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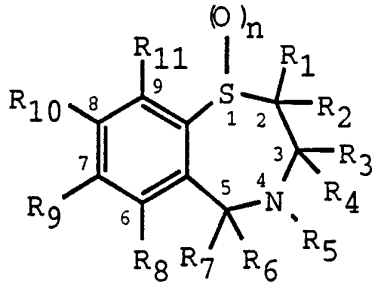

(I)

(57) Abstract

Compounds of formula (I) in which n = 0, 1 or 2; R_1, R_2, R_6 and R_7 independently represent H or alkyl (optionally substituted by one or more halo); R_3 and R_4 independently represent H or alkyl or together represent a group of formula = NR_{12} where R_{12} represents H, hydroxy, alkyl, phenyl or alkoxy; each alkyl, phenyl and alkoxy being optionally substituted with one or more halo; R_5 represents: (a) H, (b) alkyl, (c) a group of formula $-COR_{13}$ in which R_{13} is H, alkyl or phenyl, when R_3 and R_4 represent H or alkyl (optionally substituted with one or more halo), or (d) a group of formula $-S(O)_pR_{14}$ in which p = 1 or 2 and R_{14} is alkyl or phenyl, when R_3 and R_4 represent H or alkyl (optionally substituted with one or more halo); each alkyl and phenyl optionally substituted with one or more halo; and R_8 to R_{11} independently represent H, halo, cyano, nitro, alkyl alkoxy, alkanoyl, carboxy, alkanoyloxy, carbamoyl (optionally substituted with alkyl) or sulphamoyl (optionally substituted with alkyl of 1 to 4 carbon atoms); each alkyl, alkoxy, alkanoyl or alkanoyloxy optionally substituted with one or more halo; have utility in the treatment of seizures and/or neurological disorders such as epilepsy and/or as neuroprotective agents to protect against conditions such as stroke.

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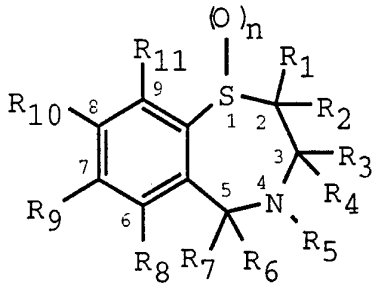
1,4-BENZOTHIAZEPINES USEFUL AS NEUROLOGICAL AGENTS

This invention relates to derivatives of 2,3,4,5-tetrahydro-1,4-benzothiazepines, to pharmaceutical compositions containing them, to processes for their preparation and to their use in the treatment of seizures and/or neurological disorders such as epilepsy and/or as neuroprotective agents to protect against conditions such as stroke.

In particular the present invention provides compounds of formula I



I

in which:

n = 0, 1 or 2;

R_1, R_2, R_6 and R_7 independently represent H or alkyl of 1 to 4 carbon atoms (optionally substituted with one or more halo);

R_3 and R_4 independently represent H or alkyl of 1 to 4 carbon atoms; or together represent a group of formula $=NR_{12}$ where R_{12} represents H, hydroxy, alkyl of 1 to 4 carbon atoms, phenyl or alkoxy of 1 to 4 carbon atoms; each alkyl, phenyl and alkoxy being optionally substituted with one or more halo;

R_5 represents: (a) H, (b) alkyl of 1 to 4 carbon atoms, (c) a group of formula $-COR_{13}$ in which R_{13} represents H, alkyl of 1 to 4 carbon atoms or phenyl, when R_3 and R_4 represent H or alkyl (optionally substituted with one or more halo), or (d) a group of formula $-S(O)_pR_{14}$ in

which p = 1 or 2 and R_{14} is alkyl of 1 to 4 carbon atoms or phenyl, when R_3 and R_4 represent H or alkyl (optionally substituted with one or more halo); each alkyl and phenyl being optionally substituted with one or more halo;

R_8 to R_{11} independently represent H, halo, cyano, nitro, alkyl of 1 to 4 carbon atoms, alkoxy of 1 to 4 carbon atoms, alkanoyl of 1 to 4 carbon atoms, carboxy, alkanoyloxy of 1 to 4 carbon atoms, carbamoyl (optionally substituted with alkyl of 1 to 4 carbon atoms) or sulphamoyl (optionally substituted with alkyl of 1 to 4 carbon atoms); each alkyl, alkoxy, alkanoyl and alkanoyloxy being optionally substituted with one or more halo;

their stereoisomers; and

pharmaceutically acceptable salts thereof;

with the proviso that when n = 0, at least one of R_1 to R_{11} is other than H;

have utility in the treatment of seizures and/or neurological disorders such as epilepsy and/or as neuroprotective agents to protect against conditions such as stroke.

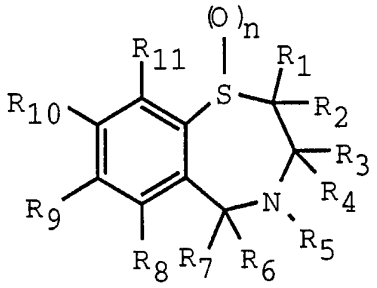
Compounds of formula I where n = 0; R_1 to R_4, R_6 to R_8 and R_{11} are all H; and either: R_5 is H or acetyl, and R_9 and R_{10} are both methoxy; or R_5 and R_{10} are both H, and R_9 is methoxy; are known from: Szabo et al Chem Ber 119, 2904-2913 (1986); and international patent application WO 92/12148 (Kanebo).

Compounds of formula I where n = 0 or 2; R_1 to R_6 and R_{10} to R_{11} are all H; R_7 is methyl; and R_8 and R_9 are both methoxy; are known from J. Org. Chem. 30(8) 2812-2813, 1965 (Eng).

Compounds of formula I where n = 0; R_1, R_2, R_5, R_6 and R_7 are all H; R_3 is a straight chain alkyl of 1 to 4 carbon atoms; R_4 is a straight chain alkyl of 2 to 4 carbon atoms; and R_8 to R_{11} are independently H, halo, nitro, alkyl of 1 to 4 carbon atoms, haloalkyl of 1 to 4 carbon atoms, alkoxy of 1 to 4 carbon atoms or haloalkoxy of 1 to 4 carbon atoms; are known as intermediates in the preparation of the compounds claimed in international patent application WO 93/16055 (Wellcome).

Compounds of formula I where n = 0; R_1 to R_3 and R_6 to R_{11} are all H; and either: R_4 is H, and R_5 is H, ethyl, acetyl or benzoyl; or R_4 is methyl, and R_5 is H; are known from Boudet et al, C. R. Acad Sc. Paris t.282 (26/01/79), Series C p 249-251; patent application DE 3,837,575 (Bayer); and Indian J. Chem. 7(9) 862-5 (Eng) 1969.

Therefore the present invention provides novel compounds of formula II



II

in which:

n = 0, 1 or 2;

R_1, R_2, R_6 and R_7 independently represent H or alkyl of 1 to 4 carbon atoms (optionally substituted with one or more halo);

R_3 and R_4 independently represent H or alkyl of 1 to 4 carbon atoms; or together represent a group of formula

$=NR_{12}$ where R_{12} represents H, hydroxy, alkyl of 1 to 4 carbon atoms, phenyl or alkoxy of 1 to 4 carbon atoms; each alkyl, phenyl and alkoxy being optionally substituted with one or more halo;

R_5 represents: (a) H, (b) alkyl of 1 to 4 carbon atoms, (c) a group of formula $-COR_{13}$ in which R_{13} represents H, alkyl of 1 to 4 carbon atoms or phenyl, when R_3 and R_4 represent H or alkyl (optionally substituted by one or more halo), or (d) a group of formula $-S(O)_pR_{14}$ in which p = 1 or 2 and R_{14} is alkyl of 1 to 4 carbon atoms or phenyl, when R_3 and R_4 represent H or alkyl (optionally substituted by one or more halo); each alkyl and phenyl being optionally substituted with one or more halo;

R_8 to R_{11} independently represent H, halo, cyano, nitro, alkyl of 1 to 4 carbon atoms, alkoxy of 1 to 4 carbon atoms, alkanoyl of 1 to 4 carbon atoms, carboxy, alkanoyloxy of 1 to 4 carbon atoms, carbamoyl (optionally substituted with alkyl of 1 to 4 carbon atoms) or sulphamoyl (optionally substituted with alkyl of 1 to 4 carbon atoms); each alkyl, alkoxy, alkanoyl and alkanoyloxy being optionally substituted with one or more halo;

their stereoisomers; and

pharmaceutically acceptable salts thereof;

with the provisos that:

when n = 0; R_1 to R_4, R_6 to R_8 and R_{11} are all H; and either: when R_5 is H or acetyl, R_9 and R_{10} are both other than methoxy; or when R_5 and R_{10} are both H, R_9 is other than methoxy;

when n = 0 or 2; R_1 to R_6 and R_{10} to R_{11} are all H; and R_7 is methyl; R_8 and R_9 are both other than methoxy;

when n = 0; R_1, R_2, R_5, R_6 and R_7 are all H; R_3 is alkyl; and R_8 to R_{11} are independently H, halo, nitro, alkyl, haloalkyl, alkoxy or haloalkoxy, R_4 is other than alkyl of 2 to 4 carbon atoms;

when n = 0; R_1 to R_3 and R_6 to R_{11} are all H; and either: when R_4 is H, R_5 is other than H, ethyl, acetyl or benzoyl; or when R_4 is methyl, R_5 is other than H.

Preferred compounds of formula I or II are those in which:

n = 0 or 1;

R_1, R_2, R_6 and R_7 are independently H or methyl;

R_3 and R_4 are independently H or methyl; or together represent imino, methylimino, phenylimino, hydroxyimino or methoxyimino;

R_5 is H or methyl, and when R_3 and R_4 are H or methyl, R_5 is formyl, acetyl, propionyl, benzoyl, methylsulphinyl, methylsulphonyl or ethylsulphonyl;

one of R_8 to R_{11} is H, fluoro, chloro, bromo, iodo, methyl (optionally substituted with one or more halo), methoxy (optionally substituted by one or more halo), nitro, cyano, carboxy, acetyl, dimethylcarbamoyl or dimethylsulphamoyl; the remainder of R_8 to R_{11} being H;

their stereoisomers; and

pharmaceutically acceptable salts thereof.

