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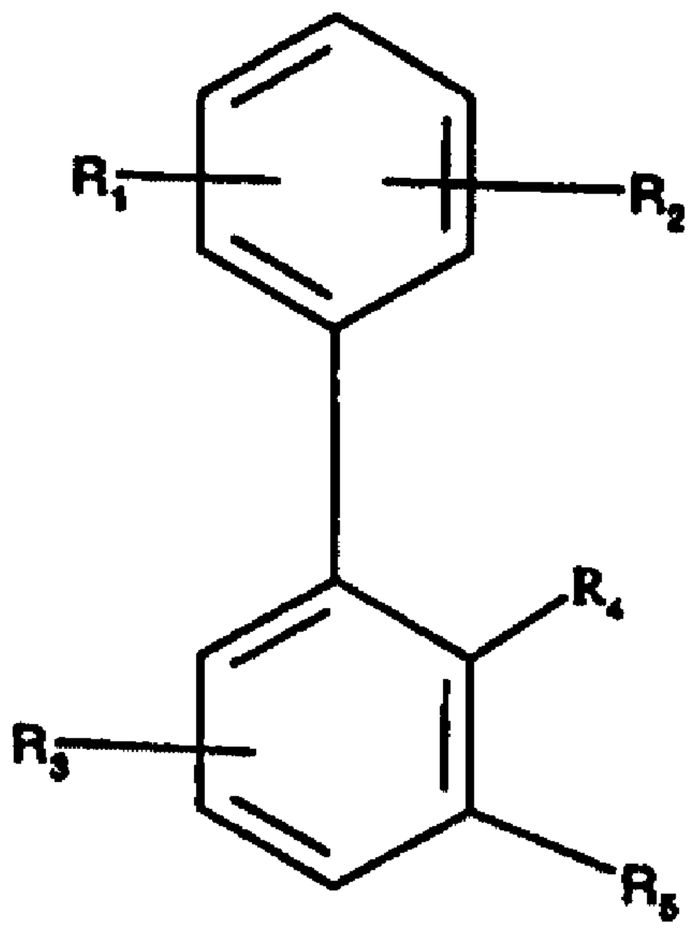
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(54) **DERIVES DE BIPHENYLE EN TANT QUE PRODUITS PHARMACEUTIQUES**

(54) **BIPHENYL DERIVATIVES AS PHARMACEUTICALS**



(I)

(57) L'invention concerne les composés présentant la formule (I) dans laquelle R_1, R_2, R_3, R_4 et R_5 sont tels que définis dans le descriptif. Ces composés constituent des produits pharmaceutiques d'une grande utilité.

(57) Compounds of formula (I) wherein R_1, R_2, R_3, R_4 and R_5 are as defined in the description, are useful as pharmaceuticals.

PCT

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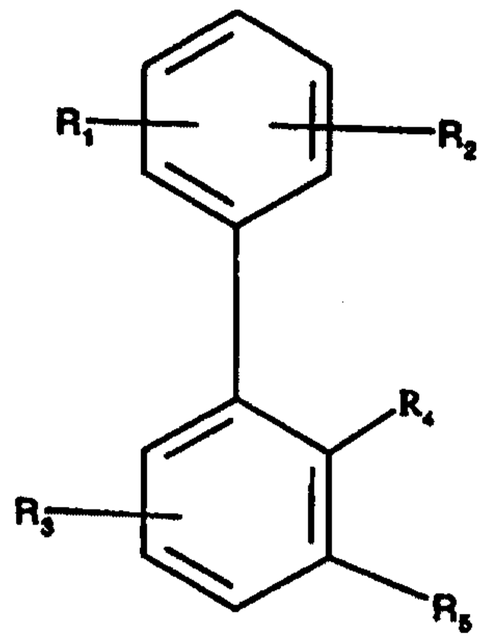
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(54) Title: BIPHENYL DERIVATIVES AS PHARMACEUTICALS

(57) Abstract

Compounds of formula (I) wherein R_1, R_2, R_3, R_4 and R_5 are as defined in the description, are useful as pharmaceuticals.

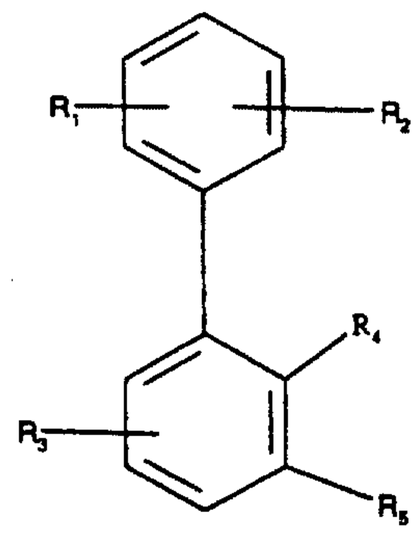


(I)

BIPHENYL DERIVATIVES AS PHARMACEUTICALS

The present invention relates to novel biphenyl derivatives, their preparation, their use as pharmaceuticals and pharmaceutical compositions containing them.

More particularly the invention provides a compound of formula I



I

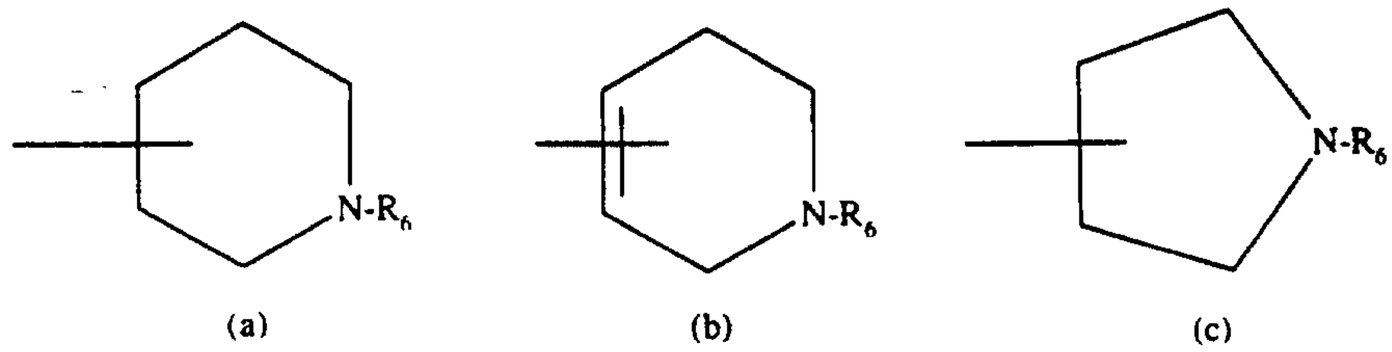
wherein

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

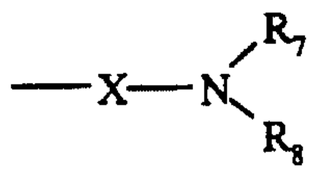
R_3 is hydrogen, hydroxy, (C_{1-4})alkyl, (C_{1-4})alkoxy, (C_{3-6})cycloalkyloxy, halogen, cyano, (C_{2-5})alkanoyl, carbamoyl, (C_{1-4})alkylsulfonyloxy or trifluoromethylsulfonyloxy,

R_4 is hydrogen, hydroxy or (C_{1-4})alkoxy, and

R_5 is a group of formula (a), (b), (c) or (d)



(a) (b) (c)



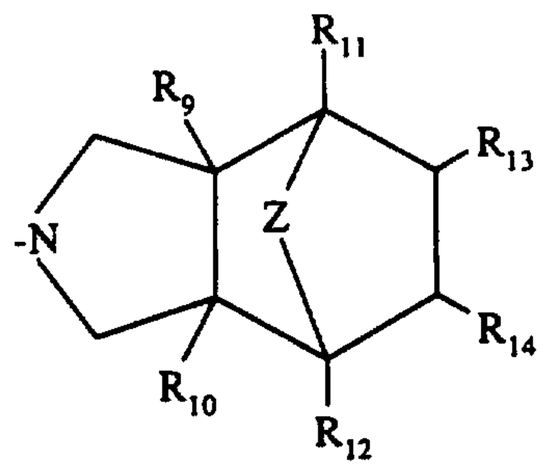
(d)

wherein

R_6 is (C_{1-4})alkyl,

X is a straight or branched alkylene chain with 1 to 4 carbon atoms, and

R_7 and R_8, 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, piperazinyl or morpholino group, or a group of formula (e)



(e)

wherein Z is O, CH_2 or CH_2-CH_2 and R_9, R_{10}, R_{11}, R_{12}, R_3 and R_{14}, independently,are H, halogen, (C_{1-4})alkyl or (C_{1-4})alkoxy,

in free base or acid addition salt form.

