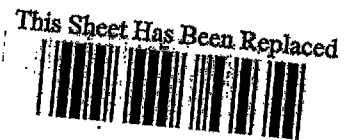


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Agent with an antidepressant activity



The present invention relates to an agent with an antidepressant activity containing 2-amino-4,5,6,7-tetrahydro-6-propylamino-benzothiazole or the (+) or (-) enantiomer thereof, the pharmacologically acceptable acid addition salts thereof and a conventional antidepressant. Of particular interest is the combination of pramipexole with sertraline.

Prior art

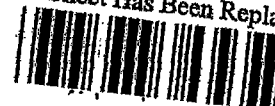
Pramipexole - (-)-2-amino-6-n-propylamino-4,5,6,7-tetrahydrobenzo-thiazole- is a dopamine-D₃/D₂ agonist, the synthesis of which is described in European Patent 186 087 and U.S. Patent 4,886,812. Pramipexole is known primarily for treating schizophrenia and particularly for the treatment of Parkinson's disease. German Patent Application DE 38 43 227 discloses that pramipexole lowers the prolactin serum level, and it is also known from German Patent Application DE 39 33 738 to use pramipexole to lower high TSH levels. Its transdermal administration is disclosed in US Patent 5,112,842, and WO Patent Application PCT/EP93/03389 describes the use of pramipexole as an antidepressant.

Details of the preparation of the title compound can be found in EP-A 85 116 016, and reference is hereby made specifically to the literature cited therein.

Description of the invention

It has now been found that, surprisingly, pramipexole, the (+) or (-) enantiomer thereof or the pharmacologically acceptable acid addition salts thereof combined with another antidepressant has a significantly greater antidepressant activity than either of the two individual components taken alone. The fact that the combination of active substances takes effect immediately should be particularly emphasised.

The improvement in the effect of pramipexole by the simultaneous administration of another antidepressant was discovered in tests on rats which had been given



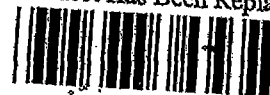
pramipexole and sertraline using the so-called "forced swimming test". Details of this test method can be found, for example, in Willner, *Psychopharmacology* 83, 1-16 (1984) or Borsini and Meli, *Psychopharmacology* 94, 147-160 (1988).

For the particularly preferred combination of pramipexole and sertraline (1S-cis)-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-N-methyl-1-naphthaleneamine, or the acid addition salts thereof, the test was carried out as follows. The animals were divided up into different groups and each group was given either a saline solution, a therapeutically effective amount of pramipexole, a therapeutic amount of sertraline or a combination of the two antidepressants in the same therapeutic amount as the animals that received only one of the two active substances.

The combination of 2-amino-4,5,6,7-tetrahydro-6-propylamino-benzothiazole, the (+) or (-) enantiomer thereof, the acceptable acid addition salts thereof and (1S-cis)-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-N-methyl-1-naphthaleneamine (sertraline) and the acid addition salts thereof is particularly preferred; the combination of pramipexole and sertraline in the form of their hydrochlorides is most particularly preferred.

Apart from sertraline, another antidepressant may be used in conjunction with pramipexole. This other antidepressant is preferably one selected from among the following:

alprazolam	mirtazapine	trimipramine
chlordiazepoxide	moclobemide	tryptophan
clomipramine	Nefazodone	venlafaxine or
chinpirol	Nortriptyline	viloxazine
dibenzepin	opipramol	
doxepin	paroxetine	
fluvoxamine	sertraline	
lofepramine	sulpiride	
maprotiline	tranylcypromine	
mianserin	trazolone	



The term combination for the purposes of the invention refers to an active substance combination of the two active substances in a formulation and also as a combination in the sense of individual formulations of the active substances administered at specified intervals from one another in a therapeutic treatment.

Orally administered pharmaceutical formulations for pramipexole are known from the prior art and are obtainable on the German or US market.

The individual active substances may also be packaged in kit form as a combined pack of the individual drugs, as well as separately.

The combination of pramipexole and another antidepressant may be formulated analogously to conventional galenic preparations, generally together with a pharmaceutical carrier. In other words an effective dose of the individual components and optionally a pharmaceutical carrier are formulated as plain or coated tablets, capsules, lozenges, powders, solutions, suspensions, emulsions, syrups, suppositories etc. For pramipexole the pharmaceutically effective dose per patient is between 0.01 and 10 mg, preferably between 0.08 and 5 mg.

The therapeutically effective doses of the second antidepressant in the combination are given in the Table which follows.

