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New derivatives of 10,11-dihydro-10-oxo-5H-dibenz[b,f]azepine-5-carboxamide

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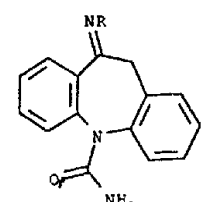
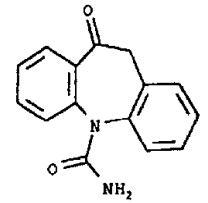
- (54) Title  
**NEW DERIVATIVES OF 10,11-DIHYDRO-10-OX O-5H-DIBENZ/B,F/AZEPINE-5-CARBOXAMIDE**
- International Patent Classification(s)  
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<p>(54) Title: NEW DERIVATIVES OF 10,11-DIHYDRO-10-OXO-5H-DIBENZ<b>b,f</b>AZEPINE-5-CARBOXAMIDE</p>		
<p>(57) Abstract</p>		
<p>Compounds of general formula (I) have valuable pharmaceutical properties especially in the treatment of some disturbances in the central and peripheral nervous system. The compounds can be formulated with a pharmaceutically acceptable carrier into pharmaceutical compositions. The compounds can be made by reacting the compound of formula (II) with hydroxylamine or a derivative thereof of the following formula (III) H<sub>2</sub>NOR<sup>2</sup>, or with a semicarbazide or thiosemicarbazide or a hydrazine derivative of the following formula (IV) H<sub>2</sub>NNR<sup>3</sup>R<sup>4</sup>, or by a reaction of a compound of formula (I) where R is OH with an acylating agent of the following formula (V): ACOR<sup>1</sup> or (VI): ClCOOR<sup>1</sup>.</p>		<p> (I)</p>
		<p> (II)</p>

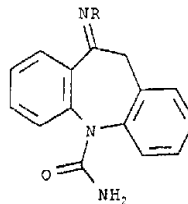
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**Description****New Derivatives of 10,11-dihydro-10-oxo-5H-dibenz/b,f/azepine-5-carboxamide**

The present invention relates to new derivatives of 10,11-dihydro-10-oxo-5H-dibenz/b,f/azepine-5-carboxamide, to a method of their preparation and to pharmaceutical compositions containing them. The compounds have valuable pharmaceutical properties in the treatment of some central and peripheral nervous system disorders.

10,11-Dihydro-10-oxo-5H-dibenz/b,f/azepine-5-carboxamide (oxcarbazepine) is a well established agent in the management of epilepsv, trigeminal neuralgia and affective disorders (see e.g. Drugs 43(6), 873 (1992)). In some patients however, oxcarbazepine precipitates severe adverse reactions, particularly allergic reactions and it also produces a decrease in serum sodium levels. Another disadvantage of oxcarbazepine is associated with its rapid metabolism; as a consequence, the drug should normally be used in a three times per day regime.

The invention aims to achieve an improvement in some of the above mentioned characteristics and relates to new compounds of general formula I;



I

wherein:

R is hydroxy, alkyl, cycloalkyl, alkylcycloalkyl, alkylaryl or an alkylheteroaryl group or R is the group  $-O-CO-R^1$  wherein  $R^1$  is hydrogen, alkyl, cycloalkyl, alkylcycloalkyl, alkylaryl, aryl or heteroaryl group or R is the group  $-O-CO-OR^1$  wherein substituent  $R^1$  is defined above or R is the group  $-O-R^2$  wherein  $R^2$  is alkyl or alkylaryl group or R is the group  $-NR^3R^4$  wherein  $R^3$  is hydrogen,  $-NH-CO-NH_2$ ,  $NH-CS-NH_2$ , alkyl or alkylaryl group and  $R^4$  is hydrogen, alkyl, alkylcycloalkyl, alkylaryl, alkylcarbonyl or arylcarbonyl group; the term alkyl means carbon chains, straight or branched, containing from one to six carbon atoms, optionally substituted by one or more alkoxy, halogen, alkoxycarbonyl or hydroxycarbonyl groups; the term cycloalkyl represents an alicyclic group with three to six carbon atoms; the term aryl represents phenyl or naphthyl group, optionally substituted by one or more alkoxy, halogen or nitro groups; the term heteroaryl represents a five or six membered ring, incorporating an atom of oxygen, sulphur or nitrogen; the term halogen represents fluorine, chlorine, bromine or iodine.