On account of the asymmetrical carbon atoms which may be present in the compounds of formula I and their salts, the compounds may exist 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.

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 or in para to the phenyl substituent is hydroxy, (C_{1-4})alkoxy, (C_{3-6}) cycloalkyloxy, cyano or carbamoyl,

R_4 is H,

R_5 is a group of formula (a) or (d).

When R_5 is a group of formula (a), R_6 is preferably methyl or propyl.

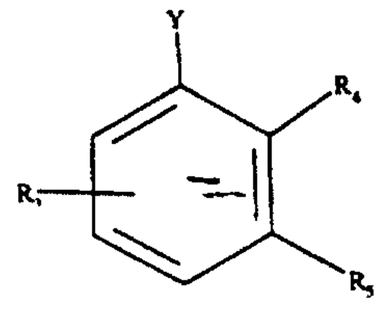
When R_5 is a group of formula (d), R_7 and R_8 are preferably hydrogen, (C_{1-4})alkyl or, together with the nitrogen atom to which they are attached, a group of formula (e).

When R_7 and R_8, together with the nitrogen atom to which they are attached, form a group of formula (e), Z is preferably O and R_9 to R_{14}, independently, are preferably hydrogen or methyl.

In one group of compounds of formula I, R_1, R_2, R_3 and R_4 are as defined above and R_5 is a group of formula (a), (b) or (c).

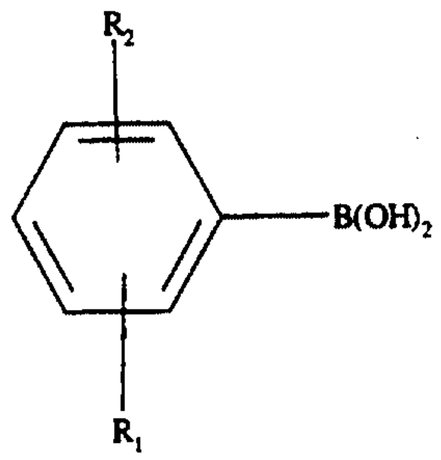
In another group of compounds of formula I, R_1, R_2, R_3 and R_4 are as defined above and R_5 is a group of formula (d).

In a further aspect, the invention provides a process for the production of the compounds of formula I and their salts, whereby a compound of formula II



II

wherein R_3, R_4, and R_5 are as defined above and Y is halogen or trifluoromethyl sulfonate, is reacted with a compound of formula III



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 iodine.

Alternatively the compounds may be obtained by other well established metal-catalysed aryl-aryl coupling procedures, using for example aryl-stannyl, -zinc, -halide or Grignard precursors.

For the preparation of compounds of formula I wherein R_5 is a group of formula (c), the nitrogen in the group of formula (c) may be protected e.g. by an alkoxycarbonyl group, which can be removed after the reaction with the compound of formula III according to well-known procedures. See for example Example 11.

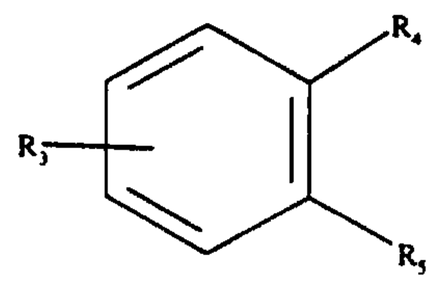
For the preparation of compounds of formula I wherein R_5 is a group of formula (b), a compound having the formula I but wherein R_5 is a 3-pyridyl group, may first be prepared as described above for the compounds of formula I, and the pyridyl group subsequently converted into the desired tetrahydropyridyl over a corresponding pyridinium salt, according to well-known procedures, for example over the pyridinium iodide as described in Example 1.

For the preparation of compounds of formula I wherein R_5 is a group of formula (a), the corresponding compounds wherein R_5 is of formula (b) may be prepared first, and subsequently hydrogenated according to well-known procedures, e.g. as described in Example 5.

Compounds of formula I in optically pure form can be obtained from the corresponding racemates according to well-known procedures, e.g. as described in Examples 9 and 10. Alternatively, optically pure starting materials can be used as described in Examples 28 and 29.

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.

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



IV

wherein R_3, R_4 and R_5 are as defined above, in accordance with known procedures.

The starting materials of formulae III and IV are known or may be produced in analogous manner to known procedures, e.g. as described in the Examples.

The compounds of formula I and their pharmaceutically acceptable acid addition salts, hereinafter referred to collectively 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 1-50 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 μM. 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 mM. 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.

The agents of the invention are accordingly indicated for use in 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 for use 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, olivopontocerebellar 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.

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: 3-(4-methoxy-4'-trifluoromethyl-biphenyl-3-yl)-1-methyl-1,2,5,6-tetrahydro-pyridine

A. 3-(5-bromo-2-methoxy-phenyl)-pyridine

A solution of bromine (12.2 g, 3.9 ml, 0.076 mol) in glacial acetic acid (40 ml) is added dropwise over 15 minutes to a solution of 3-(2-methoxyphenyl)-pyridine (14.0 g, 0.076 mol) and anhydrous sodium acetate (6.8 g, 0.083 mol) in glacial acetic acid (140 ml), held at 15-20°. A precipitate is observed, which dissolves gradually upon stirring of the suspension. This suspension is left to stir for 18 hours at room temperature, after which a clear orange solution is obtained. The acetic acid is removed under reduced pressure, and the residue taken up in EtOAc (250 ml). The extract is washed with water (150 ml), saturated agueous $NaHCO_3$ (100 ml) and brine (75 ml), dried ($MgSO_4$), and evaporated to

give the product as an orange oil. TLC (silica gel, toluene-EtOH-NH_4OH 85:15:1) Rf = 0.5.

B. 3-(4-methoxy-4'-trifluoromethyl-biphenyl-3-yl)-pyridine

A mixture of 3-(5-bromo-2-methoxy-phenyl)-pyridine (19.0 g, 0.072 mol), 4-trifluoromethylphenylboronic acid (14.3 g, 0.076 mol), palladium(II)acetate (520 mg, 0.0023 mol), tri-o-toluylphosphine (2.1 g, 0.0069 mol), 2M aqueous Na_2CO_3 (39 ml, 0.077 mol), MeOH (80 ml) and toluene (350 ml) is heated to reflux under an argon atmosphere during 18 hours. The mixture is allowed to cool, filtered through Hyflo, diluted with water (100 ml), and the phases separated. The aqueous phase is extracted with toluene (150 ml) and the combined organic phases are washed with water (100 ml) and brine (100 ml), dried ($MgSO_4$), treated with activated charcoal (1 g), filtered through Hyflo and evaporated to give a yellow oil. This oil is dissolved in EtOH (50 ml) and treated with 3N ethanolic HCl (25 ml). The hydrochloride salt precipitates upon addition of ether (20 g, 76%), m.p. 229-231°. TLC (silica gel, toluene-EtOH-NH_4OH 85:15:1) Rf = 0.55.

