APPLICATION ACCEPTED AND AMENDMENTS ALLOWED 28.11.87

AUSTRALIA

Patents Act 1952

CONVENTION APPLICATION FOR A PATENT

We, BOEHRINGER INGELHEIM INTERNATIONAL GmbH, a body corporate organised under the laws of the Federal Republic of Germany, of D-6507 Ingelheim am Rhein, Federal Republic of Germany, hereby apply for the grant of a Patent for an invention entitled "TETRAHYDROBENZOTHIAZOLES" which is described in the accompanying complete specification.

This application is a Convention application and is based on the application numbered P 36 20 813.2 for a patent or similar protection made in Federal Republic of Germany on 21st June, 1986.

Our address for service is: CALLINAN AND ASSOCIATES, Patent Attorneys, of 48-50 Bridge Road, Richmond, State of Victoria, Australia.

D A T E D this 22nd day of June, 1987.

PATENT OFFICE 100 AUSTRALIA ONE HUNDRED DOLLARS

PATENT OFFICE 40 AUSTRALIA FORTY DOLLARS

BOEHRINGER INGELHEIM INTERNATIONAL GmbH
By its Patent Attorneys:
CALLINAN AND ASSOCIATES

LODGED AT SUB-OFFICE
22 JUN 1987
Melbourne

PATENT OFFICE 40 AUSTRALIA FORTY DOLLARS

LODGED AT SUB-OFFICE 22 PATENT OFFICE Melb 5 AUSTRALIA FIVE DOLLARS

TO: The Commissioner of Patents

FEE STAMP TO VALUE OF $185.00 ATTACHED
MAIL OFFICER.....

COMMONWEALTH OF AUSTRALIA

The Patents Act 1952

DECLARATION IN SUPPORT

of the (Convention) Application made by: BOEHRINGER INGELHEIM INTERNATIONAL GmbH

(hereinafter termed "the applicant") for a patent (~~of addition~~) for an invention entitled

"TETRAHYDROBENZOTHIAZOLES"

I/~~We~~ KEITH WILLIAM CALLINAN,

of 23 Michele Drive, Scoresby, Victoria 3179, Australia

do solemnly and sincerely declare as follows:

~~I am/ We are the applicant ,~~ ~~or~~

I am/ ~~We are~~ authorised by the applicant to make this declaration on its/~~their~~ behalf.

The basic application as defined by sections 141 and 142 of the Act was/~~were~~ made

in Federal Republic of Germany on 21st June, 1986

~~in~~ ~~on~~

~~in~~ ~~on~~

by BOEHRINGER INGELHEIM KG

Tne basic application referred to in this paragraph is/~~are~~ the first application made in a Convention country in respect of the invention the subject of the application.

~~I/We am/are~~
Claus Schneider, of Albrecht-Dürer-Strasse 19, 6507 Ingelheim am Rhein, F.D.R.;
Herbert Merz, of Rotweinstrasse 53, 6507 Ingelheim am Rhein, F.D.R.;
Rainer Sobotta, of Ludwig Richter Strasse 6, 6507 Ingelheim am Rhein, F.D.R.;
Rudolf Bauer, of Aarstrasse 4, 6200 Wiesbaden, F.D.R.;
Joachim Mierau, of An den Weiden 3, 6500 Mainz 33, F.D.R.; and
Günter Schingnitz, of Unter den Gärten 18, 6550 Bad Kreuznach 14, F.D.R.

~~is~~/are the actual inventors of the invention and the facts upon which the applicant is/~~are~~ entitled to make the application are as follows:

The applicant would, if a patent were to be granted upon an application made by the said actual inventors, be entitled to have the patent assigned to it; the applicant is the assignee of priority right from BOEHRINGER INGELHEIM KG.

Declared at Richmond, Victoria this 22nd day of June 19 87.

