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REPLACED SHEETS SG
☑ Description : paged ...1... to paged ..14...
☑ Claim(s) : paged ..15... to paged ....
☐ Drawing(s) : paged ..... to paged .....
☐ Abstract : paged ..... to paged .....

19.3.1990
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ATYPICAL NEUROLEPTIC

FIELD OF THE INVENTION

The present invention relates to the use of a certain 5-substituted 1-arylindole derivative or a salt thereof for the manufacturing of a pharmaceutical preparation selectively blocking the dopamine neurones in the ventral tegmental area of the brain.

BACKGROUND OF THE INVENTION

Damping of dopamine (DA) overactivity by the use of DA-receptor blocking drugs is today the most important principle in the treatment of schizophrenia. "Classical neuroleptics" such as haloperidol, cis(Z)-flupentixol or chlorpromazine induce antipsychotic effect via DA-receptor blockade. Pharmacologically, such compounds antagonize stereotypies induced by dopaminergic compounds (i.e. methylphenidate, apomorphine, amphetamine) in mice or rats. Unfortunately, the incidence of severe extrapyramidal side effects (EPS) (dystonia, akathisia and parkinsonism) is very frequent in long term treatment with these neuroleptics and causes great concern among clinicians. The EPS are difficult to treat, and unsuccessful treatment often leads to poor medication compliance. Some of these neurological side effects, which generally involve involuntary movement disorders, have been correlated to the propensity of the drugs to induce catalepsy in rats (Arnt. et al., Neuropharmacology 20, 1331-1334 (1981)).

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A class of compounds, which does not produce EPS and which is effective in the treatment of schizophrenic disorders, is termed "atypical neuroleptics". Clozapine is the prototype of such drugs. Clozapine is an effective antipsychotic in man but, due to severe incidences of agranulocytosis it is rarely used clinically. Pharmacologically clozapine induces no catalepsy in rats, neither does it inhibit stereotypies induced by dopaminergic agonists in rodents. Clozapine blocks central serotonergic and noradrenergic receptors in animal studies.

In recent years several reports have suggested that inhibition of the spontaneous activity of DA neurones in ventral tegmental area (VTA) in the rat brain upon repeated treatment with a neuroleptic is indicative of the antipsychotic potential of the compound, whereas inhibition of the activity in substantia nigra pars compacta (SNC) should account for the development of EPS (Bunney and Grace, Life Science 25, 1715-1725 (1978), White and Wang, Science 221, 1054-1057 (1983), Chiodo and Bunney, J.Neuroscience 5, 2539-2544 (1985), Skarsfeldt, Life Science 42, 1037-1044 (1988)). "Classical neuroleptics" are active in both areas in the same dose range while "atypical neuroleptics" mainly inactivate DA-neurons in the VTA area. Clozapine has been shown to be active only in the VTA area.

U.S. Patent No. 4,710,500 , corresponding to European Patent No. 0200322, discloses a class of optionally 5-substituted 1-aryl-3-piperidinyl-, 1-aryl-3-1,2,3,6-tetrahydropyridinyl or 1-aryl-3-piperazinyl-indole derivatives having potent dopamine antagonist activity in vivo and in vitro, as tested in pharmacological tests. The tests used were methylphenidate antagonism, catalepsy and ^{3}H-spiroperidol binding tests. Accordingly, the compounds of U.S. Patent No. 4,710,500 have been shown having "Classically neuroleptic activity".

SUMMARY OF THE INVENTION

Surprisingly, it has now been found that the compound 5-chloro-1-(4-fluoro-phenyl)-3-(1-(2-(2-imidazolidinon-1-yl)ethyl)-4-piperidyl)-1H-indole, (Lu 23-174)

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known from said U.S.Patent, as well as salts thereof, selectively blocks the DA-neurones in VTA areas in rats. The selectivity is over a wide range of dose, and only at very high dose levels the active DA-neurones is also blocked in SNC areas (Table 1). This effect is outstanding and unique for this compound compared to the effects of other phenylindoles disclosed in U.S.Patent No. 4,710,500. Close analogues, such as 1-(4-fluorophenyl)-3-(4-(3-hydroxypropyl)-1-piperazino)-5-trifluoromethyl-1H-indole (Lu 24-143), inhibit the activity equipotently in both SNC and VTA areas or are inactive such as 1-(4-fluorophenyl)-3-(1-(2-(2-imidazolidinon-1-yl)ethyl)-4-piperidyl)-1H-indole (Lu 23-086) (Table 1).

