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[54] **TREATMENT OF ANXIETY WITH THE AID OF (S)-(−)-α-ETHYL-2-OXO-1-PYRROLIDINEACETAMIDE**

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[52] **U.S. Cl.** **514/424**

[58] **Field of Search** 514/424

[56] **References Cited**

U.S. PATENT DOCUMENTS

4,696,943 9/1987 Gobert et al. .
4,837,223 6/1989 Gobert et al. .
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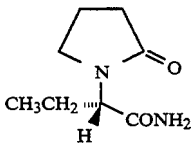
[57] **ABSTRACT**

A method is disclosed for the treatment of anxiety in a patient in need thereof, by administering to said patient an effective amount of (S)-(−)-α-ethyl-2-oxo-1-pyrrolidineacetamide of the formula

(I)



6 Claims, No Drawings

ARGENTUM Exhibit 1096
Argentum Pharmaceuticals LLC v. Research Corporation Technologies, Inc.

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TREATMENT OF ANXIETY WITH THE AID OF (S)-(−)-α-ETHYL-2-OXO-1-PYRROLIDINEACETAMIDE

The present invention relates to the use of (S)-(−)-α-ethyl-2-oxo-1-pyrrolidineacetamide for the treatment of anxiety.

The use of levorotatory (S)-α-ethyl-2-oxo-1-pyrrolidineacetamide as a protective agent for the treatment and the prevention of hypoxic and ischemic type aggressions of the central nervous system is disclosed in U.S. Pat. Nos. 4,696,943, 4,837,223 and 4,943,639, all three assigned to the assignee of the present invention. This compound is also effective in the treatment of epilepsy, a therapeutic indication for which it has been demonstrated that its dextrorotatory enantiomer (R)-(+)-α-ethyl-2-oxo-1-pyrrolidineacetamide completely lacks activity (A. J. GOWER et al., Eur. J. Pharmacol., 222, (1992), 193–203). No disclosure of the use of levorotatory (S)-α-ethyl-2-oxo-1-pyrrolidineacetamide for the treatment of anxiety is known, however.

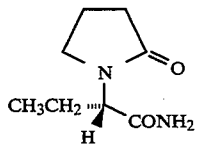
In the above-mentioned U.S. Pat. Nos. 4,696,943, 4,837,223 and 4,943,639, processes for preparing (S)-(−)-α-ethyl-2-oxo-1-pyrrolidineacetamide are also described. These processes involve the synthesis of a starting reactant obtained by resolution of the corresponding racemate. In British Patent No. 2,225,322, also assigned to the assignee of the present invention, a process for the preparation of this compound is described, which offers the advantage of using a naturally occurring amino acid with the desired stereochemical configuration as the starting material. This process thus avoids tedious separation of the enantiomers.

Continuing research work in this field, we have now found that (S)-(−)-α-ethyl-2-oxo-1-pyrrolidineacetamide possesses anxiolytic properties of considerable therapeutic interest.

Moreover, this anxiolytic activity could not be found for the dextrorotatory enantiomer, (R)-(+)-α-ethyl-2-oxo-1-pyrrolidineacetamide.

Thus, the present invention relates to a new and useful method for the treatment of anxiety in a patient in need thereof, which comprises administering to said patient an effective amount of (S)-(−)-α-ethyl-2-oxo-1pyrrolidineacetamide of the formula

(I)



The anxiolytic activity of (S)-(−)-α-ethyl-2-oxo-1-pyrrolidineacetamide is particularly pronounced in pharmacological situations in which the initial emotional state has been exacerbated, for example by choosing particularly sensitive or aged animals, or by using experimental conditions that involve the anticipation of an aversive stimulus.

