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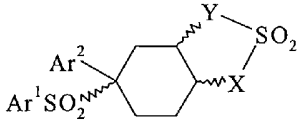
(54) Title: CYCLOHEXYL SULPHONES AS GAMMA-SECRETASE INHIBITORS



(I)

(57) Abstract: Compounds of formula (I): inhibit gamma-secretase and hence find use in treatment or prevention of Alzheimer's disease.

WO 2004/101538 A1

CYCLOHEXYL SULPHONES 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 cyclohexyl sulphones comprising an additional fused ring which contains an SO_2 group. The compounds inhibit the processing of APP by γ-secretase so as to suppress or attenuate the secretion of β-amyloid, 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.

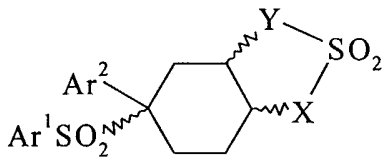
There is a growing number of reports in the literature of compounds with inhibitory activity towards γ-secretase, as measured in cell-based assays (see, for example, WO 01/70677 and references therein). Many of the relevant compounds are peptides or peptide derivatives.

WO 00/50391 discloses a broad class of sulphonamides as modulators of the production of β-amyloid, but neither discloses nor suggests the compounds of the present invention. WO 01/70677, WO 02/36555 and WO 02/081435 disclose, respectively, classes of sulphonamides, sulphamides and cyclohexyl sulphones which inhibit γ-secretase, but neither disclose nor suggest the compounds of the present invention.

The present invention provides a novel class of cyclohexyl sulphones comprising and additional fused ring which contains an SO_2 group. The compounds

inhibit the processing of APP by the putative γ-secretase so as to suppress or attenuate the production of Aβ and hence are useful in the treatment or prevention of AD.

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



I

wherein the bonds indicated by wavy lines are mutually *cis* with respect to the cyclohexane ring;

X represents O, NR^1 or CHR^1;

Y represents CHR^2-CHR^3, CR^2=CR^3, CHR^2-NR^4 or CHR^2-O;

R^1 represents H or C_{1-4}alkyl;

R^2, R^3 and R^4 independently represent H or a hydrocarbon group of up to 10 carbon atoms, optionally substituted with CF_3, CHF_2, halogen, CN, OR^5, COR^5, CO_2R^5, $OCOR^6$, $N(R^5)_2$, $CON(R^5)_2$ or NR^5COR^6; or R^2 and R^4 together complete a 5- or 6-membered ring which is optionally substituted with oxo, CF_3, CHF_2, halogen, CN, OR^5, COR^5, CO_2R^5, $OCOR^6$, $N(R^5)_2$, $CON(R^5)_2$ or NR^5COR^6;

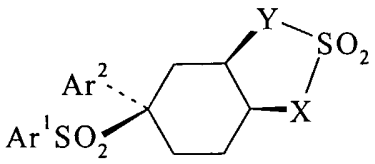
R^5 represents H or C_{1-4}alkyl;

R^6 represents C_{1-4}alkyl; and

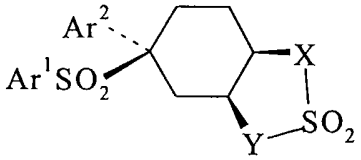
Ar^1 and Ar^2 independently represent phenyl or heteroaryl, either of which bears 0-3 substituents independently selected from halogen, CN, NO_2, CF_3, CHF_2, OH, OCF_3, CHO, CH=NOH, C_{1-4}alkoxy, C_{1-4}alkoxycarbonyl, C_{2-6}acyl, C_{2-6}alkenyl and C_{1-4}alkyl which optionally bears a substituent selected from halogen, CN, NO_2, CF_3, OH and C_{1-4}alkoxy;

or a pharmaceutically acceptable salt thereof.

The compounds of formula I exist in two enantiomeric forms, depending on whether the bonds indicated by wavy lines project upwards or downwards, corresponding to formulae IA and IB:



IA



IB

where X, Y, Ar^1 and Ar^2 have the same meanings as before. It is to be understood that any compound in accordance with the invention may exist in either of the homochiral forms IA and IB, or as a mixture of the two in any proportion.

In addition to the isomerism described above, the compounds according to the invention may comprise one or more asymmetric centres, and accordingly may 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.

Where a variable occurs more than once in formula I, the individual occurrences are independent of each other, unless otherwise indicated.

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_{2-6}acyl" as used herein refers to C_{1-5}alkylcarbonyl groups in which the alkyl portion may be straight chain, branched or cyclic, and may be halogenated. Examples include acetyl, propionyl and trifluoroacetyl.

The expression "heteroaryl" as used herein means a monocyclic system of 5 or 6 ring atoms, or fused bicyclic system of up to 10 ring atoms, selected from C, N, O and S, wherein at least one of the constituent rings is aromatic and comprises at least one ring atom which is other than carbon. Monocyclic systems of 5 or 6 members are preferred. Examples of heteroaryl groups include pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, pyrrolyl, furyl, thienyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, imidazolyl, oxadiazolyl, triazolyl and thiadiazolyl groups and benzo-fused analogues thereof. Further examples of heteroaryl groups include tetrazole, 1,2,4-triazine and 1,3,5-triazine. Pyridine rings may be in the N-oxide form.

Where a phenyl group or heteroaryl group bears more than one substituent, preferably not more than one of said substituents is other than halogen or alkyl. Where an alkyl group bears more than one substituent, preferably not more than one of said substituents is other than halogen.

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 advantageously 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, benzenesulfonic acid, methanesulfonic 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.

In the compounds of formula I, Ar^1 and Ar^2 independently represent optionally substituted phenyl or heteroaryl. Ar^1 is preferably selected from optionally substituted phenyl and optionally substituted 6-membered heteroaryl. Preferred 6-membered heteroaryl embodiments of Ar^1 include optionally substituted pyridyl, in particular optionally substituted 3-pyridyl. Ar^1 is preferably selected from 6-(trifluoromethyl)-3-pyridyl and phenyl which is optionally substituted in the 4-position with halogen, CN, vinyl, allyl, acetyl, methyl or mono-, di- or trifluoromethyl. In one preferred embodiment of the invention Ar^1 represents 4-chlorophenyl. In another preferred embodiment Ar^1 represents 4-trifluoromethylphenyl.

Ar^2 preferably represents optionally substituted phenyl, in particular phenyl bearing 2 or 3 substituents selected from halogen, CN, CF_3 and optionally-substituted alkyl. Ar^2 is typically selected from phenyl groups bearing halogen substituents (preferably fluorine) in the 2- and 5- positions, the 2- and 6-positions or in the 2-, 3- and 6-positions, or from phenyl groups bearing a fluorine substituent in the 2-position and halogen, CN, methyl or hydroxymethyl in the 5-position. In a preferred embodiment of the invention, Ar^2 represents 2,5-difluorophenyl, 2,6-difluorophenyl or 2,3,6-trifluorophenyl.

In a particular embodiment, Ar^1 is 4-chlorophenyl or 4-trifluoromethylphenyl and Ar^2 is 2,5-difluorophenyl.

In formula I, X represents O, NR^1 or CHR^1. When X represents O, Y is preferably CHR^2-NR^4 or CHR^2-O. When X represents CHR^1, Y is preferably CHR^2-CHR^3, CR^2=CR^3 or CHR^2-NR^4, especially CHR^2-CHR^3 or CHR^2-NR^4. When Y represents CR^2=CR^3, X preferably represents NR^1.

R^1 represents H or C_{1-4}alkyl, such as methyl, ethyl, n-propyl or isopropyl, but preferably R^1 represents H.

R^2 represents H or a hydrocarbon group of up to 10 carbon atoms, optionally substituted as defined previously. Hydrocarbon groups represented by R^2 are preferably non-aromatic and unsubstituted, and preferably comprise up to 6 carbon atoms. Typical examples include alkyl groups (such as methyl, ethyl, n-propyl, isopropyl and n-butyl) and alkenyl groups (such as allyl). When Y represents CHR^2-CHR^3, CR^2=CR^3 or CHR^2-O, R^2 very aptly represents H. When Y represents CHR^2-NR^4, R^2 and R^4 may combine to form a fused 5- or 6-membered ring, such as a

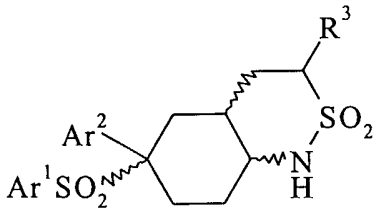
pyrrolidine, piperidine or tetrahydropyridine ring, which is optionally substituted as defined previously. Preferred rings include piperidine and tetrahydropyridine which are unsubstituted or substituted with OH.

R^3 represents H or a hydrocarbon group of up to 10 carbon atoms, optionally substituted as defined previously. In one embodiment hydrocarbon groups represented by R^3 are non-aromatic and unsubstituted, and preferably comprise up to 6 carbon atoms. Typical examples include alkyl groups (such as methyl, ethyl, n-propyl, isopropyl and n-butyl) and alkenyl groups (such as allyl and 3-methylbut-2-enyl).

In an alternative embodiment, R^3 represents C_{1-6}alkyl bearing a substituent selected from CN, OR^5, CO_2R^5, COR^5 and $CON(R^5)_2$ where R^5 is as defined previously. Preferred substituents include OH, CN, CO_2H, $COCH_3$ and $CONH_2$. When Y represents $CR^2{=}CR^3$, R^3 very aptly represents H.

R^4 represents H or a hydrocarbon group of up to 10 carbon atoms, optionally substituted as defined previously. Preferred substituents include CN, CF_3, halogen (especially F), OH and alkoxy (especially methoxy). Suitable hydrocarbon groups include optionally substituted phenylC_{1-4}alkyl (such as benzyl), C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-6}cycloalkyl and C_{3-6}cycloalkylC_{1-4}alkyl. Specific examples of groups represented by R^4 include H, methyl, ethyl, n-propyl, isopropyl, n-butyl, t-butyl, sec-butyl, 2-fluoroethyl, 2,2,2-trifluoroethyl, 2-cyanoethyl, 2-hydroxyethyl, 2-methoxyethyl, allyl, cyclopropyl, cyclobutyl, cyclopentyl and cyclopropylmethyl. Alternatively, R^4 may combine with R^2 to form a fused ring as described above.

A subset of the compounds of the invention are those of formula II and the pharmaceutically acceptable salts thereof:

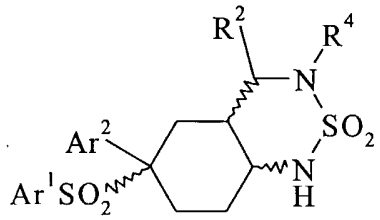


II

wherein the bonds indicated by wavy lines are mutually *cis* with respect to the cyclohexane ring, and R^3, Ar^1 and Ar^2 have the same definitions and preferred identities as before.

Specific examples of compounds within this subset include those in which Ar^1 represents 4-chlorophenyl or 4-trifluoromethylphenyl, Ar^2 represents 2,5-difluorophenyl, and R^3 represents H, methyl, ethyl, n-propyl, isopropyl, allyl, 3-methylbut-2-enyl, cyanomethyl, 2-cyanoethyl, 3-cyanopropyl, 2-hydroxyethyl, $-CH_2COCH_3$, $-CH_2CO_2H$, $-CH_2CH_2CO_2H$, $-CH_2CONH_2$ or $CH_2CH_2CONH_2$, and pharmaceutically acceptable salts thereof.

A second subset of the compounds of the invention are those of formula III and the pharmaceutically acceptable salts thereof:



III

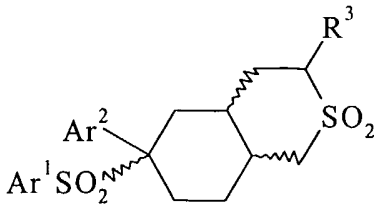
wherein the bonds indicated by wavy lines are mutually *cis* with respect to the cyclohexane ring, and R^2, R^4, Ar^1 and Ar^2 have the same definitions and preferred identities as before.

Specific compounds within this subset include those in which Ar^2 represents 2,5-difluorophenyl and Ar^1, R^2 and R^4 are as shown in the following table:

Ar^1	R^2	R^4
4-Cl-C_6H_4	H	ethyl
4-Cl-C_6H_4	H	n-propyl
4-Cl-C_6H_4	H	n-butyl
4-Cl-C_6H_4	H	cyclopropyl
4-Cl-C_6H_4	H	cyclopentyl
4-Cl-C_6H_4	H	sec-butyl
4-Cl-C_6H_4	H	cyclopropylmethyl
4-Cl-C_6H_4	H	t-butyl
4-Cl-C_6H_4	H	2,2,2-trifluoroethyl
4-Cl-C_6H_4	H	2-hydroxyethyl
4-Cl-C_6H_4	H	methyl

Ar^1	R^2	R^4
4-Cl-C_6H_4	H	isopropyl
4-Cl-C_6H_4	H	cyclobutyl
4-Cl-C_6H_4	H	2-fluoroethyl
4-CF_3-C_6H_4	H	ethyl
4-CF_3-C_6H_4	H	methyl
4-CF_3-C_6H_4	H	isopropyl
4-CF_3-C_6H_4	H	cyclopropyl
4-CF_3-C_6H_4	H	cyclobutyl
4-CF_3-C_6H_4	H	t-butyl
4-CF_3-C_6H_4	H	2,2,2-trifluoroethyl
4-CF_3-C_6H_4	H	2-hydroxyethyl
4-CF_3-C_6H_4	H	2-fluoroethyl
4-CF_3-C_6H_4	H	2-cyanoethyl
4-CF_3-C_6H_4	H	2-methoxyethyl
4-Cl-C_6H_4	allyl	allyl
4-Cl-C_6H_4	fused tetrahydropyridine	
4-Cl-C_6H_4	fused piperidine	
4-Cl-C_6H_4	allyl	isopropyl
4-Cl-C_6H_4	n-propyl	isopropyl
4-Cl-C_6H_4	fused 3-hydroxypiperidine	
4-Cl-C_6H_4	fused 4-hydroxypiperidine	
4-Cl-C_6H_4	H	H
6-CF_3-pyridin-3-yl	H	cyclopropyl
4-Cl-C_6H_4	allyl	cyclopropyl
4-Cl-C_6H_4	2-hydroxyethyl	cyclopropyl
4-Cl-C_6H_4	H	-$CH(CH_3)CH_2OH$
4-Cl-C_6H_4	H	-$CH(CH_3)CO_2H$

A third subset of the compounds of the invention are those of formula IV and the pharmaceutically acceptable salts thereof:



IV

wherein the bonds indicate by the wavy lines are mutually *cis* with respect to the cyclohexane ring, and R^3, Ar^1 and Ar^2 have the same definitions and preferred identities as before.

Specific compounds within this subset include those in which Ar^2 represents 2,5-difluorophenyl, Ar^1 represents 4-chlorophenyl or 4-trifluoromethylphenyl, and R^3 represents H, methyl, ethyl, propyl or cyclobutyl.

Further specific compounds in accordance with the invention are disclosed in the Examples appended hereto.

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 formula I 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.

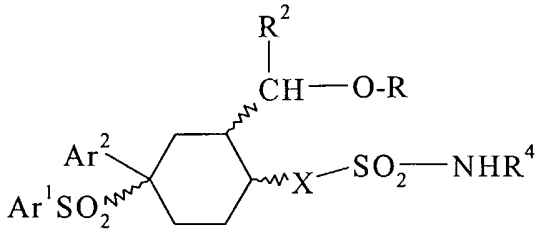
The present invention further provides the use of a compound of formula I or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for treating or preventing Alzheimer's disease.

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 0.05 to 100 mg/kg per day, more preferably about 0.1 to 50 mg/kg of body weight per day, and for the most preferred compounds, about 0.1 to 20 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.

Compounds of formula I in which Y represents CHR^2-NR^4 may be prepared by cyclisation of compounds of formula (1a):

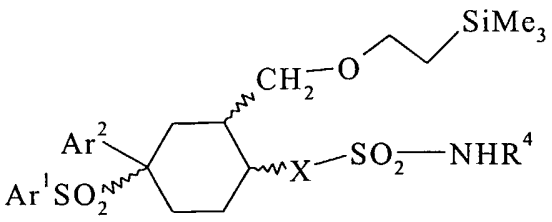


(1) (a) R = SO_2R^a (b) R = H

where R^a represents optionally-substituted alkyl or phenyl (especially methyl, tolyl or trifluoromethyl) and Ar^1, Ar^2, X, R^2 and R^4 have the same meanings as before. The reaction takes place in the presence of sodium hydride in an aprotic solvent such as THF or DMF at 0 – 20°C.

Sulphonates (1a) are obtained by treatment of alcohols (1b) with R^aSO_2Cl or $(R^aSO_2)_2O$ in the presence of base under anhydrous conditions, typically at ambient temperature.

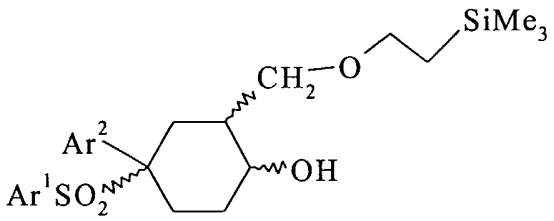
Alcohols (1b) in which R^2 is H are obtained by cleavage of the silylethyl ethers (2) with BF_3.etherate:



(2)

where Ar^1, Ar^2, X and R^4 have the same meanings as before. The reaction may be carried out in dichloromethane at ambient temperature. Secondary alcohols (1b) in which R^2 is hydrocarbon may be obtained by oxidation of the corresponding primary alcohols and reaction of the resulting aldehydes with R^2MgBr.

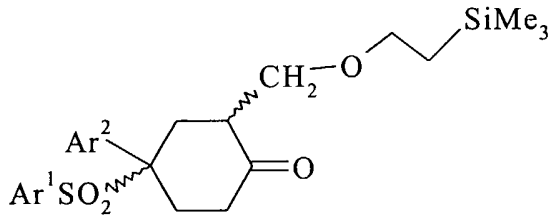
Compounds (2) in which X is O are available by reaction of alcohols (3) with R^4NHSO_2Cl:



(3)

where Ar^1, Ar^2 and R^4 have the same meanings as before. The reaction takes place in dimethylacetamide at 50°C.