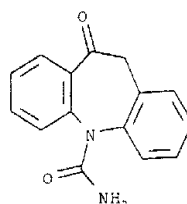
Preferred compounds of general formula I include:

1. 10,11-dihydro-10-hydroxyimino-5H-dibenz/b,f/azepine-5-carboxamide
2. 10,11-benzyloxyimino-10,11-dihydro-5H-dibenz/b,f/azepine-5-carboxamide
3. 10-acetyloxyimino-10,11-dihydro-5H-dibenz/b,f/azepine-5-carboxamide
4. 10,11-dihydro-10-propionyloxyimino-5H-dibenz/b,f/azepine-5-carboxamide
5. 10-butyroyloxyimino-10,11-dihydro-5H-dibenz/b,f/azepine-5-carboxamide
6. 10,11-dihydro-10-pivaloyloxyimino-5H-dibenz/b,f/azepine-5-carboxamide

7. 10,11-dihydro-10-[(1-naphthoxy)imino]-5H-dibenz/b,f/azepine-5-carboxamide
8. 10-benzoyloxyimino-10,11-dihydro-5H-dibenz/b,f/azepine-5-carboxamide
9. 10,11-dihydro-10-succinoyloxyimino-5H-dibenz/b,f/azepine-5-carboxamide
10. 10,11-dihydro-10-glutaroyloxyimino-5H-dibenz/b,f/azepine-5-carboxamide
11. 10,11-dihydro-10-isobutoxycarbonyloxyimino-5H-dibenz/b,f/azepine-5-carboxamide
12. 10,11-dihydro-10-methoxyimino-5H-dibenz/b,f/azepine-5-carboxamide
13. 10,11-dihydro-10-(S)-(-)-camphanoyloxyimino-5H-dibenz/b,f/azepine-5-carboxamide
14. 10,11-dihydro-10-[(3-methoxybenzoyloxyimino)]-5H-dibenz/b,f/azepine-5-carboxamide
15. 10,11-dihydro-10-nicotinoyloxyimino-5H-dibenz/b,f/azepine-5-carboxamide
16. 10,11-dihydro-10-ethoxycarbonyloxyimino-5H-dibenz/b,f/azepine-5-carboxamide
17. 10-butoxycarbonyloxyimino-10,11-dihydro-5H-dibenz/b,f/azepine-5-carboxamide
18. 10-benzyloxycarbonyloxyimino-10,11-dihydro-5H-dibenz/b,f/azepine-5-carboxamide

19. 10,11-dihydro-10-phenylhydrazono-5H-dibenz/b,f/azepine-5-carboxamide
20. 10,11-dihydro-10-hydrazono-5H-dibenz/b,f/azepine-5-carboxamide
21. 10,11-dihydro-10-(2,4-dinitrophenylhydrazono)-5H-dibenz/b,f/azepine-5-carboxamide
22. 10,11-dihydro-10-semicarbozono-5H-dibenz/b,f/azepine-5-carboxamide
23. 10,11-dihydro-10-thiosemicarbozono-5H-dibenz/b,f/azepine-5-carboxamide
24. 10-(2-chlorophenylsemicarbozono)-5H-dibenz/b,f/azepine-5-carboxamide
25. 10,11-dihydro-10-methoxycarbonylpropylimino-5H-dibenz/b,f/azepine-5-carboxamide

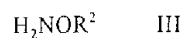
Another aspect of the invention relates to the method of preparation of compounds of formula I where substituent R is defined above, by reacting the compound of formula II



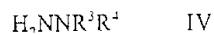
II

with hydroxylamine or a derivative thereof of formula III

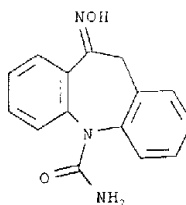
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wherein substituent  $\text{R}^2$  is defined above, or by reaction of a compound of formula II with semicarbazide, thiosemicarbazide or a derivative of hydrazine of formula IV

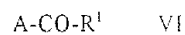


wherein substituents  $\text{R}^3$  and  $\text{R}^4$  are defined above, or by reacting the compound of formula V

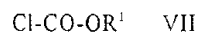


V

with an acylating reagent of formula VI



wherein  $\text{R}^1$  is the same as defined for general formula I, A is hydroxy, halogen or -O-CO-R' or -O-CO-OR', wherein R' is lower alkyl (C1 to C4), or by reacting the compound of formula V with an acylating reagent of formula VII



wherein  $\text{R}^1$  is the same as defined for general formula I; the acylation reaction can be carried out in the presence of a condensing agent such as, for example, dicyclohexylcarbodiimide, carbonyldiimidazole, ethyl or isobutylchloroformate,



and/or in the presence of an organic or inorganic base such as for example, pyridine, triethylamine or an alkali bicarbonate in an inert solvent such as a hydrocarbon, chlorinated alkane, ether or aprotic dipolar solvent, or the reaction can be run in a mixture of the above mentioned solvents or in the absence of any solvent.

Reactions as described above may be performed at various temperatures and pressures, e.g. between 0°C and the boiling temperature of the reaction mixture at the pressure used.