Signed: K S W. Callinan

(12) PATENT ABRIDGMENT (11) Document No. AU-B-74578/87
(19) AUSTRALIAN PATENT OFFICE (10) Acceptance No. 593357

(54) Title
TETRAHYDROBENZOTHIAZOLES

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(21) Application No. : **74578/87** (22) Application Date : **22.06.87**

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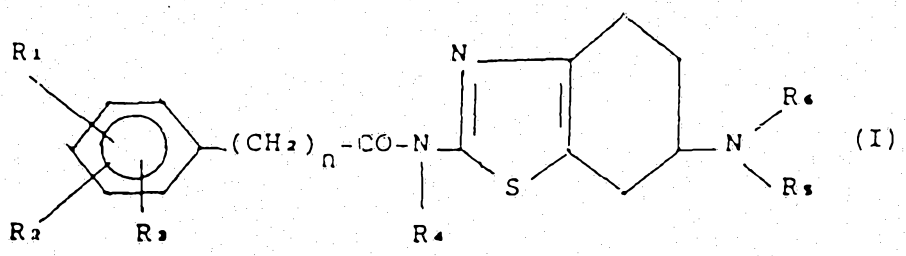
(74) Attorney or Agent
CALLINAN LAWRIE

(56) Prior Art Documents
AU 51544/85 C07D 277/60

(57) Claim

1. Tetrahydro-benzothiazole compounds of the formula



(I)

in which

n represents an integer 1, 2 or 3;

R_1 denotes an H, F, Cl or Br atom or a CH_3, C_2H_5, OCH_3, OC_2H_5, OH or CF_3 group;

R_2 denotes an H or Cl atom or a CH_3, OCH_3, OC_2H_5 or OH group;

R_3 denotes an H atom or an NH_2 group;

R_4 denotes an H atom or a CH_3 or C_2H_5 group and

R_5 and R_6, which may be the same or different, denote an H atom or C_{1-4} alkyl, phenyl-substituted C_{1-3}-alkyl, allyl or propargyl group;
and the acid-addition salts thereof.

8. A method of treatment of Parkinson's disease or Parkinsonism or of treatment of schizophrenia and for prolactine inhibition, which comprises administering to an animal or human subject an effective amount of a compound as claimed in any one of claims 1 to 6 or an acid-addition salt thereof.

Australia

Form 10

PATENTS ACT 1952

COMPLETE SPECIFICATION

(ORIGINAL)

FOR OFFICE USE

Short Title:

Int. Cl:

Application Number:
Lodged:

593357

Complete Specification—Lodged:
Accepted:
Lapsed:
Published:

Priority:

Related Art:

This document contains the amendments made under Section 49.

and is correct for printing.

TO BE COMPLETED BY APPLICANT

Name of Applicant: BOEHRINGER INGELHEIM INTERNATIONAL GmbH

Address of Applicant: D-6507 Ingelheim am Rhein, Federal Republic of Germany.

Actual Inventor: Claus Schneider, Herbert Merz, Rainer Sobotta, Rudolf Bauer, Joachim Mierau and Günter Schingnitz.

Address for Service: CALLINAN AND ASSOCIATES, Patent Attorneys, of 48-50 Bridge Road, Richmond, State of Victoria, Australia.

Complete Specification for the invention entitled: "TETRAHYDROBENZOTHIAZOLES"

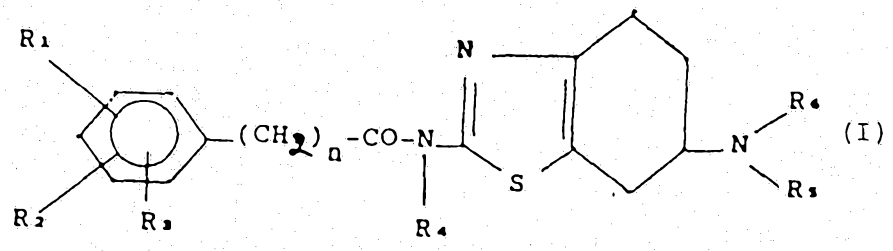
The following statement is a full description of this invention, including the best method of performing it known to me:—*

* Note: The description is to be typed in double spacing, pica type face, in an area not exceeding 250 mm in depth and 160 mm in width, on tough white paper of good quality and it is to be inserted inside this form.