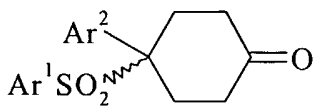
Alcohols (3) are obtained by reduction of ketones (4) and isolation of the desired *cis* isomers:



(4)

where $Ar^1$and Ar^2, have the same meanings as before. Reduction with L-Selectride™ in THF at –78°C provides the *cis* isomers preferentially, while reduction with sodium borohydride in isopropanol at –40 to 20°C provides roughly equal proportions of the *cis* and *trans* isomers which are separable by chromatography.

Ketones (4) are available by alkylation of cyclohexanones (5) with 2-(trimethylsilyl)ethoxymethyl chloride:

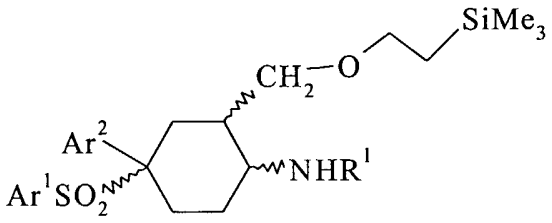


(5)

where Ar^1 and Ar^2 have the same meanings as before. The reaction may be carried out in THF at –78°C in the presence of strong base such as lithium hexamethyldisilazide.

As an alternative to lithium hexamethyldisilazide, there may be employed the product obtained from reacting BuLi with a chiral amine such as [S-(R*,R*)]-(-)-bis(α-methylbenzyl)amine. This enables the isolation of compounds (4) in homochiral form, and hence the synthesis of homochiral compounds of formula I. The preparation of cyclohexanones (5) is described in WO 02/081435 and WO 04/013090.

Compounds (2) in which X is NR^1 are obtainable by reaction of amines (6) with R^4NHSO_2Cl:

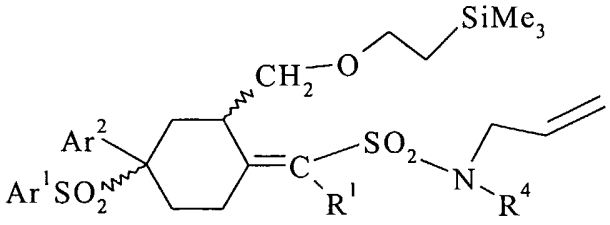


(6)

where Ar^1, Ar^2, R^1 and R^4 have the same meanings as before. The reaction may be carried out in the presence of triethylamine in a mixture of dichloromethane and dimethylacetamide at ambient temperature.

Amines (6) may be obtained by treatment of the *trans* isomers of alcohols (3) with R^aSO_2Cl or $(R^aSO_2)_2O$ in the presence of base under anhydrous conditions, followed by displacement of the resulting sulphonate esters with R^1NH_2, where R^a and R^1 have the same meanings as before. Alternatively, the sulphonate esters may be displaced using azide ion, and the product reduced to provide amines (6) in which R^1 is H. The displacement may be carried out in DMF at 95°C, and the reduction may be effected using triphenylphosphine in refluxing THF.

Compounds (2) in which X is CHR^1 may be obtained by reduction of compounds (7), using sodium borohydride and $NiCl_2$ in methanol at 0°C:



(7)

where Ar^1, Ar^2, R^1 and R^4 have the same meanings as before.

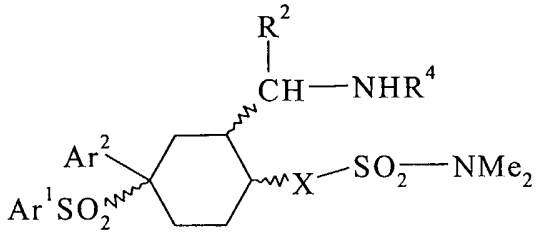
Compounds (7) are obtained via condensation of ketones (4) with:

$$(EtO)_2P(O) - CH(R^1) - SO_2N(R^4)\text{-}CH_2CH{=}CH_2$$

(8)

where R^1 and R^4 have the same meanings as before. The reaction may be carried out in THF at –78°C in the presence of BuLi. Compounds (8) are available by reaction of sulphonamides $R^1\text{-}CH_2\text{-}SO_2N(R^4)\text{-}CH_2CH{=}CH_2$ with diethylchlorophosphonate in the presence of BuLi in THF at –78°C.

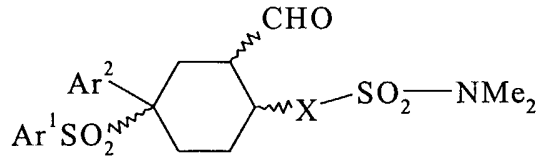
An alternative route to compounds of formula I in which Y represents $CHR^2\text{-}NR^4$ is by cyclisation of compounds of formula (9):



(9)

where Ar^1, Ar^2, X, R^2 and R^4 have the same meanings as before. The reaction takes place in refluxing tetrahydrofuran (THF), e.g. overnight. For this process, X is preferably CHR^1 or NR^1.

Compounds of formula (9) in which R^2 is H may be prepared by condensation of aldehydes (10) with R^4NH_2 and reduction of the resulting imine with sodium borohydride:

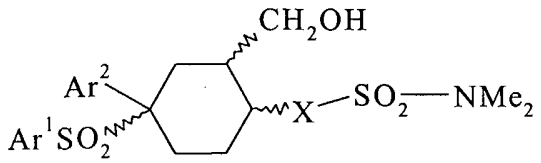


(10)

where Ar^1, Ar^2, X and R^4 have the same meanings as before. Both steps may carried out in ethanol solution at ambient temperature, and the first step is advantageously carried out in the presence of alumina.

Compounds of formula (9) in which R^2 is other than H may be prepared by reaction of aldehydes (10) with R^4NH_2 and reaction of the resulting imine with $R^2\text{-}MgBr$, e.g. in THF solution at 0°C.

The aldehydes (10) are available by oxidation of alcohols (11):

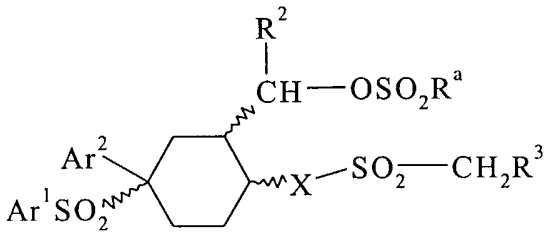


(11)

where Ar^1, Ar^2 and X have the same meanings as before. Suitable oxidation procedures include treatment with Dess-Martin periodinane in dichloromethane at ambient temperature.

Alcohols (11) are available by routes analogous to those described above for alcohols (1b).

Compounds of formula I in which Y is CHR^2-CHR^3 may be prepared by cyclisation of compounds (12):

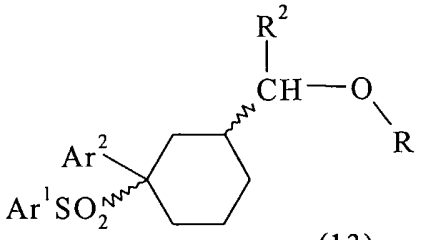


(12)

where Ar^1, Ar^2, X, R^2, R^3 and R^a have the same meanings as before. Preferably, X is NR^1 or CHR^1. The reaction takes place in THF at –30 – 20°C in the presence of BuLi. Compounds (12) in which X is NR^1 or CHR^1 may be prepared by the same methods as described above for corresponding compounds (1a), substituting (respectively) $R^3CH_2SO_2Cl$ for R^4NHSO_2Cl, and $R^1CH_2SO_2CH_2R^3$ for R^1CH_2-$SO_2N(R^4)$-$CH_2CH{=}CH_2$.

Compounds of formula I in which Y is CH_2-O and X is O may be prepared by sequential treatment of alcohols (1b) in which X is O, R^2 is H and R^4 is H with methanesulphonyl chloride and sodium hydride. The first step is carried out in pyridine in the presence of 4-dimethylaminopyridine, and the second step in THF at ambient temperature.

Compounds of formula I in which Y is CH_2-O and X is NR^1 may be prepared by treatment of compounds (13a) with iodobenzene diacetate:

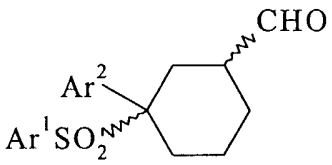


(13)

(a) R = SO_2NHR^1

(b) R = H

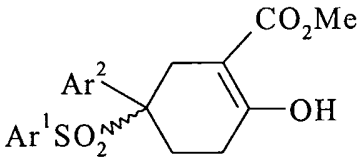
where Ar^1, Ar^2, R^1 and R^2 have the same meanings as before. Most suitably, R^1 and R^2 are both H. The reaction takes place in refluxing dichloromethane in the presence of MgO and Rh(II)diacetate dimer. Compounds (13a) are available from the treatment of alcohols (13b) with R^1NHSO_2Cl in DMF at ambient temperature. Alcohols (13b) are obtained by treatment of aldehydes (14) with sodium borohydride (when R^2 is H) or with R^2MgBr when R^2 is other than H:



(14)

where Ar^1 and Ar^2 have the same meanings as before.

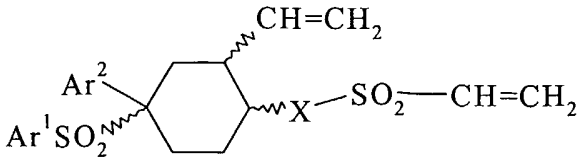
Aldehydes (14) may be prepared from enols (15) (WO 02/081435) in a process involving (i) formation of the methanesulphonate ester, (ii) reductive cleavage of the methanesulphonate group, and (iii) reduction of the carboxylate ester:



(15)

where Ar^1 and Ar^2 have the same meanings as before. Step (i) is carried out as described for the conversion of (1b) to (1a). Step (ii) involves treatment with sodium borohydride and nickel(II) chloride in a dichloromethane/methanol mixture at –10°C. Step (iii) involves treatment with diisobutylaluminium hydride in toluene at –78°C.

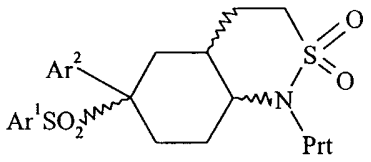
Compounds of formula I in which Y is CH=CH may be prepared by cyclisation of compounds of formula (16):



(16)

where X Ar^1 and Ar^2 have the same meanings as before. Preferably X is CHR^1 or NHR^1, most preferably NHR^1. The reaction takes place in dichloromethane in the presence of Grubb's catalyst. Compounds (16) may be prepared by the procedures described above for preparing compounds (1b), substituting chloroethanesulphonyl chloride for R^4NHSO_2Cl, or $R^1CH_2SO_2CH=CH_2$ for R^1CH_2-$SO_2N(R^4)$-$CH_2CH=CH_2$, followed by oxidation of the alcohol group and a Wittig reaction on the resulting aldehyde.

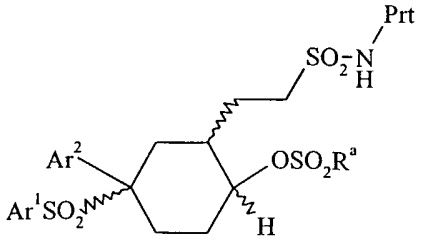
A preferred route to compounds of formula II in which R^3 is other than H comprises alkylation of compounds (17) with R^{3a} – L, followed by cleavage of the N-protecting group:



(17)

where R^{3a} is R^3 that is other than H, L is a leaving group such as halide (especially bromide or iodide), mesylate, tosylate or triflate, Prt is a protecting group such as p-methoxybenzyl, and Ar^1 and Ar^2 have the same meanings as before. The alkylation takes place in an aprotic solvent (such as THF) in the presence of strong base (such as lithium bis(trimethylsilyl)amide) at reduced temperature (e.g. -78°C). When Prt is p-methoxybenzyl, cleavage may be effected by treatment with acid, e.g. trifluoroacetic acid at ambient temperature in an inert solvent such as dichloromethane.

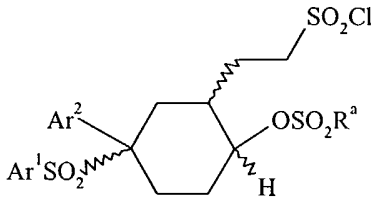
A preferred route to compounds (17) involves cyclisation of sulfonamides (18):



(18)

where R^a, Ar^1, Ar^2 and Prt have the same meanings as before. The cyclisation may be carried out by treatment with strong base such as sodium hydride in an aprotic solvent such as DMF at moderately elevated temperature (e.g. about 75°C).

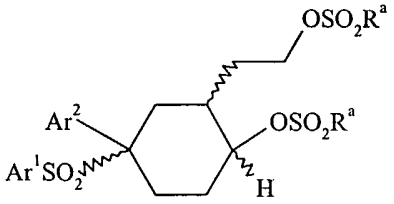
Compounds (18) are obtainable by reaction of sulfonyl chlorides (19) with $PrtNH_2$:



(19)

where R^a, Ar^1, Ar^2 and Prt have the same meanings as before. The reaction may be carried out in an inert solvent such as dichloromethane at about 0°C using an excess of the amine.

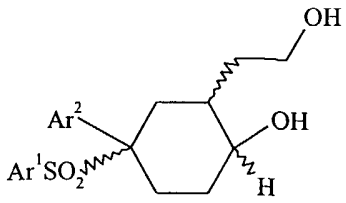
Sulfonyl chlorides (19) are obtainable by reaction of sulfonates (20) with thiourea and treatment of the resulting adducts with chlorine:



(20)

where R^a, Ar^1 and Ar^2 have the same meanings as before. The reaction with thiourea may be carried out in refluxing ethanol, and the resulting adduct may be treated with gaseous chlorine in aqueous acetic acid solution.

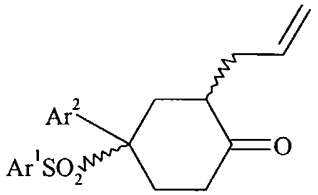
Sulfonates (20) are obtainable by treatment of diols (21) with R^aSO_2Cl or $(R^aSO_2)_2O$:



(21)

where R^a, Ar^1 and Ar^2 have the same meanings as before. The reaction is conveniently carried out in dichloromethane at about -10°C in the presence of a base such as triethylamine.

Diols (21) are obtainable by sequential treatment of ketones (22) with ozone and sodium borohydride:



(22)

where Ar^1 and Ar^2 have the same meanings as before. The ozonolysis is typically carried out at about -78°C in a dichloromethane/methanol mixture, then sodium borohydride added with warming to ambient temperature.

Ketones (21) are obtained by alkylation of cyclohexanones (5) with allyl bromide or allyl iodide under similar conditions to the conversion of (5) to (4).

Detailed procedures for the above-described routes are provided in the Examples section.

It will be apparent to those skilled in the art that individual compounds of formula I prepared by the above routes may be converted into other compounds in accordance with formula I by means of well known synthetic techniques such as alkylation, esterification, amide coupling, hydrolysis, coupling mediated by organometallic species, oxidation and reduction. Such techniques may likewise be carried out on precursors of the compounds of formula I. For example, substituents on the aromatic groups Ar^1 or Ar^2 may be added or interconverted by means of standard synthetic processes carried out on the compounds of formula I or their precursors. For example, a chlorine or bromine atom on Ar^1 or Ar^2 may be replaced by vinyl by treatment with vinyltributyltin in the presence of tri-t-butylphosphine, cesium fluoride

and tris(dibenzylideneacetone)dipalladium(0). Ozonolysis of the vinyl group provides the corresponding formyl derivative, which may be transformed in a variety of ways, including oxidation to the corresponding acid, reduction to the corresponding benzyl alcohol, and conversion to the corresponding nitrile by treatment with hydroxylamine then triphenylphosphine and carbon tetrachloride. Procedures for transformations of this type are disclosed in WO 2004/031139. Similarly, alkenyl groups represented by R^2, R^3 or R^4 (such as allyl) may be subjected to ozonolysis to provide formyl derivatives, which in turn may be converted to other functional derivatives by standard routes, such as oxidation to carboxylic acids, reduction to primary alcohols, and conversion to nitriles as described above. The aforesaid alcohols may also be converted to the corresponding sulfonate esters and subjected to nucleophilic displacement by a variety of nucleophiles. The aforesaid nitriles may be hydrated to the corresponding primary amides by standard routes.

As a further example of this protocol, compounds of formula I (or their precursors) in which one or both of R^1 and R^4 represents H can be converted to the corresponding alkyl derivatives by standard alkylation methods. Similarly, compounds of formula I in which R^2 and R^4 represent vinyl or allyl may be converted to the corresponding compounds in which R^2 and R^4 complete a heterocyclic ring by treatment with Grubb's catalyst.

Where they are not themselves commercially available, the starting materials and reagents employed in the above-described synthetic schemes may be obtained by the application of standard techniques of organic synthesis to commercially available materials.

It will be appreciated that many of the above-described synthetic schemes may give rise to mixtures of stereoisomers. Such mixtures may be separated by conventional means such as fractional crystallisation and preparative chromatography.

Certain compounds according to the invention may exist as optical isomers due to the presence of one or more chiral centres or because of the overall asymmetry of the molecule. Such 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 crystallisation 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.

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, 3rd ed., 1999. The protecting groups may be removed at a convenient subsequent stage using methods known from the art. As an example of this strategy, prior to the cyclisation of compounds of formula (12) wherein X is NH, it is advantageous to protect the sulphonamide nitrogen by alkylation with allyl bromide. The allyl group may be removed subsequently by reduction with diisobutylaluminium hydride in toluene at ambient temperature in the presence of $[Ph_2PCH_2CH_2CH_2PPh_2]NiCl_2$.

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 disclosed in WO 03/093252.

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

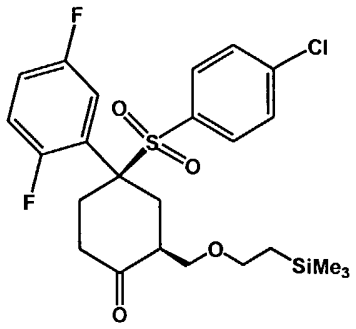
The Examples of the present invention all had an ED_{50} of less than 0.5μM, typically less than 50nM, in most cases less than 10nM, and in preferred cases less than 1.0nM, in at least one of the above assays.

The following examples illustrate the present invention. For convenience, compounds are typically depicted as being in accordance with formula IA regardless of their state of enantomeric homogeneity. Homochiral compounds are indicated by means of the R and S configurational descriptors.

