529.	1-propen-3-yl	4-(isoxazol-4-yl)-phenyl
1530.	1-propen-3-yl	4-(isoxazol-5-yl)-phenyl
1531.	1-propen-3-yl	4-([1,2,3]-triazol-1-yl)-phenyl
1532.	1-propen-3-yl	4-([1,2,4]-triazol-1-yl)-phenyl
1533.	1-propen-3-yl	4-([1,2,3]-triazol-2-yl)-phenyl
1534.	1-propen-3-yl	4-(4H-[1,2,4]-triazol-3-yl)-phenyl
1535.	1-propen-3-yl	4-([1,2,4]-triazol-4-yl)-phenyl
1536.	1-propen-3-yl	4-(2H-[1,2,3]-triazol-4-yl)-phenyl
1537.	1-propen-3-yl	4-(4-methyl-4H-[1,2,4]-triazol-3-yl)-phenyl
1538.	1-propen-3-yl	4-(2-methyl-2H-[1,2,3]-triazol-4-yl)-phenyl
1539.	1-propen-3-yl	4-([1,3,4]-oxadiazol-2-yl)-phenyl
1540.	1-propen-3-yl	4-([1,2,4]-oxadiazol-3-yl)-phenyl
1541.	1-propen-3-yl	4-([1,2,4]-oxadiazol-5-yl)-phenyl
1542.	1-propen-3-yl	4-([1,2,3]-oxadiazol-4-yl)-phenyl
1543.	1-propen-3-yl	4-([1,2,3]-oxadiazol-5-yl)-phenyl
1544.	1-propen-3-yl	4-([1,2,3]-thiadiazol-4-yl)-phenyl
1545.	1-propen-3-yl	4-(1H-tetrazol-5-yl)-phenyl
1546.	1-propen-3-yl	4-(tetrazol-1-yl)-phenyl
1547.	1-propen-3-yl	4-(2-methyl-2H-tetrazol-5-yl)-phenyl
1548.	1-propen-3-yl	4-(1-methyl-1H-tetrazol-5-yl)-phenyl
1549.	1-propen-3-yl	4-furazan-3-yl-phenyl
1550.	1-propen-3-yl	4-(pyrid-2-yl)-phenyl
1551.	1-propen-3-yl	4-(pyrid-3-yl)-phenyl
1552.	1-propen-3-yl	4-(pyrid-4-yl)-phenyl

No.	R^1	Ar
1553.	1-propen-3-yl	4-(pyrimidin-2-yl)-phenyl
1554.	1-propen-3-yl	4-(pyrimidin-4-yl)-phenyl
1555.	1-propen-3-yl	4-(pyrimidin-5-yl)-phenyl
1556.	1-propen-3-yl	5-isopropylthiophen-2-yl
1557.	1-propen-3-yl	2-chlorothiophen-5-yl
1558.	1-propen-3-yl	2,5-dichlorothiophen-4-yl
1559.	1-propen-3-yl	2,3-dichlorothiophen-5-yl
1560.	1-propen-3-yl	2-chloro-3-nitrothiophen-5-yl
1561.	1-propen-3-yl	2-(phenylsulfonyl)-thiophen-5-yl
1562.	1-propen-3-yl	2-(pyridin-2-yl)thiophen-5-yl
1563.	1-propen-3-yl	2-(5-(trifluoromethyl)isoxazol-3-yl)-thiophen-5-yl
1564.	1-propen-3-yl	2-(2-methylthiazol-4-yl)-thiophen-5-yl
1565.	1-propen-3-yl	1-methyl-1H-imidazol-4-yl
1566.	1-propen-3-yl	1,2-dimethyl-1H-imidazol-4-yl
1567.	1-propen-3-yl	3,5-dimethylisoxazol-4-yl
1568.	1-propen-3-yl	thiazol-2-yl
1569.	1-propen-3-yl	4-methylthiazol-2-yl
1570.	1-propen-3-yl	4-isopropylthiazol-2-yl
1571.	1-propen-3-yl	4-trifluoromethylthiazol-2-yl
1572.	1-propen-3-yl	5-methylthiazol-2-yl
1573.	1-propen-3-yl	5-isopropylthiazol-2-yl
1574.	1-propen-3-yl	5-trifluoromethylthiazol-2-yl
1575.	1-propen-3-yl	2,4-dimethylthiazol-5-yl
1576.	1-propen-3-yl	2-acetamido-4-methylthiazol-5-yl
1577.	1-propen-3-yl	4H-[1,2,4]triazol-3-yl
1578.	1-propen-3-yl	5-methyl-4H-[1,2,4]triazol-3-yl
1579.	1-propen-3-yl	4-methyl-4H-[1,2,4]triazol-3-yl
1580.	1-propen-3-yl	5-isopropyl-4H-[1,2,4]triazol-3-yl
1581.	1-propen-3-yl	5-trifluoromethyl-4H-[1,2,4]triazol-3-yl
1582.	1-propen-3-yl	4,5-dimethyl-4H-[1,2,4]triazol-3-yl
1583.	1-propen-3-yl	5-isopropyl-4-methyl-4H-[1,2,4]triazol-3-yl
1584.	1-propen-3-yl	5-trifluoromethyl-4-methyl-4H-[1,2,4]triazol-3-yl
1585.	1-propen-3-yl	[1,3,4]thiadiazol-2-yl
1586.	1-propen-3-yl	5-methyl-[1,3,4]thiadiazol-2-yl
1587.	1-propen-3-yl	5-isopropyl-[1,3,4]thiadiazol-2-yl
1588.	1-propen-3-yl	5-trifluoromethyl-[1,3,4]thiadiazol-2-yl

No.	R^1	Ar
1589.	1-propen-3-yl	3-bromo-2-chloropyrid-5-yl
1590.	1-propen-3-yl	2-(4-morpholino)-pyrid-5-yl
1591.	1-propen-3-yl	2-phenoxypyrid-5-yl
1592.	1-propen-3-yl	(2-isopropyl)-pyrimidin-5-yl
1593.	1-propen-3-yl	(5-isopropyl)-pyrimidin-2-yl
1594.	1-propen-3-yl	8-quinolyl
1595.	1-propen-3-yl	5-isoquinolyl
1596.	1-propen-3-yl	2-(2,2,2-trifluoroacetyl)-1,2,3,4-tetrahydroisoquinolin-7-yl
1597.	1-propen-3-yl	5-chloro-3-methylbenzothiophen-2-yl
1598.	1-propen-3-yl	3,4-dihydro-4-methyl-2H-benzo[b][1,4]oxazinyl
1599.	1-propen-3-yl	benzothiazol-6-yl
1600.	1-propen-3-yl	benzo[2,1,3]oxadiazol-4-yl
1601.	1-propen-3-yl	5-chlorobenzo[1,2,5]oxadiazolyl
1602.	1-propen-3-yl	7-chlorobenzo[2,1,3]oxadiazol-4-yl
1603.	1-propen-3-yl	benzo[2,1,3]thiadiazol-4-yl

The compounds of the formula I where E is NH and R^{1a} is hydrogen can be prepared by analogy to methods which are well known in the art, e.g. from the international patent applications cited in the introductory part. A preferred method for the preparation of compounds I is outlined in scheme 1:

Scheme 1



In scheme 1, R^1, R^2, R^{2a}, A, X, Y and Ar have the meanings as given above. Hal is halogene in particular bromine or iodine. R is C_1-C_3-alkylcarbonyl, fluorinated C_1-C_3-alkylcarbonyl or may also be also an amino-protecting group PG such as tert.-butoxycarbonyl. Suitable protecting groups are disclosed, for example, in P. Kocienski, Protecting Groups, Thieme-Verlag, Stuttgart 2000, Chapter 6.

In step a) of scheme 1 the amino group of the compound of formula II is reacted with an optionally fluorinated C_2-C_4-acyl halide in the presence of a base to obtain a compound of the formula III, wherein R is optionally fluorinated C_1-C_3-alkylcarbonyl. Acylation can be achieved by standard methods, which are discussed e.g. in J. March, Advanced Organic Chemistry, 3rd ed. J. Wiley & Sons, New York 1985, p.370 and 373 (acylation) and p. 1099 f. and in the literature cited in this publication (see also Synth. Commun. 1986, 16, p. 267). Likewise, the amino group may be protected by standard methods with a conventional amino-protecting group PG, e.g. by reacting II with pivaloyl anhydride in the presence of a tertiary amine such as triethylamine (for reaction conditions see the literature cited in P. Kocienski, Protecting Groups, loc. cit.).

The reaction depicted in step b) in scheme 2 takes place under the reaction conditions which are customary for a nitration of an aromatic radical and which are described, for

example, in J. March, Advanced Organic Chemistry, 3rd ed., John Wiley & Sons, New York 1985, pp 468-470 and the literature cited therein).

In step c), the nitro group in IV is reduced to the NH_2 group in V. Subsequently, in step c), the NH_2 group may be converted into a $-NR^{3'}H$ group, in which $R^{3'}$ has the meanings different from hydrogen which are specified for R^3. The reaction conditions which are required for step c) correspond to the customary conditions for reducing aromatic nitro groups which have been described extensively in the literature (see, for example, J. March, Advanced Organic Chemistry, 3rd ed., J. Wiley & Sons, New-York, 1985, p. 1183 and the literature cited in this reference). The reduction is achieved, for example, by reacting the nitro compound IV with a metal such as iron, zinc or tin under acidic reaction conditions, i.e. using nascent hydrogen, or using a complex hydride such as lithium aluminum hydride or sodium borohydride, preferably in the presence of transition metal compounds of nickel or cobalt such as $NiCl_2(P(phenyl)_3)_2$, or $CoCl_2$,(see Ono et al. Chem. Ind. (London), 1983 p.480), or using $NaBH_2S_3$ (see Lalancette et al. Can. J. Chem. 49, 1971, p. 2990), with it being possible to carry out these reductions, depending on the given reagent, in substance or in a solvent or diluent. Alternatively, the reduction of IV to V can be carried out with hydrogen in the presence of a transition metal catalyst, e.g. using hydrogen in the presence of catalysts based on platinum, palladium, nickel, ruthenium or rhodium. The catalysts can contain the transition metal in elemental form or in the form of a complex compound, of a salt or of an oxide of the transition metal, with it being possible, for the purpose of modifying the activity, to use customary coligands, e.g. organic phosphine compounds, such as triphenylphosphine, tricyclohexylphosphine or tri-n-butylphosphines or phosphites. The catalyst is customarily employed in quantities of from 0.001 to 1 mol per mol of compound IV, calculated as catalyst metal. In a preferred variant, the reduction is effected using tin(II) chloride in analogy with the methods described in Bioorganic and Medicinal Chemistry Letters, 2002, 12(15), pp. 1917-1919 and J. Med. Chem. 2002, 45(21), pp. 4679-4688. The reaction of IV with tin(II) chloride is preferably carried out in an inert organic solvent, preferably an alcohol such as methanol, ethanol, isopropanol or butanol.

The thus obtained compound V is reacted with an arylchlorosulfonylchloride $Cl\text{-}SO_2\text{-}Ar$, preferably in the presence of a base, according to standard procedures in the art to obtain compound VI. The reaction depicted in scheme 1 step d) takes place under the reaction conditions which are customary for preparing arylsulfonamide compounds or arylsulfonic esters, respectively, and which are described, for example, in J. March, Advanced Organic Chemistry, 3rd edition, John Wiley & Sons, New York, 1985 p 444 and the literature cited therein, European Journal of Medicinal Chemistry (1977), 12(1), 61-66, European J. Org. Chem. 2002 (13), pp. 2094-2108, Tetrahedron 2001

57 (27) pp. 5885-5895, Bioorganic and Medicinal Chemistry Letters, 2000, 10(8), pp. 835-838 and Synthesis 2000 (1), pp. 103-108. The reaction customarily takes place in an inert solvent, for example in an ether, such as diethyl ether, diisopropyl ether, methyl tert-butyl ether or tetrahydrofuran, a halohydrocarbon, such as dichloromethane, an aliphatic or cycloaliphatic hydrocarbon, such as pentane, hexane or cyclohexane, or an aromatic hydrocarbon, such as toluene, xylene, cumene and the like, or in a mixture of the abovementioned solvents. The reaction of V with Cl-SO_2-Ar is customarily carried out in the presence of an auxiliary base. Suitable bases are inorganic bases, such as sodium carbonate or potassium carbonate, or sodium hydrogencarbonate or potassium hydrogencarbonate, and organic bases, for example trialkylamines, such as triethylamine, or pyridine compounds, such as pyridine, lutidine and the like. The latter compounds can at the same time serve as solvents. The auxiliary base is customarily employed in at least equimolar quantities, based on the amine compound V.

The amino compounds of the formula V can also be prepared from the corresponding bromine compounds VIIa by reacting VIIa with an alkalimetal salt of a bis(trialkylsilyl)amine such as lithium bis(trimethylsilyl)amide in the presence of a palladium catalyst and subsequent hydrolysis. An example for a suitable palladium catalyst is tris(dibenzylideneacetone)dipalladium(0), optionally in the presence of a tri(substituted)phosphine, e.g. a triarylphosphine such as triphenylphosphine or tritolylphosphine, tri(cyclo)alkylphosphine such as tris-n-butylphosphine, tris(tert.-butyl)phosphine or tris(cyclohexylphosphine), or $PdCl_2$(dppf). The reaction of VIIa with the alkalimetal-bis(trialkylsilyl)amide can be performed by analogy to a Buchwald-Hartig coupling. the alkalimetal-bis(trialkylsilyl)amide can be generated in-situ from the corresponding amine by a strong base such an alkalimetal alkoxide, e.g. potassium tert.-butylat or an alkalimetal hydride such as lithium hydride, sodium hydride and the like. Hydrolysis is simply achieved by aqueous work-up.

If R is optionally fluorinated C_1-C_3-alkylcarbonyl, the carbonyl group in these compounds can be reduced to a CH_2-moiety either with diborane, borane-dimethylsulfide or lithium aluminium hydride to obtain compounds of the general formula I, wherein R is CH_2-(optionally fluorinated C_1-C_3-alkyl) (see e.g. see also J. Heterocycl. Chem. 1979, 16, p. 1525). The carbonyl group can also be reacted with a fluorinating agent to obtain a compound I wherein R^1 is 1,1-difluoroalkyl.

If R is a protecting group, this group can be cleaved by standard methods, whereby a compound of the formula I is obtained, wherein both R^1 and R^{1a} are hydrogen. This compound can then be reacted, in a known manner, in the sense of an alkylation, with

a compound R^1-L. In this compound, R^1 is C_2-C_4-alkyl, C_3-C_4-cycloalkyl, C_3-C_4-alkenyl, fluorinated C_1-C_4-alkyl, fluorinated C_3-C_4-cycloalkyl, fluorinated C_3-C_4-alkenyl and L is a nucleophilically displaceable leaving group, e.g. halogen, trifluoroacetate, alkylsulfonate, arylsulfonate, alkyl sulfate and the like. The reaction conditions which are required for the alkylation have been adequately disclosed, e.g. in Bioorganic and Medicinal Chemistry Lett. 2002, 12(7), pp. 2443-2446 and also 2002, 12(5), pp. 1917-1919.

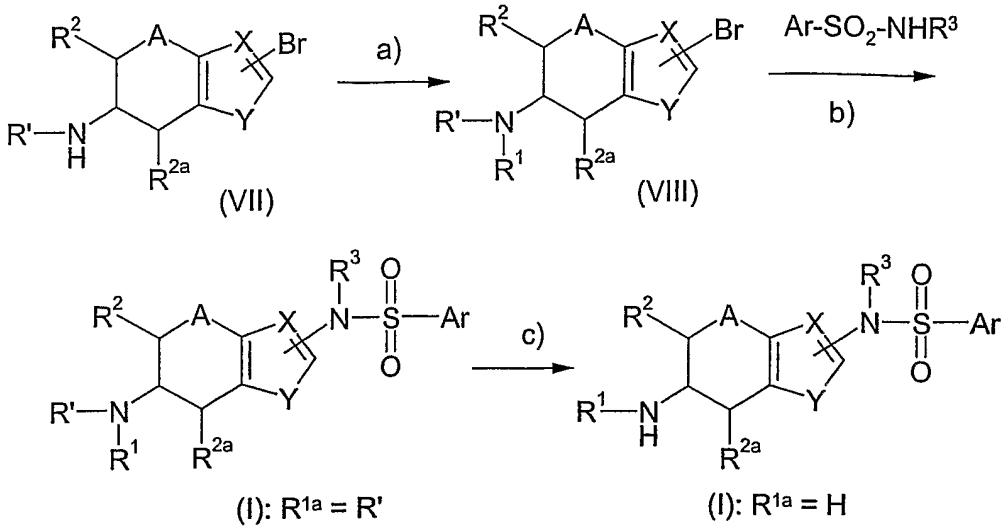
The introduction of C_2-C_4-alkyl or fluorinated C_2-C_4-alkyl as a radical R^1 into a compound of formula I, wherein both R^1 and R^{1a} are hydrogen, can also be achieved, in the sense of a reductive amination, by reacting I [$R^1 = R^{1a} = H$] with a suitable ketone or aldehyde in the presence of a reducing agent, e.g. in the presence of a borohydride such as sodium borohydride, sodium cyanoborohydride or sodium triacetoxyborohydride. The skilled person is familiar with the reaction conditions which are required for a reductive amination, e.g. from Bioorganic and Medicinal Chemistry Lett. 2002, 12(5), pp. 795-798 and 12(7) pp. 1269-1273.

A skilled person will appreciate, that a compound I, wherein R^1 is alkenyl can be converted into a compound wherein R^1 is alkyl or fluorinated alkyl by hydrogenation or by addition of hydrogen fluoride or by fluorination with suitable fluorinating agents such as XeF_2 or CoF_3.

A skilled person will further appreciate, that a radical R_3, which is different from hydrogen, can be introduced in either compound I of scheme I or at an earlier stage of the synthesis by a conventional alkylation.

Compounds of the general formula I, wherein E is N-R^3 can also be obtained by the synthetic route outlined in scheme 2.

Scheme 2:



In scheme 2, R' is an amino-protecting group or has one of the meanings given for R^{1a}, provided that R' is different from hydrogen. R^2, R^{2a}, R^3, A, X, Y and Ar have the meanings given above.

In step a) of scheme 2 a radical R^1 is introduced into compound VII either by acylation or by alkylation as outlined for scheme 1.

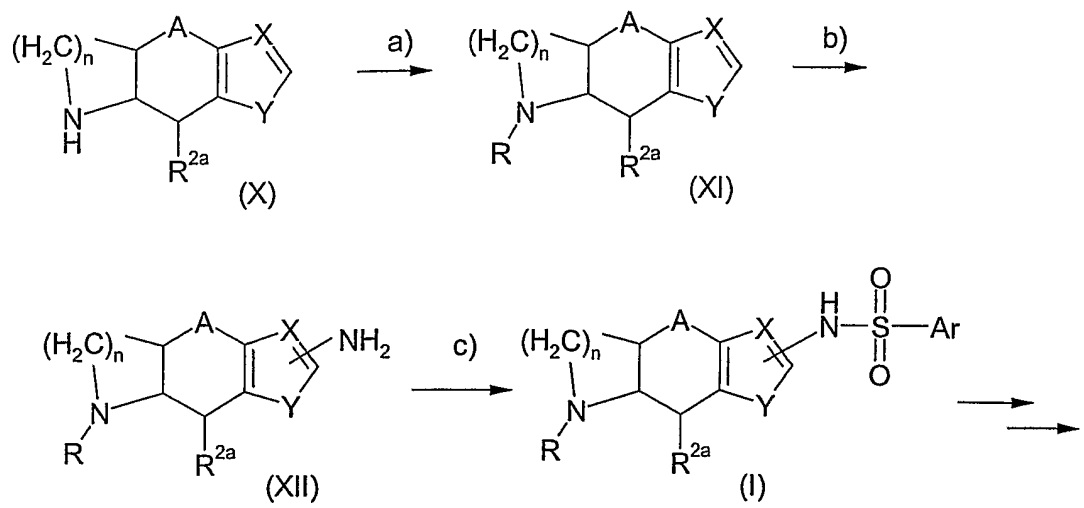
In step b) of scheme 2, compound VIII is reacted with an arylsulfonylamide Ar-SO_2-NH_2 or the lithium salt thereof in the presence of a palladium(0) compound such as tris(dibenylideneacetone)dipalladium(0) in the presence of a tri(substituted)phosphine, e.g. a triarylphosphine such as triphenylphosphine or tritolylphosphine, tri(cyclo)alkylphosphine such as tris-n-butylphosphine, tris(tert.-butyl)phosphine or tris(cyclohexylphosphine), preferably in the presence of a base such as sodium hydride according to the method described in J. Org. Chem., 68 (2993) pp 8274-8276, and outlined below.

If R' is an amino-protecting group, R' can be cleaved by standard methods to obtain a compound of the formula I, wherein R^{1a} is hydrogen (step c).

A skilled person will appreciate, that the radical R^1 compounds I shown in scheme 2, can be further modified as described for scheme 1.

Compounds of the formula I, wherein R^{1a} and R^2 together are $(CH_2)_n$ with n being 2 or 3 can be prepared in manner similar to the method outlined in scheme 1 starting from a compound of the formula IX, by the method outlined in scheme 3:

Scheme 3:

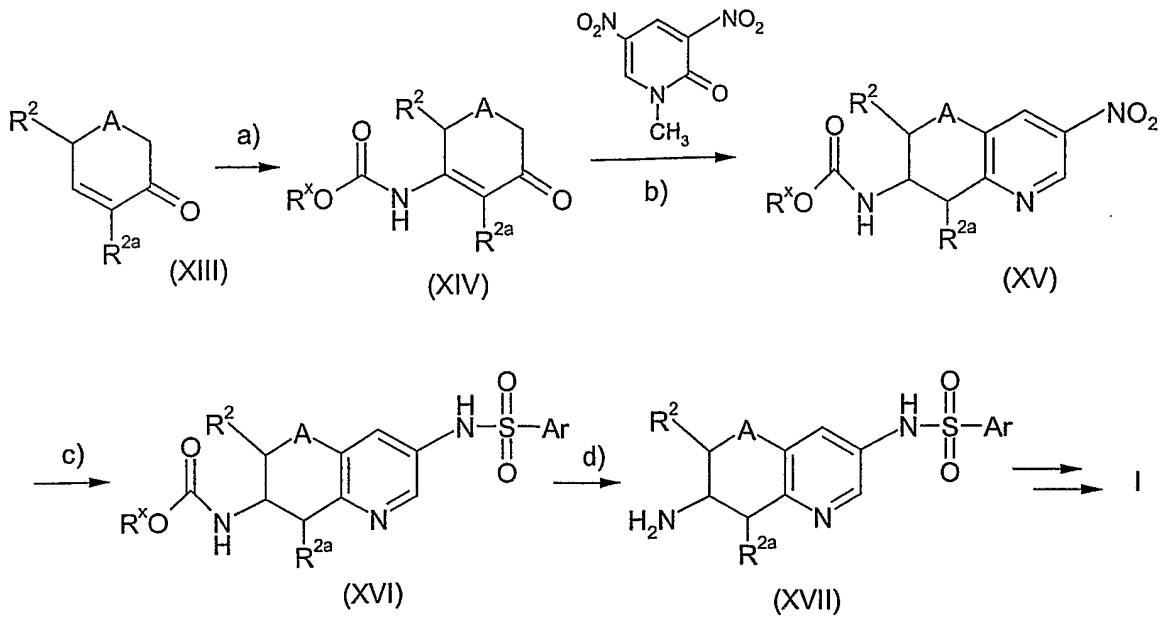


In scheme 3, R^{2a}, n, A, X, Y and Ar have the meanings given above. R is a radical R^1 or an amino protecting group. In particular R^1 is C_1-C_3-alkylcarbonyl. In step a) a radical R^1 is introduced in compound X by a method corresponding to the methods described for step e) in scheme 1. Compound XI is converted into the amino compound XII by a nitration/reduction sequence described for steps b and c of scheme 1. Step c) of scheme 3 can by performed by analogy to a method described for step d in scheme 1.

A skilled person will appreciate that compound I of scheme 3 can be further reacted as described for scheme 1. A skilled person will further appreciate, that compounds wherein R^{1a} and R^{2a} together are $(CH_2)_n$ can be prepared by a similar approach.

Compounds of the formula I, where X is CH, Y is N=CH and E is NR^3 can be also obtained by the synthetic approach outlined in scheme 4:

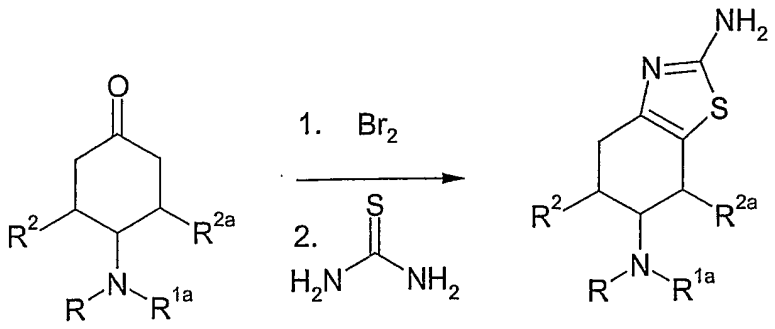
Scheme 4:



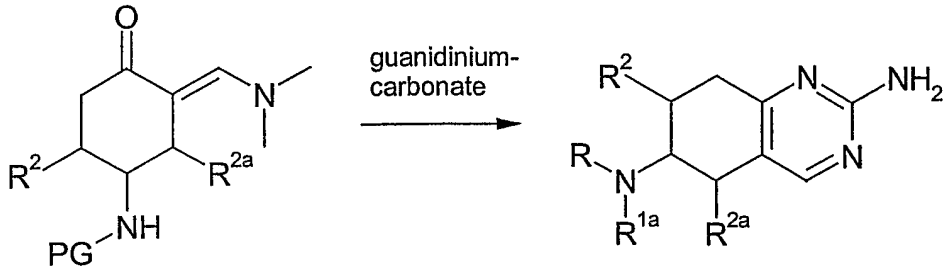
Starting from cyclohex-2-enone XIII (or the corresponding pyranon (A=O) or thianon (A=S)), selective Michael addition of a carbamate R^xO-C(O)-NH_2, in the presence of bismuth nitrate, generates the requisite β-amino ketone XIV (step a, see e.g. (*J. Org. Chem.* **2003**, *68*, 2109-2114). In step b), compound XIV undergoes Tohda reaction with dinitropyridone to give the azabicyclic nitro derivative XV (step c), see e.g. *Bull. Chem. Soc. Jpn.* **1990**, *63*, 2820-2827; *J. Med. Chem.* **1996**, *39*, 2844-2851; *Synth. Commun.* **2001**, *31*, 787-797; *Bioorg. Med. Chem. Lett.* **2003**, *13*, 529-532). This generates a mixture of the 5- and 7-amino isomers which can be separated as either the amino or sulfonamide product. The mixture can then be reduced to the amine by the methods disclosed for step b in scheme 2, e.g. via tin chloride or catalytic hydrogenation (e.g. Pd-C/H_2) and subsequently converted to the desired sulfonamide by reaction with the appropriate sulfonyl chloride as outlined for step b) in scheme 1 to yield a compound of the formula XVI. The amine XVI may be generated by cleavage of the carbamate in the presence of an acid such as trifluoroacetic acid and converted to the target N-alkyl derivatives by processes of alkylation, acylation/reduction or reductive amination as outlined for scheme 1.

Compounds of the formulae II, VII and X are known in the art or they can be prepared in case of VII by subsequent amino-protection of the corresponding amines and bromination. The preparation of compounds X can be achieved e.g. by the method disclosed in Organic Process Research and Development 7(6) (2003) 904-912.

Compounds V, wherein R is alkylcarbonyl, A is CH_2, X is N and Y is S, can be prepared by the following reaction scheme:

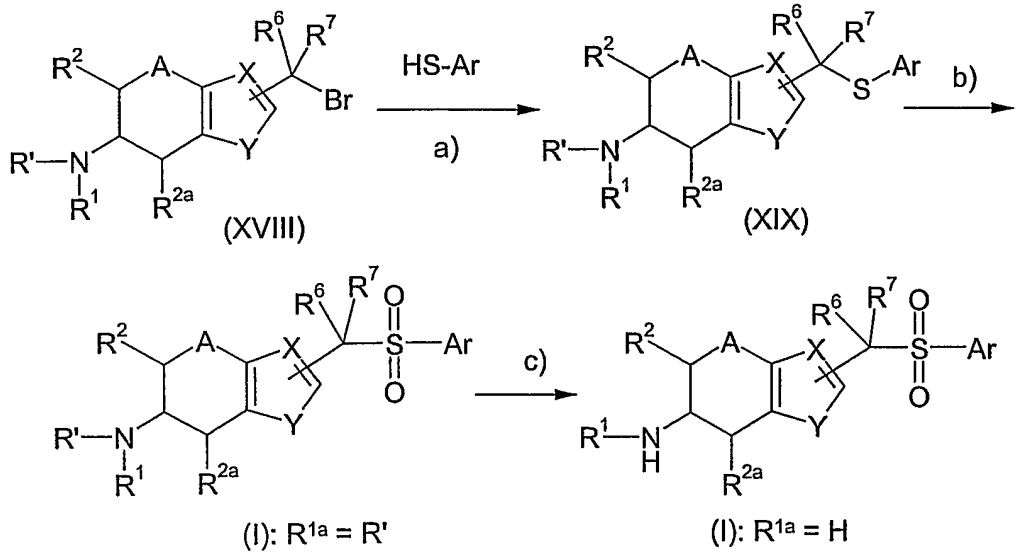


Compounds V, wherein R is an aminoprotecting group PG, A is CH_2, X is N and Y is CH=N, can be prepared by the following reaction scheme:



The compounds of the formula I where E is CR^6R^7 can be prepared as outlined in scheme 5:

Scheme 5:



In scheme 5, R^1, R^2, R^{2a}, R^6, R^7, Ar, A, X and Y have the meanings given above. R' is a radical R^{1a} or a protective group. According to scheme 5, compound XVIII is reacted in

step b) with a mercapto compound HS-Ar in the presence of a base, such as sodium hydride or sodium alkoxide or with an alkali metal salt thereof thereby yielding thioether compound XIX. The thioether moiety in compound is oxidized to a sulfone moiety, e.g. by oxone (step b). If R' is a protective group, R' can be cleaved, thereby obtaining compound I, wherein R^{1a} is H. A skilled person understands that I can be further transformed as outlined for scheme 1.

A skilled person will readily appreciate that compopunds of the formula I can also be obtained from structurally similar compounds by functional group interconversion. In particular N-bound radicals R^a can be introduced into compounds of the formula I by reacting the corresponding halogen compound, i.e. a compound of the formula I, which instead of R^a carries a halogen atom, in particular a bromine or iodine atom, with a primary or secondary amine in the presence of a base, preferably also in the presence of a palladium catalyst in terms of a Buchwald-Hartwig reaction.

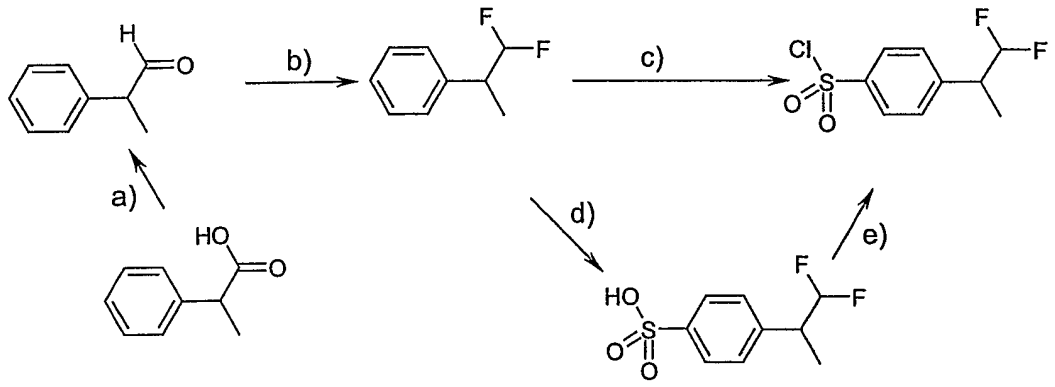
If not indicated otherwise, the above-described reactions are generally carried out in a solvent at temperatures between room temperature and the boiling temperature of the solvent employed. Alternatively, the activation energy which is required for the reaction can be introduced into the reaction mixture using microwaves, something which has proved to be of value, in particular, in the case of the reactions catalyzed by transition metals (with regard to reactions using microwaves, see Tetrahedron 2001, 57, p. 9199 ff. p. 9225 ff. and also, in a general manner, "Microwaves in Organic Synthesis", André Loupy (Ed.), Wiley-VCH 2002.

