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Australia

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Patent Request: Standard Patent

We, the Applicant(s)/Nominated Person(s) specified below, request we be granted a patent for the invention disclosed in the accompanying standard complete specification.

[70,71] Applicants/Nominated Persons:

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SWITZERLAND

[54] Invention Title:

An Imidazobenzodiazepine for the Treatment of Sleep Disorders

[72] Inventor(s):

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[74] Address for Service in Australia:

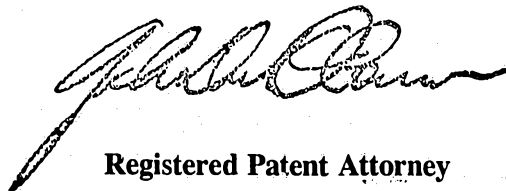
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Basic Convention Application Details

[31] Application No	[33]	Country	[32]	Date of Application
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Basic Applicant: F.Hoffmann-La Roche AG

DATED 17 August, 1994
F.Hoffmann-La Roche AG



Registered Patent Attorney



IN:196345

INSTR CODE:55540

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RAN 4008/349

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Australia

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NOTICE OF ENTITLEMENT

I, Roland Borer, of 10 Stockackerstrasse
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being authorised by the Applicant/Nominated Person in respect of an
application entitled:

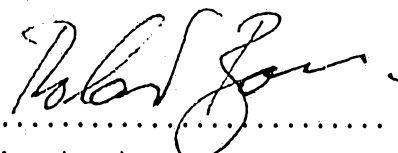
An Imidazobenzodiazepine for the Treatment of Sleep Disorders
state the following:-

The Applicant/Nominated Person has entitlement from the actual inventor(s) as
follows:-

The Applicant/Nominated Person is the assignee of the actual inventor(s).

The Applicant/Nominated Person is the applicant of the basic application(s)
listed on the Patent Request. The basic application(s) listed on the Patent
Request is/are the application(s) first made in a Convention Country in
respect of the invention.

DATED this 18th day of July 1994


.....
(Signature)

.....
(Name & Title)
Roland Borer (Mandatory)

IRN: 196345

INSTR CODE: 55541

MOC/4988D

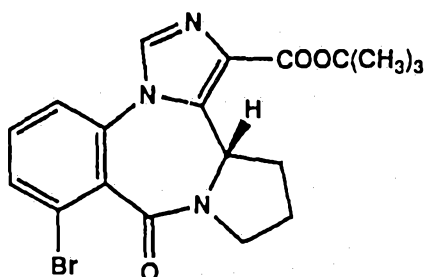


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(19) AUSTRALIAN PATENT OFFICE (10) Acceptance No. 653966

- (54) Title
AN IMIDAZOBENZODIAZEPINE FOR THE TREATMENT OF SLEEP DISORDERS
- International Patent Classification(s)
(51)⁶ **A61K 031/55**
- (21) Application No. : **88150/91** (22) Application Date : **25.11.91**
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- (71) Applicant(s)
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- (72) Inventor(s)
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- (74) Attorney or Agent
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- (56) Prior Art Documents
US 4861772
US 4914095

- (57) The present invention is concerned with the use of bretazenil, t-butyl (S)-8-bromo-11,12,13,13a-tetrahydro-9-oxo-9H-imidazo[1,5-a]pyrrolo[2,1-c][1,4]benzodiazepine-1-carboxylate, of the formula



in the treatment of sleep disorders. The use of bretazenil for the manufacture of medicaments for the treatment of sleep disorders and a method and medicament for the treatment of sleep disorders are further objects of the present invention.

CLAIMS

1. A method of inducing sleep corresponding largely to natural sleep which comprises administering to a host requiring such treatment an effective amount of bretazenil, t-butyl (S)-8-bromo-11, 12, 13, 13a-tetrahydro-9-oxo-9H-imidazo[1,5-a]pyrrolo[2,1-c][1,4]benzodiazepine-1-carboxylate.

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S & F Ref: 196345

AUSTRALIA
PATENTS ACT 1990

COMPLETE SPECIFICATION

FOR A STANDARD PATENT

ORIGINAL

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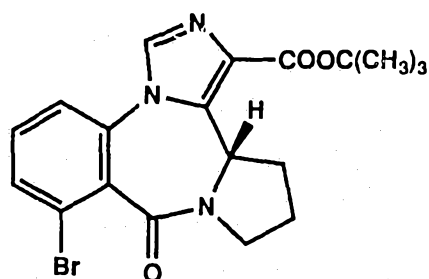
Actual Inventor(s): Roman Amrein and Jean-Paul Laurent

Address for Service: Spruson & Ferguson, Patent Attorneys
Level 33 St Martins Tower, 31 Market Street
Sydney, New South Wales, 2000, Australia

Invention Title: An Imidazobenzodiazepine for the Treatment of Sleep Disorders

The following statement is a full description of this invention, including the best method of performing it known to me/us:-

5 The present invention is concerned with the use of bretazenil, t-butyl (S)-8-bromo-11,12,13,13a-tetrahydro-9-oxo-9H-imidazo-[1,5-a]pyrrolo[2,1-c][1,4]benzodiazepine-1-carboxylate, of the formula



15 in the treatment of sleep disorders. The use of bretazenil for the manufacture of medicaments for the treatment of sleep disorders and a method and medicament for the treatment of sleep disorders are further objects of the present invention.

