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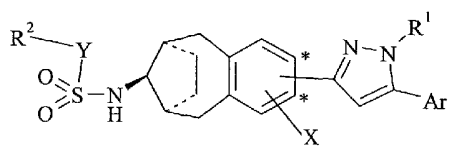
(54) Title: SULFONAMIDES, SULFAMATES AND SULFAMIDES AS GAMMA-SECRETASE INHIBITORS



(I)

(57) Abstract: Compounds of formula I inhibit the processing of APP by gamma-secretase, and hence are useful in treating or preventing Alzheimer's disease.

SULFONAMIDES, SULFAMATES AND SULFAMIDES AS GAMMA-SECRETASE INHIBITORS

The present invention relates to a novel class of compounds, their salts, pharmaceutical compositions comprising them, processes for making them and their use in therapy of the human body. In particular, the invention relates to novel sulfonamide, sulfamate and sulfamide derivatives which modulate the processing of APP by γ-secretase, and hence are useful in the treatment or prevention of Alzheimer's disease.

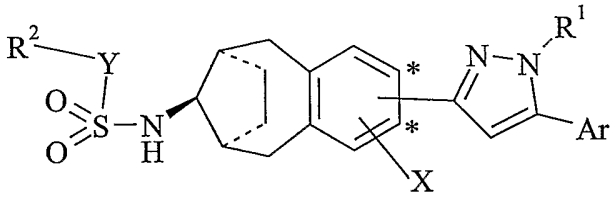
Alzheimer's disease (AD) is the most prevalent form of dementia. Although primarily a disease of the elderly, affecting up to 10% of the population over the age of 65, AD also affects significant numbers of younger patients with a genetic predisposition. It is a neurodegenerative disorder, clinically characterized by progressive loss of memory and cognitive function, and pathologically characterized by the deposition of extracellular proteinaceous plaques in the cortical and associative brain regions of sufferers. These plaques mainly comprise fibrillar aggregates of β-amyloid peptide (Aβ). The role of secretases, including the putative γ-secretase, in the processing of amyloid precursor protein (APP) to form Aβ is well documented in the literature and is reviewed, for example, in WO 01/70677.

There are relatively few reports in the literature of compounds with inhibitory activity towards γ-secretase, as measured in cell-based assays. These are reviewed in WO 01/70677. Many of the relevant compounds are peptides or peptide derivatives.

WO 01/70677 and WO 02/36555 disclose, respectively, sulfonamido- and sulfamido-substituted bridged bicycloalkyl derivatives which are believed to be useful in the treatment of Alzheimer's disease, but do not disclose or suggest compounds in accordance with the present invention.

The present invention provides a novel class of bridged bicycloalkyl sulfonamide, sulfamate and sulfamide derivatives which show a particularly strong inhibition of the processing of APP by the putative γ-secretase, and thus are useful in the treatment or prevention of AD.

According to the invention there is provided a compound of formula I:



I

wherein the pyrazole group is attached at one of the positions indicated by an asterisk and X is attached at a position adjacent thereto;

X represents H, OH, C_{1-4}alkoxy, Cl or F;

Y represents a bond, O or NR^3;

Ar represents phenyl or 6-membered heteroaryl, either of which bears 0-3 substituents independently selected from halogen, CF_3, CHF_2, CH_2F, NO_2, CN, OCF_3, C_{1-6}alkyl and C_{1-6}alkoxy;

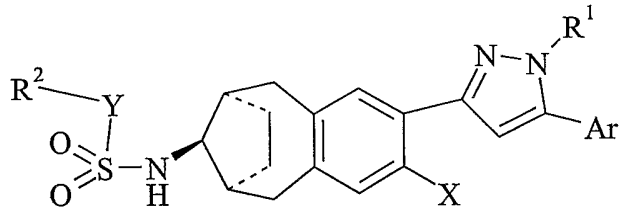
R^1 represents a hydrocarbon group of 1-5 carbon atoms which is optionally substituted with up to 3 halogen atoms; and

R^2 represents a hydrocarbon group of 1-10 carbon atoms which is optionally substituted with up to 3 halogen atoms, or heteroaryl of 5 or 6 ring atoms optionally bearing up to 3 substituents independently selected from halogen, CF_3, CHF_2, CH_2F, NO_2, CN, OCF_3, C_{1-6}alkyl and C_{1-6}alkoxy; or when Y represents NR^3, R^2 and R^3 together may complete a heterocyclic ring of up to 6 members which optionally bears up to 3 substituents independently selected from halogen, CF_3, CHF_2, CH_2F, NO_2, CN, OCF_3, C_{1-6}alkyl and C_{1-6}alkoxy;

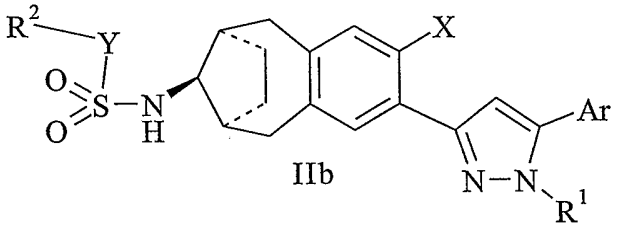
R^3 represents H or C_{1-4}alkyl, or together with R^2 completes a heterocyclic ring as defined above;

or a pharmaceutically acceptable salt thereof.

It will be readily apparent to those skilled in the art that any compound in accordance with formula I may exist in two enantiomeric forms, depending on which of the ring positions indicated by an asterisk is bonded to the pyrazole ring. Formula I thus encompasses enantiomers of formulae IIa and IIb:



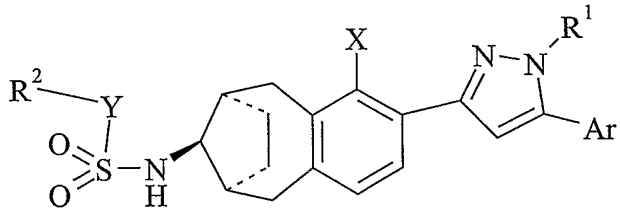
IIa



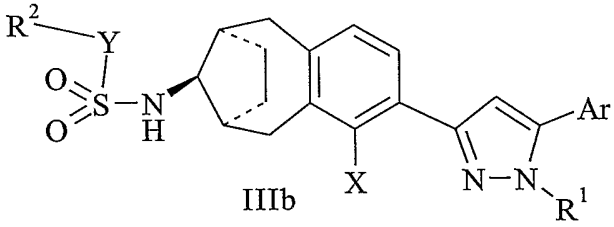
IIb

wherein X, Y, Ar, R^1 and R^2 are as defined previously;

and also enantiomers of formulae IIIa and IIIb:



IIIa



IIIb

wherein X, Y, Ar, R^1 and R^2 are as defined previously.

It will also be apparent that when X represents H formula IIa is identical to formula IIIa and formula IIb is identical to formula IIIb.

It is to be emphasised that the invention, for each compound in accordance with formula I, encompasses both enantiomeric forms, either as homochiral compounds or as mixtures of enantiomers in any proportion.

In a preferred embodiment of the invention, the compound of formula I is a homochiral compound of formula IIa or formula IIIa, or a pharmaceutically acceptable salt thereof.

Where a variable occurs more than once in formula I or in a substituent thereof, the individual occurrences of that variable are independent of each other, unless otherwise specified.