C. 3-(4-methoxy-4'-trifluoromethyl-biphenyl-3-yl)-1-methyl-pyridinium iodide

A solution of methyl iodide (9.4 g, 66 mmol) in acetone (25 ml) is added dropwise over 15 minutes to a cool (15°) solution of 3-(4-methoxy-4'-trifluoromethyl-biphenyl-3-yl)-pyridine (10.9 g, 33 mmol) in acetone (100 ml). The reaction mixture is then heated to reflux for 2 hours, after which a second portion of methyl iodide (1 ml, 2.2 g, 0.015 mmol) is added, and the mixture is allowed to reflux for a further 1.5 hours. After evaporation of the solvent, the title compound is obtained as a yellow solid, which is used directly in the following reaction. TLC (silica gel, toluene-EtOH-NH_4OH 85:15:1) Rf = 0 - 0.02.

D. 3-(4-methoxy-4'-trifluoromethyl-biphenyl-3-yl)-1-methyl-1,2,5,6-tetrahydro-pyridine

A solution of sodium hydroxide (1.5 g, 36 mmol) in water (100 ml) is added to a solution of 3-(4-methoxy-4'-trifluoromethyl-biphenyl-3-yl)-1-methyl-pyridinium iodide in MeOH (150 ml). To the resulting mixture, sodium borohydride (2.5 g, 66 mmol) are added in

portions over 30 minutes, and the mixture is left to stir for 60 hours at room temperature. The mixture is filtered through Hyflo and the filtrate concentrated to ca. 100 ml, upon which a yellow oil separates. This mixture is extracted with EtOAc (3 x 125 ml). The combined organic extracts are washed with brine (75 ml), dried ($MgSO_4$) and evaporated to yield the title compound as a yellowish-brown oil. TLC (silica gel, toluene-EtOH-NH_4OH 85:15:1) Rf = 0.4. The hydrogen maleinate has a m.p. of 123-125° (EtOH/Et_2O).

The following compounds of formula I are prepared in analogous manner to Example 1:

Example 2: 3-(4-methoxy-biphenyl-3-yl)-1-methyl-1,2,5,6-tetrahydro-pyridine

The hydrochloride has a m.p. of 187-194°.

Example 3: 3-(2'-chloro-4-methoxy-biphenyl-3-yl)-1-methyl-1,2,5,6-tetrahydro-pyridine

The hydrogen oxalate has a m.p. of 137-142°.

Example 4: 3-(4-methoxy-4'-trifluoromethyl-biphenyl-3-yl)-1-propyl-1,2,5,6-tetrahydro-pyridine

The compound is obtained as a yellow oil. TLC (silica gel, toluene-EtOH-NH_4OH 85:15:1) Rf = 0.25.

Example 5: 3-(4-methoxy-4'-trifluoromethyl-biphenyl-3-yl)-1-methyl-piperidine

Palladium on charcoal (10%, 700 mg) is added to a degassed solution of 3-(4-methoxy-4'-trifluoromethyl-biphenyl-3-yl)-1-methyl-1,2,5,6-tetrahydro-pyridine (obtained according to Example 1) (5.3 g, 15.9 mmol) in glacial acetic acid (75 ml) and the mixture hydrogenated on a Parr Hydrogenator for 18 hours at room temperature and 5 atm. hydrogen pressure, during which time 70 ml of hydrogen are taken up. The catalyst is then filtered off, and fresh catalyst added (0.800 g), and the mixture further hydrogenated for 18 hours at 45°

and 5 atm. hydrogen, after which time 400 ml of hydrogen are taken up. The suspension is then filtered, the solid washed with AcOH and the filtrates evaporated. The residue is treated with saturated aqueous K_2CO_3 until a basic solution ensues, which is extracted with EtOAc. The organic extracts are washed with brine (30 ml), dried ($MgSO_4$) and evaporated to give the product as a light brown oil. The hydrogen maleinate has a m.p. of 93-96° ($EtOH/Et_2O$, dec.).

The following compounds of formula I are prepared in analogous manner to Example 5.

Example 6: 3-(4-methoxy-biphenyl-3-yl)-1-methyl-piperidine

The hydrochloride has a m.p. of 254-262°.

Example 7: 3-(2'-chloro-4-methoxy-biphenyl-3-yl)-1-methyl-piperidine

The hydrochloride has a m.p. of 237-247°.

Example 8: 3-(4-methoxy-4'-trifluoromethyl-biphenyl-3-yl)-1-propyl-piperidine

The hydrogen fumarate of the racemate has a m.p. of 178-180° ($EtOH/Et_2O$, dec.).

The racemate is resolved into its enantiomers by HPLC on Chiralcel OJ, column 25 x 0.46 cm, Mobile phase: Hexane-EtOH 9:1 with 0.1% TFA. Flow rate: 1mL/min. The first enantiomer elutes with retention time 8.35 min and the second with 10.25 min. The enantiomers are crystallised as their corresponding fumarate salts, the first has $[\alpha]_D^{20}$ = +24.4 (c = 1.0, MeOH), and the second $[\alpha]_D^{20}$ = -24.3 (c = 1.0, MeOH).

Example 9: (-)-3-(4-methoxy-4'-trifluoromethyl-biphenyl-3-yl)-1-methyl-piperidine

A solution of 3-(4-methoxy-4'-trifluoromethyl-biphenyl-3-yl)-1-methyl-piperidine (obtained according to Example 5) (7.7 g, 22 mmol) and (-)-2,3-di-*o*-toluyltartaric acid

hydrate (8.9 g, 22 mmol) in warm (70°) EtOH (100 ml) is allowed to cool to room temperature and left to stand for 18 hours. The crystals so formed are filtered off and recrystallised from 100 ml EtOH, to give crystals with a m.p. of 155-156°; $[\alpha]_D^{20}$ = -77.8 (c = 1.0 MeOH). From the crystals thus obtained the free base is formed (oil; $[\alpha]_D^{20}$ = -9.3 (c = 0.95, MeOH). These crystals are recrystallised again from EtOH (80 ml), to give crystals with a mp of 159-160°, $[\alpha]_D^{20}$ = -83.0 (c = 1.0, MeOH); free base (oil): $[\alpha]_D^{20}$ = -12.5 (c = 0.9, MeOH). The hydrogen maleate has a mp of 124-126° (EtOH/Et_2O); $[\alpha]_D^{20}$ = -6.2 (c = 1.0, MeOH).

Example 10: (+)-3-(4-methoxy-4'-trifluoromethyl-biphenyl-3-yl)-1-methyl-piperidine

The mother liquors from Example 9 are reserved, and free base is prepared from each by treating with sat. aqueous K_2CO_3 and extraction with EtOAc. The free base obtained from the first mother liquors (2,4 g, 6.88 mmol) is treated with (+)-2,3-di-*o*-toluyltartaric acid hydrate (2.6 g, 6.88 mmol) in boiling EtOH (40 ml), which upon cooling yields crystals which are recrystallised from EtOH (25 ml) to give colourless crystals with a mp of 164-165°, $[\alpha]_D^{20}$ = + 81.1 (c = 1.1, MeOH) from which the free base has a $[\alpha]_D^{20}$ of + 11.3 (c = 1.0, MeOH). The free base from the combined second and third mother liquors (3.6 g, 10.3 mmol) are combined with (+)-2,3-di-*o*-toluyltartaric acid hydrate (3.9 g, 10.3 mmol) in boiling EtOH (50 ml). After complete crystallisation , the crystals are recrystallised from EtOH (45 ml) to give a crop of crystals having a $[\alpha]_D^{20}$ of + 85.2 (c = 1.0, MeOH) from which the free base has a $[\alpha]_D^{20}$ of + 9.8 (c = 1.4, MeOH), and are further recrystallised from EtOH (30 ml) to give crystals with a m.p. of 164-165°; $[\alpha]_D^{20}$ = +87.3 (c = 1.0, MeOH) from which the free base has a $[\alpha]_D^{20}$ of + 11.3 (c = 1.0, MeOH). The hydrogen maleate has a m.p. of 125-127° (EtOH/Et_2O); $[\alpha]_D^{20}$ = + 5.4 (c = 1.1, MeOH)

Example 11: 3-(4-methoxy-4'-trifluoromethyl-biphenyl-3-yl)-1-methyl-pyrrolidine

A. 1-ethoxycarbonyl-3-(2-methoxyphenyl)-pyrrolidine

A solution of ethylchloroformate (0.61 ml, 673 mg, 6.21 mmol) in CH_2Cl_2 (3 ml) is added dropwise over 10 minutes to a cold (0-5°, ice-bath) solution of N-ethyl-N,N-diisopropylamine (1.3 ml, 911 mg, 7.01 mmol) and 3-(2-methoxyphenyl)-pyrrolidine (1.00 g, 5.65 mmol) in CH_2Cl_2 (15 ml). The yellow reaction mixture is left to stir for 3.5 hours at room temperature, after which it is washed with 1N HCl (15 ml), saturated aqueous $NaHCO_3$ (15 ml) and brine (10 ml), dried ($MgSO_4$) and the solvent evaporated to give the product as a yellow oil. TLC (silica gel, toluene-EtOH-NH_4OH 85:15:1) Rf = 0.6.

