

**TETRALINES BEARING A PHENYL SUBSTITUENT ON THE AROMATIC RING AND THEIR USE IN THE TREATMENT OF EPILEPSY, STROKE AND BRAIN OR SPINAL TRAUMA**

The present invention relates to novel amino-tetralines (tetrahydro-naphthalenamines), their preparation, their use as pharmaceuticals and pharmaceutical compositions containing them.

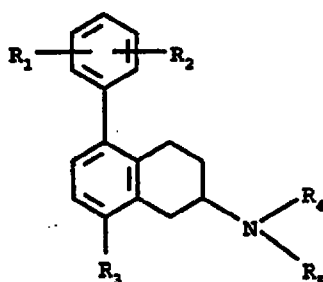
In accordance with the invention, there are provided, in a first aspect, 1,2,3,4-tetrahydro-2-naphthalenamines bearing a phenyl substituent on the aromatic ring and acid addition salts thereof.

The phenyl substituent is preferably in position 5 of the 2-naphthalenamine.

The phenyl substituent may bear further substituents, for example as in the case of formula I below.

Further substituents may also be present conveniently but not exclusively on the aromatic ring, e.g. in position 8 of the 2-naphthalenamine when the phenyl group is in position 5.

More particularly the present invention provides a compound of formula I



wherein

$R_1$  and  $R_2$ , independently, are hydrogen,  $(C_{1-4})$ alkyl,  $(C_{1-4})$ alkoxy,  $(C_{1-4})$ alkylthio, halogen, trifluoromethyl, trifluoromethoxy, cyano,  $(C_{2-5})$ alkanoyl,  $(C_{1-4})$ alkylsulfonyl or sulfamoyl,

$R_3$  is hydrogen, hydroxy,  $(C_{1-4})$ alkyl,  $(C_{1-4})$ alkoxy, halogen, cyano,  $(C_{2-5})$ alkanoyl, carbamoyl,  $(C_{1-4})$ alkylsulfonyloxy or trifluoromethylsulfonyloxy, and

$R_4$  and  $R_5$ , independently, are hydrogen,  $(C_{1-4})$ alkyl, hydroxy $(C_{2-4})$ alkyl or phenyl $(C_{1-4})$ alkyl, or form together with the nitrogen atom to which they are attached a pyrrolidinyl, piperidino or piperazinyl group,

in free base or acid addition salt form.

Halogen is fluorine, chlorine, bromine or iodine, preferably fluorine or chlorine.

Any alkyl, alkoxy and alkylthio radicals preferably are straight chain radicals. They preferably have 1 to 3 carbon atoms, more preferably they are methyl, methoxy and methylthio groups.

The following significances and their combinations are preferred:

$R_1$  and  $R_2$ , independently, are hydrogen,  $(C_{1-4})$ alkyl,  $(C_{1-4})$ alkoxy, halogen or trifluoromethyl,

$R_3$  is hydrogen, hydroxy,  $(C_{1-4})$ alkoxy, cyano or carbamoyl,

$R_4$  and  $R_5$ , independently, are hydrogen or  $(C_{1-4})$ alkyl, or form together with the nitrogen to which they are attached a piperidino group.

In a particular group of compounds of formula I,  $R_1$  and  $R_2$ , independently, are hydrogen,  $(C_{1-4})$ alkyl,  $(C_{1-4})$ alkoxy,  $(C_{1-4})$ alkylthio, halogen, trifluoromethyl, cyano or  $(C_{2-5})$ alkanoyl,  $R_3$  is as defined above and  $R_4$  and  $R_5$ , independently, are hydrogen,  $(C_{1-4})$ alkyl or phenyl $(C_{1-4})$ alkyl, or form together with the nitrogen atom to which they are attached a pyrrolidinyl, piperidino or piperazinyl group.

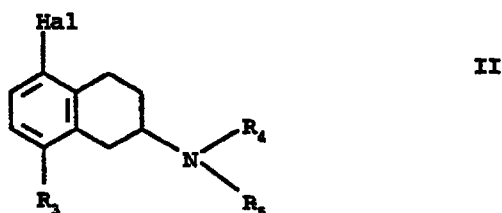
The compounds of the invention possess an asymmetrical carbon atom in position 2. They may therefore appear in optically active form or in form of mixtures of optical isomers, e.g.

in form of racemic mixtures. All optical isomers and their mixtures including the racemic mixtures are part of the present invention.

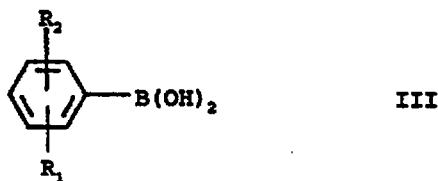
When a compound of the invention is in optically active form, the R configuration is preferred.

In a further aspect, the invention provides a process for the production of the compounds of the invention, whereby a 1,2,3,4-tetrahydro-2-naphthalenamine bearing a halogen on the aromatic ring is reacted with optionally substituted phenylboronic acid and the resulting compound is recovered in free base form or in acid addition salt form.

More particularly the invention provides a process for the production of the compounds of the invention, whereby a compound of formula II



wherein  $R_3$ ,  $R_4$  and  $R_5$  are as defined above and Hal is halogen, is reacted with a compound of formula III



wherein  $R_1$  and  $R_2$  are as defined above, and the resulting compound is recovered in free base

form or in acid addition salt form.

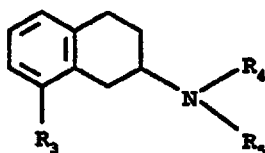
The reaction may be effected in known manner, preferably by transition metal-catalysed aryl-aryl coupling, e.g. as described in Example 1. Hal is preferably bromine or iodine, particularly bromine.

Working up of the reaction mixtures obtained according to the above process and purification of the compounds thus obtained may be carried out in accordance to known procedures.

Acid addition salts may be produced in known manner from the free base forms and vice-versa. Suitable pharmaceutically acceptable acid addition salts for use in accordance with the present invention include for example the hydrochloride, the hydrogen maleate, the hydrogen fumarate and the hydrogen malonate.