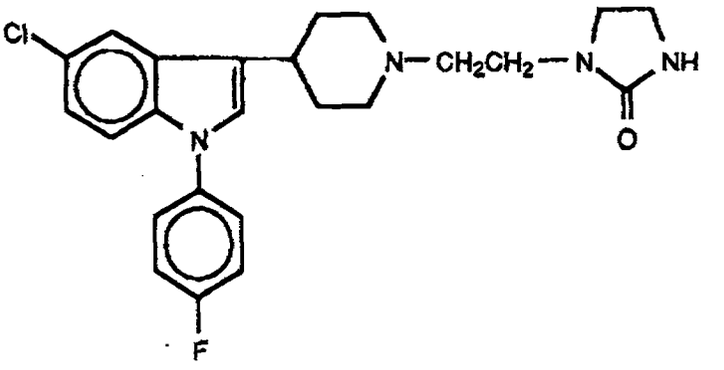
As reported for clozapine, the 5-chloro-1-(4-fluorophenyl)-3-(1-(2-(2-imidazolidinon-1-yl)ethyl)-4-piperidyl)-1H-indole, does not block dopaminergic stereotypies such as methylphenidate-induced gnawing in mice or stereotyped movements of head and forelegs in rats provoked by the administration of amphetamine (Table 2). The compound is non-cataleptic even at very high doses. (Table 2)

According to the classical tests for neuroleptic activity (i.e. catalepsy and blocking of dopaminergic stereotypies) as provided in U.S.Patent No. 4,710,500, the compound of the present invention appears relatively inactive. However, it has now been proven to have unique "atypically neuroleptic" profile and has been demonstrated to be a very promising drug for the treatment of schizophrenia and related psychic disorders.

Centrally acting serotonin 5-HT_2 antagonists are able to block the characteristic rapid shake (twitch) of the head in rats induced by administration of the 5-HT_2 agonist quipazine. 5-chloro-1-(4-fluorophenyl)-3-(1-(2-(2-imidazolidinon-1-yl)ethyl)-4-piperidyl)-1H-indole has a very potent and long-acting inhibitory activity against such quipazine-induced head twitches (Table 2). The potent central 5-HT_2 antagonistic effect may suggest that the compound additionally shows effectiveness on negative symptoms in schizophrenic patients, and improvement of the quality of sleep. (Janssen, P.A.J., Pharmacopsychiat. 21, p.33-37, 1988).

Accordingly, the present invention provides the use of 5-chloro-1-(4-fluorophenyl)-3-(1-(2-(2-imidazolidinon-1-yl)ethyl)-4-piperidyl)-1H-indole,

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or a pharmaceutically acceptable acid addition salt thereof, for the manufacturing of a pharmaceutical composition selectively blocking the dopamine neurones in the ventral tegmental area of the brain, substantially without inhibiting the activity of dopamine neurones in substantia nigra pars compacta.

Additionally, the composition of the invention may alleviate the negative symptoms of schizophrenia and/or improve the quality of sleep in a schizophrenic patient.

An effective daily dose of the compound of the invention, or a pharmaceutically acceptable salt thereof, is from 0.0001 to 1.0 mg/kg . The daily dose is administered in one or more subdoses and, accordingly, a unit dose of the compound or of the salt thereof is from 0.001 to 7.0 mg.

The term "atypical neuroleptic" as used through this specification is intended to mean a substance selectively blocking the dopamine neurones in the ventral tegmental area or in the limbic area of the brain, without inhibiting the active dopamine neurones in substantia nigra pars compacta (SNC).
The term "blocking the dopamine neurones" is through this specification with claims used in the meaning of reducing or decreasing the number of spontanously active dopamine neurones, or substantially inactivating all such neurones.

The compound of the invention, 5-chloro-1-(4-fluorophenyl)-3-(1-(2-(2-imidazolidinon-1-yl)ethyl-4-piperidyl)-1H-indole, is also designated **sertindole** (a recommended INN name), and in the following said INN name will be used for short.