EXAMPLES

Intermediate 1

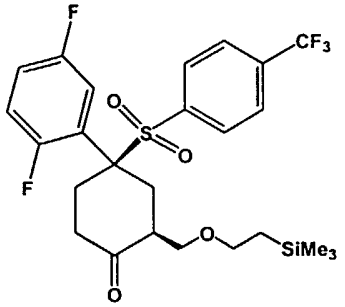
4-[(4-Chlorophenyl)sulfonyl]-4-(2,5-difluorophenyl)-2-[2-(trimethylsilyl)ethoxymethyl]cyclohexanone



4-[(4-Chlorophenyl)sulfonyl]-4-(2,5-difluorophenyl)cyclohexanone (WO 02/081435) (2.0 g, 5.2 mmol) in dry tetrahydrofuran (10 mL) was added dropwise to a cooled solution of 0.5 M lithium hexamethyldisilazide in tetrahydrofuran (11.4 mL) at –78°C. The mixture was stirred at this temperature for 2 hours before adding 2-(trimethylsilyl)ethoxymethyl chloride (1.4 mL, 7.8 mmol) and the solution allowed to warm to rt. over 16 hours. The reaction mixture was diluted with ethyl acetate (10 mL), washed with water (10 mL), and the organic phase separated, dried ($MgSO_4$) and evaporated to dryness. The product was purified on silica eluting with [9:1] hexane-ethyl acetate to yield 1.2 g of the title compound. ^1H NMR $CDCl_3$ 7.38 (4H, s), 7.24-7.16 (1H, m), 7.12-7.06 (1H, m), 6.97-6.87 (1H, m), 3.66 (1H, dd, J = 9.7 and 3.0 Hz), 3.51-3.45 (3H, m), 3.17-3.15 (1H, m), 3.05-2.98 (1H, m), 2.56-2.49 (2H, m), 2.41-2.35 (2H, m), 2.23-2.17 (1H, m), 0.91-0.87 (2H, m) and 0.03 (9H, s).

Intermediate 2

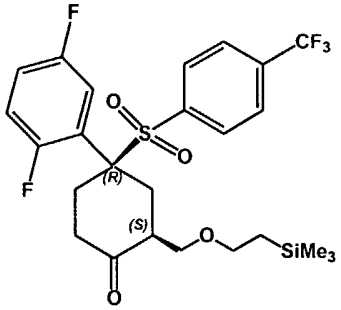
4-[(4-Trifluoromethylphenyl)sulfonyl]-4-(2,5-difluorophenyl)-2-[2-(trimethylsilyl)ethoxymethyl]cyclohexanone



Prepared as for Intermediate 1, starting from 4-[(4-trifluoromethylphenyl)sulfonyl]-4-(2,5-difluorophenyl)cyclohexanone (WO 02/081435), and obtained as a solid. 16.3 g. ^{1}H NMR $CDCl_3$ 7.69-7.59 (4H, m), 7.24-7.18 (1H, m), 7.12-7.06 (1H, m), 6.93-6.86 (1H, m), 3.67 (1H, dd, J = 9.7 and 2.9 Hz), 3.58-3.47 (3H, m), 3.20-3.16 (1H, m), 3.04-2.98 (1H, m), 2.57-2.51 (2H, m), 2.41-2.38 (2H, m), 2.24-2.16 (1H, m), 0.91-0.87 (2H, m) and 0.03 (9H, s).

Intermediate 3

(R,S)- 4-[(4-Trifluoromethylphenyl)sulfonyl]-4-(2,5-difluorophenyl)-2-[2-(trimethylsilyl)ethoxymethyl]cyclohexanone

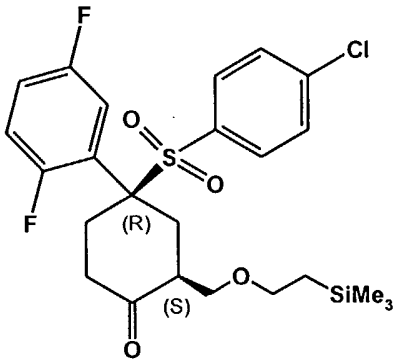


[(S-(R*, R*)]-(-)-Bis(α-methylbenzyl)amine (10 g, 44.4 mmol) and anhydrous lithium chloride (1.87 g, 44.5 mmol) were stirred in tetrahydrofuran (250 mL) under nitrogen gas, then cooled to –78°C and treated slowly with butyllithium (1.6 mol solution in hexanes, 25.9 mL). The reaction mixture was allowed to warm up to 0°C and stirred for 30min. then re-cooled to an internal temperature of –100°C, stirring for 1h. A solution of 4-[(4-trifluoromethylphenyl)sulfonyl]-4-(2,5-difluorophenyl)cyclohexanone (WO 02/081435) (12.5 g, 29.9 mmol) in tetrahydrofuran (50 mL), cooled to –78°C, was added slowly, maintaining the internal temperature at –100°C. The mixture was stirred at –100°C for 2h., then 2-(trimethylsilyl)ethoxymethyl chloride (7.9 mL, 44.7 mmol) was added, the resulting mixture warmed to –78°C, and allowed to warm up slowly overnight to –12°C. The reaction mixture was quenched with a 1M solution of citric acid then extracted with ethyl acetate. The organic extracts were washed with a 1M citric acid, 5% sodium bicarbonate solution, dried ($MgSO_4$), filtered and the solvent was removed. The resulting oil was purified by column chromatography on silica gel eluting with 2 to 10 % ethyl acetate : *iso*hexane to give the title compound as a clear oil. Yield 5g (30%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 (2H, d, *J* 8.4 Hz), 7.60 (2H, d, *J* 8.4 Hz), 7.23-7.18 (1H, m), 7.15-7.08 (1H, m), 6.96-6.86 (1H, m), 3.70-3.64 (1H, m), 3.53-3.48 (3H, m), 3.22-3.16 (1H, m), 3.08-2.98 (1H, m), 2.61-2.51 (2H, m), 2.43-2.36 (2H, m), 2.25-2.14 (1H, m), 0.94-0.83 (2H, m), 0.00 (9H, s). Chiral purity determined by chiral HPLC.

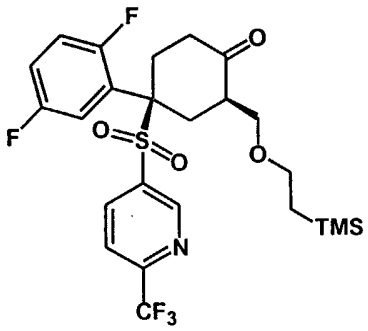
Intermediate 4 (R, S)

(R,S)-4-[(4-Chlorophenyl)sulfonyl]-4-(2,5-difluorophenyl)-2-[2-(trimethylsilyl)ethoxymethyl]cyclohexanone



Prepared in the same manner as Intermediate 3 using the 4-[(4-chlorophenyl)sulfonyl]-4-(2,5-difluorophenyl)cyclohexanone as starting material. NMR data as for Intermediate 1.

Intermediate 5



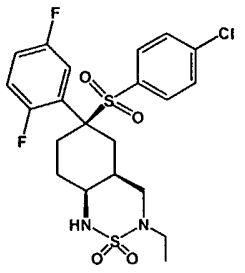
4-(2,5-Difluorophenyl)-4-(6-trifluoromethylpyridin-3-yl)cyclohexanone (WO 2004/031139) was converted to the desired product by the procedure described for Intermediate 1.

^{1}H NMR (360 MHz, $CDCl_3$) δ 0.01 (9H, s), 0.90 (2H, t, J = 7.3 Hz), 2.14-2.25 (1H, m), 2.40-2.59 (4H, m), 3.01 (1H, m), 3.14-3.19 (1H, m), 3.48-3.53 (3H, m), 3.65-3.68

(1H, m), 6.87-6.95 (1H, m), 7.13-7.18 (1H, m), 7.23-7.28 (1H, m), 7.75 (1H, d, J = 8.2 Hz), 7.95 (1H, d, J = 6.4 Hz), 8.66 (1H, s).

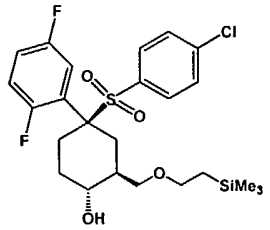
Example 1

(4a*SR*,6*RS*,8a*SR*)-6-[(4-chlorophenyl)sulfonyl]-6-(2,5-difluorophenyl)-3-ethyloctahydro-1*H*-2,1,3-benzothiadiazine 2,2-dioxide



Step 1

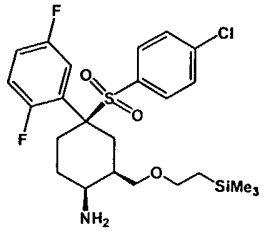
4-[(4-Chlorophenyl)sulfonyl]-4-(2,5-difluorophenyl)-2-[2-(trimethylsilyl)ethoxymethyl]cyclohexanol (*trans* isomer)



Intermediate 1 (23 g, 44.7 mmol) in isopropanol (2 L) was treated with $NaBH_4$ (6.8 g, 179 mmol) at –40°C and stirred whilst allowing to warm to rt. over 16 hours. The reaction was quenched with 8% aqueous citric acid (1 L), diluted with ethyl acetate (1 L), then the organic phase was separated, dried ($MgSO_4$) and evaporated to dryness. The *trans* product was purified on silica eluting with hexane-ethyl acetate mixtures. Yield 23.3 g. ^1H NMR $CDCl_3$ 7.39-7.31 (4H, m), 7.06-7.02 (2H, m), 6.86-6.83 (1H, m), 3.62-3.46 (5H, m), 2.90-2.42 (2H, m), 2.18-2.03 (2H, m), 1.91-1.80 (1H, m), 1.71-1.52 (1H, m), 1.24-1.20 (1H, m), 0.93-0.89 (2H, m), and 0.03 (9H, s).

Step 2

4-[(4-Chlorophenyl)sulfonyl]-4-(2, 5-difluorophenyl)-2-[2-(trimethylsilyl)ethoxymethyl]cyclohexylamine



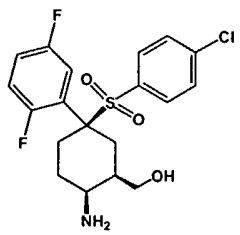
The alcohol from Step 1 (11.7 g, 22.7 mmol) in dichloromethane (100 mL) was treated with triethylamine (6.3 mL, 45 mmol) at 0°C and stirred whilst methanesulphonyl chloride (2.2 mL, 27 mmol) was added. The reaction mixture was allowed to warm to r.t. over 1 hour, washed with water (20 mL), 10% aqueous citric acid (20 mL) and saturated aqueous sodium hydrogen carbonate (50 mL), then dried ($MgSO_4$) and evaporated to dryness. The residue was filtered through silica eluting with 20% ethyl acetate in hexanes to give the mesylate (10 g).

This solid in dimethylformamide (50 mL) was treated with sodium azide (1.4 g, 29 mmol) and heated to 95°C for 8 hrs. The mixture was treated with water (80 mL) and extracted with ethyl acetate (2 x 50 mL). The combined organics were washed with brine, dried ($MgSO_4$) and evaporated to dryness. The residue (8 g, 14.7 mmol), in tetrahydrofuran (320 mL) and water (32 mL), was treated with triphenylphosphine (4.7 g, 18 mmol) at room temperature for 15 mins and then the mixture was heated at reflux for 4 hrs. The mixture was allowed to cool to rt. and then passed through SCX Varian Bond Elut™ cartridge. The basic fraction was evaporated to give the primary amine (7.2 g). ^{1}H NMR $CDCl_3$ 7.39-7.31 (4H, m), 7.09-6.96 (2H, m), 6.85-6.80 (1H, m), 3.48-3.15 (5H, m), 2.93-2.29 (4H, m), 1.74-1.19 (3H, m), 0.93-0.89 (2H, m) and 0.03 (9H, s).

MS MH+ 516(518).

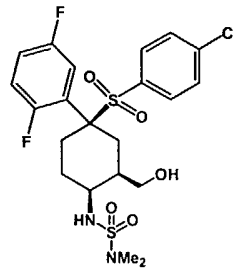
Step 3

4-[(4-Chlorophenyl)sulfonyl]-4-(2, 5-difluorophenyl)-2-(hydroxymethyl)cyclohexylamine



The product of Step 2 (5.5 g, 10.6 mmol) in dichloromethane (40 mL) was treated with boron trifluoride etherate (4 mL) and after 2 hours the mixture was cooled to 0°C and stirred during the addition of sodium hydroxide (2.5M, 20mL). The layers were separated and the organics were washed with brine, dried ($MgSO_4$) and evaporated to give an oil which was azeotroped with heptane to give the amino alcohol as a white solid (5.8g) MS ES+ 416, 418.

Step 4



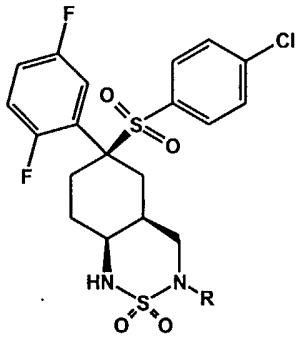
The product of Step 3 (5.3g, 10 mmol) in dichloromethane (40 mL) and dimethyl acetamide (40mL) was treated with triethylamine (3.4 mL, 24 mmol) and then with N,N-dimethylsulphamoyl chloride (1.6 mL, 14.5 mmol). After 72 hours the mixture was quenched by the addition of water (200 mL). The mixture was extracted with dichloromethane (2 x 100 mL) and the organics were washed with brine, dried ($MgSO_4$) and evaporated to give an oil which was filtered through silica to give the sulphamide (4 g). ^1H NMR $CDCl_3$ 7.38-7.31 (4H, m), 7.07-7.04 (2H, m), 6.85-6.79 (1H, m), 5.24 (1H, d, J = 11 Hz), 3.79-3.65 (2H, m), 3.58-3.50 (1H, m), 2.98-2.92 (1H, m), 2.83 (6H, s), 2.58-2.20 (3H, m), 2.09-1.98 (2H, m), and 1.56-1.52 (1H, m).

Step 5

The product of Step 4 (0.1 g, 0.2 mmol) in dichloromethane (3 mL) was treated with Dess-Martin periodinane (89 mg, 0.22 mmol) and after 1 hour the mixture was quenched by the addition of 10% aqueous sodium metabisulfite (2 mL). After stirring for 10 mins, the layers were separated, the aqueous layer was extracted with dichloromethane (2 x 10mL) and the combined organics were washed with saturated aqueous sodium bicarbonate, brine, dried ($MgSO_4$) and evaporated, azeotroping with heptane, to give the solid aldehyde (0.1 g). The crude aldehyde was dissolved in ethanol (3 mL) and treated with 2M ethylamine in ethanol (10 eq, 1 mL), and oven dried alumina (100 mg) was added. The mixture was stirred over 16 hours then filtered. Sodium borohydride (36 mg, 1 mmol) was added and after one hour the

solvent was removed *in vacuo*. The residue was partitioned between ethyl acetate (5 mL) and saturated aqueous sodium bicarbonate (5 mL). The organics were dried (Na_2SO_4) and evaporated, and the residue dissolved in tetrahydrofuran (5 mL) and refluxed overnight. The solvent was removed *in vacuo* and the residue was chromatographed on silica gel eluting with 25% ethyl acetate in hexane to give the desired cyclic sulphamide (50 mg). ^{1}H NMR $CDCl_3$ 7.39-7.30 (4H, m), 7.11-7.06 (2H, m), 6.90-6.83 (1H, m), 4.44 (1H, d, J = 11 Hz), 3.86-3.83 (1H, m), 3.46 (1H, dd, J = 12.5 and 3.5 Hz), 3.40 (1H, m), 3.00-2.93 (2H, m), 2.72-2.67 (1H, m), 2.62-2.45 (2H, m), 2.17-2.11 (1H, m), 1.96-1.92 (1H, m), 1.68-1.55 (2H, m) and 1.33-1.30 (3H, m). MS ES$^-$ 503, 505.

The following were prepared by the same procedure, substituting the appropriate amine for ethylamine in Step 5:

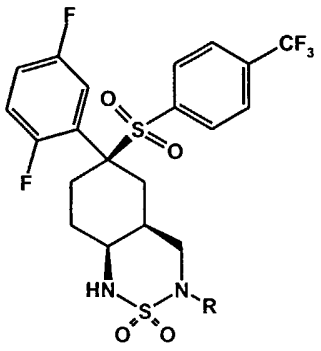


Example	R	MS (ES-)
2	n-propyl	517, 519
3	n-butyl	531, 533
4	cyclopropyl	515, 517
5	cyclopentyl	543, 545
6	sec-butyl	531, 533
7	cyclopropylmethyl	529, 531
8	t-butyl	531.533
9	2,2,2-trifluoroethyl	557, 559
10	2-hydroxyethyl	519, 521
11	methyl	489, 491
12	isopropyl	517, 519

13	cyclobutyl	529, 531
14	2-fluoroethyl	521, 523

Examples 15-25

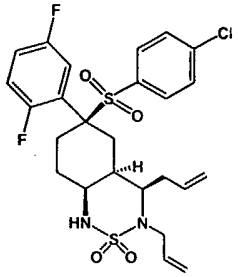
Following the procedure of Example 1, starting from Intermediate 2 and using the appropriate amine in Step 4, there were prepared:



Example	R	MS (ES-)
15	ethyl	537
16	methyl	523
17	i-propyl	551
18	cyclopropyl	549
19	cyclobutyl	563
20	t-butyl	565
21	2,2,2-trifluoroethyl	591
22	2-hydroxyethyl	553
23	2-fluoroethyl	555
24	2-cyanoethyl	562
25	2-methoxyethyl	567

Example 26

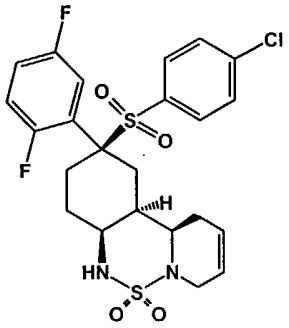
(4*RS*,4a*RS*,6*RS*,8a*SR*)-3,4-diallyl-6-[(4-chlorophenyl)sulfonyl]-6-(2,5-difluorophenyl)octahydro-1*H*-2,1,3-benzothiadiazine 2,2-dioxide



The product of Example 1 Step 4 (0.25 g, 0.5 mmol) in dichloromethane (10 mL) was treated with Dess-Martin periodinane (243 mg, 0.57 mmol) and after 1 hour the mixture was quenched with 10% aqueous sodium metabisulfite (5 mL). After stirring for 10 minutes the layers were separated, the aqueous layer extracted with dichloromethane (2 x 25 mL) and the combined organics were washed with saturated aqueous sodium bicarbonate, brine, dried ($MgSO_4$) and evaporated, azeotroping with heptane to give the aldehyde as a solid (0.25 g). The crude aldehyde was dissolved in acetonitrile (5 mL), and allylamine (75 μL, 1 mmol) and alumina (100 mg) were added. After 2 hours the mixture was filtered, evaporated, and the residue dissolved in dry tetrahydrofuran (8 mL). The solution was cooled to 0°C and then 1M allyl magnesium bromide in tetrahydrofuran (1 mL, 1 mmol) was added. After 16 hours the mixture was treated with acetic acid (1 drop), and then washed with sat. aqueous sodium hydrogen carbonate (10mL). The aqueous layer was extracted with ethyl acetate and the combined organics were washed with brine, dried ($MgSO_4$) and concentrated. The residue was then dissolved in tetrahydrofuran and refluxed for 16 hours to effect cyclisation. The solvent was removed in vacuo and the product was purified by column chromatography on silica eluting with 15% ethyl acetate in hexanes to give the desired product (195 mg). ^{1}H NMR $CDCl_3$ 7.39 (2H, d, J = 9 Hz), 7.30 (2H, d, J = 9 Hz), 7.11-6.92 (2H, m), 6.90-6.83 (1H, m), 5.85-5.78 (1H, m), 5.59-5.49 (1H, m), 5.34-5.31 (2H, m), 5.02-4.92 (2H, m), 4.53 (1H, d, J = 11 Hz), 4.26-4.19 (1H, m), 3.99-3.96 (1H, m), 3.58-3.52 (1H, m), 3.16-3.14 (1H, m), 2.72-2.18 (6H, m), 1.96-1.92 (1H, m) and 1.68-1.55 (1H, m). MS ES^- 555, 557.

