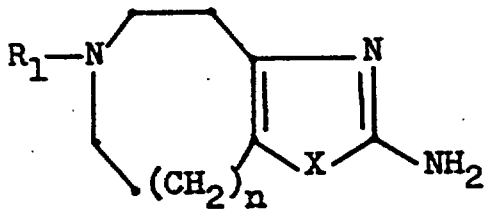
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Belgian Patents Nos. 684 515 and 771 330 describe, inter alia, thiazole and oxazole derivatives of general formula I



(I)

wherein

R_1 represents a hydrogen atom, an alkyl group with 1 to 4 carbon atoms optionally substituted by hydroxyl group, a benzyl group optionally substituted by a halogen atom or by a methyl or methoxy group, or an allyl group,

n represents the number 2 or also the number 1 if X represents a sulphur atom and

X represents an oxygen or sulphur atom, and the physiologically acceptable acid addition salts thereof with inorganic or organic acids.

It is known from Belgian Patents 684 415 and 771 330 that the compounds of general formula I and the physiologically acceptable acid addition salts thereof have valuable pharmacological properties. Thus, the compounds described in Belgian Patent 684 415 have, in particular, an analgesic, sedative, antitussive, antipyretic and antiphlogistic activity and the compounds described in Belgian Patent 771 330, depending on their substitution, have a hypotensive, sedative, antitussive and/or antiphlogistic activity. It is also apparent from the above-mentioned patent specifications

that the thiazole derivatives of general formula I wherein R_1 represents an alkyl group with 1 to 4 carbon atoms or an allyl group, n represents the number 2 and X represents a sulphur atom, have a hypotensive activity in particular and the oxazole derivatives of general formula I wherein R_1 represents a hydrogen atom, an alkyl group with 1 to 4 carbon atoms optionally substituted by a hydroxy group, or an allyl group, n represents the number 2 and X represents an oxygen atom, have antitussive properties in particular.

It is known from EP-A1-0 005 732 that the compounds of general formula I above wherein n represents the number 2 also have an anti-angina activity.

It is also known from US patent specification 4 400 378 that the compounds of general formula I also have an antiglaucoma activity.

According to the existing scientific publications, the compound 2-amino-6-allyl-5,6,7,8-tetrahydro-4H-thiazolo-[4,5-d]azepine dihydrochloride (B-HT 920) has been regarded as an agonist with a selective effect on presynaptic dopaminergic receptors (e.g. Anden et al., Acta Pharmacol. et Toxicol., 52, 51-56 (1983) and J. Neural Transmission 59, 129- 137 (1983)).

The invention is based on the surprising realisation that B-HT 920 also develops an agonistic activity on denervated or degenerate postsynaptic dopaminergic structures of the brain. This realisation marks out the compound particularly for the treatment of Parkinson's disease or Parkinsonism. These diseases are caused by the degeneration of dopaminergic neurons in the brain. The chemical messenger dopamine is therefore not released in sufficient quantities during neuron activity, resulting in the appearance of the Parkinson's

symptoms.

Nilsson & Carlsson (TIPS Reviews, Elsevier Biomedical Press, August 1982, p 322 ff.) state that the most advantageous substances for treating Parkinsonism or Parkinson's disease are those which have a specific agonistic effect on the postsynaptic dopaminergic neurons. Goodale et al., Science 210, 1141-1143 (1980) also write: "...a compound which primarily activates the postsynaptic receptors would be indicated in diseases of reduced dopamine release, such as Parkinson's disease".

The object of the invention is therefore the use of 2-amino-6-allyl-5,6,7,8-tetrahydro-4H-thiazolo[4,5-d]-azepine or one of the acid addition salts thereof for preparing pharmaceutical compositions suitable for the treatment of Parkinson's disease or Parkinsonism.

For the treatment of Parkinson's disease or Parkinsonism, the compounds A and the suitable acid addition salts thereof may be incorporated in the usual galenic preparations for oral, parenteral, rectal or transdermal application.

