

100-6939/I UK

**PSYCHO-ACTIVE PHARMACEUTICAL COMPOSITIONS CONTAINING INDOLYL
DERIVATIVES**

This invention relates to new uses and modes of administration of 5HT₂ antagonists, and in particular the compound indol-3-yl-carboxylic acid endo-8-methyl-8-aza-bicyclo [3,2,1]oct-3-yl ester, (hereinafter the compound of the invention also known as ICS 205-930).

The compound may be used in any pharmaceutically acceptable form, including the free base and in acid addition and quaternary ammonium salt forms.

The compound of the invention is known for example from Belgian patent 897,117. The compound is described therein as being a 5HT₂ receptor antagonist or serotonin M receptor antagonist (serotonin M receptors have been reclassified as 5HT₂ receptors).

The compound is indicated for use as an anti-migraine agent, anti-arrhythmic, and for treatment of serotonin-induced gastro-intestinal disorders including emesis, e.g. induced by anti-cancer agents.

We have now discovered that the compound has interesting new uses, as described and claimed below and in our copending Application GB 9008068.0 (GB 2231264A).

In a first aspect the invention provides:

- a) Use of indol-3-yl-carboxylic acid endo-8-methyl-8-aza-bicyclo [3,2,1]oct-3-yl ester, in free base form or in pharmaceutically acceptable acid addition salt form or in pharmaceutically acceptable quaternary ammonium salt form, in the manufacture of a medicament suitable for the treatment of stress-related psychiatric disorders, or
- b) Use of indol-3-yl-carboxylic acid endo-8-methyl-8-aza-bicyclo [3,2,1]oct-3-yl ester, in free base form or in pharmaceutically acceptable acid addition salt form or in pharmaceutically acceptable quaternary ammonium salt form, in the manufacture of a medicament suitable for increasing vigilance.

The antagonistic action against 5-HT₂ receptors of the preferred compound ICS 205-930 (indol-3-yl carboxylic acid endo-8-methyl-8-aza-bicyclo[3,2,1]oct-3-yl ester) on the rabbit vagus, rabbit heart and guinea pig ileum has been described (P. Donatsch et al., Br.J. Pharmacol. 1984, 81, 348) and also its topical application to humans as the first 5-HT₂ antagonist.

In the Belgian patent No. 897,117 it was also stated that the compounds disclosed therein are indicated as anti-psychotics.

We have now found e.g. from ethological and endocrinological tests that the compound of the invention is useful for the treatment of stress-related psychiatric disorders, including stress-related-social phobias and social withdrawal, affective disorders, psychoses, especially maniac depressive disorders and also promotes approach-oriented ^{social} behaviour in behaviour perturbed by stress.

The compound of the invention also increases vigilance, e.g. in geriatrics.

Trials have been carried out on the effects of the compound of the invention on approach-oriented behaviour in mice. The compound increases approach-oriented behaviour in stress-situations normally inhibitory to social responses. Thus situations involving unfamiliar surroundings, contact with foreign aggressive opponents, competition for food, were created under reversed lighting conditions whereby observations were performed during the dark phase. Under these conditions, untreated rodents exhibit high levels of flight, particularly depressive ambivalence and escape behaviour, but low levels of social behaviour involving approach activity. Anxiolytics like diazepam reduce the ambivalent behaviour and can increase social behaviour. In food deprived mice under white light, certain anti-depressants, e.g. bupropion and imipramine, but also atypical anxiolytics, e.g. buspirone as well as the compound of the invention, increase approach-oriented social behaviours.

Intruder test

Study A

A foreign male mouse (intruder), placed for 6 minutes, into the cage of an isolated male is attacked and responds with defensive escape patterns collectively known as "flight". Flight and associated defensive activities override the intruder's tendency to approach the attacker so that much of the behaviour includes social forms of ambivalence.

Intruders receiving oral doses of benzodiazepines show less of these defensive activities and more approach-oriented behaviour (A.K.Dixon Triangle 1982, 21, 95-105; M. Krisak, Br.J.Pharmacol.1975, 55, 141-150), e.g. investigation, aggression and sexual activity.

The compound of the invention is administered 1 hour before the encounter per-orally at from about 0.1 to about 10 mg/kg. Groups of 8 mice pairs are used. The frequency and duration of social and non-social behaviour of the mice were recorded using ethological

techniques.

The compounds increase social oriented activity.

In this test the compound at a dose of 1 mg/kg increased the frequency (from ca. 60 to 80) and duration of social interaction (from ca. 90 to 120 seconds).

Study B

Study A was modified using a large cage (59 x 38.5 x 20 cm) which allowed greater freedom of movement so that elements of defense could be separated more clearly from the approach-oriented social activities. The compound of the invention is given i.p. at doses from about 0.01 to about 100 microgram/kg 45 minutes before the encounter.