19V 51 761

The invention relates to tetrahydrobenzothiazole derivatives. It further relates to processes for the preparation thereof, and their use as medicaments in conventional preparations, particularly in the treatment of Parkinsonism and Parkinson's disease.

According to one aspect of the invention, we provide compounds of the formula



(I)

in which

n represents an integer 1, 2 or 3;

R_1 denotes an H, F, Cl or Br atom or a CH_3, C_2H_5, OCH_3, OC_2H_5, OH or CF_3 group;

R_2 denotes an H or Cl atom or a CH_3, OCH_3, OC_2H_5 or OH group;

R_3 denotes an H atom or an NH_2 group;

R_4 denotes an H atom or a CH_3 or C_2H_5 group; and

R_5 and R_6, which may be the same or different, denote an H atom or C_{1-4} alkyl, phenyl-substituted C_{1-3}-alkyl, allyl or propargyl group;

and the acid-addition salts thereof.

In the context of the above definitions, R_1 to

R_6 may all be the same or different and contain or represent branched or unbranched hydrocarbon radicals.

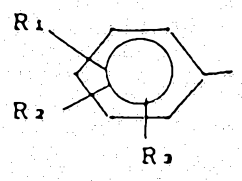
R_1 preferably represents a hydrogen, chlorine or bromine atom or an OCH_3, OH, CH_3 or C_2H_5 group; R_2 preferably represents a hydrogen or chlorine atom or a methoxy group; R_4 preferably represents a hydrogen atom or CH_3 group; R_5 preferably represents a hydrogen atom, or a C_{1-3}-alkyl, allyl or phenethyl group, and R_6 preferably represents a hydrogen atom or a C_{1-3}-alkyl or allyl group.

Those compounds in which R_1 denotes an OCH_3 or OH group; R_2, R_3 and R_4 denote a hydrogen atom, and R_5 and R_6 denote hydrogen or a C_{1-3}-alkyl group are particularly preferred.

The index n preferably represents an integer 2 or 3, most preferably 2.

If at least one of the radicals R_1 to R_4 has a meaning other than hydrogen, the 4-position is preferably substituted; any further substituent which may be present is preferably in the 3-position.

Typical radicals of the formula



(II)

include, for example, 4-methoxyphenyl, 4-chlorophenyl, 4-hydroxyphenyl, 3,4-dimethoxyphenyl, 4-hydroxy-3-methoxyphenyl, 4-methylphenyl and 3,5-dichloro-

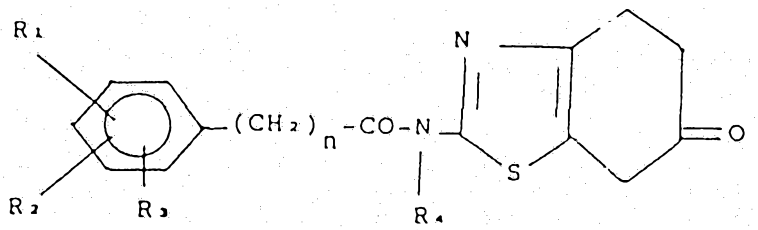
4-aminophenyl.

The new compounds can exist as racemates or pure enantiomers, but also as mixtures of the enantiomers in any ratios. In general, one of the enantiomers of the racemate is more active than the other. The invention extends to all the individual optical isomers and mixtures thereof.