More preferred compounds of formula I or II are those in which:

n = 0 or 1;

R_1, R_2, R_6 and R_7 are H;

R_3 and R_4 are H; or together are methylimino, phenylimino, hydroxyimino or methoxyimino;

R_5 is H or methyl, and when R_3 and R_4 are H, R_5 is formyl, acetyl, propionyl, benzoyl, methylsulphinyl, methylsulphonyl or ethylsulphonyl;

R_8 is methyl, fluoro or chloro;

R_9 to R_{11} are all H;

their stereoisomers; and

pharmaceutically acceptable salts thereof.

Specific compounds of formula I or II in which n = 0 are:

6-chloro-2,3,4,5-tetrahydro-1,4-benzothiazepine;
6-fluoro-2,3,4,5-tetrahydro-1,4-benzothiazepine;
6-methyl-2,3,4,5-tetrahydro-1,4-benzothiazepine;
6-chloro-4-methyl-2,3,4,5-tetrahydro-1,4-benzothiazepine;
4-formyl-2,3,4,5-tetrahydro-1,4-benzothiazepine;
4-acetyl-2,3,4,5-tetrahydro-1,4-benzothiazepine;
4-acetyl-6-chloro-2,3,4,5-tetrahydro-1,4-benzothiazepine;
4-acetyl-6-fluoro-2,3,4,5-tetrahydro-1,4-benzothiazepine;
4-acetyl-6-methyl-2,3,4,5-tetrahydro-1,4-benzothiazepine;
4-propionyl-2,3,4,5-tetrahydro-1,4-benzothiazepine;
6-chloro-4-propionyl-2,3,4,5-tetrahydro-1,4-benzothiazepine;
4-benzoyl-6-chloro-2,3,4,5-tetrahydro-1,4-benzothiazepine;
6-chloro-4-methylsulphinyl-2,3,4,5-tetrahydro-1,4-benzothiazepine;
4-methylsulphonyl-2,3,4,5-tetrahydro-1,4-benzothiazepine;
6-chloro-4-methylsulphonyl-2,3,4,5-tetrahydro-1,4-benzothiazepine;
6-fluoro-4-methylsulphonyl-2,3,4,5-tetrahydro-1,4-benzothiazepine;
6-methyl-4-methylsulphonyl-2,3,4,5-tetrahydro-1,4-benzothiazepine;
4-ethylsulphonyl-2,3,4,5-tetrahydro-1,4-benzothiazepine;
6-chloro-4-ethylsulphonyl-2,3,4,5-tetrahydro-1,4-benzothiazepine;
3-hydroxyimino-2,3,4,5-tetrahydro-1,4-benzothiazepine;
6-chloro-3-hydroxyimino-2,3,4,5-tetrahydro-1,4-benzothiazepine;

3-hydroxyimino-6-methyl-2,3,4,5-tetrahydro-1,4-benzothiazepine;
3-methoxyimino-2,3,4,5-tetrahydro-1,4-benzothiazepine;
6-chloro-3-methoxyimino-2,3,4,5-tetrahydro-1,4-benzothiazepine;
3-methylimino-2,3,4,5-tetrahydro-1,4-benzothiazepine;
6-chloro-3-phenylimino-2,3,4,5-tetrahydro-1,4-benzothiazepine;
their stereoisomers; and
pharmaceutically acceptable salts thereof.

Specific compounds of formula I or II in which n = 1 are:
6-chloro-2,3,4,5-tetrahydro-1,4-benzothiazepine 1-oxide;
4-acetyl-2,3,4,5-tetrahydro-1,4-benzothiazepine 1-oxide;
4-acetyl-6-chloro-2,3,4,5-tetrahydro-1,4-benzothiapine 1-oxide;
4-methylsulphonyl-2,3,4,5-tetrahydro-1,4-benzothiazepine 1-oxide;
6-chloro-4-methylsulphonyl-2,3,4,5-tetrahydro-1,4-benzothiazepine 1-oxide;
their stereoisomers; and
pharmaceutically acceptable salts thereof.

It will be understood that a group containing a chain of three or more carbon atoms may be straight or branched. The term 'halo' as used herein signifies fluoro, chloro, bromo or iodo.

Certain compounds of formula I or II may form salts with organic or inorganic acids. Reference hereinafter to compounds of formula I or II includes all such salts of compounds of formula I or II which are pharmaceutically acceptable. Particularly suitable

salts of compounds of formula I or II include, for example, salts with inorganic acids, for example hydrochlorides, hydrobromides, hydriodides, nitrates, sulphates and phosphates, salts with organic acids, for example maleates, acetates, citrates, fumarates, tartrates, succinates, benzoates, pamoates, palmitates, methylsulphates, dodecanoates and salts with acidic amino acids such as glutamic acid. It will be appreciated that such salts, provided they are pharmaceutically acceptable, may be used in therapy in place of the corresponding compounds of formula I or II. Such salts are prepared by reacting the compound of formula I or II with a suitable acid in a conventional manner.

Certain compounds of formula I or II or their salts may exist in more than one crystal form and the present invention includes each crystal form and mixtures thereof.

Certain compounds of formula I or II or their salts may also exist in the form of solvates, for example hydrates, and the present invention includes each solvate and mixtures thereof.

It will be appreciated by those skilled in the art that certain compounds of formula I or II contain one or more chiral centres. Thus, for example compounds of formula I or II in which n is 1 contain a chiral centre at the sulphur atom; compounds of formula I or II in which R_1 and R_2 are not identical contain a chiral centre at the 2-carbon atom; compounds of formula I or II in which R_3 and R_4 are not identical contain a chiral centre at the 3-carbon atom; and compounds of formula I or II in which R_6 and R_7 are not identical contain a chiral centre at the 5-carbon atom. A compound of

formula I or II containing a single chiral centre may exist in two enantiomeric forms. The present invention includes each enantiomer of compounds of formula I or II and mixtures thereof.

The enantiomers may be obtained by methods known to those skilled in the art. Such methods typically include:
resolution via formation of diastereoisomeric salts or complexes which may be separated, for example, by crystallisation;
formation of diastereoisomeric derivatives or complexes which may be separated, for example, by crystallisation, gas-liquid chromatography or liquid chromatography, followed by the liberation of the desired enantiomer from the separated derivative;
selective derivatisation of one enantiomer by reaction with an enantiomer-specific reagent, for example enzymatic esterification, oxidation or reduction, followed by separation of the modified and unmodified enantiomers; or
gas-liquid chromatography or liquid chromatography in a chiral environment, for example on a chiral support such as silica with a bound chiral ligand, or in the presence of a chiral solvent.

Alternatively, it may be possible to synthesise a specific enantiomer by asymmetric synthesis using optically active reagents, substrates, catalysts or solvents, or to convert one enantiomer into the other by asymmetric transformation.

When a compound of formula I or II contains more than one chiral centre it may exist in diastereoisomeric forms. The diastereoisomeric pairs may be separated by methods known to those skilled in the art, for example

chromatography or crystallisation and the individual enantiomers within each pair may be separated as described above. The present invention includes each diastereoisomer of compounds of formula I or II and mixtures thereof.

It will be appreciated that where the active moiety is transformed by the separation procedures described above, a further step may be required to convert the transformation product back to the active moiety.

Certain compounds of formula I or II may exist in different tautomeric forms or as different geometric isomers, for example when R_3 and R_4 together represent a group of formula $=NR_{12}$. The present invention includes each tautomer and/or geometric isomer and mixtures thereof.

Certain compounds of formula I or II may exist in zwitterionic form and the present invention includes each zwitterionic form and mixtures thereof.

The present invention also relates to pharmaceutical compositions comprising a therapeutically effective amount of a compound of formula I or II together with a pharmaceutically acceptable diluent or carrier. Such pharmaceutical compositions may be used as neuroprotective agents to protect against conditions such as stroke and/or for the treatment of seizures and/or neurological disorders such as epilepsy. Specific compounds which may be incorporated into the compositions of the present invention are the compounds exemplified herein.

As used hereinafter, the term 'active compound' denotes one or more compound or compounds of formula I

or II. In therapeutic use, the active compound may be administered orally, rectally or parenterally, preferably orally. Thus the therapeutic compositions of the present invention may take the form of any of the known pharmaceutical compositions for such methods of administration. The compositions may be formulated in a manner known to those skilled in the art, to give a controlled release, for example rapid release or sustained release, of the active compound. Pharmaceutically acceptable carriers suitable for use in such compositions are well known in the art of pharmacy. The compositions may contain from about 0.1% to about 99% by weight of active compound and are generally prepared in unit dosage form. Preferably the unit dosage of active ingredient is from about 1 mg to about 1000 mg. The excipients used in the preparation of these compositions are the excipients known in the pharmacist's art.

Preferably the compositions of the invention are administered orally in the known pharmaceutical forms for such administration. Dosage forms suitable for oral administration may comprise tablets, pills, capsules, caplets, granules, powders, elixirs, syrups, solutions and aqueous or oil suspensions.

Solid oral dosage forms, for example tablets, may be prepared by mixing the active compound with one or more of the following ingredients:
inert diluents, for example lactose, powdered sugar, pharmaceutical grade starch, kaolin, mannitol, calcium phosphate or calcium sulphate;
disintegrating agents, for example maize starch, methyl cellulose, agar, bentonite, cellulose, wood products, alginic acid, guar gum, citrus pulp, carboxymethylcellulose or sodium lauryl sulphate;

lubricating agents, for example magnesium stearate, boric acid, sodium benzoate, sodium acetate, sodium chloride, leucine or polyethylene glycol;
binders, for example starch, gelatin, sugars (such as sucrose, molasses or lactose), or natural and synthetic gums (such as acacia, sodium alginate, extract of Irish moss, carboxymethylcellulose, methylcellulose, ethylcellulose, polyethylene glycol, waxes, micro-crystalline cellulose or polyvinylpyrrolidone);
colouring agents, for example conventional pharmaceutically acceptable dyes;
sweetening and flavouring agents;
preservatives; and
other optional ingredients known in the art to permit production of oral dosage forms by known methods such as tabletting.

Solid oral dosage forms may be formulated in a manner known to those skilled in the art so as to give a sustained release of the compounds of the present invention. For example tablets or pills may, if desired, be provided with enteric coatings by known methods, for example by the use of cellulose acetate phthalate and/or hydroxypropylmethylcellulose phthalate.

Capsules or caplets, for example hard or soft gelatin capsules, containing the active compound with or without added excipients, for example a fatty oil, may be prepared by conventional means and, if desired, provided with enteric coatings in a known manner. The contents of the capsule or caplet may be formulated using known methods to give sustained release of the active compound. Enteric coated, solid oral dosage forms comprising compositions of the invention may be advantageous, depending on the nature of the active compound. Various materials, for example shellac

and/or sugar, may be present as coatings, or to otherwise modify the physical form of the oral dosage form.