B. 1-ethoxycarbonyl-3-(5-bromo-2-methoxyphenyl)-pyrrolidine

A solution of bromine (835 mg, 5.22 matg) in glacial acetic acid (3 ml) is added dropwise to a solution of 1-ethoxycarbonyl-3-(2-methoxyphenyl)-pyrrolidine (1.300 g, 5.22 mmol) and sodium acetate (470 mg, 5.70 mmol) in glacial acetic acid (15 ml), and the mixture is left to stir for 18 hours at room temperature. The mixture is filtered through Hyflo and the solvent evaporated. The residue is taken up in ethyl acetate (30 ml) and the solution washed with water (20 ml), saturated aqueous Na_2CO_3 (20 ml) and brine (15 ml). The aqueous phases are extracted with EtOAc (25 ml) and the combined organic extracts dried ($MgSO_4$) and evaporated to give the product as a yellow-brown oil [TLC (silica gel, toluene-EtOH-NH_4OH 85:15:1) Rf = 0.6] which is used directly in the following reaction.

C. 1-ethoxycarbonyl-3-(4-methoxy-4'-trifluoromethlyl-biphenyl-3-yl)-pyrrolidine

Obtained from 1-ethoxycarbonyl-3-(5-bromo-2-methoxyphenyl)-pyrrolidine and 4-trifluoromethylphenyl-boronic acid by palladium-catalysed coupling in analogous manner to Example 1B. TLC (silica gel, toluene-EtOH-NH_4OH 85:15:1) Rf = 0.78. The crude product is used directly in the following reaction.

D. 3-(4-methoxy-4'-trifluoromethyl-biphenyl-3-yl)-1-methyl-pyrrolidine

The crude product obtained under C (2.00 g) is dissolved in THF (15 ml) and added dropwise over 15 minutes to a cold (0-5°) suspension of lithium aluminium hydride (350 mg, 9.2 mmol) in THF (25 ml). The reaction mixture is allowed to stir at room

temperature for 1 hour and heated to reflux for 18 hours, after which it is allowed to cool to room temperature, and treated by the careful sequential addition of saturated aqueous Na_2SO_4 (2ml), 2N NaOH (2 ml), and Et_2O (50 ml). The mixture is stirred vigorously 1 hour at room temperature, and the precipitate filtered off. The precipitate is further washed with Et_2O-THF (1:1 30 ml), and the combined filtrates dried ($MgSO_4$) and evaporated to give a reddish oil. This crude product is dissolved in Et_2O (50 ml) and extracted with 2N HCl (2x 15 ml). The combined acid phases are further extracted with Et_2O (20 ml), cooled (ice-bath), made alkaline with sat. aq. K_2CO_3 and extracted with Et_2O (50 ml). The ether extracts are washed with brine (30 ml), dried ($MgSO_4$) and evaporated to give the product as a reddish oil. TLC (silica gel, toluene-EtOH-NH_4OH 85:15:1) Rf = 0.1. The hydrogen fumarate has a m.p. of 176-180° (dec.).

Example 12: 2-(4'-trifluoromethyl-biphenyl-3-yl)ethylamine

A mixture of 3-(bromophenyl)-ethylamine (1.400 g, 7.0 mmol) , 4-trifluoromethyl-phenylboronic acid (1.33 g, 7.0 mmol), tris-(*ortho*-toluyl)phosphine (212 mg, 0.70 mmol), palladium (II) acetate (160 mg, 0.7 mmol), aqueous sodium carbonate solution (2M, 3.5 ml), MeOH (2 ml) and toluene (25 ml) is heated to reflux under argon for 18 hours. The mixture is then allowed to cool to room temperature, and the phases are separated. The aqueous phase is extracted with toluene (25 ml). The combined organic phases are washed with water (25 ml) and brine (30 ml), dried ($MgSO_4$) and evaporated. The residue is purified by chromatography (silica gel, toluene-ethanol-NH_4OH 85:15:1) to yield the product as a light yellow oil. TLC (silica gel, toluene-ethanol-NH_4OH 85:15:1)Rf = 0.30.

Example 13: N,N-dimethyl-[2-(4'-trifluoromethyl-biphenyl-3-yl)ethyl]amine

Obtained analogously to Example 12. The hydrogen maleate has a m.p. of 150-153° ($EtOH/Et_2O$).

The compound can also be obtained by dimethylation of the compound of Example 12 according to known procedures, e.g. by Eschweiler-Clarke methylation.

Example 14: 2-(6-methoxy-4'-trifluoromethyl-biphenyl-3-yl)ethylamine

Obtained analogously to Example 12 as a yellow oil. TLC (silica gel, toluene-EtOH-NH_4OH 85:15:1) Rf = 0.30.

Example 15: N,N-dimethyl-[2-(6-methoxy-4'-trifluoromethyl-biphenyl-3-yl)ethyl]amine

Obtained analogously to Example 12. The hydrochloride has a m.p. of 210-212° (EtOH/Et_2O).

The compound can also be obtained by Eschweiler-Clarke methylation of the compound of Example 14.

Example 16: 2-(4-methoxy-4'-trifluoromethyl-biphenyl-3-yl)ethylamine

Obtained analogously to Example 12. The hydrogen maleate has a m.p. of 157-160° (EtOH).

Example 17: N,N-dimethyl-2-[(4-methoxy-4'-trifluoromethyl-biphenyl-3-yl)ethyl]amine

Obtained analogously to Example 12. The hydrogen maleate has a m.p. of 136-137° (EtOH).

The compound can also be obtained by Eschweiler-Clarke methylation of the compound of Example 16.

Example 18: N-propyl-2-[4-methoxy-4'-trifluoromethyl-biphenyl-3-yl)]-ethylamine

Obtained analogously to Example 12. The hydrogen maleate has a m.p. of 178-180° ($EtOH/Et_2O$).

Example 19: 1-[2-(4-methoxy-4'-trifluoromethyl-biphenyl-3-yl)ethyl]pyrrolidine

Obtained analogously to example 12. The hydrogen maleate has a m.p. of 131-133° ($EtOH/Et_2O$).

The compound can also be obtained as follows:

A. 1-[2-(4-methoxy-4'-trifluoromethyl-biphenyl-3-yl)-ethyl-pyrrolidine-2,5-dione

A solution of 2-(4-methoxy-4'-trifluoromethylbiphenyl-3-yl)-ethylamine (1.4 g, 4.74 mmol) and succinic anhydride (475 mg, 4.74 mmol) in THF (60 ml) is heated to reflux for 18 hours. The solution is then evaporated to dryness, and the residue heated to 190° to give an oil that crystallises on standing, and is recrystallised (Et_2O) to yield the product, m.p. 116-120°.