Racemic compounds of the invention may be obtained from racemic starting materials. Optically active isomers may be obtained from optically active starting materials or from the racemate. The enantiomers may be obtained from the racemate by known methods, for example by fractional crystallization of diastereoisomeric salts, e.g. their salts with (+)-di-O,p-toluoyl-D-tartaric acid or (-)-di-O,p-toluoyl-L-tartaric acid.

The starting materials of formula II may be produced by halogenating compounds of formula IV



IV

wherein R<sub>3</sub>, R<sub>4</sub> and R<sub>5</sub> are as defined above, in accordance to known procedures, e.g. as described in Example 1.

## 5

The starting materials of formulae III and IV are known or may be produced in analogous manner to known procedures.

Compounds of the invention, e.g. compounds of formula I and their pharmaceutically acceptable acid addition salts, hereinafter referred to as agents of the invention, exhibit pharmacological activity and are, therefore, useful as pharmaceuticals.

The agents of the invention provide long-lasting protection against maximal electroshock-induced convulsions in mice at doses of about 1 to 100 mg/kg p.o. and about 0.32 to 32 mg/kg i.p. [cf. E.A. Swinyard, J. Am.Pharm. Assoc. Scient. Ed. 38, 201 (1949) and J.Pharmacol. Exptl. Therap. 106, 319 (1952)].

The agents of the invention are therefore useful in the treatment of epilepsy and other convulsive states such as high pressure neurological syndrome.

Furthermore, the agents of the invention reduce ischaemia-induced neuronal damage and ensuing symptoms in the middle cerebral artery (MCA) occlusion model in rats at a dosage of 1-30 mg/kg i.p, i.v. and p.o. [cf. A. Tamura et al., J. Cereb. Blood Flow Metabol. 1, 53-60 (1981)), A. Sauter, M. Rudin, Stroke 17, 1228-1234 (1986)].

The agents of the invention are therefore useful in the treatment of any clinical condition involving a component of cerebral anoxia, hypoxia and/or ischaemia, e.g. ischemic damage to grey and white matter, stroke, reperfusion injury, subarachnoid haemorrhage, brain and spinal cord injury/trauma, high intracranial pressure, multi-infarct dementia or vascular dementia, and any surgical procedure potentially associated with cerebral anoxia, hypoxia and/or ischemia (e.g. cardiac bypass, operations on extracerebral vessels).

The agents of the invention display binding to the veratridine-sensitive sodium channel with  $IC_{50}$ s of from about 0.1 to about 100  $\mu$ M. For the binding procedure see for example J.B Brown, Journal of Neuroscience 6, 2064-2070 (1986). They block veratridine-induced glutamate release in rat hippocampal slice preparations at concentrations of about 0.1-1  $\mu$ M.

The experiment is performed according to a modification of M. J. Leach et al. in *Epilepsia* 27, 490-497 (1986) and *Stroke* 24, 1063-1067 (1993), using exogenous glutamate.

As a result the agents of the invention are indicated for the treatment of any pathology, disorder or clinical condition involving glutamate release in their etiology, including psychiatric disorders (such as schizophrenia, depression, anxiety, panic attacks, attention deficit and cognitive disorders, social withdrawal), hormonal conditions (excess GH [e.g. in the treatment of diabetes mellitus, angiopathy and acromegaly] or LH [prostate hypertrophy, menopausal syndrome] secretion, corticosterone secretion in stress), metabolic induced brain damage (hypoglycaemia, non-ketotic hyperglycinaemia [glycine encephalopathy], sulphite oxidase deficiency, hepatic encephalopathy associated with liver failure), emesis, spasticity, tinnitus, pain (e.g. cancer pain, arthritis) and drug (ethanol, opiates [including synthetics with opiate-like effects, e.g. pethidine, methadone etc.], cocaine, amphetamine, barbiturates and other sedatives, benzodiazepines) abuse and withdrawal.

Moreover the agents of the invention are indicated in the treatment of any pathology involving neuronal damage, for example neurodegenerative disorders such as Alzheimer's, Huntington's or Parkinson's diseases, virus (including HIV)-induced neurodegeneration, Amyotrophic lateral sclerosis (ALS), supra-nuclear palsy, olivoponto-cerebellar atrophy (OPCA), and the actions of environmental, exogenous neurotoxins.

For the above-mentioned indications, the appropriate dosage will of course vary depending upon, for example, the compound employed, the host, the mode of administration and the nature and severity of the condition being treated. However, in general, satisfactory results in animals are indicated to be obtained at a daily dosage of from about 0.1 to about 100, preferably from about 0.5 to about 100 mg/kg animal body weight. In larger mammals, for example humans, an indicated daily dosage is in the range from about 1 to about 500, preferably from about 1 to about 300 mg of an agent of the invention, conveniently administered, for example, in divided doses up to four times a day or in sustained release form.

For all these indications the preferred compound is (R)-1,2,3,4-tetrahydro-8-methoxy-N,N-dimethyl-5-[4-(trifluoromethyl)phenyl]-2-naphthaleneamine, which is the compound of example 21. It has for example been determined that in the above mentioned electroshock model, this compound provides protection against maximal electroshock-induced convulsions with a threshold dose of 10 mg/kg p.o. for periods up to 8 hours post-administration. In the MCA occlusion model, the compound given i.p. immediately after occlusion has been found to dose-dependently reduce infarct size at 3.2, 10 and 32 mg/kg (19, 43, and 53% respectively). In the veratridine-induced glutamate release test, the compound has been found to block the release with an  $IC_{50}$  of 0.5  $\mu$ M, which is consistent with its affinity for the veratridine binding site ( $IC_{50}$  = 125 nM).

The compound of example 21 is for example superior to the standard Lofarizine in the MCA occlusion model (infarct size reduction of 43 % versus 25 %, after 10 mg/kg i.p.). In the veratridine-induced glutamate release test it has been found to be about equipotent to Lofarizine, but more potent than the standards Riluzole and Lamotrigine ( $IC_{50}$  = 0.5  $\mu$ M versus 5  $\mu$ M and 20  $\mu$ M respectively).

The preferred indications are epilepsy, stroke and brain and spinal trauma.

The agent of the invention may be administered by any conventional route, in particular enterally, preferably orally, for example in the form of tablets or capsules, or parenterally, for example in the form of injectable solutions or suspensions.