According to a further aspect of the invention we provide a process for the preparation of compounds of formula (I)

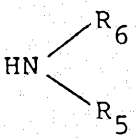
wherein

a) a compound of the formula (III)



(III)

is reacted with a compound of the formula



(IV)

under conditions of reductive amination,

or

b) for the preparation of a compound of formula I in which R_1 or R_2 comprise

a phenolic OH group, a corresponding compound having an ether group is subjected to ether cleavage,

or

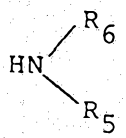
c) for the preparation of compounds of formula I in which neither radical R_5 or R_6 denotes hydrogen, a compound of the formula I where R_6 represents hydrogen is reacted with a compound

$$x - R'_6 \qquad (V)$$

serving to introduce the radical R'_6 (in which R'_6 is the same as R_6, apart from hydrogen), and x denotes a group which can be cleaved on introduction of the group R'_6 into the amino group;

followed, if necessary and/or if desired by resolution of any racemates obtained into the enantiomers; and/or followed if desired by conversion of any base obtained into an acid-addition salt, or conversion of an acid-addition salt obtained into a free base or into a salt of a different acid.

In the above processes, the reductive amination will generally be carried out using a compound of the formula



(IV)

in which R_5 and R_6 have the above meaning, and a reducing agent.

Reducing agents which can be used are hydrogen and hydrogenation catalysts, for example Raney nickel, platinum, palladium, or complex hydrides, for example sodium borohydride. Suitable reaction media include polar organic solvents which are inert under the reaction conditions, for example lower aliphatic alcohols, such as methanol or ethanol. The reaction preferably takes place with gentle cooling (for example when $NaBH_4$ is used as the reducing agent), and, if appropriate, with warming and under pressure when using hydrogen/catalyst.

In the preparation of compounds of the formula I which contain a phenolic OH group, an appropriate ether, for example the methylether, can also be subjected to conventional ether cleavage, for example using a boron bromide. Suitable solvents are, for example, halogenated hydrocarbons, such as methylene chloride or ethylene chloride. The reaction is expediently carried out at room temperature.

In the preparation of compounds of the formula I in which neither radical R_5 or R_6 denotes hydrogen, an appropriate compound in which R_6 is hydrogen can be reacted with the compound of the formula

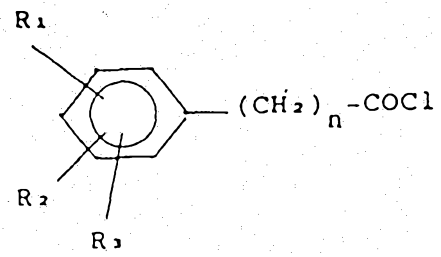
$$x - R'_6 \qquad (V)$$

in which R'_6 has the same meaning as R_6 apart from hydrogen, and x represents a group which can be eliminated on introduction of R'_6 into the amino group, for example a halogen atom.

If the starting materials are not known, they can be prepared by conventional methods.

Compounds of the formula III, for example, can

be prepared by reacting an acyl chloride of the formula



(VI)

in which n, R_1, R_2 and R_3 have the above meanings, with 6-oxo-2-aminotetrahydrobenzothiazole with heating, preferably in the presence of a tertiary aliphatic amine, such as triethylamine, in an inert organic solvent.

The final products of the formula I, which are initially obtained as bases, can be converted in conventional manner into acid-addition salts; any acid-addition salts which are initially obtained can be converted in conventional manner into bases or salts of other acids.

Suitable acids are all inorganic or organic acids which give adequately stable salts with the bases according to the invention.

The salts of physiologically tolerated acids, for example mineral acid-derived salts such as the hydrochlorides, hydrobromides, and sulphates, or organic acid-derived salts such as the methanesulphonates, succinates, fumarates, maleates, citrates and formates, are preferably used in the preparation of medicaments.

The compounds according to the invention contain a chiral centre and are therefore generally produced as racemates, which can then be separated, if desired,

into the enantiomers using conventional optically active acids, for example using tartaric acid, O,O-dibenzoyl tartaric acid, camphorsulphonic and α-methoxyphenylacetic acid.