B. 1-[2-(4-methoxy-4'-trifluoromethyl-biphenyl-3-yl)-ethyl]pyrrolidine

A solution of 1-[2-(4-methoxy-4'-trifluoromethyl-biphenyl-3-yl)-ethyl-pyrrolidine-2,5-dione (1.3 g, 3.45 mmol) in THF (10 ml) is added dropwise over 10 minutes to a suspension of lithium aluminium hydride (262 mg, 6.9 mmol) in THF (15 ml) held at 0-10°. When the addition is complete, the mixture is allowed to warm up to room temperature, and stirred for 1 hour, after which the mixture is heated to reflux for 18 hours. After cooling, the reaction mixture is treated sequentially with saturated aqueous Na_2SO_4 (2 ml) and aqueous NaOH (2N, 1 ml). After addition of Et_2O (25 ml) the resulting mixture is stirred for 1 hour, and then filtered. The precipitate is washed with Et_2O, and the washings combined with the filtrate. The Et_2O solution is dried ($MgSO_4$) and evaporated to give a yellow oil which is purified by crystallisation as its hydrogen maleate.

Example 20: (1*S,2*S**,6*R**,7*R**)- 4-[2-(4-methoxy-4'-trifluoromethyl-biphenyl-3-yl)-ethyl]-10-oxa-4-aza-tricyclo[5.2.1.0(2,6)]decane**

Obtained analogously to Example 12. The hydrogen male ate has a m.p. of 163-164° (EtOH/Et_2O). The compound can also be obtained as follows:

A. *(1S*,2R*,6S*,7R*)*-4-[2-(4-methoxy-4'-trifluoromethyl-biphenyl-3-yl)-ethyl]-10-oxa-4-aza-tricyclo[5.2.1.0(2,6)]decane-3,5-dione

A solution of 2-(4-methoxy-4'-trifluoromethyl-biphenyl-3-yl)ethylamine (1.4 g, 4.74 mmol) and *(1S*,2R*,6S*,7R*)*-4,10-dioxa-tricyclo[5.2.1.0(2,6)]decane-3,5-dione (850 mg, 5.1 mmol) in THF (60ml) is heated to reflux for 18 hours, in similar fashion to example 8A, to give the product, mp. 166-168°.

B.*(1S*,2S*,6R*,7R*)*-4-[2-(4-methoxy-4'-trifluoromethyl-biphenyl-3-yl)-ethyl]-10-oxa-4-aza-tricyclo[5.2.1.0(2,6)]decane

The product from Example 20A is reduced with lithium aluminium hydride in THF to give the product as a brown oil which is crystallised as its hydrogen maleate salt.

Example 21: *(1S*,2S*,6R*,7R*)*- 4-[2-(4-methoxy-4'-trifluoromethyl-biphenyl-3-yl)-ethyl]-10-oxa-4-aza-2,6-dimethyl-tricyclo[5.2.1.0(2,6)]decane

Obtained analogously to Example 12. The hydrochloride has a m.p. of 229-231°. The compound can also be obtained as follows:

A. *(1S*,2R*,6S*,7R*)*-4-[2-(4-methoxy-4'-trifluoromethyl-biphenyl-3-yl)-ethyl]-10-oxa-4-aza-2,6-dimethyl-tricyclo[5.2.1.0(2,6)]decane-3,5-dione

Obtained in a similar fashion to example 20A from of 2-(4-methoxy-4'-trifluoromethyl-biphenyl-3-yl)-ethylamine and *(1R*,2S*,6R*,7S*)*-2,6-dimethyl-4,10-dioxa-tricyclo [5.2.1.0(2,6)]decane-3,5-dione. Mp. 115-117° (Et_2O/hexane)

B. *(1S*,2S*,6R*,7R*)*-4-[2-(4-methoxy-4'-trifluoromethyl-biphenyl-3-yl)-ethyl]-10-oxa-4-aza-2,6-dimethyl-tricyclo[5.2.1.0(2,6)]decane

Obtained in similar fashion to Example 20B by reduction of *(1R*,2S*,6R*,7S*)*-4-[2-(4-methoxy-4'-trifluoromethyl-biphenyl-3-yl)-ethyl]-10-oxa-4-aza-2,6-dimethyl-tricyclo[5.2.1.0(2,6)]decane-3,5-dione.

Example 22 2-(4'-isopropyl-4-methoxy-biphenyl-3-yl)-ethylamine

Obtained analogously to Example 12. TLC (silica gel, EtOAc-MeOH-NH_4OH 0:20:2) Rf = 0.22.

Example 23: *N,N*-dimethyl-2-(4'-isopropyl-4-methoxy-biphenyl-3-yl)-ethylamine

Obtained analogously to Example 12. The hydrogen maleate has a m.p. of 123-124° ($EtOH/Et_2O$).
The compound can also be obtained by Eschweiler-Clarke methylation of the compound of Example 22.

Example 24: 2-(2'-chloro-4-methoxy-biphenyl-3-yl)-ethylamine

Obtained analogously to Example 12. The hydrochloride has a m.p. of 191-205°.

Example 25: N,N-dimethyl-2-(2'-chloro-4-methoxy-biphenyl-3-yl)-ethylamine

Obtained analogously to Example 12. The hydrochloride has a m.p. of 151-159°.
The compound can also be obtained by Eschweiler-Clarke methylation of the compound of Example 24.

Example 26: (2'-chloro-4-methoxy-biphenyl-3-yl-methyl)-N,N-dimethylamine

Obtained analogously to Example 12. The hydrogen oxalate has a m.p. of 145-159°.

Example 27: N,N-dimethyl-2-(2'-chloro-4-methoxy-biphenyl-3-yl)-1-methyl-ethylamine

Obtained analogously to Example 12. The hydrochloride has a m.p. of 141-145°.

Example 28: (+)-[2-(4-Methoxy-4'-trifluoromethyl-biphenyl-3-yl)-1-methyl-ethyl]-N,N-dimethyl-amine

A. Z-1-Methoxy-2-(2-nitropropenyl)-benzene

A solution of 10 g of 2-methoxybenzaldehyde, 6.07 g of nitroethane, 0.8 ml of 1-butylamine and 30 ml of ethanol is refluxed for 3 days, the ethanol evaporated and the remaining mixture dissolved in ethyl acetate. After extraction with water and brine the solvent is evaporated and the residue bulb to bulb distilled. The fraction distilling at 120 - 170° / 0.01 mbar is purified on silicagel by elution with methylenechloride / cyclohexane 1:1 giving the title compound in form of yellow plates, m.p. 39 - 42°.

B. *rac*-2-(2-Methoxy-phenyl)-1-methyl-ethylamine

A solution of 45.01 g (233 mmol) of Z-1-methoxy-2-(2-nitropropenyl)-benzene in 250 ml of ether is slowly dropped into a flask equipped with a mechanical stirrer, thermometer and reflux condenser containing 40.84 g of $LiAlH_4$ in 600 ml of diethyl ether. The exothermic reaction is cooled with ice and the temperature kept between 5 - 10°. After stirring overnight at room temperature 330 ml of 2M Na_2CO_3 are added, the resulting suspension filtered and the ether phase extracted with 2M HCl. The acidic aqueous phase is made alkaline with 1.2 equivalents of conc. ammonia and extracted with diethyl ether. The ether phase is washed with brine, dried over Na_2SO_4 and concentrated to afford the title compound as a yellow oil. ^{1}H-NMR (360 MHz, $CDCl_3$): 7.2 t, 1H; 7.1 d, 1H; 7.0 - 6.8 m, 2H; 3.9 s, 3H; 3.2 m, 1H; 2.8 m, 1H; 2.6 m, 1H; 1.1 d, 3H.

Further purification is achieved by transformation of the compound into the naphthalene-1,5-disulfonate salt.