Intruders received the drug. It was found that the compound of the invention clearly promoted the approach-oriented social activities. It also reduced escape behaviour, a special form of flight. In this test at a dose of 1 microgram/kg the compound promoted 8 elements of approach-oriented social activities by about 40 per cent. The compound also reduced escape behaviour.

Competitive feeding

Study C

In this tests 8 pairs of male OF-1 mice deprived of food for 6 hours are forced to compete over 6 minutes for a single food pellet. Because of the close proximity of the mice the tendency to eat is competitively offset by the tendency to interact socially. One partner receives a compound of the invention at an oral dose from about 0.01 to about 1 mg/kg 1 or 2 hour before the encounter. Frequencies and durations of social activities were recorded for both animals with the aid of a posture and timer machine (K.Hausamann, A.K.Dixon, Physiol. Behav. 1982, 28, 743-745).

In this test benzodiazepines increase eating behaviour more than social interactions. Antidepressants may increase such social activities. The compound of the invention increases approach-oriented social behaviour, more than eating.

The compound at a dose of 0.1 mg/kg p.o. given 2 hours before the encounter increased, relative to controls, the frequency (54 per cent) and duration (321 per cent) of social interactions. In contrast frequency of feeding increased by only 4 per cent and their duration 55 per cent.

Stretched Attend Postures (SAP) (No conflict)

Mice placed upon an unfamiliar elevated platform in a novel environment display characteristic stretched body postures called SAP's which signify ambivalence. Drugs which have putative anxiolytic reactions, e.g. benzodiazepines, barbiturates, and buspirone reduce the incidence of SAP's (H.P. Käsermann, Psychopharmacology 1986, 89, 31-37).

The compound of the invention administered p.o. at a dose of from about 0.1 to about 10 mg/kg. 2 hours before the test reduces the duration of SAP when placed on the platform for 2 minutes under conditions where no other mice are present.

The duration in the case of the compound at 0.1 mg/kg were similar to that observed with clobazam at the same dose and at higher doses the effect was less.

Corticosterone levels (Endocrinological profile)

Mice subjected to a novel environment, e.g. on transferring them from one room to another via a trolley, exhibit a rise in plasma corticosterone typical of stress-related disturbances which are reduced by benzodiazepines and barbiturates (Lahti R.A., Barsuhn C.,

Res.Comm.Chem.Path.Pharm. 11: 595-603; G.Le Fur et al., J.Pharm.exp. Ther. 211: 305-308), reduction is observed with the compound of the invention at from about 0.1 to 10 mg/kg p.o. The compound reduces such stress-induced corticosterone at about 1 to 10 mg/kg p.o. whilst lower doses from about 0.1 to about 0.3 mg/kg increase basal plasma levels of this hormone. This profile is analogous to that observed with diazepam.

Taken together, the results of these studies also show that compound of the invention promotes approach-oriented social behaviour in stressful situations. This suggests that the compounds of invention are of use in stress-related psychiatric disorders, e.g. where the treatment of social withdrawal, affective disorders, and other stress-related illnesses is desired.

The increases in corticosterone also suggests that compounds of invention increase vigilance, thus indicating a potential use for the compounds in disorders of vigilance, e.g. geriatric illnesses.

For these indications, the appropriate dosage will, of course, vary depending upon, for example, the host, the mode of administration and the nature and severity of the condition being treated. However, in general, satisfactory results are indicated to be obtained at daily dosages from about 0.001 mg/kg to about 50 mg/kg animal body weight. In humans, an indicated daily dosage is in the range from about 0.1 mg to about 50 mg of the compound of the invention conveniently administered, for example, in divided doses up to four times a day.

The compounds of the invention may be administered in similar manner to known standards, e.g. bupropion. The compound of the invention and bupropion have been found to have a pronounced effect on promoting social interaction under stress-related conditions. For example, the compound of the invention increased the mean frequency of social interactions in the competitive feeding experiment study c) by 54 per cent at 0.01 mg/kg compared to bupropion provoking an increase of 179 per cent at 2.5 mg/kg. It is indicated that the compound of the

invention will be useful in the treatment of stress-related psychiatric disorders at a daily oral dose of from 0.1 mg which could be increased up to 50 mg.

The compounds of the invention may be administered in free base form or, when they can be formed, in pharmaceutically acceptable acid addition salt form or in a quaternary ammonium salt form. Such salts may be prepared in conventional manner and are in general known. They exhibit the same order of activity as the free base form and pharmaceutical compositions comprise a compound of the invention in free base or pharmaceutically acceptable acid addition salt form or quaternary ammonium salt form in association with pharmaceutical carrier or diluent. Such compositions may be manufactured in conventional manner.