Example 27

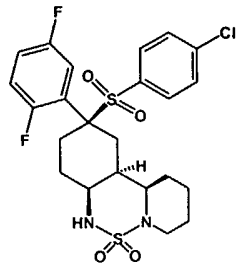
(2*RS*,4a*SR*,11a*RS*,11b*RS*)-2-[(4-chlorophenyl)sulfonyl]-2-(2,5-difluorophenyl)-1,2,3,4,4a,5,8,11,11a,11b-decahydropyrido[1,2-*c*][2,1,3]benzothiadiazine 6,6-dioxide



The product of Example 26 (190 mg, 0.34 mmol) in dichloromethane (5 mL) was treated with Grubb's catalyst (2nd generation) (1 mg). The mixture was stirred for 24 h, then evaporated and the residue was purified by column chromatography on silica eluting with 20% ethyl acetate in hexanes to give Example 27 (150 mg). ^{1}H NMR $CDCl_3$ 7.39 (2H, d, J = 9 Hz), 7.31 (2H, d, J = 9 Hz), 7.11-7.01 (2H, m), 6.90-6.83 (1H, m), 5.83-5.79 (1H, m), 5.61-5.55 (1H, m), 4.89 (1H, d, J = 11 Hz), 4.32-4.28 (1H, m), 4.08-4.05 (1H, m), 3.71-3.64 (1H, m), 3.49-3.46 (1H, m), 2.78-2.25 (5H, m), 2.06-2.01 (2H, m), 1.82-1.75 (1H, m) and 1.50-1.45 (1H, m). MS ES$^-$ 527, 529.

Example 28

(2*RS*,4a*SR*,11a*RS*,11b*RS*)-2-[(4-chlorophenyl)sulfonyl]-2-(2,5-difluorophenyl)dodecahydropyrido[1,2-*c*][2,1,3]benzothiadiazine 6,6-dioxide

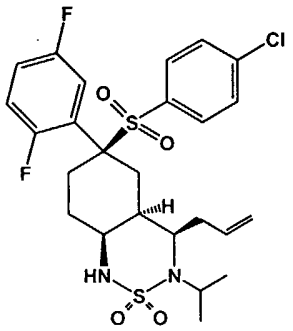


The product from Example 27 (16 mg, 0.03 mmol) in ethyl acetate (2 mL) was treated with 10% palladium on carbon [1 mg] and hydrogen gas (1 atm.). The mixture was stirred for 2 hrs and then filtered and evaporated to give Example 28 (15 mg). ^{1}H NMR $CDCl_3$ 7.39 (2H, d, J = 9 Hz), 7.32 (2H, d, J = 9 Hz), 7.11-7.01 (2H, m), 6.90-

6.83 (1H, m), 5.03 (1H, d, J = 11 Hz), 4.02-3.98 (2H, m), 3.20-3.15 (1H, m), 2.95-2.88 (1H, m), 2.72-2.18 (5H, m), 2.03-1.95 (2H, m), 1.90-1.81 (2H, m) and 1.65-1.49 (4H, m). MS ES$^-$ 529, 531.

Example 29

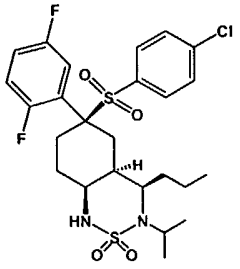
(4*RS*,4a*RS*,6*RS*,8a*SR*)-4-allyl-6-[(4-chlorophenyl)sulfonyl]-6-(2,5-difluorophenyl)-3-isopropyloctahydro-1*H*-2,1,3-benzothiadiazine 2,2-dioxide



Prepared by the procedure of Example 26, substituting isopropylamine for allylamine. ^{1}H NMR $CDCl_3$ 7.39 (2H, d, J = 8 Hz), 7.30 (2H, d, J = 8 Hz), 7.10-7.01 (2H, m), 6.89-6.85 (1H, m), 5.59-5.49 (1H, m), 5.02-4.90 (2H, m), 4.36 (1H, d, J = 11 Hz), 4.16-4.13 (1H, m), 3.97-3.95 (1H, m), 3.14-3.12 (1H, m), 2.77-2.70 (1H, m), 2.56-2.15 (5H, m), 1.96-1.92 (1H, m), 1.68-1.55 (2H, m) and 1.34-1.24 (6H, m). MS ES$^-$ 557, 559.

Example 30

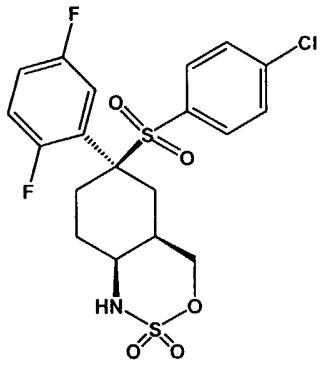
(4*RS*,4a*RS*,6*RS*,8a*SR*)-6-[(4-chlorophenyl)sulfonyl]-6-(2,5-difluorophenyl)-3-isopropyl-4-propyloctahydro-1*H*-2,1,3-benzothiadiazine 2,2-dioxide



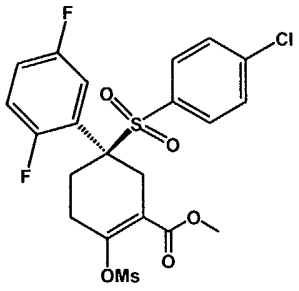
The product of Example 29 (16 mg, 0.03 mmol) was dissolved in ethyl acetate (2 mL) and treated with 10% palladium on carbon (1 mg). The mixture was stirred for 2 hrs under an atmosphere of hydrogen and then filtered and evaporated to give Example 30 (15 mg). ^{1}H NMR $CDCl_3$ 7.39 (2H, d, J = 8 Hz), 7.30 (2H, d, J = 8 Hz), 7.12 -7.05 (2H, m), 6.89-6.85 (1H, m), 4.30 (1H, d, J = 11 Hz), 4.15-4.10 (1H, m), 3.97-3.95 (1H. m), 3.04-3.02 (1H, m), 2.56-2.15 (3H, m), 1.98-1.92 (2H, m), 1.72-1.58 (4H, m), 1.34-1.24 (6H, m), 1.21-1.10 (2H, m) and 0.94-0.86 (3H, m). MS ES$^-$ 559, 561.

Example 31

(4a*RS*,6*RS*,8a*SR*)-6-[(4-chlorophenyl)sulfonyl]-6-(2,5-difluorophenyl)octahydro-3,2,1-benzoxathiazine 2,2-dioxide

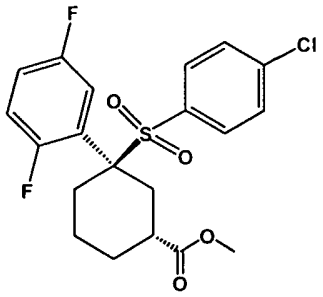


Step 1



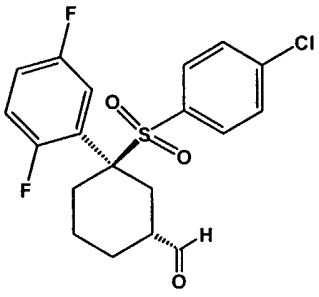
The enol from Example 1 of WO 02/081435 (18.4g, 420 mmol) in dichloromethane (100 mL) at 0°C was treated with triethylamine (8.7 mL, 620 mmol) and after 0.25 h. with methanesulphonyl chloride (4.0 mL, 0.530 mmol). After stirring for 1h. at r.t., water was added and the organics extracted into dichloromethane (3x). The organic extract was dried ($MgSO_4$), solvent removed *in vacuo* and the crude product purified by silica gel chromatography eluting with 30% ethyl acetate/ hexane to give product as a white foam (19.5g, 90%).

Step 2:



The mesylate from Step 1 (200 mg, 0.35 mmol) was dissolved in methanol / dichloromethane (10 mL) (5:1) and cooled to –10 °C. Nickel chloride hexahydrate (82 mg, 0.35 mmol) was added, followed by sodium borohydride (67 mg, 1.8 mmol) in one portion. After stirring at –10 °C for 2h the reaction was filtered through Celite™ and washed with methanol. Solvent was removed *in vacuo* and the residue dissolved in ethyl acetate, washing with 2M hydrochloric acid (2x), water (2x) and brine (2x). The organic extract was dried ($MgSO_4$) and solvent removed *in vacuo*. The crude product was purified by silica gel chromatography eluting with 20 % ethyl acetate/ hexane to give desired product (31 mg, 21%). ^1H NMR (400 MHz $CDCl_3$) δ 1.63-1.65 (1H, m), 1.84-1.89 (2H, m), 2.00-2.18 (2H, m), 2.50-2.56 (1H, m), 2.70 (1H, m), 2.93-2.95 (1H, m), 3.22-3.24 (1H, m), 3.55 (3H, s), 6.73-6.80 (1H, m, Ar-H), 6.97-7.01 (1H, m, Ar-H), 7.07-7.12 (1H, m, Ar-H), 7.28-7.37 (4H, m, Ar-H).

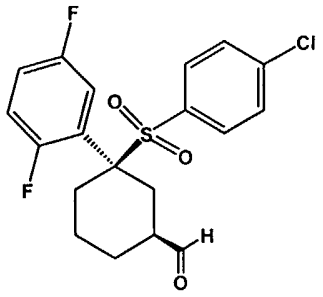
Step 3:



The foregoing ester (3.0 g, 7 mmol) was dissolved in toluene (50 mL) and cooled to -78 °C. Diisobutylaluminium hydride (1.0 M in toluene) (8.7 mmol, 8.7 mL) was added over a 0.5h period, the reaction stirred at –78 °C for 1.5 h, then quenched with methanol (0.5 mL), 2N sodium hydroxide (1 mL) and water (2 mL). The reaction mixture was warmed to r.t. and filtered through Celite™, washing with ethyl acetate (500 mL). The organic extracts were washed with water (2x), brine (2x) then dried ($MgSO_4$) and the solvent was removed *in vacuo*. The crude product was purified by silica gel chromatography eluting with 10 % ethyl acetate/ hexane and the aldehyde

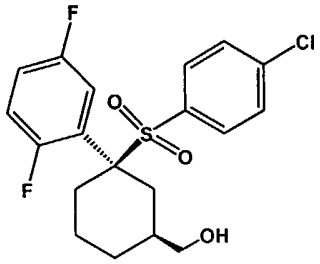
obtained as a white solid (1.86g, 67%). ^{1}H NMR (400 MHz $CDCl_3$) δ 1.62-1.74 (2H, m), 1.80 (1H, m), 2.01-2.08 (1H, m), 2.16-2.22 (1H, m), 2.61-2.75 (2H, m), 2.94-2.99 (1H, m), 3.06-3.12 (1H, m), 6.77-6.83 (1H, m, Ar-H), 6.98-7.06 (2H, m, Ar-H), 7.29-7.38 (4H, m, Ar-H), 9.57 (1H, s, CHO).

Step 4:



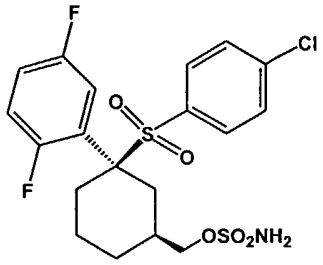
The aldehyde from Step 3 (1.86g, 4.3 mmol) in dichloromethane/ methanol (45 mL) (1:2) was treated with potassium carbonate (6.1 g, 43 mmol) and the mixture was stirred at rt. for 2h., diluted with dichloromethane (50 mL) and washed with water (3x). The organic extracts were dried ($MgSO_4$); and solvent removed *in vacuo* to give epimerised aldehyde as a white crystalline solid (1.8 g, 97%). ^{1}H NMR (400 MHz $CDCl_3$) δ 1.27-1.39 (2H, m), 1.96-2.07 (4H, m), 2.16-2.19 (1H, m), 2.71-3.1 (2H, m), 6.83-6.90 (1H, m, Ar-H), 7.03-7.09 (2H, m, Ar-H), 7.35-7.40 (4H, m, Ar-H), 9.61 (1H, s, CHO).

Step 5:



The aldehyde (1.0 g, 2.5 mmol) was suspended in methanol (20 mL) and cooled to 0 °C. Sodium borohydride (48 mg, 1.25 mmol) was added in one portion and reaction stirred for 1h. The solvent was removed *in vacuo* and the crude product was purified by silica gel chromatography eluting with 20% ethyl acetate/ hexane. The alcohol was obtained as a colourless oil (0.9 g, 90%). ^{1}H NMR (400 MHz $CDCl_3$) δ 1.3-1.5 (2H, m), 1.70 (1H, m), 1.83-1.90 (2H, m), 2.07 (1H, m), 2.60-3.0 (2H, m), 3.50-3.53 (2H, m), 6.80-6.87 (1H, m, Ar-H), 7.01-7.11 (2H, m, Ar-H), 7.36-7.39 (4H, m, Ar-H).

Step 6:



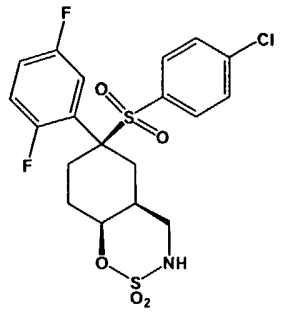
The alcohol (150 mg, 0.13 mmol) was dissolved in *N,N*-dimethylformamide (3 mL) and sulphamoyl chloride (150 mg, 0.39 mmol) was added. The reaction was stirred at rt. for 4h then dissolved in ethyl acetate (50 mL) and washed with water (3x). The organic layer was dried ($MgSO_4$) and solvent removed *in vacuo*. The residue was purified by silica gel chromatography eluting with 40% ethyl acetate/ hexane to give a white solid (90 mg, 50%). ^{1}H NMR (400 MHz $CDCl_3$) δ 1.19-1.27 (2H, m), 1.70-1.72 (2H, m), 1.86-1.97 (2H, m), 2.04 (1H, s), 2.5-3.0 (2H, m), 4.03-4.1 (2H, m), 5.0 (2H, s, NH_2), 6.85 (1H, s, Ar-H), 7.02-7.08 (2H, m, Ar-H), 7.35-7.39 (4H, m, Ar-H). MS ES$^-$ 478.

Step 7

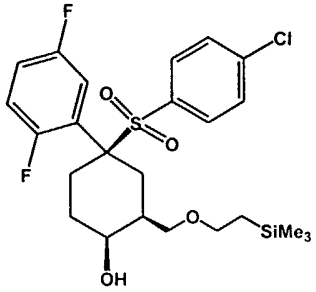
The sulphamate from Step 6 (90 mg, 0.19 mmol) was dissolved in dichloromethane (3 mL) and magnesium oxide (17 mg, 0.43 mmol) added, followed by iodobenzene diacetate (7 mg, 0.2 mmol) and rhodium (II) acetate dimer (1 mg). The mixture was heated at 40°C for 0.5 h, solvent was removed *in vacuo* and the crude product purified by silica gel chromatography eluting with 40% ethyl acetate/ hexane, followed by preparative HPLC to give a 9:1 mix of diastereomers, the major component being the title compound (7 mg, 8%). ^{1}H NMR (500 MHz $CDCl_3$) δ 1.51-1.53 (1H, m), 1.71-1.74 (1H, m), 1.93-1.96 (1H, m), 2.28-2.30 (1H, m), 2.55-2.65 (2H, m), 2.72-2.76 (1H, m), 3.92 (1H, s), 4.30-4.32 (1H, d, J = 11.6 Hz), 4.64-4.66 (1H, d, J = 8.8 Hz, NH), 4.99-5.01 (1H, d, J = 10.7 Hz), 6.84-6.89 (1H, m, Ar-H), 7.07-7.12 (2H, m, Ar-H), 7.32-7.41 (4H, m, Ar-H). MS ES$^-$ 476/478.

Example 32

(4a*SR*,6*RS*,8a*SR*)-6-[(4-chlorophenyl)sulfonyl]-6-(2,5-difluorophenyl)octahydro-1,2,3-benzoxathiazine 2,2-dioxide



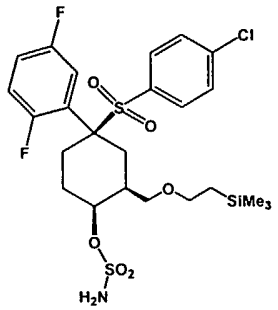
Step 1



Intermediate 1 (14.8 g, 28.7 mmol) in dry THF (500 mL) cooled to –78°C was treated dropwise with L-Selectride (1M in THF, 34.5mL, 34.5 mmol). The mixture was stirred at this temperature for 1.5h and then quenched with hydrochloric acid (2M, 50 mL), allowed to warm to room temperature and concentrated to half volume. The residue was diluted with water and extracted with ethyl acetate (3 x 100 mL). The organics were washed with brine, dried ($MgSO_4$), filtered and evaporated. The crude product was purified by flash chromatography (5:1 *iso*hexane/ethyl acetate to 2:1) to give a white solid (12.1 g).