If an optically active starting material is employed, for example in process (b) or (c), the enantiomers can also be obtained directly.

The compounds of the invention have shown valuable therapeutic properties, particularly for the treatment of Parkinson's disease or Parkinsonism. They can furthermore be used for prolactin inhibition and for treating schizophrenia.

The compounds according to the invention exhibit a particularly favourable profile of action. It is to be noted that

- the action lasts for a long time (up to about 20 hours),
- emesis has not been found to occur in the therapeutic dose range, and
- low adrenergic action is observed.

Compounds having such a profile of action have not hitherto been described.

The action can be demonstrated on apes (MPTP model).

Determination of the anti-Parkinsonism and anti-Parkinson action

The discovery of the neurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydro-pyridine (MPTP) (Langston et al., Science 219, 979 (1983)) has made available an animal model for Parkinson's disease.

In its clinical, pathological, biochemical and pharmacological character, the irreversible, neurological clirical picture initiated in humans and in apes by MPTP substantially resembles idiopathic Parkinson's disease (Markey et al., Nature 311, 464 (1984)). The cause of this agreement is that MPTP selectively destroys that small group of dopaminergic nerve cells in the cerebral substantia nigra that is also destroyed by degenerative processes in naturally occurring Parkinson's disease. It is also debated whether the cause of idiopathic Parkinson's disease is also MPTP, or a similar chemical compound, produced in the organism (Snyder, S.H., Nature 311, 514 (1984)). Possibly caused by the specific metabolism of MPTP, the clinical character of the MPTP-Parkinson picture has the term only been detectable in apes, in addition to in humans.

The MPTP model realised in rhesus apes is therefore suitable, to an excellent extent, for testing the action of anti-Parkinson medicaments. MPTP (1 x 0.15 mg/kg i.m. daily for 3 days, 3 days pause, 1 x 0.30-0.40 mg/kg daily for 3 days) was administered to rhesus apes; they exhibited the following symptoms: the animals were akinetic and not able to take water and feed. They exhibited a typical stoop; cataleptic states occurred from time to time. The extremities exhibited a rigour, which was interrupted by clonic cramps during passive movement. It was generally not possible to initiate voluntary movements of the rump and the extremities by the strongest, painful stimulae.

A few minutes after the intramuscular administration of the compound according to the invention, the first voluntary movements occur, which are followed by gradual, substantial normalisation of motoriscity.

The animals are then able to take food. They support themselves properly in the cages, which also applies with respect to vigilence and species-specific behaviour. Occasional temporary, slight passive tremor and reduction of physical strength are recorded as residual symptoms.

In some cases, the action of the compounds only falls off after about 20 hours, and the animals again take on the Parkinson symptoms described above; readministration of the compound again leads to improvement or substantial relief of the clinical pathological symptom. The advantageous action of the compounds can thus be reproduced.

According to a further feature of the invention, we provide a pharmaceutical composition which comprises a compound as hereinbefore defined in association with a pharmaceutically acceptable carrier, diluent auxiliary and/or excipient.

Conventional pharmaceutical preparations may be prepared, for example, tablets, coated tablets, suppositories, powders, suspensions and solutions. The daily dose is in general 0.1 to 10 mg/kg, preferably 0.5 to 5 mg/kg of body weight; the preparations may be administered in one or several individual doses.

Pharmaceutical Examples
(Data in parts by weight):

Coated tablets

5.0 parts of active compound according to the invention
33.5 parts of lactose
10.0 parts of maize starch
1.0 part of gelatin
0.5 part of magnesium stearate

The powdered components active compound, lactose and maize starch are granulated with aqueous gelatin solution and dried. The granules are mixed with the magnesium stearate and compressed to form coated tablet cores weighing 50 mg and are coated by known methods.