In accordance with the foregoing, the present invention also provides an agent of the invention, for use as a pharmaceutical, e.g. for the treatment of epilepsy, stroke and brain or spinal trauma.

The present invention furthermore provides a pharmaceutical composition comprising an agent of the invention in association with at least one pharmaceutical carrier or diluent. Such compositions may be manufactured in conventional manner. Unit dosage forms contain, for example, from about 0.25 to about 150, preferably from 0.25 to about 25 mg of a compound

according to the invention.

Moreover the present invention provides the use of an agent of the invention, for the manufacture of a medicament for the treatment of any condition mentioned above, e.g. epilepsy, stroke and brain or spinal trauma.

In still a further aspect the present invention provides a method for the treatment of any condition mentioned above, e.g. epilepsy, stroke and brain or spinal trauma, in a subject in need of such treatment, which comprises administering to such subject a therapeutically effective amount of an agent of the invention.

The following examples illustrate the invention. The temperatures are given in degrees Celsius and are uncorrected.

**Example 1:** (+/-)-1,2,3,4-tetrahydro-5-(4-chlorophenyl)-8-methoxy-N,N-dimethyl-2-naphthalenamine

0.57 g (2 mMol) of (+/-)-1,2,3,4-tetrahydro-5-bromo-8-methoxy-N,N-dimethyl-2-naphthalenamine are dissolved in 8 ml toluene. 0.55 g (3.54 mMol) of 4-chlorophenylboronic acid, 0.07 g (0.23 mMol) of tri(ortho-tolyl)phosphine, 3 ml of 2N aqueous sodium carbonate and 0.7 ml of methanol are added. After degassing and filling the system with argon, 0.031 g (0.14 mMol) of palladium(II)acetate are added and the mixture is stirred over night at 80°. The aqueous phase is separated and extracted with ethylacetate. The combined organic phases are extracted with 2N acetic acid, the acidic extracts basified with aqueous ammonia and again extracted with ethylacetate. After drying with sodium sulfate, filtering and evaporating the organic phase, the resulting bright-brown oil is treated with fumaric acid in methyl-tert.butylether. The resulting salt is recrystallised from isopropanol, yielding white crystals of the hydrogenfumarate of the title compound, m.p. 213-216°.

The starting material may be produced as follows:

4.1 g (20 mMol) of (+/-)-1,2,3,4-tetrahydro-8-methoxy-N,N-dimethyl-2-naphthalenamine are dissolved in 50 ml of acetic acid and 1.8 g (22 mMol) of sodium acetate are added. A solution of 1.02 ml (20 mMol) of bromine in 5 ml acetic acid is added dropwise at room temperature within about 30 minutes. A colourless precipitate is formed. After stirring over night the solvent is distilled off under vacuum, the residue taken up with water and extracted with ethylacetate. The remaining aqueous phase is made alkaline with aqueous ammonia and extracted with ethylacetate. The organic phase is dried with sodium sulfate, filtered and evaporated to dryness. The remaining oil is distilled in a bulb to bulb distillation apparatus yielding a slightly yellow oil, b.p. 170-180° at 0.04 mbar.

The following compounds are prepared analogously to example 1.

| Ex. | R <sub>1</sub>    | R <sub>2</sub> | R <sub>3</sub> | R <sub>4</sub> | R <sub>5</sub> | Config  | M.p.<br>(salt)             |
|-----|-------------------|----------------|----------------|----------------|----------------|---------|----------------------------|
| 2   | H                 | H              | OMe            | Me             | Me             | +/-     | 171-174° (1)               |
| 3   | 2-Cl              | "              | "              | "              | "              | "       | 186-190° (1)               |
| 4   | 2-Me              | "              | "              | "              | "              | "       | 190-196° (1)               |
| 5   | 2-OMe             | "              | "              | "              | "              | "       | 252-263° (2)               |
| 6   | H                 | "              | OH             | "              | "              | "       | 223-229° (3)               |
| 7   | "                 | "              | H              | "              | "              | "       | 130-133° (1)               |
| 8   | 4-Me              | "              | OMe            | "              | "              | "       | 205-209° (4)               |
| 9   | 4-CF <sub>3</sub> | "              | "              | "              | "              | "       | 202-207° (4)               |
| 10  | 2-Cl              | 4-Cl           | "              | "              | "              | "       | 250-257° (2)               |
| 11  | 2-F               | H              | "              | "              | "              | "       | 200-209° (4)               |
| 12  | 3-Cl              | "              | "              | "              | "              | "       | 187-190° (1)               |
| 13  | 2-Cl              | "              | "              | "              | "              | (-)-(S) | 200-225° (4)               |
| 14  | "                 | "              | "              | "              | H              | "       | 219-224° (4)               |
| 15  | "                 | "              | "              | "              | Me             | (+)-(R) | 221-226° (4)               |
| 16  | "                 | "              | "              | "              | H              | "       | 216-223° (4)               |
| 17  | H                 | "              | "              | piperidino     |                | +/-     | 239-245° (4)               |
| 18  | 2-Cl              | "              | "              | "              |                | "       | 204-210° (4)               |
| 19  | H                 | "              | "              | n-Propyl       | n-Propyl       | "       | 130-145° (1)               |
| 20  | 4-CF <sub>3</sub> | "              | "              | Me             | Me             | (-)-(S) | 212-215° (4)               |
| 21  | "                 | "              | "              | "              | "              | (+)-(R) | 209-216° (4)<br>75-82° (3) |
| 22  | "                 | "              | OH             | "              | "              | "       | 224-263° (2)*              |
| 23  | 2-Et              | "              | OMe            | "              | "              | +/-     | 189-197° (4)               |
| 24  | 2-Cl              | "              | CN             | "              | "              | "       | 209-215° (4)               |
| 25  | "                 | 4-F            | OMe            | "              | "              | "       | 236-240° (2)               |
| 26  | 2-F               | "              | "              | "              | "              | "       | 172-178°(1)                |