The sulfonylchlorides Cl-SO_2-Ar are either commercially available or can be prepared according to standard synthetic methods. Sulfonylchlorides containing a fluorinated radical R^a may be prepared by different synthetic routes, e.g. by reacting suitable hydroxy or oxo precursor (e.g. a compound Cl-SO_2-Ar, carrieng a hydroxy or oxo substituted radical) with fluorinating reagents like DAST (diethylaminosulfurtrifluoride), morpholine-DAST, deoxo-fluor (bis(2-methoxyethyl)aminosulfur trifluoride), Ishikawa's reagent (N,N-diethyl-(1,1,2,3,3,3-hexafluoropropyl)amine; Journal of Fluorine Chemistry, 1989, 43, 371-377). More conventionally, the hydroxy group of an aromatic compound which carries a hydroxy substituted radical but not a chlorosulfonyl group, is transformed into a leaving group which is then replace by a fluoride ion (J. Org. Chem., 1994, 59, 2898-22901; Tetrahedron Letters, 1998, 7305-6; J. Org. Chem., 1998, 63, 9587-9589, Synthesis, 1987, 920-21)). Subsequent direct chlorosulfonylation with chlorosulfonic acid (Heterocycles, 2001, 55, 9, 1789-1803; J. Org. Chem., 2000, 65, 1399-1406) or a two step process preparing first the sulfonic acid derivatives which are then transformed to the sulfonylchlorides with e.g. chlorosulfonic acid, phosphorour penta-

chloride (Eur. J. Med. Chem., 2002, 36, 809-828) and the like, yields the desired sulfonylchloride (Tetrahedron Letters, 1991, 33,50 7787-7788)) Sulfonylchlorides may also be prepared by diazotation of suitable amine precursor Ar-NH_2 with sodium nitrite under acidic conditions and reaction with sulfur dioxide in acetic acid (scheme (iii); J. Org. Chem., 1960, 25, 1824-26;); by oxidation of suitable heteroaryl-thiols HS-Ar or heteroaryl-benzyl-thioethers C_6H_5-CH_2-S-Ar with chlorine (Synthesis, 1998, 36-38; J. Am. Chem. Soc., 1950, 74, 4890-92;) directly to the corresponding sulfonyl chlorides. The further are known in the art or may be prepared by standard methods. E.g. mercapto-pyrimidines or pyrimidinyl-benzylthioether precursors can e.g. be prepared according to literature (Chemische Berichte, 1960, 1208-11; Chemische Berichte, 1960, 95, 230-235; Collection Czechoslow. Chem. Comm., 1959, 24, 1667-1671; Austr. J. Chem., 1966, 19, 2321-30; Chemiker-Zeitung, 101, 6, 1977, 305-7; Tetrahedron, 2002, 58, 887-890; Synthesis, 1983, 641-645.

In the following schemes 6 to 8 several routes are shown which are suitable to prepare benzenesulfonyl chlorides carrying a fluorinated propyl radical.

Scheme 6:

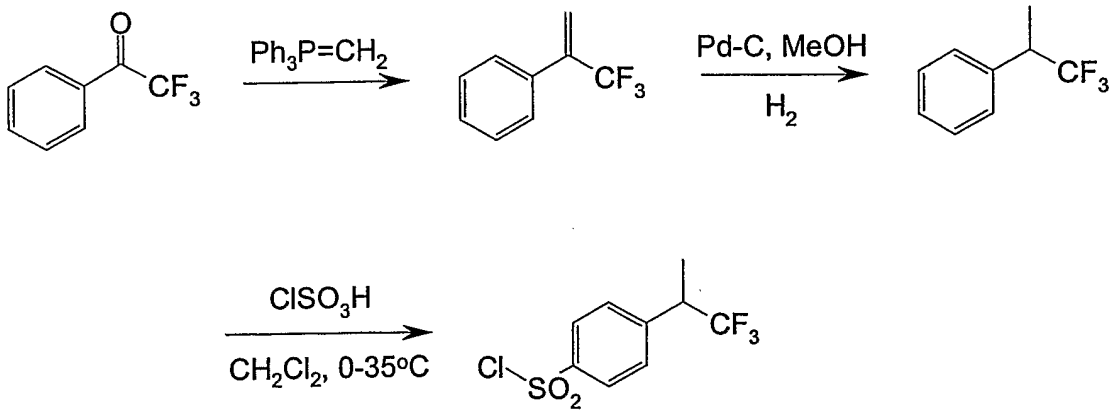


The 4-(1,1-difluoropropan-2-yl)benzene-1-sulfonyl chloride intermediate can be prepared from the commercially available 2-phenylpropanoic acid. In the first step a) the 2-phenylpropanic acid is converted to the alkyl ester by esterification with an alcohol (e.g. methanol or ethanol) under acid catalysis (e.g. HCl , SO_2Cl_2). The ester can be reduced to the corresponding 2-phenyl propanal by a reducing agent such as DIBAL (diisobutylaluminium hydride). The aldehyde is converted to the 1,1-difluoro-2-propyl derivative by reaction with a suitable fluorinating reagent like DAST (diethylaminosulfurtrifluoride), morpholine-DAST, deoxo-fluor (bis(2-methoxyethyl)aminosulfur trifluoride), Ishikawa's reagent (N,N-diethyl-(1,1,2,3,3,3-hexafluoropropyl)amine; Journal of Fluorine Chemistry, 1989, 43, 371-377) (step b). The thus obtained 1,1-difluoro-2-phenylpropane can be converted into 4-(1,1-difluoro-2-propyl)benzenesulfonyl chlo-

ride by either direct chlorosulfonylation with chlorosulfonic acid (Heterocycles, 2001, 55, 9, 1789-1803; J. Org. Chem., 2000, 65, 1399-1406) (step c) or by a two step process preparing first the sulfonic acid derivatives (step d) which are then transformed to the sulfonylchlorides (step e) by reaction with e.g. chlorosulfonic acid, phosphorous pentachloride (Eur. J. Med. Chem., 2002, 36, 809-828); through diazotisation of suitable amine precursors with sodium nitrite under acidic conditions and reaction with sulfur dioxide in acetic acid (J. Org. Chem., 1960, 25, 1824-26); oxidation of suitable heteroaryl-thiols or heteroaryl-benzyl-thioethers with chlorine (Synthesis, 1998, 36-38; J. Am. Chem. Soc., 1950, 74, 4890-92) directly to the corresponding sulfonyl chlorides.

The synthesis shown in scheme 6 can also be performed using (R)-2-phenylpropanic acid and (S)-2-phenylpropanic acid respectively to give the corresponding chiral 4-(1,1-difluoropropan-2-yl)benzene-1-sulfonyl chlorides.

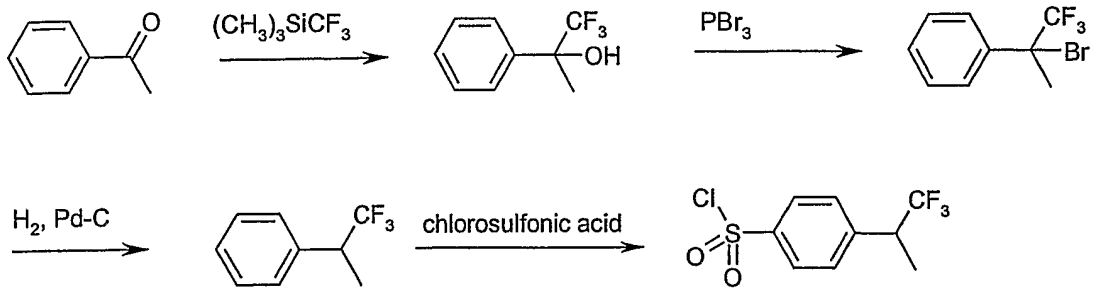
Scheme 7:



4-(1,1,1-Trifluoropropan-2-yl)benzene-1-sulfonyl chloride intermediate can be prepared from the commercially available 2,2,2-trifluoro-1-phenylethanone by a synthetic route shown in scheme 7. The ketone can be converted to the 3,3,3-trifluoro-2-phenylpropene by a Wittig reaction with a suitable ylide such as methylene-triphenylphosphane (prepared by reaction of methyltriphenylphosphonium halide and a suitable base such as lithium diisopropylamide or potassium tert-butoxide) or according to a Horner-Emmons reaction by reacting the ketone with a suitable phosphonate such as diethyl methylphosphonate and a suitable suitable base such as lithium diisopropylamide or potassium tert-butoxide. The thus obtained 3,3,3-trifluoro-2-phenylpropene can then be reduced to the saturated alkane by catalytic hydrogenation (eg Pd-C) followed by conversion to the sulfonyl chloride by the methods described in scheme 6.

The synthesis of scheme 7 can also be performed using a chiral catalyst for the alkene hydrogenation to allow the preparation of the corresponding chiral 4-(1,1,1-triifluoropropan-2-yl)benzene-1-sulfonyl chlorides.

Scheme 8:



The 4-(1,1,1-trifluoropropan-2-yl)benzene-1-sulfonyl chloride can be also prepared from the commercially available 1-phenyl-ethanone by a four step procedure as shown in scheme 8. The ketone can be converted to the trifluoromethyl hydroxyl intermediate by reaction with trimethyl-trifluoromethyl-silane (Journal of Organic Chemistry, 2000, 65, 8848-8856; Journal of Fluorine Chemistry, 2003, 122, 243-246) which can then be converted to the trifluoromethyl bromide (Journal of the American Chemical Society, 1987, 109, 2435-4). Dehalogenation by catalytic hydrogenation (eg Pd-C) can then be followed by conversion to the sulfonyl chloride by the methods discussed above.

Examples of solvents which can be used are ethers, such as diethyl ether, diisopropyl ether, methyl *tert*-butyl ether or tetrahydrofuran, aprotic polar solvent, such as dimethylformamide, dimethyl sulfoxide, dimethoxyethane, and acetonitrile, aromatic hydrocarbons, such as toluene and xylene, ketones, such as acetone or methyl ethyl ketone, halohydrocarbons, such as dichloromethane, trichloromethane and dichloroethane, esters, such as ethyl acetate and methyl butyrate, carboxylic acids, such as acetic acid or propionic acid, and alcohols, such as methanol, ethanol, n-propanol, isopropanol, n-butanol, isobutanol, 2-butanol and tert.-butanol.

If desired, it is possible for a base to be present in order to neutralize protons which are released in the reactions. Suitable bases include inorganic bases, such as sodium carbonate, potassium carbonate, sodium hydrogen carbonate or potassium hydrogen carbonate, and, in addition, alkoxides, such as sodium methoxide or sodium ethoxide, alkali metal hydrides, such as sodium hydride, and also organometallic compounds, such as butyllithium compounds or alkylmagnesium compounds, or organic nitrogen

bases, such as triethylamine or pyridine. The latter compounds can at the same time serve as solvents.

The crude product is isolated in a customary manner, for example by filtering, distilling off the solvent or extracting from the reaction mixture, etc. The resulting compounds can be purified in a customary manner, for example by means of recrystallizing from a solvent, by means of chromatography or by means of converting into an acid addition salt.

The acid addition salts are prepared in a customary manner by mixing the free base with a corresponding acid, where appropriate in solution in an organic solvent, for example a lower alcohol, such as methanol, ethanol or propanol, an ether, such as methyl *tert*-butyl ether or diisopropyl ether, a ketone, such as acetone or methyl ethyl ketone, or an ester, such as ethyl acetate.

The compounds according to the invention of the formula I are surprisingly highly selective dopamine D_3 receptor ligands which, because of their low affinity for other receptors such as D_1 receptors, D_4 receptors, α1-adrenergic and/or α2-adrenergic receptors, muscarinergic receptors, histamine receptors, opiate receptors and, in particular, dopamine D_2 receptors, give rise to fewer side-effects than do the classic neuroleptics, which are D_2 receptor antagonists. A compound of the invention can be a dopamine D_3 receptor agonist, including partial agonistic activity, or a dopamine D_3 receptor antagonist, including partial antagonistic activity.

The high affinity of the compounds according to the invention for D_3 receptors is reflected in very low in-vitro receptor binding constants ($K_i(D_3)$ values) of as a rule less than 50 nM (nmol/l), preferably of less than 10 nM and, in particular of less than 5 nM. The displacement of [^{125}I]-iodosulpride can, for example, be used in receptor binding studies for determining binding affinities for D_3 receptors.

The selectivity of the compounds according to the invention, i.e. the ratio $K_i(D_2)/K_i(D_3)$ of the receptor binding constants, is as a rule at least 50, preferably at least 100, even better at least 150. The displacement of [^{3}H]SCH23390, [^{125}I] iodosulpride or [^{125}I] spiperone can be used, for example, for carrying out receptor binding studies on D_1, D_2 and D_4 receptors.

Because of their binding profile, the compounds can be used for treating diseases which respond to dopamine D_3 receptor ligands (or which are susceptible to treatment with dopamine D_3 receptor ligand, respectively), i.e. they are effective for treating

those medical disorders or diseases in which exerting an influence on (modulating) the dopamine D_3 receptors leads to an improvement in the clinical picture or to the disease being cured. Examples of these diseases are disorders or diseases of the central nervous system.

Disorders or diseases of the central nervous system are understood as meaning disorders which affect the spinal chord and, in particular, the brain. Within the meaning of the invention, the term "disorder" denotes disturbances and/or anomalies which are as a rule regarded as being pathological conditions or functions and which can manifest themselves in the form of particular signs, symptoms and/or malfunctions. While the treatment according to the invention can be directed toward individual disorders, i.e. anomalies or pathological conditions, it is also possible for several anomalies, which may be causatively linked to each other, to be combined into patterns, i.e. syndromes, which can be treated in accordance with the invention.

The disorders which can be treated in accordance with the invention are, in particular, psychiatric and neurological disturbances. These disturbances include, in particular, organic disturbances, including symptomatic disturbances, such as psychoses of the acute exogenous reaction type or attendant psychoses of organic or exogenous cause, e.g., in association with metabolic disturbances, infections and endocrinopathogies; endogenous psychoses, such as schizophrenia and schizotype and delusional disturbances; affective disturbances, such as depressions, mania and/or manic-depressive conditions; and also mixed forms of the above-described disturbances; neurotic and somatoform disturbances and also disturbances in association with stress; dissociative disturbances, e.g. loss of consciousness, clouding of consciousness, double consciousness and personality disturbances; disturbances in attention and waking/sleeping behavior, such as behavioral disturbances and emotional disturbances whose onset lies in childhood and youth, e.g. hyperactivity in children, intellectual deficits, in particular attention disturbances (attention deficit disorders), memory disturbances and cognitive disturbances, e.g. impaired learning and memory (impaired cognitive function), dementia, narcolepsy and sleep disturbances, e.g. restless legs syndrome; development disturbances; anxiety states, delirium; sexlife disturbances, e.g. impotence in men; eating disturbances, e.g. anorexia or bulimia; addiction; and other unspecified psychiatric disturbances.

The disorders which can be treated in accordance with the invention also include Parkinson's disease and epilepsy and, in particular, the affective disturbances connected thereto.

The addiction diseases include psychic disorders and behavioral disturbances which are caused by the abuse of psychotropic substances, such as pharmaceuticals or narcotics, and also other addiction diseases, such as addiction to gaming (impulse control disorders not elsewhere classified). Examples of addictive substances are: opioids (e.g. morphine, heroin and codeine), cocaine; nicotine; alcohol; substances which interact with the GABA chloride channel complex, sedatives, hypnotics and tranquilizers, for example benzodiazepines; LSD; cannabinoids; psychomotor stimulants, such as 3,4-methylenedioxy-N-methylamphetamine (ecstasy); amphetamine and amphetamine-like substances such as methylphenidate and other stimulants including caffeine. Addictive substances which come particularly into consideration are opioids, cocaine, amphetamine or amphetamine-like substances, nicotine and alcohol.

With regard to the treatment of addiction diseases, particular preference is given to those compounds according to the invention of the formula I which themselves do not possess any psychotropic effect. This can also be observed in a test using rats, which, after having been administered compounds which can be used in accordance with the invention, reduce their self administration of psychotropic substances, for example cocaine.

According to another aspect of the present invention, the compounds according to the invention are suitable for treating disorders whose causes can at least partially be attributed to an anomalous activity of dopamine D_3 receptors.

According to another aspect of the present invention, the treatment is directed, in particular, toward those disorders which can be influenced, within the sense of an expedient medicinal treatment, by the binding of preferably exogeneously administered binding partners (ligands) to dopamine D_3 receptors.

The diseases which can be treated with the compounds according to the invention are frequently characterized by progressive development, i.e. the above-described conditions change over the course of time; as a rule, the severity increases and conditions may possibly merge into each other or other conditions may appear in addition to those which already exist.

The compounds according to the invention can be used to treat a large number of signs, symptoms and/or malfunctions which are connected with the disorders of the central nervous system and, in particular, the abovementioned conditions. These signs, symptoms and/or malfunctions include, for example, a disturbed relationship to reality,

changes in temperament, changes in individual drives, such as hunger, sleep, thirst, etc., and in mood, disturbances in the ability to observe and combine, changes in personality, in particular emotional lability, hallucinations, ego-disturbances, distractedness, ambivalence, autism, depersonalization and false perceptions, delusional ideas, chanting speech, lack of synkinesia, short-step gait, flexed posture of trunk and limbs, tremor, poverty of facial expression, monotonous speech, depressions, apathy, impeded spontaneity and decisiveness, impoverished association ability, anxiety, nervous agitation, stammering, social phobia, panic disturbances, withdrawal symptoms in association with dependency, maniform syndromes, states of excitation and confusion, dysphoria, dyskinetic syndromes and tic disorders, e.g. Huntington's chorea and Gilles-de-la-Tourette's syndrome, vertigo syndromes, e.g. peripheral positional, rotational and oscillatory vertigo, melancholia, hysteria, hypochondria and the like.

Within the meaning of the invention, a treatment also includes a preventive treatment (prophylaxis), in particular as relapse prophylaxis or phase prophylaxis, as well as the treatment of acute or chronic signs, symptoms and/or malfunctions. The treatment can be orientated symptomatically, for example as the suppression of symptoms. It can be effected over a short period, be orientated over the medium term or can be a long-term treatment, for example within the context of a maintenance therapy.

Therefore the compounds according to the invention are preferentially suitable for treating diseases of the central nervous system, in particular for treating affective disorders; neurotic disturbances, stress disturbances and somatoform disturbances and psychoses, and, in particular, for treating schizophrenia and depression. Because of their high selectivity with regard to the D_3 receptor, the compounds I according to the invention are also suitable for treating disturbances of kidney function, in particular disturbances of kidney function which are caused by diabetes mellitus (see WO 00/67847) and, especially, diabetic nephropathy.

Within the context of the treatment, the use according to the invention of the described compounds involves a method. In this method, an effective quantity of one or more compounds, as a rule formulated in accordance with pharmaceutical and veterinary practice, is administered to the individual to be treated, preferably a mammal, in particular a human being, productive animal or domestic animal. Whether such a treatment is indicated, and in which form it is to take place, depends on the individual case and is subject to medical assessment (diagnosis) which takes into consideration signs, symptoms and/or malfunctions which are present, the risks of developing particular signs, symptoms and/or malfunctions, and other factors.

As a rule, the treatment is effected by means of single or repeated daily administration, where appropriate together, or alternating, with other active compounds or active compound-containing preparations such that a daily dose of preferably from about 0.1 to 1000 mg/kg of bodyweight, in the case of oral administration, or of from about 0.1 to 100 mg/kg of bodyweight, in the case of parenteral administration, is supplied to an individual to be treated.

The invention also relates to the production of pharmaceutical compositions for treating an individual, preferably a mammal, in particular a human being, productive animal or domestic animal. Thus, the ligands are customarily administered in the form of pharmaceutical compositions which comprise a pharmaceutically acceptable excipient together with at least one compound according to the invention and, where appropriate, other active compounds. These compositions can, for example, be administered orally, rectally, transdermally, subcutaneously, intravenously, intramuscularly or intranasally.

Examples of suitable pharmaceutical formulations are solid medicinal forms, such as powders, granules, tablets, in particular film tablets, lozenges, sachets, cachets, sugar-coated tablets, capsules, such as hard gelatin capsules and soft gelatin capsules, suppositories or vaginal medicinal forms, semisolid medicinal forms, such as ointments, creams, hydrogels, pastes or plasters, and also liquid medicinal forms, such as solutions, emulsions, in particular oil-in-water emulsions, suspensions, for example lotions, injection preparations and infusion preparations, and eyedrops and eardrops. Implanted release devices can also be used for administering inhibitors according to the invention. In addition, it is also possible to use liposomes or microspheres.

When producing the compositions, the compounds according to the invention are optionally mixed or diluted with one or more excipients. Excipients can be solid, semisolid or liquid materials which serve as vehicles, carriers or medium for the active compound.

Suitable excipients are listed in the specialist medicinal monographs. In addition, the formulations can comprise pharmaceutically acceptable carriers or customary auxiliary substances, such as glidants; wetting agents; emulsifying and suspending agents; preservatives; antioxidants; antiirritants; chelating agents; coating auxiliaries; emulsion stabilizers; film formers; gel formers; odor masking agents; taste corrigents; resin; hydrocolloids; solvents; solubilizers; neutralizing agents; diffusion accelerators; pigments; quaternary ammonium compounds; refatting and overfatting agents; raw materials for ointments, creams or oils; silicone derivatives; spreading auxiliaries; stabilizers; steri-

grants or coatings; propellants; drying agents; opacifiers; thickeners; waxes; plasticizers and white mineral oils. A formulation in this regard is based on specialist knowledge as described, for example, in Fiedler, H.P., Lexikon der Hilfsstoffe für Pharmazie, Kosmetik und angrenzende Gebiete [Encyclopedia of auxiliary substances for pharmacy, cosmetics and related fields], 4th edition, Aulendorf: ECV-Editio-Kantor-Verlag, 1996.

The following examples serve to explain the invention without limiting it.

The compounds were either characterized via proton-NMR in d_6-dimethylsulfoxid or d-chloroform on a 400 MHz or 500 MHz NMR instrument (Bruker AVANCE), or by mass spectrometry, generally recorded via HPLC-MS in a fast gradient on C18-material (electrospray-ionisation (ESI) mode), or melting point.

The magnetic nuclear resonance spectral properties (NMR) refer to the chemical shifts (δ) expressed in parts per million (ppm). The relative area of the shifts in the ^{1}H NMR spectrum corresponds to the number of hydrogen atoms for a particular functional type in the molecule. The nature of the shift, as regards multiplicity, is indicated as singlet (s), broad singlet (s. br.), doublet (d), broad doublet (d br.), triplet (t), broad triplet (t br.), quartet (q), quintet (quint.) and multiplet (m).

Preparation Examples:

I. Preparation of intermediates

a. Synthesis of sulfonyl chlorides

a.1 4-((S)-2-Fluoro-1-methyl-ethyl)-benzenesulfonyl chloride

a.1.1 Toluene-4-sulfonic acid (S)-2-phenyl-propyl ester

To a solution of 20 g of (S)-(-)-2-phenyl-1-propanol in 240 ml of dichloromethane was added in portions 28 g of p-toluenesulfonyl chloride (146.8 mmol). After stirring for 18 h at room temperature, the organic phase was washed with 100 ml of water, dried over magnesium sulfate, filtered, and the solvent evaporated under reduced pressure to yield 43 g of the title compound.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ [ppm] 7.65 (d, 2H), 7.15-7.3 (m, 5H), 7.1 (d, 2H), 4.0-4.1 (m, 2H), 3.1 (m, 1H), 2.4 (s, 3H), 1.3 (d, 3H).

a.1.2 ((S)-2-Fluoro-1-methyl-ethyl)-benzene

9.62 g of toluene-4-sulfonic acid (S)-2-phenyl-propyl ester (33.13 mmol) were dissolved in 80 ml of polyethylenglycol 400. 9.62 g of potassium fluoride (165.6 mmol) were added and the reaction mixture was stirred at 50°C for 3 days and another 2 days at 55-70°C. The reaction was treated with 150 ml of saturated aqueous sodium chloride solution, extracted three times with diethyl ether, and the combined organic layers were dried over magnesium sulfate, filtered, and the solvent was evaporated under reduced pressure. The crude product was purified via silica gel chromatography using cyclohexyane/ethyl acetate 15% as eluent. 2.85 g of the desired product were isolated, containing ~ 25% of the elimination side product.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ [ppm] 7.2-7.4 (m, 5H), 4.3-4.6 (several m, 2H), 3.15 (m, 1H).1.3 (m, 3H).

a.1.3 4-((S)-2-Fluoro-1-methyl-ethyl)-benzenesulfonyl chloride

3.5 g of ((S)-2-fluoro-1-methyl-ethyl)-benzene (25.32 mmol) were dissolved in 80 ml of dichloromethane. At 0-5°C, 11.81 g of chlorosulfonic acid (101.31 mmol), dissolved in 20 ml of dichloromethane, were added dropwise. The reaction mixture was stirred for 30 min at room temperature and 2 h at 30°C. The solvent was evaporated. 150 ml of diethyl ether were added to the residue, washed once with 150 ml water, and the organic layer was dried over magnesium sulfate, filtered, and the solvent evaporated under reduced pressure. The crude product was purified via silica gel chromatography with n-heptane-dichloromethane (6:4) as eluent to give 1.5 g of the title compound.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ [ppm] 8.0 (d, 2H), 7.5 (d, 2H), 4.5 (dd, 2H), 3.25 (m, 1H), 1.4 (d, 3H).

a.2 4-((R)-2-Fluoro-1-methyl-ethyl)-benzenesulfonyl chloride

a.2.1 Toluene-4-sulfonic acid (R)-2-phenyl-propyl ester

Following the procedure analogous to that used for the synthesis of toluene-4-sulfonic acid (S)-2-phenyl-propyl ester, but using (R)-2-phenyl-1-propanol, the title compound was prepared

a.2.2 ((R)-2-Fluoro-1-methyl-ethyl)-benzene

The title compound was prepared as described above for the synthesis of ((S)-2-fluoro-1-methyl-ethyl)-benzene, but using toluene-4-sulfonic acid (R)-2-phenyl-propyl ester instead of toluene-4-sulfonic acid (S)-2-phenyl-propyl ester.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ [ppm] 7.2-7.4 (m, 5H), 4.3-4.6 (several m, 2H), 3.15 (m, 1H).1.3 (m, 3H).

a.2.3 4-((R)-2-Fluoro-1-methyl-ethyl)-benzenesulfonyl chloride

1.3 g of ((R)-2-fluoro-1-methyl-ethyl)-benzene (9.4 mmol) were dissolved in 50 ml of dichloromethane. At 0-5°C, 1.1 g of chlorosulfonic acid (9.4 mmol), dissolved in 10 ml of dichloromethane, were added dropwise. The reaction mixture was stirred for 20 min at 0-5°C and then added to a solution of 2.15 g of phosphorous pentachloride dissolved in 40 ml of dichloromethane. The reaction mixture was stirred for 30 min at 0-5°C and 1 h at room temperature. The solvent was evaporated, 100 ml of diethyl ether were added, the mixture was washed once with 150 ml of water, and the organic layer dried over magnesium sulfate, filtered, and the solvent evaporated under reduced pressure. The crude product was purified via silica gel chromatography with n-heptane-dichloromethane (1:1) as eluent to give 0.261 g of the title compound.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ [ppm] 8.0 (d, 2H), 7.5 (d, 2H), 4.5 (dd, 2H), 3.25 (m, 1H), 1.4 (d, 3H).

a.3 4-(2-Fluoro-1-methyl-ethyl)-benzenesulfonyl chloride

Following the procedures analogous to that used for the preparation of 4-((S)-2-fluoro-1-methyl-ethyl)-benzenesulfonyl chloride, but starting with 2-phenyl-1-propanol in step a.3.1, the title compound was prepared.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ [ppm] 8.0 (d, 2H), 7.5 (d, 2H), 4.5 (dd, 2H), 3.25 (m, 1H), 1.4 (d, 3H).

a.4 4-(2-Fluoro-1-fluoromethyl-ethyl)-benzenesulfonyl chloride

a.4.1 (2-Fluoro-1-fluoromethyl-ethyl)-benzene

4 g of 3-phenylglutaric acid (19.21 mmol) were suspended in 350 ml of dichloromethane. At room temperature, 6.5 g of xenon difluoride (38.42 mmol) were added and the reaction mixture was stirred at room temperature for 18 h. The organic phase was washed once with 975 ml of 6% aqueous sodium hydrogencarbonate, dried over magnesium sulfate, filtered, and the solvent evaporated. The remaining residue was distilled at a bath temperature of 123°C at 21 mm to yield 0.78 g of the title compound that contained ~ 50% of 4-(2-Fluoro-1-methyl-ethyl)-benzene.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ [ppm] 7.2-7.4 (m, 5H), 4.6-4.8 (dd, 4H), 3.3 (m, 1H).

a.4.2 4-(2-Fluoro-1-fluoromethyl-ethyl)-benzenesulfonyl chloride

Following the procedures analogous to that used for the preparation of 4-((S)-2-fluoro-1-methyl-ethyl)-benzenesulfonyl chloride, but using 5 equivalents. of chlorosulfonic acid, 0,12 g of the title compound were obtained.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ [ppm] 8.05 (d, 2H), 7.55 (d, 2H), 4.75 (dd, 4H), 3.4 (m, 1H).

a.5 4-(3,3,3-Trifluoropropyl)-benzenesulfonyl chloride

2.9 g were obtained from commercially available (3,3,3-trifluoropropyl)-benzene following the procedure used for the synthesis of 4-((S)-2-fluoro-1-methyl-ethyl)-benzenesulfonyl chloride described above.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ [ppm] 8.0 (d, 2H), 7.45 (d, 2H), 3.0 (t, 2H), 2.45 (m, 2H).

a.6 4-(2,2,2-Trifluoroethyl)-benzenesulfonyl chloride

The product was obtained from commercially available (2,2,2-trifluoroethyl)-benzene following the procedure as described in J. Org. Chem., 1960, 25, 1824-26.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ [ppm] 8.05 (d, 2H), 7.55 (d, 2H), 3.5 (q, 2H).

a.7 4-(3-Fluoropropyl)-benzenesulfonyl chloride

a.7.1 (3-Fluoropropyl)-benzene

15.6 g of diethylaminosulfurtrifluoride (DAST, 96.91 mmol) were dissolved in 18 ml of dichloromethane. At 0-5°C, 12 g of 3-phenyl-1-propanol (88.1 mmol) dissolved in 30 ml of dichloromethane, were added dropwise. The reaction mixture was stirred for 18 h, and, after addition of 30 ml of dichloromethane, poured onto 100 ml of ice water. The organic layer was separated, dried over magnesium sulfate, filtered, and the solvent evaporated. The crude product was purified by distillation at a bath temperature of 106°C at 20 mm to yield 7.4 g of the title compound.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ [ppm] 7.1-7.3 (m, 5H), 4.4 (dt, 2H), 2.7 (m, 2H).2.0 (m, 2H).

a.7.2 4-(3-Fluoropropyl)-benzenesulfonyl chloride

4.1 g of (3-fluoro-propyl)-benzene (29.67 mmol) were dissolved in 40 ml of dichloromethane. At 0-5°C, 6.91 g of chlorosulfonic acid (59.34 mmol), dissolved in 10 ml of dichloromethane, were added dropwise. The reaction mixture was stirred for 45 min at 0-5°C and then added to a solution of 6.8 g of phosphorous pentachloride (32.63 mmol) dissolved in 50 ml of dichloromethane. The reaction mixture was stirred for 1 h at 5-10°C. The solvent was evaporated, 150 ml of diethyl ether added, washed once with 150 ml of ice water, and the organic layer dried over magnesium sulfate, filtered, and the solvent evaporated under reduced pressure. The crude product was purified via silica gel chromatography with n-heptane-dichloromethane (11:9) as eluent to give 5.5 g of the title compound.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ [ppm] 7.95 (d, 2H), 7.45 (d, 2H), 4.5 (dt, 2H), 2.9 (t, 2H), 2.05 (m, 2H).

a.8 4-(2,2-Difluoro-cyclopropyl)-benzenesulfonyl chloride

2.07 g of were obtained from commercially available (2,2-difluorocyclopropyl)-benzene following the procedure used for the synthesis of (3-fluoropropyl)-benzenesulfonyl chloride with the exception that only 1.1 equivalents of phosphorous pentachloride were used.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ [ppm] 8.0 (d, 2H), 7.45 (d, 2H), 2.85 (m, 1H), 2.0 (m, 1H), 1.75 (m, 1H).

a.9 3-Bromo-4-trifluoromethoxy-benzenesulfonyl chloride

2.0 g of 1-bromo-2-(trifluoro-methoxy)benzene (8.3 mmol) were dissolved in 30 ml of dichloromethane. At 0-5°C, 1.06 g of chlorosulfonic acid (9.13 mmol), dissolved in 3 ml of dichloromethane, were added dropwise. The reaction mixture was stirred for 30 min at room temperature. Additional 5.5 equivalents of chlorosulfonic in dichloromethane were added to drive the reaction to completion. Standard work-up was followed and silica gel chromatography with n-heptane-dichloromethane (6:4) as eluent gave 2.19 g of the title compound.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ [ppm] 8.3 (d, 1H), 8.05 (dd, 1H), 7.5 (dd, 1H).

a.10 4-(2-Fluoroethyl)-benzenesulfonyl chloride

a.10.1 (2-Fluoroethyl)-benzene

6.8 g of the title compound were obtained from commercially available 2-phenyl-ethanol following the procedure used for the synthesis of (3-fluoropropyl)-benzene.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ [ppm] 7.1-7.3 (m, 5H), 4.6 (m, 1H), 4.45 (m, 1H), 2.95 (m, 1H), 2.9 (m, 1H).

a.10.2 4-(2-Fluoroethyl)-benzenesulfonyl chloride

3.55 g were obtained following the procedure used for the synthesis of 4-((R)-2-fluoro-1-methyl-ethyl)-benzenesulfonyl chloride.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ [ppm] 8.0 (d, 2H), 7.5 (d, 2H), 4.7 (dt, 2H), 3.05-3.2 (dt, 2H).

a.11 5-Propylthiophene-2-sulfonyl chloride

Following the procedures analogous to that used for the preparation of (3-fluoro-propyl)-benzenesulfonyl chloride , but using only 1 equivalent of phosphorous pentachloride, the title compound was prepared.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ [ppm] 7.7 (d, 1H), 6.85 (d, 1H), 2.9 (t, 2H), 1.75 (m, 2H), 1.0 (t, 3H).

a.12 4-(1-Methyl-1H-pyrazol-4-yl)-benzenesulfonyl chloride

a.12.1 1-Methyl-4-phenyl-1H-pyrazole

1 g of 2-phenylmalonaldehyde (6.75 mmol) were dissolved in 25 ml of ethanol. 0.36 ml of N-methyl-hydrazine (6.75 mmol) were added, the reaction mixture was stirred under reflux for 4 h, the solvent evaporated under reduced pressure to yield 1.09 g of the product.