The single dose for oral administration in man is normally between 2.5 µg and 350 µg, preferably between 100 µg and 250 µg; in the case of several administrations (e.g. 3 times a day) the daily doses may range from 15-900 µg, preferably from 30-750 µg. The parenteral and rectal doses may be of the same order of magnitude as the quantities of substance to be adminsitered by oral route.

German Patent application No. P 35 03 963.9 describes an investigation of the anti-Parkinson's effect of B-HT 920. The investigation was carried out on rats.

The following methods of investigation were used.

(A) Spontaneous motor activity in the "naive" rat

Two aspects of motor function were recorded with a known "Opto-Varimex 3":

a) "ambulatory" movements in the first 5 minutes after s.c. injection of B-HT 920; this phase of locomotor function corresponds to the so-called "exploratory activity" of rats in a new environment;

b) "non-ambulatory" movements which are made up essentially of stereotypical movements, which began to be recorded 45 minutes after the animals had been put into the recording cage (and 55 minutes after s.c. injection).

Test results

Exploratory activity and stereotypical movements

The following doses of B-HT 920 were tested: 0.02, 0.2, 2.0 mg/kg s.c.. As a comparison apomorphine was tested in a dosage of 0.1 mg/kg s.c.

The following Table contains the values found:

Table 1

Dose mg/kg	Contacts broken (exploratory activity/5 min.)	Stereotypical movements Movements/15 min.
B-HT 920		
0 (control)	680	370
0.02	380	n.t.
0.2	150	370
2.0	130	310
4.0	n.t.	340
apomorphine		
0.1	150	n.t.
4.0	n.t.	650

n.t. = not tested

The inhibitory effect of B-HT 920 on the exploratory activity was therefore almost maximum at a dosage of 0.2 mg/kg and was comparable with a corresponding effect of 0.1 mg/kg of apomorphine (which also reduced the number of breakings of the contacts to 150 per 5 minutes).

With regard to stereotypical movements, B-HT 920 did not lead to an increase in the number of stereo-typical movements at any of the doses tested.

By contrast with B-HT 920, 4.0 mg/kg of apomorphine led to an increase in the number of stereotypical movements to a level of 650.

(B) Ipsilateral rotation in the ibotenic acid model in the rat

By analogy with the correspond kainic acid model according to Schwarcz et al [Brain Res. 170 (1979)

485-495]. This model is based on the fact that unilateral intra-striatal (stereotactical) injection of the neurotoxin ibotenic acid destroys the striatum cells on which there are also post-synaptic dopamine (DA) receptors [cf. Schwarcz et al., Exper. Brain Res. 37 (1979) 199-216], so that post-synaptic DA agonists can only act on the corresponding DA receptors on the intact side and therefore cause movements of rotation of the animal to the side of the damaged striatum.

Test results

The following doses of B-HT 920 were tested: 0.2, 0.5, 1.0 and 2.0 mg/kg s.c.. As a comparison, apomorphine was tested in a dosage of 0.1 mg/kg s.c. The following Table contains the values found:

TABLE 2

	Ipsilateral rotations/duration of activity up to 3 hours (apomorphine) up to 6 hours (B-HT 920)				
Dosage mg/kg / Active substance	0.2	0.5	1.0	2.0	10.0
B-HT 920	37	54	102	96	-
apomorphine	-	265	436	-	880

A comparison between apomorphine and B-HT 920 shows that B-HT 920 has only about one eighth of the post-synaptic DA-agonistic activity of apomorphine on the normally sensitive DA receptor, i.e. it has only a weak activity in this respect.

(C) Contralateral rotation on the 6-OHDA model - according to Ungestedt (Acta physiol scand. suppl 367 (1971) 69 ff; Europ. J. Pharmacol. 98 (1984) 165-176).