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Sertindole may be synthesized as disclosed in U.S. Patent No. 4,710,500. The pharmaceutically acceptable acid addition salts of the compound may be formed with non-toxic organic or inorganic acids in an aqueous miscible solvent, such as acetone or ethanol, with isolation of the salt by concentration and cooling or an excess of the acid in aqueous immiscible solvent, such as ethyl ether or chloroform, with the desired salt separating directly.

Exemplary of such organic salts are those with maleic, fumaric, benzoic, ascorbic, embonic, succinic, oxalic, bis methylene-salicylic, methanesulfonic, ethanedisulfonic, acetic, propionic, tartaric, salicylic, citric, glucomic, lactic, malic, mandelic, cinnamic, citraconic, aspartic, stearic, palmitic, itaconic, glycolic, p-amino-benzoic, glutamic, benzene sulfonic and theophylline acetic acids as well as the 8-halotheophyllines, for example 8-bromo-theophylline. - Exemplary of such inorganic salts are those with hydrochloric, hydrobromic, sulfuric, sulfamic, phosphoric and nitric acids. Of course, these salts may also be prepared by the classical method of double decomposition of appropriate salts, which is wellknown to the art.

Sertindole and the pharmaceutically acceptable acid addition salts thereof, may be administered both orally and parenterally, for example in the form of tablets, capsules, powders, syrups or solutions for injection.

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PHARMACOLOGICAL TEST METHODS

Sertindole and reference compounds were tested according to reliable and well-known pharmacological methods as follows:

1)

Inhibition of DA cell firing in VTA and SNC areas

This test model is used to examine the effects on spontaneously active DA neurones in ventral tegmental area (VTA) and substantia nigra pars compacta (SNC) upon repeated oral treatment. Inhibition of the number of active DA neurones in VTA indicates an antipsychotic effect of a compound, while inhibition of the number of active DA neurones in SNC accounts for the development of neurological side effects.
For further information see Skarsfeldt (1988) which information is incorporated herein by reference.

Rats weighing 250 g at the start of the experiment are used. After 21 days of oral treatment with different doses of test compound the rats are anaesthetized and mounted in a stereotaxic instrument. A hole (3 x 3 mm) is drilled in the skull. Recording of DA neurone activity is performed with a single barrel glass electrode. Eight electrode penetrations are made through VTA and SNC. Data from the experiments consist of neurone/counts which may be regarded as approximately Poisson distributed. The data are expressed as per cent inhibition of the activity in non-treated animals.
ED_{50} values were calculated by log-probit analysis.

Ref.:
Skarsfeldt, T.: Eur. J. Pharmacol. 145, 239-243 (1988).

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2)

Methylphenidate antagonism

The inhibiting effect of test substances on the methylphenidate-induced gnawing in mice is determined as described by Pedersen and Christensen (1972). The test substance is given s.c. in different doses while methylphenidate is given s.c. in the dose of 60 mg/kg 2 hours after injection of test substance. 3 x 2 mice (18 -25 grams) are used per dose of the test substance The results are given in fractions: 0/3, 1/3, 2/3 and 3/3, where 0, 1, 2 and 3 are the number of pairs which has not been gnawing on receipt of the test substance. ED_{50} values were calculated by log-probit analyses and are expressed as µmol /kg , s.c.

Ref: Pedersen, V. and Christensen, A.V.: Acta pharmacol. et toxicol. 31, 488-496, 1972.

3)

Amphetamine antagonism

The inhibiting effect of test substances on the amphetamine-induced stereotyped movements of head and forelegs in rats is determined as described by Møller Nielsen et al. (1973).

The test substance is given s.c. in different doses, while amphetamine is given s.c. in the dose of 10 mg/kg 2 hours after the injection of test substance. Five rats (230 - 270 g) are used for each dose of test substance. The results are stated in fractions: 0/3, 1/3, 2/3 and 3/3, where 0, 1, 2 and 3 are the number of rats which has not shown stereotypies on receipt of test substance. ED_{50} values were calculated by log-probit analyses and are expressed as µmol /kg , s.c.

Ref.: Møller Nielsen, I. et al.:Acta Pharmacol. et Toxicol. 33, 353-362, 1973.