The relation between anxiolytic activity of the compound of the formula I and the intensity of the initial emotional state, suggests that the therapeutic application of this compound will preferably be directed towards the treatment of pathological anxiety states. This selectivity clearly distinguishes the compound used according to the invention from known anxiolytic medicaments of the benzodiazepine type, and offers an important advantage over these other classes of products, which act without distinguishing between an anxious animal and a normal animal. In the latter case, the anxiolytic activity is accompanied by disinhibition of the normal general behavior, thereby inducing an inadequate adaptative response in healthy subjects, that should be avoided. In this context, (S)-(−)-α-ethyl-2-oxo-1-pyrrolidineacetamide facilitates recovery and return to a more normal situation from pathological anxiety states caused by disorders of a neuroendocrine origin produced by stress in aged subjects, as opposed to the benzodiazepines which do not favor this recovery. Contrary to benzodiazepines, for which amnesia and neuromotor disturbances such as ataxia, muscular relaxation and sedation are well known and undesirable side-effects (J. H. WOODS et al., Pharmacol. Rev.,39 (1987), 251–419), therapeutic doses of (S)-(−)-α-ethyl-2-oxo-1-pyrrolidineacetamide do not produce the slightest harmful effect on memory and do not cause awkward neuromotor effects. Indeed, there is a large safety margin between the anxiolytic doses and the neurotoxic or sedative doses in animals (A. J. GOWER et al., loc.cit.).

Furthermore, (S)-(−)-α-ethyl-2-oxo-1-pyrrolidineacetamide also reduces the anxiety induced by the withdrawal from chronic administration of benzodiazepines.

The result of this unexpected range of properties is that the use of (S)-(−)-α-ethyl-2-oxo-1-pyrrolidineacetamide is particularly suited in the treatment of anxiety states, such as general anxiety, panic, agoraphobia, social phobia, obsessive-compulsive disorders, anxiety due to acute posttraumatic stress, feelings of impending danger, absence of tonus, fear and tension, which are sometimes accompanied by physiological symptoms such as tachycardia, dyspnea, sweating, trembling, weakness and fatigue (International Statistical Classification of Diseases and Related Health Problems—Tenth Revision, Vol. 1, World Health Organization, Geneva, 1992).

The present invention requires administration of a dose of the compound of the formula I effective to treat anxiety. The dose required according to the present invention should be sufficiently high to permit the relief of anxiety. Pharmaceutical compositions containing the compound of the formula I may be administered, for example, orally or parenterally, i.e. intravenously, intramuscularly and subcutaneously.

The pharmaceutical compositions which can be used for oral administration may be solid or liquid, for example, in the form of tablets, pills, dragees, gelatine capsules, solutions, syrups, and the like.

For this purpose, the active compound can be mixed with an inert diluent or a pharmaceutically acceptable non-toxic carrier, such as for example starch or lactose. Optionally, these pharmaceutical compositions can also contain a binder such as microcrystalline cellulose, gum tragacanth or gelatine, a disintegrating agent such as alginic acid, a lubricant such as magnesium stearate, a glidant such as colloidal silicon dioxide, a sweetening agent such as sucrose or saccharin, a coloring agent or a flavoring agent such as peppermint or methyl salicylate. These compositions also include compositions that allow controlled release of the active substance.

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The pharmaceutical compositions which can be used for parenteral administration are the pharmaceutical forms known for this mode of administration, for example, aqueous or oily solutions or suspensions generally contained in ampules, disposable syringes, vials made of glass or plastic, or infusion containers.

Besides the active compound, these solutions or suspensions can optionally also contain a sterile diluent such as water for injection, physiologic saline solution, oils, polyethylene glycols, glycerine, propylene glycol or other synthetic solvents, antibacterial agents such as benzyl alcohol, antioxidants such as ascorbic acid or sodium bisulfite, chelating agents such as ethylenediaminetetraacetic acid, buffers such as acetates, citrates or phosphates and agents for adjusting the osmolality such as sodium chloride or dextrose.

These pharmaceutical forms can be prepared according to conventional methods used by pharmacists.

The percentage of active compound in the pharmaceutical compositions can vary within very wide concentration limits and depends on a variety of factors such as the sex, age, weight and medical condition of the patient, as well as the method of administration. Thus the amount of active compound in compositions intended for oral administration, is at least 0.5% by weight, and can reach 80% by weight with respect to the weight of the composition. In the preferred oral compositions, the dosage unit is between 50 mg and 1000 mg of active compound.