This model is based on the fact that stereotactical unilateral injection of the neurotoxin 6-OHDA destroys the nigrostriatal DA path on one side so that the post-synaptic DA receptors in the ipsilateral striatum are robbed of their DA innervation, i.e. they are denervated, and consequently have a (denervation) hypersensitivity. In this model, DA-agonists with a post-synaptic activity cause rotational movements to the contralateral side even at fairly low doses by a preferential activity on the hypersensitive DA receptors.

Test results

The following doses of B-HT 920 were tested: 0.02, 0.05, 0.5, 1.0 mg/kg. As a comparison, apomorphine was tested in a dosage of 0.05 mg/kg s.c. The following Table contains the values found:

	Contralateral rotations up to 6 hours	
Dosage mg/kg	B-HT 920	apomorphine
0.02	168	-
0.05	582	557
0.5	1282	-
1.0	1443	-

Compared with B-HT 920, 0.05 mg/kg of apomorphine resulted in 557 contralateral rotations per period of activity. It can therefore be concluded that, by contrast with its weak effect on normal DA receptors, B-HT 920 has an exceptionally strong activity on denervated receptors.

The discovery of the neurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) 18 months ago [Langston et al., Science 219, 979 (1983)] has provided a further animal model for Parkinson's disease.

The irreversible neurological syndrome triggered in monkeys and humans by MPTP largely resembles idiopathic Parkinson's disease in its clinical, pathological, biochemical and pharmacological features [Markey et al., Nature 311, 464 (1984)]. The reason for this strong similarity is the fact that MPTP selectively destroys the small group of dopaminergic nerve cells in the substantia nigra of the brain which are also destroyed by degenerative processes in naturally occurring Parkinson's disease. There is thus even some discussion to the effect that idiopathic Parkinson's disease might be caused by MPTP or a similar chemical compound formed in the organism [Snyder, S.H., Nature 311, 514 (1984)]. Possibly as a result of the specific metabolism of MPTP, the clinical features of the MPTP Parkinsonism syndrome have hitherto only been detected in monkeys as well as man.

The MPTP model produced in Rhesus monkeys is therefore exceptionally suitable for testing the effect of anti-Parkinson's drugs. Seven Rhesus monkeys were given MPTP for three days at a daily dosage of 1 x 0.15 mg/kg by intramuscular route, then there was an interval of 3 days, then they were given the drug again for a further 3 days in a dosage of 1 x 0.30 - 0.40 mg/kg per day and showed the following symptoms: The animals were akinetic and incapable of taking water and food. They showed a typically bent posture; occasionally, cataleptic states occurred. The extremities showed rigor which was interspersed with clonic spasms during passive movement. Voluntary movements of the hind-quarters and extremities could not generally be

initiated even by extreme and painful stimulation.

After the intramuscular administration of B-HT 920 (50-100 µg/kg) the first voluntary movements occurred at a time interval of 5 to 10 minutes, followed in the next 10 to 30 minutes by a gradual, extensive normalisation of motor function. The animals were capable of taking food. They maintained their normal posture within their cages and also behaved normally in terms of vigilance and species-specific behaviour. The residual symptoms recorded were an occasional, transient, slight resting tremor and a reduction in brute strength. There was no sedation. The blood supply to the skin appeared to be increased compared with the state before the B-HT 920 was administered.

The effect of B-HT 920 diminished after about 3 hours and the animals reverted to the Parkinson's symptoms described above; fresh administration of B-HT 920 again resulted in an improvement or substantial removal of the clinical pathological symptoms. The advantageous effect of B-HT 920 was thus reproduced several times in each single animal.

No side effects were discovered at the dosages used.

The use of the compound and the acid addition salts thereof has the advantage over the hitherto conventional DA agonists that this substance will only act on the denervated post-synaptic DA receptors in the brain, so that in Parkinson patients the pharmacological (motor) effect of B-HT 920 would be restricted primarily to those DA systems of the brain which are affected by the disease. In other words:

The compound and the acid addition salts thereof have a particularly powerful effect in <u>severe Parkinson cases</u>

(high degree of denervation of the striatum DA receptors).