(25-100mg)	alprazolam,	(100-300mg)	nefazodone,
(5mg)	chlordiazepoxide,	(10-25mg)	nortriptyline,
(10-25mg)	clomipramine,	(50mg)	opipramol,
(1-5mg)	chinpirol,	(20mg)	paroxetin,
(10-250mg)	dibenzepin,	(50mg)	sertraline,
(5-50mg)	doxepin,	(50-200mg)	sulpiride,
(50-100mg)	fluvoxamine,	(10 mg)	tranylcypromine,
(35-75mg)	lofepramine,	(25-100mg)	trazodone,
(10-75mg)	maprotiline,	(25-250mg)	trimipramine,
(10-30mg)	mianserin,	(500mg-2.5g)	tryptophan,
(30mg)	mirtazapine,	(30-75mg)	venlafaxine or
(150-300 mg)	moclobemide,	(100mg)	viloxazine.

In the combination according to the invention the recommended dose may in individual cases be below the single dose previously recommended for the monopreparation.

Description of the tests

Pramipexole was used in doses of 0.1 and 0.3 mg/kg. In addition, tests were carried out using 0.05 mg/kg of pramipexole. Sertraline was used in doses of 5 and 10 mg/kg, as shown in the Tables. The tests were carried out on rats (male Wistar, 250-270 g) at RT while maintaining a natural night-day rhythm. Pramipexole (HCl) was dissolved in a physiological saline solution and sertraline (HCl) was dissolved in distilled water. Both substances were injected in a volume of 2 ml/kg.

Forced swimming test in rats

The entire immobility time was determined according to Porsolt et al. (1978) within a five-minute observation period. Pramipexole (0.05, 0.1 and 0.3 mg/kg) and sertraline (5 or 10 mg/kg) were given three times at intervals of 24.5 and 1 hour before the test.

In separate groups, pramipexole was again injected three times in the dose specified above together with sertraline (5 or 10 mg/kg) as described above. Each group consisted of 10 rats.

Results

Pramipexole – 0.1 mg/kg – does not change the immobility time in the forced swimming test, whereas higher doses (0.3 mg) bring about a significant reduction in the immobility time.

A dosage of 5 mg/kg of sertraline on its own does not reduce the immobility time either. However, the combined administration of 5 mg/kg of sertraline and 0.1 mg/kg

of pramipexole noticeably reduces the immobility time. This effect is considerably more marked when sertraline is given in higher doses.

Sertraline on its own in a dosage of 10 mg/kg was inactive in the forced swimming test, but given in combination with pramipexole (0.1, 0.3 mg/kg). This effect is intensified at higher doses of pramipexole. Pramipexole in a dosage of 0.05 mg/kg has no influence on the immobility time, but in combination with sertraline there is a reduction in the immobility time.

These results demonstrate the unexpected synergistic effect of pramipexole in conjunction with sertraline as antidepressant.

Table 1: Effect of pramipexole (0.1 and 0.3 mg/kg) on its own or combined with sertraline (5 mg/kg) on the immobility time in the forced swimming test in rats.

Compounds (mg/kg)	immobility time(s)	
	mean $\pm$ SEM	P
1. vehicle	239.9 $\pm$ 3.1	-
2. sertraline 5	257.0 $\pm$ 7.0	ns vs 1
3. pramipexole 0.1	223.4 $\pm$ 6.2	ns vs 1
4. pramipexole 0.3	171.5 $\pm$ 9.2	<0.001 vs 1
5. sertraline 5 + pramipexole 0.1	96.1 $\pm$ 10.3	<0.001 vs 3
6. sertraline 5 + pramipexole 0.3	18.1 $\pm$ 3.5	<0.001 vs 4

Pramipexole (0.1 or 0.3 mg/kg s.c.) and sertraline (5 mg/kg i.p.) are administered 3 times (24 hours, 5 hours and 1 hour) before the test.

Table 2: Effect of pramipexole (0.1 and 0.3 mg/kg) on its own or combined with sertraline (10 mg/kg) on the immobility time in the forced swimming test in rats.

Compounds (mg/kg)	immobility time(s)	
	mean $\pm$ SEM	P
1. vehicle	237.9 $\pm$ 2.7	-
2. sertraline 10	223.6 $\pm$ 9.9	ns vs 1
3. pramipexole 0.1	212.5 $\pm$ 6.9	ns vs 1
4. pramipexole 0.3	142.9 $\pm$ 7.9	<0.001 vs 1
5. sertraline 10 + pramipexole 0.1	133.3 $\pm$ 6.9	<0.001 vs 3
6. sertraline 10 + pramipexole 0.3	11.8 $\pm$ 2.3	<0.001 vs 4

Pramipexole (0.1 or 0.3 mg/kg s.c.) and sertraline (10 mg/kg i.p.) are administered 3 times (24 hours, 5 hours and 1 hour) before the test.