As used herein, the expression "hydrocarbon group" refers to groups consisting solely of carbon and hydrogen atoms. Such groups may comprise linear, branched or cyclic structures, singly or in any combination consistent with the indicated maximum number of carbon atoms, and may be saturated or unsaturated, including aromatic when the indicated maximum number of carbon atoms so permits.

As used herein, the expression "C_{1-x}alkyl" where x is an integer greater than 1 refers to straight-chained and branched alkyl groups wherein the number of constituent carbon atoms is in the range 1 to x. Particular alkyl groups are methyl, ethyl, n-propyl, isopropyl and t-butyl. Derived expressions such as "C_{2-6}alkenyl", "hydroxyC_{1-6}alkyl", "heteroarylC_{1-6}alkyl", "C_{2-6}alkynyl" and "C_{1-6}alkoxy" are to be construed in an analogous manner. Most suitably, the number of carbon atoms in such groups is not more than 6.

The expression "C_{3-6}cycloalkyl" as used herein refers to nonaromatic monocyclic hydrocarbon ring systems comprising from 3 to 6 ring atoms. Examples include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cyclohexenyl.

The expression "cycloalkylalkyl" as used herein includes groups such as cyclopropylmethyl, cyclobutylmethyl, cyclopentylmethyl and cyclohexylmethyl.

The term "halogen" as used herein includes fluorine, chlorine, bromine and iodine, of which fluorine and chlorine are preferred.

For use in medicine, the compounds of formula I may be in the form of pharmaceutically acceptable salts. Other salts may, however, be useful in the preparation of the compounds of formula I or of their pharmaceutically acceptable salts. Suitable pharmaceutically acceptable salts of the compounds of this invention include acid addition salts which may, for example, be formed by mixing a solution of the compound according to the invention with a solution of a pharmaceutically acceptable acid such as hydrochloric acid, sulfuric acid, methanesulfonic acid,

benzenesulfonic acid, fumaric acid, maleic acid, succinic acid, acetic acid, benzoic acid, oxalic acid, citric acid, tartaric acid, carbonic acid or phosphoric acid. Alternatively, where the compound of the invention carries an acidic moiety, a pharmaceutically acceptable salt may be formed by neutralisation of said acidic moiety with a suitable base. Examples of pharmaceutically acceptable salts thus formed include alkali metal salts such as sodium or potassium salts; ammonium salts; alkaline earth metal salts such as calcium or magnesium salts; and salts formed with suitable organic bases, such as amine salts (including pyridinium salts) and quaternary ammonium salts.

Where the compounds according to the invention have at least one asymmetric centre, they may accordingly exist as enantiomers. Where the compounds according to the invention possess two or more asymmetric centres, they may additionally exist as diastereoisomers. It is to be understood that all such isomers and mixtures thereof in any proportion are encompassed within the scope of the present invention.

In the compounds of formula I, X preferably represents H, OH or F, more preferably H or F. In one particular embodiment, X is H. In another particular embodiment, X is F. Most preferably, X is H.

Ar represents phenyl or 6-membered heteroaryl, either of which bears 0-3 substituents independently selected from halogen, CF_3, CHF_2, CH_2F, NO_2, CN, OCF_3, C_{1-6}alkyl and C_{1-6}alkoxy. Examples of suitable 6-membered heteroaryl groups represented by Ar include pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl and triazinyl, of which pyridyl is a preferred example. Preferably, the phenyl or heteroaryl ring bears 0 to 2 substituents. Preferred substituents include halogen (especially chlorine and fluorine), CN, C_{1-6}alkyl (especially methyl), C_{1-6}alkoxy (especially methoxy), OCF_3 and CF_3. If two or more substituents are present, preferably not more than one of them is other than halogen or alkyl. Examples of groups represented by Ar include phenyl, monohalophenyl, dihalophenyl, trihalophenyl, cyanophenyl, methylphenyl, methoxyphenyl, trifluoromethylphenyl, trifluoromethoxyphenyl, pyridyl, monohalopyridyl and trifluoromethylpyridyl, wherein "halo" refers to fluoro or chloro. Suitable specific values for Ar include 2-fluorophenyl, 2-chlorophenyl, 3-fluorophenyl, 4-fluorophenyl, 4-chlorophenyl, 2,4-difluorophenyl, 2,4-dichlorophenyl, 3,4-difluorophenyl, 3,4-dichlorophenyl, 3-chloro-4-fluorophenyl, 3,4,5-

trifluorophenyl, 4-cyanophenyl, 4-methylphenyl, 4-methoxyphenyl, 2-(trifluoromethyl)phenyl, 4-(trifluoromethyl)phenyl, 4-(trifluoromethoxy)phenyl, pyridin-2-yl, pyridin-3-yl, pyridin-4-yl, pyrazin-2-yl, 5-methylpyridin-2-yl, 5-fluoropyridin-2-yl, 5-chloropyridin-2-yl, 5-(trifluoromethyl)pyridin-2-yl and 6-(trifluoromethyl)pyridin-3-yl. Preferred examples include 2-fluorophenyl, 2-chlorophenyl, 3-fluorophenyl, 4-fluorophenyl, 4-chlorophenyl, 2,4-difluorophenyl, 2,4-dichlorophenyl, 3,4-difluorophenyl, 3,4-dichlorophenyl, 3-chloro-4-fluorophenyl, 4-(trifluoromethyl)phenyl, pyridin-2-yl, pyridin-3-yl and pyridin-4-yl.

In a particularly preferred embodiment, Ar represents 4-fluorophenyl.

R^1 represents a hydrocarbon group of 1-5 carbon atoms which is optionally substituted with up to 3 halogen atoms, and thus may comprise cyclic or acyclic hydrocarbon residues or combinations thereof, saturated or unsaturated, up to a maximum of 5 carbon atoms in total. The hydrocarbon group represented by R^1 is preferably unsubstituted or is substituted with up to 3 fluorine atoms Examples include methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, t-butyl, fluoromethyl, difluoromethyl, trifluoromethyl, 2,2,2-trifluoroethyl, cyclopropyl, cyclopropylmethyl and allyl. Preferred examples include methyl, ethyl and 2,2,2-trifluoroethyl. Most preferably, R^1 represents methyl.

Suitable hydrocarbon groups represented by R^2 include alkyl, cycloalkyl, cycloalkylalkyl, alkenyl, phenyl and benzyl groups optionally bearing up to 3 halogen substituents, the preferred halogen substituent being fluorine or chlorine, especially fluorine. Said alkyl, cycloalkyl, cycloalkylalkyl and alkenyl groups typically comprise up to 6 carbon atoms. Examples of hydrocarbon and fluorinated hydrocarbon groups represented by R^2 include 4-fluorophenyl, benzyl, n-propyl, 2,2-dimethylpropyl, n-butyl, isopropyl, t-butyl, 2,2,2-trifluoroethyl, 3,3,3-trifluoropropyl, allyl, cyclopropyl, cyclobutyl and cyclopropylmethyl.

Heteroaryl groups represented by R^2 are either 5-membered or 6-membered and are optionally substituted as defined previously. Preferred 5-membered heteroaryl groups include those containing a sulfur atom, such as thienyl, thiazolyl and isothiazolyl. Preferred 6-membered heteroaryl groups include pyridyl, in particular 3-pyridyl. Preferred substituents include halogen (especially chlorine or fluorine), CF_3 and alkyl (such as methyl). If two or more substituents are present, preferably not

more than one of them is other than halogen or alkyl. Preferred heteroaryl groups are unsubstituted or monosubstituted with halogen.