4)

Catalepsy

This effect is used to evaluate the ability of a compound to induce extra-pyramidal side effects. Evaluation of catalepsy is made according to Arnt (1983).

Test compound is given s.c. in different doses. The rat (170 - 240 g) is placed on a vertical wire mesh (mesh diameter 12 mm). The rat is considered cataleptic if it remains immobile for more than 15 seconds. The maximum number of rats showing catalepsy within the first 6 hours is recorded for each dose group. The results are recorded in fractions, and an ED_{50} value is calculated by means of log-probit analysis.

Ref.: Arnt, J.: Eur. J. Pharmacol. 90, 47-55 (1983).

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5)

Quipazine antagonism

The test compound or saline is injected subcutaneously 2 hours or 24 hours before s.c. injection of quipazine hemimaleate (6.8 mg/kg). At least 3 dose groups, each consisting of at least 4 rats, are used. The rats are individually placed in observation cages (12 x 25 cm). The number of head twitches is counted 30-40 minutes after quipazine administration. Inhibition of head twitches is expressed in per cent of the number of head twitches in the control group.
ED_{50} values are calculated by log-probit analysis.

Ref.: Arnt, J. et al: Drug Development Research, 1989, 16, 59-70.

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Table 1

Inhibition of firing rate of DA neurones after repeated treatment (21 days).

Compound	VTA area ED_{50}(µmol/kg/day) (*po*)	SNC area ED_{50}(µmol/kg/day) (*po*)	SNC/VTA ratio
sertindole	0.015	1.6	107
Lu 24-143	0.048	0.033	0.7
Lu 23-086	>12	>12	
clozapine	56	>120	>2.2
haloperidol	0.043	0.033	0.8
cis(Z)-flupentixol	0.037	0.044	1.2

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Table 2

Effects of different neuroleptics on methylphenidate-induced gnawing (MePh. antg.) in mice, amphetamine-induced stereotypies (Amph. antg.) in rats, cataleptic effect in rats and inhibition of quipazine-induced head twitches in rats (2 and 24 hours after drug treatment). ED_{50} values were calculated by log-probit analyses and are expressed as µmol/kg, *sc*.

Compound	MePh. antg. ED_{50}(µmol/kg)(*sc*)	Amph.antg. ED_{50}(µmol/kg)(*sc*)	Catalepsy ED_{50}(µmol/kg)(*sc*)	Quipazine inhibition ED_{50}(µmol/kg)(*sc*)	
				2 hrs	24 hrs
sertindole	>180	>45	>91	0.04	0.03
Lu 24-143	0.08	0.02	0.07	0.005	0.22
Lu 23-086	>98	NT*	>98	0.04	0.08
clozapine	>120	>120	>120	1.1	>7.6
chlorpromazine	5.1	20 (*ip*)	19	0.37	NT
haloperidol	0.19	0.15	0.33	0.99	NT
cis(Z)-flupentixol	0.10	0.06	0.16	0.04	>4.9

*) NT : Not tested

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It appears from Table 1 that sertindole has a very high SNC/VTA ratio and thus is very selectively blocking the DA-neurones in the VTA area as compared to the most closely related compounds of U.S.Patent No. 4,710,500, 1-(4-fluorophenyl)-3-(4-(3-hydroxypropyl)-1-piperazino)-5-trifluoromethyl-1H-indole (Lu 24-143) and 1-(4-fluorophenyl)-3-(1-(2-(2-imidazolidinon-1-yl)ethyl-4-piperidyl)-1H-indole (Lu 23-086) and the classical neuroleptics haloperidol and cis(Z)-flupentixol. Furthermore it is seen that sertindole is far more selective and more potent than the reference compound clozapine.

From Table 2 it will appear that sertindole is relatively inactive in the classical neuroleptic tests and, therefore, is expected to be substantially without the EPS.

Additionally, sertindole is showing potent and long lasting quipazine inhibition and, accordingly, $5HT_2$ antagonist activity.

In vivo activity in rats.

The "atypical neuroleptic" profile of sertindole has also been established in an in vivo dopamine infusion model in rats (see B. Costall et al., Br.J.Pharmacol. 90. p.89 (1987) and B. Costall et al., Reviews in the Neurosciences 2 (1), 41-65 (1988) for a detailed description of this animal model).