ESI-MS: 159.1 $[M+H]^+$

^{1}H-NMR ($CDCl_3$, 400 MHz): δ [ppm] 7.75 (s, 1H), 7.6 (s, 1H), 7.45 (d, 2H), 7.35 (t, 2H), 7.2 (t, 1H), 3.9 (s, 3H)

a.12.2 4-(1-Methyl-1H-pyrazol-4-yl)-benzenesulfonyl chloride

0.5 g of 1-methyl-4-phenyl-1H-pyrazole (3.16 mmol) were dissolved in 20ml of dichloromethane. At 0°C, 0.232 ml of chlorosulfonic acid were added and the reaction mixture was stirred for 1 h under ice cooling. Additional 0.7 ml of chlorosulfonic acid were added, the mixture was stirred at 0°C for 30 minutes and then 90 minutes at 50°C. The two phases were separated and the lower layer put on ice, extracted twice with diethyl ether, dried over magnesium sulfate, filtered, and the solvent evaporated under reduced pressure to yield 0.496 g of the product.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ [ppm] 8.0 (d, 2H), 7.85 (s, 1H), 7.75 (s, 1H), 7.65 (d, 2H), 4.0 (s, 3H).

a.13 4-(1,1,1-Trifluoropropan-2-yl)benzenesulfonyl chloride and 2-(1,1,1-trifluoropropan-2-yl)benzenesulfonyl chloride

Prepared on a 14 g scale following the procedure outlined in Scheme 7. 2-(1,1,1-Trifluoropropan-2-yl)benzenesulfonyl chloride is a by-product of the reaction.

4-(1,1,1-Trifluoropropan-2-yl)benzenesulfonyl chloride:
MS (ESI) m/z: 273.1 $[M+H]^+$
^{1}H-NMR (DMSO): δ [ppm] 7.62 (d, 2H), 7.33 (d, 2H), 3.81 (m, 1H), 1.42 (d, 3H).

2-(1,1,1-Trifluoropropan-2-yl)benzenesulfonyl chloride:
MS (ESI) m/z: 273.1 $[M+H]^+$

a.14 4-(1,1-Difluoropropan-2-yl)benzenesulfonyl chloride and
2-(1,1-Difluoropropan-2-yl)benzene-1-sulfonyl chloride

Prepared on an 11 g scale following the procedure outlined in Scheme 6. 2-(1,1-Difluoropropan-2-yl)benzene-1-sulfonyl chloride is a by-product of the reaction.

4-(1,1-Difluoropropan-2-yl)benzenesulfonyl chloride:
MS (ESI) m/z: 255.0 $[M+H]^+$
^{1}H-NMR (DMSO): δ [ppm] 8.03 (d, 2H), 7.55 (d, 2H), 5.88 (dt, 1H), 3.34 (m, 1H), 1.47 (d, 3H).
^{13}C-NMR (DMSO): δ [ppm] 146.43, 143.54, 129.77, 127.28, 117.06 (t), 43.76, 13.78.

2-(1,1-difluoropropan-2-yl)benzene-1-sulfonyl chloride:
Isolated by chromatography on 110 mg scale.
MS (ESI) m/z: 255.0 $[M+H]^+$
^{1}H-NMR (DMSO-d_6): δ [ppm] 8.15 (d, 1H), 7.77 (t, 1H), 7.70 (d, 1H), 7.54 (t, 1H), 5.99 (dt, 1H), 4.43 (m, 1H), 1.51 (d, 3H).
^{13}C-NMR (DMSO-d_6): δ [ppm] 143.45, 138.63, 135.53, 130.93, 129.04, 128.17, 116.61 (t), 38.38, 13.68.

II. Preparation of compounds I

EXAMPLE 1

(R)-N-[7-(4-Isopropyl-benzenesulfonylamino)-1,2,3,4-tetrahydro-naphthalen-2-yl]-propionamide

1.1 (R)-N-(1,2,3,4-Tetrahydro-naphthalen-2-yl)-propionamide

A solution of (R)-2-aminotetralin hydrochloride (2.50 g, 13.6 mmol) and triethylamine (3.42 g, 33.77 mmol) in tetrahydrofuran (THF) (30 mL) was stirred at -5°C and propionic anhydride (1.78 g, 13.7 mmol) added dropwise. After the mixture was stirred for 18 h at room temperature, the solvent was removed and ethyl acetate / water were added. The organic layer was washed with citric acid solution (5%) and dried over $MgSO_4$. The filtered solution was concentrated to give a white solid (2.69 g, 97%).

^{1}H-NMR ($CDCl_3$): δ [ppm] 7.12 (m, 4H), 5.49 (br s, 1H), 4.30 (m, 1H), 3.12 (m, 1H), 2.87 (m, 1H), 2.63 (m, 1H), 2.18 (q, 2H), 2.03 (m, 1H), 1.76 (m, 1H), 1.13 (t, 3H).
MS (ESI) m/z: 204.1 $[M+H]^+$

1.2 (R)-N-(7-Nitro-1,2,3,4-tetrahydro-naphthalen-2-yl)-propionamide and 5-nitro isomer, 6-nitro isomer and 8-nitro isomer

N-(1,2,3,4-Tetrahydro-naphthalen-2-yl)-propionamide (3.00 g, 14.8 mmol) was dissolved in nitromethane (45 mL) and cooled to 5°C. A solution of concentrated H_2SO_4 (14.5 mL), nitric acid (1.05 mL, 65%) and water (2.40 mL) was added dropwise over 30 mins. After stirring for a further 2 hours, the solution was poured into water and and extracted with ethyl acetate. The organic phase was dried over $MgSO_4$, filtered, and the filtrate was evaporated in vacuo to give the product as a yellow oil (3.56 g, 97%).
^{1}H-NMR ($CDCl_3$): δ [ppm] regioisomers (1:1) 9.15 (br s, 1H), 7.92 (m, 3H), 7.70 (d, 1H), 7.20 (m, 3H), 6.15 (br m, 1H), 4.26 (m, 4H), 3.20 (m, 2H), 3.10 (m, 1H), 2.98 (m, 3H), 2.72 (m, 2H), 2.25 (q, 4H), 2.15 (m, 2H), 1.60 (m, 2H), 1.15 (t, 6H).
MS (ESI) m/z: 249.1 $[M+H]^+$

1.3 (R)-N-(7-Amino-1,2,3,4-tetrahydro-naphthalen-2-yl)-propionamide and 5-amino isomer, 6-amino isomer and 8-amino isomer

The mixture of nitro isomers (3.50 g, 14.1 mmol) were dissolved in methanol (MeOH) (100 mL) and Pd-C (0.40 g, 10%) added. The solution was stirred under an H_2 atmosphere for 6 h. The solution was filtered and the filtrate concentrated to give an oil which was separated by preparative HPLC (20-95% MeOH) to all 4 amino isomers. The products were obtained as yellow oils: 8-amino isomer (0.05 g, 2%), 7-amino isomer (0.38 g, 12%), 6-amino isomer (0.19 g, 6%) and 5-amino isomer(0.34 g, 10%).

8-Amino isomer:
MS (ESI) m/z: 219.1 $[M+H]^+$

7-Amino isomer:
MS (ESI) m/z: 219.1 $[M+H]^+$

^{1}H-NMR (DMSO-d_6): δ [ppm] 7.72 (d, NH), 6.71 (d, 2H), 6.35 (d, 1H), 6.25 (s, 1H), 4.72 (s, NH_2), 3.84 (m, 1H), 2.75 (m, 1H), 2.62 (m, 2H), 2.48 (m, 1H), 2.05 (q, 2H), 1.85 (m, 1H), 1.51 (m, 1H), 0.98 (t, 3H).

6-Amino isomer:
MS (ESI) m/z: 219.1 $[M+H]^+$
^{1}H-NMR (DMSO-d_6): δ [ppm] 7.74 (d, 1H), 6.71 (d, 2H), 6.50 (br s, NH), 6.33 (d, 1H), 6.31 (s, 1H), 3.84 (m, 1H), 2.75 (m, 1H), 2.68 (m, 2H), 2.42 (m, 1H), 2.08 (q, 2H), 1.85 (m, 1H), 1.51 (m, 1H), 0.99 (t, 3H).

5-Amino isomer:
MS (ESI) m/z: 219.1 $[M+H]^+$
^{1}H-NMR (DMSO): δ [ppm] 7.74 (d, NH), 6.79 (t, 1H), 6.44 (d, 1H), 6.26 (d, 1H), 4.71 (s, NH_2), 3.84 (m, 1H), 2.81 (m, 1H), 2.52 (m, 2H), 2.36 (m, 1H), 2.07 (q, 2H), 1.94 (m, 1H), 1.59 (m, 1H), 1.00 (t, 3H).

1.4 (R)-N-[7-(4-Isopropyl-benzenesulfonylamino)-1,2,3,4-tetrahydro-naphthalen-2-yl]-propionamide

(R)-N-(7-Amino-1,2,3,4-tetrahydro-naphthalen-2-yl)-propionamide (0.34 g, 1.56 mmol) was dissolved in pyridine-dichloromethane (1:2, 30 mL) and cooled to 5°C. 4-Isopropylbenzenesulfonyl chloride (0.37 g, 1.69 mmol) was added and the solution stirred at 5°C for 3h. Solution was evaporated, partitioned between ethyl acetate and water, and the organic phase separated and dried over $MgSO_4$. The filtered solution was concentrated to give the product as a yellow oil (0.56 g, 90%).
7-Amino: MS (ESI) m/z: 401.1 $[M+H]^+$

EXAMPLE 2

(R)-4-Isopropyl-N-((*R*)-7-propylamino-5,6,7,8-tetrahydro-naphthalen-2-yl)-benzenesulfonamide

(R)-N-[7-(4-Isopropyl-benzenesulfonylamino)-1,2,3,4-tetrahydro-naphthalen-2-yl]-propionamide (0.56 g, 1.40 mmol) was dissolved in 15 mL of tetrahydrofuran (THF) and 7.5 mL (78.4 mmol) of a borane-THF complex was introduced dropwise over 15 min. The resulting mixture was stirred at reflux for 1 h. The solution was cooled, 5 mL of 2 N HCl was added slowly, and the mixture was stirred at 40°C for 2 h. The cooled solution was quenched with water, then NaOH (2N) and

extracted with ethyl acetate. The organic phase was dried over $MgSO_4$, filtered, and the filtrate was evaporated in vacuo to give product as a white solid which was further purified recrystallization from MeOH- isopropanol to give a white solid (100 mg, 18%).

MS (ESI) m/z: 387.2 $[M+H]^+$

^{1}H-NMR (DMSO-d_6): δ [ppm] 14.3 (br s, 1H), 12.0 (br s, 1H), 7.68 (d, 2H), 7.43 (d, 2H), 6.88 (m, 2H), 6.76 (s, 1H), 2.82 (m, 2H), 2.65 (m, 1H), 2.52 (m, 3H), 2.36 (m, 1H), 1.88 (m, 1H), 1.40 (m, 3H), 1.15 (d, 6H), 0.84 (t, 3H).

^{13}C-NMR (DMSO): δ [ppm] 153.4 (s), 137.4 (s), 136.0 (s), 135.3 (s), 131.8 (s), 129.0 (d), 127.1 (d), 126.7 (d), 120.4 (d), 117.5 (d), 52.7 (d), 48.2 (t), 35.7 (t), 33.2 (d), 28.5 (t), 26.5 (t), 23.3 (q), 22.6 (t), 11.8 (q).

EXAMPLE 3

4-Isopropyl-N-((*R*)-6-propylamino-5,6,7,8-tetrahydro-naphthalen-2-yl)-benzenesulfonamide

N-[6-(4-Isopropyl-benzenesulfonylamino)-1,2,3,4-tetrahydro-naphthalen-2-yl]-propionamide (0.19 g, 0.47 mmol) was dissolved in 10 mL of tetrahydrofuran (THF) and 3 mL (31.3 mmol) of a borane-THF complex was introduced dropwise over 20 min. The resulting mixture was stirred at reflux for 3 h. The solution was cooled, 3 mL of 2 N HCl was added slowly, and the mixture was stirred at 40°C for 1 h. The cooled solution was quenched with water, then NaOH (2N) and extracted with ethyl acetate. The organic phase was dried over $MgSO_4$, filtered, and the filtrate was evaporated in vacuo to give the product as a colorless oil (100 mg, 55%).

MS (ESI) m/z: 387.1 $[M+H]^+$

^{1}H-NMR (DMSO-d_6): δ [ppm] 7.68 (d, J 8.4, 2H), 7.39 (d, J 8.4, 2H), 6.90-6.75 (m, 3H), 2.92 (m, 2H), 2.69 (m, 1H), 2.52 (m, 3H), 2.38 (m, 1H), 1.88 (m, 1H), 1.40 (m, 3H), 1.15 (d, 6H), 0.84 (t, 3H).

EXAMPLE 4

(R)-N-[5-(4-Isopropyl-benzenesulfonylamino)-1,2,3,4-tetrahydro-naphthalen-2-yl]-propionamide

The 5-amine isomer (0.26 g, 1.19 mmol) from 1.3 was dissolved in pyridine-dichloromethane (1:2, 30 mL) and cooled to 5°C. 4-Isopropylbenzenesulfonyl chloride (0.29 g, 1.31 mmol) was added and the solution stirred at 5°C for 3h. Solution was evaporated, partitioned between ethyl acetate and water, and the or-

ganic phase separated and dried over $MgSO_4$. The filtered solution was concentrated to give the product as a yellow oil (0.61 g, 100%).
MS (ESI) m/z: 401.1 $[M+H]^+$

EXAMPLE 5

(R)-4-Isopropyl-N-(6-propylamino-5,6,7,8-tetrahydro-naphthalen-1-yl)-benzenesulfonamide

(R)-N-[5-(4-Isopropyl-benzenesulfonylamino)-1,2,3,4-tetrahydro-naphthalen-2-yl]-propionamide (0.48 g, 1.20 mmol) was dissolved in 10 mL of THF and 5 mL (8.36 mmol) of a borane-THF complex was introduced dropwise over 20 min. The resulting mixture was stirred at reflux for 3 h. The solution was cooled, 5 mL of 2 N HCl was added slowly, and the mixture was stirred at 40°C for 1 h. The cooled solution was quenched with water, then NaOH (2N) and extracted with ethyl acetate. The organic phase was dried over $MgSO_4$, filtered, and the filtrate was evaporated in vacuo to give the product as a colorless oil (130 mg, 28 %).
MS (ESI) m/z: 387.4 $[M+H]^+$
^{1}H-NMR (DMSO-d_6): δ [ppm] 7.56 (d, J 8.4, 2H), 7.39 (d, J 8.4, 2H), 6.98 (m, 1H), 6.83 (m, 2H), 2.83 (m, 1H), 2.70-2.52 (m, 3H), 2.37 (m, 1H), 2.15 (m, 1H), 1.75 (m, 1H), 1.40 (m, 2H), 1.15 (d, 6H), 0.82 (t, 3H).
^{13}C-NMR (DMSO-d_6): δ [ppm] 153.1 (s), 138.7 (s), 136.6 (s), 135.2 (s), 132.4 (s), 126.8 (d), 126.5 (d), 125.5 (d), 123.2 (d), 52.4 (d), 48.3 (t), 35.2 (t), 33.3 (d), 28.3 (t), 23.5 (q), 23.0 (t), 22.8 (t), 11.8 (q).

EXAMPLE 6

N-((*R*)-6-Allylamino-5,6,7,8-tetrahydro-naphthalen-2-yl)-4-isopropyl-benzenesulfonamide, hydrochloride

6.1 ((*R*)-6-Bromo-1,2,3,4-tetrahydro-naphthalen-2-yl)-carbamic acid tert-butyl ester

(*R*)-6-Bromo-1,2,3,4-tetrahydro-naphthalen-2-ylamine hydrochloride (5.25 g, 20 mmol) was dissolved in dichloromethane (100 ml). Subsequently, triethylamine (11.14 ml, 80 mmol) and di-tert-butyldicarbonate (5.45 g, 25 mmol) were added and the reaction mixture was stirred at room temperature overnight. The reaction mixture was extracted with aqueous $NaHCO_3$ solution. The organic layer was dried over magnesium sulfate, filtered, and evaporated to dryness to yield the desired crystalline product (6.4 g, 98 %).

6.2 Allyl-((*R*)-6-Bromo-1,2,3,4-tetrahydro-naphthalen-2-yl)-carbamic acid tert-butyl ester

((*R*)-6-Bromo-1,2,3,4-tetrahydro-naphthalen-2-yl)-carbamic acid tert-butyl ester (3.26 g, 10 mmol) was dissolved in dimethylformamide (30 ml). Sodium hydride (50 % in oil) (528 mg, 11 mmol) was added and stirred for 15 minutes at room temperature. Allyl bromide (0.95 ml, 11 mmol) was added and the reaction mixture was stirred at room temperature overnight. To the reaction mixture was added H_2O (400 ml) and extracted twice with 150 ml diethylether. The organic layer was dried over magnesium sulfate, filtered, and evaporated to dryness to yield the crude product (3.25 g). The crude product was purified with silica gel chromatography with cyclohexane/ethyl acetate (9:1) as eluent, yielding the purified product (2.7 g, 66 %).

6.3 Allyl-[(*R*)-6-(4-isopropyl-benzenesulfonylamino)-1,2,3,4-tetrahydro-naphthalen-2-yl]-carbamic acid tert-butyl ester

In an inert atmosphere (argon), allyl-((*R*)-6-bromo-1,2,3,4-tetrahydro-naphthalen-2-yl)-carbamic acid tert-butyl ester (2.04 g, 5.5 mmol) was dissolved in trifluortoluol (10 ml) at room temperature. Tris(dibenzylideneacetone)dipalladium (230 mg, 0.25 mmol) and tri-tert-butyl-phosphane (152 mg, 0.75 mmol) were added to the reaction mixture. In a separate flask, 4-isopropyl-benzenesulfonamide (996 mg, 5 mmol) was dissolved in trifluortoluol (20 ml) at 65 °C. Sodium hydride (50 % in oil) (240 mg, 5 mmol) was added, stirred for 5 minutes and added to the reaction mixture. The reaction mixture was dispensed into 5 vials and stirred for 1 hour at 160 °C in the microwave (CEM). The combined reaction mixture was evaporated to dryness. H_20 (50 ml) was added and extracted three times with 50 ml diethylether. The organic layer was dried over magnesium sulfate, filtered, and evaporated to dryness to yield 2.8 g of crude product. The crude product was purified with silica gel chromatography with cyclohexane/ethyl acetate (85:15) as eluent, yielding the purified product (1.13 g, 45 %).

6.4 N-((*R*)-6-Allylamino-5,6,7,8-tetrahydro-naphthalen-2-yl)-4-isopropyl-benzenesulfonamide, hydrochloride

Allyl-[(*R*)-6-(4-isopropyl-benzenesulfonylamino)-1,2,3,4-tetrahydro-naphthalen-2-yl]-carbamic acid tert-butyl ester (2.04 g, 5.5 mmol) was dissolved in dichloromethane (50 ml). Trifluoroacetic acid (2 ml) was added and the reaction mixture

rated to dryness. Ethyl acetate (100 ml) was added and extracted with NaOH (2M). The organic layer was dried over magnesium sulfate, filtered, and evaporated to dryness to yield 790 mg of crude product. The crude product was purified with silica gel chromatography with ethyl acetate/methanol (90:10) as eluent, yielding the purified product (300 mg, 30 % yield).

50 mg were dissolved in diethyl ether and dichloromethane. A solution of 1 N HCl in diethyl ether was added, and after formation of a precipitate, the suspension evaporated under reduced pressure to yield 36 mg of a white precipitate.
ESI-MS: 385.1 $[M+H]^+$
^{1}H-NMR (DMSO-d_6): δ [ppm] 10.2 (s, 1H), 9.2 (bs, 2H), 7.7 (d, 2H), 7.4 (d, 2H), 7.0 (d, 1H), 6.9 (d, 1H), 6.8 (s, 1H), 6.0 (m, 1H), 5.5 (d, 1H), 5.4 (d, 1H), 3.7 (d, 2H), 3.3 (bs, 1H), 3.1 (dd, 1H), 2.9 (m, 1H), 2.7 (m, 3H), 2.2 (m, 1H), 1.7 (m, 1H), 1.2 (d, 6H).

EXAMPLE 7

N-((*S*)-6-Allylamino-5,6,7,8-tetrahydro-naphthalen-2-yl)-4-isopropyl-benzenesulfonamide, hydrochloride

7.1 ((*S*)-6-Bromo-1,2,3,4-tetrahydro-naphthalen-2-yl)-carbamic acid tert-butyl ester

(*S*)-6-Bromo-1,2,3,4-tetrahydro-naphthalen-2-ylamine hydrochloride (3.94 g, 15 mmol) was dissolved in dichloromethane (75 ml). Subsequently, triethylamine (8.32 ml, 60 mmol) and di-tert-butyldicarbonate (4.09 g, 18.75 mmol) were added and the reaction mixture was stirred at room temperature overnight. The reaction mixture was extracted with aqueous $NaHCO_3$ solution. The organic layer was dried over magnesium sulfate, filtered, and evaporated to dryness to yield the desired crystalline product (4.85 g, 99 %).

7.2 Allyl-((*S*)-6-Bromo-1,2,3,4-tetrahydro-naphthalen-2-yl)-carbamic acid tert-butyl ester

((*S*)-6-Bromo-1,2,3,4-tetrahydro-naphthalen-2-yl)-carbamic acid tert-butyl ester (4.85 g, 14.87 mmol) was dissolved in dimethylformamide (40 ml). Sodium hydride (50 % in oil) (785 mg, 16.35 mmol) was added and stirred for 15 minutes at room temperature. Allyl bromide (1.41 ml, 16.35 mmol) was added and the reaction mixture was stirred at room temperature overnight. To the reaction mixture was added H_20 (500 ml) and extracted three times with 100 ml diethylether. The

organic layer was dried over magnesium sulfate, filtered, and evaporated to dryness to yield 5.5 g of crude product. The crude product was purified with silica gel chromatography with cyclohexane/ethyl acetate (95:5) as eluent, yielding the purified product (3.9 g, 68 %).

7.3 Allyl-[(*S*)-6-(4-isopropyl-benzenesulfonylamino)-1,2,3,4-tetrahydro-naphthalen-2-yl]-carbamic acid tert-butyl ester

In an inert atmosphere (argon), allyl-((*S*)-6-bromo-1,2,3,4-tetrahydro-naphthalen-2-yl)-carbamic acid tert-butyl ester (1.94 g, 5.3 mmol) was dissolved in trifluortoluol (10 ml) at room temperature. Tris(dibenzylideneacetone)dipalladium (230 mg, 0.25 mmol) and tri-tert-butyl-phosphane (152 mg, 0.75 mmol) were added to the reaction mixture. In a separate flask, 4-Isopropyl-benzenesulfonamide (996 mg, 5 mmol) was dissolved in trifluortoluol (20 ml) at 65 °C. Sodium hydride (50 % in oil) (240 mg, 5 mmol) was added, stirred for 5 minutes and added to the reaction mixture. The reaction mixture was dispensed into 8 vials and stirred for 1 hour at 150 °C in the microwave (CEM). The combined reaction mixture was evaporated to dryness. H_20 (50 ml) was added and extracted three times with 50 ml diethylether. The organic layer was dried over magnesium sulfate, filtered, and evaporated to dryness to yield 4.3 g of crude product. The crude product was purified with silica gel chromatography with cyclohexane/ethyl acetate (85:15) as eluent, yielding the product (1.5 g, 50 % purity, 31 % yield).

7.4 N-((*S*)-6-Allylamino-5,6,7,8-tetrahydro-naphthalen-2-yl)-4-isopropyl-benzenesulfonamide, hydrochloride

Allyl-[(*R*)-6-(4-isopropyl-benzenesulfonylamino)-1,2,3,4-tetrahydro-naphthalen-2-yl]-carbamic acid tert-butyl ester (1.5 g, 1.5 mmol) was dissolved in dichloromethane (50 ml). Trifluoroacetic acid (2 ml) was added and the reaction mixture was stirred at room temperature for 3 hours. The reaction mixture was evaporated to dryness. Ethyl acetate (100 ml) was added and extracted with NaOH (2M). The organic layer was dried over magnesium sulfate, filtered, and evaporated to dryness to yield 1.05 g of crude product. The crude product was purified with silica gel chromatography with ethyl acetate/methanol (90:10) as eluent, yielding the purified product (290 mg, 34 % yield).

50 mg were dissolved in diethyl ether and dichloromethane. A solution of 1 N HCl in diethyl ether was added, and after formation of a precipitate, the suspension

ESI-MS: 385.1 $[M+H]^+$

^{1}H-NMR (DMSO-d_6): δ [ppm] 10.2 (s, 1H), 9.2 (bs, 2H), 7.7 (d, 2H), 7.4 (d, 2H), 7.0 (d, 1H), 6.9 (d, 1H), 6.8 (s, 1H), 6.0 (m, 1H), 5.5 (d, 1H), 5.4 (d, 1H), 3.7 (d, 2H), 3.1 (dd, 1H), 2.9 (m, 1H), 2.7 (m, 3H), 2.5 (m, 1H), 2.2 (m, 1H), 1.7 (m, 1H), 1.2 (d, 6H).

EXAMPLE 8

4-Isopropyl-N-((*S*)-6-propylamino-5,6,7,8-tetrahydro-naphthalen-2-yl)-benzenesulfonamide, hydrochloride

A mixture of N-((*S*)-6-Allylamino-5,6,7,8-tetrahydro-naphthalen-2-yl)-4-isopropyl-benzensulfonamide (240 mg, 0.48 mmol) and 10 % palladium on carbon (25 mg) in ethyl acetate (25 ml) was hydrogenated overnight. The catalyst was filtered, and the solvent was removed under vaccum to yield an oil (190 mg). The residue was dissolved in H_2O (20 ml) and HCl (1N, 1 ml)and extracted twice with ethyl ether (20 ml). The aqueous phase was made alkaline and extracted with ethyl acetate. The organic phase was separated, dried over magnesium sulfate, filtered, and evaporated to dryness to yield a foam (120 mg, 58 %). 50 mg of this foam were dissolved in destilled H_2O (30 ml) and a few drops of concentrated HCl were added. This solution was lyophilisated to yield the desired product.

ESI-MS: 387.4 $[M+H]^+$

^{1}H-NMR (DMSO-d_6): δ [ppm] 10.2 (s, 1H), 8.9 (m, 2H), 7.7 (d, 2H), 7.4 (d, 2H), 7.0 (d, 1H), 6.9 (d, 1H), 6.8 (s, 1H), 3.1 (dd, 1H), 3.0 (m 3H), 2.8 (m, 3H), 2.5 (m, 1H), 2.2 (m, 1H), 1.7 (m, 3H), 1.2 (d, 6H), 0.9 (t, 3H).

EXAMPLE 9

N-((*S*)-6-Allylamino-5,6,7,8-tetrahydro-naphthalen-2-yl)-4-isopropyl-N-methyl-benzenesulfonamide

9.1 Allyl-{(*S*)-6-[(4-isopropyl-benzenesulfonyl)-methyl-amino]-1,2,3,4-tetrahydro-naphthalen-2-yl}-carbamic acid tert-butyl ester

In an inert atmosphere (argon), allyl-((*S*)-6-bromo-1,2,3,4-tetrahydro-naphthalen-2-yl)-carbamic acid tert-butyl ester (749 mg, 2.0 mmol) was dissolved in trifluortoluol (20 ml) at room temperature. Tris(dibenzylideneacetone)dipalladium (92 mg, 0.1 mmol) and tri-tert-butyl-phosphane (61 mg, 0.3 mmol) were added to the reaction mixture. In a separate flask, 4-Isopropyl-N-methyl-benzenesulfonamide

(427 mg, 2 mmol) was dissolved in trifluortoluol (20 ml) at 65 °C. Sodium hydride (50 % in oil) (96 mg, 2 mmol) was added, stirred for 5 minutes and added to the reaction mixture. The reaction mixture was dispensed into 3 vials and stirred for 1 hour at 150 °C in the microwave (CEM). The combined reaction mixture was evaporated to dryness. H_20 (50 ml) was added and extracted three times with 50 ml diethylether. The organic layer was dried over magnesium sulfate, filtered, and evaporated to dryness to yield crude product (1.12 g, 68 %).

9.2 N-((*S*)-6-Allylamino-5,6,7,8-tetrahydro-naphthalen-2-yl)-4-isopropyl-N-methyl-benzenesulfonamide

Allyl-{(*S*)-6-[(4-isopropyl-benzenesulfonyl)-methyl-amino]-1,2,3,4-tetrahydro-naphthalen-2-yl}-carbamic acid tert-butyl ester (672 mg, 1.35 mmol) was dissolved in dichloromethane (30 ml). Trifluoroacetic acid (1 ml) was added and the reaction mixture was stirred at room temperature overnight. The reaction mixture was evaporated to dryness. Ethyl acetate (100 ml) was added and extracted with NaOH (2M). The organic layer was dried over magnesium sulfate, filtered, and evaporated to dryness to yield 1.05 g of crude product. The crude product was dissolved in ethyl acetate (20 ml) and the precipitate was collected to yield the desired compound (270 mg, 50 %). The mother liquid was reduced in vacuo to yield an oil (840 mg, 54 % purity).
ESI-MS: 399.1 $[M+H]^+$
^{1}H-NMR ($CDCl_3$): δ [ppm] 9.8 (bs, 2H), 7.5 (d, 2H), 7.3 (d, 2H), 7.0 (d, 1H), 6.9 (s, 1H), 6.8 (dd, 1H), 6.0 (m, 1H), 5.5 (m, 2H), 3.7 (m, 2H), 3.4 (m, 1H), 3.2 (dd, 1H), 3.1 (s, 3H), 3.0-2.8 (m, 4H), 2.3 (m, 1H), 1.9 (m, 1H), 1.3 (d, 6H).

EXAMPLE 10

4-Isopropyl-N-methyl-N-((*S*)-6-propylamino-5,6,7,8-tetrahydro-naphthalen-2-yl)-benzenesulfonamide

A mixture of N-((*S*)-6-Allylamino-5,6,7,8-tetrahydro-naphthalen-2-yl)-4-isopropyl-N-methyl-benzensulfonamide (840 mg, 54 % purity, 1.13 mmol) and 10 % palladium on carbon (50 mg) in ethyl acetate (25 ml) was hydrogenated overnight. The catalyst was filtered, and the solvent was removed under vaccum to yield an oil (720 mg). The crude product was dissolved in ethyl acetate (20 ml) and the precipitate was collected to yield the desired compound (100 mg, 22 %).
ESI-MS: 401.2 $[M+H]^+$

^{1}H-NMR ($CDCl_3$): δ [ppm] 9.5 (bs, 2H), 7.5 (d, 2H), 7.3 (d, 2H), 7.0 (d, 1H), 6.9 (s, 1H), 6.8 (d, 1H), 3.4 (m, 1H), 3.2 (dd, 1H), 3.1 (s 3H), 3.0-2.8 (m, 6H), 2.3 (m, 1H), 1.9 (m, 1H), 1.8 (m, 2H), 1.3 (d, 6H), 1.0 (t, 3H).

EXAMPLE 11 (reference)

N-[3-(4-Trifluoromethoxy-benzenesulfonylamino)-5,6,7,8-tetrahydro-quinolin-7-yl]-propionamide and its 5-regioisomer

11.1 (3-Oxo-cyclohexyl)-carbamic acid benzyl ester

Bismuth nitrate pentahydrate (1.02 g, 2.10 mmol) was added to a mixture of benzylcarbamate (3.2 g, 21.16 mmol) and cyclohex-2-enone (2 ml, 20.59 mmol) in CH_2Cl_2 (2 ml) and the resulting syrup was vigorously stirred at room temperature overnight. CH_2Cl_2 (20 ml) was then added to the mix and it was filtered through a pad of celite. The filtrate was washed with saturated aqueous $NaHCO_3$, the organic layer was dried over Na_2SO_4 and evaporated. Purification of the crude product by flash column chromatography (heptane:ethyl acetate, 3:1) provides the title compound (4.81 g, 94%) as a pale yellow gum.