When R^2 represents an optionally substituted phenyl or heteroaryl group, Y is preferably a bond.

When Y represents NR^3, R^2 may combine with R^3 to complete a heterocyclic ring of up to 6 members which is optionally substituted as defined previously. Said ring preferably comprises at most one heteroatom selected from O, N and S in addition to the nitrogen to which R^2 and R^3 are mutually attached. Suitable rings include azetidinyl, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl and thiomorpholinyl. Preferred substituents include CF_3, halogen (especially chlorine or fluorine) and alkyl such as methyl. If two or more substituents are present, preferably not more than one of them is other than halogen or alkyl..

R^3 may alternatively represent H or C_{1-4}alkyl, such as methyl. Preferably, R^3 represents H or completes a ring with R^2.

In one subset of the compounds of formula I, Y is a bond and R^2 is hydrocarbon of up to 6 carbon atoms, optionally bearing up to 3 fluorine or chlorine substituents, or 5- or 6-membered heteroaryl which is optionally substituted as described previously. Within this embodiment, suitable identities for R^2 include n-butyl, 4-fluorophenyl, 2-thienyl, 5-chloro-2-thienyl, 5-isothiazolyl and 6-chloro-3-pyridyl.

In a second subset of the compounds of formula I, Y is O and R^2 represents alkyl, alkenyl, cycloalkyl or cycloalkylalkyl of up to 6 carbon atoms which is optionally substituted with up to 3 fluorine atoms.

In a third subset of the compounds of formula I, Y is NH or NMe and R^2 represents alkyl, alkenyl, cycloalkyl or cycloalkylalkyl of up to 6 carbon atoms which is optionally substituted with up to 3 fluorine atoms.

In a fourth subset of the compounds of formula I, Y represents NR^3 and R^2 and R^3 complete a heterocyclic ring as described previously.

Specific examples of compounds in accordance with the invention include the compounds of formula IIIa or formula IIa in which X is H, Ar is 4-fluorophenyl, R^1 is methyl and Y, R^2 and (where relevant) R^3 are as shown in the following table:

Y	R^2	R^3
bond	n-butyl	-
bond	4-fluorophenyl	-
bond	5-chloro-2-thienyl	-
bond	5-isothiazolyl	-
bond	6-chloropyridin-3-yl	-
bond	2-thienyl	-
O	n-propyl	-
O	cyclobutyl	-
NR^3	2,2,2-trifluoroethyl	H
NR^3	n-propyl	H
NR^3	n-propyl	methyl
NR^3	cyclobutyl	H
NR^3	methyl	methyl
NR^3	pyrrolidinyl	
NR^3	4-(trifluoromethyl)piperidinyl	
NR^3	cyclopropyl	H

The compounds of the present invention have an activity as inhibitors of γ secretase.

The invention also provides pharmaceutical compositions comprising one or more compounds of this invention and a pharmaceutically acceptable carrier. Preferably these compositions are in unit dosage forms such as tablets, pills, capsules, powders, granules, sterile parenteral solutions or suspensions, metered aerosol or liquid sprays, drops, ampoules, transdermal patches, auto-injector devices or suppositories; for oral, parenteral, intranasal, sublingual or rectal administration, or for administration by inhalation or insufflation. The principal active ingredient typically is mixed with a pharmaceutical carrier, e.g. conventional tableting ingredients such as corn starch, lactose, sucrose, sorbitol, talc, stearic acid, magnesium stearate and dicalcium phosphate, or gums, dispersing agents, suspending agents or surfactants such as sorbitan monooleate and polyethylene glycol, and other pharmaceutical

diluents, e.g. water, to form a homogeneous preformulation composition containing a compound of the present invention, or a pharmaceutically acceptable salt thereof. When referring to these preformulation compositions as homogeneous, it is meant that the active ingredient is dispersed evenly throughout the composition so that the composition may be readily subdivided into equally effective unit dosage forms such as tablets, pills and capsules. This preformulation composition is then subdivided into unit dosage forms of the type described above containing from 0.1 to about 500 mg of the active ingredient of the present invention. Typical unit dosage forms contain from 1 to 100 mg, for example 1, 2, 5, 10, 25, 50 or 100 mg, of the active ingredient. Tablets or pills of the novel composition can be coated or otherwise compounded to provide a dosage form affording the advantage of prolonged action. For example, the tablet or pill can comprise an inner dosage and an outer dosage component, the latter being in the form of an envelope over the former. The two components can be separated by an enteric layer which serves to resist disintegration in the stomach and permits the inner component to pass intact into the duodenum or to be delayed in release. A variety of materials can be used for such enteric layers or coatings, such materials including a number of polymeric acids and mixtures of polymeric acids with such materials as shellac, cetyl alcohol and cellulose acetate.

The liquid forms in which the novel compositions of the present invention may be incorporated for administration orally or by injection include aqueous solutions, liquid- or gel-filled capsules, suitably flavoured syrups, aqueous or oil suspensions, and flavoured emulsions with edible oils such as cottonseed oil, sesame oil or coconut oil, as well as elixirs and similar pharmaceutical vehicles. Suitable dispersing or suspending agents for aqueous suspensions include synthetic and natural gums such as tragacanth, acacia, alginate, dextran, sodium carboxymethylcellulose, methylcellulose, poly(ethylene glycol), poly(vinylpyrrolidone) or gelatin.

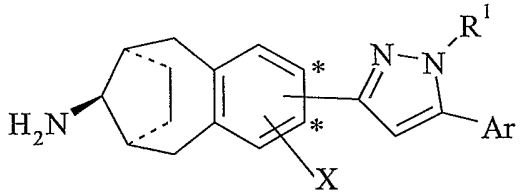
The present invention also provides a compound of the invention or a pharmaceutically acceptable salt thereof for use in a method of treatment of the human body. Preferably the treatment is for a condition associated with the deposition of β-amyloid. Preferably the condition is a neurological disease having associated β-amyloid deposition such as Alzheimer's disease.

The present invention further provides the use of a compound of the present invention or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for treating or preventing Alzheimer's disease.

Also disclosed is a method of treatment of a subject suffering from or prone to Alzheimer's disease which comprises administering to that subject an effective amount of a compound according to the present invention or a pharmaceutically acceptable salt thereof.

For treating or preventing Alzheimer's disease, a suitable dosage level is about 0.01 to 250 mg/kg per day, preferably about 0.01 to 100 mg/kg per day, more preferably about 0.05 to 50 mg/kg of body weight per day, and for the most preferred compounds, about 0.1 to 10 mg/kg of body weight per day. The compounds may be administered on a regimen of 1 to 4 times per day. In some cases, however, a dosage outside these limits may be used.

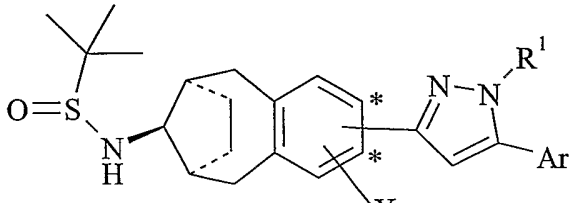
The compounds of formula I may be prepared by reaction of an amine (1) with R^2-Y-SO_2Cl:



(1)

where X, Y, Ar, R^1 and R^2 have the same meanings as before. The reaction takes place in an aprotic solvent such as dichloromethane in the presence of a base such as triethylamine or pyridine.