Suppositories

10 parts of active compound according to the invention
1690 parts of suppository material (for example Witepsol W 45)

The finely powdered substance is distributed uniformly, by means of a homogeniser, in the molten suppository material, cooled to 40°C. Suppositories weighing 1.7 g are shaped from the mixture.

The following non-limiting Examples below illustrate the invention in greater detail:

Example 1

2-(4-Methoxyphenylpropionyl)amino-6-n-propylamino-4,5,6,7-tetrahydrobenzothiazole

a) Preparation of the racemate

15.1 g (0.09 mol) of 6-oxo-2-amino-tetrahydrobenzothiazole and 20.5 g (0.1 mol) of 4-methoxyphenylpropionyl chloride are refluxed for 2 hours in 450 ml of tetrahydrofuran and 0.1 mol of triethylamine, subsequently poured onto ice and extracted with ethyl acetate. After drying, 2-(4-methoxyphenylpropionyl)amino-6-oxo-tetrahydrobenzothiazole (17.5 g) crystallises out on concentrating, and, is dissolved in methanol and is reductively aminated, without further purification, in an autoclave using propylamine (Raney nickel, 5 bar, 60°C). After filtering off the catalyst under suction, the solvent is removed by distillation. The residue crystallises from i-propyl ether.
Yield: 12.5 g (63% of theory)
Base: Melting point 105-106°C (recrystallised from ethyl acetate)
Dihydrochloride: Melting point 259-261°C.

b) Resolution of the racemate

3.75 g (0.025 mol) of L-(+)-tartaric acid [Aldrich: $[\alpha]_D^{20}$ + 12° (c = 20 H_2O)] are added to a suspension of the product obtained according to a) (9.3 g, 0.025 mol) in 200 ml of water. The mixture is refluxed for 15 minutes and filtered. The colourless crystals which precipitate after one day are filtered off under suction. This L-(+)-tartaric acid salt is recrystallised five times from 75 ml of water. The optical rotation $[\alpha]_D^{20}$ of - 45.5°C (c = 1,

CH_3OH) of the liberated base does not change further on further recrystallisation.

From the pure L-(+)-tartaric acid salt, the base is liberated using concentrated ammonia and extracted with ethyl acetate. After washing and drying (magnesium sulphate), the solvent is removed in vacuo. The dihydrochloride of the (-)-enantiomer crystallises through treatment with ethereal hydrochloric acid.

Yield: 0.9 g, melting point 261 - 262°C

$[\alpha]_D^{20}$ - 41.1° (c = 1, CH_3OH)

Example 2

2-(4-Hydroxyphenylpropionyl)amino-6-n-propylamino-4,5,6,7-tetrahydrobenzothiazole

9.6 g (0.026 mol) of the compound obtained according to Example 1 are dissolved in 300 ml of methylene chloride and stirred for 3 hours at 15°C with 90 ml of boron tribromide. Water is added to the reaction mixture, which is then rendered alkaline using concentrated ammonia. The organic phase is extracted with methylene chloride dried and concentrated. The dihydrobromide of the title compound is obtained from the residue using ethanolic hydrobromic acid.

Yield: 4.95 g (49% of theory)
melting point 228-229°C.