MS (ESI+) m/z = 248.3 $[M+H]^+$

^{1}H NMR (400 MHz, $CDCl_3$) : δ (ppm) 1.71 (m, 2H), 1.97 (m, 1H), 2.10 (m, 1H), 2.27 (m, 2H), 2.37 (m, 1H), 2.71 (dd, *J* = 14.0, 4.4 Hz, 1H), 3.99 (bs, 1H), 4.77 (bs, 1H), 5.09 (s, 2H), 7.35 (m, 5 H).

11.2 (3-Nitro-5,6,7,8-tetrahydro-quinolin-5 and 7-yl)-carbamic acid benzyl ester

A mixture of 1-methyl-3,5-dinitro-2-pyridone (3.66 g, 18.38 mmol) and (3-oxo-cyclohexyl)-carbamic acid benzyl ester (4.55 g, 18.39 mmol) in methanolic ammonia (1 M, 140 ml) was heated at 65°C for 1.5 h. It was then concentrated and digested in CH_2Cl_2. The organic layer was washed with H_2O (x2), dried (Na_2SO_4) and evaporated. The residue was chromatographed on silica gel (heptane:ethyl acetate, 3:1) to afford a mixture 1/2 of the 5 and 7 regioisomers (4.51 g, 75% for two steps) as a pale yellow gum.

MS (ESI+) m/z = 328.1 $[M+H]^+$

^{1}H NMR (400 MHz, $CDCl_3$) : δ (ppm) 1.83 (m, 1.5H), 2.01 (m, 1H), 2.20 (m, 1.5H), 2.90 (dd, *J* = 18.1, 8.7 Hz, 1H), 3.00 (t, *J* = 6.4 Hz, 2H), 3.05 (t, *J* = 6.4 Hz, 1H), 3.43 (dd, *J* = 18.1, 5.2 Hz, 1H), 4.16 (m, 1H), 4.81 (bs, 1H), 5.03 (bs, 1H), 5.12 (s, 2H), 5.19 (s, 1H), 7.36 (m, 7.5 H), 8.19 (bs, 1H), 8.46 (bs, 0.5H), 9.20 (d, *J* = 1.9 Hz, 1H), 9.23 (d, *J* = 2.1 Hz, 0.5H).

11.3 [3-(4-Trifluoromethoxy-benzenesulfonylamino)-5,6,7,8-tetrahydro-quinolin-5 and 7-yl]-carbamic acid benzyl ester

(3-Nitro-5,6,7,8-tetrahydro-quinolin-5 and 7-yl)-carbamic acid benzyl ester (1 g, 3.05 mmol) was dissolved in EtOH (25 ml) and $SnCl_2.2H_2O$ (3.44 g, 15.24 mmol) was added. The resulting mixture was refluxed for 14 h and the solvent next removed under vacuum. The raw material was dissolved in ethyl acetate and washed successively with 2N aqueous NaOH (x2) and water. The organic layer was dried (Na_2SO_4), filtered through a pad of celite and evaporated. The crude material was then dissolved in CH_2Cl_2 (60 ml) and pyridine (370 µl, 4.53 mmol) followed by 4-(trifluoromethoxy)benzensulfonyl chloride (620 µl, 3.65 mmol) were added dropwise. After stirring at room temperature overnight, the reaction mixture was diluted with CH_2Cl_2 and washed successively with 1N aqueous HCl, saturated aqueous $NaHCO_3$ and water. The organic layer was dried (Na_2SO_4) and evaporated. The residue was chromatographied on silica gel (heptane:ethyl acetate, 1:1) to afford a mixture 1/2 of the 5 and 7 regioisomers (1.32 g, 83% for two steps) as a light yellow gum.

MS (ESI+) m/z = 522.2 $[M+H]^+$

^1H NMR (400 MHz, $CDCl_3$) : δ (ppm) 1.74 (m, 1.5H), 1.89 (m, 1H), 2.08 (m, 1.5H), 2.72 (dd, *J* = 17.2, 8.6 Hz, 1H), 2.82 (m, 3H), 3.21 (dd, *J* = 17.2, 5.0 Hz, 1H), 4.06 (m, 1H), 4.86 (d, *J* = 7.2 Hz, 1.5H), 5.10 (m, 3.5H), 7.23 (d, *J* = 8.5 Hz, 1H), 7.27 (d, *J* = 8.5 Hz, 2H), 7.34 (m, 8.5H), 7.47 (s, 0.5H), 7.81 (d, *J* = 8.6 Hz, 3H), 7.99 (s, 1H), 8.15 (s, 0.5H).

11.4 N-[3-(4-Trifluoromethoxy-benzenesulfonylamino)-5,6,7,8-tetrahydro-quinolin-7-yl]-propionamide and its 5-regioisomer

10% Pd/C (150 mg) was suspended in a solution of [3-(4-trifluoromethoxy-benzenesulfonylamino)-5,6,7,8-tetrahydro-quinolin-5 and 7-yl]-carbamic acid benzyl ester (558 mg, 1.07 mmol) in MeOH (25 ml) and the resulting mixture stirred under H_2 (1 atm) at room temperature for 3 h. It was then filtered through celite and concentrated in vacuo to yield the free base. The latter was next dissolved in THF (20 ml) and the solution cooled to 0°C. Propionyl chloride (94 µl, 1.07 mmol) and triethylamine (150 µl, 1.07 mmol) were next added, the mixture allowed to reach 20°C and stirred for a further 2 h. It was then diluted with CH_2Cl_2 and washed successively with 1N aqueous HCl, saturated aqueous $NaHCO_3$ and water. The organic layer was dried (Na_2SO_4) and evaporated. The residue was

chromatographied on silica gel (heptane:ethyl acetate, 1:4) to afford the title compound (268 mg, 56% for two steps) as a white solid and its 5-regioisomer (130 mg, 27% for two steps) as a gum.

N-[3-(4-Trifluoromethoxy-benzenesulfonylamino)-5,6,7,8-tetrahydro-quinolin-7-yl]-propionamide:
MS (ESI+) m/z = 444.0 $[M+H]^+$
^1H NMR (400 MHz, $CDCl_3$) : δ (ppm) 1.17 (t, *J* = 7.6 Hz, 3H), 1.71 (m, 1H), 2.08 (m, 1H), 2.23 (q, *J* = 7.6 Hz, 2H), 2.68 (dd, *J* = 17.1, 9.2 Hz, 1H), 2.82 (m, 2H), 3.18 (dd, *J* = 17.2, 5.2 Hz, 1H), 4.28 (m, 1H), 5.51 (d, *J* = 7.6 Hz, 1H), 7.29 (d, *J* = 8.3 Hz, 2H), 7.34 (d, *J* = 1.7 Hz, 1H), 7.82 (d, *J* = 8.8 Hz, 2H), 8.02 (d, *J* = 2.0 Hz, 1H).

N-[3-(4-Trifluoromethoxy-benzenesulfonylamino)-5,6,7,8-tetrahydro-quinolin-5-yl]-propionamide:
MS (ESI+) m/z = 444.0 $[M+H]^+$
^1H NMR (400 MHz, $CDCl_3$) : δ (ppm) 1.19 (t, *J* = 7.6 Hz, 3H), 1.70 (m, 2H), 1.92 (m, 2H), 2.07 (m, 1H), 2.25 (m, 2H), 2.88 (m, 2H), 5.16 (dd, *J* = 14.0, 8.2 Hz, 1H), 5.69 (d, *J* = 8.7 Hz, 1H), 7.29 (d, *J* = 8.4 Hz, 2H), 7.41 (bs, 1H), 7.85 (d, *J* = 8.8 Hz, 2H), 8.18 (d, *J* = 1.8 Hz, 1H).

EXAMPLE 12 (reference)

N-(7-Propylamino-5,6,7,8-tetrahydro-quinolin-3-yl)-4-trifluoromethoxy-benzenesulfonamide

To a solution of N-[3-(4-trifluoromethoxy-benzenesulfonylamino)-5,6,7,8-tetrahydro-quinolin-7-yl]-propionamide (260 mg, 0.58 mmol) in THF (10 ml) was added dropwise 1M BH_3.THF (5.8 ml) and the mixture was stirred at room temperature for 6 h. It was then quenched by careful addition of 1N aqueous HCl (10 ml) and the resulting solution was heated at reflux for 4 h. The solution was next cooled to room temperature , adjusted to pH~8 with 2 N NaOH solution and diluted with CH_2Cl_2. Separation of the layers, drying (Na_2SO_4) of the organic phase and evaporation in vacuo provided the crude material, which was purified by flash column chromatography (CH_2Cl_2:MeOH, 95:5) to give the title compound (160 mg, 64%) as a white solid.
MS (ESI+) m/z = 430.1 $[M+H]^+$

^{1}H NMR (400 MHz, $CDCl_3$) : δ (ppm) 0.93 (t, J = 7.4 Hz, 3H), 1.53 (m, 2H), 1.65 (m, 1H), 2.04 (m, 1H), 2.69 (m, 4H), 2.84 (m, 1H), 3.10 (m, 2H), 3.67 (bs, 2H), 7.27 (m, 3H), 7.81 (d, J = 8.6 Hz, 2H), 7.95 (bs, 1H).

EXAMPLE 13 (reference)

N-(5-Propylamino-5,6,7,8-tetrahydro-quinolin-3-yl)-4-trifluoromethoxy-benzenesulfonamide

Following the same procedure as described previously, N-[3-(4-trifluoromethoxy-benzenesulfonylamino)-5,6,7,8-tetrahydro-quinolin-5-yl]-propionamide (120 mg, 0.27 mmol) in THF (10 ml) was treated with 1M BH_3.THF (2.7 ml). Purification of the crude product by flash column chromatography (heptane:ethyl acetate, 1:2) provides the title compound (66 mg, 57%) as a white solid.

MS (ESI+) m/z = 430.1 $[M+H]^+$

^{1}H NMR (400 MHz, $(CD_3)_2SO$) : δ (ppm) 0.85 (t, J = 7.4 Hz, 3H), 1.40 (m, 3H), 1.67 (m, 2H), 2.86 (m, 2H), 2.43 (m, 2H), 2.68 (m, 2H), 3.68 (bs, 1H), 7.46 (d, J = 2.0 Hz, 1H), 7.53 (d, J = 8.4 Hz, 2H), 7.85 (d, J = 8.8 Hz, 2H), 8.04 (d, J = 2.3Hz, 1H).

EXAMPLE 14

N-[3-(4-Isopropyl-benzenesulfonylamino)-5,6,7,8-tetrahydro-quinolin-7-yl]-propionamide and N-[3-(4-Isopropyl-benzenesulfonylamino)-5,6,7,8-tetrahydro-quinolin-5-yl]-propionamide (reference)

14.1 [3-(4-Isopropyl-benzenesulfonylamino)-5,6,7,8-tetrahydro-quinolin-5 and 7-yl]-carbamic acid benzyl ester and its 5-regioisomer

Following the same procedure as described in example 11.3, (3-nitro-5,6,7,8-tetrahydro-quinolin-5 and 7-yl)-carbamic acid benzyl ester (1 g, 3.05 mmol) in EtOH (25 ml) was treated with $SnCl_2.2H_2O$ (3.44 g, 15.24 mmol). The resulting amine in CH_2Cl_2 (50 ml) was then treated with pyridine (500 µl, 6.13 mmol) and 4-isopropylbenzensulfonylchloride (655 µl, 3.65 mmol). Purification of the crude product by flash column chromatography (heptane:ethyl acetate, 1:1) provides a mixture 1/2 of the 5 and 7 regioisomers (872 mg, 60% for two steps) as a light yellow gum.

MS (ESI+) m/z = 480.1 $[M+H]^+$.

14.2 N-[3-(4-Isopropyl-benzenesulfonylamino)-5,6,7,8-tetrahydro-quinolin-7-yl]-propionamide and N-[3-(4-Isopropyl-benzenesulfonylamino)-5,6,7,8-tetrahydro-quinolin-5-yl]-propionamide

Following the same procedure as described previously, [3-(4-isopropyl-benzenesulfonylamino)-5,6,7,8-tetrahydro-quinolin-5 and 7-yl]-carbamic acid benzyl ester (412 mg, 0.86 mmol) in MeOH (18 ml) was hydrogenated in the presence of 10% Pd/C (100 mg) under H_2 (1 atm). The resulting amine in THF (15 ml) was next treated with propionyl chloride (75 µl, 0.86 mmol) and triethyl-amine (120 µl, 0.86 mmol). Purification of the crude product by flash column chromatography (heptane:ethyl acetate, 1:9) provides the title compound (290 mg, 58% for two steps) as a white solid and its 5-regioisomer (136 mg, 27% for two steps) as a white solid.

N-[3-(4-Isopropyl-benzenesulfonylamino)-5,6,7,8-tetrahydro-quinolin-7-yl]-propionamide:
MS (ESI+) m/z = 402.1 $[M+H]^+$
^{1}H NMR (400 MHz, $CDCl_3$) : δ (ppm) 1.16 (t, *J* = 7.6 Hz, 3H), 1.24 (d, *J* = 6.9 Hz, 6H), 1.72 (m, 1H), 2.07 (m, 1H), 2.21 (q, *J* = 7.6 Hz, 2H), 2.68 (dd, *J* = 17.1, 8.9 Hz, 1H), 2.81 (m, 2H), 2.95 (m, 1H), 3.17 (dd, *J* = 17.1, 5.2 Hz, 1H), 4.30 (m, 1H), 5.53 (d, *J* = 7.6 Hz, 1H), 7.31 (d, *J* = 8.3 Hz, 2H), 7.35 (d, *J* = 1.9 Hz, 1H), 7.68 (d, *J* = 8.4 Hz, 2H), 7.99 (d, *J* = 2.1 Hz, 1H).

N-[3-(4-Isopropyl-benzenesulfonylamino)-5,6,7,8-tetrahydro-quinolin-5-yl]-propionamide:
MS (ESI+) m/z = 402.1 $[M+H]^+$
^{1}H NMR (400 MHz, $CDCl_3$) : δ (ppm) 1.19 (t, *J* = 7.6 Hz, 3H), 1.24 (d, *J* = 7.0 Hz, 6H), 1.70 (m, 2H), 1.91 (m, 2H), 2.06 (m, 1H), 2.26 (q, *J* = 7.6 Hz, 2H), 2.86 (m, 2H), 2.94 (m, 1H), 5.16 (dd, *J* = 13.8, 8.2 Hz, 1H), 5.75 (d, *J* = 8.7 Hz, 1H), 7.31 (d, *J* = 8.3 Hz, 2H), 7.41 (d, *J* = 2.1 Hz, 1H), 7.71 (d, *J* = 8.4 Hz, 2H), 8.14 (d, *J* = 2.3 Hz, 1H).

EXAMPLE 15

4-Isopropyl-N-(7-propylamino-5,6,7,8-tetrahydro-quinolin-3-yl)-benzenesulfonamide

Following the same procedure as described above, N-[3-(4-isopropyl-benzenesulfonylamino)-5,6,7,8-tetrahydro-quinolin-7-yl]-propionamide (90 mg, 0.22 mmol) in THF (5 ml) was treated with 1M BH_3.THF (2.2 ml). Purification of

the crude product by flash column chromatography (CH_2Cl_2:MeOH, 95:5) provides the title compound (52 mg, 60%) as a white solid.

MS (ESI+) m/z = 388.1 $[M+H]^+$

^{1}H NMR (400 MHz, $CDCl_3$) : δ (ppm) 0.94 (t, *J* = 7.4 Hz, 3H), 1.24 (d, *J* = 6.9 Hz, 6H), 1.56 (m, 2H), 1.66 (m, 1H), 2.06 (m, 1H), 2.72 (m, 4H), 2.85 (dt, *J* = 17.1, 5.3 Hz, 1H), 2.94 (m, 1H), 3.06 (m, 1H), 3.14 (dd, *J* = 16.8, 4.6 Hz, 1H), 3.62 (bs, 2H), 7.30 (d, *J* = 8.3 Hz, 2H), 7.32 (d, *J* = 2.1 Hz, 1H), 7.68 (d, *J* = 8.4 Hz, 2H), 7.94 (d, *J* = 2.3 Hz, 1H).

EXAMPLE 16 (reference)

4-Isopropyl-N-(5-propylamino-5,6,7,8-tetrahydro-quinolin-3-yl)-benzenesulfonamide

Following the same procedure as described above, N-[3-(4-isopropyl-benzenesulfonylamino)-5,6,7,8-tetrahydro-quinolin-5-yl]-propionamide (136 mg, 0.33 mmol) in THF (10 ml) was treated with 1M BH_3•THF (3.3 ml). Purification of the crude product by flash column chromatography (heptane:ethyl acetate, 1:2) provides the title compound (74 mg, 56%) as a white solid.

MS (ESI+) m/z = 388.1 $[M+H]^+$

^{1}H NMR (400 MHz, $CDCl_3$) : δ (ppm) 0.94 (t, *J* = 7.4 Hz, 3H), 1.24 (d, *J* = 6.9 Hz, 6H), 1.51 (m, 2H), 1.75 (m, 3H), 1.96 (m, 3H), 2.59 (m, 2H), 2.86 (m, 3H), 3.73 (m, 1H), 7.30 (d, *J* = 8.3 Hz, 2H), 7.68 (d, *J* = 1.9 Hz, 1H), 7.68 (d, *J* = 8.3 Hz, 2H), 8.02 (d, *J* = 2.2 Hz, 1H).

EXAMPLE 17

N-[6-(4-Isopropyl-benzenesulfonylamino)-chroman-3-yl]-propionamide

17.1 N-Chroman-3-yl-propionamide

A solution of chroman-3-ylamine (5.00 g, 33.5 mmol) and triethylamine (5.09 g, 50.27 mmol) in THF (70 mL) was stirred at -5°C and propionic anhydride (4.36 g, 33.5 mmol) added dropwise. After the mixture was stirred for 2 h at room temperature, the solvent was removed and ethyl acetate / water were added. The organic layer was washed with citric acid solution (5%) and dried over $MgSO_4$. The filtered solution was concentrated to give a yellow-brown solid (5.40 g, 78%).

MS (ESI) m/z: 206.1 $[M+H]^+$

^{1}H-NMR ($CDCl_3$): δ [ppm] 7.15 (t, 1H), 7.06 (d, 1H), 6.88 (t, 1H), 6.82 (d, 1H), 5.76 (br s, 1H), 4.50 (m, 1H), 4.12 (m, 2H), 3.12 (dd, 1H), 2.72 (d, 1H), 2.16 (q, 2H), 1.25 (t, 3H).

17.2 N-(6-Nitro-chroman-3-yl)-propionamide

The nitration was carried out by the aforementioned procedure. The product was obtained as a red oil (1.40 g).
MS (ESI) m/z: 251.1 $[M+H]^+$
^{1}H-NMR (DMSO-d_6): δ [ppm] 8.07 (s, 1H), 8.00 (m, 2H), 6.97 (d, 1H), 4.22 (m, 2H), 3.12 (dd, 1H), 2.80 (dd, 1H), 2.14 (q, 2H), 1.16 (t, 3H).

17.3 N-(6-Amino-chroman-3-yl)-propionamide

The $SnCl_2$ reduction was carried out by the aforementioned procedure. The product was obtained as a brown solid (3.63 g, 65%).
MS (ESI) m/z: 221.1 [M+H]+

17.4 N-[6-(4-Isopropyl-benzenesulfonylamino)-chroman-3-yl]-propionamide

The sulfonamide coupling was carried out by the aforementioned procedure. The product was obtained as a yellow oil (0.46 g, 31%).
MS (ESI) m/z: 403.1 $[M+H]^+$
^{1}H-NMR (DMSO-d_6): δ [ppm] 7.66 (d, J 8.2, 2H), 7.39 (d, J 8.2, 2H), 7.00 (s, 1H), 6.81 (m, 2H), 6.70 (m, 1H), 5.83 (d, 1H), 4.40 (m, 1H), 2.92 (m, 2H), 2.65 (m, 1H), 2.15 (m, 2H), 1.15 (m, 9H).

EXAMPLE 18

4-Isopropyl-N-(3-propylamino-chroman-6-yl)-benzenesulfonamide

N-[6-(4-Isopropyl-benzenesulfonylamino)-chroman-3-yl]-propionamide (0.48 g, 1.20 mmol) was dissolved in THF (5 mL) and added dropwise to a stirred suspension of LiAlH4 (0.43 g, 11.3 mmol) in THF (5 mL) at 0°C. The resulting mixture was stirred at room temperature for 18 h. The solution was heated to reflux for 3 h, cooled and quenched by addition of water and 2 N HCl. The mixture was extracted with ethyl acetate and the organic phase dried over $MgSO_4$, filtered, and the filtrate was evaporated in vacuo to give the product which was further purified by preparative HPLC (20-90% MeOH) to give a white solid (10 mg, 6 %).
MS (ESI) m/z: 389.1 $[M+H]^+$

EXAMPLE 19

N-((4aS,10bS)-4-Allyl-1,2,3,4,4a,5,6,10b-octahydro-benzo[f]quinolin-8-yl)-4-isopropyl-benzenesulfonamide

19.1 (4aS,10bS)-8-Nitro-1,2,3,4,4a,5,6,10b-octahydro-benzo[f]quinoline

Trans-(4a,10b)-1,2,3,4,4a,5,6,10b-octahydrobenzo[f]quinoline (5.00 g, 26.7 mmol) was dissolved in concentrated H_2SO_4 (14.2 mL) cooled to 5°C. After stirring for 15 min, potassium nitrate (2.90 g, 29.0 mmol) was added in small portions as a solid so that the temperature was maintained below 5°C. The reaction mixture was stirred at 5°C for 1 h then allowed to reach room temperature and stirred for 18 hours. The reaction solution was poured over ice (200 g) and a yellow precipitate (3.92 g) collected. This was determined to be the sulfate salt of the desired product. The solution was adjusted to pH 11 with 50% NaOH/H_2O, extracted with ethyl acetate (150 mL) and the organic phase separated and dried over $MgSO_4$. The filtered solution was concentrated to give a red oil (1.96 g). Total yield 76%.

MS (ESI) m/z: 233.1 $[M+H]^+$

^{1}H-NMR (DMSO-d_6): δ [ppm] regioisomers 8.08-7.95 (m, 1H), 7.73-7.58 (m, 1H), 7.41 (m, 1H), 3.05 (m, 3H), 2.60 (m, 2H), 2.42 (m, 2H), 1.92 (m, 1H), 1.80 (m, 1H), 1.64 (m, 2H), 1.22 (m, 1H).

19.2 (4aS,10bS)-4-Allyl-8-nitro-1,2,3,4,4a,5,6,10b-octahydro-benzo[f]quinoline

(4aS,10bS)-8-Nitro-1,2,3,4,4a,5,6,10b-octahydro-benzo[f]quinoline (0.50 g, 1.51 mmol) was dissolved in THF (30 mL) and allyl bromide (0.40 g, 3.30 mmol) added. The solution was stirred at 50°C for 8 h, room temperature for 18 h and then evaporated. The residue was partitioned between ethyl acetate and NaOH (2M), and the organic phase separated and dried over $MgSO_4$. The filtered solution was concentrated and separated by column chromatography (dichloromethane:0-3% MeOH) to give the product as a yellow oil (0.40 g, 97%).

MS (ESI) m/z: 273.2 $[M+H]^+$

19.3 (4aS,10bS)-4-Allyl-1,2,3,4,4a,5,6,10b-octahydro-benzo[f]quinolin-8-ylamine

(4aS,10bS)-4-Allyl-8-nitro-1,2,3,4,4a,5,6,10b-octahydro-benzo[f]quinoline (0.85 g, 3.12 mmol) was dissolved in MeOH (50 mL) and tin chloride (3.50 g, 15.5 mmol) added. The solution was heated to reflux for 3 h and then evaporated. The residue was partitioned between ethyl acetate and NaOH (2M), and the organic

phase separated and dried over $MgSO_4$. The filtered solution was concentrated and separated by preparative HPLC (20-90% MeOH) to give the 3 amino isomers. The product was obtained as a yellow oil (0.35 g, 46%).

MS (ESI) m/z: 243.3 $[M+H]^+$

^{1}H-NMR (DMSO-d_6): δ [ppm] 6.90 (d, 1H), 6.35 (d, 1H), 6.25 (s, 1H), 5.87 (m, 1H), 5.12 (m, 2H), 3.42 (m, 1H), 3.04 (m, 1H), 2.90 (m, 1H), 2.64 (m, 2H), 2.34 (m, 2H), 2.13 (m, 2H), 1.95 (m, 1H), 1.62 (m, 2H), 1.39 (m, 1H), 1.00 (m, 1H).

^{13}C-NMR (DMSO-d_6): δ [ppm] 146.1 (s), 135.7 (s), 135.3 (d), 126.4 (s), 125.6 (d), 117.1 (t), 113.2 (d), 112.2 (d), 63.9 (d), 55.4 (t), 52.8 (t), 41.3 (d), 29.4 (t), 28.6 (t), 26.3 (t), 24.9 (t).

19.4 N-((4aS,10bS)-4-Allyl-1,2,3,4,4a,5,6,10b-octahydro-benzo[f]quinolin-8-yl)-4-isopropyl-benzenesulfonamide

(4aS,10bS)-4-Allyl-1,2,3,4,4a,5,6,10b-octahydro-benzo[f]quinolin-8-ylamine (60 mg, 0.23 mmol) was dissolved in pyridine-dichloromethane (1:2, 7.5 mL) and cooled to 5°C. 4-Isopropylbenzenesulfonyl chloride (50 mg, 0.24 mmol) was added and the solution stirred at 5°C for 3h. Solution was evaporated, partitioned between ethyl acetate and water, and the organic phase separated and dried over $MgSO_4$. The filtered solution was concentrated and separated by column chromatography (dichloromethane-3% MeOH) to give an oil. The oil was dissolved in ethyl acetate and HCl (4M, dioxane) was added to give the product as a white solid (20 mg, 15%).

MS (ESI) m/z: 425.2 $[M+H]^+$

The procedure described in example 19 was used to prepare the compounds of examples 20 and 21. The compounds were characterized by the following physical data:

EXAMPLE 20

N-((4aS,10bS)-4-Allyl-1,2,3,4,4a,5,6,10b-octahydro-benzo[f]quinolin-9-yl)-4-isopropyl-benzenesulfonamide

20.1 (4aS,10bS)-9-Nitro-1,2,3,4,4a,5,6,10b-octahydro-benzo[f]quinoline

MS (ESI) m/z: 233.1 $[M+H]^+$

^{1}H-NMR (DMSO-d_6): δ [ppm] 8.13 (s, 1H), 8.03 (d, 1H), 7.43 (d, 1H), 4.05 (br s, 1H), 3.38 (m, 1H), 2.97 (m, 3H), 2.64 (m, 1H), 2.15 (d, 1H), 1.99 (m, 1H), 1.88 (m, 2H), 1.46 (m, 2H).

^{13}C-NMR (DMSO-d_6): δ [ppm] 146.1 (s), 143.7 (s), 138.2 (d), 130.1 (d), 121.3 (d), 120.6 (d), 56.3 (d), 43.7 (t), 27.6 (t), 26.4 (t), 25.5 (t), 22.1 (t).

20.2 (4aS,10bS)-4-Allyl-9-nitro-1,2,3,4,4a,5,6,10b-octahydro-benzo[f]quinoline

Scale 1.51 g. Yield: 97%
MS (ESI) m/z: 273.0 [M+H]+

20.3 (4aS,10bS)-4-Allyl-1,2,3,4,4a,5,6,10b-octahydro-benzo[f]quinolin-9-ylamine

Scale 0.73 g. Yield 59 %
MS (ESI) m/z: 243.3 $[M+H]^+$
^{1}H-NMR (DMSO-d_6): δ [ppm] 6.47 (d, 1H), 6.28 (s, 1H), 6.13 (d, 1H), 5.67 (m, 1H), 5.40 (br s, 2H), 4.93 (m, 2H), 3.18 (m, 1H), 2.82 (m, 1H), 2.70 (d, 1H), 2.41 (m, 2H), 2.11 (m, 2H), 1.93 (m, 2H), 1.85 (m, 1H), 1.47 (m, 2H), 1.15 (m, 1H), 0.82 (m, 1H).
^{13}C-NMR (DMSO-d_6): δ [ppm] 146.2 (s), 139.1 (s), 135.1 (d), 128.4 (d), 122.8 (s), 117.2 (t), 112.2 (d), 110.9 (d), 63.7 (d), 55.4 (t), 52.7 (t), 41.9 (d), 29.3 (t), 27.6 (t), 26.5 (t), 24.9 (t).

20.4 N-((4aS,10bS)-4-Allyl-1,2,3,4,4a,5,6,10b-octahydro-benzo[f]quinolin-9-yl)-4-isopropyl-benzenesulfonamide

Procedure described above. Scale 0.73 g. Yield 45 %.
MS (ESI) m/z: 425.2 $[M+H]^+$
^{1}H-NMR (DMSO-d_6): δ [ppm] 7.68 (d, 2H), 7.42 (d, 2H), 6.92 (m, 3H), 6.00 (m, 1H), 5.52 (m, 2H), 3.90 (m, 1H), 3.78 (m, 1H), 3.41 (m, 1H), 3.05-2.85 (m, 4H), 2.75 (m, 2H), 2.40 (m, 1H), 2.22 (m, 1H), 2.00 (m, 2H), 1.78 (m, 1H), 1.30 (m, 1H), 1.19 (d, 6H).

EXAMPLE 21

N-((4aS,10bS)-4-Allyl-1,2,3,4,4a,5,6,10b-octahydro-benzo[f]quinolin-7-yl)-4-isopropyl-benzenesulfonamide

21.1 (4aS,10bS)-4-Allyl-7-nitro-1,2,3,4,4a,5,6,10b-octahydro-benzo[f]quinoline

Procedure described above except: room temperature reaction for 18h. Yield 51%.

MS (ESI) m/z: 273.0 $[M+H]^+$

21.2 (4aS,10bS)-4-Allyl-1,2,3,4,4a,5,6,10b-octahydro-benzo[f]quinolin-7-ylamine

Scale 0.85 g. Yield : 46 %
MS (ESI) m/z: 243.3 $[M+H]^+$

21.3 N-((4aS,10bS)-4-Allyl-1,2,3,4,4a,5,6,10b-octahydro-benzo[f]quinolin-7-yl)-4-isopropyl-benzenesulfonamide

Procedure described above. Scale 0.26 g. Yield 53% . Converted to HCl salt.
MS (ESI) m/z: 425.1 $[M+H]^+$
^{1}H-NMR (DMSO-d_6): δ [ppm] 11.38 (br s, 1H), 9.56 (br s, 1H), 7.60 (d, 2H), 7.44 (d, 2H), 7.21 (d, 2H), 7.11 (t, 1H), 6.84 (d, 1H), 6.00 (m, 1H), 5.50 (m, 2H), 3.85 (m, 1H), 3.75 (m, 1H), 3.15 (m, 1H), 2.95 (m, 3H), 2.60 (m, 2H), 2.28 (m, 1H), 2.00 (m, 2H), 1.68 (m, 1H), 1.40 (m, 1H), 1.19 (d, 6H).
^{13}C-NMR (DMSO-d_6): δ [ppm] 153.5 (s), 138.0 (s), 134.1 (s), 132.0 (s), 127.0 (d), 126.5 (d), 126.3 (d), 124.6 (t), 124.4 (d), 123.9 (d), 62.8 (d), 53.8 (t), 51.2 (t), 35.2 (t), 33.3 (d), 26.8 (t), 23.3 (q), 22.6 (t), 22.1 (t).

EXAMPLE 22

trans-4-Isopropyl-N-(1-propionyl-1,2,3,4,4a,5,10,10a-octahydro-benzo[g]quinolin-7-yl)-benzenesulfonamide

22.1 trans-1,2,3,4,4a,5,10,10a-Octahydro-benzo[g]quinoline

This compound was prepared as described for (4aR,10aR)-9-methoxy-1-methyl-6-trimethylsilanyl-1,2,3,4,4a,5,10,10a-octahydrobenzo[g]quinoline in Organic Process Research & Development, 2003, 904-12.

ESI-MS: $[M+H]^+$
^{1}H-NMR ($CDCl_3$): δ [ppm] 7.1-8.0 (several m, 4H), 3.15 (m, 1H), 3.0 (m, 1H), 2.9 (m, 1H), 2.6-2.8 (several m, 3H), 2.55 (m, 1H), 2.0 (m, 1H), 1.75 (m, 1H), 1.6 (m, 2H), 1.2 (m, 1H).
^{1}H-NMR (DMSO-d_6): δ [ppm] 7.0-7.1 (several m, 4H), 2.95 (m, 1H), 2.8 (m, 1H), 2.7 (m, 1H), 2.3-2.6 (several m, 4H), 1.85 (m, 1H), 1.55 (m, 1H), 1.45 (m, 1H), 1.35 (m, 1H), 1.05 (m, 1H).