Administration of sertindole in an amount of 0.0025 - 1.25 mg/kg/day (s.c.) significantly reduced the locomotor hyperactivity induced by bilaterally infused dopamine in the nucleus accumbens. No "rebound" hyperactivity was found after termination of the sertindole treatment. On the other hand, termination of treatment with classical neuroleptics such as fluphenazine results in a marked and persistent increase of locomotor activity.

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Typical examples of formulas for composition containing **sertindole** or an pharmaceutically acceptable acid addition salt thereof as an active ingredient, are as follows:

1) Tablets containing 0.5 milligrams of **sertindole** calculated as the free base:

Sertindole	0.5 mg
Lactose	18 mg
Potato starch	27 mg
Saccharose	58 mg
Sorbitol	3 mg
Talcum	5 mg
Gelatine	2 mg
Povidone	1 mg
Magnesium stearate	0.5 mg

2) Tablets containing 5.0 milligrams of **sertindole** calculated as the free base:

Sertindole	5.0 mg
Lactose	16 mg
Potato starch	45 mg
Saccharose	106 mg
Sorbitol	6 mg
Talcum	9 mg
Gelatine	4 mg
Povidone	3 mg
Magnesium stearate	0.6 mg

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3) Syrup containing per milliliter:

Sertindole	1.0 mg
Sorbitol	500 mg
Tragacanth	7 mg
Glycerol	50 mg
Methyl-paraben	1 mg
Propyl-paraben	0.1 mg
Ethanol	0.005 ml
Water	ad 1 ml

4) Solution for injection containing per milliliter:

Sertindole	2.0 mg
Acetic acid	17.9 mg
Sterile water	ad 1 ml

5) Solution for injection containing per milliliter:

Sertindole	1.0 mg
Sorbitol	42.9 mg
Acetic acid	0.63 mg
Sodium hydroxide	22 mg
Sterile water	ad 1 ml

Any other pharmaceutical tableting adjuvants may be used provided that they are compatible with the active ingredient, and additional compositions and dosage forms may be similar to those presently used for neuroleptics, such as clopenthixol, flupentixol or fluphenazine.

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Also combinations of **sertindole** as well as its non-toxic acid salts with other active ingredients, especially other neuroleptics, thymoleptics, tranquilizers, analgetics or the like, fall within the scope of the present invention.

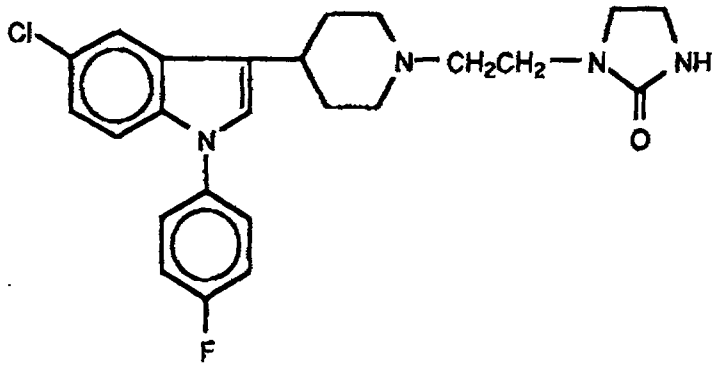
It is to be understood that the invention is not limited to the exact details of operation or exact compositions shown and described, as obvious modifications and equivalents will be apparent to one skilled in the art.

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CLAIMS

1. A use of 5-chloro-1-(4-fluorophenyl)-3-(1-(2-(2-imidazolidinon-1-yl)ethyl)-4-piperidyl)-1H-indole,



or a pharmaceutically acceptable acid addition salt thereof, for the manufacturing of a pharmaceutical composition selectively blocking dopamine neurones in the ventral tegmental area of the brain, substantially without inhibiting the activity of dopamine neurones in substantia nigra pars compacta.

2. A use according to Claim 1, characterized in that the pharmaceutical composition additionally alleviates the negative symptoms of schizophrenia.

3. A use according to Claim 1 or 2, characterized in that the pharmaceutical composition additionally improves the quality of sleep in a schizophrenic patient.

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