Further Examples

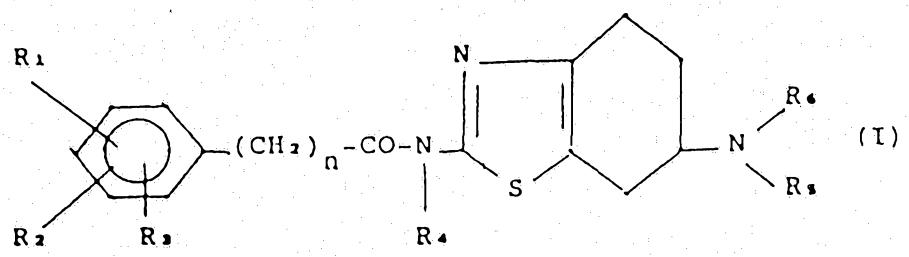
NO.	R_1	R_2	R_3	R_4	R_5	R_6	n	Mp.(°C)
3	4-OCH_3	H	H	H	C_2H_5	H	2	224-225 (Fumarate)
4	4-OCH_3	H	H	H	CH_3	H	2	202-204 (Fumarate)
5	4-OH	H	H	H	C_2H_5	H	2	164-165 (Dihydro-bromide)
6	4-OH	H	H	H	CH_3	H	2	239-240 (Base)
7	4-CH_3	H	H	H	n-C_3H_7	H	2	>260 (Fumarate)
8	2-OCH_3	H	H	H	n-C_3H_7	H	2	216-217 (Oxalate)
9	3-OCH_3	H	H	H	n-C_3H_7	H	2	
10	4-OCH_3	H	H	CH_3	n-C_3H_7	H	2	
11	4-OCH_3	H	H	H	n-C_3H_7	C_6H_5 C_2H_5	2	
12	4-OCH_3	H	H	H	n-C_3H_7	n-C_3H_7	2	
13	4-Cl	H	H	H	n-C_3H_7	H	2	
14	3-Cl	4-Cl	H	H	n-C_3H_7	H	2	
15	H	H	H	H	n-C_3H_7	H	2	>260 (Fumarate)
16	4-OH	H	H	H	CH_3	CH_3	2	259-260 Dihydro-bromide)
17	4-CF_3	H	H	H	n-C_3H_7	H	2	

No.	R_1	R_2	R_3	R_4	R_5	R_6	n	Mp.[°C]
18	4-OCH_3	H	H	H	CH_3	CH_3	2	> 260 (Mono-hydro-chloride)
19	4-OCH_3	H	H	H	H	H	2	115-117 (Base)
20	4-OCH_3	3-OCH_3	H	H	n-C_3H_7	H	2	
21	4-C_2H_5	H	H	C_2H_5	CH_2=CH-CH_2	CH_2=CH-CH_2	2	
22	3-Cl	5-Cl	4-NH_2	H	n-C_3H_7	H	2	
23	4-CF_3	H	H	H	CH_3	C_2H_5	2	
24	2-F	4-OCH_3	H	H	i-C_3H_7	H	2	
25	4-OH	2-CH_3	H	H	n-C_4H_9	H	1	
26	4-OCH_3	H	H	H	n-C_3H_7	H	3	93-94 Dihydro-chloride
27	4-Br	H	H	CH_3	t-C_4H_9	H	2	
28	3-OH	H	H	H	i-C_3H_7	H	3	
29	4-OCH_3	H	H	H	n-C_3H_7	n-C_3H_7	3	
30	4-OC_2H_5	H	H	H	n-C_4H_9	H	2	
31	4-C_2H_5	H	H	H	n-C_4H_9	H	2	
32	4-C_2H_5	H	H	H	i-C_4H_9	H	3	

No.	R_1	R_2	R_3	R_4	R_5	R_6	n	Mp.[°C]
33	3-OC_2H_5	4-OC_2H_5	H	H	n-C_4H_9	H	3	
34	3-OH	5-OH	H	H	C_2H_5	CH_3	2	
35	4-OCH_3	H	H	H	n-C_4H_9	n-C_4H_9	2	
36	n-OCH_3	H	H	H	n-C_3H_7	H	1	167-168 Difumarate
37	3-OCH_3	4-OCH_3	H	H	C_2H_5	C_2H_5	3	

The claims defining the invention are as follows:

1. Tetrahydro-benzothiazole compounds of the formula



(I)

in which

n represents an integer 1, 2 or 3;

R_1 denotes an H, F, Cl or Br atom or a CH_3, C_2H_5, OCH_3, OC_2H_5, OH or CF_3 group;

R_2 denotes an H or Cl atom or a CH_3, OCH_3, OC_2H_5 or OH group;

R_3 denotes an H atom or an NH_2 group;

R_4 denotes an H atom or a CH_3 or C_2H_5 group; and

R_5 and R_6, which may be the same or different, denote an H atom or C_{1-4} alkyl, phenyl-substituted C_{1-3}-alkyl, allyl or propargyl group;

and the acid-addition salts thereof.