22.2 trans-1-(3,4,4a,5,10,10a-Hexahydro-2H-benzo[g]quinolin-1-yl)-propan-1-one

5.33 g of trans-1,2,3,4,4a,5,10,10a-Octahydro-benzo[g]quinoline (28.46 mmol) were dissolved in 70 ml tetrahydrofuran, and subsequently 5.76 g of triethylamine (56.9 mmol) and, at –5°C, 4.07 g propionic acid anhydride (31.3 mmol) in 10 ml of tetrahydrofuran were added. After stirring for 2 h at –5°C, 4 ml of concentrated aqueous ammonia were added, the reaction mixture evaporated to dryness, 100 ml ethyl acetate added, and washed with 60 ml water. The organic layer was dried over magnesium sulfate, filtered, and evaportated to dryness to yield 7.79 g of the desired product.

ESI-MS: 244.2 $[M+H]^+$

^{1}H-NMR ($CDCl_3$): δ [ppm]

22.3 trans-1-(7-Nitro-3,4,4a,5,10,10a-hexahydro-2H-benzo[g]quinolin-1-yl)-propan-1-one

2.5 g trans-1-(3,4,4a,5,10,10a-Hexahydro-2H-benzo[g]quinolin-1-yl)-propan-1-one (10.27 mmol) were dissolved in 25 ml nitromethane. At –5°C to –10°C, a mixture of 0.71 ml of nitric acid (10.27 mmol), 1.5 ml of water, and 9.5 ml of sulphuric acid (170 mmol) were added within 30 minutes. Stirring continued for 1.5 h under cooling conditions before the mixture was poured onto crushed ice. The aqueous phase was extracted twice with ethyl acetate, the combined organic layer was dried over magnesium sulfate, filtered, and the solvent evaporated under reduced pressure to yield 2.7 g of the nitrated product as a mixture of several nitro-isomers, which was used in the subsequent reaction without further separation.

ESI-MS: 289.1 $[M+H]^+$

22.4 trans-1-(7-amino-3,4,4a,5,10,10a-hexahydro-2H-benzo[g]quinolin-1-yl)-propan-1-one

2.7 g trans-1-(7-Nitro-3,4,4a,5,10,10a-hexahydro-2H-benzo[g]quinolin-1-yl)-propan-1-one including its regioisomers (9.36 mmol) were dissolved in 100 ml of methanol, 11 g of stannous dichloride (48.75 mmol) added, and the reaction mixture stirred under reflux for 1.5 h. Methanol was removed, the residue treated with 1 N aqueous sodium hydroxide and ethyl acetate, filtered through celite, the phases separated and the aqueous phase extracted twice with ethyl acetate. The combined organic layers were dried over magnesium sulfate, filtered, and the solvent evaporated under reduced pressure. The crude product was purified via

preparative HPLC (DeltaPak, 40 mm diameter) with methanol/water/1%acetic acid as eluent to yield 0.04 g of the 6-amino-isomer, 0.1 g of the 7-amino-isomer, 0.14 g of the 8-amino-isomer, and 0.19 g of the 9-amino-isomer.

6-amino-isomer:

ESI-MS: 259.1 $[M+H]^+$

^{1}H-NMR ($CDCl_3$): δ [ppm] 6.95 (m, 1H), 6.5 (m, 2H), 3.8 (m, very broad, 2H), 3.55 (m, very broad, 2H), 3.1 (m, very broad, 2H), 2.6-2.8 (m, 2H), 2.3-2.5 (m, 2H), 2.15 (m, 1H), 1.7-2.0 (several m, 4H), 1.3 (m, 1H), 1.15 (m, 3H).

7-amino-isomer:

ESI-MS: 259.1 $[M+H]^+$

^{1}H-NMR ($CDCl_3$): δ [ppm] 6.9 (m, 1H), 6.5 (m, 1H), 6.4 (m, 1H), 3.7 (m, very broad, 2H), 3.55 (m, very broad, 2H), 3.1 (m, very broad, 2H), 2.3-2.8 (several m, 5H), 1.65-2.0 (several m, 4H), 1.3 (m, 1H), 1.15 (m, 3H).

8-amino-isomer:

ESI-MS: 259.1 $[M+H]^+$

^{1}H-NMR ($CDCl_3$): δ [ppm] 6.85 (m, 1H), 6.5 (m, 1H), 6.4 (m, 1H), 3.3-4.2 (m, very broad, 4H), 3.1 (m, very broad, 2H), 2.55-2.8 (m, 2H), 2.25-2.5 (m, 3H), 1.9 (m, 2H), 1.75 (m, 2H), 1.25 (m, 1H), 1.15 (m, 3H).

9-amino-isomer:

ESI-MS: 259.1 $[M+H]^+$

^{1}H-NMR ($CDCl_3$): δ [ppm] 6.95 (m, 1H), 6.5 (m, 2H), 3.4-4.0 (m, very broad, 4H), 3.0-3.3 (m, very broad, 2H), 2.8 (m, 1H), 2.55 (m, 1H), 2.2-2.45 (m, 3H), 1.95 (m, 2H), 1.75 (m, 2H), 1.25 (m, 1H), 1.15 (m, 3H).

22.5 trans-4-Isopropyl-N-(1-propionyl-1,2,3,4,4a,5,10,10a-octahydro-benzo[g]quinolin-7-yl)-benzenesulfonamide

1.21 g of trans-1-(7-amino-3,4,4a,5,10,10a-hexahydro-2H-benzo[g]quinolin-1-yl)-propan-1-one (0.38 mmol) were dissolved in 2 ml of pyridine. At 0-4°C, 0.08 g of 4-isopropyl-benzene sulfonylchloride (0.4 mmol) were added, and the reaction stirred for 1 h under cooling. 40 ml of aqueous 1 N hydrochlorid acid and diethyl ether were added, the phases separated, and the aqueous layer extracted twice with diethyl ether. The organic phases were combined, washed three times with water acidified with 1 N aqueous hydrochloric acid, dried over magnesium sul-

fate, filtered, and the solvent evaporated under reduced pressure to yield 0.118 g of the product.

ESI-MS: 441.1 $[M+H]^+$

EXAMPLE 23

trans-4-Isopropyl-N-(1-propyl-1,2,3,4,4a,5,10,10a-octahydro-benzo[g]quinolin-7-yl)-benzenesulfonamide

0.18 mg of trans-4-isopropyl-N-(1-propionyl-1,2,3,4,4a,5,10,10a-octahydro-benzo[g]quinolin-7-yl)-benzenesulfonamide (0.268 mmol) were dissolved in 7 ml of tetrahydrofuran. 1.4 ml of 1 M borane-tetrahydrofuran-complex in tetrahydrofurane were added and the reaction stirred under reflux for 30 min. 2 ml of 2 N aqueous hydrochloric acid were added, the reaction further stirred for 3 h under reflux, and the solvent removed under reduced pressare. Water adjusted to pH 9 with sodium hydroxide was added and the aqueous phase extracted three times with diethyl ether. The combined organic layers were dried over magnesium sulfate, filtered, and the solvent removed. The residue was purified via silica gel chromatography on chromabond column with cyclohexane / ethyl acetate 1:3 as eluent to yield 0.0155 g of the desired product

ESI-MS: 427.1 $[M+H]^+$

^{1}H-NMR ($CDCl_3$): δ [ppm] 7.6 (d, 2H), 7.2 (d, 2H), 6.9 (m, 1H), 6.7 (m, 3H), 3.05 (m, 1H), 2.95 (m, 1H), 2.85 (m, 1H), 2.5-2.75 (several m, 3H), 2.05-2.5 (several m, 4H), 1.8 (m, 1H), 1.6 (m, 3H), 1.45 (m, 2H), 1.2 (m, 6H), 0.8 (m, 3H).

EXAMPLE 24

trans-4-Isopropyl-N-(1,2,3,4,4a,5,10,10a-octahydro-benzo[g]quinolin-7-yl)-benzenesulfonamide

From that same chromatography of example 20, 0.0227 g of the secondary amine could be obtained.

ESI-MS: 385.1 $[M+H]^+$

^{1}H-NMR ($CDCl_3$): δ [ppm] 7.7 (d, 2H), 7.25 (d, 2H), 6.9 (m, 1H), 6.75 (m, 2H), 3.1 (m, 1H), 2.9 (m, 1H), 2.8 (m, 1H), 2.7 (m, 2H), 2.6 (m, 2H), 2.35 (m, 1H), 1.9 (m, 1H), 1.7 (m, 1H), 1.6 (m, 1H), 1.45 (m, 1H), 1.2 (m, 6H), 1.1 (m, 1H).

EXAMPLE 25

trans-4-trifluoromethyl-N-(1-propionyl-1,2,3,4,4a,5,10,10a-octahydro-benzo[g]quinolin-7-yl)-benzenesulfonamide

0.792 g (3.065 mmol) of a 1:1 mixture trans-(7-amino-3,4,4a,5,10,10a-hexahydro-2H-benzo[g]quinolin-1-yl)-propan-1-one and trans-(8-amino-3,4,4a,5,10,10a-hexahydro-2H-benzo[g]quinolin-1-yl)-propan-1-one were dissolved in 20 ml pyridine. At 0-4°C, 0.75 g of 4-trifluoromethyl-benzene sulfonyl-chloride (3.066 mmol) were added, and the reaction stirred for 2 h under cooling. Pyridine was evaporated and the residue partitioned between 20 % aqueous citric acid and diethylether. The aqueous layer was extracted twice with diethylether, the combined organic phases washed with 20% aqueous citric acid, dried over magnesium sulfate, filtered, and the solvent evaporated under reduced pressure to yield 1.327 g of the product. MSD: 467.1g/mol

ESI-MS: 467.1 $[M]^+$

EXAMPLE 26

trans-4-trifluoromethyl-N-(1-propyl-1,2,3,4,4a,5,10,10a-octahydro-benzo[g]quinolin-7-yl)-benzenesulfonamide

22.5 mg of the compound were obtained from the chromatographic purification of example 27 which describes the reduction of a 1:1 mixture of the 7- and 8-isomers of the corresponding propionyl precursors

EXAMPLE 27

trans-4-trifluoromethyl-N-(1-propyl-1,2,3,4,4a,5,10,10a-octahydro-benzo[g]quinolin-8-yl)-benzenesulfonamide

To a suspension of 0.035 g of lithium aluminium hydride (0.922 mmol) in 2.5 ml tetrahydrofurane were added at 4°C a solution of 0.2 g of the 1:1 mixture of trans-4-trifluoromethyl-N-(1-propionyl-1,2,3,4,4a,5,10,10a-octahydro-benzo[g]quinolin-7-yl)-benzenesulfonamide and trans-4-trifluoromethyl-N-(1-propionyl-1,2,3,4,4a,5,10,10a-octahydro-benzo[g]quinolin-8-yl)-benzenesulfonamide (0.429 mmol) in 2.5 ml tetrahydrofuran. After stirring for 5 minutes at 10°C, 1mL water was cautiously added, the solvent evaporated and the residue treated with diethyl ether and water. The aqueous phase was reextracted with diethylether, and the combined organic layers dried over magnesium sulfate, filtered and the solvent evaporated under reduced pressure. The crude product was purified via preparative HPLC (compression column, Delta Pack 40mm diameter) using a gradient consisting of methanol/ water / 0.1% acetic as eluent; fraction 3, m=31.9mg (8-isomer), fraction. 4, m=22.4mg, fractions. 5-7, m=22.5mg (7-isomer),

EXAMPLE 28

N-((*S*)-6-Amino-5,6,7,8-tetrahydro-naphthalen-2-yl)-4-isopropyl-benzenesulfonamide, hydrochloride

A mixture of N-((*S*)-6-Allylamino-5,6,7,8-tetrahydro-naphthalen-2-yl)-4-isopropyl-benzenesulfonamide (108 mg, 0.26 mmol) and 10 % palladium on carbon (25 mg) in a misture of ethyl acetate (12 ml) and methanol (3 ml) was hydrogenated overnight. The catalyst was filtered, and the solvent was removed under vaccum to yield an oil. This oil was dissolved in destilled H_2O (30 ml) and a few drops of concentrated HCl were added. This solution was lyophilisated to yield the deallylated product (60 mg, 61 %).

ESI-MS: 345.2 $[M+H]^+$

^{1}H-NMR (DMSO-d_6): δ [ppm] 10.2 (bs, 1H), 8.2 (bs, 1H), 7.7 (d, 2H), 7.4 (d, 2H), 7.0 (d, 1H), 6.9 (d, 1H), 6.8 (s, 1H), 3.7 (m, 1H), 3.0 (m, 2H), 2.7 (m, 3H), 2.1 (m, 1H), 1.7 (m, 1H), 1.2 (d, 6H).

EXAMPLE 29

N-((*R*)-6-Dipropylamino-5,6,7,8-tetrahydro-naphthalen-2-yl)-4-isopropyl-benzenesulfonamide, hydrochloride

4-Isopropyl-N-((*R*)-6-propylamino-5,6,7,8-tetrahydro-naphthalen-2-yl)-benzenesulfonamide (150 mg, 0.39 mmol) and propionaldehyde (42 µl, 0.58 mmol) were dissolved in THF (20 ml). Acetic acid (30 µl, 0.58 mmol) and sodium trisacetoxyborohydride (165 mg, 0.78 mmol) were sequentially added to the reaction mixture and stirred overnight. The reaction mixture was concentrated and the residue was dissolved in H_2O (10 ml) and ethyl acetate (50 ml). With NaOH (2M) the ph was adjusted to 9. The organic phase was separated, dried over magnesium sulfate, filtered, and evaporated to dryness to yield an oil (95 mg). This oil was dissolved in destilled H_2O (30 ml) and a few drops of concentrated HCl were added. This solution was lyophilisated to yield the desired product (92 mg, 54 %).

ESI-MS: 429.2 $[M+H]^+$

^{1}H-NMR (DMSO-d_6): δ [ppm] 10.2 (s, 1H), 9.9 (bs, 1H), 7.7 (d, 2H), 7.4 (d, 2H), 7.0 (d, 1H), 6.9 (d, 1H), 6.8 (s, 1H), 3.6 (m, 1H), 3.1-2.9 (m, 6H), 2.8 (m, 2H), 2.5 (m, 1H), 2.2 (m, 1H), 1.7 (m, 5H), 1.2 (d, 6H), 0.9 (t, 6H).

EXAMPLE 30

N-((*S*)-6-Dipropylamino-5,6,7,8-tetrahydro-naphthalen-2-yl)-4-isopropyl-benzenesulfonamide, hydrochloride

4-Isopropyl-N-((*S*)-6-propylamino-5,6,7,8-tetrahydro-naphthalen-2-yl)-benzenesulfonamide (70 mg, 0.18 mmol) and propionaldehyde (42 µl, 0.58 mmol) was dissolved in THF (20 ml). Acetic acid (19 µl, 0.27 mmol) and sodium trisacetoxyborohydride (75 mg, 0.35 mmol) were sequentially added to the reaction mixture and stirred overnight. The reaction mixture was concentrated and the residue was dissolved in H_2O (10 ml) and ethyl acetate (50 ml). With NaOH (2M) the ph was adjusted to 9. The organic phase was separated, dried over magnesium sulfate, filtered, and evaporated to dryness to yield an oil (95 mg). This oil was dissolved in destilled H_2O (30 ml) and a few drops of concentrated HCl were added. This solution was lyophilisated to yield the desired product (21 mg, 25 %).
ESI-MS: 429.2 $[M+H]^+$
^{1}H-NMR (DMSO-d_6): δ [ppm] 10.2 (s, 1H), 9.9 (bs, 1H), 7.7 (d, 2H), 7.4 (d, 2H), 7.0 (d, 1H), 6.9 (d, 1H), 6.8 (s, 1H), 3.6 (m, 1H), 3.1-2.9 (m, 6H), 2.8 (m, 2H), 2.5 (m, 1H), 2.2 (m, 1H), 1.7 (m, 5H), 1.2 (d, 6H), 0.9 (t, 6H).

EXAMPLE 31

N-[7-(4-Trifluoromethoxy-benzenesulfonylamino)-3,4-dihydro-2H-pyrano[3,2-b]pyridin-3-yl]-propionamide

31.1 (5-Oxo-tetrahydro-pyran-3-yl)-carbamic acid benzyl ester

Following the same procedure as described in example 11.1, 6H-pyran-3-one (5 g, 50.96 mmol) in CH_2Cl_2 (5 ml) was treated with bismuth nitrate pentahydrate (5 g, 10.30 mmol) and benzylcarbamate (8.5 g, 56.22 mmol). Purification of the crude product by flash column chromatography (heptane:ethyl acetate, 3:1) gave the title compound (8.11 g, 64%) as a colorless oil.
MS (ESI+) m/z = 250.1 $[M+H]^+$
^{1}H NMR (400 MHz, $CDCl_3$) δ 2.67 (dd, *J* = 16.6, 2.5 Hz, 1H), 2.75 (dd, *J* = 16.6, 5.4 Hz, 1H), 3.84 (br d, *J* = 11.5 Hz, 1H), 3.92 (dd, *J* = 11.8, 2.7 Hz, 1H), 3.99 (d, *J* = 16.1 Hz, 1H), 4.06 (d, *J* = 16.2 Hz, 1H), 4.30 (br s, 1H), 5.10 (m, 2H), 5.19 (m, 1H), 7.35 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) □44.1, 47.9, 67.0, 69.3, 74.9, 128.1 (2C), 128.2, 128.5 (2C), 136.0, 155.4, 204.7.

31.2 Benzyl 3,4-dihydro-7-nitro-2H-pyrano[3,2-b]pyridin-3-ylcarbamate and benzyl 6,8-dihydro-3-nitro-5H-pyrano[3,4-b]pyridin-5-ylcarbamate

A solution of (5-oxo-tetrahydro-pyran-3-yl)-carbamic acid benzyl ester (750 mg, 3 mmol) and 1-methyl-3,5-dinitro-2-pyridone (660 g, 3.31 mmol) in methanolic ammonia (1M, 6 ml) was irradiated in a sealed vial at 120°C for 20 min. The mixture was then concentrated and the resulting residue was dissolved in CH_2Cl_2. The organic layer was washed with saturated aqueous $NaHCO_3$ and water, dried over Na_2SO_4 and evaporated. Purification of the resulting residue by chromatography on silica gel (heptane:ethyl acetate, 3:1) afforded a mixture 7.5/1 (632 mg, 64%) of benzyl 6,8-dihydro-3-nitro-5H-pyrano[3,4-b]pyridin-5-ylcarbamate as major product along with benzyl 3,4-dihydro-7-nitro-2H-pyrano[3,2-b]pyridin-3-ylcarbamate as minor adduct. A small fraction of each was isolated to afford full characterization.

Benzyl 3,4-dihydro-7-nitro-2H-pyrano[3,2-b]pyridin-3-yl-carbamate: white solid
MS (ESI+) m/z = 330.1 $[M+H]^+$.
^1H NMR (400 MHz, $CDCl_3$) δ 3.10 (dd, *J* = 18.1, 3.5 Hz, 1H), 3.34 (dd, *J* = 18.2, 5.3 Hz, 1H), 4.25 (s, 2H), 4.39 (br s, 1H), 5.02 (br s, 1H), 5.10 (s, 2H), 7.33 (m, 5H), 7.90 (d, *J* = 2.0 Hz, 1H), 8.98 (d, *J* = 2.0 Hz, 1H);
^{13}C NMR (100 MHz, $CDCl_3$) δ 34.9, 43.7, 67.2, 68.7, 118.6, 128.2 (2C), 128.3, 128.5 (2C), 135.8, 137.2, 143.6, 148.0, 150.3, 155.4.
Anal. calcd. for $C_{16}H_{15}N_3O_5$: C, 58.36; H, 4.59; N, 12.76; O, 24.29. Found: C, 58.76; H, 5.00; N, 12.23; O, 24.12.

Benzyl 6,8-dihydro-3-nitro-5H-pyrano[3,4-b]pyridin-5-yl-carbamate: light yellow solid
MS (ESI+) m/z = 330.1 $[M+H]^+$.
^1H NMR (400 MHz, $CDCl_3$) δ 3.96 (dd, *J* = 11.9, 3.2 Hz, 1H), 4.07 (dd, *J* = 11.9, 2.9 Hz, 1H), 4.80 (d, *J* = 17.4 Hz, 1H), 4.94 (d, *J* = 17.4 Hz, 1H), 5.00 (m, 1H), 5.13 (d, *J* = 12.3 Hz, 1H), 5.17 (d, *J* = 12.3 Hz, 1H), 5.38 (d, *J* = 9.0 Hz, 1H), 7.35 (m, 5H), 8.61 (d, *J* = 1.6 Hz, 1H), 9.29 (d, *J* = 1.9 Hz, 1H);
^{13}C NMR (100 MHz, $CDCl_3$) δ 46.7, 67.3, 68.8, 69.8, 128.1 (2C), 128.3, 128.5 (2C), 130.9, 131.8, 135.8, 143.2, 144.1, 155.8, 160.8;
Anal. calcd for $C_{16}H_{15}N_3O_5$: C, 58.36; H, 4.59; N, 12.76; O, 24.29. Found: C, 58.46; H, 4.80; N, 12.59; O, 23.98.

31.3 N-(3,4-dihydro-7-nitro-2H-pyrano[3,2-b]pyridin-3-yl)propionamide and N-(6,8-dihydro-3-nitro-5*H*-pyrano[3,4-*b*]pyridin-5-yl)propionamide

A mixture of benzyl 3,4-dihydro-7-nitro-2*H*-pyrano[3,2-*b*]pyridin-3-ylcarbamate and benzyl 6,8-dihydro-3-nitro-5*H*-pyrano[3,4-*b*]pyridine-5-ylcarbamate (6.54 g, 26.23 mmol) in CH_2Cl_2 (55 ml) was stirred at 0°C and 33% HBr in acetic acid (45 ml) was added. The solution was further stirred at 0°C for 1 h then at room temperature for 2 h. The solvents were then removed. The crude mixture was dissolved in CH_2Cl_2/H_2O 1/1 (80 ml) and the aqueous mixture adjusted to pH~10 with 2N NaOH solution. After separation of the layers, the organic phase was washed with H_2O (x2), dried over Na_2SO_4 and evaporated. The residue was dissolved in CH_2Cl_2 (400 ml) and the solution cooled to 0°C. Propionyl chloride (4,54 ml, 52 mmol) and triethylamine (7.22 ml, 52 mmol) were added and then the mixture was allowed to reach 20°C and stirred for 4.5 h. The solution was washed successively with 1 N aqueous HCl, saturated aqueous $NaHCO_3$ and water. The organic layer was dried (Na_2SO_4) and evaporated. Immediate recrystallization in acetone gave a pure fraction of N-(6,8-dihydro-3-nitro-5*H*-pyrano[3,4-*b*]pyridin-5-yl)propionamide (2.2 g, 33% for two steps) as a white solid. The remaining mixture was subjected to chromatography on silica gel (heptane:ethyl acetate, 1.5:3.5 then CH_2Cl_2:CH_3OH, 95:5) to afford another portion of N-(6,8-dihydro-3-nitro-5*H*-pyrano[3,4-*b*]pyridin-5-yl)propionamide (1.15 mg, 17% for two steps) and N-(3,4-dihydro-7-nitro-2H-pyrano[3,2-b]pyridin-3-yl)propionamide (445 mg, 7% for two steps) as a white solid.

N-(3,4-dihydro-7-nitro-2H-pyrano[3,2-b]pyridin-3-yl)propionamide:
MS (ESI+) m/z = 252.1 $[M+H]^+$
^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.14 (t, *J* = 7.6 Hz, 3H), 2.21 (q, *J* = 7.6 Hz, 2H), 3.08 (dd, *J* = 18.3, 4.0 Hz, 1H), 3.35 (dd, *J* = 18.3, 5.5 Hz, 1H), 4.25 (m, 2H), 4.65 (m, 1H), 5.57 (br s, 1H), 7.93 (d, *J* = 1.9 Hz, 1H), 9.01 (d, *J* = 2.0 Hz, 1H).

31.4 N-(7-Amino-3,4-dihydro-2H-pyrano[3,2-b]pyridin-3-yl)-propionamide

N-(3,4-Dihydro-7-nitro-2H-pyrano[3,2-b]pyridin-3-yl)propionamide (445 mg, 1.76 mmol) was dissolved in ethanol (80 ml) and $SnCl_2 \cdot 2H_2O$ (2 g, 8.82 mmol) was added. The resulting mixture was refluxed for 8 h and then the solvent was removed under vacuum. The raw material was dissolved in ethyl acetate and washed successively with 2 N aqueous NaOH (2x) and water. The organic layer was dried (Na_2SO_4), filtered through a pad of celite and evaporated to afford the crude N-(7-amino-3,4-dihydro-2H-pyrano[3,2-b]pyridin-3-yl)-propionamide (390 mg, 99%) as a pale yellow powder.

31.5 N-[7-(4-Trifluoromethoxy-benzenesulfonylamino)-3,4-dihydro-2H-pyrano[3,2-b]pyridin-3-yl]-propionamide

A portion of the raw N-(7-amino-3,4-dihydro-2H-pyrano[3,2-b]pyridin-3-yl)-propionamide (100 mg, 0.45 mmol) was dissolved in CH_2Cl_2/pyridine 9/1 (20 ml) and 4-(trifluoromethoxy)benzensulfonyl chloride (100 µl, 0.58 mmol) was added dropwise. After stirring at room temperature over night, the reaction mixture was concentrated and the purification of the residue by chromatography on silica gel (CH_2Cl_2:CH_3OH, 97:3) gave the title compound (94 mg, 47% for steps 31.4 and 31.5) as a gum.
MS (ESI+) m/z = 446.1 $[M+H]^+$

EXAMPLE 32
N-[7-(4-Isopropyl-benzenesulfonylamino)-3,4-dihydro-2H-pyrano[3,2-b]pyridin-3-yl]-propionamide

Following the same procedure as described in example 31.5, a portion of crude N-(7-amino-3,4-dihydro-2H-pyrano[3,2-b]pyridin-3-yl)-propionamide (100 mg, 0.45 mmol) in CH_2Cl_2/pyridine 9/1 (20 ml) was treated with 4-isopropylbenzensulfonyl chloride (130 µl, 0.72 mmol). Purification by flash column chromatography (CH_2Cl_2:methanol, 97:3) gave the title compound (85 mg, 47% for steps 31.4 and this step) as a gum.
MS (ESI+) m/z = 404.1 $[M+H]^+$

EXAMPLE 33
N-{7-[4-((S)-2-Fluoro-1-methyl-ethyl)-benzenesulfonylamino]-3,4-dihydro-2H-pyrano[3,2-b]pyridin-3-yl}-propionamide

Following the same procedure as described in example 31.5, a portion of crude N-(7-amino-3,4-dihydro-2H-pyrano[3,2-b]pyridin-3-yl)-propionamide (95 mg, 0.43 mmol) in CH_2Cl_2/pyridine 9/1 (10 ml) was treated with 4-((S)-2-fluoro-1-methyl-ethyl)-benzenesulfonyl chloride (132 mg, 0.55 mmol). Purification by flash column chromatography (CH_2Cl_2:MeOH, 97:3) gave the title compound (100 mg, 55% for step 31.4 and this step) as a gum.
MS (ESI+) m/z = 422.1 $[M+H]^+$

EXAMPLE 34
N-(3-Propylamino-3,4-dihydro-2H-pyrano[3,2-b]pyridin-7-yl)-4-trifluoromethoxy-benzenesulfonamide

To a solution of N-[7-(4-trifluoromethoxy-benzenesulfonylamino)-3,4-dihydro-2H-pyrano[3,2-b]pyridin-3-yl]-propionamide (93 mg, 0.20 mmol) in THF (20 ml) was added dropwise 1M BH_3•THF (2.08 ml, 2.08 mmol) and the mixture was stirred at room temperature for 12 h. It was then quenched by adding carefully 1N aqueous HCl (8 ml) and then the resulting solution was heated at reflux for 4 h. The solution was cooled to room temperature, the aqueous mixture was adjusted to pH~8 with 2 N NaOH solution and diluted with CH_2Cl_2. Separation of the layers, drying (Na_2SO_4) of the organic phase and evaporation in vacuo provided the crude material, which was purified by flash column chromatography (CH_2Cl_2:methanol, 97:3) to give the title compound (70 mg, 78%) as a white amorphous solid.

MS (ESI+) m/z = 432.1 $[M+H]^+$

^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 0.92 (t, *J* = 7.3 Hz, 3H), 1.53 (m, 2H), 2.69 (t, 1H, *J* = 7.3 Hz, 2H), 2.78 (dd, *J* = 16.9, 6.5 Hz, 1H), 3.10 (dd, *J* = 16.9, 4.8 Hz, 1H), 3.24 (m, 1H), 3.96 (dd, *J* = 10.8, 6.4 Hz, 1H), 4.16 (m, 3H), 6.97 (d, *J* = 1.7 Hz, 1H), 7.27 (d, *J* = 8.3 Hz, 2H), 7.77 (d, *J* = 1.2 Hz, 1H), 7.84 (d, *J* = 8.7 Hz, 2H).

EXAMPLE 35

4-Isopropyl-N-(3-propylamino-3,4-dihydro-2H-pyrano[3,2-b]pyridin-7-yl)-benzenesulfonamide

Following the same procedure as described in example 34, N-[7-(4-isopropyl-benzenesulfonylamino)-3,4-dihydro-2H-pyrano[3,2-b]pyridin-3-yl]-propionamide (85 mg, 0.21 mmol) in THF (10 ml) was treated with 1M BH_3•THF (2.1 ml, 2,1 mmol). Purification of the crude product by flash column chromatography (CH_2Cl_2:methanol, 97:3) gave the title compound (50 mg, 61%) as a white amorphous solid.

MS (ESI+) m/z = 390.1 $[M+H]^+$

^1H NMR (400 MHz, $CDCl_3$) : δ (ppm) 0.92 (t, *J* = 7.4 Hz, 3H), 1.23 (d, *J* = 6.9 Hz, 6H), 1.52 (m, 2H), 2.69 (t, 1H, *J* = 7.3 Hz, 2H), 2.78 (dd, *J* = 16.9, 6.9 Hz, 1H), 2.93 (m, 1H), 3.09 (dd, *J* = 16.8, 4.8 Hz, 1H), 3.28 (m, 1H), 3.90 (m, 1H), 3.92 (dd, *J* = 10.8, 6.8 Hz, 1H), 4.17 (d, *J* = 10.1 Hz, 1H), 7.02 (d, *J* = 2.1 Hz, 1H), 7.30 (d, *J* = 8.3 Hz, 2H), 7.71 (d, *J* = 8.3 Hz, 2H), 7.79 (d, *J* = 2.0 Hz, 1H).

EXAMPLE 36

4-((S)-2-Fluoro-1-methyl-ethyl)-N-(3-propylamino-3,4-dihydro-2H-pyrano[3,2-b]pyridin-7-yl)-benzenesulfonamide

Following the same procedure as described in example 34, N-{7-[4-((S)-2-fluoro-1-methyl-ethyl)-benzenesulfonylamino]-3,4-dihydro-2H-pyrano[3,2-b]pyridin-3-yl}-propionamide (100 mg, 0.27 mmol) in THF (15 ml) was treated with 1M BH_3•THF (2.3 ml, 2.3 mmol). Purification of the crude product by flash column chromatography (CH_2Cl_2:methanol, 97:3) gave the title compound (50 mg, 52%) as a white solid.

MS (ESI+) m/z = 408.1 $[M+H]^+$

^1H NMR (400 MHz, CH_3OH-d_4) : δ (ppm) 0.92 (t, *J* = 7.4 Hz, 3H), 1.18 (d, *J* = 6.9 Hz, 3H), 1.61 (m, 2H), 2.93 (m, 1H), 3.00 (m, 2H), 3.09 (m, 1H), 3.28 (dd, *J* = 18.1, 5.9 Hz, 1H), 3.81 (m, 1H), 4.18 (m, 1H), 4.31 (d, *J* = 6.2 Hz, 1H), 4.34 (m, 1H), 4.43 (d, *J* = 6.2 Hz, 1H), 7.11 (d, *J* = 1.9 Hz, 1H), 7.36 (d, *J* = 8.3 Hz, 2H), 7.67 (d, *J* = 8.3 Hz, 2 H), 7.83 (bs, 1m).

EXAMPLE 37

4-Oxazol-5-yl-N-((S)-6-propylamino-5,6,7,8-tetrahydro-naphthalen-2-yl)-benzenesulfonamide

Step 1. Sulfonamide coupling; following a procedure described above, e.g. example 6.3. yield: 1.57 g (88%)

Step 2. Removal of the BOC (tert-butoxycarbonyl) group was achieved by following a procedure as described above, e.g. example 6.4 (HCl / dioxane / CH_2Cl_2). Scale 0.59 g. Yield: 40% .

HCl salt.

MS (ESI) m/z: 449.1 $[M+H]^+$

^1H-NMR (DMSO-d_6): δ [ppm] 10.24 (s, 1H), 8.80 (m, 2H), 8.53 (s, 1H), 7.84 (m, 4H), 6.98 (d, 1H), 6.88 (m, 2H), 3.39 (m, 1H), 3.07 (m, 1H), 2.91 (m, 2H), 2.72 (m, 3H), 2.16 (m, 1H), 1.63 (m, 3H), 0.91 (t, J = 7.3 Hz, 3H).