Liquid oral dosage forms comprising compositions of the invention may be elixirs, solutions, suspensions or syrups, for example, aqueous suspensions containing the active compound in an aqueous medium in the presence of a non-toxic suspending agent such as sodium carboxymethylcellulose; or oily suspensions containing a compound of the present invention in a suitable vegetable oil, for example arachis oil or sunflower oil. Liquid oral dosage forms may also comprise sweetening agents, flavouring agents and/or preservatives.

The active compound may be formulated into granules or powders with or without additional excipients. The granules or powders may be ingested directly by the patient or they may be added to a suitable liquid carrier (for example water) before ingestion. The granules or powders may contain disintegrants (for example a pharmaceutically acceptable effervescent couple formed from an acid and a carbonate or bicarbonate salt) to facilitate dispersion in the liquid medium.

Each of the above oral dosage forms may conveniently contain from about 1 mg to about 1000 mg of the active compound.

Compositions of the invention may be administered rectally in the known pharmaceutical forms for such administration, for example, suppositories with hard fat, semi-synthetic glyceride, cocoa butter or polyethylene glycol bases.

Compositions of the invention may also be administered parenterally, for example by intravenous injection, in the known pharmaceutical forms for such administration, for example sterile suspensions in aqueous or oily media, or sterile solutions in a suitable solvent.

The active compound may also be administered by continuous infusion either from an external source, for example by intravenous infusion, or from a source of the compound placed within the body. Internal sources include implanted reservoirs containing the compound to be infused which is continuously released (for example by osmosis) or implants. Implants may be liquid, such as a suspension or solution in a pharmaceutically acceptable oil of the compound to be infused (for example in the form of a very sparingly water-soluble derivative such as a dodecanoate salt or ester). Implants may be solid in the form of an implanted support (for example a synthetic resin or waxy material) for the compound to be infused. The support may be a single body containing all the compound or a series of several bodies each containing part of the compound to be delivered. The amount of active compound present in an internal source should be such that a therapeutically effective amount of the compound is delivered over a long period of time.

In some formulations it may be beneficial to use the active compound, or pharmaceutical compositions containing the active compound, in the form of particles of very small size, for example as obtained by fluid energy milling.

In the above compositions the active compound may, if desired, be associated with other compatible pharmacologically active ingredients.

A further aspect of the present invention provides use of compounds of formula I or II in the preparation of a medicament for the treatment of seizures and/or neurological disorders such as epilepsy and/or for neuroprotection to protect against conditions such as stroke.

A still further aspect of the present invention provides a method of treating seizures and/or neurological disorders such as epilepsy and/or a method of neuroprotection to protect against conditions such as stroke, which comprises the administration to patient in need thereof a therapeutically effective amount of compounds of formula I or II and/or a pharmaceutical compositions containing a therapeutically effective amount of compounds of formula I or II. Thus compounds of formula I or II are useful for the inhibition of seizures and/or neurological disorders such as epilepsy and/or as neuroprotective agents to protect against conditions such as stroke.

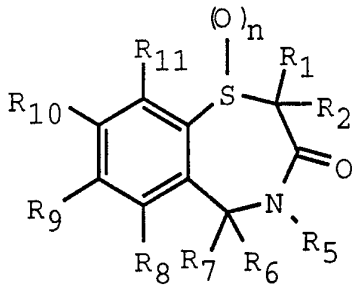
Whilst the precise amount of the active compound administered in the treatments outlined above will depend on a number of factors, for example the severity of the condition, the age and past medical history of the patient, and always lies within the sound discretion of the administering physician, a suitable daily dose of compounds of formula I or II for administration to human beings, is generally from about 1 mg to about 5000 mg, more usually from about 5 mg to about 1000 mg, given in a single dose or in divided doses at one or more times during the day. Oral administration is preferred.

Compounds of formula I or II may be used in adjunctive therapy with one or more other compounds having activity in the treatment of seizures and/or neurological disorders such as epilepsy and/or as neuroprotective agents to protect against conditions such as stroke. It will be appreciated that the term therapy as used herein includes prophylactic use of compounds of formula I or II and pharmaceutical compositions containing compounds of formula I or II, for example as neuroprotective agents to protect against conditions such as stroke or to prevent the onset of epileptic seizures. Compounds of formula I or II and pharmaceutical compositions containing compounds of formula I or II may be used to provide a local and/or systemic therapeutic effect.

The therapeutic activity of compounds of formula I or II has been demonstrated by means of tests in standard laboratory animals. Such tests include, for example, the tests of anticonvulsant activity in mice described below.

Processes for the preparation of compounds of formula I or II will now be described. These processes form a further aspect of the present invention.

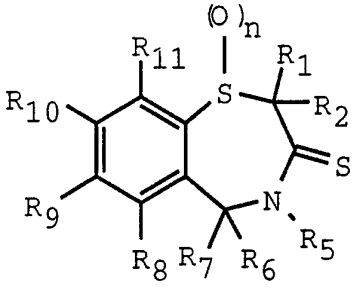
Compounds of formula I or II, in which R_3 and R_4 are both H and R_5 is H or alkyl may be prepared by reducing a compound of formula III



III

in which R_5 is H or alkyl, with a reducing agent, for example lithium aluminium hydride or borane-dimethyl-sulphide complex. Compounds of formula III are known and can be prepared as described in international patent application WO 92/21668.

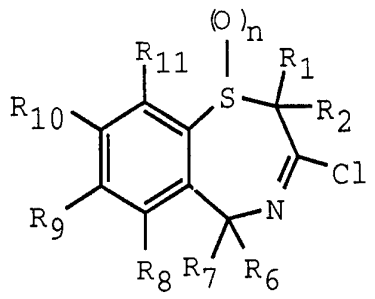
Compounds of formula I or II in which R_3 and R_4 together are a group of formula $=NR_{12}$ may be prepared by the reaction of compounds of formula IV



IV

with a compound of formula $R_{12}NH_2$.

Compounds of formula I or II in which R_3 and R_4 together are a group of formula $=NR_{12}$ and R_5 is H may be prepared by the reaction of compounds of formula V



V

with a compound of formula $R_{12}NH_2$.

Compounds of formula I or II in which R_3 and R_4 together are alkoxyimino may be prepared by the reaction between compounds of formula I or II in which R_3 and R_4 together are hydroxyimino with an alkylating agent such as an alkylsulphate.

Compounds of formula I or II in which R_3 and R_4 are H or alkyl and R_5 is alkyl may be prepared by alkylation of compounds of formula I or II in which R_5 is H for example; by using an alkylating agent such as an alkyl halide; or by reductive alkylation with an aldehyde or a ketone and formic acid, or a reducing agent such as sodium cyanoborohydride; or by reducing a compound of formula I or II in which R_5 is a group of formula $-COR_{13}$.

Compounds of formula I or II in which R_5 is a group of formula $-COR_{13}$ may be prepared by acylation of compounds of formula I or II in which n = 0 or 2 and R_5 is H, for example with an acid chloride of formula $R_{13}COCl$, an acid anhydride of formula $(R_{13}CO)_2O$ or an acid of formula $R_{13}CO_2H$.

Compounds of formula I or II in which R_5 is a group of formula $-S(O)_pR_{14}$ may be prepared by the reaction of compounds of formula I or II in which R_5 is H, with a

sulphonylating agent such as a sulphonyl chloride of formula $R_{14}SO_2Cl$, or a sulphinylating agent such as a sulphinyl chloride of formula $R_{14}SOCl$. For example, compounds of formula I or II in which R_5 is $-SO_2Me$ may be prepared by the reaction of a compound of formula I or II in which R_5 is H with methanesulphonyl chloride.

Compounds of formula I or II in which n = 1 may be prepared by the oxidation of compounds of formula I or II in which n = 0, for example using sodium periodate or 3-chloroperbenzoic acid.

Compounds of formula I or II in which n = 2 may be prepared by the oxidation of compounds of formula I or II in which n = 0 or 1, for example using peracetic acid or 3-chloroperbenzoic acid.

Compounds of formula IV may be prepared by the reaction of compounds of formula III with reagents such as phosphorus pentasulphide or Lawesson's reagent [which is the known compound 2,4-bis(4-methoxyphenyl)-1,3-dithia-2,4-diphosphetane-2,4 disulphide].

Compounds of formula V may be prepared by the reaction of compounds of formula III with a chlorinating agent, for example phosphorus pentachloride or phosphoryl chloride.

The anticonvulsant activity of compounds of formula I or II was demonstrated by the following pharmacological tests.

Firstly, by observing the ability of the compound of formula I or II to antagonise the myoclonic seizures induced by the administration of (+)-bicuculline. Hereinafter, this test is referred to as 'BICM'.

In the BICM experiments groups of female mice in the weight range 25 to 30 grammes had free access to food and water until one hour before administration of the compound of formula I or II to be tested. The compound to be tested was orally administered at one or more doses in 1% aqueous methylcellulose solution. One hour later (+)- bicuculline at a dose of 0.55 mg/kg was administered intravenously into a tail vein. Such a dose of (+)-bicuculline would generally be expected to induce a seizure in the mice.

During the following two minutes the animals were observed and the percentage of animals in which seizures had been inhibited was recorded. Thus, the greater the anticonvulsant activity of the compound, the higher was the percentage recorded in the BICM test. If results at more than one dose were available, then a value for the dose inhibiting the seizures in 50% of the animals (ED_{50}) was calculated from the regression straight line plot of the percentage of animals in which seizures were inhibited against the dose of the compound of formula I or II administered.

The second test of anticonvulsant activity involved observing the ability of a compound to inhibit seizures in mice induced by a maximal electroshock. Hereinafter, this test is referred to as 'MESM'.

In the MESM experiments, groups of male mice in the weight range 25 to 30 grammes had free access to food and water until one hour before administration of the compound of formula I or II to be tested. The compound to be tested was orally administered at one or more doses in 1% aqueous methylcellulose solution. One hour later an electroshock of duration 1.0 second was administered to the mice through ear clip electrodes.

The electroshock had an intensity of 99 mA, frequency of 50 Hz and pulse width of 0.4 ms. Such a shock would generally be expected to induce a seizure in the mice.

During the following two minutes the animals were observed and the percentage of animals in which seizures had been inhibited was recorded. Thus, the greater the anticonvulsant activity of the compound, the higher was the percentage recorded in the MESM test. If results at more than one dose were available, then a value for the dose inhibiting seizures in 50% of the animals (ED_{50}) was calculated from the regression straight line plot of the percentage of animals in which seizures were inhibited against the dose of the compound of formula I or II administered.