Compound II is known (see e.g. German Patent 2 001 087) and compounds of formulae III, IV, VI and VII can be made by those skilled in the art by methods described for example in the book "Comprehensive Organic Transformations" by R.C.Larock, VCH Publishers, 1989.

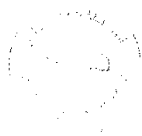
Still another aspect of the invention comprises a method of making pharmaceutical compositions consisting of mixing a compound of formula I with a pharmaceutically acceptable carrier.

The invention also includes a pharmaceutical composition for the treatment of central and peripheral nervous system disorders which comprises a compound of the invention and a pharmaceutically acceptable carrier therefor.

The invention further includes a method of treating central and peripheral nervous system disorders which comprises administering a compound of the invention such as in, for example, a pharmaceutical composition of the invention.

Some compounds of formula I are useful in the treatment of epilepsy, trigeminal neuralgia and affective cerebral disorders and alterations of the nervous function in degenerative and postischaemic diseases.

Epilepsy is one of the most common afflictions of man with a prevalence of



approximately 1%. Since the time of Hughlings Jackson more than 100 years ago, epileptic seizures have been known to represent "occasional, sudden, excessive, rapid and local discharges of nerve tissue". Epileptic seizures are divided fundamentally into two groups: partial and generalised. Partial seizures are those in which the discharge begins locally, and often remains localised. Generalised seizures involve the whole brain, including the reticular system, thus producing abnormal electrical activity throughout both hemispheres and immediate loss of consciousness. Partial seizures are divided in (a) *partial simple seizures*, (b) *complex partial seizures* and (c) *partial seizures secondarily generalised*. The generalised seizures include (1) tonic-clonic seizures (grand mal), (2) absence seizures (petit mal), (3) myoclonic seizures, (4) atonic seizures, (5) clonic seizures and (6) tonic seizures. Epilepsy, in contradistinction to seizures, is a chronic disorder characterised by recurrent seizures (Gastaut, H.: Dictionary of epilepsy. World Health Organization, Geneva, 1973).

There are two ways in which drugs might abolish or attenuate seizures: (a) through effects on altered neurones of seizure foci to prevent or reduce their excessive discharge, and (b) through effects that would reduce the spread of excitation from seizure foci and prevent disruption of function of normal aggregates of neurones. The majority, if not all, of the available antiepileptic drugs work at least by the second mechanism, since all modify the ability of the brain to respond to various seizure-evoking stimuli. Convulsant drugs, such as pentylenetetrazol (metrazol) are often used, particularly in the testing of anticonvulsant agents, and seizures caused by electrical stimulation of the whole brain are used for the same purpose. It has been found empirically that activity in inhibiting metrazol-induced seizures and in raising the threshold for production of electrically induced seizures is a fairly good index of effectiveness against absence seizures. On the other hand, activity in reducing the duration and spread of electrically induced convulsions correlates with effectiveness in controlling other types of epilepsy, such as tonic-clonic seizures.

The anticonvulsant effect of compounds of formulae I was studied in a model of

electrically induced convulsions, the maximal electroshock (MES) test, and in a model of chemical induced convulsions, the metrazol test. The MES test allows the evaluation of the ability of drugs to prevent electrically induced tonic hindlimb extension in rats, the efficacy of which is thought to be predictive of anticonvulsant efficacy against generalised tonic-clonic seizures in man (grand mal). The metrazol test predicts the ability of potential antiepileptic agents to prevent clonic seizures and to be effective against absence seizures (petit mal).

#### Materials and methods

Male Wistar rats obtained from the animal house of the Harlan Interfauna Ibérica (Barcelona, Spain) and weighing 180 to 280 g were used. Animals were kept two per cage under controlled environmental conditions (12 hr light/dark cycle and room temperature 24°C). Food and tap water were allowed *ad libitum* and the experiments were all carried out during daylight hours.

#### 1 - MES test

MES stimulation was applied for 0.2 s. using a Ugo Basile ECT unit 7801, with a frequency of 100 Hz, pulse width of 0.6 ms and a current of 150 mA through bipolar corneal electrodes. A drop of electrolyte/anaesthetic, oxibuprocaine chloride, was applied in the eyes of all animals immediately before placement of corneal electrodes. Abolition of the hindleg tonic extensor component, was used as the endpoint. These experimental conditions produced tonic-clonic convulsions in 97% of animals tested and only rats showing typical tonic-clonic convulsions were used. All rats were submitted to a maximum of 3 MES sessions: the first MES session was performed to screen the animals and select those rats presenting a typical convulsive behaviour. The day after, rats were given the compounds to be tested or the vehicle and submitted to a second MES session 2 or 4 hours after the administration of test drugs. The third MES session was performed at 6, 8 or 12 hours after the administration of test drugs. The time interval between each MES session was at

least 4 hours (rats tested at 2 hours were retested at 6 hours and rats tested at 4 hours were retested at 8 hours). The evaluation of the anticonvulsive profile of test drugs was based on the duration of the tonic phase (in seconds) being each rat its own control (internal control) as obtained in the first MES session. An external control group was also studied; in this particular case, rats were given the vehicle and submitted to the three MES sessions procedure, as described above. All drugs used were suspended in 0.5% carboxymethylcellulose (4 ml/kg) and given by stomach tube.