C.1 (-)-2-(2-Methoxy-phenyl)-1-methyl-ethylamine

To 19.16 g of *rac*-2-(2-methoxy-phenyl)-1-methyl-ethylamine dissolved in 300 ml of methanol a solution of 17.49 g of D-(-)-tartaric acid in 334 ml of methanol is added and the mixture kept at 4° for 3 hours. The solid is filtered, the mother liquor put aside and the filter cake washed with ice-cold methanol and recristallised twice from methanol until the optical rotation remained constant. One obtains 11.11 g of (-)-2-(2-methoxy-phenyl)-1-methyl-ethylamine D-tartaric acid salt as fine white plates, m.p. 144 - 149°. The free base show a specific rotation of $[\alpha]_{589}$ = -35.4° (c=1, MeOH). Analytical chiral capillary electrophoresis of the free base reveals an optical purity of >98%.

C.2 (+)-2-(2-Methoxy-phenyl)-1-methyl-ethylamine

The first mother liquor obtained in the preparation of the (-)-enantiomer of C.1 is concentrated and the residue liberated from the tartrate by treatment with conc. ammonia and ethyl acetate. After evaporation of the organic layer, 11.14 g of a yellow oil are obtained and combined with 10.12 g of L-(+)-tartaric acid in a total volume of 140 ml of methanol. After 3 h at 4°, the formed solid is collected, washed with ice-cold methanol and recristallised from methanol until the specific rotation remains constant. One obtains 11.92 g of (+)-2-(2-methoxy-phenyl)-1-methyl-ethylamine-L-tartaric acid salt as white plates. The free base show a specific rotation of $[\alpha]_{589}$ = +37.7° (c=1, MeOH). Analytical chiral capillary electrophoresis reveals an optical purity of >98%.

D. (-)-[2-(2-Methoxy-phenyl)-1-methyl-ethyl]-N,N-dimethyl-amine

11.8 g of the tartaric acid salt of (+)-2-(2-methoxy-phenyl)-1-methyl-ethylamine are liberated with conc. ammonia in ethyl acetate and the obtained oil is dissolved in 56 ml of methanol. To this solution 22.3 ml of 36.5% aqueous formaldehyde solution are added, the mixture cooled to 3° and treated in small portions with 10.66 g of $NaCNBH_3$. After 22 h of stirring at room temperature, the solvent is evaporated and the residue distributed between ethyl acetate and water. The organic phase is washed with water and brine, dried over Na_2SO_4, concentrated and the residue purified on silicagel by elution with toluene / ethyl acetate / methanol / conc. ammonia 60:30:10:1 yielding 5.02 g of the title compound as a yellow oil with $[\alpha]_{589}$ = -19.9° (c = 1,

MeOH). ^{1}H-NMR (360 MHz, $CDCl_3$): 7.2 dxt, 1H; 7.1 dxd, 1H; 7.0 - 6.8 m, 2H; 3.85 s, 3H; 3.1 - 3.0 m, 1H; 2.95 - 2.85 m, 1H; 2.4 br s, 7H; 0.95 d, 3H.

E. (+)-[2-(5-bromo-2-methoxy-phenyl)-1-methyl-ethyl]-N,N-dimethyl-amine

To a mixture of 4.47 g of (-)-[2-(2-methoxy-phenyl)-1-methyl-ethyl]-dimethyl-amine, 2.09 g of sodium acetate and 40 ml of glacial acetic acid in a mechanically stirred flask, 1.19 ml of bromine in 8.5 ml of glacial acetic acid are added dropwise at 20 - 30°. The reaction mixture is stirred for 16 h, neutralised with conc. ammonia and extracted with ethyl acetate. Drying of the organic layer with brine and Na_2SO_4, evaporation of the solvent and purification of the obtained residue on silicagel with toluene / ethyl acetate / methanol / conc. ammonia 60:30:10:1 give 4.32 g of the title compound as a brown oil, $[\alpha]_{589}$ = +1.5° (c = 1.01, MeOH). ^{1}H-NMR (360 MHz, $CDCl_3$): 7.2 - 7.0 m, 2H; 6.60 d, 1H; 3.70 s, 3H; 2.95 - 2.75 m, 2H; 2.3 - 2.2 m+s, 7H; 0.85 d, 3H.

F. (+)-[2-(4-methoxy-4'-trifluoromethyl-biphenyl-3-yl)-1-methyl-ethyl]-N,N-dimethyl-amine

A 500 ml-flask is charged with 140 ml of toluene and 28 ml of 2M Na_2CO_3 and gased with argon for 1 h. Then 3.94 g of (+)-[2-(5-bromo-2-methoxy-phenyl)-1-methyl-ethyl]-dimethyl-amine, 4.95 g of 4-trifluoromethyl-phenylboronic acid and 374 mg of tetrakis(triphenylphosphine)palladium are added and the mixture is refluxed for 12 h. The aqueous layer is extracted with ethyl acetate and the combined organic phases are washed with brine, dried over Na_2SO_4 and concentrated to afford a brown oil. Formation of the naphthalene-1,5-disulfonate salt of this oil and liberation of the free base allow to cristallise the product as hydrochloride salt from HCl in diethyl ether. Recristallisation from ethanol / ether afford the hydrochloride of the title compound as fine white plates, m.p. 155 - 163°.

The free base solidifies with a m.p. of 36 - 37° and shows a specific rotation of $[\alpha]_{589}$ = +13.0° (c = 0.995, MeOH). Analytical chiral HPLC (Chiracel OJ) reveals an optical purity of >99%. ^{1}H-NMR (360 MHz, $CDCl_3$): 7.70 s, 4H; 7.45 dxd, 1H; 7.40 d, 1H;

6.95 d, 1H; 3.90 s, 3H; 3.25 - 3.20 m, 1H; 3.0 - 2.9 m, 1H; 2.55 - 2.45 m, 1H; 2.40 s, 6H; 1.00 d, 1H.

Example 29: (-)-[2-(4-methoxy-4'-trifluoromethyl-biphenyl-3-yl)-1-methyl-ethyl]-N,N-dimethyl-amine

A. (+)-[2-(2-methoxy-phenyl)-1-methyl-ethyl]-N,N-dimethyl-amine

The product prepared as described in example 28C.1 is reduced with $NaCNBH_3$ and formaldehyde according to the description in example 28D to afford the title compound as a yellow oil, $[\alpha]_{589}$ = +21.6° (c = 1.03, MeOH).

B. (-)-[2-(5-bromo-2-methoxy-phenyl)-1-methyl-ethyl]-N,N-dimethyl-amine

The product prepared under A is brominated as described in example 28E to afford the title compound as a yellow oil, $[\alpha]_{589}$ = -1.0 (c = 1.05, MeOH).

C. (-)-[2-(4-methoxy-4'-trifluoromethyl-biphenyl-3-yl)-1-methyl-ethyl]-N,N-dimethyl-amine

The product prepared under B is arylated with 4-trifluoromethyl-phenylboronic acid according to example 28F to afford the hydrochloride of the title compound as white plates, m.p. 148 - 163°.

The free base solidifies with a m.p. of 31° and shows a specific rotation of $[\alpha]_{589}$ = -12.8° (c = 1.0, MeOH). Analytical chiral HPLC (Chiracel OJ) reveals an optical purity of >99%.

Example 30: [1-(4-methoxy-4'-trifluoromethyl-biphenyl-3-ylmethyl)-propyl]-N,N-dimethyl-amine

A. 1-methoxy-2-(2-nitro-but-1-enyl)-benzene

A solution of 2.72 g of 2-methoxybenzaldehyde, 1.96 g of 1-nitropropane, 0.4 ml of 1-butylamine and 10 ml of toluene is refluxed for 16 h. The toluene is evaporated and the residue dissolved in ethyl acetate and extracted with water and brine.

Concentration of the organic phase affords the title compound as yellow oil, sufficiently pure for the next step. ^{1}H-NMR (360 MHz, $CDCl_3$): 8.6 s (olefinic H of E-isomer); 8.2 s (olefinic H of Z-isomer).