In compositions intended for parenteral administration, the amount of active compound present is at least 0.5% by weight and can reach 33% by weight of the composition. In the preferred parenteral compositions, the dosage unit is between 1 mg and 200 mg of active compound.

As regards the daily dosage, this can vary within a wide range of dosage units and is preferably between 5 and 70 mg/kg. An average dose of 250 mg, twice a day, has proved to be effective in relief of anxiety in man. It is to be understood, however, that the specific doses can be adapted for particular cases, depending on individual need, at the discretion of the responsible physician. The above-mentioned dosages are given exemplary only and by no means limit the scope of practice of the invention.

As non-limiting examples of compositions containing (S)-(−)-α-ethyl-2-oxo-1-pyrrolidineacetamide, which can be administered orally, four compositions are given hereinafter for white and opaque gelatine capsules:

	Number of the capsules			
	1	1	1	0
Compound I	62.5 mg	125 mg	250 mg	500 mg
Lactose	362.5 mg	264 mg	89 mg	50 mg
Magnesium stearate	1 mg	1 mg	1 mg	2 mg

The efficacy of (S)-(−)-α-ethyl-2-oxo-1-pyrrolidineacetamide for the treatment of anxiety is demonstrated by its activity in the following pharmacological tests performed on animals, using standard tests, which are recognized for their capacity to demonstrate the anxiolytic activity of new compounds.

Anxiety can exist in different physiological and pathological forms. The heterogeneous nature of anxiety disorders is clinically accepted in the same way that it is accepted that various anxiety tests, performed on animals and based on behavioral changes are sensitive to different types of anxiety (S. E. FILE, "Animal models of anxiety" in "Biological Psychiatry", Vol. 2, G. Racagui et al. (eds), Excerpta Medica, Amsterdam, (1991), p. 596–599).

However, to be sure that a given behavioral test actually permits to detect anxiolytic activity, the latter must also be confirmed by clinical tests. A test in man has enabled to confirm the therapeutic activity of (S)- (−)-α-ethyl-2-oxo-1-pyrrolidineacetamide for the treatment of various types of anxiety.

1. Hole-board Test (Exploratory Activity)

The hole-board test offers a simple method for studying the behavior of a rodent and for measuring the response of an animal to an unfamiliar environment. This reaction, known as the "exploratory behavior", relates both to the curiosity of the animal and to its natural fight-or-flight reaction and is influenced by psychoactive drugs. In particular, this method has proved useful in predicting the potential anxiolytic activity of benzodiazepines (N. A. NOLAN and M. W. PARKES, Psychopharmacologia (Berl.) 29, (1973), 277–288). Using the methodology of J. R. BOISSIER and P. SIMON (Arch. Int. Pharmacodyn. 147, (1964), 372–387), the test consists of placing a mouse in the center of a square board, perforated by 16 regularly spaced holes, and counting the number of times the animal dips its head into a hole during a five-minute exploration period. Three genetically distinct strains of mice are used in this test; a normal strain of NMRI mice and two strains which are emotionally more sensitive, one being prone to audiogenic seizure (Dilute Brown Agouti-derived (DBA-derived)), and the other having the normal fight-or-flight reaction blocked by fear (C57 Black Mice strain).

The activities of (S)-(−)-α-ethyl-2-oxo-1-pyrrolidineacetamide (compound I), of its dextrorotatory enantiomer (R)-(+)-α-ethyl-2-oxo-1-pyrrolidineacetamide (compound II) and of diazepam are compared on these three strains.

The compounds are administered to the animals by intraperitoneal injection (10 ml/kg of mouse) 30 minutes before exposure to the board. Animals in the control group receive the carrier only.

Table I shows the mean of the number of holes explored per group of 16 animals (X±SEM) for each of the strains (control and treated animals) at the doses indicated (SEM: Standard Deviation from the Mean). It also gives the percentage change of the score with respect to the score of the control groups.