20 Bretazenil is a known substance. Its manufacture is described, for example, in European Patent Publication No. 59 391. The anticonvulsive and anxiolytic properties of this compound are also described in this publication.

25 Bretazenil has a high affinity to the benzodiazepine receptor (BZR), the modulatory part of the receptor for the amino acid GABA. GABA is an inhibiting messenger (neurotransmitter) of certain nerve cells (neurones) of the brain. The distribution of GABA by one type of neurone causes inhibition of the excitability of other neurones, which can manifest itself, for example, in an anxiolytic, anticonvulsive, muscle relaxant or sedative-hypnotic activity.

30 Three main types of substances have been found which bind to the BZR and which are denoted as ligands: (1) The agonists, which intensify the inhibition by GABA; (2) the so-called inverse agonists which reduce the activity of GABA; and (3) the antagonists which do not influence the activity of GABA, but which prevent its

intensification or reduction by agonists or inverse agonists at the BZR (see Haefely, W., handbook of Anxiety 3: 165-188, 1990). Substances from the three groups of ligands which are active on the BZR generally have a high affinity to this receptor, but differ by the so-called relative intrinsic effectiveness, i.e. the capability of influencing the activity of GABA. while pure antagonists occupy the BZR, but do not influence the activity of GABA, full agonists or inverse agonists produce at the BZR maximum intensification or reduction of the inhibiting activity of GABA. It is conceivable that between the extremes there are substances with different degrees of intrinsic effectiveness and that such substances would also be found. They themselves behave as weak agonists or inverse agonists, significantly weaker than the activity of the actual full agonists. Such substances are therefore partial agonists or partial inverse agonists.

It has been found that bretazenil is such a partial agonist or partial agonist at the BZR. In animal experiments it has been established that bretazenil has a high affinity to the BZR, but that with the substance there are only achieved effects which correspond to those of lower dosages of benzodiazepines (BZD) such as, for example, diazepam. The characteristic effects and side-effects of higher and higher dosages of the BZD such as sedation, muscle relaxation, ataxia and amnesia could not be shown or could be shown only in subtoxic dosages for bretazenil in classical animal experiments.

It has now surprisingly been found that bretazenil can induce sleep in healthy male and female volunteers even in low dosages and that the induced sleep corresponds largely to natural sleep.

Accordingly, there is provided a method of inducing sleep corresponding largely to natural sleep which comprises administering to a host requiring such treatment an effective amount of bretazenil, t-butyl (S)-8-bromo-11, 12, 13, 13a-tetrahydro-9-oxo-9H-imidazo[1,5-a]pyrrolo[2,1-c][1,4]benzodiazepine-1-carboxylate.

The amount of bretazenil may be between about 0.25mg to about 5mg and may preferably be between about 0.5mg and about 2mg.

This property of bretazenil can be determined on the basis of the double blind study described hereinafter:

Six male volunteers and six female volunteers with an average age of 24 years and an average weight of 58 kg took part in the study. The volunteers were required to take 0.5, 1 or 2 mg of bretazenil in tablet form after 21 hours. This took place after the volunteers had taken placebo tablets on two previous



evenings. The second placebo night served as the reference (pre-control). Placebo was again administered on the evening of the day after bretazenil (post-control). The volunteers spent the four nights of one session in a sleep laboratory. Their brain current curves
5 (EEG) and body movements were recorded on magnetic tape and thereafter evaluated using a computer. This method permits the exact recording of the sleep profile.

The results determined in this study (see Table I) show quite
10 clearly that bretazenil was effective in all tested dosages. Bretazenil shortened drastically the time taken to fall asleep (sleep latency) and lengthened the total sleep per night by lengthening the normal sleep (non REM sleep) and reducing the number of intermittent short waking phases. Likewise, bretazenil reduced the
15 number of body movements during sleep. Thus, bretazenil brought about a more rapid falling asleep and a lengthening and stabilization of the sleep. During normal sleep bretazenil did not reduce the deep sleep stages 3 and 4 or reduced these stages only insignificantly, but lengthened altogether the duration of the middle sleep
20 stage 2. This is characterized by the appearance of so-called sleep spikes, a characteristic pattern in the EEG. Their number was, however, unaltered. However, the number of K complexes, another characteristic pattern in the EEG, was reduced in stage 2. These can be traced back to disturbing acoustic signals which reach the
25 sleeping brain. Their reduction therefore points to a deepening of the sleep. The superficial sleep of stage 1 was shortened by bretazenil.

The sleep of a healthy human being is usually structured in
30 five sleep cycles, with each cycle being terminated with a dream phase. Bretazenil does not alter the number of cycles, but lengthens the first cycle and at the same time the period until the first dream phase occurs (REM sleep latency). The dream sleep, also referred to as REM sleep because rapid eye movements occur
35 therein, was, however, only immaterially shortened overall by bretazenil. The closeness of the rapid eye movements (REMs) in the REM sleep was decreased.