B. 1-(2-methoxybenzyl)-propylamine

To a magnetically stirred mixture of 2.28 g of $LiAlH_4$ and 35 ml of diethyl ether a solution of 3.79 g of 1-methoxy-2-(2-nitro-but-1-enyl)-benzene in 15 ml of diethyl ether is dropped at 0 - 5°. After stirring overnight at room temperature 20 ml of 2M Na_2CO_3 are added, the resulting suspension is filtered and the organic phase extracted with 2M HCl. The acidic aqueous phase is made alkaline with 2M NaOH and extracted with methyl-t-butyl ether. The organic phase is washed with brine, dried over Na_2SO_4 and concentrated to give the title compound as a yellow oil. ^{1}H-NMR (360 MHz, $CDCl_3$): 7.2 - 7.0 m, 2H; 6.9 - 6.7 m, 2H; 3.8 s, 3H; 2.9 m, 1H; 2.8 dxd, 1H; 2.4 dxd, 1H; 1.5 m, 1H; 1.3 m, 1H; 0.9 t, 3H.

C. 1-(5-bromo-2-methoxy-benzyl)-propylamine

To a mixture of 2.25 g of 1-(2-methoxybenzyl)-propylamine, 1.13 g of sodium acetate and 57 ml of glacial acetic acid in a magnetically stirred flask, 0.65 ml of bromine in 3 ml of glacial acetic acid are added dropwise at 20 - 30°. The reaction mixture is stirred for 4 h, concentrated and the obtained residue distributed between water and ethyl acetate. The organic phase is extracted with 2M acetic acid and the combined acidic aqueous phases are made alkaline with conc. ammonia. Re-extraction with ethyl acetate, drying of the organic phase over Na_2SO_4 and concentration give the title compound as colorless powder. ^{1}H-NMR (360 MHz, $CDCl_3$): 7.2 d, 1H; 7.1 s, 1H; 6.7 d, 1H; 3.8 s, 3H; 2.9 m, 1H; 2.7 m, 1H; 2.5 m, 1H; 1.6 - 1.3 m, 2H; 1.0 t, 3H.

D. 1-(4-methoxy-4'-trifluoromethyl-biphenyl-3-ylmethyl)-propyl]-amine

A mixture of 1.91 g of 1-(5-bromo-2-methoxy-benzyl)-propylamine, 0.3 g of tetrakis(triphenylphosphine)palladium, 2.61 g of 4-trifluoromethyl-phenylboronic acid, 24 ml of 2M Na_2CO_3 and 25 ml of toluene is refluxed under argon for 7 h. After extraction of the water phase with diethyl ether, the organic phases are combined,

dried over Na_2SO_4 and concentrated to afford the title compound as a brown oil which is purified on silicagel by elution with toluene / ethanol / conc. ammonia 85:15:1. ^{1}H-NMR (360 MHz, $CDCl_3$): 7.65 s, 4H; 7.5 dxd, 1H; 7.4 d, 1H; 7.0 d, 1H; 3.9 s, 3H; 3.1 m, 1H; 2.9 dxd, 1H; 2.6 dxd, 1H; 1.6 m, 1H; 1.4 m, 1H, 1.1 t, 3H.

E. [1-(4-methoxy-4'-trifluoromethyl-biphenyl-3-ylmethyl)-propyl]-N,N-dimethyl-amine hydrochloride

To a mixture of 1.25 g of 1-(4-methoxy-4'-trifluoromethyl-biphenyl-3-ylmethyl)-propyl]-amine, 2.5 ml of 36.5% formaline solution and 10 ml of methanol under argon 1.66 g of $NaCNBH_3$ are added in several portions at 3°. After stirring overnight at room temperature the solvent is evaporated and the residue distributed between ethyl acetate and water. The organic phase is washed with water and brine and concentrated to afford the crude product which is treated with HCl in diethyl ether. The formed solid is filtered and recristallised from aceton / diethyl ether to give the title compound as white needles, m.p. 155 - 172°.

Example 31: 1-[2-(4-methoxy-4'-trifluoromethyl-biphenyl-3-yl)-1-methyl-ethyl]-piperidine

A. 2-(5-Bromo-2-methoxy-phenyl)-1-methyl-ethylamine

A mixture of 6.54 g of 2-(2-methoxy-phenyl)-1-methyl-ethylamine (free base, prepared as described in example 28B), 3.56 g of sodium acetate and 180 ml of glacial acetic acid is treated with 6.31 g of bromine as described in example 30C, affording the title compound as a yellow oil. ^{1}H-NMR (360 MHz, $CDCl_3$): 7.4 - 7.2 m, 2H; 6.7 d, 1H; 3.8 s, 3H; 3.2 hex, 1H; 2.8 - 2.5 m, 2H; 1.1 d, 3H.

B. 2-(4-methoxy-4'-trifluoromethyl-biphenyl-3-yl)-1-methyl-ethylamine hydrochloride

A mixture of 7.62 g of 2-(5-bromo-2-methoxy-phenyl)-1-methyl-ethylamine, 0.71 g of tetrakis(triphenylphosphine)palladium, 7.98 g of 4-trifluoromethyl-phenylboronic acid, 24 ml of 2M Na_2CO_3, 40 ml of toluene and 10 ml of ethanol is refluxed for 9 h under argon. After workup similar to Example 30D, the crude oil is purified by

transformation into the hydrochloride salt which is obtained in form of white plates. ^{1}H-NMR (360 MHz, DMSO-d_6): 7.90 - 7.75 dxd, 4H; 7.65 dxd, 1H; 7.60 d, 1H; 7.15 d, 1H; 3.85 s, 3H; 3.5 m, 1H; 3.1 - 2.8 m, 2H; 1.15 d, 3H.

C. 4-[2-(4-methoxy-4'-trifluoromethyl-biphenyl-3-yl)-1-methyl-ethyl-carbamoyl]butyric acid

The base of 1.1 g of 2-(4-methoxy-4'-trifluoromethyl-biphenyl-3-yl)-1-methyl-ethylamine hydrochloride is liberated and reacted with 0.37 g of glutaric anhydride in THF under reflux for 20 h. The solvent is evaporated and the residue dissolved in ethyl acetate. After extraction of the organic phase with 1M HCl, water and brine, drying over Na_2SO_4 and evaporation the title compound is obtained as a white powder, m.p. 88° (dec.).

D. 1-[2-(4-methoxy-4'-trifluoromethyl-biphenyl-3-yl)-1-methyl-ethyl]-piperidine-2,6-dione

A mixture of 1.02 g of the carboxylic acid obtained under C and 4.3 g of acetyl chloride in 20 ml of chloroform was refluxed for 17 h and, after cooling, extracted with water and 2M Na_2CO_3. After drying of the organic phase over Na_2SO_4 the solvent is evaporated and the residue purified on silicagel by elution with ethyl acetate / cyclohexane 1:2, yielding the title compound as a bright yellow oil, solidifying in the refrigerator. ^{1}H-NMR (360 MHz, $CDCl_3$): 7.6 - 7.5 m, 4H; 7.4 dxd, 1H; 7.2 d, 1H; 6.8 d, 1H; 5.2 m, 1H; 3.8 s, 3H; 3.2 - 3.0 m, 2H; 2.4 - 2.3 m, 4H; 1.5 br m, ca. 2H (+HOD); 1.35 d, 3H.

E. 1-[2-(4-methoxy-4'-trifluoromethyl-biphenyl-3-yl)-1-methyl-ethyl]-piperidine hydrochloride

To a suspension of 0.054 g of $LiAlH_4$ in 6 ml of diethyl ether under argon a solution of 0.3 g of 1-[2-(4-methoxy-4'-trifluoromethyl-biphenyl-3-yl)-1-methyl-ethyl]-piperidine-2,6-dione in 2 ml of diethyl ether is dropped under slight cooling. After stirring for 30 min 0.5 ml of 2M Na_2CO_3 are added, the resulting mixture is filtered and the filtrate acidified and extracted with 1M HCl. The aqueous phase is made alkaline with conc.

ammonia and extracted with diethyl ether. The organic phase, after drying over Na_2SO_4, is concentrated and the residue treated with a solution of HCl in diethyl ether thereby affording the title compound as colorless plates, m.p.185° (dec.).