TABLE I

		Hole-board test					
	Dose	DBA-derived strain		C57 Black Mice strain		NMRI strain	
Compound	(mg/kg)	X ± SEM	% Change	X ± SEM	% Change	X ± SEM	% Change
Compound I	9.5	16.1 ± 3.1	80.9	22.5 ± 3.1	47.1	NT	
	17.0	21.5 ± 3.4*	141.6	21.0 ± 2.7	37.3	NT	
	30.6	17.1 ± 2.1*	92.1	24.9 ± 3.3*	62.7	29.4 ± 2.8	−10.1
	Control	8.9 ± 1.4	—	15.3 ± 2.6	—	32.7 ± 2.5	—
Compound II	9.5	9.9 ± 1.4	0				
	17.0	7.9 ± 2.0	−20.2	NT		NT	

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TABLE I-continued

Compound	Dose (mg/kg)	Hole-board test: DBA-derived strain X ± SEM	% Change	C57 Black Mice strain X ± SEM	% Change	NMRI strain X ± SEM	% Change
	30.6	10.1 ± 2.7	2.0				
	Control	9.9 ± 2.4	—				
Diazepam	0.5	19.7 ± 2.7*	45.9	33.7 ± 3.0*	60.5	49.8 ± 3.8*	25.4
	1.0	14.9 ± 3.0	10.4	42.1 ± 3.4*	100.5	51.1 ± 2.9*	28.7
	Control	13.5 ± 1.9	—	21.0 ± 3.3	—	39.7 ± 2.8	—

NT: not treated

(*): significant increase in activity compared with the control group: P ≦ 0.05; Mann-Whitney U-test

The results show that the three strains of mice tested differ from one another by their baseline levels (control tests), which are much higher for the normal NMRI mice than for the other two strains. It is known that the number of holes explored is considerably reduced under the influence of anxiogenic agents, such as caffeine and yohimbine (R. LISTER, Pharmacol. Ther., 46, (1990), 321–340). Consequently, the low level observed for the control groups of unhealthy DBA-derived and C57 Black Mice strains correctly reflects the increased level of intrinsic anxiety in these two strains.

As with diazepam, (S)-(−)-α-ethyl-2-oxo-1-pyrrolidineacetamide considerably increases the score achieved by the DBA-derived and C57 Black Mice strains, but unlike diazepam, compound I has practically no anxiolytic effect on the normal NMRI strain. Diazepam is also very active on the latter strain and the increase in score reflects very well the disinhibition effect which is specific to benzodiazepines. The dependence of the anxiolytic effect of compound I on the nature of the strain, and the pronounced selectivity of this effect for strains which exhibit unhealthy anxiety, suggests that compound I is particularly useful in the treatment of exacerbated emotional states, independently of any disinhibiting effect on the behavior. The (R)-(+)-α-ethyl-2-oxo-1-pyrrolidineacetamide enantiomer (compound II) is inactive on these strains.

2. Four-Plates Test (Punished Behavior)

The general approach used in this type of experiment consists of inducing the inhibition of a specific response by applying a stimulus which produces aversion at the time of that specific response. The "four-plates" test is an easy method described for the first time by J. R. BOISSIER et al., in Eur. J. Pharmacol., 4, (1968), 145–151, for evaluating the potential anxiolytic activity of new compounds in laboratory animals. In a first stage, it involves placing a mouse in an unfamiliar environment, which consists of a surface covered by four metal plates which can be electrified, and during a specific period of time, the number of times that the animal crosses the surface, passing from one plate to another is counted (unpunished crossings). In a second stage, the animal is punished by an electric shock to the paws, each time it crosses right over the surface (punished crossings), which induces on the animal an immobilizing reaction. Under conditions with punishment (punished crossings), the number of crossings over the surface to explore the environment is strongly reduced. On the other hand, the reduction in the number of crossings under conditions with punishment is inhibited in animals which have been previously treated with an anxiolytic agent.