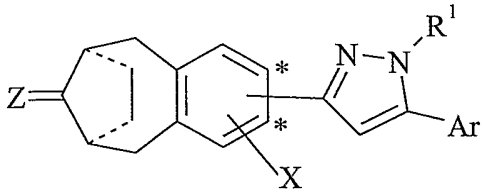
The amines (1) may be prepared by treatment of the sulfinamides (2) with acid:



(2)

where X, Ar and R^1 have the same meanings as before. The reaction may be carried out at 0°C using anhydrous HCl in dioxan.

The sulfinamides (2) are available from the reduction of imines (3a), which are in turn available from the condensation of ketones (3b) with t-Bu-SO-NH_2:



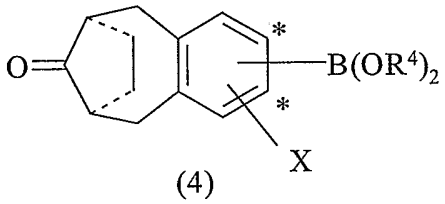
(a) Z = t-Bu-S(O)-N

(b) Z = O

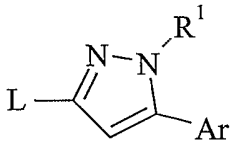
(3)

where X, Ar and R^1 have the same meanings as before. The condensation takes place in refluxing THF in the presence of titanium(IV) ethoxide, while the reduction may be effected using sodium borohydride in methanol at 0°C.

The ketones (3b) may be prepared by coupling of boronates (4) with pyrazole derivatives (5):



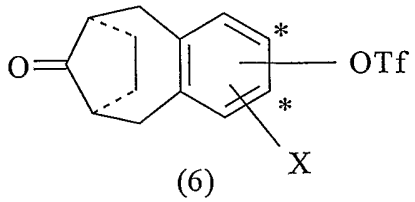
(4)



(5)

wherein R^4 represents H or C_{1-6}alkyl, or the two OR^4 groups complete a cyclic boronate ester such as the pinacolate, L represents a leaving group such as triflate, bromide or iodide (preferably triflate), and X, Ar and R^1 have the same meanings as before. The coupling takes place in the presence of a Pd catalyst such as *tetrakis*(triphenylphosphine)palladium(0), typically in the presence of an inorganic base such as potassium acetate or potassium carbonate in DMF at 100°C.

Boronates (4) may be prepared by reaction of triflates (6) with a suitable boron reagent, such as bis(pinacolato)diboron:

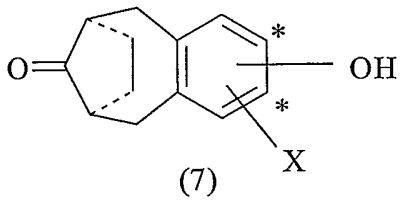


(6)

wherein Tf represents trifluoromethanesulfonyl and X has the same meaning as before. The reaction takes place under the same conditions as the coupling of (4) and

(5), although the preferred catalyst is [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II).

Triflates (6) are prepared from phenols (7) by reaction with triflic anhydride:

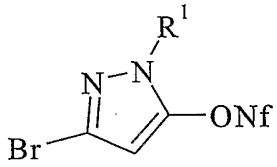


(7)

where and X has the same meaning as before. The reaction takes place in dichloromethane solution at 0°C in the presence of a base such as pyridine.

The phenols (7) in which X is H are known in the literature (*J. Org, Chem.* 1982, **47**, 4329), and the other compounds of formula (7) may be prepared analogously, or by suitable manipulation (e.g. halogenation) of (7) (X = H).

Pyrazoles (5) in which L is triflate are accessible from the reaction of alkynes Ar-C≡C-CO_2Me with R^1NHNH_2 and treatment of the resulting pyrazolones with triflic anhydride. Pyrazoles (5) in which L is Br are available by reaction of nonaflates (8) with ArZnBr:



(8)

where Nf represents nonafluorobutanesulfonyl, and Ar and R^1 have the same meaning as before.

Compounds of formula I in which Y represents NR^3 may also be prepared by condensation of ketones (3b) with $R^2R^3NSO_2NH_2$, followed by reduction of the resulting sulfamoyl imine. The condensation may be carried out by refluxing the reagents in THF in the presence of titanium(IV) ethoxide for 16 hours, while the reduction may be carried out using sodium borohydride in methanol at 0°C.

A further route to compounds of formula I in which Y represents O or NR^3 comprises reaction of amines (1) with catechol sulfate and treatment of the resulting (2-hydroxyphenyl)sulfamates with R^2OH or R^2R^3NH as appropriate.

It will also be appreciated that where more than one isomer can be obtained from a reaction then the resulting mixture of isomers can be separated by conventional means.

Where the above-described process for the preparation of the compounds according to the invention gives rise to mixtures of stereoisomers, these isomers may be separated by conventional techniques such as preparative chromatography. The novel compounds may be prepared in racemic form, or individual enantiomers may be prepared either by enantiospecific synthesis or by resolution. The novel compounds may, for example, be resolved into their component enantiomers by standard techniques such as preparative HPLC, or the formation of diastereomeric pairs by salt formation with an optically active acid, such as (-)-di-p-toluoyl-d-tartaric acid and/or (+)-di-p-toluoyl-l-tartaric acid, followed by fractional crystallization and regeneration of the free base. The novel compounds may also be resolved by formation of diastereomeric esters or amides, followed by chromatographic separation and removal of the chiral auxiliary. Alternatively, such techniques may be carried out on racemic synthetic precursors of the compounds of interest.

In a preferred route to enantiomerically pure compounds of formula I, racemic intermediates (7) are subjected to preparative chiral HPLC to provide the corresponding homochiral intermediates, which are then converted to homochiral compounds of formula I by the routes indicated above.

Where they are not commercially available, the starting materials and reagents used in the above-described synthetic schemes may be prepared by conventional means.

During any of the above synthetic sequences it may be necessary and/or desirable to protect sensitive or reactive groups on any of the molecules concerned. This may be achieved by means of conventional protecting groups, such as those described in Protective Groups in Organic Chemistry, ed. J.F.W. McOmie, Plenum Press, 1973; and T.W. Greene & P.G.M. Wuts, Protective Groups in Organic Synthesis, John Wiley & Sons, 1991. The protecting groups may be removed at a convenient subsequent stage using methods known from the art.

An assay which can be used to determine the level of activity of compounds of the present invention is described in WO01/70677. A preferred assay to determine such activity is as follows:

1) SH-SY5Y cells stably overexpressing the βAPP C-terminal fragment SPA4CT, are cultured at 50-70% confluency. 10mM sodium butyrate is added 4 hours prior to plating.

2) Cells are plated in 96-well plates at 35,000 cells/well/100μL in Dulbeccos minimal essential medium (DMEM) (phenol red-free) + 10% foetal bovine serum (FBS), 50mM HEPES buffer (pH7.3), 1% glutamine.

3) Make dilutions of the compound plate. Dilute stock solution 18.2x to 5.5% DMSO and 11x final compound concentration. Mix compounds vigorously and store at 4°C until use.

4) Add 10μL compound/well, gently mix and leave for 18h at 37°C, 5% CO_2.

5) Prepare reagents necessary to determine amyloid peptide levels, for example by Homogeneous Time Resolved Fluorescence (HTRF) assay.

6) Plate 160μL aliquots of HTRF reagent mixture to each well of a black 96-well HTRF plate.