EXAMPLE 38

5-Oxazol-5-yl-thiophene-2-sulfonic acid ((S)-6-propylamino-5,6,7,8-tetrahydro-naphthalen-2-yl)-amide

Step 1. Sulfonamide coupling; following a procedure described above, e.g. example 6.3

Step 2. Removal of the BOC (tert-butoxycarbonyl) group was achieved by following a procedure as described above, e.g. example 6.4. Yield: 110 mg (74% based for two steps

MS (ESI) m/z: 418.0 $[M+H]^+$

^{1}H-NMR (DMSO-d_6): δ [ppm] 10.50 (s, 1H), 8.62 (br s, 1H), 8.48 (s, 1H), 7.72 (s, 1H), 7.50 (m, 2H), 7.00 (m, 4H), 3.12 (m, 1H), 2.93 (m, 2H), 2.76 (t, 1H, J = 7.3 Hz, 2H), 2.16 (m, 1H), 1.63 (m, 3H), 1.47 (m, 1H), 0.92 (t, J = 7.3 Hz, 3H).

EXAMPLE 39

5-Isoxazol-5-yl-thiophene-2-sulfonic acid ((S)-6-propylamino-5,6,7,8-tetrahydro-naphthalen-2-yl)-amide

Step 1. Sulfonamide coupling; following a procedure described above, e.g. example 6.3.

Step 2. BOC deprotection; following a procedure described above, e.g. example 6.4. Amount 130 mg. Yield: 87% calculated for two steps.

Converted to HCl salt.

MS (ESI) m/z: 418.1 $[M+H]^+$

^{1}H-NMR (DMSO-d_6): δ [ppm] 10.55 (s, 1H), 8.70 (br s, 2H), 7.67 (d, 1H), 7.62 (d, 1H), 7.06 (m, 2H), 6.96 (m, 2H), 3.10 (m, 1H), 2.92 (m, 2H), 2.76 (m, 3H), 2.15 (m, 1H), 1.63 (m, 3H), 0.93 (t, J = 7.3 Hz, 3H).

EXAMPLE 40

N-((S)-6-Propylamino-5,6,7,8-tetrahydro-naphthalen-2-yl)-4-(2,2,2-trifluoro-1-methyl-ethyl)-benzenesulfonamide – racemate

Step 1. Sulfonamide coupling; following a procedure described above, e.g. example 6.3 Amount 900 mg. Yield 100%

Step 2. BOC deprotection; following a procedure described above, e.g. example 6.4. Amount 700 mg. Yield: 88%

Converted to HCl salt.

MS (ESI) m/z: 441.1 $[M+H]^+$

^{1}H-NMR (DMSO-d_6): δ [ppm] 10.23 (br s, 1H), 8.72 (br s, 1H), 7.78 (d, 2H), 7.59 (d, 2H), 6.88 (m, 3H), 3.92 (m, 1H), 3.32 (m, 1H), 3.08 (m, 1H), 2.90 (m, 2H), 2.70 (m, 3H), 2.16 (m, 1H), 1.63 (m, 3H), 1.41 (d, 3H), 0.91 (t, J = 7.3 Hz, 3H).

EXAMPLE 41

N-((S)-6-Propylamino-5,6,7,8-tetrahydro-naphthalen-2-yl)-4-((R)-2,2,2-trifluoro-1-methyl-ethyl)-benzenesulfonamide

The racemic compound obtained in example 40 was separated by chiral HPLC. Amount 40 mg. 80% recovery.

MS (ESI) m/z: 441.1 $[M+H]^+$

^{1}H-NMR (DMSO-d_6): δ [ppm] 10.23 (br s, 1H), 8.72 (br s, 1H), 7.78 (d, 2H), 7.59 (d, 2H), 6.88 (m, 3H), 3.92 (m, 1H), 3.32 (m, 1H), 3.08 (m, 1H), 2.90 (m, 2H), 2.70 (m, 3H), 2.16 (m, 1H), 1.63 (m, 3H), 1.41 (d, 3H), 0.91 (t, J = 7.3 Hz, 3H).

EXAMPLE 42

N-((S)-6-Propylamino-5,6,7,8-tetrahydro-naphthalen-2-yl)-4-((S)-2,2,2-trifluoro-1-methyl-ethyl)-benzenesulfonamide

The racemic compound of example 40 was separated by chiral HPLC. Amount 50 mg. 100% recovery.

MS (ESI) m/z: 441.1 $[M+H]^+$

^{1}H-NMR (DMSO-d_6): δ [ppm] 10.23 (br s, 1H), 8.72 (br s, 1H), 7.78 (d, 2H), 7.59 (d, 2H), 6.88 (m, 3H), 3.92 (m, 1H), 3.32 (m, 1H), 3.08 (m, 1H), 2.90 (m, 2H), 2.70 (m, 3H), 2.16 (m, 1H), 1.63 (m, 3H), 1.41 (d, 3H), 0.91 (t, J = 7.3 Hz, 3H).

EXAMPLE 43

5-Isoxazol-3-yl-thiophene-2-sulfonic acid ((S)-6-propylamino-5,6,7,8-tetrahydro-naphthalen-2-yl)-amide

Step 1. Sulfonamide coupling; following a procedure described above, e.g. example 6.3 Amount 100 mg. Yield: 59%

Step 2. BOC deprotection; following a procedure described above, e.g. example 6.4 Amount 50 mg. Yield: 57%

MS (ESI) m/z: 418.0 $[M+H]^+$

^{1}H-NMR (DMSO-d_6): δ [ppm] 7.28 (d, 1H), 7.07 (br s, 1H), 6.90 (m, 4H), 6.60 (d, 2H), 4.10 (m, 1H), 3.94 (m, 1H), 3.03 (m, 1H), 2.75 (m, 5H), 2.06 (m, 2H), 1.53 (m, 3H), 0.92 (t, J = 7.3 Hz, 3H).

EXAMPLE 44

4-((R)-3-Fluoro-pyrrolidin-1-yl)-N-((S)-6-propylamino-5,6,7,8-tetrahydro-naphthalen-2-yl)-benzenesulfonamide

Step 1. Buchwald coupling reaction using (R)-3-fluoropyrrolidine,

Reaction of 0.200 g of [(S)-6-(4-bromo-benzenesulfonylamino)-1,2,3,4-tetrahydro-naphthalen-2-yl]-propyl-carbamic acid tert-butyl ester (0.38 mmol), 72 mg of (R)-3-fluoropyrrolidine (0.57 mmol), 51 mg of $NaOtC_4H_9$ (1.53 mmol), 39 mg of $Pd_2(dba)_3$ (tris(dibenzylideneacetone) dipalladium(0) (0.04 mmol)), 47 mg of BINAP (2,2'-bis(diphenylphosphino)-1,1'-binaphthyl) (0.08 mmol) in 5 ml tetrahydrofuran at 80°C for 48 hours yielded 95 mg (47 %) of {(S)-6-[4-((R)-3-fluoro-

pyrrolidin-1-yl)-benzenesulfonylamino]-1,2,3,4-tetrahydro-naphthalen-2-yl}-propyl-carbamic acid tert-butyl ester as a yellow solid.

Step 2. BOC deprotection; following a procedure described below, see example 47.2. Amount: 39 mg. Yield: 49%

MS (ESI) m/z: 432.0 $[M+H]^+$

EXAMPLE 45

4-Morpholin-4-yl-N-((S)-6-propylamino-5,6,7,8-tetrahydro-naphthalen-2-yl)-benzenesulfonamide

Step 1. Buchwald coupling using morpholine, following a procedure as described in example 44, step1. Amount: 40 mg. Yield 20%

Step 2. BOC deprotection; following a procedure described below, see example 47.2. Amount: 11 mg. Yield 31%

MS (ESI) m/z: 430.0 $[M+H]^+$

EXAMPLE 46

4-Difluoromethoxy-N-((*S*)-6-propylamino-5,6,7,8-tetrahydro-naphthalen-2-yl)-benzenesulfonamide, hydrochloride

46.1 ((*S*)-6-Bromo-1,2,3,4-tetrahydro-naphthalen-2-yl)-propyl-carbamic acid tert-butyl ester

((*S*)-6-Bromo-1,2,3,4-tetrahydro-naphthalen-2-yl)-carbamic acid tert-butyl ester (12.2 g, 37.4 mmol) was dissolved in N,N-dimethylformamide (1000 ml). Sodium hydride (50 % in oil) (1.975 g, 41.14 mmol) was added and the mixture was stirred for 15 minutes at room temperature. Propyl bromide (3.74 ml, 41.14 mmol) was added and the reaction mixture was stirred at room temperature over night. The reaction mixture was poured into a mixture of ice and H_2O (400 ml) and extracted twice with 200 ml of diethyl ether. The organic layer was dried over magnesium sulfate, filtered, and evaporated to dryness to yield 14.4 g of crude product. The crude product was purified by chromatography on silica gel using cyclohexane/ethyl acetate (95:5) as eluent, yielding the title compound (10.5 g, 76 %).

46.2 ((*S*)-6-Amino-1,2,3,4-tetrahydro-naphthalen-2-yl)-propyl-carbamic acid tert-butyl ester

In an inert atmosphere (argon), ((*S*)-6-bromo-1,2,3,4-tetrahydro-naphthalen-2-yl)-

(150 ml) at room temperature. Tris(dibenzylideneacetone) dipalladium (622 mg, 0.68 mmol) and tri-tert-butyl-phosphane (412 mg, 2.04 mmol) were added to the reaction mixture. After 15 minutes bis-(trimethylsilyl)lithiumamide (29.86 ml of a 1 M solution in THF) was added slowly and the reaction mixture was stirred for 1 hour at 100 °C. The reaction mixture was cooled and H_2O (150 ml) was added slowly and the aqueous mixture was extracted several times with diethyl ether. The organic layer was dried over magnesium sulfate, filtered, and evaporated to dryness to yield 6.9 g of crude product (95 % yield, 57 % purity).

46.3 [(*S*)-6-(4-Difluoromethoxy-benzenesulfonylamino)-1,2,3,4-tetrahydro-naphthalen-2-yl]-propyl-carbamic acid tert-butyl ester

((*S*)-6-Amino-1,2,3,4-tetrahydro-naphthalen-2-yl)-propyl-carbamic acid tert-butyl ester (1.5 g, 4.93 mmol) was dissolved in tetrahydrofuran (50 ml). Then, dimethylaminopyridine (100 mg, 0.82 mmol) and difluoromethoxy-benzenesulfonyl chloride (1.195 g, 4.93 mmol) were added and the reaction mixture was stirred over night at room temperature. The solvent was evaporated under reduced pressure, the residue treated with water and diethyl ether. The organic layer was dried over magnesium sulfate, filtered, and the solvent evaporated under reduced pressure to give the crude product (2.5 g). The crude product was purified by chromatography on silica gel using dichloromethane/methanol (100:0 to 96:4) as eluent, yielding the purified product (2.08 g, 83 %).

46.4 4-Difluoromethoxy-N-((*S*)-6-propylamino-5,6,7,8-tetrahydro-naphthalen-2-yl)-benzenesulfonamide, hydrochloride

[(*S*)-6-(4-Difluoromethoxy-benzenesulfonylamino)-1,2,3,4-tetrahydro-naphthalen-2-yl]-propyl-carbamic acid tert-butyl ester (2.08 g, 4.07 mmol) were dissolved in dichloromethane (100 ml). Trifluoroacetic acid (10 ml) was added and the reaction mixture was stirred at room temperature for 1 hour. The reaction mixture was evaporated to dryness. Diethyl ether (100 ml) was added and the mixture was extracted with saturated $NaHCO_3$ solution. To the organic layer was added ethereal hydrochloride solution and the solvent evaporated. To the residue was added diethyl ether (25 ml) and the resulting crystalline product was filtered off to give pure product (1.41 g, 77 % yield).
ESI-MS: 411.15 $[M+H]^+$

^{1}H-NMR (DMSO-d_6, 400 MHz): δ [ppm] 10.25 (s, 1H), 9.0 (m, 2H), 7.8 (d, 2H), 7.35 (t, *J* = 70 Hz, 1H), 7.3 (d, 2H), 7.0 (d, 1H), 6.9 (d, 1H), 6.85 (s, 1H), 3.4 (m, 1H), 3.1 (dd, 1H), 2.95 (m, 2H), 2.75 (m, 3H), 2.2 (m, 1H), 1.7 (m, 3H), 0.9 (t, 3H).

EXAMPLE 47

N-((*S*)-6-Propylamino-5,6,7,8-tetrahydro-naphthalen-2-yl)-4-(2,2,2-trifluoro-ethyl)-benzenesulfonamide, hydrochloride

47.1 Propyl-{(*S*)-6-[4-(2,2,2-trifluoro-ethyl)-benzenesulfonylamino]-1,2,3,4-tetrahydro-naphthalen-2-yl}-carbamic acid tert-butyl ester

((*S*)-6-Amino-1,2,3,4-tetrahydro-naphthalen-2-yl)-propyl-carbamic acid tert-butyl ester (720 mg, 2.37 mmol) was dissolved in tetrahydrofurane (50 ml). Then, dimethylamino pyridine (100 mg, 0.82 mmol) and 4-(2,2,2-trifluoro-ethyl)-benzenesulfonyl chloride (761 mg, 2.37 mmol) were added and the reaction mixture wasstirred for 30 minutes at room temperature. The solvent was evaporated under reduced pressure, the residue treated with water and diethyl ether. The organic layer was dried over magnesium sulfate, filtered, and the solvent evaporated under reduced pressure to give the crude product (1.22 g, 95 % purity, 93 % yield).

47.2 N-((*S*)-6-Propylamino-5,6,7,8-tetrahydro-naphthalen-2-yl)-4-(2,2,2-trifluoro-ethyl)-benzenesulfonamide, hydrochloride

Propyl-{(*S*)-6-[4-(2,2,2-trifluoro-ethyl)-benzenesulfonylamino]-1,2,3,4-tetrahydro-naphthalen-2-yl}-carbamic acid tert-butyl ester (1.22 g, 2.07 mmol) was dissolved in dichloromethane (40 ml). Trifluoroacetic acid (2 ml) was added and the reaction mixture was stirred at room temperature for 1 hour. The reaction mixture was evaporated to dryness. Diethyl ether (100 ml) was added and the mixture was extracted with saturated $NaHCO_3$ solution. The organic layer was dried over magnesium sulfate, filtered, and the solvent evaporated under reduced pressure. The residue was dissolved with ethyl acetate and ethereal hydrochloride solution was added. The crystalline product was filtered off to give pure product (625 mg, 65 % yield).

ESI-MS: 427.15 $[M+H]^+$

^{1}H-NMR (DMSO-d_6, 400 MHz): δ [ppm] 10.25 (s, 1H), 8.9 (m, 2H), 7.8 (d, 2H), 7.55 (d, 2H), 7.0 (d, 1H), 6.9 (d, 1H), 6.85 (s, 1H), 3.75 (q, 2H), 3.35 (m, 1H), 3.1 (dd, 1H), 2.95 (m, 2H), 2.75 (m, 3H), 2.2 (m, 1H), 1.95 (m, 4H), 1.7 (m, 3H), 0.95 (t, 3H)

The procedure described in example 46 was used to prepare the compounds of examples 48 to 57. The compounds were characterized by the following physical data:

EXAMPLE 48

4-(2,2-Difluoro-cyclopropyl)-N-((*S*)-6-propylamino-5,6,7,8-tetrahydro-naphthalen-2-yl)-benzenesulfonamide, hydrochloride

ESI-MS: 421.35 $[M+H]^+$

EXAMPLE 49

N-((*S*)-6-Propylamino-5,6,7,8-tetrahydro-naphthalen-2-yl)-4-pyrrolidin-1-yl-benzenesulfonamide, hydrochloride

ESI-MS: 414.25 $[M+H]^+$

^{1}H-NMR (DMSO-d_6, 400 MHz): δ [ppm] 9.8 (s, 1H), 8.85 (m, 2H), 7.5 (d, 2H), 6.95 (d, 1H), 6.9 (d, 1H), 6.85 (s, 1H), 6.55 (d, 1H), 3.35 (m, 1H), 3.25 (m, 4H), 3.1 (dd, 1H), 2.95 (m, 2H), 2.75 (m, 3H), 2.2 (m, 1H), 1.95 (m, 4H), 1.7 (m, 3H), 0.95 (t, 3H).

EXAMPLE 50

4-Dimethylamino-N-((*S*)-6-propylamino-5,6,7,8-tetrahydro-naphthalen-2-yl)-benzenesulfonamide, hydrochloride

ESI-MS: 388.25 $[M+H]^+$

^{1}H-NMR (DMSO-d_6, 400 MHz): δ [ppm] 9.85 (s, 1H), 9.05 (m, 2H), 7.55 (d, 2H), 6.95 (d, 1H), 6.9 (d, 1H), 6.85 (s, 1H), 6.7 (d, 2H), 3.35 (m, 1H), 3.1 (dd, 1H), 2.95 (m, 7H), 2.75 (m, 4H), 2.2 (m, 1H), 1.65 (m, 3H), 0.95 (t, 3H).

EXAMPLE 51

4-(3-Fluoro-propyl)-N-((*S*)-6-propylamino-5,6,7,8-tetrahydro-naphthalen-2-yl)-benzenesulfonamide

ESI-MS: 405.2 $[M+H]^+$

^{1}H-NMR (DMSO-d_6, 400 MHz): δ [ppm] 10.1 (m, 1H), 8.9 (m, 1H), 7.7 (d, 2H), 7.4 (d, 2H), 7.0 (d, 1H), 6.9 (d, 1H), 6.85 (s, 1H), 4.5 (t, 1H), 4.4 (t, 1H), 3.35 (m, 1H), 3.05 (dd, 1H), 2.9 (m, 2H), 2.75 (m, 5H), 2.2 (m, 1H), 1.95(m, 2H), 1.65 (m, 3H), 0.95 (t, 3H).

EXAMPLE 52
5-Propyl-thiophene-sulfonic acid ((*S*)-6-propylamino-5,6,7,8-tetrahydro-naphthalen-2-yl)-amide, hydrochloride

The crude product was purified by chromatography on silica gel using dichloro-methane/methanol (9:1) as eluent and subsequently convertion into the hydro-chloride salt.
ESI-MS: 393.15 $[M+H]^+$
^{1}H-NMR (DMSO-d_6, 400 MHz): δ [ppm] 10.25 (s, 1H), 8.95 (m, 2H), 7.35 (d, 1H), 7.05 (d, 1H), 6.95 (d, 1H), 6.85 (m, 2H), 3.4 (m, 1H), 3.1 (dd, 1H), 2.95 (m, 2H), 2.8 (m, 5H), 2.2 (m, 1H), 1.8 –1.55 (m, 5H), 0.95 (t, 3H), 0.9 (t, 3H).

EXAMPLE 53 reference
4-Chloro-N-((*S*)-6-propylamino-5,6,7,8-tetrahydro-naphthalen-2-yl)-benzenesulfonamide, hydrochloride

ESI-MS: 379.15 $[M+H]^+$
^{1}H-NMR (DMSO-d_6, 400 MHz): δ [ppm] 10.3 (s, 1H), 8.9 (m, 2H), 7.75 (d, 2H), 7.65 (d, 2H), 7.0 (d, 1H), 6.9 (d, 1H), 6.85 (s, 1H), 3.4 (m, 1H), 3.1 (dd, 1H), 2.95 (m, 2H), 2.75 (m, 3H), 2.2 (m, 1H), 1.7 (m, 3H), 0.95 (t, 3H).

EXAMPLE 54 reference
N-((*S*)-6-Propylamino-5,6,7,8-tetrahydro-naphthalen-2-yl)-4-trifluoromethylbenzenesulfonamide, hydrochloride

ESI-MS: 413.15 $[M+H]^+$
^{1}H-NMR (DMSO-d_6, 400 MHz): δ [ppm] 10.45 (s, 1H), 8.9 (m, 2H), 8.0 (s, 4H), 7.0 (d, 1H), 6.9 (d, 1H), 6.85 (s, 1H), 3.4 (m, 1H), 3.1 (dd, 1H), 2.95 (m, 2H), 2.75 (m, 3H), 2.2 (m, 1H), 1.65 (m, 3H), 0.95 (t, 3H).

EXAMPLE 55
4-((*S*)-2-Fluoro-1-methyl-ethyl)-N-((*S*)-6-propylamino-5,6,7,8-tetrahydro-naphthalen-2-yl)-benzenesulfonamide, hydrochloride

ESI-MS: 405.15 $[M+H]^+$
^{1}H-NMR (DMSO-d_6, 400 MHz): δ [ppm] 10.2 (s, 1H), 8.9 (m, 2H), 7.75 (d, 2H), 7.5 (d, 2H), 7.0 (d, 1H), 6.9 (d, 1H), 6.85 (s, 1H), 4.6 (d, 1H), 4.45 (d, 1H), 3.4 (m,

1H), 3.2 (m, 1H), 3.1 (dd, 1H), 2.9 (m, 2H), 2.75 (m, 3H), 2.2 (m, 1H), 1.7 (m, 3H), 1.2 (d, 3H), 0.95 (t, 3H).

EXAMPLE 56

4-((*R*)-2-Fluoro-1-methyl-ethyl)-N-((*S*)-6-propylamino-5,6,7,8-tetrahydro-naphthalen-2-yl)-benzenesulfonamide, hydrochloride

ESI-MS: 405.15 $[M+H]^+$

^{1}H-NMR (DMSO-d_6, 400 MHz): δ [ppm] 10.2 (s, 1H), 8.85 (m, 2H), 7.75 (d, 2H), 7.5 (d, 2H), 7.0 (d, 1H), 6.9 (d, 1H), 6.85 (s, 1H), 4.6 (d, 1H), 4.45 (d, 1H), 3.4 (m, 1H), 3.2 (m, 1H), 3.1 (dd, 1H), 2.95 (m, 2H), 2.75 (m, 3H), 2.2 (m, 1H), 1.7 (m, 3H), 1.2 (d, 3H), 0.95 (t, 3H).

EXAMPLE 57

4-(1-Methyl-1H-pyrazol-4-yl)-N-((*S*)-6-propylamino-5,6,7,8-tetrahydro-naphthalen-2-yl)-benzenesulfonamide, hydrochloride

ESI-MS: 425.15 $[M+H]^+$

^{1}H-NMR (DMSO-d_6, 400 MHz): δ [ppm] 10.15 (s, 1H), 9.0 (m, 2H), 8.35 (s, 1H), 7.7 (s, 4H), 7.0 (d, 1H), 6.9 (d, 1H), 6.85 (s, 1H), 3.9 (s, 3H), 3.35 (m, 1H), 3.1 (dd, 1H), 2.9 (m, 2H), 2.75 (m, 3H), 2.2 (m, 1H), 1.65 (m, 3H), 0.95 (t, 3H).

EXAMPLE 58

4-(3-Fluoro-propyl)-N-((*R*)-6-propylamino-5,6,7,8-tetrahydro-naphthalen-2-yl)-benzenesulfonamide, hydrochloride

58.1 ((*R*)-6-Bromo-1,2,3,4-tetrahydro-naphthalen-2-yl)-carbamic acid tert-butyl ester

To (*R*)-6-bromo-1,2,3,4-tetrahydro-naphthalen-2-ylamine (5.252 g, 20.0 mmol) and di-tert-butyldicarbonate (5.456 g, 25.0 mmol) in dichloromethane (100 ml) was added triethylamine (21.12 ml, 152.34 mmol). The reaction mixture was stirred over night at room temperature and then extracted twice with aqueous $NaHCO_3$ solution. The organic layer was dried over magnesium sulfate, filtered, and evaporated to dryness to yield the pure product (6.4 g, 98 % yield).

ESI-MS: 270.05/272.05 $[M+H-C(CH_3)_3]^+$

58.2 ((*R*)-6-Bromo-1,2,3,4-tetrahydro-naphthalen-2-yl)-propyl-carbamic acid tert-butyl ester

((*R*)-6-Bromo-1,2,3,4-tetrahydro-naphthalen-2-yl)-carbamic acid tert-butyl ester (3.4 g, 10.42 mmol) was dissolved in dimethylformamide (40 ml). Sodium hydride (60 % in oil) (625 mg, 15.63 mmol) was added and stirred for 1 hour at 0 °C. Propyl bromide (1.04 ml, 11.46 mmol) dissolved in N,N-dimethylformamide (DMF) was added at 0 °C to the reaction mixture. After 2 hours propyl bromide was added (0.2 ml, 2.20 mmol) and the reaction mixture was stirred at room temperature over night. To the reaction mixture was added water and three times extracted with diethyl ether. The organic layer was dried over magnesium sulfate, filtered, and evaporated to dryness to yield the crude product. The crude product was purified by chromatography on silica gel using cyclohexane/ethyl acetate (92:8) as eluent, yielding the purified product (3.54 g, 92 %).
ESI-MS: 312.05/314.05 $[M+H-C(CH_3)_3]^+$

58.3 ((*R*)-6-Amino-1,2,3,4-tetrahydro-naphthalen-2-yl)-propyl-carbamic acid tert-butyl ester

Under an inert atmosphere (argon), ((*R*)-6-bromo-1,2,3,4-tetrahydro-naphthalen-2-yl)-propyl-carbamic acid tert-butyl ester (3.54 g, 9.61 mmol) was dissolved in toluene (50 ml) at room temperature. Tris(dibenzylideneacetone)dipalladium (440 mg, 0.48 mmol) and tri-tert-butyl-phosphane (292 mg, 1.44 mmol) were added to the reaction mixture. After 10 minutes bis-(trimethylsilyl)lithiumamide (21.14 ml of a 1 molar solution in THF) was added slowly and the reaction mixture was stirred for 1 hour at 100 °C. The reaction mixture was cooled and slowly water was added. The organic phase was extracted twice with water. The organic layer was dried over magnesium sulfate, filtered, and evaporated to dryness to yield 6.06 g of crude product (93 % yield, 45 % purity).
ESI-MS: 249.15 $[M+H-C(CH_3)_3]^+$

58.4 {(*R*)-6-[4-(3-Fluoro-propyl)-benzenesulfonylamino]-1,2,3,4-tetrahydro-naphthalen-2-yl}-propyl-carbamic acid tert-butyl ester

((*R*)-6-Amino-1,2,3,4-tetrahydro-naphthalen-2-yl)-propyl-carbamic acid tert-butyl ester (200 mg, 0.66 mmol) was dissolved in tetrahydrofuran (10 ml). Then, dimethylamino pyridine (80 mg, 0.66 mmol) and 4-(3-fluoro-propyl)-benzenesulfonyl chloride (156 mg, 0.66 mmol) were added and the reaction mixture was stirred over night at room temperature. The solvent was evaporated under reduced pressure, the residue treated with water and ethyl acetate. The organic layer was dried over magnesium sulfate, filtered, and the solvent evapo-

purified with silica gel chromatography with dichloromethane/methanol (100:0 to 96:4) as eluent, yielding the purified product (150 mg, 45 %).
ESI-MS: 455.15 $[M+H-C(CH_3)_3]^+$

58.5 4-(3-Fluoro-propyl)-N-((*R*)-6-propylamino-5,6,7,8-tetrahydro-naphthalen-2-yl)-benzenesulfonamide, hydrochloride

Following the procedure analogous to that described in example 46.4, the title compound was obtained.
ESI-MS: 405.55 $[M+H]^+$
^{1}H-NMR (CH_3OH-d_4, 400 MHz): δ [ppm] 7.55 (d, 2H), 7.25 (d, 2H), 6.9 (d, 2H), 6.8 (s, 1H), 4.35 (t, 1H), 4.25 (t, 1H), 3.35 (m, 1H), 3.1 (dd, 1H), 3.0 (t, 2H), 2.75 (m, 3H), 2.65 (m, 3H), 2.2 (m, 1H), 1.85 (m, 2H), 1.65 (m, 3H), 0.95 (t, 3H).

EXAMPLE 59
4-(2-Fluoro-ethyl)-N-((*R*)-6-propylamino-5,6,7,8-tetrahydro-naphthalen-2-yl)-benzenesulfonamide, hydrochloride

Following the procedure analogous to that described in example 46, the title compound was obtained.
ESI-MS: 391.15 $[M+H]^+$
^{1}H-NMR (CH_3OH-d_4, 400 MHz): δ [ppm] 7.6 (d, 2H), 7.3 (d, 2H), 6.9 (d, 1H), 6.8 (m, 2H), 4.6 (t, 1H), 4.45 (t, 1H), 3.35 (m, 1H), 3.1 (dd, 1H), 2.95 (m, 3H), 2.9 (m, 1H), 2.75 (m, 3H), 2.2 (m, 1H), 1.65 (m, 3H), 0.95 (t, 3H).

EXAMPLE 60
4-Acetyl-N-((*S*)-6-propylamino-5,6,7,8-tetrahydro-naphthalen-2-yl)-benzenesulfonamide

Following the procedure analogous to that described in example 46, the title compound was obtained.
ESI-MS: 387.15 $[M+H]^+$

^{1}H-NMR (DMSO-d_6, 400 MHz): δ [ppm] 8.05 (d, 2H), 7.85 (d, 2H), 6.9 (d, 1H), 6.8 (d, 1H), 6.75 (s, 1H), 3.4 (m, 1H), 2.9 (m, 2H), 2.65 (m, 6H), 2.45 (m, 1H), 1.95 (m, 1H), 1.45 (m, 3H), 0.85 (t, 3H).

EXAMPLE 61

4-(1-Hydroxy-1-methyl-ethyl)-N-((*S*)-6-propylamino-5,6,7,8-tetrahydro-naphthalen-2-yl)-benzenesulfonamide, acetate

61.1 {(*S*)-6-[4-(1-Hydroxy-1-methyl-ethyl)-benzenesulfonylamino]-1,2,3,4-tetrahydro-naphthalen-2-yl}-propyl-carbamic acid tert-butyl ester

[(*S*)-6-(4-Acetyl-benzenesulfonylamino)-1,2,3,4-tetrahydro-naphthalen-2-yl]-propyl-carbamic acid tert-butyl ester (400 mg, 0.71 mmol) was dissolved in tetrahydrofuran (15 ml) at 0°C. A 3 molar solution of methylmagnesium bromide in diethyl ether (2.82 ml, 7.12 mmol) was added slowly and the reaction mixture was stirred for 3 hours at room temperature. Another portion of a 3 molar solution of methylmagnesium bromide in diethyl ether (0.5 ml, 1.26 mmol) was added. Since no further conversion was observed, the reaction mixture was evaporated to dryness. Water (20 ml) was added to the residue and the aqueous phase was extracted with diethyl ether (50 ml) twice. The organic layer was dried over magnesium sulfate, filtered, and evaporated to dryness to yield the crude product. The crude product was purified by MPLC chromatography using dichloromethane/methanol (100:0 – 70:30) as eluent, yielding the product (300 mg, 47 % purity, 39 %).

61.2 4-(1-Hydroxy-1-methyl-ethyl)-N-((*S*)-6-propylamino-5,6,7,8-tetrahydro-naphthalen-2-yl)-benzenesulfonamide, acetate

{(*S*)-6-[4-(1-Hydroxy-1-methyl-ethyl)-benzenesulfonylamino]-1,2,3,4-tetrahydro-naphthalen-2-yl}-propyl-carbamic acid tert-butyl ester (115 mg, 47 % purity, 0.11 mmol) was dissolved in dichloromethane (10 ml). Trifluoroacetic acid (1 ml) was added and the reaction mixture was stirred at room temperature for 1 hour. The reaction mixture was evaporated to dryness. Ethyl acetate (15 ml) was added and extracted with saturated $NaHCO_3$ solution (5 ml). The organic layer was dried over magnesium sulfate, filtered, and evaporated to dryness to yield the crude product (65 mg). The crude product was purified via HPLC chromatography yielding the purified product (22 mg, 42 %).
ESI-MS: 403.2 $[M+H]^+$

EXAMPLE 62

4-(1-Fluoro-1-methyl-ethyl)-N-((*S*)-6-propylamino-5,6,7,8-tetrahydro-naphthalen-2-yl)-benzenesulfonamide, trifluoro acetate

62.1 {(*S*)-6-[4-(1-Fluoro-1-methyl-ethyl)-benzenesulfonylamino]-1,2,3,4-tetrahydro-naphthalen-2-yl}-propyl-carbamic acid tert-butyl ester

{(*S*)-6-[4-(1-Hydroxy-1-methyl-ethyl)-benzenesulfonylamino]-1,2,3,4-tetrahydro-naphthalen-2-yl}-propyl-carbamic acid tert-butyl ester (50 mg, 92 % purity, 0.09 mmol) was dissolved in dichloromethane (10 ml) and cooled to –78°C. Diethylaminosulfurtrifluoride (59 mg, 0.36 mmol) was added and the reaction mixture was allowed to reach 0°C over 30 minutes. The reaction mixture was evaporated to dryness. The residue was dissolved in saturated $NaHCO_3$ solution (10 ml) and extracted with diethyl ether (20 ml). The organic layer was dried over magnesium sulfate, filtered, and evaporated to dryness to yield the crude product (49 mg, 83 % purity, 88 %).