Table 3: Effect of pramipexole (0.05 mg/kg) on its own or combined with sertraline (5 and 10 mg/kg) on the immobility time in the forced swimming test in rats.

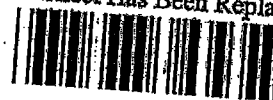
Compounds (mg/kg)	immobility time(s)	
	mean $\pm$ SEM	P
1. vehicle	235.3 $\pm$ 4.8	-
2. pramipexole 0.05	245.5 $\pm$ 7.8	ns vs 1
3. sertraline 5	247.5 $\pm$ 3.0	ns vs 1
4. sertraline 10	223.7 $\pm$ 2.8	ns vs 1
5. sertraline 5 + pramipexole 0.05	187.7 $\pm$ 11.2	<0.001 vs 2
6. sertraline 10 + pramipexole 0.05	163.9 $\pm$ 10.0	<0.001 vs 2

Pramipexole (0.05 mg/kg s.c.) and sertraline (5 and 10 mg/kg i.p.) are administered 3 times (24 hours, 5 hours and 1 hour) before the test.



Patent Claims

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1. Agent for treating depression, containing 2-amino-4,5,6,7-tetrahydro-6-propylamino-benzothizole, one of the enantiomers or acid addition salts thereof in conjunction with a conventional antidepressant selected from among

alprazolam	mirtazapine	trimipramine
chlordiazepoxide	moclobemide	tryptophan
clomipramine	Nefazodone	venlafaxine or
chinpirol	Nortriptyline	viloxazine
dibenzepin	opipramol	
doxepin	paroxetine	
fluvoxamine	sertraline	
lofepramine	sulpiride	
maprotiline	tranylcypromine	
mianserin	trazolone	

or one of the pharmacologically acceptable salts thereof.

2. Agent according to claim 1, characterised in that it contains the (+)-enantiomer of 2-amino-4,5,6,7-tetrahydro-6-propylamino-benzothizole or one of the acid addition salts thereof.
3. Agent according to claim 1, characterised in that it contains the (-)-enantiomer of 2-amino-4,5,6,7-tetrahydro-6-propylamino-benzothizole or one of the pharmacologically acceptable acid addition salts thereof.
4. Agent according to one of claims 1 to 3, characterised in that it contains 2-amino-4,5,6,7-tetrahydro-6-propylamino-benzothizole-dihydrochloride,



particularly 2-amino-4,5,6,7-tetrahydro-6-propylamino-benzothizole-dihydrochloride monohydrate.

5. Agent according to claim 1, characterised in that the formulation contains 0.05 – 10 mg of 2-amino-4,5,6,7-tetrahydro-6-propylamino-benzothizole, one of the enantiomers or one of the acid addition salts thereof, pramipexole or pramipexole dihydrochloride monohydrate.
6. Pharmaceutical formulation according to claim 1, characterised in that the formulation contains 0.088 – 1.5 mg of 2-amino-4,5,6,7-tetrahydro-6-propylamino-benzothizole, one of the enantiomers or one of the acid addition salts thereof, pramipexole or pramipexole-dihydrochloride-monohydrate.
7. Agent containing 2-amino-4,5,6,7-tetrahydro-6-propylamino-benzothizole, one of the enantiomers or one of the acid addition salts thereof, pramipexole or pramipexole-dihydrochloride-monohydrate and sertraline or a pharmaceutically acceptable acid addition salt thereof.
8. Agent containing pramipexole or pramipexole dihydrochloride and sertraline or a pharmacologically acceptable acid addition salt thereof.
9. Agent according to claim 8, characterised in that it contains between 0.088 and 1.1 mg of pramipexole or between 0.125 and 1.5 mg of pramipexole dihydrochloride monohydrate monohydrate.
10. Agent according to one of claims 8 to 9, characterised in that it contains between 25 and 200mg of sertraline.
11. Agent according to claim 10, characterised in that it contains 50 mg of sertraline.
12. Use of an agent according to one of the preceding claims for treating depression or depressive states.

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13. Use of an agent according to one of the preceding claims for preparing a pharmaceutical composition for treating depression.
14. Method of treating depression in patients suffering from such a complaint, characterised in that a combination of active substances according to one of the preceding claims is administered.
15. Method according to claim 14, characterised in that the active substances are taken as individual compounds one after the other over time.

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