The compounds of formula I or II described hereinafter in Examples 1 to 31 have been found to have anticonvulsant activity in at least one of the BICM and MESM tests.

The invention will now be illustrated by the following non-limiting examples. The final product of each example was characterised by one or more of the following; elemental analysis; infra-red spectroscopy; nuclear magnetic resonance spectroscopy; and/or liquid chromatography. Temperatures are given in degrees Celsius.

Example 1

6-Chloro-4,5-dihydro-1,4-benzothiazepin-3(2H)-one (9.8 g, prepared in a similar manner to example 11 of international patent application WO 92/21668) was added to a stirred solution of lithium aluminium hydride (5.01 g) in dry tetrahydrofuran (400 ml), After the addition, the reaction mixture was heated under reflux for five minutes and cooled. Excess lithium aluminium hydride was decomposed by adding a saturated aqueous solution of sodium sulphate. The mixture was filtered and the solvent removed from the filtrate by evaporation. The residue was dissolved in diethyl ether, acidified with hydrogen chloride gas and the precipitated 6-chloro-2,3,4,5-tetrahydro-1,4-benzothiazepine hydrochloride was collected by filtration, and was recrystallised from ethanol. Yield 6.5 g (m.p. 244-246°C).

The ED_{50}, in the BICM test described above, for this compound was 8.2 mg/kg.

Example 2

6-Chloro-4,5-dihydro-1,4-benzothiazepin-3(2H)-one (9.8 g, prepared in a similar manner to example 11 of international patent application WO 92/21668) was added to a stirred solution of lithium aluminium hydride (5.01 g) in dry tetrahydrofuran (400 ml). After the addition, the reaction mixture was heated under reflux for five minutes and then cooled. Excess lithium aluminium hydride was decomposed by adding of a saturated aqueous solution of sodium sulphate. The mixture was filtered and the solvent evaporated from the

filtrate to give 6-chloro-2,3,4,5-tetrahydro-1,4-benzothiazepine as an oil.

A solution of sodium periodate (3.09 g) in water (25 ml) was added dropwise with cooling to a stirred solution of 6-chloro-2,3,4,5-tetrahydro-1,4-benzothiazepine (2.88 g, prepared in a similar manner to that described in the preceding paragraph) in dichloromethane (75 ml). The stirring was continued at room temperature for 19 hours. Solvent was removed from the mixture by evaporation at reduced pressure. Purification of the residue by flash chromatography using dichloromethane/ethanol (95:5) as eluent gave 6-chloro-2,3,4,5-tetrahydro-1,4-benzothiazepine 1-oxide, which was recrystallised from ethyl acetate. Yield 2.15 g (m.p. 125-126°C).

The ED_{50}, in the BICM test described above, for this compound was 2.7 mg/kg.

Example 3

6-Fluoro-4,5-dihydro-1,4-benzothiazepin-3(2H)-one (9 g, prepared in a similar manner to example 5 of international patent application WO 92/21668) was added to a stirred solution of lithium aluminium hydride (5 g) in dry tetrahydrofuran (500 ml). After the addition, the reaction mixture was heated under reflux for ten minutes and cooled. Excess lithium aluminium hydride was decomposed by adding a saturated aqueous solution of sodium sulphate. The mixture was filtered and the solvent removed from the filtrate by evaporation to give an oil, which was dissolved in diethyl ether and acidified with hydrogen chloride gas. The precipitated 6-fluoro-2,3,4,5-tetrahydro-1,4-benzothiazepine

hydrochloride was collected by filtration and was recrystallised from ethanol. Yield 7.43 g (m.p. 265-268°C).

The ED_{50}, in the BICM test described above, for this compound was 17.7 mg/kg.

Example 4

6-Methyl-4,5-dihydro-1,4-benzothiazepin-3(2H)-one (6 g, prepared in a similar manner to example 13 of international patent application WO 92/21668) was added to a stirred solution of lithium aluminium hydride (3.38 g) in dry tetrahydrofuran (340 ml). After the addition, the reaction mixture was heated under reflux for ten minutes, and cooled. Excess lithium aluminium hydride was decomposed by adding a saturated aqueous solution of sodium sulphate. The mixture was filtered and the solvent was removed from the filtrate by evaporation. The residue was dissolved in diethyl ether, acidified with hydrogen chloride gas and the precipitated 6-methyl-2,3,4,5-tetrahydro-1-1,4-benzothiazepine hydrochloride was collected by filtration and was recrystallised from ethanol. Yield 2.87 g (m.p. 248-250°C).

The ED_{50}, in the BICM test described above, for this compound was 66.5 mg/kg.

Example 5

A solution of 6-chloro-4,5-dihydro-1,4-benzothiazepine-3(2H)-one (5.33 g, prepared in a similar manner to example 11 of international patent application

WO 92/21668) in dry dimethylsulphoxide (60 ml) was added slowly at room temperature to a stirred suspension of sodium hydride (0.6 g) in dimethylsulphoxide (20 ml). After the addition was completed, the mixture was stirred for 30 minutes before adding methyl iodide (6 ml) dropwise. The reaction mixture was stirred at room temperature for one hour, water (160 ml) was added and the mixture was extracted with diethyl ether. The organic layer was washed with water and the solvent was removed by evaporation. Purification of the residue by flash chromatography using dichloromethane/ethyl acetate (9.8:0.2) as eluent gave 6-chloro-4-methyl-4,5-dihydro-1,4-benzothiazepin-3(2H)-one. Yield 3.8 g (m.p. 122-125°C).

6-Chloro-4-methyl-4,5-dihydro-1,4-benzothiazepin-3(2H)-one (3.8 g) was added to a stirred solution of lithium aluminium hydride (1.92 g) in dry tetrahydrofuran (160 ml). After the addition, the reaction was heated under reflux for 15 minutes and cooled. Excess lithium aluminium hydride was decomposed by adding a saturated aqueous solution of sodium sulphate. The mixture was filtered and the solvent was removed from the filtrate by evaporation. Purification of the residue by flash chromatography using dichloromethane/ethanol (9.5:0.5) as eluent gave an oil (2.62 g) which was dissolved in diethyl ether and acidified with hydrogen chloride gas. The precipitated 6-chloro-4-methyl-2,3,4,5-tetrahydro-1,4-benzothiazepine hydrochloride was collected by filtration and was recrystallised from ethanol/diethyl ether. Yield 2.38 g (m.p. 209-211°C).

In the BICM test described above, a dosage of 100 mg/kg of this compound inhibited 50% of the mice tested from seizures.

Example 6

4,5-Dihydro-1,4-benzothiazepin-3(2H)-one (12 g, prepared in a similar manner to example 1 of international patent application WO 92/21668) was added to a stirred solution of lithium aluminium hydride (6.3 g) in dry tetrahydrofuran (400 ml). After the addition, the reaction mixture was heated under reflux for ten minutes and cooled. Excess of lithium aluminium hydride was decomposed by adding a saturated aqueous solution of sodium sulphate. The mixture was filtered and the solvent was removed from the filtrate by evaporation to give 2,3,4,5-tetrahydro-1,4-benzothiazepine as an oil which was used without further purification. Yield 9.4 g.

A mixture of 2,3,4,5-tetrahydro-1,4-benzothiazepine (4.56 g), formic acid (20 ml) and toluene (60 ml) was heated under reflux at 90°C for four hours and then at 120°C for a further three hours. The solvent was removed from the mixture by evaporation at reduced pressure. Purification of the residue by flash chromatography using dichloromethane as eluent gave 4-formyl-2,3,4,5-tetrahydro-1,4-benzothiazepine, which was recrystallised from hexane. Yield 3.73 g (m.p. 84-87°C).

The ED_{50}, in the BICM test described above, for this compound was 17.9 mg/kg.

Example 7

A solution of 2,3,4,5-tetrahydro-1,4-benzothiazepine (1.5 g, prepared as described in the first paragraph of Example 6 above) in acetic anhydride

(15 ml) was stirred at room temperature for one hour. The reaction mixture was poured into ice and extracted with dichloromethane. The organic layer was dried and the solvent removed by evaporation to give 4-acetyl-2,3,4,5-tetrahydro-1,4-benzothiazepine, which was recrystallised from hexane. Yield 1.55 g (m.p. 69-70°C).

The ED_{50}, in the BICM test described above, for this compound was 65.7 mg/kg.

Example 8

A solution of 3-chloroperbenzoic acid (1.03 g) in dichloromethane (100 ml) was added dropwise with cooling from 0°C to -2°C to a stirred solution of 4-acetyl-2,3,4,5-tetrahydro-1,4-benzothiazepine (1.03 g, prepared as Example 7 above) in dichloromethane (50 ml). The reaction mixture was stirred for 15 minutes, then washed with water, dried and the solvent was removed by evaporation at reduced pressure. Purification of the residue by flash chromatography using dichloromethane/ethanol (9:1) as eluent gave 4-acetyl-2,3,4,5-tetrahydro-1,4-benzothiazepine 1-oxide, which was recrystallised from ethyl acetate. Yield 0.67 g (m.p. 156-157°C).

The ED_{50}, in the BICM test described above, for this compound was 37.8 mg/kg.

Example 9

A solution of 6-chloro-2,3,4,5-tetrahydro-1,4-benzothiazepine (1.6 g, prepared in a similar manner to

its hydrochloride, Example 1 above) in acetic anhydride (15 ml) was stirred at room temperature for one hour. The reaction mixture was poured into ice and extracted with dichloromethane. The organic layer was dried and the solvent was removed by evaporation to give 4-acetyl-6-chloro-2,3,4,5-tetrahydro-1,4-benzothiazepine, which was recrystallised from hexane. Yield 1.68 g (m.p. 79-81°C).

The ED_{50}, in the BICM test described above, for this compound was 4.6 mg/kg.

The ED_{50}, in the MESM test described above, for this compound was 48.5 mg/kg.

Example 10

A solution of 3-chloroperbenzoic acid (1.14 g) in dichloromethane (100 ml) was added dropwise with cooling from 0°C to -2°C to a stirred solution of 4-acetyl-6-chloro-2,3,4,5-tetrahydro-1,4-benzothiazepine (1.34 g, prepared as Example 9 above) in dichloromethane (50 ml). The reaction mixture was stirred for 15 minutes, washed with water, dried and the solvent was removed by evaporation at reduced pressure. Purification of the residue by flash chromatography using dichloromethane/ethanol (95:5) as eluent gave 4-acetyl-6-chloro-2,3,4,5-tetrahydro-1,4-benzothiazepine 1-oxide, which was recrystallised from ethyl acetate. Yield 1.15 g (m.p. 119-121°C).