7) Transfer 40μL conditioned supernatant from cell plate to HTRF plate. Mix and store at 4°C for 18 hours.

8) To determine if compounds are cytotoxic following compound administration, cell viability is assessed by the use of redox dye reduction. A typical example is a combination of redox dye MTS (Promega) and the electron coupling reagent PES. This mixture is made up according to the manufacturer's instructions and left at room temperature.

9) Add 10μL/well MTS/PES solution to the cells; mix and leave at 37°C.

10) Read plate when the absorbance values are approximately 0.4 – 0.8. (Mix briefly before reading to disperse the reduced formazan product).

11) Quantitate amyloid beta 40 peptide using an HTRF plate reader.

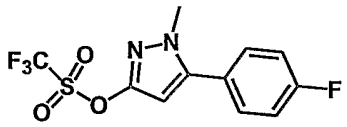
Alternative assays are described in *Biochemistry*, 2000, **39(30)**, 8698-8704. See also, *J. Neuroscience Methods*, 2000, **102**, 61-68.

The compounds of the present invention show unexpectedly high affinities as measured by the above assays. Thus the following Examples all had an ED_{50} of less than 50nM, typically less than 10nM, and frequently less than 1nM in at least one of the above assays. In general, the compounds also exhibit good oral bioavailability and/or brain penetration.

The following examples illustrate the present invention.

EXAMPLES

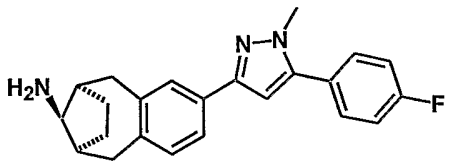
Intermediate A



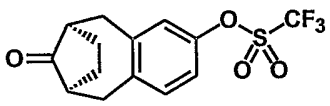
To a solution of methyl 4-(fluorophenyl)propynoate (*J. Org. Chem.* 1987, **52(16)**, 3662-8) (13g , 73mmol) in methanol (60ml) was added water (60ml) followed by methylhydrazine (4ml, 77mmol), the mixture was stirred for 6hrs at 60°C then left to stand overnight. The solid was filtered and washed with water then a minimum volume of methanol and dried overnight, affording 7.7g of 5-(4-fluorophenyl)-1-methyl-1,2-dihydropyrazol-3-one (55%). δ (^{1}H, 500MHz, $CDCl_3$) 3.68 (3H, s), 5.68 (1H, s), 7.13-7.17 (2H, m), 7.37-7.40 (2H, m).

To a cooled suspension of the above pyrazolone (15.5g, 81 mmol) in dry pyridine (100ml) was added in three portions trifluoromethanesulfonic anhydride (24g, 85 mmol) maintaining the temperature below 5°C. The cooling bath was then removed and the reaction was stirred for two hours before pouring into 2M hydrochloric acid and extracting into ethyl acetate. The organic layer was washed with brine, saturated sodium hydrogen carbonate, and dried (sodium sulfate), filtered and evaporated to yield a residue which was dissolved in toluene and evaporated and then dissolved in isohexane and filtered through a plug of silica, eluting with dichloromethane. The solvent was evaporated to yield product as a colourless oil (23.4g, 89%) δ (^{1}H, 500MHz, $CDCl_3$) 3.80 (3H,s), 6.14 (1H, s), 7.15-7.19 (2H, m), 7.38-7.42 (2H, m).

Intermediate B



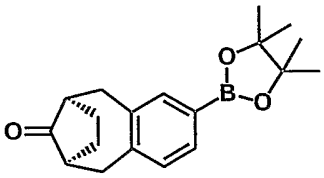
Step1



Racemic 2-hydroxy-5,6,7,8,9,10-hexahydro-6,9-methanobenzo[*a*][8]annulen-11-one (*J. Org. Chem,* 1982, **47**, 4329) was resolved using a Berger SFC semi-preparative instrument (chiralpak AS (25 x 2 cm, 20 um); 15% MeOH/CO_2 @ 50 mL/min; 35°C; 100 bar), retaining the second eluted enantiomer.

To a stirred solution of the homochiral phenol (6.83g, 34 mmol) in dry DCM (40 mL) at 0°C under nitrogen was added pyridine (3.8 mL, 47 mmol) followed by triflic anhydride (8.0 mL, 47 mmol). The reaction was stirred at 0°C for 2 hours, water (40 mL) added, the layers separated, and the aqueous layer extracted with DCM (x2). The combined extracts were washed with brine (x1), dried ($MgSO_4$), filtered and evaporated. The residue was purified by chromatography on silica, eluting with 10-15% EtOAc/hexane, to give the triflate (9.64g, 85%). (400MHz ^1H, δ-$CDCl_3$) 1.28 (2H, m), 1.92 (2H, m), 2.64 (2H, m), 2.85-3.05 (4H, m), 7.13 (2H, m), 7.29 (1H, m).

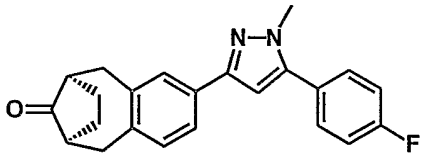
Step 2



A solution of the triflate from Step 1 (9.64 g, 29 mmol), 1,1′-bis (diphenylphosphino)ferrocene (1.60 g, 2.8 mmol), bis(pinacolato)diboron (8.05 g, 32 mmol) and KOAc (8.49 g, 86 mmol) in dry DMF (200 mL) was deoxygenated by bubbling nitrogen through the solution for 20 minutes. [1,1′-Bis (diphenylphosphino)ferrocene] palladium (II) chloride (2.354 g, 2.9 mmol) was added and deoxygenation was continued for a further 10 minutes. The reaction was heated at 10°C for 4 hours, then allowed to cool and diluted with water (400 mL). The catalyst

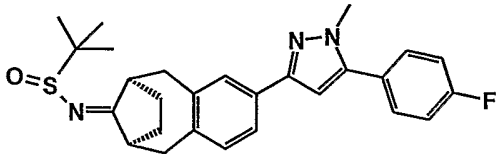
was removed by filtration through Hyflo® and the filtrate was extracted with EtOAc (x3). The combined extracts were washed with water then brine, dried ($MgSO_4$), filtered and evaporated. The residue was purified by chromatography on silica, eluting with 10-20% EtOAc/hexane to give the product (7.39 g, 82%). (360MHz ^1H, δ-$CDCl_3$) 1.29 (2H, m), 1.35 (12H, s), 1.85 (2H, m), 2.59 (2H, m), 2.84-3.01 (4H, m), 7.21 (1H, m), 7.63 (2H, m).

Step 3



A solution of the boronate from Step 2 (2.06 g, 6.6 mmol), Intermediate A (1.95 g, 6.0 mmol), and sodium carbonate (0.70 g, 6.6 mmol) in dry DMF (30 mL) was deoxygenated by bubbling nitrogen through the solution for 30 minutes. Tetrakis (triphenylphosphine) palladium (0) (0.52 g, 0.45 mmol) was added and deoxygenation was continued for a further 10 minutes. The reaction was heated at 100°C for 16 hours then allowed to cool and diluted with water (40 mL). The catalyst was removed by filtration through Hyflo® and the filtrate was extracted with EtOAc (x3). The combined extracts were washed with water then brine, dried ($MgSO_4$), filtered and evaporated. The residue was purified by chromatography on silica, eluting with 10-40% EtOAc/hexane to give the product (1.52 g, 64%). (400MHz ^1H, δ-$CDCl_3$) 1.37 (2H, m), 1.87 (2H, m), 2.61 (2H, m), 2.89-3.09 (4H, m), 3.91 (3H, s), 6.58 (1H, s), 7.15-7.26 (3H, m), 7.44 (2H, m), 7.61 (1H, m), 7.71 (1H, m). MS (ES+) 361, MH^+.