## 2 - Metrazol test

Administration of compounds of formula I was performed 2 hours before the administration of metrazol. Metrazol (75 mg/kg) was given subcutaneously in the back; this dose of metrazol was found to produce convulsions in 95% of the animals. The parameters observed concern the duration of seizures in a 30 minute observation period following the administration of metrazol.  $ED_{50}$  (mg/kg) is the dose giving 50% reduction of duration of the seizure

## Results

### 1 - MES test

At the highest dose tested (30 mg/kg), compounds of formula I produced a complete protection against MES after 2 hours of administration. At 4 and 8 hours the protection conferred by compounds of formula I was similar to that produced by the reference compound carbamazepine. At the highest dose tested (30 mg/kg), carbamazepine produced a complete protection against MES after 2 hours of administration; at 4 and 8 hours after administration the protection conferred was still above 80%. The  $ED_{50}$  values for carbamazepine at 2, 4 and 8 hours after the administration was 5.6, 11.3 and 20.6 mg/kg, respectively. The  $ED_{50}$  values for compounds of formula I at 2, 4 and 8 hours after the administration were 6.9, 19.8

and 18.9 mg/kg, respectively. Oxcarbazepine performed not so potently as did carbamazepine and compounds of formula I. The ED<sub>50</sub> values for oxcarbazepine at 2, 4 and 8 hours after the administration were 9.7, 20.2 and 22.3 mg/kg, respectively.

## 2 - Metrazol test

Compounds of formula I were effective in protecting rats against convulsions induced by metrazol. The highest effective dose of compounds of formula I was 30 mg/kg and reduced the total seizure time by 44%. Carbamazepine at 30 and 60 mg/kg produced a 41% and 44%, respectively, decrease in total seizure time. Oxcarbazepine performed less potently than did carbamazepine. At 30 and 60 mg/kg oxcarbazepine a 3% and 32% decrease in total seizure time was observed, respectively.

## Conclusion

Compounds of formula I possess valuable antiepileptic activity as screened in the MES and metrazol tests and are endowed with greater or similar anticonvulsant potency to that of reference compounds carbamazepine or oxcarbazepine.

The utilisation of compounds of formula I have proved useful in man for the treatment of some other central and peripheral nervous system disorders, e.g. for trigeminal neuralgia and brain affective disorders nervous function alterations in degenerative and post-ischemic diseases.

For the preparation of pharmaceutical compositions from the compounds of formula I, inert pharmaceutically acceptable carriers are admixed with the active compounds. The pharmaceutically acceptable carriers may be either solid or liquid. Solid form preparations include powders, tablets, dispersible granules and capsules. A solid carrier can be one or more substances which may also act as diluents,

flavouring agents, solubilizers, lubricants, suspending agents, binders or tablet disintegrating agents; it may also be an encapsulating material.

Preferably, the pharmaceutical preparation is in unit dosage form, e.g. packaged preparation, the package containing discrete quantities of preparation such as packed tablets, capsules and powders in vials or ampoules.

The dosages may be varied depending on the requirement of the patient, the severity of the disease and the particular compound being employed. For convenience, the total daily dosage may be divided and administered in portions throughout the day. Determination of the proper dosage for a particular situation is within the skill of those in the medical art.

The invention disclosed herein is exemplified by the following examples of preparation which should not be construed to limit the scope of the disclosure. Alternative pathways and analogous structures may be apparent to those skilled in the art.

#### EXAMPLES

EXAMPLE 1: 10,11-dihydro-10-hydroxyimino-5H-dibenz[b,f]azepine-5-carboxamide

A suspension of 4.0 g (15.86 mmol) of 10,11-dihydro-10-oxo-5H-dibenz[b,f]azepine-5-carboxamide and 3.86 g (55.49 mmol) of hydroxylamine hydrochloride in 100 mL of absolute alcohol was treated with 3.76 g (47.57 mmol) of pyridine. The mixture was heated at reflux for 1 hour and then the ethanol was removed by evaporation under reduced pressure. The residue was partitioned between 150 mL of water and 150 mL of dichloromethane. The organic layer was separated and washed with 50 mL of 1 M aqueous HCl, a saturated solution of NaHCO<sub>3</sub> and brine, then dried by sodium sulphate. Filtration and evaporation of the

solvent under reduced pressure gave an off-white solid which was triturated with hot ethanol to give the desired compound as a white powder of m.p. 230.4 to 231.5° C.