^{1}H NMR $CDCl_3$ -0.03 (9H, s), 0.98-0.82 (4H, m), 1.45-1.29 (4H, m), 1.91-1.84 (1H, brs), 2.61-2.57 (2H, m), 3.18 (1H, br), 3.55-3.41 (3H, m), 6.91-6.80 (1H, m), 7.14-6.98 (2H, m), 7.35 (4H, s).

Step 2

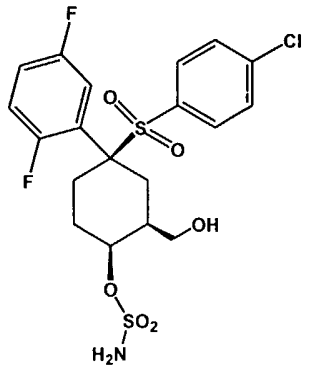


The product from Step 1 (980 mg, 1.9 mmol) was dissolved in *N,N*-dimethylacetamide (15 mL) and sulphamoyl chloride (875 mg, 7.6 mmol) was added in one portion. The

reaction was heated at 50°C overnight, allowed to cool and diluted with water (150 mL). After extraction with ethyl acetate (3 x 50 mL), the organics were washed with brine, dried ($MgSO_4$), filtered and evaporated. The crude product was purified by flash chromatography (5:1 *iso*hexane/ethyl acetate to 2:1) to give a white foam (720 mg).

MS MH- 594

Step 3



Prepared from the product of Step 2 by the procedure of Example 1 Step 3.

MS ES^- 494

Step 4

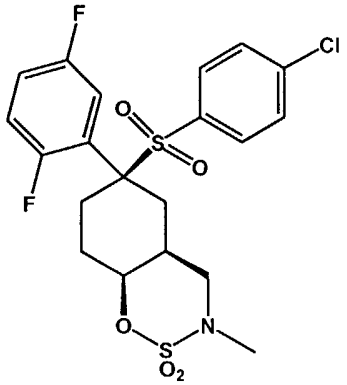
The alcohol from Step 3 (900 mg, 1.81 mmol) in dry pyridine (5 mL) was treated with *N,N*-dimethylaminopyridine (110 mg, 0.6 mmol) and *p*-toluenesulfonyl chloride (1.0g, 5.4 mmol) and the reaction stirred overnight at 40°C. The mixture was diluted with water (50 mL) and extracted with ethyl acetate (3 x 50 mL). The organics were washed with 2M hydrochloric acid (x2), water, brine, dried ($MgSO_4$), filtered and evaporated. The crude tosylate was purified by flash chromatography (4:1 *iso*hexane/ethyl acetate to 1:1) to give a white solid (910 mg).

To this tosylate (660 mg, 1.15 mmol) in dry THF (8 mL) was added sodium hydride (60% dispersion, 60 mg, 1.5 mmol). The reaction was allowed to stir overnight, then quenched with saturated aqueous ammonium chloride (5 mL), diluted with water (50 mL) and extracted with ethyl acetate (3 x 50 mL). The organics were washed with brine, dried ($MgSO_4$), filtered and evaporated. The crude product was purified by flash chromatography (9:1 dichloromethane/methanol) to give the desired product as a white foam (520 mg). ^1H NMR (MeOD) 0.82-0.91 (3H, m), 1.52-1.72 (2H, m), 2.03-

2.08 (1H, m), 2.34-2.74 (4H, m), 3.72 (1H, dd, J = 3.4, 14.7 Hz), 6.97-7.04 (1H, m), 7.18-7.23 (2H, m), 7.40 (2H, d, J = 8.7 Hz), 7.51 (2H, d, J = 8.7 Hz)

Example 33

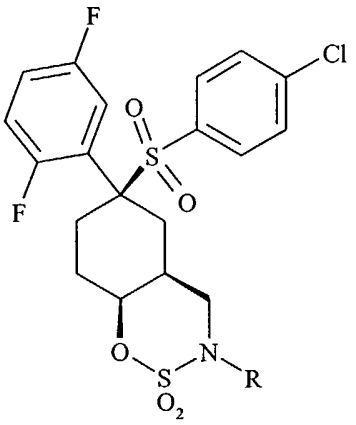
(4a*SR*,6*RS*,8a*SR*)-6-[(4-chlorophenyl)sulfonyl]-6-(2,5-difluorophenyl)-3-methyloctahydro-1,2,3-benzoxathiazine 2,2-dioxide



To the product of Example 32 (40 mg, 0.083 mmol) in dry THF (2 mL) was added sodium hydride (60% dispersion, 4 mg, 0.1 mmol) followed by iodomethane (8 µl, 0.17 mmol). The mixture was allowed to stir overnight, quenched with saturated aqueous ammonium chloride (10 mL) and extracted with ethyl acetate (3 x 50 mL). The organics were washed with brine, dried ($MgSO_4$), filtered and evaporated. The crude product was purified by flash chromatography (2:1 *iso*hexane /ethyl acetate) to give a white solid (34 mg).

^{1}H NMR $CDCl_3$ 1.43 (1H, s), 1.67-1.75 (1H, m), 2.20 (1H, dd, J = 2.9, 15.4 Hz), 2.44-2.64 (3H, m), 2.86 (3H, s), 2.89-2.99 (2H, m), 3.55 (1H, dd, J = 3.2, 12.7 Hz), 4.90 (1H, s), 6.85-6.91 (1H, m), 7.02-7.12 (2H, m), 7.35 (2H, d, J = 8.5 Hz), 7.37 (2H, d, J = 8.5 Hz).

Examples 34-37

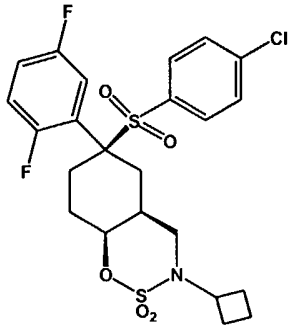


Following the procedure of Example 33, substituting the appropriate alkyl halide for iodomethane and refluxing the reaction mixture for 5 hours, the following were prepared:

Example	R
34	ethyl
35	n-propyl
36	allyl
37	cyclopropylmethyl

Example 38

(4a*SR*,6*RS*,8a*SR*)-6-[(4-chlorophenyl)sulfonyl]-3-cyclobutyl-6-(2,5-difluorophenyl)octahydro-1,2,3-benzoxathiazine 2,2-dioxide

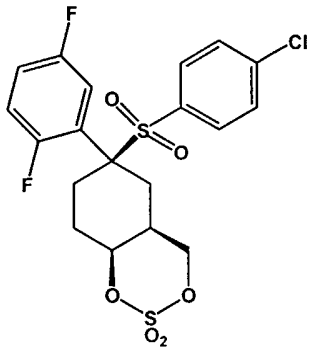


Steps 1-4 of Example 32 were repeated, using cyclobutylsulfamoyl chloride in place of sulphamoyl chloride in Step 2. Cyclisation was effected as in Step 5 of Example 32 except the reaction was performed at reflux.

^{1}H NMR $CDCl_3$ 1.55 (2H, m), 1.65-1.89 (2H, m), 2.14-2.17 (2H, m), 2.17 (1H, m), 2.27-2.99 (6H, m), 3.00-3.09 (1H, m), 3.34-3.37 (1H, m), 3.86-3.93 (1H, m), 4.84 (1H, s), 6.80-7.09 (3H, m), 7.35 (2H, d, J = 8 Hz), 7.39-7.41 (2H, d, J = 8 Hz).

Example 39

(4a*SR*,6*RS*,8a*SR*)-6-[(4-chlorophenyl)sulfonyl]-6-(2,5-difluorophenyl)hexahydro-4*H*-1,3,2-benzodioxathiine 2,2-dioxide

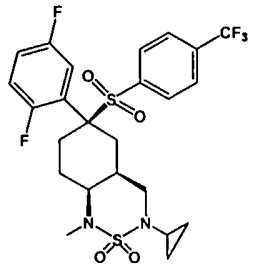


Step 4 of Example 32 was repeated, substituting methanesulfonyl chloride for toluenesulfonyl chloride. Treatment of the crude mesylate by the procedure of Example 32 Step 5 provided the sulfate rather than the sulfamate.

^{1}H NMR $CDCl_3$ 1.45-1.52 (1H, m), 1.94 (1H, s), 2.55-2.67 (4H, m), 3.02-3.10 (1H, m), 3.95 (1H, dd, J = 1.2, 5.6 Hz), 4.73 (1H, t, J = 4.6 Hz), 4.79 (1H, t, J = 5.3 Hz), 6.83-6.88 (1H, m), 6.99-7.07 (2H, m), 7.38-7.42 (4H, m).

Example 40

(4a*SR*,6*RS*,8a*SR*)-3-cyclopropyl-6-(2,5-difluorophenyl)-1-methyl-6-{[4-(trifluoromethyl)phenyl]sulfonyl}octahydro-1*H*-2,1,3-benzothiadiazine 2,2-dioxide



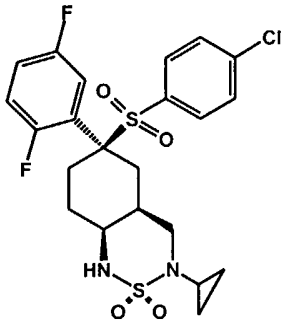
The product of Example 18 (7 mg, 0.012 mmol) was dissolved in dimethyl formamide (1mL) and sodium hydride (60% suspension in mineral oil, 3 mg) was added. The

mixture was heated to 90°C for 2 hours before adding methyl iodide (8μL), heating at 50°C for 3 hours, then pouring into ethyl acetate (20 mL) and washing with water (3 x 30 mL). The organic phase was dried and evaporated to give an oil which was purified by preparative t.l.c. to give the desired product. ^{1}H NMR $CDCl_3$ 7.69-7.52 (4H, m), 7.12-7.07 (2H, m), 6.87-6.80 (1H, m), 3.78-3.72 (1H, m), 3.49-3.48 (1H, m), 3.13-3.07 (2H, m), 2.76 (3H, s), 2.68-2.63 (1H, m), 2.60-2.35 (3H, m), 2.21-2.17 (1H, m), 1.65-1.59 (1H, m), 1.45-1.35 (1H, m), 0.95-0.83 (2H, m) and 0.78-0.72 (2H, m).

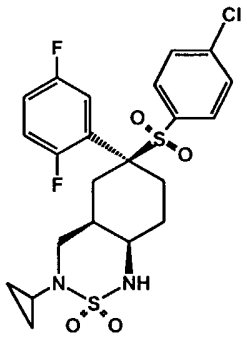
Examples 41 and 42

(4a*S*,6*R*,8a*S*)-6-[(4-chlorophenyl)sulfonyl]-3-cyclopropyl-6-(2,5-difluorophenyl)octahydro-1*H*-2,1,3-benzothiadiazine 2,2-dioxide

and (4a*R*,6*S*,8a*R*)-6-[(4-chlorophenyl)sulfonyl]-3-cyclopropyl-6-(2,5-difluorophenyl)octahydro-1*H*-2,1,3-benzothiadiazine 2,2-dioxide



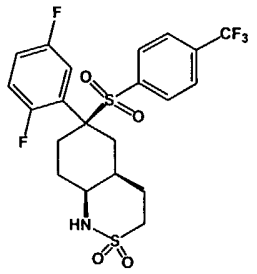
and



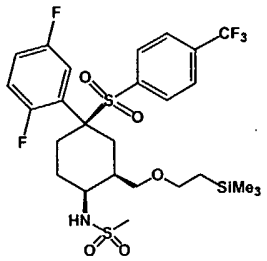
The product from Example 4 (5 mg) was separated by chiral HPLC into its constituent enantiomers using a CHIRACEL OD-H (250 x 4.5 mm) column eluting with 15% ethanol in *iso*hexanes (2 mL / min) to give Example 41 (2 mg) and Example 42 (2 mg) MS (ES^-) 515, 517.

Example 43

(4a*RS*,6*RS*,8a*SR*)-6-(2,5-difluorophenyl)-6-{[4-(trifluoromethyl)phenyl]sulfonyl}octahydro-1*H*-2,1-benzothiazine 2,2-dioxide

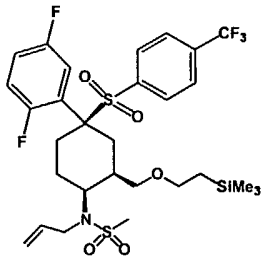


Step 1



Triethylamine (175 μL, 1.26 mmol) was added to a solution of the product of Example 15 Step 1 (230 mg, 0.419 mmol) and methanesulfonyl chloride (65 μL, 0.838 mmol) in dichloromethane (5 mL). The mixture was stirred at room temperature for 3h., evaporated to dryness and the residue partitioned between ethyl acetate and 2 M hydrochloric acid. The organic layer was washed with 2 M hydrochloric acid, and then 4 M sodium hydroxide, dried ($MgSO_4$), filtered and the solvent removed to give the desired methanesulfonamide as a light yellow foam.

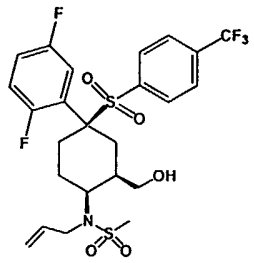
Step 2



The product of Step 1 (263 mg, 0.419 mmol) in dimethylformamide (5 mL) was treated with sodium hydride (60% dispersion in mineral oil, 90 mg, 2.25 mmol), the reaction mixture was stirred at room temperature for 30 min., then allyl bromide (382 μL, 4.51 mmol) was added. The reaction mixture was then heated to 65°C and stirred overnight. The cooled reaction mixture was quenched with water and extracted with ethyl acetate. The organic extract was washed with water, dried ($MgSO_4$), filtered and the solvent was removed. The residue was purified by column chromatography on

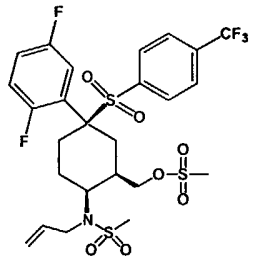
silica gel eluting with 25% ethyl acetate : 75% *iso*hexane to give the N-allyl derivative as a yellow foam. Yield 150 mg.

Step 3



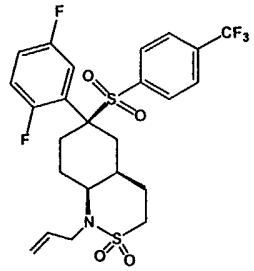
The product of Step 2 (150 mg, 0.225 mmol) was treated with boron trifluoride diethyl etherate (250 μL, 1.99 mmol) as described in Example 1 Step 3 to yield the alcohol (115 mg).

Step 4



The alcohol from Step 3 (115 mg, 0, 203 mmol) and methanesulfonyl chloride (47μL, 0.609 mmol) in dichloromethane (5 mL) were treated with triethylamine (141μL, 1.01 mmol) and the mixture stirred at room temperature for 3h. The solvent was removed under reduced pressure, and the residue partitioned between ethyl acetate and 2 M hydrochloric acid. The organics were collected, washed with 2 M hydrochloric acid, and then 4 M sodium hydroxide, dried ($MgSO_4$), filtered and the solvent was removed, azeotroping with toluene to remove all traces of ethyl acetate, to give the mesylate as a white foam. Yield 130 mg.

Step 5



The mesylate from Step 4 (130 mg, 0.202 mmol) in tetrahydrofuran (5 mL) at –30 °C under nitrogen gas was treated with butyllithium (1.6 M solution in hexanes, 252 μL) and the reaction mixture was allowed to warm up slowly to room temperature, then quenched with water and extracted with ethyl acetate. The organic extract was washed with water, dried ($MgSO_4$), filtered and evaporated. The residue was purified by column chromatography on silica gel eluting with 25% ethyl acetate : 75% *iso*hexane to give the desired cyclic sulfonamide as a white powder. Yield 15 mg (14%).

Step 6

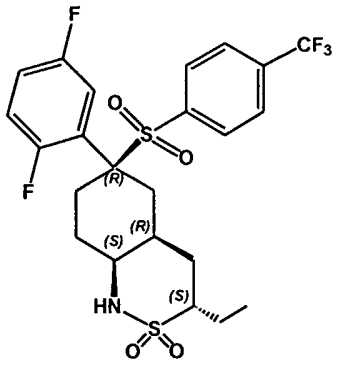
The product of Step 5 (12 mg, 0.022 mmol) in toluene (2 mL) was treated with [1.3-bis(diphenylphosphino)propane]dichloronickel(II) (1.2 mg, 0.0022 mmol) then di*iso*butylaluminum hydride (1.5 M solution in toluene, 30 μL). The mixture was stirred at room temperature for 3h., then quenched with 4 M sodium hydroxide and extracted with ethyl acetate. The organic extracts were dried ($MgSO_4$), filtered through a plug of silica gel eluting with ethyl acetate and evaporated to dryness. The residue was triturated in diethyl ether and the solid was collected to give the title compound as a white solid. Yield 6 mg (55%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.67 (2H, d, *J* 8.1 Hz), 7.53 (2H, d, *J* 8.1 Hz), 7.12-7.07 (2H, m), 6.90-6.78 (1H, m), 4.45-4.37 (1H, m), 3.76-3.71 (1H, m), 3.20-3.11 (1H, m), 3.10-3.04 (1H, m), 2.71-2.61 (1H, m), 2.55-2.42 (2H, m), 2.40-2.29 (1H, m), 2.10-1.98 (1H, m), 1.91-1.84 (1H, m), 1.72-1.60 (2H, m), 0.98-0.91 (1H, m).

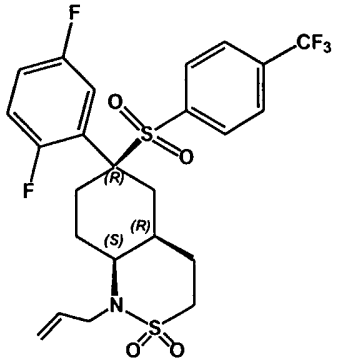
m/z (ES^-) (M-1) 508.