Table I: Effects of bretazenil on the sleep of healthy volunteers

	Dosage administered in mg p.o.		
	0.5	1	2
Sleep latency	33*	30*	20*
Total sleep	+ 45 min*	+ 44 min*	+ 45 min*
Intermittent waking phases	32*	25*	22*
Movements	80*	74*	69*
Non REM sleep	+ 60 min*	+ 60 min*	+ 62 min*
Stage 1	98	65*	79
Stage 2	130*	128*	136*
Stage 3	90	90	87
Stage 4	87*	103	79*
Spikes in stage 2	101	107	107
K complexes in stage 2	71*	63*	61*
Duration of first sleep cycle	154*	189*	198*
REM sleep latency	165*	206*	217*
REM sleep duration	91	83	85
REMs in REM sleep	84	49*	31*

5 All values, except total sleep and non REM sleep, are in % and relate to the pre-control. The absolute increase in minutes is given for total sleep and non REM sleep.

*p<0.05

10 In the scope of the present invention bretazenil can be used in the form of pharmaceutical preparations for peroral, rectal and parenteral administration. Tablets, coated tablets, dragees, hard and soft gelatine capsules, suppositories, solutions, emulsions or suspensions are examples of such preparations. Perorally admin-
15 istrable forms, especially tablets, are preferred dosage forms.

Bretazenil is processed with pharmaceutically inert, inorganic or organic carrier materials in order to manufacture pharmaceutical preparations. Suitable carrier materials for tablets, coated tablets,
20 dragees and hard gelatine capsules are, for example, lactose, maize

starch or derivatives thereof, talc, stearic acid or its salts and the like. Vegetable oils, waxes, fats, semi-solid and liquid polyols and the like are, for example, suitable for soft gelatine capsules. Natural or hardened oils, waxes, fats, semi-solid and liquid polyols and the like are, for example, suitable for suppositories. Suitable carrier materials for the manufacture of solutions, emulsions and suspensions are, for example, water, polyols, saccharose, invert sugar, glucose and the like.

Moreover, the pharmaceutical preparations can contain the usual preservatives, solubilizers, stabilizers, wetting agents, emulsifiers, sweeteners, colorants, flavorants, salts for varying the osmotic pressure, buffers, coating agents and/or antioxidants.

As already mentioned, bretazenil can be used in the treatment of sleep disorders. The dosages can vary according to the severity of the sleep disorders and the age and weight of the patient and will, of course, be fitted to the individual requirements in each particular case. In general, in the case of peroral administration a dosage of about 0.25 to about 5 mg should be appropriate.

The following Example describes a dosage form which is suitable for the practical application of the present invention. It is, however, in no way intended to limit the scope of the present invention.

Example (tablet)

Bretazenil	0.5 mg
Lactose	126.5 mg
Maize starch	54.0 mg
Polyvinylpyrrolidone	8.0 mg
Sodium carboxymethylstarch	10.0 mg
Magnesium stearate	<u>1.0 mg</u>
Tablet weight	200.0 mg

Bretazenil, the lactose and the maize starch are mixed and granulated with an aqueous solution of polyvinylpyrrolidone. The

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dried and pulverized granulate is mixed with the sodium carboxymethylstarch and the magnesium stearate, whereupon the mixture is pressed to tablets having a weight of 200 mg.

The claims defining the invention are as follows:

1. A method of inducing sleep corresponding largely to natural sleep which comprises administering to a host requiring such treatment an effective amount of bretazenil, t-butyl (S)-8-bromo-11, 12, 13, 13a-tetrahydro-9-oxo-9H-imidazo[1,5-
5 a]pyrrolo[2,1-c][1,4]benzodiazepine-1-carboxylate.

2. A method according to claim 1 wherein the effective amount is from about 0.25mg to about 5mg of bretazenil.

3. A method according to claim 1 wherein the effective amount is from about 0.5mg to about 2mg of bretazenil.

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Dated 19 August, 1994
F.Hoffmann-La Roche AG

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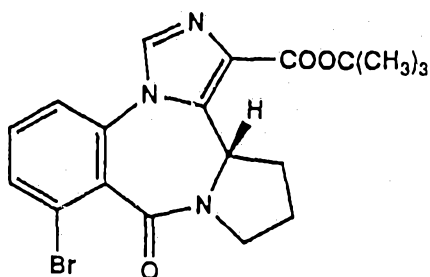
Patent Attorneys for the Applicant/Nominated Person
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An Imidazobenzodiazepine for the Treatment of Sleep
Disorders

Abstract

5 The compound *t*-butyl (S)-8-bromo-11,12,13,13a-tetrahydro-
9-oxo-9H-imidazo[1,5-a]pyrrolo[2,1-c][1,4]benzodiazepine-1-
carboxylate of the formula



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can be used for the manufacture of medicaments for the treatment
of sleep disorders and also as a medicament for the treatment of
sleep disorders.

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