EXAMPLE 2: Using a similar procedure to that described in the preceding example but employing the appropriate hydroxylamine, 10-benzyloxyimino-10,11-dihydro-5H-dibenz[b,f]azepine-5-carboxamide was prepared.

EXAMPLE 3: 10-acetyloxyimino-10,11-dihydro-5H-dibenz[b,f]azepine-5-carboxamide

A suspension of 0.5 g (1.87 mmol) of 10,11-dihydro-10-hydroxyimino-5H-dibenz[b,f]azepine-5-carboxamide in 25 mL of dichloromethane and 0.72 g (9.16 mmol) of pyridine was treated with 0.57 g (5.61 mmol) of acetic anhydride. The resulting mixture was stirred at room temperature overnight and then diluted with 10 mL of dichloromethane. The organic phase was extracted with 20 mL of 1 M aqueous HCl, a saturated solution of NaHCO<sub>3</sub> and brine, then dried by sodium sulphate. The solvent was then removed by evaporation under reduced pressure and the crude product was crystallised from a mixture of dichloromethane and ethyl acetate to give the desired product as white crystals of m.p. 175.8-176.9° C.

EXAMPLE 4-11: By the application of the above described technique but using the appropriate anhydrides, the following compounds were prepared:

10,11-dihydro-10-propionyloxyimino-5H-dibenz[b,f]azepine-5-carboxamide

10-butyroyloxyimino-10,11-dihydro-5H-dibenz[b,f]azepine-5-carboxamide

10,11-dihydro-10-pivaloyloxyimino-5H-dibenz[b,f]azepine-5-carboxamide

10,11-dihydro-10-[(1-naphthoyloxy)imino]-5H-dibenz[b,f]azepine-5-carboxamide

10-benzoyloxyimino-10,11-dihydro-5H-dibenz[b,f]azepine-5-carboxamide

10,11-dihydro-10-succinoyloxyimino-5H-dibenz[b,f]azepine-5-carboxamide

10,11-dihydro-10-glutaroyloxyimino-5H-dibenz[b,f]azepine-5-carboxamide

10,11-dihydro-10-isobutoxycarbonyloxyimino-5H-dibenz[b,f]azepine-5-carboxamide

EXAMPLE 12: 10,11-dihydro-10-methoxyimino-5H-dibenz[b,f]azepine-5-carboxamide

To a suspension of 0.2 g (0.75 mmol) of 10,11-dihydro-10-hydroxyimino-5H-dibenz[b,f]azepine-5-carboxamide in 2 mL of acetone cooled to 0° C was added a solution of 0.065 g (1.16 mmol) of potassium hydroxide in 1 mL of water followed by 0.164 g (1.16 mmol) of iodomethane. The resulting mixture was stirred at room temperature overnight then 10 mL of water was added. The mixture was extracted with ether and the organic layer was washed with water and brine, then dried by sodium sulphate and filtered. The solvent was removed by evaporation under reduced pressure and the residue chromatographed on silica gel with a 3% methanol-dichloromethane mixture. Chromatographically homogenous fractions were pooled, the solvents were removed under reduced pressure and the residue was crystallised from toluene to give the product as off-white crystals of m.p. 157.9-159.4° C.

EXAMPLE 13: 10,11-dihydro-10-(S)-(-)-camphanoyloxyimino-5H-dibenz[b,f]azepine-5-carboxamide

To a suspension of 0.15 g (0.56 mmol) of 10,11-dihydro-10-hydroxyimino-5H-dibenz[b,f]azepine-5-carboxamide and 0.01 g (0.08mmol) of 4-dimethylaminopyridine in 5 mL of dichloromethane and 0.22 g (2.8 mmol) of



pyridine was added 0.15 g (0.67 mmol) of (S)-(-)-camphanic chloride in portions. The resulting mixture was stirred for 2 hours at room temperature whereupon a further portion of 0.1 g, (0.46 mmol) of (S)-(-)-camphanic chloride was added. After stirring for a further 1.5 hours, 5 mL of dichloromethane followed by 5 mL of ice-water was added. The organic layer was separated and washed with 10 mL of 2 M aqueous HCl, a saturated solution of NaHCO<sub>3</sub> and brine, then dried by sodium sulphate and filtered. The solvent was removed by evaporation under reduced pressure and the residue triturated with ether to give an off-white solid which was crystallised from a mixture of dichloromethane and ethyl acetate to give the desired product as white crystals of m.p. 187 to 187.9° C.