Example 44

(3*S*,4a*R*,6*R*,8a*S*)-6-(2,5-difluorophenyl)-3-ethyl-6-{[4-(trifluoromethyl)phenyl]sulfonyl}octahydro-1*H*-2,1-benzothiazine 2,2-dioxide



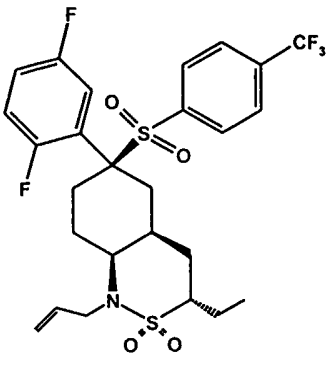
Step 1



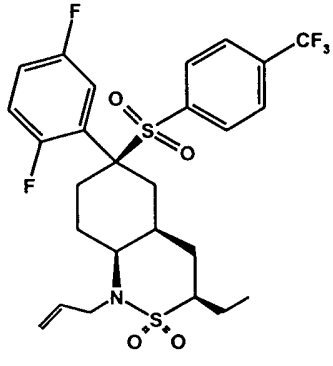
Intermediate 3 (830 mg, 1.29 mmol) was treated as described in Example 15 Step 1 and Example 43 to give the chiral N-allyl sulfonamide as a white solid. Yield 300 mg (42%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.67 (2H, d, *J* 8.1 Hz), 7.53 (2H, d, *J* 8.1 Hz), 7.12-7.06 (2H, m), 6.88-6.77 (1H, m), 6.07-5.98 (1H, m), 5.28 (1H, dd, *J* 0.5 and 17.6 Hz), 5.23 (1H, dd, *J* 0.5 and 10.5 Hz), 4.41-4.31 (1H, m), 3.71-3.61 (1H, m), 3.28-3.20 (1H, m), 3.10-3.02 (1H, m), 2.91-2.80 (1H, m), 2.56-2.25 (5H, m), 1.98-1.90 (1H, m), 1.81-1.66 (1H, m), 1.45-1.30 (2H, m).

Step 2



and



The product of Step 1 (80 mg, 0.146 mmol) in tetrahydrofuran (5 mL) at 0°C was treated with lithium bis(trimethylsilyl)amide (1M solution in tetrahydrofuran, 292 μL) and the mixture was stirred at 0°C for 30min. before addition of iodoethane (15 μL, 0.188 mmol). The resulting mixture was allowed to warm up slowly overnight, quenched with water then extracted with ethyl acetate. The organic extracts were dried ($MgSO_4$), filtered and the solvent was removed. The residue was purified by column chromatography on silica gel eluting with 10 to 15% ethyl acetate : *iso*hexane to give a less polar product (white solid, yield 28 mg, 33%):

^{1}H NMR (500 MHz, CD_3OH) δ 7.81 (2H, d, *J* 8.3 Hz), 7.66 (2H, d, *J* 8.3 Hz), 7.24-7.15 (2H, m), 7.02-6.93 (1H, m), 6.04-5.93 (1H, m), 5.32 (1H, d, *J* 17.2 Hz), 5.19 (1H, d, *J* 10.1 Hz), 4.26 (1H, dd, *J* 5.1 & 17.2 Hz), 3.77 (1H, dd, *J* 7.0 & 17.2 Hz), 3.54 (1H, brs), 3.16-3.11 (1H, m), 2.83-2.68 (1H, m), 2.61-2.39 (2H, m), 2.33-2.02 (2H, m), 2.08-1.85 (2H, m), 1.55-1.28 (3H, m), 1.11-0.98 (3H, m), 0.93-0.82 (1H, m);

and also a more polar product (white solid, yield 23 mg 27%):

^{1}H NMR (500 MHz, CD_3OH) δ 7.83 (2H, d, *J* 8.3 Hz), 7.66 (2H, d, *J* 8.3 Hz), 7.24-7.14 (2H, m), 7.04-6.94 (1H, m), 5.92-5.81 (1H, m), 5.24 (1H, dd, *J* 1.1 & 17.2 Hz), 5.13 (1H, dd, *J* 1.1 & 10.3 Hz), 4.13-4.05 (1H, dd, m), 3.75 (1H, dd, *J* 6.8 & 16.7 Hz), 3.59-3.53 (1H, m), 3.00-2.93 (1H, m), 2.70-2.55 (2H, m), 2.48-2.22 (4H, m), 2.13-2.03 (1H, m), 1.93-1.85 (1H, m), 1.75-1.66 (1H, m), 1.59-1.47 (1H, m), 1.17-1.07 (3H, m), 0.95-0.84 (1H, m).

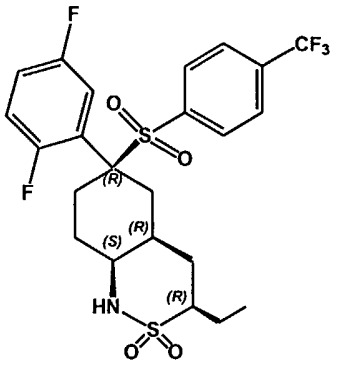
Step 3

The less polar product from Step 2 (25 mg, 0.0433 mmol) was treated as described in Example 43 Step 6 to give the desired chiral sulfonamide as a white solid. Yield 20 mg (86%).

^{1}H NMR (500 MHz, CD_3OH) δ 7.82 (2H, d, *J* 8.2 Hz), 7.64 (2H, d, *J* 8.2 Hz), 7.23-7.08 (2H, m), 7.01-6.93 (1H, m), 3.57-3.52 (1H, m), 3.06-2.98 (1H, m), 2.75-2.56 (2H, m), 2.51-2.37 (2H, m), 2.00-1.91 (2H, m), 1.90-1.82 (1H, m), 1.74-1.55 (2H, m), 1.51-1.42 (1H, m), 1.23-1.20 (1H, m), 1.15-1.07 (3H, m), 0.97-0.84 (1H, m). m/z (ES^-) (M-1) 536.

Example 45

(3*R*,4a*R*,6*R*,8a*S*)-6-(2,5-difluorophenyl)-3-ethyl-6-{[4-(trifluoromethyl)phenyl]sulfonyl}octahydro-1*H*-2,1-benzothiazine 2,2-dioxide

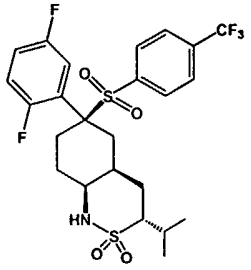


The more polar isomer from Example 44 Step 2 (23 mg, 0.0433 mmol) was treated as described in Example 43 Step 6 to give the desired chiral sulfonamide as a white solid. Yield 10 mg (46%).

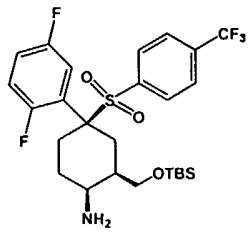
^{1}H NMR (500 MHz, CD_3OH) δ 7.84 (2H, d, *J* 8.2 Hz), 7.65 (2H, d, *J* 8.2 Hz), 7.27-7.08 (2H, m), 7.04-6.94 (1H, m), 3.62-3.57 (1H, m), 2.93-2.86 (1H, m), 2.75-2.63 (1H, m), 2.56-2.49 (2H, m), 2.48-2.41 (1H, m), 2.40-2.32 (1H, m), 2.17-2.07 (1H, m), 2.00-1.93 (1H, m), 1.91-1.84 (1H, m), 1.79-1.70 (1H, m), 1.68-1.55 (1H, m), 1.32-1.25 (1H, m), 1.20-1.14 (3H, m), 0.98-0.85 (1H, m). m/z (ES^-) (M-1) 536.

Example 46

(3*RS*,4a*RS*,6*RS*,8a*SR*)-6-(2,5-difluorophenyl)-3-isopropyl-6-{[4-(trifluoromethyl)phenyl]sulfonyl}octahydro-1*H*-2,1-benzothiazine 2,2-dioxide

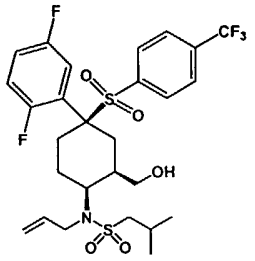


Step 1



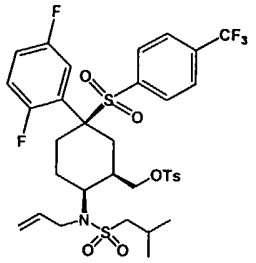
The product from Example 15 Step 2 (2 g, 3.1 mmol) in dichloromethane (25 mL) was treated with triethylamine (1.7 mL, 12.4 mmol), 4-dimethylaminopyridine (cat.) and ^{t}butyldimethylsilyl chloride (1.16g, 7.75 mmol). After 16 hours the mixture was washed with 10% citric acid (10 mL), sodium bicarbonate (sat., 20 mL) and brine (sat. 15mL). The organics were dried ($MgSO_4$) and evaporated and the residue was filtered through silica eluting with 1% ammonia in ethyl acetate to give the desired t-butyldimethylsilyl ether as a white solid (1.8 g) MS ES+ 564.

Step 2



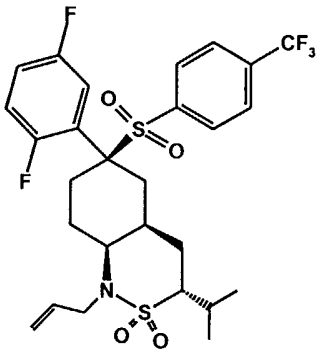
The silyl ether from Step 1 (1.8 g, 3.2 mmol) and isobutanesulfonyl chloride (1.12g, 8 mmol) were stirred in dichloromethane (20 mL) and triethylamine (1.34 mL, 9.5 mmol) was added. After stirring at room temperature for 16h., the mixture was evaporated to dryness and the residue was partitioned between ethyl acetate and 2 M hydrochloric acid. The organic layer was collected, washed with 2 M hydrochloric acid and then 4 M sodium hydroxide, dried ($MgSO_4$), filtered and the solvent removed in vacuo. The residue was purified by column chromatography (eluting with 20% ethyl acetate in hexanes) to give the sulphonamide (900 mg). This product was dissolved in dimethylformamide (6 mL) and sodium hydride (60% dispersion in mineral oil, 132 mg, 3.3 mmol) was added. The mixture was stirred at room temperature for 30 min., allyl bromide (1.1 mL, 13 mmol) was added, then the mixture was heated to 65°C over 72 hrs. After cooling to room temperature and quenching with water, the mixture was extracted with ethyl acetate. The organic extract was washed with water, dried ($MgSO_4$), filtered and the solvent was removed. The residue was purified by column chromatography on silica gel eluting with 20% ethyl acetate : 80% *iso*hexane to give the N-allyl derivative (400 mg).

Step 3

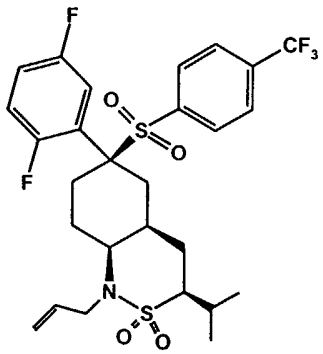


Prepared from the product of Step 2 (0.2g) and p-toluenesulfonyl chloride by the procedure of Example 32 Step 4. Purified by column chromatography on silica, eluting with 30% ethyl acetate in hexanes to give the tosylate (185 mg).

Step 4



and



The tosylate from Step 3 (186 mg, 0.24 mmol) in tetrahydrofuran (9 mL) at –40°C under nitrogen was treated with lithium hexamethyldisilazide (1.0 M solution in tetrahydrofuran, 480 μL) and the reaction mixture was allowed to warm up slowly to room temperature, then quenched with saturated aqueous ammonium chloride and extracted with ethyl acetate. The organic extract was washed with water, dried ($MgSO_4$), filtered and the solvent was removed. The residue was purified by column chromatography on silica gel eluting with 15% ethyl acetate : 85% *iso*-hexane. to give a less polar product as a white solid (48 mg):

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.66 (2H, d, *J* 8 Hz), 7.52 (2H, d, *J* 8 Hz), 7.11-7.07 (1H, m), 6.93-6.75 (2H, m), 6.06-5.96 (1H, m), 5.29-5.22 (2H, m), 4.41-4.33 (1H, m), 3.69-3.48 (2H, m), 3.07-2.99 (1H, m), 2.89-2.72 (1H, m), 2.61-2.20 (5H, m), 1.90-1.73 (2H, m), 1.48-1.30 (2H, m), 1.17 (3H, d, J = 7 Hz) and 1.05 (3H, d, J = 7 Hz);

and also a more polar product as a white solid. (67 mg):

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.65 (2H, d, *J* 8 Hz), 7.54 (2H, d, *J* 8 Hz), 7.07-7.03 (2H, m), 6.86-6.78 (1H, m), 5.75-5.65 (1H, m), 5.04-4.99 (2H, m), 3.95 (1H, dd, J =

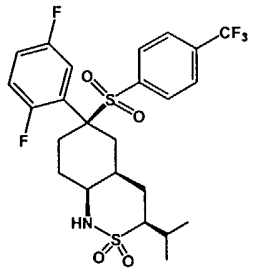
15.5 and 4.5 Hz), 3.63 (1H, dd, J = 15.5 and 6.5 Hz), 3.29-3.24 (1H, m), 2.76-2.72 (1H, m), 2.61-2.52 (4H, m), 2.49-2.42 (1H, m), 2.40-2.18 (3H, m), 2.09-2.00 (1H, m), 1.75-1.68 (1H, m), 1.17 (3H, d, J = 6.8 Hz) and 1.09 (3H, d, J = 6.8 Hz).

Step 5

The less polar product from Step 4 (40 mg, 0.067 mmol) was treated as described in Example 43 Step 6 to give the title compound as a white solid. 23 mg . ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.67 (2H, d, *J* 8.3 Hz), 7.53 (2H, d, *J* 8.0 Hz), 7.25-6.88 (2H, m), 7.11-7.06 (1H, m), 4.68-4.50 (1H, brs), 3.69-3.68 (1H, m), 3.00-2.96 (1H, m), 2.71-2.65 (1H, m), 2.60-2.27 (3H, m), 2.18-2.13 (1H, m), 2.02-1.87 (2H, m), 1.80-1.52 (3H, m), 1.22 (3H, d, *J* 6.9 Hz), 1.07 (3H, d, *J* 6.9 Hz). m/z (ES^-) (M-1) 550.

Example 47

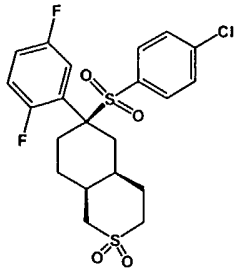
(3*SR*,4a*RS*,6*RS*,8a*SR*)-6-(2,5-difluorophenyl)-3-isopropyl-6-{[4-(trifluoromethyl)phenyl]sulfonyl}octahydro-1*H*-2,1-benzothiazine 2,2-dioxide



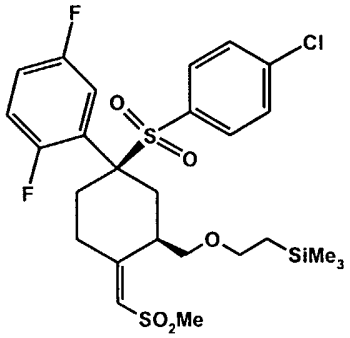
Step 5 of Example 46 was repeated, using the more polar isomer from Step 4 (40 mg, 0.067 mmol) to give the title compound as a white solid. (23 mg). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.68 (2H, d, *J* 8.3 Hz), 7.54 (2H, d, *J* 8.2 Hz), 7.10-7.06 (2H, m), 6.87-6.82 (1H, m), 4.47 (1H, d, *J* 8.9 Hz), 3.60-3.57 (1H, m), 2.82-2.77 (1H, m), 2.71-2.52 (2H, m), 2.40-2.20 (4H, m), 1.98 (1H, dd, *J* 15.1 and 2 Hz), 1.81-1.77 (2H, m), 1.76-1.74 (1H, m), 1.26 (3H, d, *J* 6.4 Hz), 1.11 (3H, d, *J* 6.8 Hz). m/z (ES^-) (M-1) 550.

Example 48

(4a*RS*,6*RS*,8a*SR*)-6-[(4-chlorophenyl)sulfonyl]-6-(2,5-difluorophenyl)octahydro-1*H*-isothiochromene 2,2-dioxide

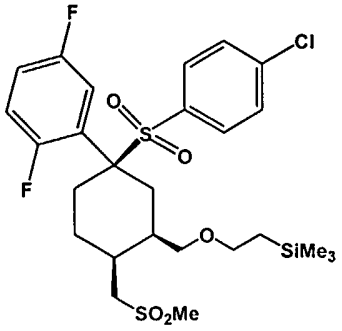


Step 1



Diethyl (methylsulphonylmethyl)phosphonate [*J.Org.Chem.* 1972, **37**(22), 3547-9] (0.49 g, 2.1 mmol) in dry tetrahydrofuran (10 mL) was treated dropwise with 1.0 M butyl lithium (1.25 mL, 2 mmol) at –78°C. The mixture was allowed to warm to –50°C over 1 hour before adding Intermediate 1 (1.0 g, 1.9 mmol), then allowing the mixture to warm to r.t. over 16 hours. The mixture was diluted with ethyl acetate (10 mL), washed with water (10 mL), and the organic phase separated, dried (Na_2SO_4) and evaporated to dryness. The residue was purified on silica eluting with [7:3] hexane-ethyl acetate to give the vinyl sulfone (0.7 g).

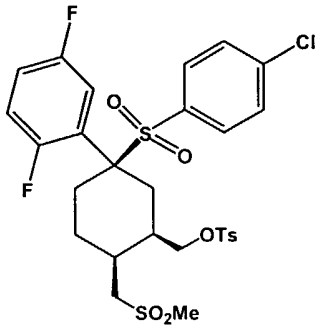
Step 2



The product from Step 1 (0.7 g, 1.2 mmol) in dry tetrahydrofuran (90 mL) was treated dropwise with 1.0 M L-Selectride (1.8 mL, 1.8 mmol) at –40°C. The mixture was held at this temperature for 2 hours and then allowed to warm to 0°C over 1 hour before adding ethanol (3 drops). The reaction mixture was diluted with ethyl acetate

(10 mL), washed with water (10 mL), and the organic phase washed with brine (sat), separated, dried (Na_2SO_4) and evaporated to dryness. The residue was purified on silica eluting with [3:1] hexane-ethyl acetate to give the desired product (0.7 g). ^1H NMR $CDCl_3$ 7.35-7.28 (4H, m), 7.11-6.79 (2H, m), 7.06-7.02 (1H, m), 3.47-3.11 (6H, m), 2.92 (3H, s), 2.70-2.20 (5H, m), 1.97-1.79 (2H, m), 1.49-1.38 (1H, m), 0.91-0.84 (2H, m) and 0.03 (9H, s).