|    |                   |       |                   |                                     |    |       |              |
|----|-------------------|-------|-------------------|-------------------------------------|----|-------|--------------|
| 27 | 2-OMe             | 4-OMe | "                 | "                                   | "  | "     | 182-189° (4) |
| 28 | 2-F               | 3-F   | "                 | "                                   | "  | "     | 193-211° (4) |
| 29 | 2-OMe             | 3-OMe | "                 | "                                   | "  | "     | 213-229° (4) |
| 30 | 2-Me              | 5-Me  | "                 | "                                   | "  | "     | 212-220° (4) |
| 31 | 2-Cl              | 3-Cl  | "                 | "                                   | "  | "     | 198-208° (4) |
| 32 | 2-F               | 5-F   | "                 | "                                   | "  | "     | 189-195° (1) |
| 33 | 2-Me              | 4-Me  | "                 | "                                   | "  | "     | 232-238° (2) |
| 34 | 2-Cl              | H     | CONH <sub>2</sub> | "                                   | "  | "     | 186-189° (3) |
| 35 | 4-CF <sub>3</sub> | "     | OMe               | "                                   | H  | (+)-R | 205-208°(4)  |
| 36 | H                 | "     | "                 | "                                   | Me | "     | 198-211° (4) |
| 37 | 4-Me              | "     | "                 | "                                   | "  | "     | 194-202° (4) |
| 38 | 4-Cl              | "     | "                 | "                                   | "  | "     | 196-203° (4) |
| 39 | 4-OMe             | "     | "                 | "                                   | "  | "     | 235-239° (4) |
| 40 | 4-F               | "     | "                 | "                                   | "  | "     | 199-212° (1) |
| 41 | 4-CF <sub>3</sub> | "     | "                 | (CH <sub>2</sub> ) <sub>2</sub> -OH | "  | "     | 185-112° (4) |
| 42 | "                 | "     | H                 | Me                                  | "  | "     | 140-143° (5) |

Me = methyl

Et = ethyl

\* decomposition

(1) hydrogen maleate

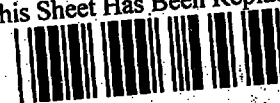
(2) hydrochloride

(3) free base

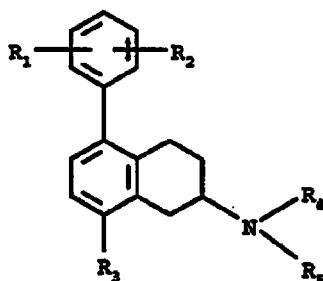
(4) hydrogen fumarate

(5) hydrogen malonate

This Sheet Has Been Replaced

**CLAIMS**

1. A 1,2,3,4,-tetrahydro-2-naphthalenamine bearing a phenyl substituent on the aromatic ring, in free base or acid addition salt form.
2. A compound of formula I



I

wherein

- $R_1$  and  $R_2$ , independently, are hydrogen,  $(C_{1-4})$ alkyl,  $(C_{1-4})$ alkoxy,  $(C_{1-4})$ alkylthio, halogen, trifluoromethyl, trifluoromethoxy, cyano,  $(C_{2-5})$ alkanoyl,  $(C_{1-4})$ alkylsulfonyl or sulfamoyl,
- $R_3$  is hydrogen, hydroxy,  $(C_{1-4})$ alkyl,  $(C_{1-4})$ alkoxy, halogen, cyano,  $(C_{2-5})$ alkanoyl, carbamoyl,  $(C_{1-4})$ alkylsulfonyloxy or trifluoromethylsulfonyloxy, and
- $R_4$  and  $R_5$ , independently, are hydrogen,  $(C_{1-4})$ alkyl, hydroxy $(C_{2-4})$ alkyl or phenyl $(C_{1-4})$ alkyl, or form together with the nitrogen atom to which they are attached a pyrrolidinyl, piperidino or piperazinyl group,
- in free base or acid addition salt form.



\* C L M S \*



## 3. A compound of claim 2 wherein

$R_1$  and  $R_2$ , independently, are hydrogen,  $(C_{1-4})$ alkyl,  $(C_{1-4})$ alkoxy, halogen, trifluoromethyl, cyano,  $(C_{2-5})$ alkanoyl or  $(C_{1-4})$ alkylthio,

$R_3$  is hydrogen, hydroxy,  $(C_{1-4})$ alkyl,  $(C_{1-4})$ alkoxy, halogen, cyano,  $(C_{2-5})$ alkanoyl, carbamoyl,  $(C_{1-4})$ alkylsulfonyloxy or trifluoromethylsulfonyloxy, and

$R_4$  and  $R_5$ , independently, are hydrogen,  $(C_{1-4})$ alkyl or phenyl $(C_{1-4})$ alkyl, or form together with the nitrogen atom to which they are attached a pyrrolidiny, piperidino or piperazinyl group,

in free base or acid addition salt form.