62.1 4-(1-Fluoro-1-methyl-ethyl)-N-((*S*)-6-propylamino-5,6,7,8-tetrahydro-naphthalen-2-yl)-benzenesulfonamide, trifluoro acetate

{(*S*)-6-[4-(1-Fluoro-1-methyl-ethyl)-benzenesulfonylamino]-1,2,3,4-tetrahydro-naphthalen-2-yl}-propyl-carbamic acid tert-butyl ester (49 mg, 83 % purity, 0.08 mmol) was dissolved in dichloromethane (10 ml). Trifluoroacetic acid (1 ml) was added and the reaction mixture was stirred at room temperature for 1 hour. The reaction mixture was evaporated to dryness. Ethyl acetate (15 ml) was added and extracted with saturated $NaHCO_3$ solution (5 ml). The organic layer was dried over magnesium sulfate, filtered, and evaporated to dryness to yield the crude product (33 mg). The crude product was purified via HPLC chromatography yielding the purified product (19 mg, 46 %).
ESI-MS: 405.25 $[M+H]^+$
^{1}H-NMR (DMSO-d_6, 400 MHz): δ [ppm] 10.25 (s, 1H), 8.45 (m, 2H), 7.8 (d, 2H), 7.6 (d, 2H), 7.0 (d, 1H), 6.9 (d, 1H), 6.85 (s, 1H), 3.4 (m, 1H), 3.05 (dd, 1H), 2.95 (m, 2H), 2.75 (m, 3H), 2.15 (m, 1H), 1.65 (m, 9H), 0.95 (t, 3H).

The procedure described in example 46 was used to prepare the compounds of examples 63 to 70. The compounds were characterized by the following physical data:

EXAMPLE 63

N-((*S*)-6-Ethylamino-5,6,7,8-tetrahydro-naphthalen-2-yl)-4-trifluoromethoxy-benzenesulfonamide, hydrochloride

ESI-MS: 415.15 $[M+H]^+$

^{1}H-NMR (DMSO-d_6, 400 MHz): δ [ppm] 10.35 (s, 1H), 8.95 (m, 2H), 7.9 (d, 2H), 7.55 (d, 2H), 7.0 (d, 1H), 6.9 (d, 1H), 6.85 (s, 1H), 3.35 (m, 1H), 3.05 (m, 3H), 2.75 (m, 3H), 2.2 (m, 1H), 1.7 (m, 1H), 1.25 (t, 3H).

EXAMPLE 64

N-((*S*)-6-Ethylamino-5,6,7,8-tetrahydro-naphthalen-2-yl)-4-isopropyl-benzenesulfonamide, hydrochloride

ESI-MS: 373.15 $[M+H]^+$

^{1}H-NMR (DMSO-d_6, 400 MHz): δ [ppm] 10.15 (s, 1H), 8.95 (m, 2H), 7.7 (d, 2H), 7.45 (d, 2H), 7.0 (d, 1H), 6.9 (d, 1H), 6.85 (s, 1H), 3.4 (m, 1H), 3.05 (m, 3H), 2.95 (sept, 1H), 2.75 (m, 3H), 2.2 (m, 1H), 1.7 (m, 1H), 1.25 (t, 3H), 1.2 (d, 6H).

EXAMPLE 65

N-[(*S*)-6-(2-Fluoro-ethylamino)-5,6,7,8-tetrahydro-naphthalen-2-yl]-4-trifluoromethoxy-benzenesulfonamide, hydrochloride

ESI-MS: 433.15 $[M+H]^+$

^{1}H-NMR (DMSO-d_6, 400 MHz): δ [ppm] 10.35 (s, 1H), 9.3 (m, 2H), 7.9 (d, 2H), 7.55 (d, 2H), 7.0 (d, 1H), 6.9 (d, 1H), 6.85 (s, 1H), 4.85 (t, 1H), 4.75 (t, 1H), 3.45 (m, 2H), 3.15 (dd, 1H), 2.75 (m, 4H), 2.25 (m, 1H), 1.75 (m, 1H).

EXAMPLE 66

N-[(*S*)-6-(2-Fluoro-ethylamino)-5,6,7,8-tetrahydro-naphthalen-2-yl]-4-isopropyl-benzenesulfonamide, hydrochloride

ESI-MS: 391.15 $[M+H]^+$

^{1}H-NMR (DMSO-d_6, 400 MHz): δ [ppm] 10.15 (s, 1H), 9.3 (m, 2H), 7.7 (d, 2H), 7.45 (d, 2H), 7.0 (d, 1H), 6.9 (d, 1H), 6.85 (s, 1H), 4.85 (t, 1H), 4.75 (t, 1H), 3.4 (m, 2H), 3.1 (dd, 1H), 2.95 (m, 1H), 2.75 (m, 4H), 2.25 (m, 1H), 1.75 (m, 1H), 1.2 (d, 6H).

EXAMPLE 67

N-[(*S*)-6-(3-Fluoro-propylamino)-5,6,7,8-tetrahydro-naphthalen-2-yl]-4-trifluoromethoxy-benzenesulfonamide, hydrochloride

ESI-MS: 447.15 $[M+H]^+$

^{1}H-NMR (DMSO-d_6, 400 MHz): δ [ppm] 10.35 (s, 1H), 9.05 (m, 2H), 7.9 (d, 2H), 7.55 (d, 2H), 7.0 (d, 1H), 6.9 (d, 1H), 6.85 (s, 1H), 4.65 (t, 1H), 4.5 (t, 1H), 3.45 (m, 1H), 3.1 (m, 3H), 2.75 (m, 3H), 2.2 (m, 1H), 2.05 (m, 2H), 1.75 (m, 1H).

EXAMPLE 68

N-[(*S*)-6-(3-Fluoro-propylamino)-5,6,7,8-tetrahydro-naphthalen-2-yl]-4-isopropyl-benzenesulfonamide, hydrochloride

ESI-MS: 405.15 $[M+H]^+$

^{1}H-NMR (DMSO-d_6, 400 MHz): δ [ppm] 10.15 (s, 1H), 9.1 (m, 2H), 7.7 (d, 2H), 7.45 (d, 2H), 7.0 (d, 1H), 6.9 (d, 1H), 6.85 (s, 1H), 4.65 (t, 1H), 4.5 (t, 1H), 3.4 (m, 1H), 3.1 (m, 3H), 2.95 (sept, 1H), 2.75 (m, 3H), 2.2 (m, 1H), 2.1 (m, 2H), 1.75 (m, 1H), 1.2 (d, 6H).

EXAMPLE 69

N-((*S*)-6-Ethylamino-5,6,7,8-tetrahydro-naphthalen-2-yl)-4-(2-oxo-pyrrolidin-1-yl)-benzenesulfonamide, hydrochloride

ESI-MS: 414.2 $[M+H]^+$

EXAMPLE 70

N-((*S*)-6-Ethylamino-5,6,7,8-tetrahydro-naphthalen-2-yl)-4-pyrrolidin-1-yl-benzenesulfonamide, hydrochloride

ESI-MS: 400.15 $[M+H]^+$

^{1}H-NMR (DMSO-d_6, 400 MHz): δ [ppm] 9.8 (s, 1H), 8.95 (m, 2H), 7.55 (d, 2H), 6.95 (d, 1H), 6.9 (d, 1H), 6.85 (s, 1H), 6.55 (d, 2H), 3.4 (m, 1H), 3.25 (m, 4H), 3.05 (m, 3H), 2.75 (m, 3H), 2.2 (m, 1H), 1.95 (m, 4H), 1.7 (m, 1H), 1.25 (t, 3H).

EXAMPLE 71

4-Isopropyl-N-(3-propylamino-chroman-7-yl)-benzenesulfonamide, hydrochloride

71.1 7-Methoxy-2H-chromene-3-carbonitrile

To 2-hydroxy-4-methoxy-benzaldehyde (10.0 g, 65.72 mmol) and DABCO (1,4-diazabicyclo[2.2.2]octane) (1.84 g, 16.43 mmol) was added acrylonitrile (17.44 g, 328.62 mmol). The reaction mixture was refluxed for 20 h. The reaction mixture was diluted with ethyl acetate and the resulting rheum was separated. The or-

ganic phase was washed with a 1 molar solution of NaOH and then with a 1 molar solution of HCl. The organic layer was dried over magnesium sulfate, filtered, and the solvent evaporated under reduced pressure to give the crude product (8.89 g, 72 % yield).

71.2 7-Methoxy-2H-chromene-3-carboxylic acid

To 7-methoxy-2H-chromene-3-carbonitrile (8.89 g, 47.49 mmol) was added a 10 molar solution of NaOH (40 ml). The reaction mixture was refluxed for 6 h. After cooling to room temperature, the reaction mixture was adjusted to pH = 2 with concentrated HCl. The precipitate was filtered off and washed with water to give the pure product (6.07 g, 62 % yield).

71.3 7-Methoxy-chroman-3-one

7- Methoxy-2H-chromene-3-carboxylic acid (6.07 g, 29.44 mmol) and triethylamine (4.8 ml, 34.48 mmol) were dissolved in dichloromethane (60 ml). Diphenylphosphoryl azide (6.54 ml, 29.44 mmol) was dissolved in toluene (24 ml) and added dropwise to the reaction mixture while slowly increasing the temperature to 60 °C. 60 ml of toluene were added and the reaction mixture was stirred at 70 °C for 90 minutes. A 10 molar HCl solution (28 ml) was then added and the reaction mixture was stirred at reflux for 2 hours. After cooling to room temperature the phases were separated. The organic phase was extracted with an aq. $NaHCO_3$ solution. The organic layer was dried over magnesium sulfate, filtered, and the solvent evaporated under reduced pressure. The crude product was purified by chromatography using silica gel with cyclohexane/ethyl acetate (100:0 to 95:5) as eluent, yielding the title product (1.47 g, 24 % yield).
ESI-MS: 179.05 $[M+H]^+$

71.4 (7-Methoxy-chroman-3-yl)-propyl-amine

7-Methoxy-chroman-3-one (1.47 g, 8.25 mmol) and propylamine (748 µl, 9.07 mmol) were dissolved in dichloromethane (20 ml). Acetic acid (710 µl, 12.37 mmol) and sodium trisacetoxyborohydride (3.5 g, 16.51 mmol) were sequentially added to the reaction mixture and the mixture was stirred for 1 hour at room temperature. To the reaction mixture was added dichloromethane and water. The aqueous phase was made alkaline with a 1 molar solution of NaOH. The aqueous phase was separated and extracted (3 times) with dichloromethane. The

combined organic phases were dried over magnesium sulfate, filtered, and evaporated to dryness to yield the crude product (1.68 g, 92 % yield).
ESI-MS: 222.15 $[M+H]^+$

71.5 3-Propylamino-chroman-7-ol, hydrobromide

(7-Methoxy-chroman-3-yl)-propyl-amine (1.3 g, 5.87 mmol) was dissolved in dichloromethane (100 ml) and cooled to –78 °C. Boron tribromide (11.7 ml, 122.52 mmol) was added and the reaction mixture was allowed to reach room temperature over night. The reaction mixture was cooled to – 78 °C and a mixture of methanol and dichloromethane (2:3) was slowly added. The reaction mixture was allowed to reach room temperature and was then evaporated to dryness to yield the crude product (1.69 g, 5.86 mmol)
ESI-MS: 208.15 $[M+H]^+$

71.6 (7-Hydroxy-chroman-3-yl)-propyl-carbamic acid tert-butyl ester

3-Propylamino-chroman-7-ol, hydrobromide (1.69 g, 5.86 mmol) was dissolved in dichloromethane (50 ml). Subsequently, triethylamine (4.08 ml, 29.32 mmol) and di-tert-butyldicarbonate (1.28 g, 5.86 mmol) were added and the reaction mixture was stirred at room temperature over night. The reaction mixture was concentrated in vacuo and then dissolved in diethyl ether and water. The aqueous phase was adjusted to pH = 4 with a 5 % citric acid solution. The organic phase was then separated and washed with water and brine. The organic layer was dried over magnesium sulfate, filtered, and evaporated to dryness to yield the desired product (1.61 g, 89 %).
ESI-MS: 252.15 $[M+H-C(CH_3)_3]^+$

71.7 Trifluoro-methanesulfonic acid 3-(tert-butoxycarbonyl-propyl-amino)-chroman-7-yl ester

(7-Hydroxy-chroman-3-yl)-propyl-carbamic acid tert-butyl ester (1.58 g, 5.14 mmol) and triethylamine (2.15 ml, 15.42 mmol) were dissolved in dichloromethane (40 ml) and cooled to -78 °C. Trifluoromethanesulfonic anhydride (1.45 g, 5.14 mmol) was dissolved in dichloromethane (10 ml) and slowly added to the reaction mixture. Stirring was continued for 2 hours. The reaction mixture was allowed to reach room temperature, diluted with dichloromethane and washed twice with aqueous citric acid solution (pH = 4). The organic phase was then

sulfate, filtered, and evaporated to dryness to yield the desired product (2.57 g, 88 % purity, 100 % yield).
ESI-MS: 384.05 $[M+H-C(CH_3)_3]^+$

71.8 Trifluoro-methanesulfonic acid 3-propylamino-chroman-7-yl ester

Trifluoro-methanesulfonic acid 3-(tert-butoxycarbonyl-propyl-amino)-chroman-7-yl ester (2.1 g, 4.78 mmol) was dissolved in dichloromethane (30 ml). Trifluoroacetic acid (3 ml) was added and the reaction mixture was stirred at room temperature for 3 hours. The reaction mixture was evaporated to dryness. Dichloromethane was added (twice) and the reaction mixture was evaporated to dryness to give the product (2.6 g, 65 % purity).
ESI-MS: 340.05 $[M+H]^+$

71.9 Trifluoro-methanesulfonic acid 3-(benzyl-propyl-amino)-chroman-7-yl ester

Trifluoro-methanesulfonic acid 3-propylamino-chroman-7-yl ester (1.62 g, 4.78 mmol) and benzaldehyde (975 µl, 9.56 mmol) were dissolved in dichloromethane (60 ml). Acetic acid (710 µl, 12.37 mmol) and sodium trisacetoxyborohydride (3.04 g, 14.34 mmol) were sequentially added to the reaction mixture and stirred over the weekend at room temperature. Dichloromethane and water were added to the reaction mixture. The aqueous phase was adjusted to a pH = 6 with a 1 molar solution of NaOH. The organic phase was separated, dried over magnesium sulfate, filtered, and evaporated to dryness to yield the crude product. The crude product was purified by chromatography on silica gel using cyclohexane/ethyl acetate (100:0 to 95:5) as eluent, yielding the purified product (1.24 g, 50 % purity, 30 % yield).
ESI-MS: 430.15 $[M+H]^+$

71.10 N-3-Benzyl-N-3-propyl-chroman-3,7-yl-diamine

In an inert atmosphere (argon), trifluoromethanesulfonic acid 3-(benzyl-propyl-amino)-chroman-7-yl ester (1.25 g, 2.91 mmol), benzhydrylideneamine (528 mg, 2.91 mmol) and sodium tert.-butoxide (420 mg, 4.37 mmol) were dissolved in toluene (15 ml) at room temperature. Tris(dibenzylideneacetone)dipalladium (320 mg, 0.35 mmol) and BINAP (2,2'-bis(diphenylphosphino)-1,1'-binaphthyl) (326 mg, 0.52 mmol) were dissolved in toluene (5 ml) and then added to the reaction mixture. The reaction mixture was refluxed under stirring for 4 hours. The reac-

ness. The residue was treated with tetrahydrofuran and a 1 molar solution of HCl (40 ml). The tetrahydrofuran was evaporated and diethyl ether was added. The aqueous phase was separated and twice extracted with diethyl ether. The aqueous phase was made alkaline with a 1 molar solution of NaOH and then extracted several times with diethyl ether. The combined organic layers were dried over magnesium sulfate, filtered, and evaporated to dryness to yield the crude product. The crude product was purified by chromatography on silica gel with dichloromethane/methanol (100:0 to 95:5) as eluent, yielding the product (110 mg, 35 % purity, 5 % yield).
ESI-MS: 297.15 $[M+H]^+$

71.11 N-[3-(Benzyl-propyl-amino)-chroman-7-yl]-4-isopropyl-benzenesulfonamide

N-3-Benzyl-N-3-propyl-chroman-3,7-yl-diamine (110 mg, 0.13 mmol) was dissolved in tetrahydrofuran (5 ml). Subsequently, dimethylaminopyridine (17 mg, 0.13 mmol) and 4-isopropyl-benzenesulfonyl chloride (57 mg, 0.26 mmol) were added and the reaction mixture stirred was over night at room temperature. The solvent was evaporated under reduced pressure, the residue treated with water and diethyl ether. The organic layer was dried over magnesium sulfate, filtered, and the solvent evaporated under reduced pressure to give the crude product (2.5 g). The crude product was purified by chromatography on silica gel using dichloromethane/methanol (100:0 to 0:100) as eluent, yielding the purified product (25 mg, 40 %).
ESI-MS: 479.25 $[M+H]^+$

71.12 4-Isopropyl-N-(3-propylamino-chroman-7-yl)-benzenesulfonamide, hydrochloride

A mixture of N-[3-(benzylpropyl-amino)-chroman-7-yl]-4-isopropyl-benzenesulfonamide (25 mg, 0.05 mmol) and 10 % palladium on carbon (3 mg) in methanol (5 ml) was hydrogenated over night. The catalyst was filtered off, and the solvent was removed under vaccum to yield the crude product. The crude product was purified by reversed phase chromatography. The purified product was then converted into its hydrochloride salt (5.8 mg, 26 % yield).
ESI-MS: 389.15 $[M+H]^+$
^{1}H-NMR, measured from free base: ^{1}H-NMR (CH_3OH-d_4, 400 MHz): δ [ppm] 7.75 (d, 2H), 7.4 (d, 2H), 7.05 (d, 1H), 6.75 (m, 2H), 4.35 (m, 1H), 4.25 (m, 1H), 3.8

(m, 1H), 3.35 (dd, 1H), 3.1 (m, 2H), 2.95 (m, 2H), 1.75 (m, 2H), 1.25 (d, 6H), 1.05 (t, 3H).

The procedure described in example 46 was used to prepare the compounds of examples 72 and 73. The compounds were characterized by the following physical data

EXAMPLE 72

4-((*S*)-2-Fluoro-1-methyl-ethyl)-N-((*R*)-6-propylamino-5,6,7,8-tetrahydro-naphthalen-2-yl)-benzenesulfonamide, hydrochloride

ESI-MS: 405.15 $[M+H]^+$

^{1}H-NMR (CH_3OH-d_4, 400 MHz): δ [ppm] 7.6 (d, 2H), 7.3 (d, 2H), 6.9 (d, 1H), 6.85 (d, 1H), 6.8 (s, 1H), 4.45 (d, 1H), 4.3 (d, 1H), 3.35 (m, 1H), 3.1 (m, 2H), 3.0 (m, 2H), 2.75 (m, 3H), 2.2 (m, 1H), 1.65 (m, 3H), 1.2 (d, 3H), 0.95 (t, 3H).

EXAMPLE 73

N-((*R*)-6-Propylamino-5,6,7,8-tetrahydro-naphthalen-2-yl)-4-(2,2,2-trifluoro-1-methyl-ethyl)-benzenesulfonamide

ESI-MS: 441.15 $[M+H]^+$

^{1}H-NMR (CH_3OH-d_4, 400 MHz): δ [ppm] 7.75 (d, 2H), 7.5 (d, 2H), 6.95 (d, 1H), 6.85 (d, 1H), 6.8 (s, 1H), 3.7 (m, 1H), 2.95 (m, 2H), 2.7 (m, 4H), 2.5 (m, 1H), 2.1 (m, 1H), 1.55 (m, 3H), 1.5 (d, 3H), 1.0 (t, 3H).

EXAMPLE 74

4-Difluoromethoxy-N-((*S*)-6-propylamino-5,6,7,8-tetrahydro-naphthalen-2-yl)-benzenesulfonamide, hydrochloride

74.1 ((*S*)-6-Bromo-1,2,3,4-tetrahydro-naphthalen-2-yl)-carbamic acid tert-butyl ester

To (*S*)-6-bromo-1,2,3,4-tetrahydro-naphthalen-2-ylamine (10.0 g, 38.08 mmol) and di-tert-butyldicarbonate (10.39 g, 47.6 mmol) in dichloromethane (200 ml) was added triethylamine (21.12 ml, 152.34 mmol). The reaction mixture was stirred for 1 hour at room temperature and then extracted twice with water (50 ml). The organic layer was dried over magnesium sulfate, filtered, and evaporated to dryness to yield pure product (12.2 g, 98 % yield).

ESI-MS: 310.95/312.95 $[M+H-CH_3]^+$

74.2 ((*S*)-6-Bromo-1,2,3,4-tetrahydro-naphthalen-2-yl)-propyl-carbamic acid tert-butyl ester

((*S*)-6-Bromo-1,2,3,4-tetrahydro-naphthalen-2-yl)-carbamic acid tert-butyl ester (12.2 g, 37.4 mmol) was dissolved in N,N-dimethylformamide (1000 ml). Sodium hydride (50 % in oil) (1.975 g, 41.14 mmol) was added and stirred for 15 minutes at room temperature. Propyl bromide (3.74 ml, 41.14 mmol) was added and the reaction mixture was stirred at room temperature overnight. The reaction mixture was poured into a mixture of ice and H_2O (400 ml) and twice extracted with 200 ml diethyl ether. The organic layer was dried over magnesium sulfate, filtered, and evaporated to dryness to yield 14.4 g of crude product. The crude product was purified with silica gel chromatography with cyclohexane/ethyl acetate (95:5) as eluent, yielding the purified product (10.5 g, 76 %).

74.3 ((*S*)-6-Amino-1,2,3,4-tetrahydro-naphthalen-2-yl)-propyl-carbamic acid tert-butyl ester

In an inert atmosphere (argon), ((*S*)-6-bromo-1,2,3,4-tetrahydro-naphthalen-2-yl)-propyl-carbamic acid tert-butyl ester (5.0 g, 13.58 mmol) was dissolved in toluene (150 ml) at room temperature. Tris(dibenzylideneacetone)dipalladium (622 mg, 0.68 mmol) and tri-tert-butyl-phosphane (412 mg, 2.04 mmol) were added to the reaction mixture. After 15 minutes bis-(trimethylsilyl)lithiumamide (29.86 ml of a 1 molar solution in tetrahydrofuran) was added slowly and the reaction mixture was stirred for 1 hour at 100 °C. The reaction mixture was cooled and slowly H_2O (150 ml) was added and extracted several times with diethyl ether. The organic layer was dried over magnesium sulfate, filtered, and evaporated to dryness to yield 6.9 g of crude product (95 % yield, 57 % purity).
ESI-MS: 249.15 $[M+H-C(CH_3)_3]^+$

74.4 [(*S*)-6-(4-Difluoromethoxy-benzenesulfonylamino)-1,2,3,4-tetrahydro-naphthalen-2-yl]-propyl-carbamic acid tert-butyl ester

((*S*)-6-Amino-1,2,3,4-tetrahydro-naphthalen-2-yl)-propyl-carbamic acid tert-butyl ester (1.5 g, 4.93 mmol) was dissolved in tetrahydrofuran (50 ml). Subsequently, dimethylamino pyridine (100 mg, 0.82 mmol) and difluoro-methoxy-benzenesulfonyl chloride (1.195 g, 4.93 mmol) were added and the reaction mixture stirred over night at room temperature. The solvent was evaporated under reduced pressure, the residue treated with water

and diethyl ether. The organic layer was dried over magnesium sulfate, filtered, and the solvent evaporated under reduced pressure to give the crude product (2.5 g). The crude product was purified with silica gel chromatography with dichloromethane/methanol (100:0 to 96:4) as eluent, yielding the purified product (2.08 g, 83 %).

74.5 4-Difluoromethoxy-N-((*S*)-6-propylamino-5,6,7,8-tetrahydro-naphthalen-2-yl)-benzenesulfonamide, hydrochloride

[(*S*)-6-(4-Difluoromethoxy-benzenesulfonylamino)-1,2,3,4-tetrahydro-naphthalen-2-yl]-propyl-carbamic acid tert-butyl ester (2.08 g, 4.07 mmol) was dissolved in dichloromethane (100 ml). Trifluoroacetic acid (10 ml) was added and the reaction mixture was stirred at room temperature for 1 hour. The reaction mixture was evaporated to dryness. Diethyl ether (100 ml) was added and extracted with saturated $NaHCO_3$ solution. To the organic layer was added ethereal hydrochloride solution and the solvent evaporated. To the residue was added diethyl ether (25 ml) and the crystalline product was filtered off to give pure product (1.41 g, 77 % yield).

ESI-MS: 411.15 $[M+H]^+$

^{1}H-NMR (DMSO-d_6, 400 MHz): δ [ppm] 10.25 (s, 1H), 9.0 (m, 2H), 7.8 (d, 2H), 7.35 (t, *J* = 70 Hz, 1H), 7.3 (d, 2H), 7.0 (d, 1H), 6.9 (d, 1H), 6.85 (s, 1H), 3.4 (m, 1H), 3.1 (dd, 1H), 2.95 (m, 2H), 2.75 (m, 3H), 2.2 (m, 1H), 1.7 (m, 3H), 0.9 (t, 3H).

EXAMPLE 75

4-Difluoromethoxy-N-((R)-6-propylamino-5,6,7,8-tetrahydro-naphthalen-2-yl)-benzenesulfonamide, hydrochloride

Example 75 was prepared analogous to the procedure described for Example 74, except that in step 75.1 (R)-6-bromo-1,2,3,4-tetrahydro-naphthalen-2-ylamine was used instead of (*S*)-6-bromo-1,2,3,4-tetrahydro-naphthalen-2-ylamine.

The procedure described in example 47 was used to prepare the compounds of examples 76 to 81. The compounds were characterized by the following physical data.

EXAMPLE 76

N-((S)-6-Propylamino-5,6,7,8-tetrahydro-naphthalen-2-yl)-4-pyrazol-1-yl-benzenesulfonamide, hydrochloride

Sulfonamid coupling: yield 14% (amount 24 mg); removal of tert-butoxy carbonyl protection group : yield: 45% (amount 12 mg);

ESI-MS: 411.2 $[M+H]^+$;
^{1}H-NMR (DMSO-d_6, 400 MHz): δ [ppm] 10.22 (s, 1H), 8.70 (br m, 2H), 8.59 (s, 1H), 8.03 (d, 2H), 7.84 (d, 2H), 7.82 (s, 1H), 6.90 (m, 3H), 6.60 (s, 1H), 2.92 (m, 2H), 2.72 (m, 2H), 2.15 (m, 1H), 1.68 (m, 2H), 0.92 (t, 3H).

EXAMPLE 77

4-(2,2-Difluoro-1-methyl-ethyl)-N-((S)-6-propylamino-5,6,7,8-tetrahydro-naphthalen-2-yl)-benzenesulfonamide, hydrochloride

Sulfonamid coupling: amount obtained 300 mg; yield 97%; removal of tert-butoxy carbonyl protection group : amount obtained 190 mg; yield: 72%.

ESI-MS: 423.1 $[M+H]^+$
^{1}H-NMR (DMSO-d_6, 400 MHz): δ [ppm] 10.22 (s, 1H), 8.75 (br m, 2H), 7.74 (d, 2H), 7.50 (d, 2H), 6.92 (m, 3H), 6.19 (t, 1H), 3.36 (m, 1H), 3.09 (m, 1H), 2.93 (m, 2H), 2.72 (m, 2H), 2.18 (m, 1H), 1.68 (m, 3H), 1.30 (m, 3H), 0.92 (t, 3H).

EXAMPLE 78

4-Oxazol-5-yl-N-((R)-6-propylamino-5,6,7,8-tetrahydro-naphthalen-2-yl)-benzenesulfonamide

78.1 [(R)-6-(4-Oxazol-5-yl-benzenesulfonylamino)-1,2,3,4-tetrahydro-naphthalen-2-yl]-propyl-carbamic acid tert-butyl ester

Amount obtained: 165 mg, yield 75%.
ESI-MS: 512.1 $[M+H]^+$

78.2 4-Oxazol-5-yl-N-((R)-6-propylamino-5,6,7,8-tetrahydro-naphthalen-2-yl)-benzenesulfonamide

Amount obtained: 150 mg, yield 100%.
ESI-MS: 412.1 $[M+H]^+$

EXAMPLE 79

5-Oxazol-5-yl-thiophene-2-sulfonic acid ((R)-6-propylamino-5,6,7,8-tetrahydro-

79.1 [(R)-6-(5-Oxazol-5-yl-thiophene-2-sulfonylamino)-1,2,3,4-tetrahydro-naphthalen-2-yl]-propyl-carbamic acid tert-butyl ester

Amount obtained: 201 mg, yield 91%.
ESI-MS: 518.1 $[M+H]^+$

79.2 5-Oxazol-5-yl-thiophene-2-sulfonic acid ((R)-6-propylamino-5,6,7,8-tetrahydro-naphthalen-2-yl)-amide

Amount obtained: 172 mg; yield: 100%
ESI-MS: 418.1 $[M+H]^+$

EXAMPLE 80

4-(2,2-Difluoro-1-methyl-ethyl)-N-((R)-6-propylamino-5,6,7,8-tetrahydro-naphthalen-2-yl)-benzenesulfonamide

80.1 {(R)-6-[4-(2,2-Difluoro-1-methyl-ethyl)-benzenesulfonylamino]-1,2,3,4-tetrahydro-naphthalen-2-yl}-propyl-carbamic acid tert-butyl ester

Amount obtained: 247 mg; yield: 100%.
ESI-MS: 523.1 $[M+H]^+$

80.2 4-(2,2-Difluoro-1-methyl-ethyl)-N-((R)-6-propylamino-5,6,7,8-tetrahydro-naphthalen-2-yl)-benzenesulfonamide

Amount obtained: 235 mg; yield: 100%.
ESI-MS: 423.1 $[M+H]^+$

EXAMPLE 81

4-(Bromo)-N-((R)-6-propylamino-5,6,7,8-tetrahydronaphthalen-2-yl)-benzenesulfonamide

81.1 [(R)-6-(4-Bromo-benzenesulfonylamino)-1,2,3,4-tetrahydronaphthalen-2-yl]-propyl-carbamic acid tert-butyl ester

Amount obtained: 317 mg; yield: 62%.
ESI-MS: 523.1, 525.1 1 $[M+H]^+$

81.2 4-(Bromo)-N-((R)-6-propylamino-5,6,7,8-tetrahydro-naphthalen-2-yl)-benzenesulfonamide

Examples of galenic administration forms

A) Tablets

Tablets of the following composition are pressed on a tablet press in the customary manner:

40 mg of substance from Example 8
120 mg of corn starch
13.5 mg of gelatin
45 mg of lactose
2.25 mg of Aerosil® (chemically pure silicic acid in submicroscopically fine dispersion)
6.75 mg of potato starch (as a 6% paste)

B) Sugar-coated tablets

20 mg of substance from Example 8
60 mg of core composition
70 mg of saccharification composition

The core composition consists of 9 parts of corn starch, 3 parts of lactose and 1 part of 60:40 vinylpyrrolidone/vinyl acetate copolymer. The saccharification composition consists of 5 parts of cane sugar, 2 parts of corn starch, 2 parts of calcium carbonate and 1 part of talc. The sugar-coated tablets which had been prepared in this way are subsequently provided with a gastric juice-resistant coating.

Biological investigations

Receptor binding studies:
The substance to be tested was either dissolved in methanol/Chremophor® (BASF-AG) or in dimethyl sulfoxide and then diluted with water to the desired concentration.

Dopamine D_3 receptor:

The assay mixture (0.250 ml) was composed of membranes derived from ~ 10^6 HEK-293 cells possessing stably expressed human dopamine D_3 receptors, 0.1 nM [^{125}I]-iodosulpride and incubation buffer (total binding) or, in addition, test substance (inhibition curve) or 1µM spiperone (nonspecific binding). Each assay mixture was run in triplicate.

The incubation buffer contained 50 mM tris, 120 mM NaCl, 5 mM KCl, 2 mM $CaCl_2$, 2 mM $MgCl_2$ and 0.1% bovine serum albumin, 10 µM quinolone and 0.1% ascorbic acid (prepared fresh daily). The buffer was adjusted to pH 7.4 with HCl.

Dopamine D_{2L} receptor:

The assay mixture (1 ml) was composed of membranes from ~ 10^6 HEK-293 cells possessing stably expressed human dopamine D_{2L} receptors (long isoform) and 0.01 nM [^{125}I] iodospiperone and incubation buffer (total binding) or, in addition, test substance (inhibition curve) or 1µM haloperidol (nonspecific binding). Each assay mixture was run in triplicate.

The incubation buffer contained 50 mM tris, 120 mM NaCl, 5 mM KCl, 2 mM $CaCl_2$, 2 mM $MgCl_2$ and 0.1% bovine serum albumin. The buffer was adjusted to pH 7.4 with HCl.

Measurement and analysis:

After having been incubated at 25°C for 60 minutes, the assay mixtures were filtered through a Whatman GF/B glass fiber filter under vacuum using a cell collecting device. The filters were transferred to scintillation viols using a filter transfer system. After 4 ml of Ultima Gold® (Packard) have been added, the samples were shaken for one hour and the radioactivity was then counted in a Beta-Counter (Packard, Tricarb 2000 or 2200CA). The cpm values were converted into dpm using a standard quench series and the program belonging to the instrument.

The inhibition curves were analyzed by means of iterative nonlinear regression analysis using the Statistical Analysis System (SAS) which is similar to the "LIGAND" program described by Munson and Rodbard.

The results of the receptro binding studies are expressed as receptor binding constants $K_i(D_2)$ and $K_i(D_3)$, respectively, as herein before described, and given in table 2.