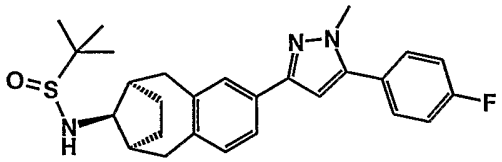
Step 4



1,1-Dimethylethylsulfinamide (392 mg, 6.0 mmol) followed by titanium tetraethoxide (1.2 ml, 5.6 mmol) were added to a solution of the product from Step 3 (1.0 g, 2.8 mmol) in THF (20 ml), under a nitrogen atmosphere, and the mixture was heated at

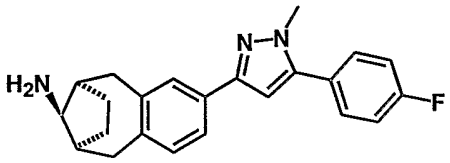
reflux for 24 hours. The mixture was cooled to room temperature and poured onto rapidly stirring brine. After 30 minutes ethyl acetate (100ml) was added and the mixture was filtered through a bed of Hyflo®, the phases were separated and the aqueous layer extracted with ethyl acetate (100ml). The organics were washed with brine, dried ($MgSO_4$) and evaporated *in vacuo* to give the desired imine as a yellowish foam (1.3 g, 99%) M/Z ES+ (464) $(MH)^+$.

Step 5



A solution of the imine from Step 4 (1.3 g, 2.8 mmol) in methanol (40 ml) at 0°C, under a nitrogen atmosphere, was treated with sodium borohydride (212 mg, 5.6 mmol) and the mixture was stirred at 0°C for 45 minutes and at 4°C for 16 hours. The reaction was concentrated *in vacuo*, the residue was diluted with water (40 ml) and extracted with ethyl acetate (2 x 40 ml). The organics were washed with brine, dried ($MgSO_4$) and evaporated *in vacuo* to give the desired sulfinamide as a brown foam (1.3 g, 99%) M/Z ES+ (466) $(MH)^+$.

Step 6

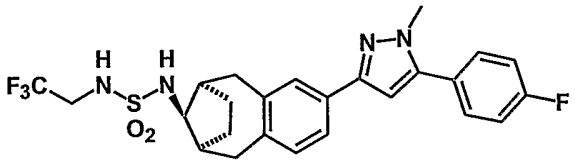


A solution of the sulfinamide from Step 5 (1.3 g, 2.8 mmol) in anhydrous methanol (20 ml) at 0°C was treated with hydrogen chloride (4N in dioxane, 8 ml, 32 mmol) and the reaction was stirred at 0°C for one hour. The reaction was evaporated *in vacuo*, the residue was diluted with sodium bicarbonate (sat, 40 ml) and extracted with ethyl acetate (2 x 30 ml). The organics were washed with brine, dried ($MgSO_4$) and evaporated *in vacuo* to a brown gum which was purified by ion exchange chromatography (SCX, washing with methanol and eluting with ammonia in methanol

(2M)) to give the desired amine as a white foam (911mg, 90%). M/Z ES+ (362) $(MH)^+$.

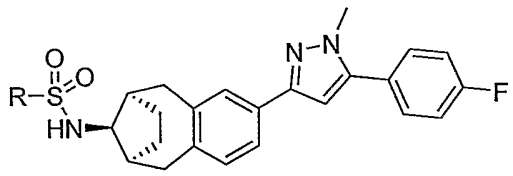
Example 1

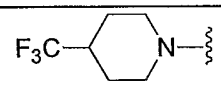
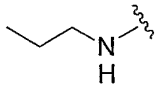
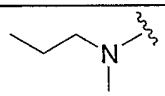
N-{(6*S*,9*R*,11*R*)-2-[5-(4-fluorophenyl)-1-methyl-1*H*-pyrazol-3-yl]-5,6,7,8,9,10-hexahydro-6,9-methanobenzo[*a*][8]annulen-11-yl}-*N'*-(2,2,2-trifluoroethyl)sulfamide

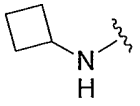


A solution of Intermediate B (50 mg, 0.14 mmol) in dichloromethane (1 ml) was added to trifluoroethylsulfamoyl chloride (41 mg, 0.2 mmol), triethylamine (78 Tl, 0.56 mmol) was added and the mixture was stirred at room temperature for 16 hours. The reaction was quenched by the addition of water (2ml) and the phases were separated via a Bond Elute™ phase separation cartridge. The aqueous phase was extracted with dichloromethane and the combined organics were evaporated and purified by Mass Directed LCMS to give the title compound a white foam (42 mg, 58 %). M/Z ES+ (523) $(MH)^+$.

The following examples were prepared in an analogous fashion, using the appropriate sulfamoyl chloride:

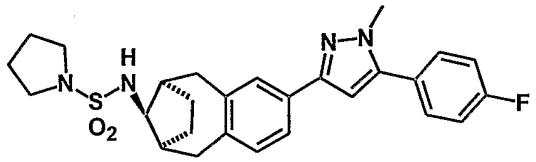


Example	R	*m/z* $(MH)^+$
2		577
3		483
4		497

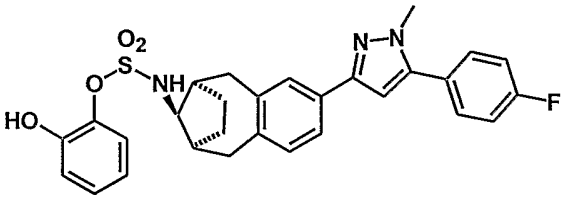
Example	R	*m/z* $(MH)^+$
5		495

Example 6

N-{(6*S*,9*R*,11*R*)-2-[5-(4-fluorophenyl)-1-methyl-1*H*-pyrazol-3-yl]-5,6,7,8,9,10-hexahydro-6,9-methanobenzo[*a*][8]annulen-11-yl}pyrrolidine-1-sulfonamide

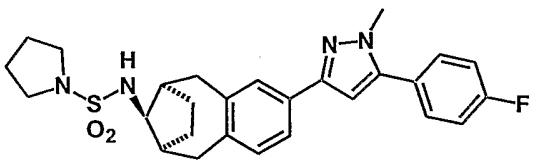


Step1



A solution of Intermediate B (400 mg, 1.1 mmol) in THF (8 ml), under a nitrogen atmosphere, was treated with catchol sulfate (200 mg, 1.2 mmol) and the mixture was stirred at room temperature for 65 hours. More catchol sulfate (200 mg, 1.2 mmol) was added and the mixture was stirred at room temperature for 20 hours. The reaction was diluted with ammonium chloride solution (sat, 40 ml) and extracted with ethyl acetate (2 x 20 ml). The organics were washed with brine, dried ($MgSO_4$) and evaporated *in vacuo* to give a purple gum, which was purified by chromatography on silica [ethyl acetate:isohexane 1:2] to give the desired sulfamate as a white foam (368 mg, 68%) M/Z ES+ (534) $(MH)^+$.