## 4. A compound of claim 2 selected from the compounds of formula I, in optically active or racemic form, wherein:

|                        |                      |                     |                                  |                      |
|------------------------|----------------------|---------------------|----------------------------------|----------------------|
| $R_1 = 4\text{-Cl,}$   | $R_2 = \text{H,}$    | $R_3 = \text{OMe,}$ | $R_4 = \text{Me,}$               | $R_5 = \text{Me,}$   |
| $R_1 = \text{H,}$      | $R_2 = \text{H,}$    | $R_3 = \text{OMe,}$ | $R_4 = \text{Me,}$               | $R_5 = \text{Me,}$   |
| $R_1 = 2\text{-Cl,}$   | $R_2 = \text{H,}$    | $R_3 = \text{OMe,}$ | $R_4 = \text{Me,}$               | $R_5 = \text{Me,}$   |
| $R_1 = 2\text{-Me,}$   | $R_2 = \text{H,}$    | $R_3 = \text{OMe,}$ | $R_4 = \text{Me,}$               | $R_5 = \text{Me,}$   |
| $R_1 = 2\text{-OMe,}$  | $R_2 = \text{H,}$    | $R_3 = \text{OMe,}$ | $R_4 = \text{Me,}$               | $R_5 = \text{Me,}$   |
| $R_1 = \text{H,}$      | $R_2 = \text{H,}$    | $R_3 = \text{OH,}$  | $R_4 = \text{Me,}$               | $R_5 = \text{Me,}$   |
| $R_1 = \text{H,}$      | $R_2 = \text{H,}$    | $R_3 = \text{H,}$   | $R_4 = \text{Me,}$               | $R_5 = \text{Me,}$   |
| $R_1 = 4\text{-Me,}$   | $R_2 = \text{H,}$    | $R_3 = \text{OMe,}$ | $R_4 = \text{Me,}$               | $R_5 = \text{Me,}$   |
| $R_1 = 4\text{-CF}_3,$ | $R_2 = \text{H,}$    | $R_3 = \text{OMe,}$ | $R_4 = \text{Me,}$               | $R_5 = \text{Me,}$   |
| $R_1 = 2\text{-Cl,}$   | $R_2 = 4\text{-Cl,}$ | $R_3 = \text{OMe,}$ | $R_4 = \text{Me,}$               | $R_5 = \text{Me,}$   |
| $R_1 = 2\text{-F,}$    | $R_2 = \text{H,}$    | $R_3 = \text{OMe,}$ | $R_4 = \text{Me,}$               | $R_5 = \text{Me,}$   |
| $R_1 = 3\text{-Cl,}$   | $R_2 = \text{H,}$    | $R_3 = \text{OMe,}$ | $R_4 = \text{Me,}$               | $R_5 = \text{Me,}$   |
| $R_1 = 2\text{-Cl,}$   | $R_2 = \text{H,}$    | $R_3 = \text{OMe,}$ | $R_4 = \text{Me,}$               | $R_5 = \text{H,}$    |
| $R_1 = \text{H,}$      | $R_2 = \text{H,}$    | $R_3 = \text{OMe,}$ | $R_4 + R_5 = \text{piperidino,}$ |                      |
| $R_1 = 2\text{-Cl,}$   | $R_2 = \text{H,}$    | $R_3 = \text{OMe,}$ | $R_4 + R_5 = \text{piperidino,}$ |                      |
| $R_1 = \text{H,}$      | $R_2 = \text{H,}$    | $R_3 = \text{OMe,}$ | $R_4 = \text{n-Pr,}$             | $R_5 = \text{n-Pr,}$ |
| $R_1 = 4\text{-CF}_3,$ | $R_2 = \text{H,}$    | $R_3 = \text{OH,}$  | $R_4 = \text{Me,}$               | $R_5 = \text{Me,}$   |



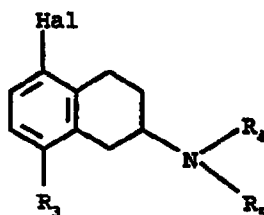


|                        |                       |                        |                       |                        |
|------------------------|-----------------------|------------------------|-----------------------|------------------------|
| $R_1 = 2\text{-Et,}$   | $R_2 = \text{H,}$     | $R_3 = \text{OMe,}$    | $R_4 = \text{Me,}$    | $R_5 = \text{Me,}$     |
| $R_1 = 2\text{-Cl,}$   | $R_2 = \text{H,}$     | $R_3 = \text{CN,}$     | $R_4 = \text{Me,}$    | $R_5 = \text{Me,}$     |
| $R_1 = 2\text{-Cl,}$   | $R_2 = 4\text{-F,}$   | $R_3 = \text{OMe,}$    | $R_4 = \text{Me,}$    | $R_5 = \text{Me,}$     |
| $R_1 = 2\text{-F,}$    | $R_2 = 4\text{-F,}$   | $R_3 = \text{OMe,}$    | $R_4 = \text{Me,}$    | $R_5 = \text{Me,}$     |
| $R_1 = 2\text{-OMe,}$  | $R_2 = 4\text{-OMe,}$ | $R_3 = \text{OMe,}$    | $R_4 = \text{Me,}$    | $R_5 = \text{Me,}$     |
| $R_1 = 2\text{-F,}$    | $R_2 = 3\text{-F,}$   | $R_3 = \text{OMe,}$    | $R_4 = \text{Me,}$    | $R_5 = \text{Me,}$     |
| $R_1 = 2\text{-OMe,}$  | $R_2 = 3\text{-OMe,}$ | $R_3 = \text{OMe,}$    | $R_4 = \text{Me,}$    | $R_5 = \text{Me,}$     |
| $R_1 = 2\text{-Me,}$   | $R_2 = 5\text{-Me,}$  | $R_3 = \text{OMe,}$    | $R_4 = \text{Me,}$    | $R_5 = \text{Me,}$     |
| $R_1 = 2\text{-Cl,}$   | $R_2 = 3\text{-Cl,}$  | $R_3 = \text{OMe,}$    | $R_4 = \text{Me,}$    | $R_5 = \text{Me,}$     |
| $R_1 = 2\text{-F,}$    | $R_2 = 5\text{-F,}$   | $R_3 = \text{OMe,}$    | $R_4 = \text{Me,}$    | $R_5 = \text{Me,}$     |
| $R_1 = 2\text{-Me,}$   | $R_2 = 4\text{-Me,}$  | $R_3 = \text{OMe,}$    | $R_4 = \text{Me,}$    | $R_5 = \text{Me,}$     |
| $R_1 = 2\text{-Cl,}$   | $R_2 = \text{H,}$     | $R_3 = \text{CONH}_2,$ | $R_4 = \text{Me,}$    | $R_5 = \text{Me,}$     |
| $R_1 = 4\text{-CF}_3,$ | $R_2 = \text{H,}$     | $R_3 = \text{OMe,}$    | $R_4 = \text{Me,}$    | $R_5 = \text{H,}$      |
| $R_1 = 4\text{-OMe,}$  | $R_2 = \text{H,}$     | $R_3 = \text{OMe,}$    | $R_4 = \text{Me,}$    | $R_5 = \text{Me,}$     |
| $R_1 = 4\text{-F,}$    | $R_2 = \text{H,}$     | $R_3 = \text{OMe,}$    | $R_4 = \text{Me,}$    | $R_5 = \text{Me,}$     |
| $R_1 = 4\text{-CF}_3,$ | $R_2 = \text{H,}$     | $R_3 = \text{OMe,}$    | $R_4 = \text{Et-OH,}$ | $R_5 = \text{Me, and}$ |
| $R_1 = 4\text{-CF}_3,$ | $R_2 = \text{H,}$     | $R_3 = \text{H,}$      | $R_4 = \text{Me,}$    | $R_5 = \text{Me}$      |

Me being methyl, Et ethyl and Pr propyl, in free base or acid addition salt form.