In these tests, the compounds according to the invention exhibit very good affinities for the D_3 receptor (frequently < 20 nM, in particular < 5 nM) and bind selectively to the D_3 receptor.

The results of the binding tests are given in table %.

Table 5:

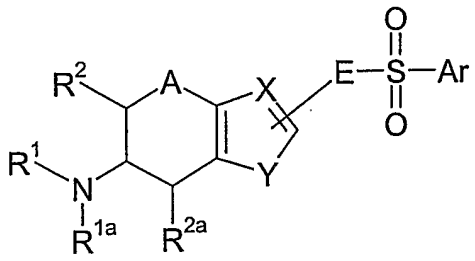
Example	$K_i(D3)^*$ [nM]	$K_i(D2)^*$ [nM]	$K_i(D2)^*/K_i(D3)^*$
2	14	442	32
3	0.34	10.3	30
6	0.28	14.5	52
7	1.97	152	77
8	0.50	50.6	102
9	15.3	416	27
10	8.2	238	29
15	11.3	476	42
19	2.5	51	21
20	7.5	339	45
22	19.0	1829	96
23	2.3	116	50
29	0.37	1.39	4
30	0.39	11.3	29
35	30.4	12342	406
38	4.81	727	151
40	1.40	309	221
41	12.2	1232.27	101
42	1.95	514	263
43	30.7	3477	113
44	0.62	258	416
45	13.9	1309	94
46	2.5		100
47	5.1		70
48	1.5		128

Example	$K_i(D3)^*$ [nM]	$K_i(D2)^*$ [nM]	$K_i(D2)^*/K_i(D3)^*$
49	1.3		63
50	1.8		95
51	1.7		56
52	0.7		71
55	1.7		230
56	2.4		161
58	0.15		229
60	9.4		274
62	6.2		77
63	30.9		40
64	3.4		70
68	2		42
70	3.6		61
74	2.5	250	100
76	8.62	728	84
77	1.65	501	304

* Receptor binding constants obtained according to the assays described herein before

We claim:

1. An aromatic compound of the formula I



(I)

wherein

Ar is phenyl or an aromatic 5- or 6-membered C-bound heteroaromatic radical, wherein Ar may carry 1 radical R^a and wherein Ar may also carry 1 or 2 radicals R^b;

R^a being selected from the group consisting of C_1-C_6-alkyl, C_2-C_6-alkenyl, fluorinated C_2-C_6-alkenyl, C_3-C_6-cycloalkyl, C_1-C_6-alkoxy, fluorinated C_1-C_6-alkyl, fluorinated C_3-C_6-cycloalkyl, fluorinated C_1-C_6-alkoxy, C_1-C_6-hydroxyalkyl, C_1-C_6-alkoxy-C_1-C_4-alkyl, C_1-C_6-hydroxyalkoxy, C_1-C_6-alkoxy-C_1-C_4-alkoxy, COOH, NR^4R^5, $CH_2NR^4R^5$, ONR^4R^5, $NHC(O)NR^4R^5$, $C(O)NR^4R^5$, $SO_2NR^4R^5$, C_1-C_6-alkylcarbonyl, fluorinated C_1-C_6-alkylcarbonyl, C_1-C_6-alkylcarbonylamino, fluorinated C_1-C_6-alkylcarbonylamino, C_1-C_6-alkylcarbonyloxy, fluorinated C_1-C_6-alkylcarbonyloxy, C_1-C_6-alkoxycarbonyl, C_1-C_6-alkylthio, fluorinated C_1-C_6-alkylthio, C_1-C_6-alkylsulfinyl, C_1-C_6-alkylsulfonyl, fluorinated C_1-C_6-alkylsulfinyl, fluorinated C_1-C_6-alkylsulfonyl, phenylsulfonyl, phenyl, phenoxy, benzyloxy and a 3- to 7-membered heterocyclic radical, wherein the five last mentioned radicals may carry 1, 2, 3 or 4 radicals selected from halogen, cyano, OH, oxo, CN, and the radicals R^a,

R^b being, independently from each other, selected from halogen, cyano, nitro, OH, methyl, methoxy, fluoromethyl, difluoromethyl, trifluoromethyl, fluormethoxy, difluoromethoxy and trifluoromethoxy,

the radical R^a and one radical R^b, if present and bound to two adjacent carbon atoms of phenyl, may form a 5-or 6-memberd heterocyclic or carbocylic ring which is fused to the phenyl ring and which is unsubstituted or which may carry 1, 2 or 3 radicals selected from halogen, NO_2, NH_2, OH, CN, C_1-C_6-alkyl, C_3-C_6-cycloalkyl, C_1-C_6-alkoxy, fluorinated C_1-C_6-alkyl, fluorinated C_3-C_6-cycloalkyl, fluorinated C_1-C_6-alkoxy, C_1-C_6-hydroxyalkyl, C_1-C_4-alkoxy-C_2-

C_4-alkyl, C_1-C_6-hydroxyalkoxy, C_1-C_4-alkoxy-C_2-C_4-alkoxy, C_1-C_6-alkylcarbonyl, C_1-C_6-alkylamino, di-C_1-C_6-alkylamino, C_1-C_6-alkylaminocarbonyl, di-C_1-C_6-alkylaminocarbonyl, fluorinated C_1-C_6-alkylcarbonyl, C_1-C_6-alkylcarbonylamino, fluorinated C_1-C_6-alkylcarbonyl-amino, C_1-C_6-alkylcarbonyloxy, fluorinated C_1-C_6-alkylcarbonyloxy, C_1-C_6-alkoxycarbonyl, C_1-C_6-alkylthio, fluorinated C_1-C_6-alkylthio, C_1-C_6-alkylsulfinyl, C_1-C_6-alkylsulfonyl, fluorinated C_1-C_6-alkylsulfinyl and fluorinated C_1-C_6-alkylsulfonyl,

provided that if Ar is phenyl, R^{2a} is hydrogen and R^{2b} is hydrogen and A is CH_2, Ar carries 1 radical R^a which is different from methyl, methoxy, trifluormethyl and trifluoromethoxy, and optionally 1 or 2 radicals R^b;

X is N or CH;

Y is O, S, -CH=N-, -CH=CH- or -N=CH-;

A is CH_2, O or S;

E is CR^6R^7 or NR^3;

R^1 is C_1-C_4-alkyl, C_3-C_4-cycloalkyl, C_3-C_4-cycloalkylmethyl, C_3-C_4-alkenyl, fluorinated C_1-C_4-alkyl, fluorinated C_3-C_4-cycloalkyl, fluorinated C_3-C_4-cycloalkylmethyl, fluorinated C_3-C_4-alkenyl, formyl or C_1-C_3-alkylcarbonyl;

R^{1a} is H, C_2-C_4-alkyl, C_3-C_4-cycloalkyl, C_3-C_4-alkenyl, fluorinated C_1-C_4-alkyl, fluorinated C_3-C_4-cycloalkyl, or R^{1a} and R^2 together are $(CH_2)_n$ with n being 2 or 3, or R^{1a} and R^{2a} together are $(CH_2)_n$ with n being 2 or 3;

R^2 and R^{2a} are independently of each other H, CH_3, CH_2F, CHF_2 or CF_3;

R^3 is H or C_1-C_4-alkyl;

R^4, R^5 independently of each other are selected from H, C_1-C_2-alkyl, C_1-C_2-alkoxy and fluorinated C_1-C_2-alkyl; and

R^6, R^7 independently of each other are selected from H, C_1-C_2-alkyl and fluorinated C_1-C_2-alkyl;

and the physiologically tolerated acid addition salts thereof.

2. The compounds as claimed in claim 1, wherein

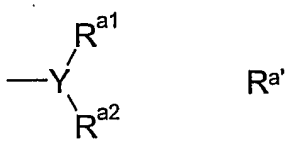
Ar is phenyl or an aromatic 5- or 6-membered C-bound heteroaromatic radical, comprising 1 nitrogen atom as ring member and 0, 1, 2 or 3 further heteroatoms, independently of each other, selected from O, S and N, as ring members, wherein Ar carries 1 radical R^a which selected from the group consisting of C_2-C_6-alkyl, C_3-C_6-cycloalkyl, C_2-C_6-alkoxy, fluorinated C_2-C_6-alkyl, fluorinated C_3-C_6-cycloalkyl, fluorinated C_2-C_6-alkoxy, NR^4R^5, 1-aziridinyl, azetidin-1-yl, pyrrolidin-1-yl or piperidin-1-yl, wherein the last four mentioned radicals may be fluorinated, a phenyl group and an aromatic 5- or 6-membered C-bound heteroaromatic radical, comprising 1 nitrogen atom as ring member and 0, 1, 2 or 3 further heteroatoms, independently of each other, selected from O, S and N, wherein the last two mentioned radicals may carry 1, 2, 3 or 4 radicals selected from Halogen and the radicals R^a, and wherein Ar may carry 1 or 2 further radicals R^b, which are independently from each other selected from halogen, cyano, methyl, fluoromethyl, difluoromethyl, trifluoromethyl, difluoromethoxy and trifluoromethoxy and wherein

E is CH_2 or NR^3, R^3 being H or C_1-C_4-alkyl, and

R^1 is C_2-C_4-alkyl, C_3-C_4-cycloalkyl, C_3-C_4-cycloalkylmethyl, C_3-C_4-alkenyl, fluorinated C_1-C_4-alkyl, fluorinated C_3-C_4-cycloalkyl, fluorinated C_3-C_4-cycloalkylmethyl, fluorinated C_3-C_4-alkenyl, formyl or C_1-C_3-alkylcarbonyl;

R^4, R^5 are, independently of each other, selected from H, C_1-C_2-alkyl and fluorinated C_1-C_2-alkyl.

3. The compounds as claimed in claim 1 or 2, wherein Ar carries one radical R^a of the formula $R^{a'}$



wherein

Y is N, CH or CF,

R^{a1} and R^{a2} are independently of each other selected from C_1-C_2-alkyl, C_1-C_2-alkoxy, fluorinanted C_1-C_2-alkyl, provided for Y being CH or CF one of the radicals R^{a1} or R^{a2} may also be hydrogen or fluorine, or
R^{a1} and R^{a2} together form a radical $(CH_2)_m$ wherein 1 or 2 of the hydrogen atoms may be replaced by fluorine, hydroxy, oxo, C_1-C_2-alkyl or C_1-C_2-alkoxy, wherein one CH_2 moiety may be replaced by O, S, S=O, SO_2 or N-R^c, R^c being hydrogen or C_1-C_2-alkyl and wherein m is 2, 3, 4, 5 or 6;

4. The compounds as claimed in claim 3, wherein the radical $R^{a'}$ is selected from isopropyl, (R)-1-fluoroethyl, (S)-1-fluoroethyl, 2-fluoroethyl, 1,1-difluoroethyl, 2,2-difluoroethyl, 2,2,2-trifluoroethyl, (R)-1-fluoropropyl, (S)-1-fluoropropyl, 2-fluoropropyl, 3-fluoropropyl, 1,1-difluoropropyl, 2,2-difluoropropyl, 3,3-difluoropropyl, 3,3,3-trifluoropropyl, (R)-2-fluoro-1-methylethyl, (S)-2-fluoro-1-methylethyl, (R)-2,2-difluoro-1-methylethyl, (S)-2,2-difluoro-1-methylethyl, (R)-1,2-difluoro-1-methylethyl, (S)-1,2-difluoro-1-methylethyl, (R)-2,2,2-trifluoro-1-methylethyl, (S)-2,2,2-trifluoro-1-methylethyl, 2-fluoro-1-(fluoromethyl)ethyl, 1-(difluoromethyl)-2,2-difluoroethyl, 1-fluoro-1-methylethyl cyclopropyl, cyclobutyl, 1-fluorocyclopropyl, (R)-2,2-difluorocyclopropyl, (S)-2,2-difluorocyclopropyl (R)- and (S)-2-fluorocyclopropyl.

5. The compounds as claimed in claim 3, wherein the radical $R^{a'}$ is selected from 4-morpholinyl, 4-thiomorpholinyl, 4-(1,1-dioxo)thiomorpholinyl, piperazin-1-yl, 4-methylpiperazin-1-yl, azetidin-1-yl, 2-methylazetidin-1-yl, (S)-2-methylazetidin-1-yl, (R)-2-methylazetidin-1-yl, 3-fluoroazetidin-1-yl, 3-methoxyazetidin-1-yl, 3-hydroxyazetidin-1-yl, pyrrolidin-1-yl, pyrrolidin-2-yl, (S)-pyrrolidin-2-yl, (R)-pyrrolidin-2-yl, pyrrolidin-3-yl, (S)-pyrrolidin-3-yl, (R)-pyrrolidin-3-yl, 2-fluoropyrrolidin-1-yl, (S)-2-fluoropyrrolidin-1-yl, (R)-2-fluoropyrrolidin-1-yl, 3-fluoropyrrolidin-1-yl, (S)-3-fluoropyrrolidin-1-yl, (R)-3-fluoropyrrolidin-1-yl, 2,2-difluoropyrrolidin-1-yl, 3,3-difluoropyrrolidin-1-yl, 2-methylpyrrolidin-1-yl, (S)-2-methylpyrrolidin-1-yl, (R)-2-methylpyrrolidin-1-yl, 3-methylpyrrolidin-1-yl, (S)-3-methylpyrrolidin-1-yl, (R)-3-methylpyrrolidin-1-yl, 1-methylpyrrolidin-2-yl, (S)-1-methylpyrrolidin-2-yl, (R)-1-methylpyrrolidin-2-yl, 1-methylpyrrolidin-3-yl, (S)-1-methylpyrrolidin-3-yl, (R)-1-methylpyrrolidin-3-yl, 2,2-dimethylpyrrolidin-1-yl, 3,3-dimethylpyrrolidin-1-yl, 2-trifluoromethylpyrrolidin-1-yl, (S)-2-trifluoromethylpyrrolidin-1-yl, (R)-2-trifluoromethylpyrrolidin-1-yl, 3-trifluoromethylpyrrolidin-1-yl, (S)-3-trifluoromethylpyrrolidin-1-yl, (R)-3-trifluoromethylpyrrolidin-1-yl, 2-oxopyrrolidin-1-yl, 2-oxo-oxazolidin-3-yl, piperidin-1-yl, 2-methylpiperidin-1-yl, (S)-2-methylpiperidin-1-yl and (R)-2-methylpiperidin-1-yl.

6. The compounds as claimed in any of the claims 3, 4 or 5, wherein the radical $R^{a'}$ carries 1, 2, 3 or 4 fluorine atoms.

7. The compounds as claimed in claim 1, wherein Ar carries one radical R^a, which is selected from CHF_2, CH_2F, $OCHF_2$ and OCH_2F.

8. The compounds as claimed in claim 1, wherein Ar carries one radical R^a, which is selected from 5- or 6-membered heteroaromatic radicals having as ring members 1 heteroatom selected from O, S and N and which may further have 1, 2 or 3 nitrogen atoms as ring members, and wherein the 5- or 6-membered heteroaromatic radical may carry 1, 2 or 3 substituents selected from halogen, NO_2, NH_2, OH, CN, C_1-C_6-alkyl, C_3-C_6-cycloalkyl, C_1-C_6-alkoxy, fluorinated C_1-C_6-alkyl, fluorinated C_3-C_6-cycloalkyl, fluorinated C_1-C_6-alkoxy, C_1-C_6-hydroxyalkyl, C_1-C_4-alkoxy-C_2-C_4-alkyl, C_1-C_6-hydroxyalkoxy, C_1-C_4-alkoxy-C_2-C_4-alkoxy, C_1-C_6-alkylcarbonyl, C_1-C_6-alkylamino, di-C_1-C_6-alkylamino, C_1-C_6-alkylaminocarbonyl, di-C_1-C_6-alkylaminocarbonyl, fluorinated C_1-C_6-alkylcarbonyl, C_1-C_6-alkylcarbonylamino, fluorinated C_1-C_6-alkylcarbonylamino, C_1-C_6-alkylcarbonyloxy, fluorinated C_1-C_6-alkylcarbonyloxy, C_1-C_6-alkoxycarbonyl, C_1-C_6-alkylthio, fluorinated C_1-C_6-alkylthio, C_1-C_6-alkylsulfinyl, C_1-C_6-alkylsulfonyl, fluorinated C_1-C_6-alkylsulfinyl and fluorinated C_1-C_6-alkylsulfonyl.

9. The compounds as claimed in claim 8, wherein Ar carries one heteroaromatic radical R^a, which is selected from furanyl, thienyl, pyrrolyl, pyrazolyl, imidazolyl, oxazolyl, isoxazolyl, 1,3,4-thiadiazolyl, 1,2,4-triazolyl, 1,2,3-triazolyl and tetrazolyl, where the heteroaromatic radical may be unsubstituted or may carry 1 to 3 substituents selected from halogen, C_1-C_4-alkyl, C_1-C_4-alkoxy, fluorinated C_1-C_4-alkyl and fluorinated C_1-C_4-alkoxy.

10. The compounds as claimed in any of the preceding claims, wherein Ar is phenyl.

11. The compounds as claimed in any of the preceding claims, wherein Ar is phenyl that carries a radical R^a in the 4-position of the phenyl ring.

12. The compounds as claimed in any of the preceding claims, wherein E is NR^3.

13. The compounds as claimed in any of claims 1 to 11, wherein E is CH_2.

14. The compounds as claimed in any of the preceding claims, wherein R^1 is n-propyl, fluorinated linear C_2-C_3-alkyl or 1-propen-3-yl.

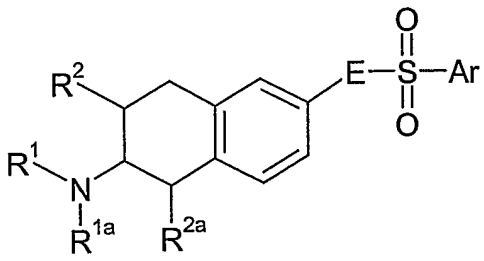
15. The compounds as claimed in any of the preceding claims, wherein R^{1a} is hydrogen.

16. The compounds as claimed in any of claims 1 to 14, wherein R^{1a} is n-propyl, 1-propen-3-yl.

17. The compounds as claimed in any of claims 1 to 14, wherein either R^{1a} and R^2 or R^{1a} and R^{2a} form a moiety $(CH_2)_n$ with n being 2 or 3.

18. The compounds as claimed in any of the preceding claims, wherein Y is -CH=CH- and X is CH.

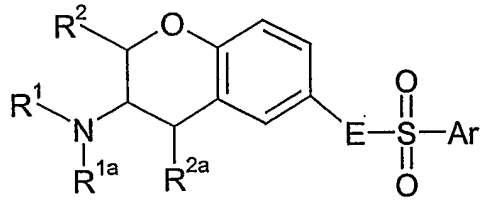
19. The compounds as claimed in claim 18 of the formula Ia



(Ia)

wherein R^1, R^{1a}, R^2, R^{2a}, R^3, E and Ar have the meanings given in claim 1 or 2 and the physiologically tolerated acid addition salts thereof.

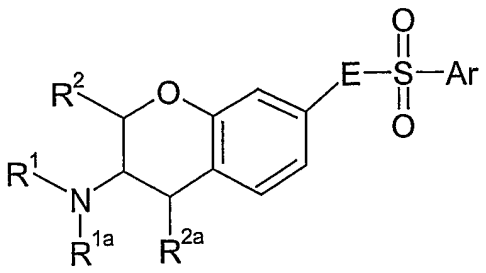
20. The compounds as claimed in claim 18 of the formula Ib



(Ib)

wherein R^1, R^{1a}, R^2, R^{2a}, R^3, E and Ar have the meanings given in claim 1 or 2 and the physiologically tolerated acid addition salts thereof.

21. The compounds as claimed in claim 18 of the formula Ic

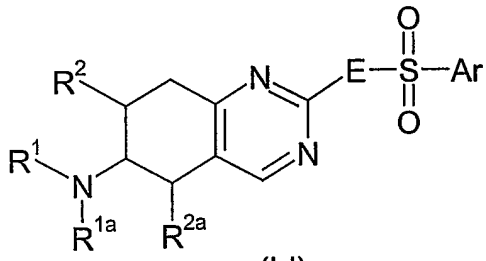


(Ic)

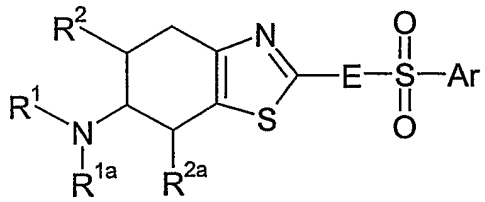
wherein R^1, R^{1a}, R^2, R^{2a}, R^3, E and Ar have the meanings given in claim 1 or 2 and the physiologically tolerated acid addition salts thereof.

22. The compounds as claimed in any of claims 1 to 17, wherein Y is -CH=CH-, -CH=N- or S and X is N.

23. The compound as claimed in claim 22 of the formulae Id or Ie



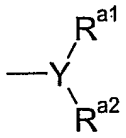
(Id)



(Ie)

wherein R^1, R^{1a}, R^2, R^{2a}, R^3, E and Ar have the meanings given in claim 1.

24. The compounds of the formulae Ia, Ib, Ic, Id or Ie and the physiologically tolerated acid addition salts thereof, as claimed in claims 19, 20, 21 or 23, wherein Ar carries one radical R^a of the formula $R^{a'}$



$R^{a'}$

wherein

Y is N, CH or CF,

R^{a1} and R^{a2} are independently of each other selected from C_1-C_2-alkyl, C_1-C_2-alkoxy, fluorinanted C_1-C_2-alkyl, provided for Y being CH or CF one of the radicals R^{a1} or R^{a2} may also be hydrogen or fluorine, or

R^{a1} and R^{a2} together form a radical $(CH_2)_m$ wherein 1 or 2 of the hydrogen atoms may be replaced by fluorine, hydroxy, C_1-C_2-alkyl or C_1-C_2-alkoxy, wherein 1 CH_2 moiety may be

replaced by O, S, S=O, SO_2 or N-R^c, R^c being hydrogen or C_1-C_2-alkyl and wherein m is 2, 3, 4, 5 or 6;

25. The compounds as claimed in claim 24, wherein the radical $R^{a'}$ is selected from isopropyl, (R)-1-fluoroethyl, (S)-1-fluoroethyl, 2-fluoroethyl, 1,1-difluoroethyl, 2,2-difluoroethyl, 2,2,2-trifluoroethyl, (R)-1-fluoropropyl, (S)-1-fluoropropyl, 2-fluoropropyl, 3-fluoropropyl, 1,1-difluoropropyl, 2,2-difluoropropyl, 3,3-difluoropropyl, 3,3,3-trifluoropropyl, (R)-2-fluoro-1-methylethyl, (S)-2-fluoro-1-methylethyl, (R)-2,2-difluoro-1-methylethyl, (S)-2,2-difluoro-1-methylethyl, (R)-1,2-difluoro-1-methylethyl, (S)-1,2-difluoro-1-methylethyl, (R)-2,2,2-trifluoro-1-methylethyl, (S)-2,2,2-trifluoro-1-methylethyl, 2-fluoro-1-(fluoromethyl)ethyl, 1-(difluoromethyl)-2,2-difluoroethyl, 1-fluoro-1-methylethyl cyclopropyl, cyclobutyl, 1-fluorocyclopropyl, (R)-2,2-difluorocyclopropyl, (S)-2,2-difluorocyclopropyl (R)- and (S)-2-fluorocyclopropyl.

26. The compounds as claimed in claim 24, wherein the radical $R^{a'}$ is selected from 4-morpholinyl, 4-thiomorpholinyl, 4-(1,1-dioxo)thiomorpholinyl, piperazin-1-yl, 4-methylpiperazin-1-yl, azetidin-1-yl, 2-methylazetidin-1-yl, (S)-2-methylazetidin-1-yl, (R)-2-methylazetidin-1-yl, 3-fluoroazetidin-1-yl, 3-methoxyazetidin-1-yl, 3-hydroxyazetidin-1-yl, pyrrolidin-1-yl, pyrrolidin-2-yl, (S)-pyrrolidin-2-yl, (R)-pyrrolidin-2-yl, pyrrolidin-3-yl, (S)-pyrrolidin-3-yl, (R)-pyrrolidin-3-yl, 2-fluoropyrrolidin-1-yl, (S)-2-fluoropyrrolidin-1-yl, (R)-2-fluoropyrrolidin-1-yl, 3-fluoropyrrolidin-1-yl, (S)-3-fluoropyrrolidin-1-yl, (R)-3-fluoropyrrolidin-1-yl, 2,2-difluoropyrrolidin-1-yl, 3,3-difluoropyrrolidin-1-yl, 2-methylpyrrolidin-1-yl, (S)-2-methylpyrrolidin-1-yl, (R)-2-methylpyrrolidin-1-yl, 3-methylpyrrolidin-1-yl, (S)-3-methylpyrrolidin-1-yl, (R)-3-methylpyrrolidin-1-yl, 1-methylpyrrolidin-2-yl, (S)-1-methylpyrrolidin-2-yl, (R)-1-methylpyrrolidin-2-yl, 1-methylpyrrolidin-3-yl, (S)-1-methylpyrrolidin-3-yl, (R)-1-methylpyrrolidin-3-yl, 2,2-dimethylpyrrolidin-1-yl, 3,3-dimethylpyrrolidin-1-yl, 2-trifluoromethylpyrrolidin-1-yl, (S)-2-trifluoromethylpyrrolidin-1-yl, (R)-2-trifluoromethylpyrrolidin-1-yl, 3-trifluoromethylpyrrolidin-1-yl, (S)-3-trifluoromethylpyrrolidin-1-yl, (R)-3-trifluoromethylpyrrolidin-1-yl, 2-oxopyrrolidin-1-yl, 2-oxo-oxazolidin-3-yl, piperidin-1-yl, 2-methylpiperidin-1-yl, (S)-2-methylpiperidin-1-yl and (R)-2-methylpiperidin-1-yl.

27. The compounds as claimed in any of the claims 24, 25 or 26, wherein the radical $R^{a'}$ carries 1, 2, 3 or 4 fluorine atoms.

28. The compounds of the formulae Ia, Ib, Ic, Id or Ie and the physiologically tolerated acid addition salts thereof, as claimed in claims 19, 20, 21 or 23, wherein Ar is phenyl, which carries one radical R^a, which is selected from CHF_2, CH_2F, $OCHF_2$ and OCH_2F.

29. The compounds of the formulae Ia, Ib, Ic, Id or Ie and the physiologically tolerated acid addition salts thereof, as claimed in claims 19, 20, 21 or 23, wherein Ar carries one radical R^a, which is selected from 5- or 6-membered heteroaromatic radicals having as ring members 1 heteroatom selected from O, S and N and which may further have 1, 2 or 3 nitrogen atoms as ring members, and wherein the 5- or 6-membered heteroaromatic radical may carry 1, 2 or 3 substituents selected from halogen, NO_2, NH_2, OH, CN, C_1-C_6-alkyl, C_3-C_6-cycloalkyl, C_1-C_6-alkoxy, fluorinated C_1-C_6-alkyl, fluorinated C_3-C_6-cycloalkyl, fluorinated C_1-C_6-alkoxy, C_1-C_6-hydroxyalkyl, C_1-C_4-alkoxy-C_2-C_4-alkyl, C_1-C_6-hydroxyalkoxy, C_1-C_4-alkoxy-C_2-C_4-alkoxy, C_1-C_6-alkylcarbonyl, C_1-C_6-alkylamino, di-C_1-C_6-alkylamino, C_1-C_6-alkylaminocarbonyl, di-C_1-C_6-alkylaminocarbonyl, fluorinated C_1-C_6-alkylcarbonyl, C_1-C_6-alkylcarbonylamino, fluorinated C_1-C_6-alkylcarbonylamino, C_1-C_6-alkylcarbonyloxy, fluorinated C_1-C_6-alkylcarbonyloxy, C_1-C_6-alkoxycarbonyl, C_1-C_6-alkylthio, fluorinated C_1-C_6-alkylthio, C_1-C_6-alkylsulfinyl, C_1-C_6-alkylsulfonyl, fluorinated C_1-C_6-alkylsulfinyl and fluorinated C_1-C_6-alkylsulfonyl.

30. The compounds as claimed in claim 29, wherein Ar carries one heteroaromatic radical R^a, which is selected from furanyl, thienyl, pyrrolyl, pyrazolyl, imidazolyl, oxazolyl, isoxazolyl, 1,3,4-thiadiazolyl, 1,2,4-triazolyl, 1,2,3-triazolyl and tetrazolyl, where the heteroaromatic radical may be unsubstituted or may carry 1 to 3 substituents selected from halogen, C_1-C_4-alkyl, C_1-C_4-alkoxy, fluorinated C_1-C_4-alkyl and fluorinated C_1-C_4-alkoxy.

31. The compounds as claimed in any of claims 19 to 30, wherein Ar is phenyl that carries a radical R^a in the 4-position of the phenyl ring.

32. The compounds as claimed in any of claims 19 to 31, wherein E is NR^3.

33. The compounds as claimed in any of claims 19 to 31, wherein E is CH_2.

34. The compounds as claimed in any of claims 19 to 33, wherein R^1 is n-propyl, fluorinated linear C_2-C_3-alkyl or 1-propen-3-yl.

35. The compounds as claimed in any of claims 19 to 34, wherein R^{1a} is hydrogen.

36. The compounds as claimed in any of claims 19 to 35, wherein R^{1a} is n-propyl, 1-propen-3-yl.

37. The compounds as claimed in any of claims 19 to 36, wherein either R^{1a} and R^2 or R^{1a} and R^{2a} form a moiety $(CH_2)_n$ with n being 2 or 3.

38. The compounds as claimed in any of claims 19 to 36, wherein R^2 and R^{2a} are hydrogen.

39. The compounds of the formulae Ia, Ib, Ic, Id and Ie and the physiologically tolerated acid addition salts thereof as claimed in claim 38, wherein Ar is 4-difluormethoxyphenyl.

40. The compounds as claimed in claim 38 or 39, wherein R^1 is n-propyl, fluorinated linear C_2-C_3-alkyl or 1-propen-3-yl.

41. The compounds as claimed in claims 38 to 40, wherein R^{1a} is hydrogen.

42. The compounds of the formula Ia and the physiologically tolerated acid addition salts thereof as claimed in claim 19, wherein R^2 and R^{2a} are hydrogen, Ar is 4-difluormethoxyphenyl, R^1 is n-propyl, fluorinated linear C_2-C_3-alkyl or 1-propen-3-yl.

43. The compounds as claimed in claim 42, wherein R^{1a} is hydrogen.

44. The compounds as claimed in claim 42 or 43, wherein R^1 is propyl.

45. A pharmaceutical composition comprising at least one compound of the formula I or a pharmaceutically acceptable salt thereof as claimed in any of the preceding claims, optionally together with at least one physiologically acceptable carrier or auxiliary substance.

46. A method for treating a medical disorder susceptible to treatment with a dopamine D3 receptor ligand, said method comprising administering an effective amount of at least one compound of the formula I or a pharmaceutically acceptable salt thereof as claimed in any of the preceding claims to a subject in need thereof.

47. The method as claimed in claim 46, wherein the medical disorder is a disease of the central nervous system.

48. The use of a compound of the formula I or a pharmaceutically acceptable salt thereof as claimed in any of the preceding claims for preparing a pharmaceutical composition for the treatment of a medical disorder susceptible to treatment with a dopamine D3 receptor ligand.

49. The use as claimed in claim 48, wherein the medical disorder is a disease of the central nervous system.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2005/011091

A. CLASSIFICATION OF SUBJECT MATTER
C07D311/04 C07D215/38 C07C211/19 A61K31/13 A61K31/47
A61K31/35 A61P25/16

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D 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 practical, search terms used)
EPO-Internal, PAJ, 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.
P,X	WO 2004/112785 A (BIOVITRUM AB; NILSSON, CECILIA; DREIFELDT, CATRINE) 29 December 2004 (2004-12-29) page 1, lines 4-6, page 4, lines 26-27	1-3, 10-12, 15,23, 24,31, 32,38,45
X	WO 03/013507 A (THE UNITED STATES OF AMERICA AS REPRESENTED BY DEPARTMENT OF VETERANS) 20 February 2003 (2003-02-20) page 21, 1st complete paragraph; claim 2	1-4,12, 18,19, 23-25, 31-33, 35,36, 38,40, 41,45-49

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[X] Further documents are listed in the continuation of Box C.

[X] 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 document 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
14 February 2006	01/03/2006

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, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Schmid, A

Form PCT/ISA/210 (second sheet) (April 2005)

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	D. CUSSAC ET AL: "The novel antagonist, S33084 , and GR218,231 interact selectively with cloned and native, rat dopamine D3 receptors as compared with native, rat dopamine D2 receptors" EUROPEAN JOURNAL OF PHARMACOLOGY, vol. 394, 2000, pages 47-50, XP002367384 abstract	1-4,12, 18,19, 23-25, 31-33, 35,36, 38,40, 41,45-49
A	WO 97/45403 A (PHARMACIA & UPJOHN COMPANY; HAADSMA-SVENSSON, SUSANNE, R; CLEEK, KERRY) 4 December 1997 (1997-12-04) cited in the application the whole document	1-49

INTERNATIONAL SEARCH REPORT

ıational application No.
PCT/EP2005/011091

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 46 and 47 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
/EP2005/011091

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