The compounds tested, (S)-(−)-α-ethyl-2-oxo-1-pyrrolidineacetamide (compound I) and chlordiazepoxide, are administered to the animals by intraperitoneal injection (10 ml/kg of mouse) 30 minutes before the beginning of the test. The animals in the control groups receive the carrier only. Table II gives the mean (X±SEM) of the number of crossings made under punished conditions and under unpunished conditions for groups of 30 NMRI mice, over a period of 1 minute and at the doses indicated.

It also gives the percentage change of the score with respect to the score of the control groups.

TABLE II

Compound	Dose (mg/kg)	Four-plates test: Number of crossings: Punished crossings X ± SEM	% Change	Unpunished crossing X ± SEM	% Change
Compound I	30.6	7.8 ± 0.6	16.4	14.7 ± 0.7	3.5
	54.0	8.9 ± 0.6*	32.8	12.7 ± 0.7	−10.6
	95.2	8.5 ± 0.5*	26.9	13.7 ± 0.6	−3.5
	Control	6.7 ± 0.4	—	14.2 ± 0.8	—
Chlordiazepoxide	2.0	10.9 ± 0.5	18.5	17.4 ± 1.0	13.7
	4.0	10.9 ± 0.5*	18.5	16.1 ± 0.7	5.2
	8.0	13.2 ± 0.6*	43.5	22.7 ± 0.8*	48.4
	16.0	13.7 ± 0.7*	48.9	22.8 ± 1.0*	49.0
	Control	9.2 ± 0.5	—	15.3 ± 0.8	—

(*): significant increase in activity with respect to the control group: P ≦ 0.05; Mann-Whitney U-test

The results show that, under punished conditions, the number of crossings is lower than under unpunished conditions, both for the control groups and for the treated groups.

Compound I and chlordiazepoxide increase the number of crossings under punished conditions but, unlike compound I, chlordiazepoxide also has the same effect under unpunished conditions by disinhibiting normal behavior.

These results show that (S)-(−)-α-ethyl-2-oxo-1-pyrrolidineacetamide (compound I) offers an advantage over existing drugs because it only exhibits its anxiolytic activity under conditions which induce severe anxiety and not under normal conditions.

This selectivity of compound I enables to distinguish an anxiolytic effect from an effect which would result in an increase of activity per se.

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3. Elevated Plus-Maze Test

This test is a simple and rapid method, widely used for detecting the anxiolytic activity of new compounds. Unlike most anxiety tests which use nociceptive stimuli, for example an electric shock, this test relies solely on measuring the spontaneous activity of an animal confronted with a natural anxiogenic situation, which causes a conflict between two opposed tendencies: the desire to explore a novel environment and the desire to flee from an open elevated area. Relative exploration of the open or closed arms of a maze is a reflection of an anxiety state of the animal, exploration of the open arms being strongly reduced in animals that exhibit a high anxiety state (S. PELLOW et al., J. Neurosci. Methods, 14, (1985), 149–167).

An anxiolytic compound increases the number of visits to the open arms and the time spent to explore them, whereas with benzodiazepines, part of this increase has been attributed to induction of stereotypy by the drug at the doses used (U. FALTER et al., Behav. Processes, 29, (1993), 128–129). The technique used in this test is that described by S. PELLOW (loc. cit) modified by R. J. RODGERS et al. (Psychopharmacology, 106 (1992), 102–110). This modification consists of enhancing the anxiety state of the animals, by previously placing them on an elevated maze (pre-test) of which the four arms are open, which has the effect of reducing the number of explorations into the open arms (baseline) when the animal is placed, 24 hours later, on a conventional maze having 2 open and 2 closed arms.

The activities of (S)-(−)-α-ethyl-2-oxo-1-pyrrolidineacetamide (compound I), of the dextrorotatory enantiomer (compound II) and of chlordiazepoxide have been examined using this test. The compounds are administered to Sprague-Dawley rats by intraperitoneal injection (10 ml/kg of rat) 60 minutes before the beginning of the test. The animals in the control group received a saline solution (0.9% NaCl). Table III gives the mean values for the total number of entries into the arms of the maze, the percentage of entries into the open arms with respect to the total number of entries, and the time spent exploring these open arms, for groups of 15 rats (control groups and groups treated with the doses indicated), each in the maze for 4 minutes.

