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(54) Title: NOVEL USE OF 1-[4-(5-CYANOINDOL-3-YL)BUTYL]-4-(2-CARBAMOYL-BENZOFURAN-5-YL)-PIPERAZINE AND ITS PHYSIOLOGICALLY ACCEPTABLE SALTS

(57) Abstract: 1-[4-(5-cyanoindol-3-yl)butyl]-4-(2-carbamoyl-benzofuran-5-yl)-piperazine or a physiologically acceptable salt thereof is used for the manufacture of a medicament for the treatment of sub-type anxiety disorders chosen from the sub-types panic disorder with or without agoraphobia, agoraphobia, obsessive-compulsive spectrum disorders, social phobia, posttraumatic stress disorder, acute stress indication or generalized-anxiety disorder, bipolar disorders, mania, dementia, substance-related disorders, sexual dysfunctions, eating disorders, obesity, anorexia and fibromyalgia. A preferred salt is

Novel use of 1-[4-(5-cyanoindol-3-yl)butyl]-4-(2-carbamoyl-benzofuran-5-yl)-piperazine and its physiologically acceptable salts

The present invention relates to the use of 1-[4-(5-cyanoindol-3-yl)butyl]-4-(2-carbamoyl-benzofuran-5-yl)-piperazine or a physiologically acceptable salt thereof, for the manufacture of a medicament for the treatment of sub-type anxiety disorders.

1-[4-(5-cyanoindol-3-yl)butyl]-4-(2-carbamoyl-benzofuran-5-yl)-piperazine, physiologically acceptable salts thereof (US 5,532,241, column 7, lines 30 to 58) and a process (US 5,532,241, Example 4) by which it/they can be prepared are known from U.S. Patent US 5,532,241. The compound which is referred to herein is described in the patent as a combined selective serotonin (5-HT) reuptake inhibitor (SSRI) and 5-HT_{1A} receptor agonist. Therefore, the use of 1-[4-(5-cyanoindol-3-yl)butyl]-4-(2-carbamoyl-benzofuran-5-yl)-piperazine and its physiologically acceptable acid addition salts for the manufacture of a medicament for the treatment of depressive disorders, including the sub-type disorders major depressive disorder and dysthymic disorder, for the treatment of anxiety disorders, for the treatment of psychiatric disorders like psychoses, schizophrenia or schizoaffective disorder, for the treatment of cerebral infarct like stroke and cerebral ischemia, for the treatment of CNS disorders such as tension, for the therapy of side-effects in the treatment of hypertension (e.g. with α-methyldopa) and for the prophylaxis and therapy of cerebral disorders (e.g. migraine) is disclosed. Additionally, the use in endocrinology and gynecology is described, e.g. for the treatment of acromegaly, hypogonadism, secondary amenorrhea, premenstrual syndrome or undesired puerperal lactation.

Furthermore, it is known that they have a useful potential utility for the treatment of sleep disorders, including dyssomnias and narcolepsy.

The invention had the object of providing novel uses for 1-[4-(5-cyanoindol-3-yl)butyl]-4-(2-carbamoyl-benzofuran-5-yl)-piperazine and its physiologically acceptable salts having significantly better pharmacological properties than compounds of the prior art.

It has been found that 1-[4-(5-cyanoindol-3-yl)butyl]-4-(2-carbamoyl-benzofuran-5-yl)-piperazine also has activity against sub-type anxiety disorders chosen from the sub-types panic disorder with and/or without agoraphobia, agoraphobia, obsessive-compulsive spectrum disorders, social phobia, specific phobia including neophobia, posttraumatic stress disorder, acute stress indication or generalized-anxiety disorder.

Accordingly, the present invention relates to the use of 1-[4-(5-cyanoindol-3-yl)butyl]-4-(2-carbamoyl-benzofuran-5-yl)-piperazine or a physiologically acceptable salt thereof, for the manufacture of a medicament for the treatment of sub-type anxiety disorders chosen from the sub-types panic disorder with or without agoraphobia, agoraphobia, obsessive-compulsive spectrum disorders including obsessive compulsive disorders, social phobia, specific phobia including neophobia, posttraumatic stress disorder, acute stress indication and/or generalized-anxiety disorder.