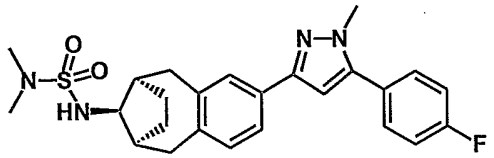
Step2



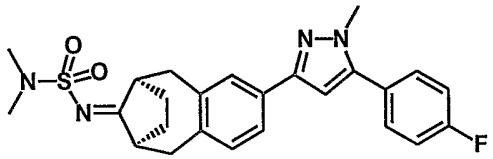
A solution of the sulfamate from step 1 (50 mg, 0.09 mmol), and pyrrolidine (40 Tl, 0.46 mmol) in dioxane (1 ml), under a nitrogen atmosphere was heated at 80°C for 1

hour. The reaction was diluted with water and extracted with DCM (3 x 20 ml). The extracts were dried (MgSO4) and evaporated *in vacuo* to a brown gum which was purified by chromatography on silica [ethyl acetate:isohexane 1:2] to give the desired sulfamide as a white foam (40 mg, 91%) M/Z ES+ (495) $(MH)^+$.

Example 7



Step 1



A solution of the ketone from Step 3 of the preparation of Intermediate B (0.360 g, 1.0 mmol), N,N-dimethylsulfamide (0.620 g, 5.0 mmol) and titanium(IV) ethoxide (tech., 0.63 mL, 3.0 mmol) in dry THF (5 mL) was stirred and heated at reflux under nitrogen for 16 hours. The reaction was allowed to cool to room temperature and poured into rapidly stirred brine (60 mL). The mixture was stirred for 1 hour, then filtered through Hyflo□, washing with EtOAc. The layers of the filtrate were separated, and the aqueous layer was extracted with EtOAc. The combined organic extracts were washed with brine, dried ($MgSO_4$), filtered and evaporated. The residue was purified by chromatography on silica, eluting with 5-20% EtOAc / DCM, to give the imine (0.383 g, 82%). MS (ES+) 467, MH^+.

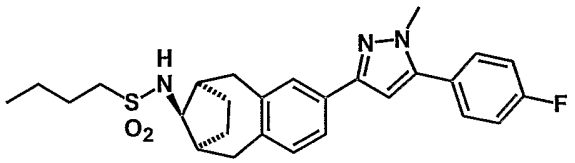
Step 2

A solution of the imine from Step 1 (60 mg, 0.13 mmol) and sodium borohydride (10 mg, 0.26 mmol) in MeOH (5 mL) was stirred at 0°C for 1 hour. The reaction was concentrated *in vacuo* and water (10 mL) was added, then the mixture was extracted with EtOAc, and the combined organic extracts were washed with brine, dried ($MgSO_4$), filtered and evaporated. The residue was purified by chromatography on silica, eluting with 30% EtOAc / hexane, to give the sulfamide (43 mg, 73%).

(360MHz ^{1}H, δ-$CDCl_3$) 1.25 (2H, m), 1.70 (2H, m), 2.50 (2H, m), 2.71 (2H, m), 2.87 (6H, s), 3.10 (2H, m), 3.80 (1H, m), 3.90 (3H, s), 4.59 (1H, m), 6.56 (1H, s), 7.15 (3H, m), 7.43 (2H, m), 7.51 (1H, m), 7.60 (1H, m). MS (ES+) 469, MH^+.

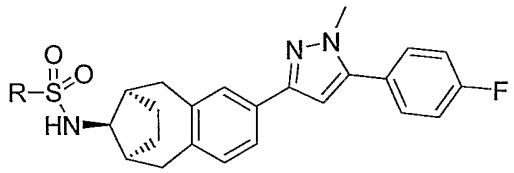
Example 8

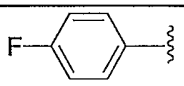
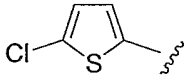
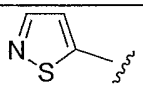
N-{(6*S*,9*R*,11*R*)-2-[5-(4-fluorophenyl)-1-methyl-1*H*-pyrazol-3-yl]-5,6,7,8,9,10-hexahydro-6,9-methanobenzo[*a*][8]annulen-11-yl}butane-1-sulfonamide

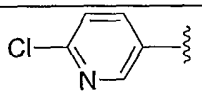
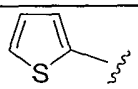


A solution of Intermediate B (50 mg, 0.14 mmol) in dichloromethane (1 ml) was added to n-butanesulfonyl chloride (44 mg, 0.28 mmol), followed by triethylamine (78 Tl, 0.56 mmol), and the mixture was stirred at room temperature for 16 hours. The reaction was quenched by the addition of water (2ml) and the phases were separated via Bond Elute™ phase separation cartridge. The aqueous phase was extracted with dichloromethane, the combined organics were evaporated and the residue purified by Mass Directed LCMS to give the title compound a white foam M/Z ES+ (482) $(MH)^+$.

The following examples were prepared in an analogous fashion using the appropriate sulfonyl chloride:

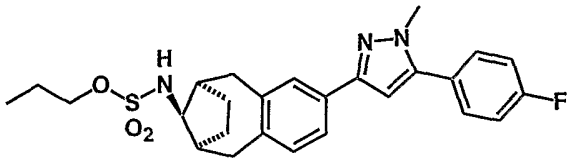


Example	R	*m/z* $(MH)^+$
9		520
10		542
11		509

Example	R	*m/z* $(MH)^+$
12		537
13		508

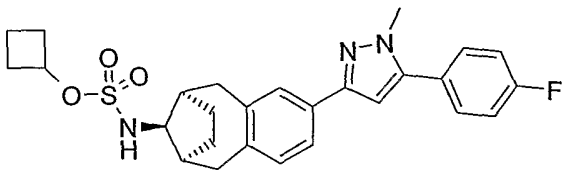
Example 14

Propyl (6*S*,9*R*,11*R*)-2-[5-(4-fluorophenyl)-1-methyl-1*H*-pyrazol-3-yl]-5,6,7,8,9,10-hexahydro-6,9-methanobenzo[*a*][8]annulen-11-ylsulfamate



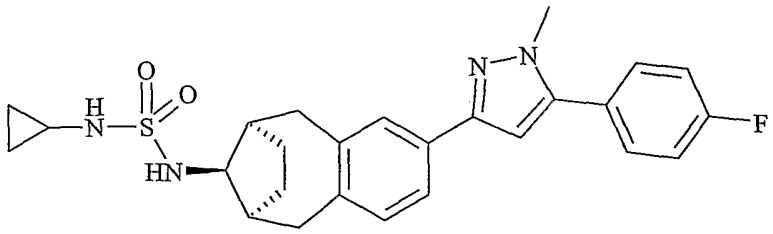
A solution of the sulfamate from Example 6 step 1 (43 mg, 0.08 mmol) and triethylamine (14 Tl, 0.1 mmol) in n-propanol (1ml), under a nitrogen atmosphere, was heated at 80 °C for 16 hours. The reaction was cooled to room temperature, diluted with ethyl acetate and washed with sodium hydroxide solution (1N, 3 x 10 ml), followed by water (10 ml) and brine. The organics were dried (MgSO4) and evaporated *in vacuo* to a brown gum, which was purified by chromatography on silica [ethyl acetate:isohexane 1:2] to give the desired sulfamate as a white foam (36 mg, 93%) M/Z ES+ (484) $(MH)^+$.