EXAMPLE 14-15: By the application of the above described technique but using the appropriate acid halogenides, the following compounds were prepared:

10,11-dihydro-10-[(3-methoxybenzoyloxy)imino]-5H-dibenz[b,f]azepine-5-carboxamide

10,11-dihydro-10-nicotinoyloxyimino-5H-dibenz[b,f]azepine-5-carboxamide

EXAMPLE 16: 10,11-dihydro-10-ethoxycarbonyloxyimino-5H-dibenz[b,f]azepine-5-carboxamide

To a suspension of 0.2 g (0.74 mmol) of 10,11-dihydro-10-hydroxyimino-5H-dibenz[b,f]azepine-5-carboxamide and 0.01 g (0.08 mmol) of 4-dimethylaminopyridine in 10 mL of dichloromethane and 0.29 g (3.7 mmol) of pyridine was added 0.28 g (2.6 mmol) of ethyl chloroformate dropwise. The resulting mixture was stirred at room temperature for 2 hours whereupon it was extracted with 20 mL of 1 M aqueous HCl and a saturated solution of NaHCO<sub>3</sub>, then dried by sodium sulphate and filtered. The solvent was removed by evaporation under reduced pressure and the residue was crystallised from a mixture of dichloromethane and ethyl acetate to give white crystals of m.p. 188.9-190° C.

EXAMPLE 17-18: By the application of the above described technique but using the appropriate chloroformates, the following compounds were prepared:

10-butoxycarbonyloxyimino-10,11-dihydro-5H-dibenz[b,f]azepine-5-carboxamide

10-benzyloxycarbonyloxyimino-10,11-dihydro-5H-dibenz[b,f]azepine-5-carboxamide

EXAMPLE 19: 10,11-dihydro-10-phenylhydrazono-5H-dibenz[b,f]azepine-5-carboxamide

A mixture of 0.2 g (0.8 mmol) of 10,11-dihydro-10-oxo-5H-dibenz[b,f]azepine-5-carboxamide, 0.5 g (4.6 mmol) of phenylhydrazine and 0.5 g (6 mmol) of sodium acetate in a mixture of 5 mL of water, 5 mL of ethanol and 3 drops of concentrated hydrochloric acid was heated at 60° C for thirty minutes and then allowed to cool to room temperature. The precipitate was then filtered and washed with cold water and dilute ethanol to give the desired product as yellow crystals of m.p. 220 to 220.8° C.

EXAMPLE 20-21: By the application of the above described technique but using the appropriate hydrazines, the following compounds were prepared:

10,11-dihydro-10-hydrazono-5H-dibenz[b,f]azepine-5-carboxamide

10,11-dihydro-10-(2,4-dinitrophenylhydrazono)-5H-dibenz[b,f]azepine-5-carboxamide

EXAMPLE 22: 10,11-dihydro-10-semicarbozono-5H-dibenz[b,f]azepine-5-carboxamide

To a stirred solution of 0.4 g (3.59 mmol) of semicarbazide hydrochloride and 0.6 g

(7.32 mmol) of sodium acetate in 4 mL of water was added 0.2 g (0.8 mmol) of 10,11-dihydro-10-oxo-5H-dibenz[b,f]azepine-5-carboxamide. The resulting suspension was warmed on a water bath and 6 mL of ethanol was added until a solution was obtained. The solution was heated at 60° C for 1.5 hours and then cooled to room temperature. The ethanol was removed by evaporation under reduced pressure and the residue cooled to 5° C for 2 hours. The crystalline precipitate was filtered and washed with cold water to give the desired product as pale yellow crystals of m.p. 247.2-248.6° C.

EXAMPLE 23-24: By the application of the above described technique but using the appropriate semicarbazides, the following compounds were prepared:

10,11-dihydro-10-thiosemicarbozono-5H-dibenz[b,f]azepine-5-carboxamide

10-(2-chlorophenylsemicarbozono)-10,11-dihydro-5H-dibenz[b,f]azepine-5-carboxamide

EXAMPLE 25: 10,11-dihydro-10-methoxycarbonylpropylimino-5H-dibenz[b,f]azepine-5-carboxamide

To a suspension of 0.2 g (0.79 mmol) of 10,11-dihydro-10-oxo-5H-dibenz[b,f]azepine-5-carboxamide and 0.1 g (0.67 mmol) of methyl-4-aminobutyrate hydrochloride in 5 mL of xylene was added 0.07g (0.49 mmol) of boron trifluoride diethyl etherate. The resulting mixture was heated at 135° C for seven hours and then allowed to cool to room temperature. The mixture was then filtered and the residue was extracted with toluene. The combined extracts were evaporated under reduced pressure and the residue chromatographed on silica gel using a 4:1 mixture of petroleum ether-ethyl acetate. Chromatographically homogenous fractions were pooled and the solvents were removed under reduced pressure to give the desired product as a yellow oil which crystallised on standing to give yellow crystals which decomposed on heating without melting.