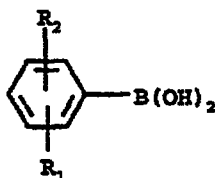
5. A compound of claim 2 which is (R)-1,2,3,4-tetrahydro-8-methoxy-N,N-dimethyl-5-[4-(trifluoromethyl)phenyl]-2-naphthalenamine, in free base or acid addition salt form.
6. A process for the production of a 1,2,3,4-tetrahydro-2-naphthalenamine bearing a phenyl substituent on the aromatic ring, and acid addition salts thereof, whereby a 1,2,3,4-tetrahydro-2-naphthalenamine bearing a halogen on the aromatic ring is reacted with optionally substituted phenylboronic acid and the resulting compound is recovered in free base form or in acid addition salt form.
7. A process for the production of a compound of formula I as defined in claim 1, in free base or acid addition salt form, whereby a compound of formula II,





II

wherein  $R_3$ ,  $R_4$  and  $R_5$  are as defined in claim 2 and Hal is halogen, is reacted with a compound of formula III



III

wherein  $R_1$  and  $R_2$  are as defined in claim 2, and the resulting compound is recovered in free base form or in acid addition salt form.

8. A compound of anyone of claims 1 to 5, in free base or pharmaceutically acceptable acid addition salt form, for use as a pharmaceutical.
9. A compound of anyone of claims 1 to 5 in free base or pharmaceutically acceptable acid addition salt form, for use in the treatment of epilepsy, stroke and brain or spinal trauma.
10. A pharmaceutical composition comprising a compound of anyone of claims 1 to 5 in free base or pharmaceutically acceptable acid addition salt form, in association with a pharmaceutical carrier or diluent.



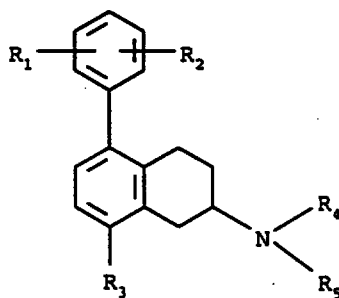


11. The use of a compound of anyone of claims 1 to 5 in free base or pharmaceutically acceptable acid addition salt form, for the manufacture of a medicament for the treatment of epilepsy, stroke and brain or spinal trauma.
12. A method for the treatment of epilepsy, stroke and brain or spinal trauma, in a subject in need of such treatment, which comprises administering to such subject a therapeutically effective amount of an agent of a compound of anyone of claims 1 to 5 in free base or pharmaceutically acceptable acid addition salt form.



**CLAIMS**

1. A 1,2,3,4-tetrahydro-2-naphthalenamine bearing a phenyl substituent on the aromatic ring, in free base or acid addition salt form, for use in the treatment of epilepsy, stroke and brain or spinal trauma.
2. A compound of formula I



I

wherein

- $R_1$  and  $R_2$ , independently, are hydrogen,  $(C_{1-4})$ alkyl,  $(C_{1-4})$ alkoxy,  $(C_{1-4})$ alkylthio, halogen, trifluoromethyl, trifluoromethoxy, cyano,  $(C_{2-5})$ alkanoyl,  $(C_{1-4})$ alkylsulfonyl or sulfamoyl,
- $R_3$  is hydrogen, hydroxy,  $(C_{1-4})$ alkyl,  $(C_{1-4})$ alkoxy, halogen, cyano,  $(C_{2-5})$ alkanoyl, carbamoyl,  $(C_{1-4})$ alkylsulfonyloxy or trifluoromethylsulfonyloxy, and
- $R_4$  and  $R_5$ , independently, are hydrogen,  $(C_{1-4})$ alkyl, hydroxy $(C_{2-4})$ alkyl or phenyl $(C_{1-4})$ alkyl, or form together with the nitrogen atom to which they are attached a pyrrolidiny, piperidino or piperaziny group,
- in free base or acid addition salt form.



## 3. A compound of claim 2 wherein

$R_1$  and  $R_2$ , independently, are hydrogen,  $(C_{1-4})$ alkyl,  $(C_{1-4})$ alkoxy, halogen, trifluoromethyl, cyano,  $(C_{2-5})$ alkanoyl or  $(C_{1-4})$ alkylthio,

$R_3$  is hydrogen, hydroxy,  $(C_{1-4})$ alkyl,  $(C_{1-4})$ alkoxy, halogen, cyano,  $(C_{2-5})$ alkanoyl, carbamoyl,  $(C_{1-4})$ alkylsulfonyloxy or trifluoromethylsulfonyloxy, and

$R_4$  and  $R_5$ , independently, are hydrogen,  $(C_{1-4})$ alkyl or phenyl $(C_{1-4})$ alkyl, or form together with the nitrogen atom to which they are attached a pyrrolidinyl, piperidino or piperazinyl group,

in free base or acid addition salt form.