Example 15



Prepared by the method of Example 14, substituting cyclobutanol for n-propanol. M/Z ES+ (496) $(MH)^+$.

Examples 16

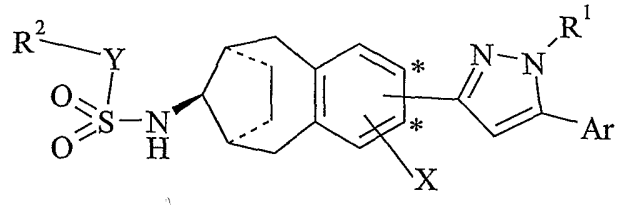


Prepared by the method of Example 6, substituting cyclopropylamine for pyrrolidine.

M/Z ES+ (481) $(MH)^+$.

CLAIMS:

1. A compound of formula I:



I

wherein the pyrazole group is attached at one of the positions indicated by an asterisk and X is attached at a position adjacent thereto;

X represents H, OH, C_{1-4}alkoxy, Cl or F;

Y represents a bond, O or NR^3;

Ar represents phenyl or 6-membered heteroaryl, either of which bears 0-3 substituents independently selected from halogen, CF_3, CHF_2, CH_2F, NO_2, CN, OCF_3, C_{1-6}alkyl and C_{1-6}alkoxy;

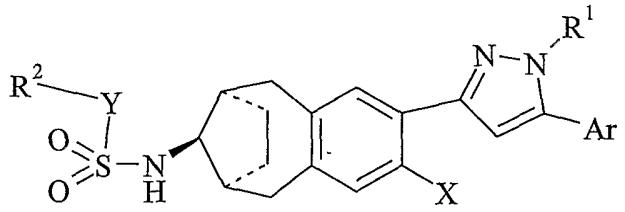
R^1 represents a hydrocarbon group of 1-5 carbon atoms which is optionally substituted with up to 3 halogen atoms; and

R^2 represents a hydrocarbon group of 1-10 carbon atoms which is optionally substituted with up to 3 halogen atoms, or heteroaryl of 5 or 6 ring atoms optionally bearing up to 3 substituents independently selected from halogen, CF_3, CHF_2, CH_2F, NO_2, CN, OCF_3, C_{1-6}alkyl and C_{1-6}alkoxy; or when Y represents NR^3, R^2 and R^3 together may complete a heterocyclic ring of up to 6 members which optionally bears up to 3 substituents independently selected from halogen, CF_3, CHF_2, CH_2F, NO_2, CN, OCF_3, C_{1-6}alkyl and C_{1-6}alkoxy;

R^3 represents H or C_{1-4}alkyl, or together with R^2 completes a heterocyclic ring as defined above;

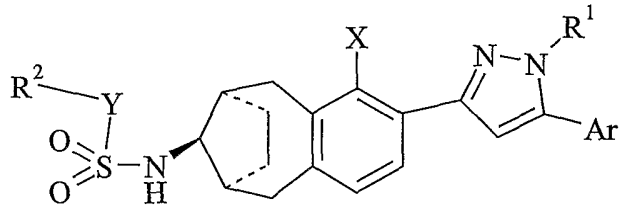
or a pharmaceutically acceptable salt thereof.

2. A compound according to claim 1 of formula IIa:



IIa

or formula IIIa:



IIIa

wherein X, Y, Ar, R^1 and R^2 are as defined in claim 1;
or a pharmaceutically acceptable salt thereof.

3. A compound according to any previous claim wherein X represents H.

4. A compound according to any previous claim wherein Y is a bond and R^2 represents optionally substituted phenyl or heteroaryl or C_{1-6}alkyl.

5. A compound according to any of claims 1-3 wherein Y is O and R^2 represents alkyl or cycloalkyl of up to 6 carbon atoms.

6. A compound according to any of claims 1-3 wherein Y is NH or NMe and R^2 represents alkyl or cycloalkyl of up to 6 carbon atoms which is optionally substituted with up to 3 fluorine atoms.

7. A compound according to any of claims 1-8 wherein Y is NR^3 and R^2 and R^3 complete a heterocyclic ring.

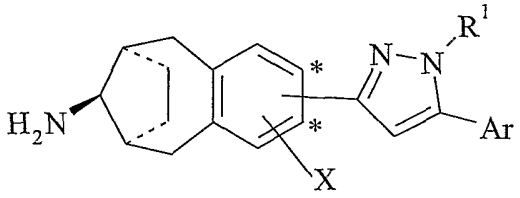
8. A pharmaceutical composition comprising a compound according to any previous claim and a pharmaceutically acceptable carrier.

9. A compound according to any of claims 1-7 for use in therapy.

10. The use of a compound according to any of claims 1-7 for the manufacture of a medicament for treatment or prevention of Alzheimer's disease.

11. A method of treatment of a subject suffering from or prone to Alzheimer's disease which comprises administering to that subject an effective amount of a compound according to any of claims 1-7.

12. A method of preparing a compound according to claim 1 comprising reaction of an amine (1) with R^2-Y-SO_2Cl:



(1)

where X, Y, Ar, R^1 and R^2 and as defined in claim 1.

INTERNATIONAL SEARCH REPORT

Int al Application No
PCT/GB 03/04707

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/415 C07D231/12 C07D401/12 C07D409/12 C07D417/12
A61P25/28

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)
IPC 7 C07D

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, WPI Data, PAJ, BEILSTEIN 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.
X	WO 02 36555 A (COLLINS IAN JAMES ;MERCK SHARP & DOHME (GB); WILLIAMS BRIAN JOHN () 10 May 2002 (2002-05-10) cited in the application page 2, line 21 - line 25; claims 1,8,9,16 page 20, line 3 - line 17 page 43, line 4 - line 13; examples 40,41,143	1-12
X	WO 01 70677 A (MERCK FROSST CANADA INC ;BELANGER PATRICE CHARLES (CA); COLLINS IA) 27 September 2001 (2001-09-27) cited in the application page 2, line 24 - line 27; claims 9,14,16 page 10, line 21 - line 30 page 23, line 22 - line 27; examples 95-102,177,178,200,201	1-12

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

☒ Patent family members are listed in 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
20 January 2004	26/01/2004

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	Seymour, L

INTERNATIONAL SEARCH REPORT

International application No.
PCT/GB 03/04707

Box I Observations where certain claims were found unsearchable (Continuation of item 1 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 claim 11 is 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 II Observations where unity of invention is lacking (Continuation of item 2 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

Inte ɪnal Application No
PCT/GB 03/04707

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 0236555 A	10-05-2002	AU 1074702 A	15-05-2002
		AU 4086101 A	03-10-2001
		CA 2404125 A1	27-09-2001
		CA 2427206 A1	10-05-2002
		EP 1268412 A1	02-01-2003
		EP 1334085 A1	13-08-2003
		WO 0170677 A1	27-09-2001
		WO 0236555 A1	10-05-2002
		JP 2003528076 T	24-09-2003
WO 0170677 A	27-09-2001	AU 4086101 A	03-10-2001
		CA 2404125 A1	27-09-2001
		EP 1268412 A1	02-01-2003
		WO 0170677 A1	27-09-2001
		JP 2003528076 T	24-09-2003
		AU 1074702 A	15-05-2002
		CA 2427206 A1	10-05-2002
		EP 1334085 A1	13-08-2003
		WO 0236555 A1	10-05-2002