Where the terms "comprise", "comprises", "comprised" or "comprising" are used in this specification, they are to be interpreted as specifying the presence of the stated features, integers, steps or components referred to, but not to preclude the presence or addition of one or more other feature, integer, step, component or group thereof.

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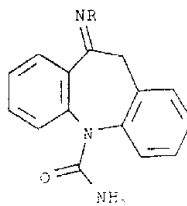
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## Claims

1. Compounds of general formula I



I

wherein: R is hydroxy, alkyl, cycloalkyl, alkylaryl or alkylheteroaryl group or R is the group  $-O-CO-R^1$  wherein  $R^1$  is hydrogen, alkyl, cycloalkyl, alkylcycloalkyl, alkylaryl or heteroaryl group or R is the group  $-O-CO-OR^1$  where substituent  $R^1$  is defined above. or group R is the group  $-O-R^2$  wherein  $R^2$  is an alkyl or alkylaryl group, or R is the group  $NR^3R^4$  wherein  $R^3$  is hydrogen,  $-NH-CO-NH_2$ ,  $-NH-CS-NH_2$ , alkyl or alkylaryl group and  $R^4$  is hydrogen, alkyl, alkylcycloalkyl, alkylcarbonyl or arylcarbonyl group; the term alkyl means a carbon chain, straight or branched, containing from one to six carbon atoms, optionally substituted by one or more alkoxy, halogen, alkoxy carbonyl or hydroxycarbonyl groups; the term cycloalkyl represents an alicyclic group with three to six carbon atoms; the term aryl represents a phenyl or naphthyl group optionally substituted by one or more alkoxy, halogen or nitro groups; the term heteroaryl represents a five or six membered aromatic ring incorporating an atom of oxygen, sulphur or nitrogen; the term halogen represents fluorine, chlorine, bromine or iodine.

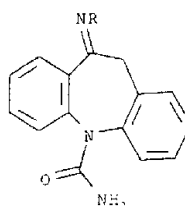
2. A compound as defined in claim 1 which is:

- (1) 10,11-dihydro-10-hydroxyimino-5H-dibenz/b,f/azepine-5-carboxamide
- (2) 10-benzyloxyimino-10,11-dihydro-5H-dibenz/b,f/azepine-5-carboxamide
- (3) 10-acetyloxyimino-10,11-dihydro-5H-dibenz/b,f/azepine-5-carboxamide
- (4) 10,11-dihydro-10-propionyloxyimino-5H-dibenz/b,f/azepine-5-carboxamide
- (5) 10-butyroyloxyimino-10,11-dihydro-5H-dibenz/b,f/azepine-5-carboxamide
- (6) 10,11-dihydro-10-pivaloyloxyimino-5H-dibenz/b,f/azepine-5-carboxamide
- (7) 10,11-dihydro-10-[(1-naphthoyloxyimino)]-5H-dibenz/b,f/azepine-5-carboxamide
- (8) 10-benzoyloxyimino-10,11-dihydro-5H-dibenz/b,f/azepine-5-carboxamide
- (9) 10,11-dihydro-10-succinoyloxy-5H-dibenz/b,f/azepine-5-carboxamide
- (10) 10,11-dihydro-10-glutaroyloxyimino-5H-dibenz/b,f/azepine-5-carboxamide
- (11) 10,11-dihydro-10-isobutoxycarbonyloxyimino-5H-dibenz/b,f/azepine-5-carboxamide
- (12) 10,11-dihydro-10-methoxyimino-5H-dibenz/b,f/azepine-5-carboxamide
- (13) 10,11-dihydro-10-(S)-(-)-camphanoyloxyimino-5H-dibenz/b,f/azepine-5-carboxamide

- (14) 10,11-dihydro-10-[(3-methoxybenzoyloxy)imino]-5H-dibenz/b,f/azepine-5-carboxamide
- (15) 10,11-dihydro-10-nicotinoyloxyimino-5H-dibenz/b,f/azepine-5-carboxamide
- (16) 10,11-dihydro-10-ethoxycarbonyloxyimino-5H-dibenz/b,f/azepine-5-carboxamide
- (17) 10-butoxycarbonyloxyimino-10,11-dihydro-5H-dibenz/b,f/azepine-5-carboxamide
- (18) 10-benzyloxycarbonyloxyimino-10,11-dihydro-5H-dibenz/b,f/azepine-5-carboxamide
- (19) 10,11-dihydro-10-phenylhydrazono-5H-dibenz/b,f/azepine-5-carboxamide
- (20) 10,11-dihydro-10-hydrazono-5H-dibenz/b,f/azepine-5-carboxamide
- (21) 10,11-dihydro-10-(2,4-dinitrophenylhydrazono)-5H-dibenz/b,f/azepine-5-carboxamide
- (22) 10,11-dihydro-10-semicarbozono-5H-dibenz/b,f/azepine-5-carboxamide
- (23) 10,11-dihydro-10-thiosemicarbozono-5H-dibenz/b,f/azepine-5-carboxamide
- (24) 10-(2-chlorophenylsemicarbozono)-5H-dibenz/b,f/azepine-5-carboxamide