It is known that 5-HT reuptake inhibitors such as fluoxetine (L. Solyom, C. Solyom, B. Ledwidge, Can. J. Psychiatry, 1991, **36:** 378-380) or 5-HT_{1A} receptor agonists such as geprione (J.C. Pecknold, L. Luthe, M.H. Scott-Fleury, S. Jenkins, J. Clin. Psychopharmacology, 1993, **13:** 145-149) are clinically effective in panic disorders. It has been found that a combined

selective 5-HT reuptake inhibitor and 5-HT_{1A} receptor agonist which includes both mechanisms leads to an advantage in clinical practice.

A typical model for panic disorder is the Mouse Defense Test Battery according to G. Griebel, D.C. Blanchard, R.J. Blanchard, Prog. Neuropsychopharmacol. & Biol. Psychiat., 1996, **20:** 185-205.
The mouse defence battery test consists of an oval runway of 2 m straight segments joint by two 0.4 m curved segments separated by a median wall. A mouse is placed in the runway for a 3 min familiarization period. Then, a hand-held anaesthetized rat is introduced into the runway and brought up to the mouse. Approach is terminated when contact with the mouse was made or the mouse runs away from the approaching rat. If the subject runs away, avoidance distance and the number of avoidances after five approaches are recorded. Immediately after these approaches, the rat chases the mouse for a distance of 15 m, and flight speed is recorded.

A typical model for Agoraphobia is named Elevated Plus Maze according to S. Pellow, P. Chopin, S.E. File, M. Briley, J. Neurosci. Meth., 1985, **14**: 145-167.
The apparatus consists of an X-shaped platform elevated from the floor, with two "open" unprotected arms and two "closed" protected arms, with animals having free access to both arms. The rat or mouse is placed in the centre of the arms, and the number of entires made and the time spent on the open arms is measured in a 3 min test period. Normal animals have very low basal levels, i.e. avoid entering the open arms and stay only a for a very brief period on open arms.
1-[4-(5-cyanoindol-3-yl)butyl]-4-(2-carbamoyl-benzofuran-5-yl)-piperazine or one of its physiologically acceptable salts, in particular 1-[4-(5-cyanoindol-3-yl)butyl]-4-(2-carbamoyl-benzofuran-5-yl)-piperazine hydrochloride, following oral application dose-dependently increased both

the number of entries and the time spend on open arms. For example, in mice the dose of 10 mg/kg p.o. increased the number of entires by 157% and time spent on open arms by 105%. In rats, a dose of 10 mg/kg p.o. increased number of entries by 56% and time spent on open arms by 76%.

It is known that 5-HT reuptake inhibitors such as paroxetine (A.K. Cardogan, I.K. Wright, I. Combs, C.A. Marsden, D.A. Kendall, I. Tulloch, Neurosci. Lett. **42:** S8) or 5-HT_{1A} receptor agonists such as geprione (V. Motta, S. Maisonnette; S. Morato; P. Castrechini; M.L. Brandao, Psychopharmacology, 1992; **107:** 135-139) or 8-OH-DPAT (8-hydroxy-dipropylaminotetralin) (N. Collinson, G.R. Dawson, Psychopharmacology, 1997, **132:** 35-43) have been shown to be effective in the elevated plus maze test. It has been found that a combined selective 5-HT reuptake inhibitor and 5-HT_{1A} receptor agonist which includes both mechanisms leads to therapeutic advantages.

Obsessive Compulsive Disorders (OCDs) are characterized by unwanted intrusive, recurring thoughts, images, or actions which generate an irrational dread (obsession) of germs, dirt, contamination, apprehension of acting on violent or aggressive impulses, feeling overly responsible for the safety of others, e.g. unreasonable dread of having run over someone with a car, abhorrent religious (blasphemous) and sexual thoughts, inordinate concern with order, arrangement, or symmetry, inability to discard useless or worn out possessions.
This often results in the repetitive performance of rituals (compulsions), such as excessive washing (particularly hand-washing or bathing), touching, counting, arranging and ordering, checking, cleaning and hoarding which persons suffering from OCD feel they can not control. Performing these rituals, however, provides only temporary relief. This person is almost always aware that their strange compulsive behaviour

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