The ED_{50}, in the BICM test described above, for this compound was 22.6 mg/kg.

The ED_{50}, in the MESM test described above, for this compound was 52.8 mg/kg.

Example 11

A solution of 6-fluoro-2,3,4,5-tetrahydro-1,4-benzothiazepine (2.04 g, prepared in a similar manner to its hydrochloride, Example 3 above) in acetic anhydride (22 ml) was stirred at room temperature for one hour. The reaction mixture was poured into ice and extracted with dichloromethane. The organic layer was dried and the solvent removed by evaporation. Purification of the residue by flash chromatography using dichloromethane/ethanol (97:3) as eluent gave 4-acetyl-6-fluoro-2,3,4,5-tetrahydro-1,4-benzothiazepine as an oil. Yield 1.7 g.

The ED_{50}, in the BICM test described above, for this compound was 21.5 mg/kg.

Example 12

A solution of 6-methyl-2,3,4,5-tetrahydro-1,4-benzothiazepine (0.91 g, prepared in a similar manner to its hydrochloride, Example 4 above) in acetic anhydride (10 ml) was stirred at room temperature for one hour. The reaction mixture was poured into ice and extracted with dichloromethane. The organic layer was dried and the solvent removed by evaporation to give 4-acetyl-6-methyl-2,3,4,5-tetrahydro-1,4-benzothiazepine, which was recrystallised from hexane. Yield 0.93 g (m.p. 71-73°C).

The ED_{50}, in the BICM test described above, for this compound was 49.4 mg/kg.

In the MESM test described above, a dosage of 100 mg/kg of this compound inhibited 50% of the mice tested from seizures.

Example 13

A solution of propionyl chloride (2.39 g) in dichloromethane (50 ml) was added dropwise at room temperature to a stirred solution of 2,3,4,5-tetrahydro-1,4-benzothiazepine (8.58 g, prepared as described in the first paragraph of Example 6 above) in dichloromethane (100 ml). The reaction mixture was stirred at room temperature for 45 minutes, washed with water, dried and the solvent was removed by evaporation. Purification of the residue by flash chromatography using dichloromethane/ethanol (98:2) as eluent gave 4-propionyl-2,3,4,5-tetrahydro-1,4-benzothiazepine as an oil. Yield 2.9 g.

The ED_{50}, in the BICM test described above, for this compound was 48.1 mg/kg.

Example 14

A solution of propionyl chloride (0.92 g) in dichloromethane (10 ml) was added dropwise at room temperature to a stirred solution of 6-chloro-2,3,4,5-tetrahydro-1,4-benzothiazepine (1.99 g, prepared in a similar manner to its hydrochloride, Example 1 above) and triethylamine (1.01 g) in dichloromethane (50 ml). The reaction mixture was stirred at room temperature for

30 minutes, washed with water, dried and the solvent was removed by evaporation. Purification of the residue by flash chromatography using dichloromethane as eluent gave 6-chloro-4-propionyl-2,3,4,5-tetrahydro-1,4-benzothiazepine, which was recrystallised from hexane. Yield 1.14 g (m.p. 55-57°C).

The ED_{50}, in the BICM test described above, for this compound was 44.7 mg/kg.

Example 15

A solution of benzoyl chloride (3.93 g) in dichloromethane (50 ml) was added dropwise at room temperature to a stirred solution of 6-chloro-2,3,4,5-tetrahydro-1,4-benzothiazepine (4.5 g, prepared in a similar manner to its hydrochloride, Example 1 above) and triethylamine (2.82 g) in dichloromethane (100 ml). The reaction mixture was stirred at room temperature for 15 minutes, washed with water, dried and the solvent was removed by evaporation. Purification of the residue by flash chromatography using dichloromethane as eluent gave 4-benzoyl-6-chloro-2,3,4,5-tetrahydro-1,4-benzothiazepine, which was recrystallised from ethanol/water. Yield 5.93 g (m.p. 64-72°C).

The ED_{50}, in the BICM test described above, for this compound was 49.2 mg/kg.

Example 16

A solution of methanesulphinyl chloride (0.98 g) in dichloromethane (10 ml) was added dropwise at room temperature to a stirred solution of 6-chloro-2,3,4,5-

tetrahydro-1,4-benzothiazepine (1.99 g, prepared in a similar manner to its hydrochloride, Example 1 above) and triethylamine (1.01 g) in dichloromethane (50 ml). The reaction mixture was stirred at room temperature for one hour, washed with water, dried and the solvent was removed by evaporation. Purification of the residue by flash chromatography using dichloromethane/ethanol (98:2) as eluent gave 6-chloro-4-methylsulphinyl-2,3,4,5-tetrahydro-1,4-benzothiazepine, which was recrystallised from ethylacetate/hexane. Yield 2.1 g (m.p. 82-84°C).

The ED_{50}, in the BICM test described above, for this compound was 19.6 mg/kg.

Example 17

A solution of methanesulphonyl chloride (3.3 g) in dichloromethane (15 ml) was added dropwise at room temperature to a stirred solution of 2,3,4,5-tetrahydro-1,4-benzothiazepine (4.8 g, prepared as described in the first paragraph of Example 6 above) and triethylamine (2.9 g) in dichloromethane (100 ml). The reaction mixture was stirred at room temperature for one hour, washed with water, dried and the solvent was removed by evaporation. Purification of the residue by flash chromatography using dichloromethane as eluent gave 4-methylsulphonyl-2,3,4,5-tetrahydro-1,4-benzothiazepine which was recrystallised from hexane. Yield 3 g. (m.p. 98-100°C).

The ED_{50}, in the BICM test described above, for this compound was 40.8 mg/kg.

The ED_{50}, in the MESM test described above, for this compound was 51.6 mg/kg.

Example 18

A solution of 3-chloroperbenzoic acid (1.4 g) in dichloromethane (200 ml) was added dropwise with cooling from 0°C to -2°C to a stirred solution of 4-methylsulphonyl-2,3,4,5-tetrahydro-1,4-benzothiazepine (2 g, prepared as Example 17 above) in dichloromethane (50 ml). The reaction mixture was stirred for 15 minutes, washed with water, dried and the solvent was removed by evaporation at reduced pressure. Purification of the residue by flash chromatography using dichloromethane/ethanol (95:5) as eluent gave 4-methylsulphonyl-2,3,4,5-tetrahydro-1,4-benzothiazepine 1-oxide, which was recrystallised from ethanol. Yield 1.65 g (m.p. 195-197°C).

The ED_{50}, in the BICM test described above, for this compound was 27.4 mg/kg.

Example 19

A solution of methanesulphonyl chloride (3.43 g) in dichloromethane (30 ml) was added dropwise at room temperature to a stirred solution of 6-chloro-2,3,4,5-tetrahydro-1,4-benzothiazepine (5.2 g, prepared in a similar manner to its hydrochloride, Example 1 above) and triethylamine (3.03 g, 0.03 ml) in dichloromethane (100 ml). The reaction mixture was stirred at room temperature for one hour, washed with water, dried and the solvent was removed by evaporation. Purification of the residue by flash chromatography using

dichloromethane as eluent gave 6-chloro-4-methylsulphonyl-2,3,4,5-tetrahydro-1,4-benzothiazepine, which was recrystallised from hexane. Yield 6.06 g (m.p. 85-86°C).

The ED_{50}, in the BICM test described above, for this compound was 41.3 mg/kg.

The ED_{50}, in the MESM test described above, for this compound was 19.5 mg/kg.

Example 20

A solution of 3-chloroperbenzoic acid (2.26 g) in dichloromethane (150 ml) was added dropwise with cooling from 0°C to -2°C to a stirred solution of 6-chloro-4-methylsulphonyl-2,3,4,5-tetrahydro-1,4-benzothiazepine (3.05 g, prepared as Example 19 above) in dichloromethane (100 ml). The reaction mixture was stirred for 15 minutes, washed with water and dried, and the solvent was removed by evaporation at reduced pressure. Purification of the residue by flash chromatography using dichloromethane/ethanol (95:5) as eluent gave 6-chloro-4-methylsulphonyl-2,3,4,5-tetrahydro-1,4-benzothiazepine 1-oxide, which was recrystallised from ethyl acetate. Yield 2.86 g (m.p. 167-169°C).

The ED_{50}, in the BICM test described above, for this compound was 36.2 mg/kg.

The ED_{50}, in the MESM test described above, for this compound was 31.9 mg/kg.

Example 21

A solution of methanesulphonyl chloride (1.83 g) in dichloromethane (30 ml) was added dropwise at room temperature to a stirred solution of 6-fluoro-2,3,4,5-tetrahydro-1,4-benzothiazepine (2.65 g, prepared in a similar manner to its hydrochloride, Example 3 above) and triethylamine (1.6 g) in dichloromethane (60 ml). The reaction mixture was stirred at room temperature for 20 minutes, washed with water, dried and the solvent was removed by evaporation. Purification of the residue by flash chromatography using dichloromethane as eluent gave 6-fluoro-4-methylsulphonyl-2,3,4,5-tetrahydro-1,4-benzothiazepine, which was recrystallised from hexane. Yield 3.3 g (m.p. 115-117°C).

The ED_{50}, in the BICM test described above, for this compound was 33.8 mg/kg.

The ED_{50}, in the MESM test described above, for this compound was 30.5 mg/kg.

Example 22

A solution of methanesulphonyl chloride (1.69 g) in dichloromethane (20 ml) was added dropwise at room temperature to a stirred solution to 6-methyl-2,3,4,5-tetrahydro-1,4-benzothiazepine (2 g, prepared in a similar manner to its hydrochloride, Example 4 above) and triethylamine (1.51 g) in dichloromethane (30 ml). The reaction mixture was stirred at room temperature for one hour, washed with water, dried and the solvent was removed by evaporation. Purification of the residue by flash chromatography using dichloromethane as eluent gave 6-methyl-4-methylsulphonyl-2,3,4,5-tetrahydro-1,4-

benzothiazepine, which was recrystallised from ethyl acetate/hexane. Yield 2.48 g (m.p. 128-130°C).

The ED_{50}, in the BICM test described above, for this compound was 116.3 mg/kg.

The ED_{50}, in the MESM test described above, for this compound was 102.2 mg/kg.