2. Compounds as claimed in claim 1, in which

R_1 represents a hydrogen, chlorine or bromine atom or an OCH_3, OH, CH_3 or C_2H_5 group;

R_2 represents a hydrogen or chlorine atom or a methoxy group;

R_3 is as defined in claim 1;

R_4 represents a hydrogen atom or CH_3 group;

R_5 represents a hydrogen atom, or a C_{1-3}-alkyl, allyl or phenethyl group, and

R_6 represents a hydrogen atom or a C_{1-3}-alkyl or allyl group; and n is as defined in claim 1.

3. Compounds as claimed in claim 1 or claim 2, in which R_1 represents an OCH_3 or OH group; R_2, R_3 and R_4 represents a hydrogen atom; R_5 and R_6 represent a hydrogen atom or C_{1-3}-alkyl group, and n is as defined in claim 1.

4. Compounds as claimed in any preceding claim in which n denotes 2 or 3.

5. Compounds as claimed in any preceding claim in which n denotes 2.

6. 2-(4-Methoxyphenlpropionyl)amino-6-n-propylamino-4,5,6,7-tertahydrobenzothiazole, in the form of a racemate or in the form of an active enantiomer, in each case as a free base or in the form of an acid-addition salt.

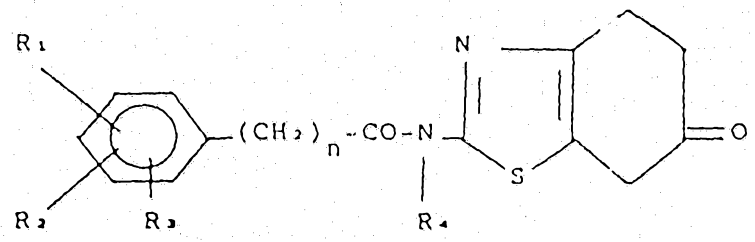
7. A pharmaceutical composition which comprises a compound as claimed in any of claims 1 to 6, in association with a pharmaceutically acceptable carrier, diluent auxiliary and/or excipient.

8. A method of treatment of Parkinson's disease or Parkinsonism or of treatment of schizophrenia and for prolactine inhibition, which comprises administering to an animal or human subject an effective amount of a compound as claimed in any one of claims 1 to 6 or an acid-addition salt thereof.

9. A process for the preparation of a compound of formula (I) as defined in claim 1

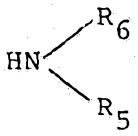
wherein

a) a compound of the formula (III)



(III)

is reacted with a compound of the formula



(IV)

under conditions of reductive amination,

or

b) for the preparation of a compound of formula I in which R_1 or R_2 comprise a phenolic OH group, a corresponding compound having an ether group is subjected to ether cleavage,

or

c) for the preparation of compounds of formula I in which neither radical R_5 or R_6 denotes hydrogen, a compound of the formula I where R_6 represents hydrogen is reacted with a compound

$$x - R'_6 \qquad (V)$$

serving to introduce the radical R'_6 (in which R'_6 is the same as R_6, apart

from hydrogen), and x denotes a group which can be cleaved on introduction of the group R'_6 into the amino group;

followed, if necessary and/or if desired by resolution of any racemates obtained into the enantiomers; and/or followed if desired by conversion of any base obtained into an acid-addition salt, or conversion of an acid-addition salt obtained into a free base or into a salt of a different acid.

10. A process as claimed in claim 9 substantially as hereinbefore described and with reference to any of the Examples.

~~11. Each and every novel process, compound, composition and method herein disclosed.~~

D A T E D this 22nd day of June, 1987.

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