(25) 10,11-dihydro-10-methoxycarbonylpropylimino-5H-dibenz/b,f/azepine-  
-5-carboxamide

3. A process for producing a compound having the general formula I



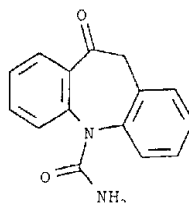
I

wherein:

R is hydroxy, alkyl, alkylcycloalkyl, alkylaryl or alkylheteroaryl group or R is the group -O-CO-R<sup>1</sup> wherein R<sup>1</sup> is hydrogen, alkyl, cycloalkyl, alkylcycloalkyl, alkylaryl or heteroaryl group, or R is the group -O-CO-OR<sup>1</sup> wherein substituent R<sup>1</sup> is defined above or the group R is -O-R<sup>2</sup> wherein R<sup>2</sup> is an alkyl or alkylaryl group, or R is the group NR<sup>3</sup>R<sup>4</sup> wherein R<sup>3</sup> is hydrogen, -NH-CO-NH<sub>2</sub>, -NH-CS-NH<sub>2</sub>, alkyl or alkylaryl group and R<sup>4</sup> is hydrogen, alkyl, alkylcycloalkyl, alkylaryl, alkylcarbonyl or arylcarbonyl group; the term alkyl means a carbon chain, straight or branched, containing from one to six carbon atoms optionally substituted by alkoxy, halogen, alkoxycarbonyl or hydroxycarbonyl groups; the term cycloalkyl represents an alicyclic group with three to six carbon atoms; the term aryl represents a phenyl or naphthyl group optionally substituted by alkoxy, halogen or nitro groups; the term heteroaryl represents a five or six membered aromatic ring incorporating an atom of oxygen, sulphur or nitrogen; the term halogen represents fluorine, chlorine, bromine

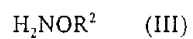


or iodine, by reacting the compound of formula II

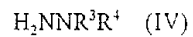


II

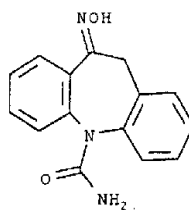
with hydroxylamine or a derivative thereof of formula III



wherein substituent  $\text{R}^2$  is defined above, or by reacting a compound of formula II with thiocarbazide, thiosemicarbazide or a derivative of hydrazine of formula IV

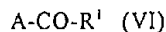


wherein substituents  $\text{R}^3$  and  $\text{R}^4$  are defined above, or by reacting a compound of formula V



V

with an acylating reagent of formula VI



wherein  $R^1$  is the same as defined for general formula I; A is hydroxy, halogen or -O-CO- $R^1$  group or -O-CO-OR' group wherein  $R^1$  is lower alkyl (C1 to C4), or by reacting the compound of formula V with an acylating reagent of formula VII



wherein  $R^1$  is the same as defined for general formula I.

4. A process according to claim 3, wherein the reaction is conducted in the presence of a condensing agent and/or a base.

5. The use of a compound as claimed in claims 1 or 2, for the preparation of a pharmaceutical composition useful in the treatment of central and peripheral nervous system disorders, such as in the treatment of epilepsy, trigeminal neuralgia, affective brain disorders and nervous function alterations in degenerative and post-ischaemic diseases.

6. A pharmaceutical composition for the treatment of central and peripheral nervous system disorders, which comprises a compound of formula I as defined in claim 1, and a pharmaceutically acceptable carrier.

7. A composition according to claim 6 wherein the said compound is as claimed in claim 2.

8. A method of treating central and peripheral nervous system disorders which comprises administering a compound as claimed in claim 1 or 2, or a pharmaceutical composition as claimed in claim 6 or 7.

9. Compounds of general formula I according to claim 1 or claim 2 substantially as hereinbefore described with reference to any one of the accompanying Examples.

5 10. A process for producing a compound having the general formula I according to claim 3 or claim 4 substantially as hereinbefore described with reference to any one of the accompanying Examples.

10 11. A pharmaceutical composition according to claim 6 or claim 7 substantially as hereinbefore described with reference to any one of the accompanying Examples.

12. Use of the pharmaceutical composition according to claim 6 or claim 7 substantially as hereinbefore described.

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DATED this 8<sup>th</sup> day of October, 1999

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**PORTELA & C.A. S.A.**

By their Patent Attorneys:

CALLINAN LAWRIE

*Michael J. Houlihan.*