Example 23

A solution of ethanesulphonyl chloride (3.8 g) in dichloromethane (50 ml) was added dropwise at room temperature to a stirred solution of 2,3,4,5-tetrahydro-1,4-benzothiazepine (4.29 g, prepared as described in the first paragraph of Example 6 above) in dichloromethane (100 ml). The reaction mixture was stirred at room temperature for one hour, washed with water, dried and the solvent was removed by evaporation. Purification of the residue by flash chromatography using trichloromethane as eluent gave 4-ethylsulphonyl-2,3,4,5-tetrahydro-1,4-benzothiazepine, which was recrystallised from hexane. Yield 4.25 g (m.p. 78-80°C).

The ED_{50}, in the MESM test described above, for this compound was 22.3 mg/kg.

Example 24

A solution of ethanesulphonyl chloride (1.28 g) in dichloromethane (10 ml) was added dropwise at room temperature to a stirred solution of 6-chloro-2,3,4,5-tetrahydro-1,4-benzothiazepine (1.99 g, prepared in a

similar manner to its hydrochloride, Example 1 above) and triethylamine (1.01 g) in dichloromethane (50 ml). The reaction mixture was stirred at room temperature for one hour, washed with water, dried and the solvent was removed by evaporation. Purification of the residue by flash chromatography using dichloromethane as eluent gave 4-ethylsulphonyl-6-chloro-2,3,4,5-tetrahydro-1,4-benzothiazepine, which was recrystallised from ethyl acetate/hexane. Yield 2.53 g (m.p. 126-128°C).

The ED_{50}, in the BICM test described above, for this compound was 90.4 mg/kg.

The ED_{50}, in the MESM test described above, for this compound was 35.1 mg/kg.

Example 25

A stirred mixture of 4,5-dihydro-1,4-benzothiazepin-3(2H)-one (1.79 g, prepared as example 1 of international patent application WO 92/21668) and Lawesson's reagent (2.22 g) in dry toluene (100 ml) was heated at 100°C for three hours. The mixture was allowed to cool to room temperature. The precipitated solid was collected by filtration, washed with toluene and dried to give 4,5-dihydro-1,4-benzothiazepin-3(2H)-thione. Yield 1.78 g (m.p. 215-219°C).

A mixture of 4,5-dihydro-1,4-benzothiazepin-3(2H)-thione (1.56 g), hydroxylamine hydrochloride (0.83 g) and sodium acetate (0.98 g) in dry ethanol (100 ml) was heated under reflux for three hours. The mixture was cooled, and the precipitated solid was collected by filtration and washed with water. Purification of the precipitate by flash chromatography using

dichloromethane/ethanol (95:5) as eluent gave 3-hydroxyimino-2,3,4,5-tetrahydro-1,4-benzothiazepine, which was recrystallised from ethanol. Yield 1.2 g (m.p. 208-210°C).

The ED_{50}, in the BICM test described above, for this compound was 31.5 mg/kg.

Example 26

A stirred mixture of 6-chloro-4,5-dihydro-1,4-benzothiazepin-3(2H)-one (4.27 g, prepared as example 11 of international patent application WO 92/21668) and Lawesson's reagent (4.90 g) in dry toluene (170 ml) was heated under reflux for one hour. The reaction mixture was cooled to room temperature and the precipitated 6-chloro-4,5-dihydro-1,4-benzothiazepin-3(2H)-thione was collected by filtration, washed with toluene and dried. Yield 4.16 g (m.p. 210-212°C).

A stirred mixture of 6-chloro-4,5-dihydro-1,4-benzothiazepin-3(2H)-thione (3.90 g), hydroxylamine hydrochloride (1.77 g) and sodium acetate (2.09 g) in dry ethanol (175 ml) was heated under reflux for one hour. The reaction mixture was cooled and the precipitated 6-chloro-3-hydroxyimino-2,3,4,5-tetrahydro-1,4-benzothiazepine was collected by filtration, washed with water and recrystallised from ethanol. Yield 2.6 g (m.p. 180-183°C).

The ED_{50}, in the BICM test described above, for this compound was 5.0 mg/kg.

Example 27

A stirred mixture of 6-methyl-4,5-dihydro-1,4-benzothiazepin-3(2H)-one (3.26 g, prepared in a similar manner to example 13 of international patent application WO 92/21668) and Lawesson's reagent (3.93 g) in dry toluene (170 ml) was heated under reflux for one hour. The reaction mixture was cooled to room temperature and the precipitated 6-methyl-4,5-dihydro-1,4-benzothiazepin-3(2H)-thione was collected by filtration, washed with toluene and dried. Yield 3.30 g (m.p. 228-230°C).

A stirred mixture of 6-methyl-4,5-dihydro-1,4-benzothiazepin-3(2H)-thione (3.13 g), hydroxylamine hydrochloride (1.56 g) and sodium acetate (1.84 g) in dry ethanol (175 ml) was heated under reflux for one hour. The reaction mixture was cooled and the precipitated 3-hydroxyimino-6-methyl-2,3,4,5-tetrahydro-1,4-benzothiazepine was collected by filtration, washed with water and recrystallised from ethanol. Yield 2.23 g (m.p. 188-190°C).

The ED_{50}, in the BICM test described above, for this compound was 20.1 mg/kg.

Example 28

Dimethylsulphate (1.26 g) was added dropwise to a vigorously stirred suspension of 3-hydroxyimino-2,3,4,5-tetrahydro-1,4-benzothiazepine (2 g, prepared in a similar manner to Example 25 above) in a mixture of a 10% aqueous solution of sodium hydroxide (4 ml) and ethanol (150 ml). The reaction mixture was kept at room temperature for 24 hours and then extracted with

dichloromethane. The organic layer was dried and the solvent was removed by evaporation. Purification of the solid residue by flash chromatography using dichloromethane as eluent gave 3-methoxyimino-2,3,4,5-tetrahydro-1,4-benzothiazepine, which was recrystallised from hexane. Yield 1.51 g (m.p. 101-102°C).

The ED_{50}, in the BICM test described above, for this compound was 58.2 mg/kg.

Example 29

A 10% aqueous solution of sodium hydroxide (4 ml) was added to a suspension of 6-chloro-3-hydroxyimino-2,3,4,5-tetrahdyro-1,4-benzothiazepine (2.29 g, prepared as Example 26 above) in ethanol (150 ml). After 15 minutes dimethylsulphate (1.33 g) was added dropwise to the mixture. The reaction mixture was stirred at room temperature for 22 hours and then the solvent was removed by evaporation at reduced pressure. Purification of the residue by chromatography on a silica gel support using dichloromethane followed by dichloromethane/ethanol (97:3) as successive eluents gave 6-chloro-3-methoxyimino-2,3,4,5-tetrahydro-1,4-benzothiazepine, which was recrystallised from n-hexane. Yield 1.21 g (m.p. 120-121°C).

In the BICM test described above, a dosage of 100 mg/kg of this compound inhibited 50% of the mice tested from seizures.

Example 30

A mixture of 4,5-dihydro-1,4,benzothiazepine-3(2H)-one (5.37 g, prepared as example 1 of international patent application WO 92/21668) and phosphorus pentachloride (6.3 g) in dry toluene was heated at 50°C for two hours. The precipitated product was collected by filtration, washed with toluene and dried to give 3-chloro-2,5-dihydro-1,4-benzothiazepine. Yield 5.2 g (m.p. 164-168°C). This crude product was used in the next step without further purification.

3-Chloro-2,5-dihydro-1,4-benzothiazepine (5 g) and a 33% solution of methylamine in absolute ethanol (150 ml) were heated under reflux for one hour. The mixture was cooled and filtered. Purification of the residue by flash chromatography using ethyl acetate/ethanol (1:1) as eluent gave 3-methylimino-2,3,4,5-tetrahydro-1,4-benzothiazepine, which was recrystallised from ethanol. Yield 0.51 g (m.p. 278-280°C).

The ED_{50}, in the BICM test described above, for this compound was 20.8 mg/kg.

Example 31

Phosphorus pentachloride (5.84 g) was added in portions to a stirred suspension of 6-chloro-4,5-dihydro-1,4-benzothiazepin-3(2H)-one (6.0 g, prepared as example 1 of international patent application WO 92/21668) in dry toluene (450 ml). The reaction mixture was then heated in an oil bath at 50-60°C for 5½ hours. After cooling, the crude precipitate of 3,6-dichloro-2,5-dihydro-1,4-benzothiazepine was collected by

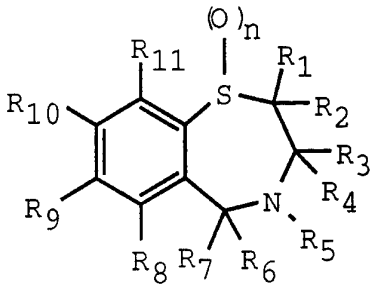
filtration, and washed with toluene. Yield 4.85 g. This crude product was used in the next step without further purification.

A solution of aniline (4.8 ml) in dry ethanol (10 ml) was added dropwise at room temperature to a stirred solution of 3,6-dichloro-2,5-dihydro-1,4-benzothiazepine (2.5 g) in dry ethanol (65 ml). The reaction mixture was heated under reflux for 9½ hours, cooled to room temperature, filtered and the solvent was removed from the filtrate by evaporation at reduced pressure. The oily residue was separated into fractions by chromatography on a silica gel support using chloroform/ethanol (50:1) as eluent. Purification of those fractions containing the product by flash chromatography using ethyl acetate/hexane (2:3) as eluent gave 6-chloro-3-phenylimino-2,3,4,5-tetrahydro-1,4-benzothiazepine, which was recrystallised from ethyl acetate/hexane. Yield 0.27 g (m.p. 150-152°C).

The ED_{50}, in the BICM test described above, for this compound was 16.3 mg/kg.