The compounds may be administered by any conventional route, in particular enterally, preferably orally, e.g. in the form of tablets or capsules or parenterally, e.g. in the form of injectable solutions or suspensions.

Suitable pharmaceutical carriers and diluents for oral administration include polyethylene glycol, polyvinylpyrrolidone, mannitol, lactose etc. granulating agents, and disintegrating agents such as starch and algenic acid, binding agents such as stearic and gelatine, lubricating agents such as magnesium stearate, stearic acid and talc. Suspensions may contain conserving agents like ethyl p-hydroxy-benzoate, suspending agents such as methyl-cellulose, tenside etc. For parenteral forms the compositions are preferably buffered, aqueous solutions (pH between 4 and 5).

For all these indications, the compound may be administered in the same manner as described in European Patent Publication No. 189002.

Toxicity and Tolerability:

Toxicity and Tolerability studies may be effected in conventional manner with the compound of the invention to determine the upper dosage.

Toxicity studies may be effected for example in the rat and the dog over for example 26 weeks.

For the compound of the invention over 26 weeks the no toxic effect level in the dog was 5-20 mg/kg/daily p.o. For the rat it was 16 to 45 mg/kg per day p.o. In healthy human volunteers single doses up to 150 mg were well tolerated without relevant side effects.

The following examples illustrate the invention.

EXAMPLE 1: Tablets for oral administration

Tablets concerning the constituents as specified below were produced in conventional manner and are used in the indications specified above.

Compound of the invention in form of hydrochloride	16.9 mg
(corresponding to 15 mg free base)	
Hydroxy-propyl-cellulose	1.2 mg
Corn Starch	12.0 mg
Lactose	92.8 mg
Silica	0.6 mg
Magnesium stearate	<u>1.5 mg</u>
Tablet weight	125.0 mg

EXAMPLE 2: Injection solution for i.v. administration

A composition for injection is made up in conventional manner and is used at a dose of 10 mg a day.

	A	B	C
Compound of the invention in form of hydrochloride	1.13 ¹	2.256 ²	11.282 ³
Acetic acid (99 to 100%)*	1.2	0.6	0.6
Sodium acetate 3. H ₂ O*	1.8	3.18	3.18
Sodium chloride	8	7.5	6.5
Water for injection to	1.0 ml		

¹ = 1 mg free base

² = 2 mg free base

³ = 10 mg free base

pH value 4.3; *Buffer used 1/30 molar

EXAMPLE 3: Capsules for oral administration

5 mg and 15 mg capsules (A and B respectively) containing the constituents as specified below were produced in conventional manner and are used in the indication specified above 2 - 4 times a day in the case of A and once a day in the case of B.

	A mg	B mg
Compound of the invention in form of hydrochloride	5.641	16.92
Lactose 200 mesh	84.929	79.29
Lactose 100 mesh	84.43	79.29
Corn starch	120.00	120.00
Silica	1.5	1.5
Magnesium stearate	<u>3.0</u>	<u>3.0</u>
	300 mg	300 mg

Capsules containing other weights can be formulated in conventional manner.

EXAMPLE 4: Nasal liquid Compositions

<u>Components</u>	<u>Quantity of components</u>
Indol-3-yl carboxylic acid-endo-8-methyl-8-aza-bicyclo[3,2,1]oct-3-yl ester. HCl	100 mg
benzalkonium chloride	0.1 mg
NaCl (0.9% aqueous solution)	0.6 ml
distilled water	0.4 ml

The solution obtained is filtered (e.g. through a 0.2 um filter) and filled into a nasal canister, or a gelatinous form (SPONGOSTAN) is soaked with the solution.

CLAIMS



1. Use of indol-3-yl-carboxylic acid endo-8-methyl-8-aza-bicyclo [3,2,1]oct-3-yl ester, in free base form or in pharmaceutically acceptable acid addition salt form or in pharmaceutically acceptable quaternary ammonium salt form, in the manufacture of a medicament suitable for the treatment of stress-related psychiatric disorders.
 2. Use according to claim 1 for the manufacture of a medicament suitable for treatment of impaired approach oriented behaviour in stressful situations.
 3. Use according to claim 1 for the manufacture of a medicament suitable for *promoting* approach oriented social behaviour in stressful situations.
 4. Use according to claim 1 for the manufacture of a medicament suitable for treatment of stress-induced anxiety.
 5. Use of indol-3-yl-carboxylic acid endo-8-methyl-8-aza-bicyclo [3,2,1]oct-3-yl ester in free base form or in pharmaceutically acceptable acid addition salt form or in pharmaceutically acceptable quaternary ammonium salt form, in the manufacture of a medicament suitable for increasing vigilance.
 6. Use according to any preceeding claim wherein the compound is in hydrochloride salt form.
-