Step 3



Prepared from the product of Step 2 by treatment with BF_3 etherate, following the procedure of Example 1 Step 3, then tosylation by the procedure of Example 32 Step 4. Yield 0.425 g

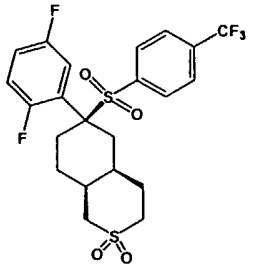
Step 4

The procedure of Example 43 Step 5 was followed, using the tosylate from Step 3 (106 mg, 0.16 mmol), to give the desired cyclic sulfone (75 mg).

^1H NMR (500 MHz, $CDCl_3$) δ 7.38 (2H, d, *J* 8.7 Hz), 7.30 (2H, d, *J* 8.5 Hz), 7.15-6.80 (2H, m), 7.09-7.06 (1H, m), 3.37 (1H, t, J = 14 Hz), 3.08-3.02 (1H, m), 2.96-2.90 (1H, m), 2.80 (1H, dt, J = 14.5 and 3.5 Hz), 2.70-2.15 (6H, m), 2.02-1.93 (1H, m), and 1.87-1.62 (3H, m).

Example 49

(4a*RS*,6*RS*,8a*SR*)-6-(2,5-difluorophenyl)-2,2-dioxidooctahydro-1*H*-isothiochromen-6-yl 4-(trifluoromethyl)phenyl sulfone

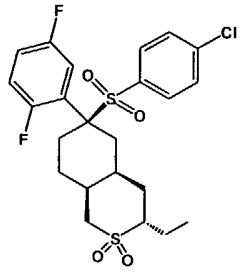


Prepared as described for Example 48, substituting Intermediate 2 for Intermediate 1 in the initial step.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.66 (2H, d, *J* 8.2 Hz), 7.51 (2H, d, *J* 8.2 Hz), 7.25-6.78 (2H, m), 7.10-7.07 (1H, m), 3.38 (1H, t, J = 13.9 Hz), 3.08-3.02 (1H, m), 2.96-2.90 (1H, m), 2.80 (1H, dt, J = 14.5 and 3.5 Hz), 2.70-2.19 (6H, m), 2.02-1.93 (1H, m), and 1.87-1.62 (3H, m).

Example 50

(3*SR*,4a*RS*,6*RS*,8a*SR*)-6-[(4-chlorophenyl)sulfonyl]-6-(2,5-difluorophenyl)-3-ethyloctahydro-1*H*-isothiochromene 2,2-dioxide

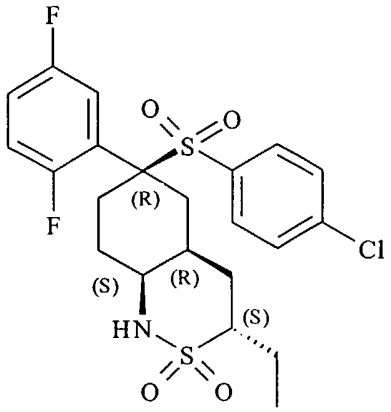


Prepared as described in Example 48, substituting diethyl (propanesulfonylmethyl)phosphonate for diethyl (methanesulfonylmethyl)phosphonate in Step 1.

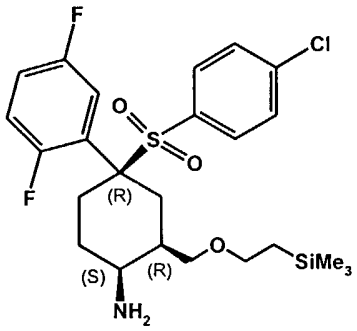
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39-7.37 (2H, m), 7.31-7.29 (2H, m), 7.22-6.78 (2H, m), 7.09-7.05 (1H, m), 3.37 (1H, t, J = 13.9 Hz), 2.86-2.82 (1H, m), 2.80 (1H, dd, J = 14.3 and 3.7 Hz), 2.68-2.13 (6H, m), 2.02-1.49 (6H, m), and 1.11 (3H, t, J = 7.5 Hz).

Example 51

(3*S*,4a*R*,6*R*,8a*S*)-6-[(4-chlorophenyl)sulfonyl]-6-(2,5-difluorophenyl)-3-ethyloctahydro-1*H*-2,1-benzothiazine 2,2-dioxide



Step 1



Intermediate 4 was treated as described in Example 1 Steps 1 and 2. The resulting product (80% e.e) (3.6 g, 6.96 mmol) was dissolved in *iso*-propanol (34 mL) and (1S)-(+)-camphor sulfonic acid (1.37 g, 5.91 mmol) was added. The mixture was heated to reflux, allowed to cool to room temperature slowly, and then left in the refrigerator overnight. The resulting solid was collected, washed with pre-cooled (~5°C) *iso*propanol, then suspended in ethyl acetate and washed with 4M sodium hydroxide. The organics were dried ($MgSO_4$), filtered and the solvent removed to give the chiral amine (98% e.e). Yield 3 g, NMR data identical to those observed for the product of Example 1 Step 2.

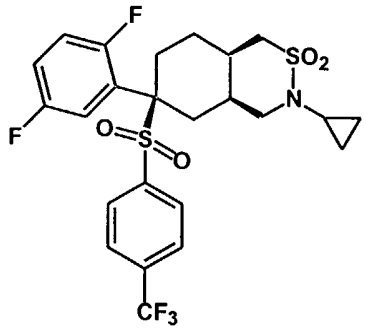
Step 2

The amine from Step 1 (3g) was elaborated as described for Example 43 Steps 1-5 to provide the desired homochiral sulfonamide (60mg).

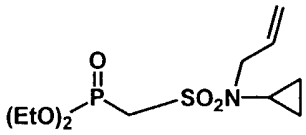
^{1}H NMR (500 MHz, CD_3OH) δ 7.51 (2H, d, *J* 8.7 Hz), 7.40 (2H, d, *J* 7.9 Hz), 7.25-7.11 (2H, m), 7.04-6.94 (1H, m), 3.55-3.51 (1H, m), 3.03-2.97 (1H, m), 2.75-2.32 (4H, m), 2.17-2.07 (1H, m), 2.01-1.93 (2H, m), 1.91-1.84 (1H, m), 1.75-1.57 (2H, m), 1.50-1.44 (1H, m) and 1.11 (3H, t, *J* 7.6 Hz).

Example 52

(4a*RS*,6*RS*,8a*SR*)-3-cyclopropyl-6-(2,5-difluorophenyl)-6-{[4-(trifluoromethyl)phenyl]sulfonyl}octahydro-1*H*-2,3-benzothiazine 2,2-dioxide

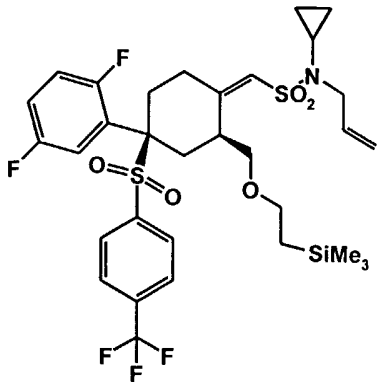


Step 1



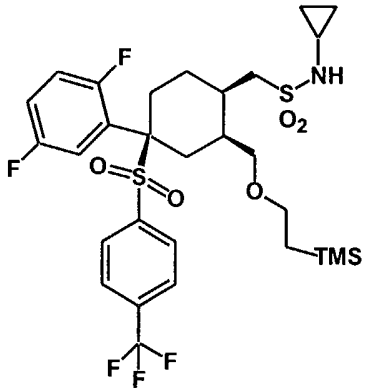
The methanesulfonyl derivative of cyclopropylamine was N-alkylated with allyl bromide by the procedure described in Example 43 Step 2. The resulting product (3.6 g, 0.021 moles) in THF (40 mL) at -78^0C under a nitrogen atmosphere was treated with a 1.6 M solution of butyl lithium in hexanes (14.1 mL, 0.023 moles). After 20 minutes, diethylchlorophosphonate (3.9 g, 0.023 moles) was added and stirring continued for 2 hr. The reaction was quenched (water), extracted (ethyl acetate), and the extracts washed (water, brine), dried (magnesium sulphate) and evaporated *in vacuo*. Purification by flash silica chromatography, using 40% ethyl acetate / isohexane to elute, gave the desired product (2.9 g, 44% yield).

Step 2



The product of Step 1 (1.0 g, 3.2 mmoles) in THF (10 mL) at -78^0C under a nitrogen atmosphere was treated with butyl lithium (1.6M in hexanes, 2.2 mL, 3.5 mmoles), then aged for 10 minutes before addition of Intermediate 2 (1.76 g, 3.2 mmoles) in THF (10 mL). After stirring for 16 h., the reaction was quenched with water, extracted into ether, washed (brine), dried (magnesium sulphate) and evaporated *in vacuo*. The residue was purified by flash silica chromatography, using 10-20% ethyl acetate / isohexane to elute, giving the vinyl sulfonamide, 0.6 g, 27% yield.

Step 3



The product of Step 2 (0.4 g, 0.56 mmoles) in methanol (10 mL) at 0^0C under N_2 was treated with nickel (II) chloride (0.02 g, 0.112 mmoles) followed by portionwise addition of sodium borohydride (0.22 g, 5.6 mmoles). After 3 hours, the reaction mixture was filtered and evaporated *in vacuo*, and the residue partitioned between ethyl acetate and water. The organic layer was washed (brine), dried (magnesium sulphate) and evaporated *in vacuo*. Purification of the residue by flash silica chromatography, using 20% ethyl acetate / *iso*-hexane to elute, gave the desired product. (0.031 g, 8% yield).

Step 4

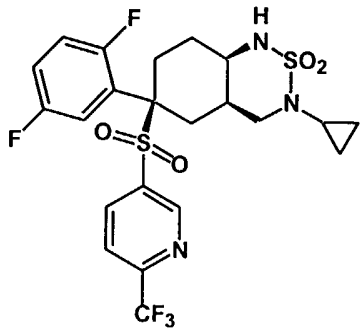
The product of Step 3 was treated with BF_3 etherate by the procedure of Example 1 Step 3. The resulting alcohol (0.042 g, 0.079 mmoles) in dichloromethane (0.6 mL) at 0^0C was treated with triethylamine (0.012 g, 0.12 mmoles) in dichloromethane (0.2 mL) followed by methanesulfonyl chloride (0.011 g, 0.095 mmoles) in dichloromethane (0.2 mL). The mixture was stirred for 60 minutes, diluted with dichloromethane (2 mL), washed (water, brine), dried (magnesium sulphate), passed through a plug of silica (eluting with ethyl acetate) and evaporated *in vacuo*.

The resulting crude mesylate in N,N-dimethylformamide (1.0 mL) under nitrogen at 0^0C was treated with a 60% dispersion of sodium hydride in mineral oil (0.004 mg, 0.093 mmoles) and stirred for 60 minutes. The reaction was quenched (0.5 M citric acid solution), extracted into ethyl acetate, washed (water, brine), dried (magnesium sulphate), and evaporated *in vacuo*. Purification of the residue by flash silica chromatography, using ethyl acetate / isohexane mixtures to elute, gave the desired cyclic sulfonamide, 0.006g, 18% yield.

^{1}H NMR (400 MHz, $CDCl_3$) δ 0.45 (1H, vbrs), 0.70-0.78 (1H, m), 0.85-0.96 (1H, m), 1.08-1.15 (1H, m), 1.60-1.75 (2H, m), 2.14-2.61 (7H, m), 2.83-3.06 (1H, m), 3.04-3.39 (1H, m), 3.32-3.39 (1H, m), 3.59-3.63 (1H, m), 6.84 (1H, vbrs), 7.06-7.12 (2H, m), 7.50 (2H, d, J = 8.2 Hz), 7.67 (2H, d, J = 8.2 Hz). MS (ES^+) MH^+ = 550.

Example 53

(4a*SR*,6*RS*,8a*SR*)-3-cyclopropyl-6-(2,5-difluorophenyl)-6-{[6-(trifluoromethyl)pyridin-3-yl]sulfonyl}octahydro-1*H*-2,1,3-benzothiadiazine 2,2-dioxide

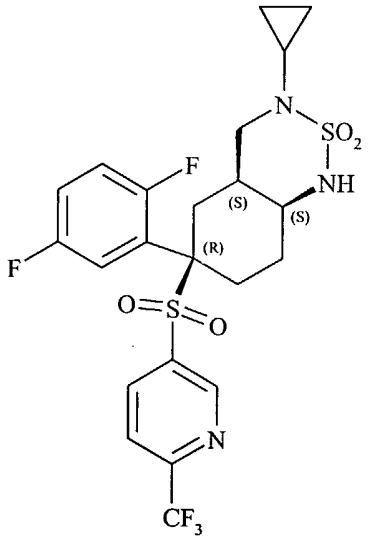


Prepared from Intermediate 5 (100 mg, 0.17 mmol) using the procedure detailed for Example 4. Yield 69 mg (71%).

^{1}H NMR (360 MHz, $CDCl_3$) δ 0.39-0.50 (1H, m), 0.65-0.74 (1H, m), 0.71-0.93 (3H, m), 1.58-1.75 (2H, m), 1.98 (1H, bd, J = 14.4 Hz), 2.14-2.22 (1H, m), 2.26-2.33 (1H, m), 2.45-2.70 (2H, m), 3.04-3.15 (1H, m), 3.55 (1H, bd, J = 14.4 Hz), 3.84 (1H, bd, J = 14.4 Hz), 4.45 (1H, d, J = 10.8 Hz), 6.78-6.92 (1H, m), 7.10-7.20 (2H, m), 7.74 (1H, d, J = 8.3 Hz), 7.84-7.90 (1H, m), 8.60 (1H, bs).

Example 54

(4a*S*,6*R*,8a*S*)-3-cyclopropyl-6-(2,5-difluorophenyl)-6-{[6-(trifluoromethyl)pyridin-3-yl]sulfonyl}octahydro-1*H*-2,1,3-benzothiadiazine 2,2-dioxide

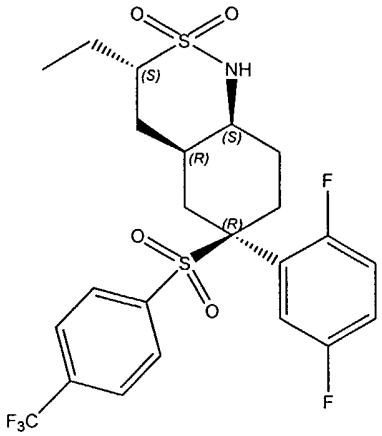


The product of Example 53 was separated into its constituent enantiomers by chiral HPLC (Chiralpak AD, column dimensions 250 x 21.0 mm i.d.).

The racemate (70 mg) was dissolved in 2mL ethanol, and using 50 µl injections, column loadings of 1.75 mg were achieved eluting with 30% ethanol in isohexanes The second eluting peak was Example 54 (12 mg) and NMR data were identical to those specified for Example 53.

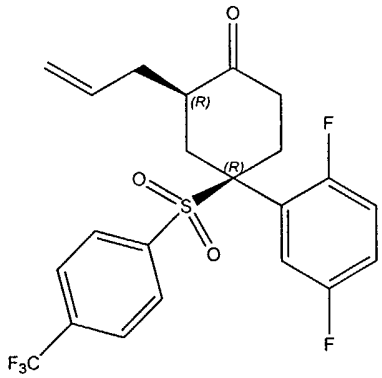
Example 55

(3S,4aR,6R,8aS)-6-(2,5-difluorophenyl)-3-ethyl-6-{[4-(trifluoromethyl)phenyl]sulfonyl}octahydro-1H-2,1-benzothiazine 2,2-dioxide



- alternative route.

Step1

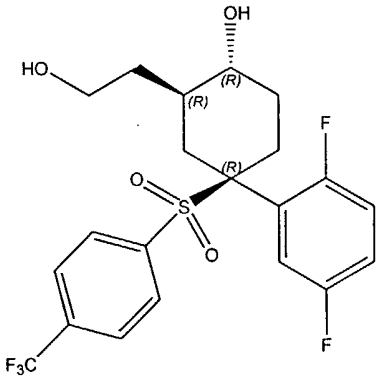


A solution of (1S)-1-phenyl-N-[(1S)-1-phenylethyl] ethanamine (10.8 g, 47.85 mmol) and oven-dried lithium chloride (3.0 g, 71.80 mmol) in tetrahydrofuran (200 ml) was degassed under nitrogen. The reaction mixture was cooled to -78 °C (internal temperature) and treated with n-butyl lithium (1.6M in hexane, 30 ml, 47.85 mmol), dropwise over 25 minutes. After the addition, the reaction was warmed to -20 °C and then cooled to -100 °C and stirred for 2 hours. A solution of 4-(2,5-difluorophenyl)-4-[[4-(trifluoromethyl)phenyl]sulfonyl]-cyclohexanone (20 g, 47.85 mmol) in tetrahydrofuran (100 ml) (cooled to -78 °C) was cannulated into the reaction vessel over 20 minutes. After a further 30 minutes at -100 °C, allyl iodide (8.80 ml, 95.60 mmol) was added and the reaction mixture was allowed to warm to room temperature over 18 hours. The reaction mixture was acidified with citric acid solution (200 ml) and diluted with ethyl actetate (300 ml). The ethyl acetate layer was separated and re-

washed with citric acid solution (200 ml), 10% ammonia solution (200 ml), brine, dried over $MgSO_4$, filtered and evaporated in vacuo. Purification by column chromatography gave the title compound as a white solid (8.97 g, 41%, 70% ee).