CLAIMS

1. Compounds of formula II



II

in which:

n = 0, 1 or 2;

R_1, R_2, R_6 and R_7 independently represent H or alkyl of 1 to 4 carbon atoms (optionally substituted with one or more halo);

R_3 and R_4 independently represent H or alkyl of 1 to 4 carbon atoms; or together represent a group of formula $=NR_{12}$ where R_{12} represents H, hydroxy, alkyl of 1 to 4 carbon atoms, phenyl or alkoxy of 1 to 4 carbon atoms; each alkyl, phenyl and alkoxy being optionally substituted with one or more halo;

R_5 represents: (a) H, (b) alkyl of 1 to 4 carbon atoms, (c) a group of formula $-COR_{13}$ in which R_{13} represents H, alkyl of 1 to 4 carbon atoms or phenyl, when R_3 and R_4 represent H or alkyl (optionally substituted with one or more halo), or (d) a group of formula $-S(O)_pR_{14}$ in which p = 1 or 2 and R_{14} is alkyl of 1 to 4 carbon atoms or phenyl, when R_3 and R_4 represent H or alkyl (optionally substituted with one or more halo); each alkyl and phenyl being optionally substituted with one or more halo;

R_8 to R_{11} independently represent H, halo, cyano, nitro, alkyl of 1 to 4 carbon atoms, alkoxy of 1 to 4 carbon

atoms, alkanoyl of 1 to 4 carbon atoms, carboxy, alkanoyloxy of 1 to 4 carbon atoms, carbamoyl (optionally substituted with alkyl of 1 to 4 carbon atoms) or sulphamoyl (optionally substituted with alkyl of 1 to 4 carbon atoms); each alkyl, alkoxy, alkanoyl or alkanoyloxy optionally substituted with one or more halo;

their stereoisomers; and

pharmaceutically acceptable salts thereof;

with the provisos that:

when n = 0; R_1 to R_4, R_6 to R_8 and R_{11} are all H; and either: when R_5 is H or acetyl, R_9 and R_{10} are both other than methoxy; or when R_5 and R_{10} are both H, R_9 is other than methoxy;

when n = 0 or 2; R_1 to R_6 and R_{10} to R_{11} are all H; and R_7 is methyl; R_8 and R_9 are both other than methoxy;

when n = 0; R_1, R_2, R_5, R_6, R_7 are all H; R_3 is alkyl; and R_8 to R_{11} are independently H, halo, nitro, alkyl, haloalkyl, alkoxy or haloalkyl; R_4 is other than alkyl of 2 to 4 carbon atoms;

when n = 0; R_1 to R_3 and R_6 to R_{11} are all H; and either: when R_4 is other than H, R_5 is H, ethyl, acetyl or benzoyl; or when R_4 is methyl, R_5 is other than H.

2. Compounds of formula II as claimed in claim 1, in which:

n = 0 or 1;

R_1, R_2, R_6 and R_7 are independently H or methyl;

R_3 and R_4 are independently H or methyl; or together represent imino, methylimino, phenylimino, hydroxyimino or methoxyimino;

R_5 is H or methyl, and when R_3 and R_4 are H or methyl, R_5 is formyl, acetyl, propionyl, benzoyl, methylsulphinyl, methylsulphonyl or ethylsulphonyl;

one of R_8 to R_{11} is H, fluoro, chloro, bromo, iodo, methyl (optionally substituted with one or more halo),

methoxy (optionally substituted by one or more halo), nitro, cyano, carboxy, acetyl, dimethylcarbamoyl or dimethylsulphamoyl; the remainder of R_8 to R_{11} being H; their stereoisomers; and pharmaceutically acceptable salts thereof.

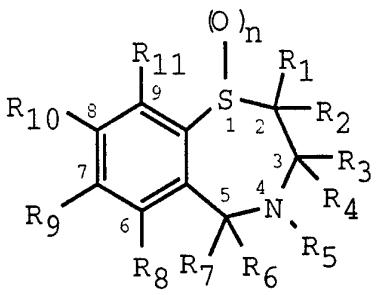
3. Compounds of formula II as claimed in either preceding claim, in which:
n = 0 or 1;
R_1, R_2, R_6 and R_7 are H;
R_3 and R_4 are H, or together are methylimino, phenylimino, hydroxyimino or methoxyimino;
R_5 is H or methyl, and when R_3 and R_4 are H, R_5 is formyl, acetyl, propionyl, benzoyl, methylsulphinyl, methylsulphonyl, or ethylsulphonyl;
R_8 is methyl, fluoro or chloro;
R_9 to R_{11} are all H;
their stereoisomers; and
pharmaceutically acceptable salts thereof.

4. Compounds of formula II as claimed in any preceding claim selected from:
6-chloro-2,3,4,5-tetrahydro-1,4-benzothiazepine;
6-chloro-2,3,4,5-tetrahydro-1,4-benzothiazepine 1-oxide;
6-fluoro-2,3,4,5-tetrahydro-1,4-benzothiazepine;
6-methyl-2,3,4,5-tetrahydro-1,4-benzothiazepine;
6-chloro-4-methyl-2,3,4,5-tetrahydro-1,4-benzothiazepine;
4-formyl-2,3,4,5-tetrahydro-1,4-benzothiazepine;
4-acetyl-2,3,4,5-tetrahydro-1,4-benzothiazepine;
4-acetyl-2,3,4,5-tetrahydro-1,4-benzothiazepine 1-oxide;
4-acetyl-6-chloro-2,3,4,5-tetrahydro-1,4-benzothiazepine;

4-acetyl-6-chloro-2,3,4,5-tetrahydro-1,4-benzothiapine 1-oxide;
4-acetyl-6-fluoro-2,3,4,5-tetrahydro-1,4-benzothiazepine;
4-acetyl-6-methyl-2,3,4,5-tetrahydro-1,4-benzothiazepine;
4-propionyl-2,3,4,5-tetrahydro-1,4-benzothiazepine;
6-chloro-4-propionyl-2,3,4,5-tetrahydro-1,4-benzothiazepine;
4-benzoyl-6-chloro-2,3,4,5-tetrahydro-1,4-benzothiazepine;
6-chloro-4-methylsulphinyl-2,3,4,5-tetrahydro-1,4-benzothiazepine;
4-methylsulphonyl-2,3,4,5-tetrahydro-1,4-benzothiazepine;
4-methylsulphonyl-2,3,4,5-tetrahydro-1,4-benzothiazepine 1-oxide;
6-chloro-4-methylsulphonyl-2,3,4,5-tetrahydro-1,4-benzothiazepine;
6-chloro-4-methylsulphonyl-2,3,4,5-tetrahydro-1,4-benzothiazepine 1-oxide;
6-fluoro-4-methylsulphonyl-2,3,4,5-tetrahydro-1,4-benzothiazepine;
6-methyl-4-methylsulphonyl-2,3,4,5-tetrahydro-1,4-benzothiazepine;
4-ethylsulphonyl-2,3,4,5-tetrahydro-1,4-benzothiazepine;
6-chloro-4-ethylsulphonyl-2,3,4,5-tetrahydro-1,4-benzothiazepine;
3-hydroxyimino-2,3,4,5-tetrahydro-1,4-benzothiazepine;
6-chloro-3-hydroxyimino-2,3,4,5-tetrahydro-1,4-benzothiazepine;
3-hydroxyimino-6-methyl-2,3,4,5-tetrahydro-1,4-benzothiazepine;
3-methoxyimino-2,3,4,5-tetrahydro-1,4-benzothiazepine;
6-chloro-3-methoxyimino-2,3,4,5-tetrahydro-1,4-benzothiazepine;

3-methylimino-2,3,4,5-tetrahydro-1,4-benzothiazepine;
6-chloro-3-phenylimino-2,3,4,5-tetrahydro-1,4-benzothiazepine;
their stereoisomers; and
pharmaceutically acceptable salts thereof.

5. Pharmaceutical compositions comprising a therapeutically effective amount of compounds of formula I



I

in which:
n = 0, 1 or 2;
R_1, R_2, R_6 and R_7 independently represent H or alkyl of 1 to 4 carbon atoms (optionally substituted by one or more halo);
R_3 and R_4 independently represent H or alkyl of 1 to 4 carbon atoms; or together represent a group of formula $=NR_{12}$ where R_{12} represents H, hydroxy, alkyl of 1 to 4 carbon atoms, phenyl or alkoxy of 1 to 4 carbon atoms; each alkyl, phenyl and alkoxy being optionally substituted with one or more halo;
R_5 represents: (a) H, (b) alkyl of 1 to 4 carbon atoms, (c) a group of formula $-COR_{13}$ in which R_{13} represents H, alkyl of 1 to 4 carbon atoms or phenyl, when R_3 and R_4 represent H or alkyl (optionally substituted with one or more halo, or (d) or a group of formula $-S(O)_pR_{14}$ in which p = 1 or 2 and R_{14} is alkyl of 1 to 4 carbon atoms or phenyl, when R_3 and R_4 represent H or alkyl

(optionally substituted with one or more halo); each alkyl and phenyl being optionally substituted with one or more halo;

R_8 to R_{11} independently represent H, halo, cyano, nitro, alkyl of 1 to 4 carbon atoms, alkoxy of 1 to 4 carbon atoms, alkanoyl of 1 to 4 carbon atoms, carboxy, alkanoyloxy of 1 to 4 carbon atoms, carbamoyl (optionally substituted with alkyl of 1 to 4 carbon atoms), or sulphamoyl (optionally substituted with alkyl of 1 to 4 carbon atoms); each alkyl, alkoxy, alkanoyl or alkanoyloxy optionally substituted with one or more halo;

their stereoisomers; and

pharmaceutically acceptable salts thereof;

with the proviso that when n = 0, at least one of R_1 to R_{11} is other than H;

together with a pharmaceutically acceptable diluent or carrier.

6. Pharmaceutical compositions as claimed in claim 5, comprising a therapeutically effective amount of compounds of formula I in which:

n = 0 or 1;

R_1, R_2, R_6 and R_7 are independently H or methyl;

R_3 and R_4 are independently H or methyl; or together represent imino, methylimino, phenylimino, hydroxyimino or methoxyimino;

R_5 is H or methyl, and when R_3 and R_4 are H or methyl, R_5 is formyl, acetyl, propionyl, benzoyl, methylsulphinyl, methylsulphonyl or ethylsulphonyl;

one of R_8 to R_{11} is H, fluoro, chloro, bromo, iodo, methyl (optionally substituted with one or more halo), methoxy (optionally substituted by one or more halo), nitro, cyano, carboxy, acetyl, dimethylcarbamoyl or dimethylsulphamoyl; the remainder of R_8 to R_{11} being H;

their stereoisomers; and
pharmaceutically acceptable salts thereof.

7. Pharmaceutical compositions as claimed in either claim 5 or 6, comprising a therapeutically effective amount of compounds of formula I in which:
n = 0 or 1;
R_1, R_2, R_6 and R_7 are H;
R_3 and R_4 are H, or together are methylimino, phenylimino, hydroxyimino or methoxyimino;
R_5 is H or methyl, and when R_3 and R_4 are H, R_5 is formyl, acetyl, propionyl, benzoyl, methylsulphinyl, methylsulphonyl, or ethylsulphonyl;
R_8 is methyl, fluoro or chloro;
R_9 to R_{11} are all H;
their stereoisomers; and
pharmaceutically acceptable salts thereof.