Example 32: N,N-diethyl-[2-(4-methoxy-4'-trifluoromethyl-biphenyl-3-yl)-1-methyl-ethyl]-amine

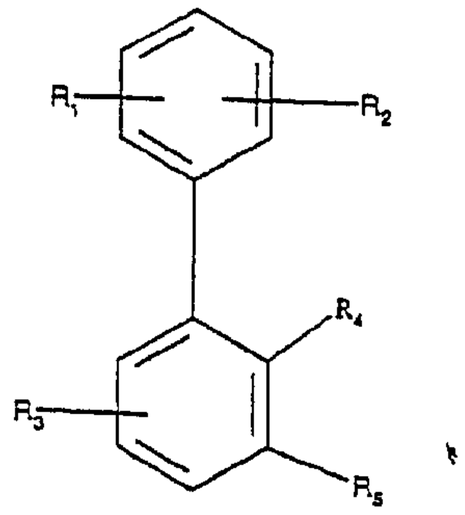
Obtained by reductive alkylation of 2-(4-methoxy-4'-trifluoromethyl-biphenyl-3-yl)-1-methyl-ethylamine (obtained as described in Example 31B) with acetaldehyde over 10% Pd/C in ethylacetate. The hydrochloride has a m.p. of 105-107°.

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CLAIMS

1. A compound of formula I



I

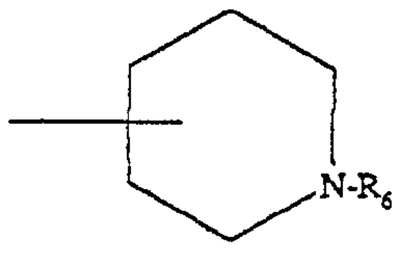
wherein

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

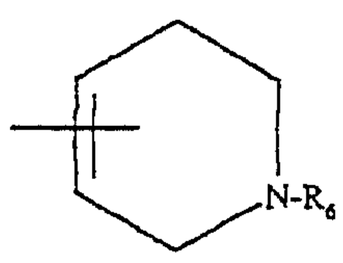
R_3 is hydrogen, hydroxy, (C_{1-4})alkyl, (C_{1-4})alkoxy, (C_{3-6})cycloalkyloxy, halogen, cyano, (C_{2-5})alkanoyl, carbamoyl, (C_{1-4})alkylsulfonyloxy or trifluoromethyl-sulfonyloxy,

R_4 is hydrogen, hydroxy or (C_{1-4})alkoxy, and

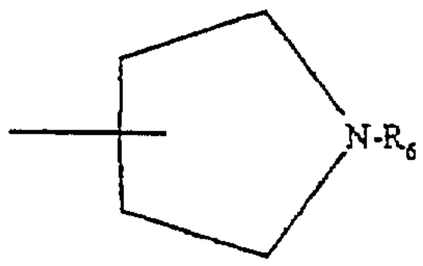
R_5 is a group of formula (a), (b), (c) or (d)



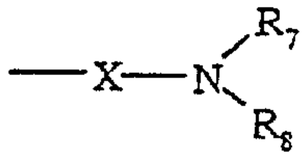
(a)



(b)



(c)



(d)

AMENDED SHEET

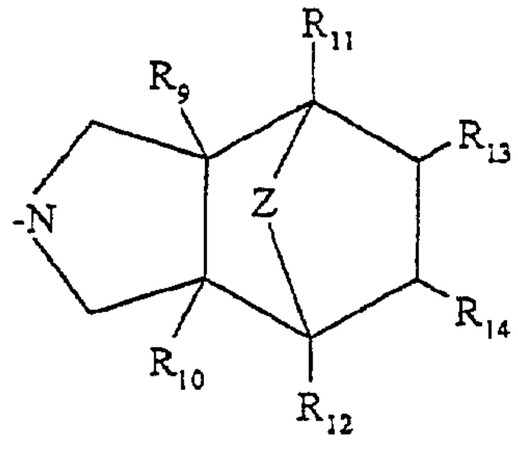
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wherein

R_6 is (C_{1-4})alkyl,

X is a straight or branched alkylene chain with 1 to 4 carbon atoms, and

R_7 and R_8 form together with the nitrogen atom to which they are attached a group of formula (e)



(e)

wherein Z is O, CH_2 or CH_2-CH_2 and R_9, R_{10}, R_{11}, R_{12}, R_3 and R_{14}, independently,are H, halogen, (C_{1-4})alkyl or (C_{1-4})alkoxy,

in free base or acid addition salt form.

2. A compound of formula I as defined in claim 1, wherein R_1, R_2, R_3 and R_4 are as defined in claim 1 and R_5 is a group of formula (a), (b) or (c) as defined in claim 1, in free base or acid addition salt form.

3. A compound of formula I as defined in claim 1, wherein R_1, R_2, R_3 and R_4 are as defined in claim 1 and R_5 is a group of formula (d) as defined in claim 1, in free base or acid addition salt form

4. A compound of claim 1 selected from

(+)-3-(4-methoxy-4'-trifluoromethyl-biphenyl-3-yl)-1-propyl-piperidine,

(-)-3-(4-methoxy-4'-trifluoromethyl-biphenyl-3-yl)-1-propyl-piperidine,

(-)-3-(4-methoxy-4'-trifluoromethyl-biphenyl-3-yl)-1-methyl-piperidine,

(+)-3-(4-methoxy-4'-trifluoromethyl-biphenyl-3-yl)-1-methyl-piperidine,

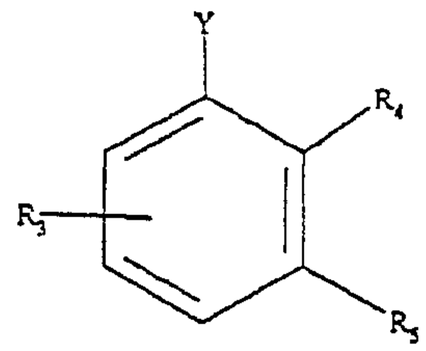
(1S*,2S*,6R*,7R*)-4-[2-(4-methoxy-4'-trifluoromethyl-biphenyl-3-yl)-ethyl]-10-oxa-4-aza-tricyclo[5.2.1.0(2,6)]decane,

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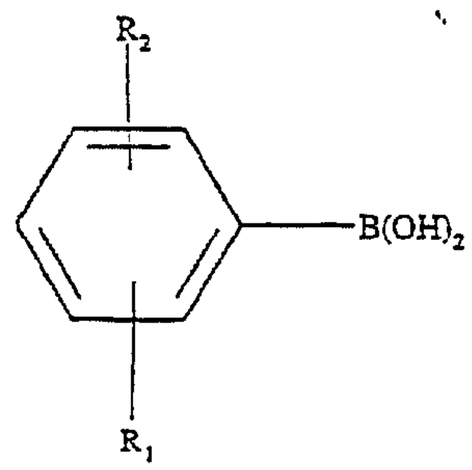
in free base or acid addition salt form.

5. 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 1 and Y is halogen or trifluoromethylsulfonate, is reacted with a compound of formula III



III

wherein R_1 and R_2 are as defined in claim 1, and the resulting compound is recovered in free base form or in acid addition salt form.

6. A compound of anyone of claims 1 to 4 in free base or pharmaceutically acceptable acid addition salt form, for use as a pharmaceutical.

7. A compound of anyone of claims 1 to 4 in free base or pharmaceutically acceptable acid addition salt form, for use in the treatment of epilepsy, stroke and brain or spinal trauma.

AMENDED SHEET

8. A pharmaceutical composition comprising a compound of anyone of claims 1 to 4 in free base or pharmaceutically acceptable acid addition salt form, in association with a pharmaceutical carrier or diluent.

9. The use of a compound of anyone of claims 1 to 4 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.

10. 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 a compound of anyone of claims 1 to 4 in free base or pharmaceutically acceptable acid addition salt form.