TABLE III

	Elevated plus-maze test			
		Total number	Open arms	
Compounds	Dose (mg/kg)	of entries X ± SEM	% entries X ± SEM	Time (sec) X ± SEM
Control		8.6 ± 1.0	10.3 ± 3.0	5.2 ± 2.0
Compound I	17.0	11.9 ± 0.7*	20.2 ± 3.0*	16.1 ± 3.1*
Compound II	17.0	8.3 ± 0.9	10.9 ± 3.1	5.7 ± 2.2
	54.0	9.2 ± 0.7	11.8 ± 2.7	6.8 ± 1.6
Chlordiazepoxide	5.0	15.0 ± 1.3*	27.1 ± 2.7*	27.1 ± 3.7*

(*) significant increase in activity compared with the control group: P ≦ 0.05; Mann-Whitney U-test.

The results show that, for the control group, the number of entries into the open arms only represents a very low percentage of the total number of entries.

Treatment of animals with compound I or with chlordiazepoxide significantly increases the number of entries into the open arms as well as the time spent to explore them. On the other hand, compound II has no activity.

These results confirm the value of compound I in the treatment of pathological anxiety states.

4. Potentiated Startle Test

The startle response to a loud sound (sound aggression) is potentiated by simultaneous presentation of a light stimulus that has been previously paired with an electric shock to the paws of the animals. In this case, the anxiety induced by the combined sound and light aggressions (potentiated startle) originates from the premonition of a painful and unpleasant event (M. DAVIS, Psychopharmacology, 62, (1979), 1–7).

Anxiolytic compounds, such as benzodiazepines or buspirone, reduce the amplitude of the potentiated startle response proportionally to the dose used (S. GREEN et al, "Animal Models of Anxiety" in "Behavioural Models in Psychopharmacology", P. Willner (ed.), Cambridge Univ. Press, 21–49, 1991; M. DAVIS, Trends Pharmacol. Sci., 13, (1992), 35–41). The technique used in this test is based upon that proposed by M. DAVIS (loc. cit.) and comprises essentially two stages:

1st stage: Training—the animals are trained to react to a light stimulus accompanied by an electric shock to the paws;

2nd stage: Main test—the amplitude of the startle response of the animals to a sound aggression accompanied by a light stimulus without electric shock is measured—20 tests—(potentiated startle response or PSR), and the amplitude of the startle response of the animals to sound aggression, neither accompanied by a light stimulus, nor by an electric shock, is also measured—20 tests—(acoustic startle response or ASR).

Groups of 10 male untrained Sprague-Dawley rats are used. The compounds tested are (S)-(−)-α-ethyl-2-oxo-1-pyrrolidineacetamide (compound I) and chlordiazepoxide. They are administered by intraperitoneal injection (1 ml/kg of rat) 60 minutes before the main test. Animals in the control group receive only the saline solution (0.9% NaCl). At the time of the test, each animal is placed in a cage connected to accelerometers which record automatically the startles of the animals and express the amplitude of the response in arbitrary units.

Table IV gives the mean of the amplitudes obtained for ASR and PSR responses at the doses indicated.

TABLE IV

		Potentiated startle test	
	Dose in	PSR	ASR
Compound	mg/kg	X ± SEM	X ± SEM
Control		22965 ± 4760*	17326 ± 3126
Compound I	17.0	14817 ± 3056**	14388 ± 2214
Chlordiazepoxide	5.0	10393 ± 2079**	8759 ± 2352**

(*) Significant difference between PSR and ASR: P ≦ 0.05, paired t-test
(*) Significant difference between treated and control groups: P ≦ 0.05; Student's t-test

The results for the animals in the control group show that the PSR response is, as expected, more intense than the ASR response. Compound I strongly reduces the amplitude of the potentiated startle response (PSR) but

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