8. Pharmaceutical compositions as claimed in any of claims 5 to 7, comprising a therapeutically effective amount of compounds of formula I selected from:

6-chloro-2,3,4,5-tetrahydro-1,4-benzothiazepine;
6-chloro-2,3,4,5-tetrahydro-1,4-benzothiazepine 1-oxide;
6-fluoro-2,3,4,5-tetrahydro-1,4-benzothiazepine;
6-methyl-2,3,4,5-tetrahydro-1,4-benzothiazepine;
6-chloro-4-methyl-2,3,4,5-tetrahydro-1,4-benzothiazepine;
4-formyl-2,3,4,5-tetrahydro-1,4-benzothiazepine;
4-acetyl-2,3,4,5-tetrahydro-1,4-benzothiazepine;
4-acetyl-2,3,4,5-tetrahydro-1,4-benzothiapine 1-oxide;
4-acetyl-6-chloro-2,3,4,5-tetrahydro-1,4-benzothiazepine;
4-acetyl-6-chloro-2,3,4,5-tetrahydro-1,4-

benzothiazepine 1-oxide;
4-acetyl-6-fluoro-2,3,4,5-tetrahydro-1,4-benzothiazepine;
4-acetyl-6-methyl-2,3,4,5-tetrahydro-1,4-benzothiazepine;
4-propionyl-2,3,4,5-tetrahydro-1,4-benzothiazepine;
6-chloro-4-propionyl-2,3,4,5-tetrahydro-1,4-benzothiazepine;
4-benzoyl-6-chloro-2,3,4,5-tetrahydro-1,4-benzothiazepine;
6-chloro-4-methylsulphinyl-2,3,4,5-tetrahydro-1,4-benzothiazepine;
4-methylsulphonyl-2,3,4,5-tetrahydro-1,4-benzothiazepine;
4-methylsulphonyl-2,3,4,5-tetrahydro-1,4-benzothiazepine 1-oxide;
6-chloro-4-methylsulphonyl-2,3,4,5-tetrahydro-1,4-benzothiazepine;
6-chloro-4-methylsulphonyl-2,3,4,5-tetrahydro-1,4-benzothiazepine 1-oxide;
6-fluoro-4-methylsulphonyl-2,3,4,5-tetrahydro-1,4-benzothiazepine;
6-methyl-4-methylsulphonyl-2,3,4,5-tetrahydro-1,4-benzothiazepine;
4-ethylsulphonyl-2,3,4,5-tetrahydro-1,4-benzothiazepine;
6-chloro-4-ethylsulphonyl-2,3,4,5-tetrahydro-1,4-benzothiazepine;
3-hydroxyimino-2,3,4,5-tetrahydro-1,4-benzothiazepine;
6-chloro-3-hydroxyimino-2,3,4,5-tetrahydro-1,4-benzothiazepine;
3-hydroxyimino-6-methyl-2,3,4,5-tetrahydro-1,4-benzothiazepine;
3-methoxyimino-2,3,4,5-tetrahydro-1,4-benzothiazepine;
6-chloro-3-methoxyimino-2,3,4,5-tetrahydro-1,4-benzothiazepine;
3-methylimino-2,3,4,5-tetrahydro-1,4-benzothiazepine;

6-chloro-3-phenylimino-2,3,4,5-tetrahydro-1,4-benzothiazepine;
their stereoisomers; and
pharmaceutically acceptable salts thereof.

9. A method of treating seizures, comprising administering to a patient in need thereof a therapeutically effective amount of compounds of formula I as described in any of claims 5 to 8.

10. A method of treating neurological disorders, comprising administering to a patient in need thereof a therapeutically effective amount of compounds of formula I as described in any of claims 5 to 8.

11. A method of treating epilepsy, comprising administering to a patient in need thereof a therapeutically effective amount of compounds of formula I as described in any of claims 5 to 8.

12. A method of neuroprotection, comprising administering to a patient in need thereof a therapeutically effective amount of compounds of formula I as described in any of claims 5 to 8.

13. A method of protecting against stroke, comprising administering to a patient in need thereof a therapeutically effective amount of compounds of formula I as described in any of claims 5 to 8.

14. Use of compounds of formula I as described in any of claims 5 to 8, in the treatment of seizures.

15. Use of compounds of formula I as described in any of claims 5 to 8, in the treatment of neurological disorders.

16. Use of compounds of formula I as described in any of claims 5 to 8, in the treatment of epilepsy.

17. Use of compounds of formula I as described in any of claims 5 to 8, as a neuroprotective agent.

18. Use of compounds of formula I as described in any of claims 5 to 8, to protect against stroke.

19. Use of compounds of formula I as described in any of claims 5 to 8, in the preparation of a medicament for the treatment of seizures.

20. Use of compounds of formula I as described in any of claims 5 to 8, in the preparation of a medicament for the treatment of neurological disorders.

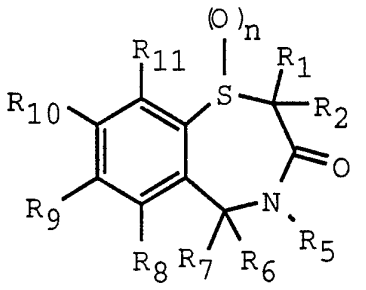
21. Use of compounds of formula I as described in any of claims 5 to 8, in the preparation of a medicament for the treatment of epilepsy.

22. Use of compounds of formula I as described in any of claims 5 to 8, in the preparation of a medicament for neuroprotection.

23. Use of compounds of formula I as described in any of claims 5 to 8, in the preparation of a medicament for protection against stroke.

24. A process for the preparation of compounds of formula II as claimed in any of claims 1 to 5, comprising one or more of the following steps A) to I)

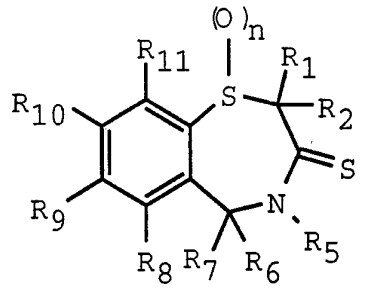
A) the reduction of compounds of formula III



III

in which R_5 is H or alkyl to give compounds of formula II in which R_3 and R_4 are H or alkyl;

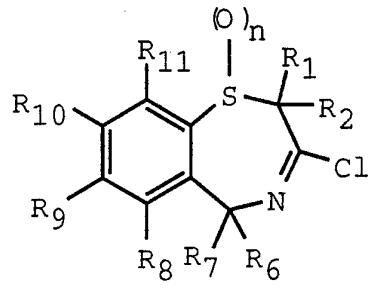
B) the reaction between compounds of formula $R_{12}NH_2$ and compounds of formula IV



IV

to give compounds of formula II in which R_3 and R_4 together represent a group of formula $=NR_{12}$;

C) the reaction between compounds of formula $R_{12}NH_2$ compounds of formula V



V

to give compounds of formula II in which R_3 and R_4 together represent a group of formula $=NR_{12}$, and R_5 is H;

D) the reaction between an alkylating agent such as an alkylsulphate and compounds of formula II in which R_3 and R_4 together are hydroxyamino to give compounds of formula I or II in which R_3 and R_4 together are alkoxyimino;

E) the alkylation of compounds of formula II in which R_5 is H to give compounds of formula II in which R_5 is alkyl;

F) the acylation of compounds of formula II in which R_5 is H and n = 0 or 2 to give compounds of formula II in which R_5 is a group of formula $-COR_{13}$;

G) the reaction between compounds of formula II in which R_5 is H and a sulphonylating or a sulphinylating agent to give compounds of formula II in which R_5 is a group of formula $-S(O)_pR_{14}$;

H) the oxidation of compounds of formula II in which n = 0, to produce compounds of formula II in which n = 1;

I) the oxidation of compounds of formula II in which n = 0 or 1, to give compounds of formula II in which n = 2.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 93/03123

A. CLASSIFICATION OF SUBJECT MATTER
IPC 5 C07D281/10 A61K31/55

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 5 C07D A61K

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)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO,A,92 12148 (N. KANEKO) 23 July 1992 cited in the application see the whole document, particularly page 5, formulae 1 and 4, pages 10, experimental example 3 and page 11, experimental example 4	1
P,X	& EP,A,0 565 721 (N. KANEKO) 20 October 1993	1

X	EP,A,0 368 063 (BAYER AG) 16 May 1990 cited in the application see page 9, lines 20, 21, page 10, lines 1-3, page 22, example 37, pages 24, 25, examples 46 and 47	1,2,4

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[X] Further documents are listed in the continuation of box C.

[X] 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

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Date of the actual completion of the international search	Date of mailing of the international search report
6 April 1994	14. 04. 94

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	Allard, M

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO,A,92 21668 (THE BOOTS COMPANY PLC) 10 December 1992 cited in the application see the whole document	1-24
X	FR,M,4 916 (F. HOFFMANN-LA ROCHE & CIE) 24 April 1967 see the whole document, particularly page 7, paragraph bridging the two columns and page 15, examples 43 and 44	1-24
A	US,A,3 682 962 (W.B. DICKINSON) 8 August 1972 see the whole document	1-24
X	COMPTES RENDUS HEBDOMADAIRES DES SéANCES DE L'ACADéMIE DES SCIENCES, SéRIE C vol. 282 , 26 January 1976 , PARIS FR pages 249 - 251 R. BOUDET ET AL. 'Recherche dans la série des thiazépines. Synthèse et étude de la benzo-6.7 tétrahydrothiazépine-1.4.' cited in the application	1,2,24
X	CHEMICAL ABSTRACTS, vol. 71, no. 25, 22 December 1969, Columbus, Ohio, US; abstract no. 124391p, M.D. NAIR ET AL. 'Synthesis and reactions of 1,4-benzothiazepine derivatives' page 456 ; cited in the application see abstract & CHEMICAL ABSTRACTS, 8TH COLLECTIVE SUBJECT INDEX page 4452S '1,4-Benzothiazepine, 4-(dichloroacetyl)-2,3,4,5-tetrahydro-; -2,3,4,5-tetrahydro-, 1-oxide, hydrochloride and -2,3,4,5-tetrahydro-, 1,1-dioxide, hydrochloride' & INDIAN J. CHEM. vol. 7, no. 9 , 1969 pages 862 - 865	1

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 93/03123

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 9-18 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 compounds/compositions.

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

nternational Application No
PCT/EP 93/03123

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
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		CN-A-	1063491	12-08-92
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		GB-A-	1091182	
		NL-A-	6500817	26-07-65
		US-A-	3362962	
		US-A-	3503985	31-03-70
		US-A-	3523974	11-08-70
		US-A-	3530139	22-09-70
		US-A-	3631089	28-12-71
US-A-3682962	08-08-72	NONE		