## 4. A compound of claim 2 selected from the compounds of formula I, in optically active or racemic form, wherein:

|                        |                      |                     |                                  |                      |
|------------------------|----------------------|---------------------|----------------------------------|----------------------|
| $R_1 = 4\text{-Cl,}$   | $R_2 = \text{H,}$    | $R_3 = \text{OMe,}$ | $R_4 = \text{Me,}$               | $R_5 = \text{Me,}$   |
| $R_1 = \text{H,}$      | $R_2 = \text{H,}$    | $R_3 = \text{OMe,}$ | $R_4 = \text{Me,}$               | $R_5 = \text{Me,}$   |
| $R_1 = 2\text{-Cl,}$   | $R_2 = \text{H,}$    | $R_3 = \text{OMe,}$ | $R_4 = \text{Me,}$               | $R_5 = \text{Me,}$   |
| $R_1 = 2\text{-Me,}$   | $R_2 = \text{H,}$    | $R_3 = \text{OMe,}$ | $R_4 = \text{Me,}$               | $R_5 = \text{Me,}$   |
| $R_1 = 2\text{-OMe,}$  | $R_2 = \text{H,}$    | $R_3 = \text{OMe,}$ | $R_4 = \text{Me,}$               | $R_5 = \text{Me,}$   |
| $R_1 = \text{H,}$      | $R_2 = \text{H,}$    | $R_3 = \text{OH,}$  | $R_4 = \text{Me,}$               | $R_5 = \text{Me,}$   |
| $R_1 = \text{H,}$      | $R_2 = \text{H,}$    | $R_3 = \text{H,}$   | $R_4 = \text{Me,}$               | $R_5 = \text{Me,}$   |
| $R_1 = 4\text{-Me,}$   | $R_2 = \text{H,}$    | $R_3 = \text{OMe,}$ | $R_4 = \text{Me,}$               | $R_5 = \text{Me,}$   |
| $R_1 = 4\text{-CF}_3,$ | $R_2 = \text{H,}$    | $R_3 = \text{OMe,}$ | $R_4 = \text{Me,}$               | $R_5 = \text{Me,}$   |
| $R_1 = 2\text{-Cl,}$   | $R_2 = 4\text{-Cl,}$ | $R_3 = \text{OMe,}$ | $R_4 = \text{Me,}$               | $R_5 = \text{Me,}$   |
| $R_1 = 2\text{-F,}$    | $R_2 = \text{H,}$    | $R_3 = \text{OMe,}$ | $R_4 = \text{Me,}$               | $R_5 = \text{Me,}$   |
| $R_1 = 3\text{-Cl,}$   | $R_2 = \text{H,}$    | $R_3 = \text{OMe,}$ | $R_4 = \text{Me,}$               | $R_5 = \text{Me,}$   |
| $R_1 = 2\text{-Cl,}$   | $R_2 = \text{H,}$    | $R_3 = \text{OMe,}$ | $R_4 = \text{Me,}$               | $R_5 = \text{H,}$    |
| $R_1 = \text{H,}$      | $R_2 = \text{H,}$    | $R_3 = \text{OMe,}$ | $R_4 + R_5 = \text{piperidino,}$ |                      |
| $R_1 = 2\text{-Cl,}$   | $R_2 = \text{H,}$    | $R_3 = \text{OMe,}$ | $R_4 + R_5 = \text{piperidino,}$ |                      |
| $R_1 = \text{H,}$      | $R_2 = \text{H,}$    | $R_3 = \text{OMe,}$ | $R_4 = \text{n-Pr,}$             | $R_5 = \text{n-Pr,}$ |
| $R_1 = 4\text{-CF}_3,$ | $R_2 = \text{H,}$    | $R_3 = \text{OH,}$  | $R_4 = \text{Me,}$               | $R_5 = \text{Me,}$   |

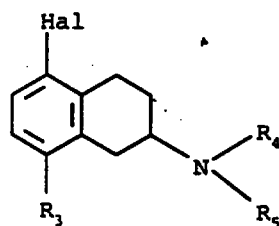


|                        |                       |                        |                       |                        |
|------------------------|-----------------------|------------------------|-----------------------|------------------------|
| $R_1 = 2\text{-Et,}$   | $R_2 = \text{H,}$     | $R_3 = \text{OMe,}$    | $R_4 = \text{Me,}$    | $R_5 = \text{Me,}$     |
| $R_1 = 2\text{-Cl,}$   | $R_2 = \text{H,}$     | $R_3 = \text{CN,}$     | $R_4 = \text{Me,}$    | $R_5 = \text{Me,}$     |
| $R_1 = 2\text{-Cl,}$   | $R_2 = 4\text{-F,}$   | $R_3 = \text{OMe,}$    | $R_4 = \text{Me,}$    | $R_5 = \text{Me,}$     |
| $R_1 = 2\text{-F,}$    | $R_2 = 4\text{-F,}$   | $R_3 = \text{OMe,}$    | $R_4 = \text{Me,}$    | $R_5 = \text{Me,}$     |
| $R_1 = 2\text{-OMe,}$  | $R_2 = 4\text{-OMe,}$ | $R_3 = \text{OMe,}$    | $R_4 = \text{Me,}$    | $R_5 = \text{Me,}$     |
| $R_1 = 2\text{-F,}$    | $R_2 = 3\text{-F,}$   | $R_3 = \text{OMe,}$    | $R_4 = \text{Me,}$    | $R_5 = \text{Me,}$     |
| $R_1 = 2\text{-OMe,}$  | $R_2 = 3\text{-OMe,}$ | $R_3 = \text{OMe,}$    | $R_4 = \text{Me,}$    | $R_5 = \text{Me,}$     |
| $R_1 = 2\text{-Me,}$   | $R_2 = 5\text{-Me,}$  | $R_3 = \text{OMe,}$    | $R_4 = \text{Me,}$    | $R_5 = \text{Me,}$     |
| $R_1 = 2\text{-Cl,}$   | $R_2 = 3\text{-Cl,}$  | $R_3 = \text{OMe,}$    | $R_4 = \text{Me,}$    | $R_5 = \text{Me,}$     |
| $R_1 = 2\text{-F,}$    | $R_2 = 5\text{-F,}$   | $R_3 = \text{OMe,}$    | $R_4 = \text{Me,}$    | $R_5 = \text{Me,}$     |
| $R_1 = 2\text{-Me,}$   | $R_2 = 4\text{-Me,}$  | $R_3 = \text{OMe,}$    | $R_4 = \text{Me,}$    | $R_5 = \text{Me,}$     |
| $R_1 = 2\text{-Cl,}$   | $R_2 = \text{H,}$     | $R_3 = \text{CONH}_2,$ | $R_4 = \text{Me,}$    | $R_5 = \text{Me,}$     |
| $R_1 = 4\text{-CF}_3,$ | $R_2 = \text{H,}$     | $R_3 = \text{OMe,}$    | $R_4 = \text{Me,}$    | $R_5 = \text{H,}$      |
| $R_1 = 4\text{-OMe,}$  | $R_2 = \text{H,}$     | $R_3 = \text{OMe,}$    | $R_4 = \text{Me,}$    | $R_5 = \text{Me,}$     |
| $R_1 = 4\text{-F,}$    | $R_2 = \text{H,}$     | $R_3 = \text{OMe,}$    | $R_4 = \text{Me,}$    | $R_5 = \text{Me,}$     |
| $R_1 = 4\text{-CF}_3,$ | $R_2 = \text{H,}$     | $R_3 = \text{OMe,}$    | $R_4 = \text{Et-OH,}$ | $R_5 = \text{Me, and}$ |
| $R_1 = 4\text{-CF}_3,$ | $R_2 = \text{H,}$     | $R_3 = \text{H,}$      | $R_4 = \text{Me,}$    | $R_5 = \text{Me}$      |

Me being methyl, Et ethyl and Pr propyl, in free base or acid addition salt form.