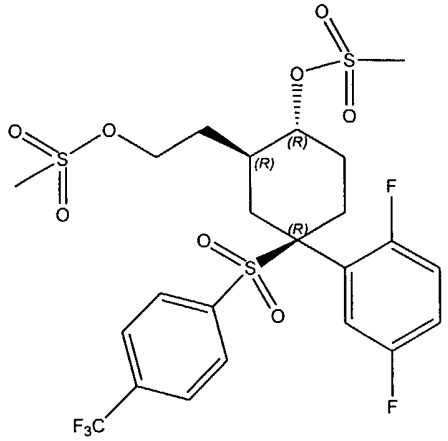
A solution of this material (73.1 g, 61%ee) in toluene (181 ml) was added dropwise to isohexane (760 ml) stirring at 70 °C, over 45 minutes. The reaction mixture was seeded with racemic product (100 mg) and was cooled slowly over 2 ½ hours. The resultant solid was filtered and the filtrate was evaporated in vacuo resulting in clear gummy oil (49 g, 95% ee).

Step2



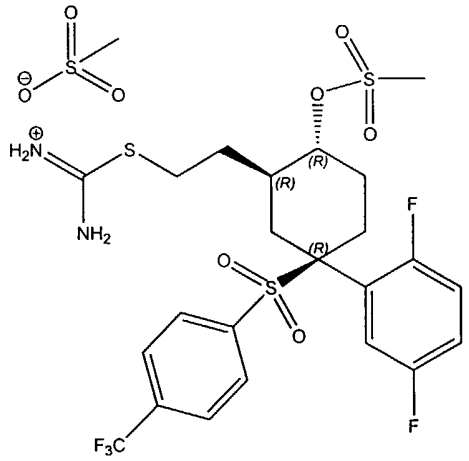
Oxygen was bubbled through a stirred solution of the product of Step 1 (67.8 g, 148 mmol) in dichloromethane (750 ml) and methanol (150 ml) at -78 °C for 10 minutes. Ozone was bubbled into the reaction mixture until a blue coloration persisted (3 ½ hours), followed by oxygen and then nitrogen until the blue color disappeared. Sodium borohydride (14 g, 370 mmol) was added to the reaction mixture, which was then allowed to warm to room temperature slowly. The mixture was acidified with citric acid solution (200 ml) and 2N hydrochloric acid, until pH 2, and diluted with dichloromethane (800 ml). The dichloromethane layer was separated and washed with water, brine, dried over $MgSO_4$, filtered and evaporated in vacuo. Purification by recrystallization from ether and isohexane (50:50), gave the diol as a white solid (50 g, 73%, 97% ee).

Step 3



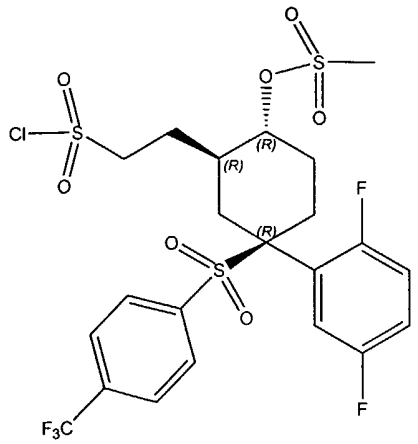
Methanesulfonyl chloride (20 ml, 259 mmol) was added slowly to a solution of the product of Step 2 (50 g, 108 mmol) in dichloromethane (700 ml) and triethylamine (45 ml, 324 mmol), stirring at -10 °C. The reaction mixture was allowed to stir at -10 °C for 2 hours. The reaction was acidified with citric acid solution (500 ml) and diluted with dichloromethane (500 ml). The dichloromethane layer was separated and washed with sodium hydrogen carbonate solution (500 ml), brine, dried over $MgSO_4$, filtered and evaporated in vacuo to give the bis-mesylate as white foam (67.7 g, >100%), which was used without further purification.

Step 4



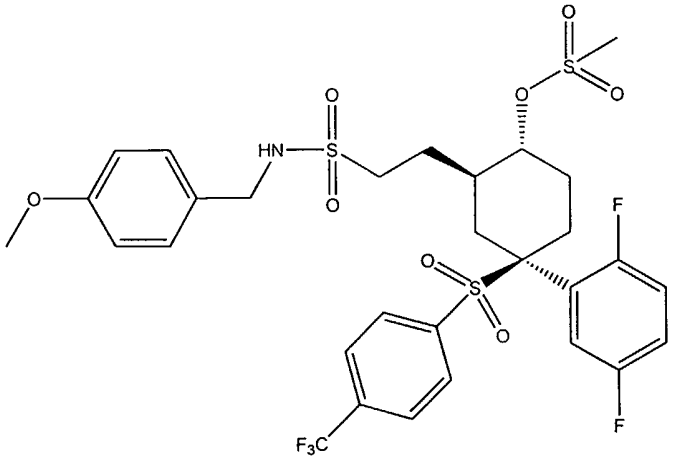
A solution of the product of Step 3 (67.7 g, 109 mmol) in ethanol was treated with thiourea (8.7 g, 115 mmol). The reaction mixture was stirred at 80 °C for 18 hours, cooled to room temperature and evaporated in vacuo to give the desired product as pale yellow foam (80.6 g, >100%).

Step 5



Acetic acid (500 ml) was added to a solution of the product of Step 4 (80.7 g) in water (100 ml) at room temperature. Chlorine gas (approximately 55 g) was bubbled through the reaction mixture for 30 minutes, until the reaction mixture turned a dark yellow. The reaction mixture was diluted with diethyl ether (1000 ml) and water (1000 ml). The ether layer was separated and washed with a further portion of water (1000 ml), sodium sulfite solution (500 ml), sodium hydrogen carbonate solution (3x500 ml), brine, dried over $MgSO_4$, filtered and evaporated in vacuo to give the sulfonyl chloride as a white foam 65.7 g (>100%).

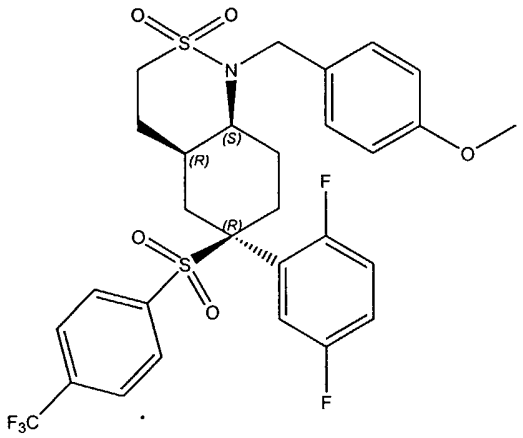
Step 6



4-Methoxybenzylamine (35 ml, 263 mmol) was added dropwise over 10 minutes to a solution of the product of Step 5 (65.7 g, 105 mmol in dichloromethane (500 ml) stirred at 0 °C, under nitrogen. The reaction mixture was warmed to room temperature over 90 minutes, diluted with dichloromethane (500 ml) and acidified with citric acid solution (500 ml). The dichloromethane layer was separated and washed with brine, water (700 ml), dried over $MgSO_4$, filtered and evaporated in vacuo. Purification by

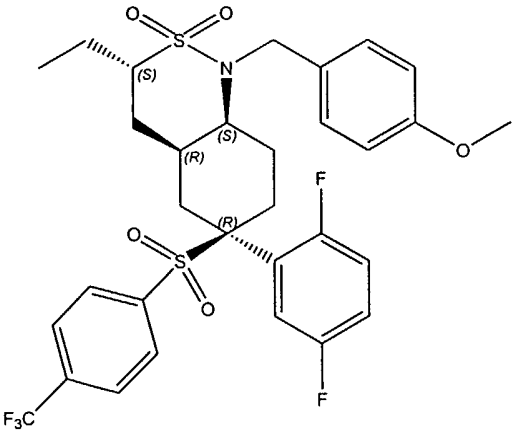
column chromatography gave the title intermediate as a pale brown foam (59.3 g, 88% over 4 steps).

Step 7



Sodium hydride (4.90 g, 127 mmol) was added to a solution of the product of Step 6 (59.3 g, 82 mmol) dissolved in dimethylformamide (700 ml). After stirring at room temperature for 10 minutes the reaction mixture was heated to 75 °C. After 2 hours the reaction mixture was cooled to room temperature, acidified with citric acid solution (500 ml) and diluted with ethyl acetate (800 ml). The ethyl acetate layer was separated, washed with water (3x500 ml), brine, dried over $MgSO_4$, filtered and evaporated in vacuo. Purification by column chromatography gave the cyclised intermediate as white solid (28.7 g, 56%).

Step 8



Lithium bis(trimethylsilyl)amide (1M in THF, 114 ml, 114 mmol) was added dropwise to a solution the product of Step 7 (28.7 g, 45.5 mmol) in tetrahydrofuran (300 ml) stirring at -2 °C (internal temperature). The reaction mixture was stirred for 1 hour at 0 °C under nitrogen, then cooled to -78 °C and treated with ethyl iodide (4.7

ml, 59.2 mmol). The reaction mixture was stirred at -25 °C for 18 hours then warmed to -8 °C and then to room temperature over 2 hours. The reaction was diluted with ethyl acetate (500 ml), water (500 ml) and acidified with citric acid solution (500 ml). The ethyl acetate layer separated and the aqueous layer was extracted with ethyl acetate (3x500 ml). The organics combined, washed with brine, dried over $MgSO_4$, filtered and evaporated in vacuo. Purification by column chromatography gave the alkylated intermediate as a white foam (23.1 g, 77%).

Step 9: (3S,4aR,6R,8aS)-6-(2,5-difluorophenyl)-3-ethyl-6-{[4-(trifluoromethyl)phenyl] sulfonyl}octahydro-1H-2,1-benzothiazine 2,2-dioxide

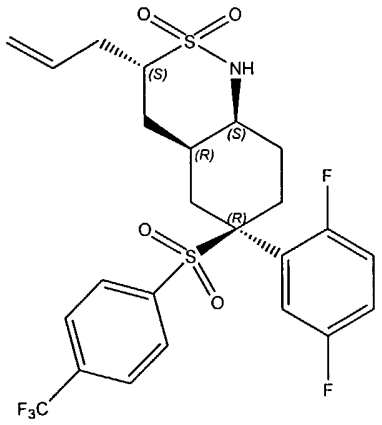
A solution of the product of Step 8 (23.1 g) in dichloromethane (115ml) was treated with trifluoroacetic acid (60ml) dropwise over 5 minutes, and stirred at room temperature under nitrogen for 30 minutes. The reaction mixture was evaporated in vacuo and purified by column chromatography gave the title product as white foam (17 g, 90%, 98.5% ee).

The white foam (17 g, 98.5%ee) was dissolved in ethyl acetate (34ml) and heated to 70 °C. Heptane (136ml) was added portionwise to the stirred solution under nitrogen. After 2 hours the reaction solution was seeded with a homochiral sample of the title compound and allowed to stir for a further 1 hour and then cooled to room temperature. The resulting white solid was collected by filtration (12 g, 99.5% ee).

^{1}H NMR δ (ppm)($CDCl_3$): 7.67 (2 H, d, J = 8.3 Hz), 7.56 (2 H, s), 7.11-7.07 (1 H, m), 6.98-6.83 (2 H, m), 4.71-4.58 (1 H, m), 3.68 (1 H, s), 3.12 (1 H, q, J = 9.8 Hz), 2.73 (1 H, t, J = 13.5 Hz), 2.54-2.40 (3 H, m), 2.17-1.91 (4 H, m), 1.65-1.48 (3 H, m), 1.14 (3 H, t, J = 7.5 Hz).

Example 56

(3S,4aR,6R,8aS)-6-(2,5-difluorophenyl)-3-(2-propenyl)-6-{[4-(trifluoromethyl)phenyl]sulfonyl}-octahydro-1H-2,1-benzothiazine 2,2-dioxide

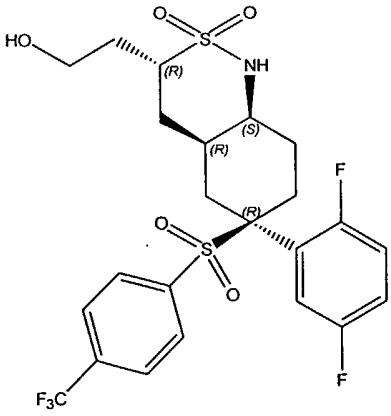


Prepared by the method of Example 55, substituting allyl iodide for ethyl iodide in Step 8.

^{1}H NMR δ (ppm)($CDCl_3$): 7.72-7.58 (4H, m), 7.20-6.75 (3H, m), 5.90-5.80 (1H, m), 5.37-5.16 (3H, m), 3.70 (1H, s), 3.37 (1H, s), 2.90-2.70 (2H, m), 2.54-2.40 (3H, m), 2.33-2.15 (1H, m), 2.00-1.94 (3H, m), 1.80-1.52 (2H, m).

Example 57

(3R,4aR,6R,8aS)-6-(2,5-difluorophenyl)-3-(2-hydroxyethyl)-6-{[4-(trifluoromethyl)phenyl]sulfonyl}-octahydro-1H-2,1-benzothiazine 2,2-dioxide

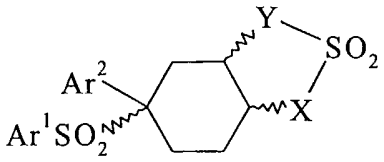


Prepared from the product of Example 56 by treatment with ozone followed by sodium borohydride using the procedure described in Example 55 Step 2.

^{1}H NMR δ (ppm)(CD_3OD): 7.81 (2H, d, J = 8.2Hz), 7.64 (2H, d, J = 8.0Hz), 7.19 (2H, t, J = 7.9Hz), 7.00-6.94 (1H, m), 3.82-3.70 (2H, m), 3.57 (1H, s), 3.35 (2H, s), 2.80-2.40 (4H, m), 2.21-2.13 (2H, m), 2.01 (2H, s), 1.88 (1H, d, J = 14.6Hz), 1.63-1.53 (3H, m).

CLAIMS

1. A compound according to formula I:



I

wherein the bonds indicated by wavy lines are mutually *cis* with respect to the cyclohexane ring;

X represents O, NR^1 or CHR^1;

Y represents CHR^2-CHR^3, CR^2=CR^3, CHR^2-NR^4 or CHR^2-O;

R^1 represents H or C_{1-4}alkyl;

R^2, R^3 and R^4 independently represent H or a hydrocarbon group of up to 10 carbon atoms, optionally substituted with CF_3, CHF_2, halogen, CN, OR^5, COR^5, CO_2R^5, $OCOR^6$, $N(R^5)_2$, $CON(R^5)_2$ or NR^5COR^6; or R^2 and R^4 together complete a 5- or 6-membered ring which is optionally substituted with oxo, CF_3, CHF_2, halogen, CN, OR^5, COR^5, CO_2R^5, $OCOR^6$, $N(R^5)_2$, $CON(R^5)_2$ or NR^5COR^6;

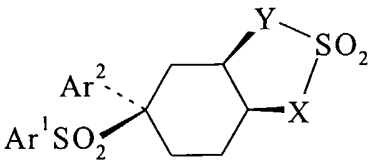
R^5 represents H or C_{1-4}alkyl;

R^6 represents C_{1-4}alkyl; and

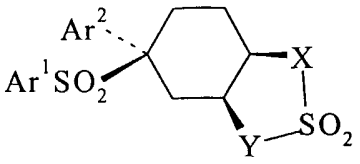
Ar^1 and Ar^2 independently represent phenyl or heteroaryl, either of which bears 0-3 substituents independently selected from halogen, CN, NO_2, CF_3, CHF_2, OH, OCF_3, CHO, CH=NOH, C_{1-4}alkoxy, C_{1-4}alkoxycarbonyl, C_{2-6}acyl, C_{2-6}alkenyl and C_{1-4}alkyl which optionally bears a substituent selected from halogen, CN, NO_2, CF_3, OH and C_{1-4}alkoxy;

or a pharmaceutically acceptable salt thereof.

2. A compound according to claim 1 for formula IA or IB:



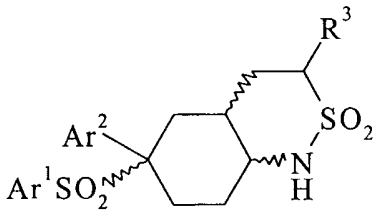
IA



IB

or a pharmaceutically acceptable salt thereof.

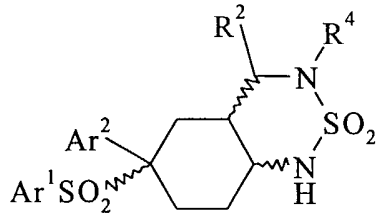
3. A compound according to claim 1 or claim 2 of formula II:



II

or a pharmaceutically acceptable salt thereof.

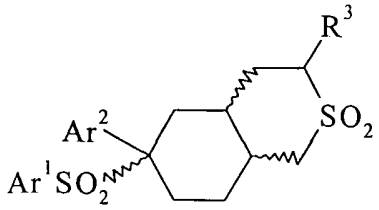
4. A compound according to claim 1 or claim 2 of formula III:



III

or a pharmaceutically acceptable salt thereof.

5. A compound according to claim 1 or claim 2 of formula IV:



IV

or a pharmaceutically acceptable salt thereof.

6. A compound according to any previous claim wherein Ar^1 is selected from 6-(trifluoromethyl)-3-pyridyl and phenyl which is optionally substituted in the 4-position with halogen, CN, vinyl, allyl, acetyl, methyl or mono-, di- or trifluoromethyl; and Ar^2 represents 2,5-difluorophenyl, 2,6-difluorophenyl or 2,3,6-trifluorophenyl.

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

8. A compound according to any of claims 1-6 for use in a method of treatment of the human body.

9. Use of a compound according to any of claims 1-6 in the manufacture of a medicament for treating or preventing Alzheimer's disease.

10. 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 1-6.

INTERNATIONAL SEARCH REPORT

rnational Application No
PCT/GB2004/001973

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D285/16 C07D513/04 C07D335/06 C07D279/02 A61K31/382 A61K31/5415

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, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 01/70677 A (MERCK FROSST CANADA INC ; BELANGER PATRICE CHARLES (CA); COLLINS IAN J) 27 September 2001 (2001-09-27) page 2, line 24 - line 27 claim 1	1,9

☐ 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
6 August 2004	17/08/2004

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	Fanni, S

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.: 8, 10
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 8 and 10 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

national Application No
..T/GB2004/001973

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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
		US 2004029862 A1	12-02-2004
		AU 1074702 A	15-05-2002
		CA 2427206 A1	10-05-2002
		EP 1334085 A1	13-08-2003
		WO 0236555 A1	10-05-2002
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		US 2004049038 A1	11-03-2004