Furthermore, the compound and the physiologically acceptable acid addition salts thereof are well tolerated; for example, the oral LD_{50} in the mouse is 455 mg/kg.

Example I

Tablet core

Composition:

1 Tablet core contains:

B-HT 920	50 µg
Lactose	38.45 mg
Corn starch	10.00 mg
Gelatine	1.00 mg
Magnesium stearate	0.50 mg
	50.00 mg

Method of preparation:

A mixture of the active substance with lactose and corn starch is granulated with a 10% aqueous gelatine solution through a 1 mm screen, dried at 40°C and passed through the same screen again. The granulate thus obtained is mixed with magnesium stearate and compressed to form tablet cores. The operation must be carried out in a darkened room.

Weight of core:	50 mg
Die:	5 mm, convex

The tablet cores thus obtained are coated in known manner with a coating consisting essentially of sugar and talc. The finnished coated tablets are polished with bees wax.

Weight of coated tablet:	100 mg

Example II

Suppositories

1 Suppository contains:	
B-HT 920	100.0 µg
Suppository mass (e.g. Witepsol W 45)	1690.0 mg

Method of preparation:

The finely powdered substance is stirred into the molten suppository mass, which has been cooled to 40°C, with an immersion homogeniser. At 35°C the mass is poured into slightly chilled moulds.

Example III

Ampoules containing 200 µg of B-HT 920

1 Ampoule contains:		
B-HT 920		200 µg
Citric acid		7 mg
sec. sodium phosphate. 2 H_2O		3 mg
sodium pyrosulfite		1 mg
Distilled water	ad.	1 ml

Method of preparation:

The buffer substances, active substance and sodium pyrosulfite are dissolved successively in decocted water which has been cooled under a current of CO_2. The solution is made up to the specified volume with decocted water and filtered free from pyrogens.

Packaging:	in brown ampoules under protective gas
Sterilisation:	20 minutes at 120°C.

The preparation and packaging of the ampoule solution must be carried out in a darkened room.

Example IV

Coated tablets containing 1 mg of B-HT 920

1 tablet core contains:

B-HT 920	100 µg
Lactose	36.0 mg
Corn starch	12.4 mg
Gelatine	1.0 mg
Magnesium stearate	0.5 mg
	50.0 mg

Method of preparation:

Analogously to Example I.

Weight of core:	50 mg
Die:	5 mm, convex
Weight of coated tablet:	100 mg

Example V

Coated tablets containing 0.2 mg of B-HT 920

1 tablet core contains:

B-HT 920	0.2 mg
Digoxin	0.25mg
Lactose	66.55mg
Potato starch	25.0 mg
Polyvinyl pyrrolidone	2.0 mg
Magnesium stearate	1.0 mg
	120.0 mg

Method of preparation:

A thorough mixture of the active substances with lactose and potato starch is granulated with a 10% solution of the polyvinyl pyrrolidone in ethanol through a 1.5 mm screen, then dried at 40°C and passed through a 1.0 mm screen. The granulate thus obtained is mixed with magnesium stearate and compressed to form tablet cores.

Weight of core:	120 mg
Punch:	7 mm, convex

The tablet cores thus produced are coated in known manner with a coating consisting essentially of sugar and talc. The finished coated tablets are polished with beeswax.

Weight of coated tablet:	200 mg.

Example VI

Gelatine capsules containing 300 µg of B-HT 920

1 Capsule contains:

B-HT 920	0.3 mg
Codeine phosphate	10.0 mg
tartaric acid	3.0 mg
Corn starch	85.7 mg
	100.0 mg

Method of preparation:

The substances are intensively mixed and packed into opaque capsules of suitable size.

Capsule content:	100 mg.



Claim

Use of 2-amino-6-allyl-5,6,7,8-tetrahydro-4H-thiazolo[4,5-d]azepine (B-HT 920) or of one of the acid addition salts thereof for preparing a pharmaceutical compositions suitable for the treatment of Parkinson's disease or Parkinsonism.