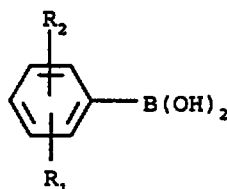
5. A compound of claim 2 which is (R)-1,2,3,4-tetrahydro-8-methoxy-N,N-dimethyl-5-[4-(trifluoromethyl)phenyl]-2-naphthalenamine, in free base or acid addition salt form.
6. A process for the production of a compound of formula I as defined in claim 2, in free base or acid addition salt form, whereby a compound of formula II,





II

wherein  $R_3$ ,  $R_4$  and  $R_5$  are as defined in claim 2 and Hal is halogen, is reacted with a compound of formula III



III

wherein  $R_1$  and  $R_2$  are as defined in claim 2, and the resulting compound is recovered in free base form or in acid addition salt form.

7. A compound of anyone of claims 2 to 5, in free base or pharmaceutically acceptable acid addition salt form, for use as a pharmaceutical.
8. A compound of anyone of claims 2 to 5 in free base or pharmaceutically acceptable acid addition salt form, for use in the treatment of epilepsy, stroke and brain or spinal trauma.
9. A pharmaceutical composition comprising a compound of anyone of claims 2 to 5 in free base or pharmaceutically acceptable acid addition salt form, in association with a pharmaceutical carrier or diluent.



**THIS SHEET HAS BEEN  
REPLACED**

10. The use of a compound of anyone of claims 1 to 5 in free base or pharmaceutically acceptable acid addition salt form, for the manufacture of a medicament for the treatment of epilepsy, stroke and brain or spinal trauma.
11. A method for the treatment of epilepsy, stroke and brain or spinal trauma, in a subject in need of such treatment, which comprises administering to such subject a therapeutically effective amount of an agent of a compound of anyone of claims 1 to 5 in free base or pharmaceutically acceptable acid addition salt form.

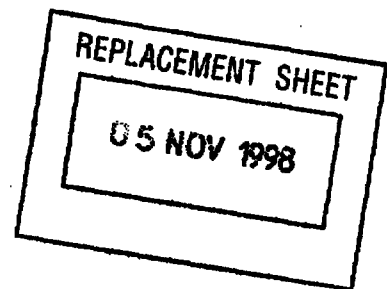
---

This Sheet Has Been Replaced



\* C L M S \*

10. The use of a compound of anyone of claims 1 to 5 in free base or pharmaceutically acceptable acid addition salt form, for the manufacture of a medicament for the treatment of epilepsy, stroke and brain or spinal trauma.



9709998-5

RTMP's copy



PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION  
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification<sup>6</sup>:C07C 217/54, 211/42, 215/46, 255/58,  
237/48, C07D 295/033, 295/073, A61K  
31/135, 31/445, 31/275, 31/165

A1

(11) International Publication Number:

WO 96/34849

(43) International Publication Date:

7 November 1996 (07.11.96)

(21) International Application Number: PCT/EP96/01841

(22) International Filing Date: 3 May 1996 (03.05.96)

(30) Priority Data:

9509156.7

5 May 1995 (05.05.95)

GB

(71) Applicant (for all designated States except AT/DE/US): SANDOZ LTD. [CH/CH]; Lichtstrasse 35, CH-4002 Basle (CH).

(71) Applicant (for DE only): SANDOZ-PATENT-GMBH [DE/DE]; Humboldtstrasse 3, D-79539 Lörrach (DE).

(71) Applicant (for AT only): SANDOZ-ERFINDUNGEN VERWALTUNGSGESELLSCHAFT MBH [AT/AT]; Brunner Strasse 59, A-1230 Vienna (AT).

(72) Inventor; and

(75) Inventor/Applicant (for US only): SWOBODA, Robert [CH/CH]; Möslweg 30, CH-3098 Köniz (CH).

(74) Common Representative: SANDOZ LTD.; Patents &amp; Trade-marks Division, Lichtstrasse 35, CH-4002 Basle (CH).

(81) Designated States: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, ARIPO patent (KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

Published

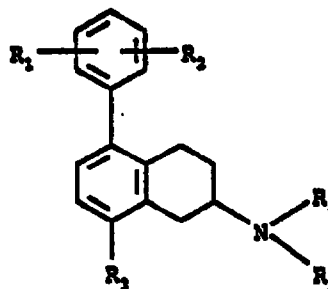
With international search report.

Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(54) Title: TETRALINES BEARING A PHENYL SUBSTITUENT ON THE AROMATIC RING AND THEIR USE IN THE TREATMENT OF EPILEPSY, STROKE AND BRAIN OR SPINAL TRAUMA

(57) Abstract

Compounds of formula (I) wherein R<sub>1</sub> and R<sub>2</sub>, independently, are hydrogen (C<sub>1-4</sub>)alkyl, (C<sub>1-4</sub>)alkoxy, (C<sub>1-4</sub>)alkylthio, halogen, trifluoromethyl, trifluoromethoxy, cyano, (C<sub>2-5</sub>)alkanoyl, (C<sub>1-4</sub>)alkylsulfonyl or sulfamoyl; R<sub>3</sub> is hydrogen, hydroxy, (C<sub>1-4</sub>)alkyl, (C<sub>1-4</sub>)alkoxy, halogen, cyano, (C<sub>2-5</sub>)alkanoyl, carbamoyl, (C<sub>1-4</sub>)alkylsulfonyloxy or trifluoromethylsulfonyloxy; and R<sub>4</sub> and R<sub>5</sub>, independently, are hydrogen, (C<sub>1-4</sub>)alkyl, hydroxy(C<sub>2-4</sub>)alkyl or phenyl(C<sub>1-4</sub>)alkyl, or form together with the nitrogen atom to which they are attached a pyrrolidinyl, piperidino or piperazinyl group, in free base or acid addition salt form. Compounds according to formula (I) are useful in the treatment of epilepsy, stroke and brain or spinal trauma.



(I)