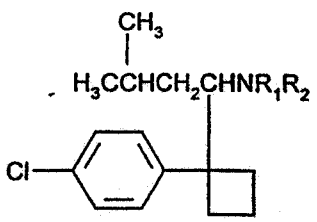
Method of Treating Sleep Apnoea

This invention relates to a method of treating sleeping disorders for example sleep apnoea and snoring.

Patients with sleep apnoea experience transient episodes of breathing-cessation while they are asleep. When this disturbed respiration is associated with obstruction of the upper airways it is known as obstructive sleep apnoea. If the cause of the cessation of breathing is due to some neurogenic mechanism then it is known as the central sleep apnoea (see Martindale, The Extra Pharmacopoeia, 31st edition, p. 1545). Although several drugs have been used to combat this condition there remains a need for a more efficacious treatment with fewer side effects.

According to the present invention there is provided a method of treating sleeping disorders including sleep apnoea and snoring in which a therapeutically effective amount of a compound of formula I



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including enantiomers and pharmaceutically acceptable salts thereof, in which R_1 and R_2 are independently H or methyl, is administered in conjunction with a pharmaceutically acceptable diluent or carrier to a human in need thereof.

The term sleeping disorders includes sleep apnoea, snoring, daytime sleepiness resulting from poor sleep during the night which is recognised as a significant cause of accidents, particularly road accidents, and other sleeping

disorders known to those skilled in the art. In a preferred aspect the present invention provides a method of treating sleep apnoea.

The compounds of formula I are advantageous in that they may be used to provide a higher degree of efficacy and a lower degree of side effects compared to the conventional treatments.

A preferred compound of formula I is N,N-dimethyl-1-[1-(4-chlorophenyl)cyclobutyl]-3-methylbutylamine or a salt thereof, for example the hydrochloride salt. A preferred form of this hydrochloride is its monohydrate.

The preparation and use of compounds of formula I, such as N,N-dimethyl-1-[1-(4-chlorophenyl)cyclobutyl]-3-methylbutylamine and salts thereof, in the treatment of depression is described in British Patent Specification 2098602. The use of compounds of formula I such as N,N-dimethyl-1-[1-(4-chlorophenyl)cyclobutyl]-3-methylbutylamine and salts thereof in the treatment of Parkinson's disease is described in published PCT application WO 88/06444. The use of N,N-dimethyl-1-[1-(4-chlorophenyl)cyclobutyl]-3-methylbutylamine and salts thereof in the treatment of cerebral function disorders is described in US Patent 4939175. The use of N,N-dimethyl-1-[1-(4-chlorophenyl)cyclobutyl]-3-methylbutylamine hydrochloride in the treatment of obesity is described in published PCT application WO90/06110. A particularly preferred form of this compound is N,N-dimethyl-1-[1-(4-chlorophenyl)cyclobutyl]-3-methylbutylamine hydrochloride monohydrate (sibutramine hydrochloride) which is described in European Patent Number 230742. The use of N,N-dimethyl-1-[1-(4-chlorophenyl)cyclobutyl]-3-methylbutylamine and salts thereof for improving the glucose tolerance of humans having Impaired Glucose Tolerance or Non-Insulin Dependent Diabetes Mellitus is described in published PCT application WO95/20949.

It will be appreciated by those skilled in the art that compounds of formula I contain a chiral centre. When a compound of formula I contains a single chiral

centre it may exist in two enantiomeric forms. The present invention includes the use of the individual enantiomers and mixtures of the enantiomers. The enantiomers may be resolved by methods known to those skilled in the art, for example by formation of diastereoisomeric salts or complexes which may be separated, for example, by crystallisation; via formation of diastereoisomeric derivatives which may be separated, for example, by crystallisation, gas-liquid or liquid chromatography; selective reaction of one enantiomer with an enantiomer-specific reagent, for example enzymatic oxidation or reduction, followed by separation of the modified and unmodified enantiomers; or gas-liquid or liquid chromatography in a chiral environment, for example on a chiral support, for example silica with a bound chiral ligand or in the presence of a chiral solvent. It will be appreciated that where the desired enantiomer is converted into another chemical entity by one of the separation procedures described above, a further step is required to liberate the desired enantiomeric form. Alternatively, specific enantiomers may be synthesised by asymmetric synthesis using optically active reagents, substrates, catalysts or solvents, or by converting one enantiomer to the other by asymmetric transformation.

Preferred compounds of formula I are N,N-dimethyl-1-[1-(4-chlorophenyl)-cyclobutyl]-3-methylbutylamine, N-{1-[1-(4-chlorophenyl)cyclobutyl]-3-methylbutyl}-N- methylamine, and 1-[1-(4-chlorophenyl)cyclobutyl]-3-methylbutylamine including racemates, individual enantiomers and mixtures thereof, and pharmaceutically acceptable salts thereof.

The individual enantiomers can be prepared by enantioselective synthesis from optically active precursors, or by resolving the racemic compound which can be prepared as described above. Enantiomers of secondary amines of the formula I can also be prepared by preparing the racemate of the corresponding primary amine, resolving the latter into the individual enantiomers, and then converting the optically pure primary amine enantiomer into the required secondary amine by methods described in British Patent Specification 2098602.

Specific examples of compounds of formula I are:

(+)-N-[1-[1-(4-chlorophenyl)cyclobutyl]-3-methylbutyl}-N-methylamine;
(-)-N-{1-[1-(4-chlorophenyl)cyclobutyl-3-methylbutyl}-N-methylamine;
(+)-1-[1-(4-chlorophenyl)cyclobutyl]-3-methylbutylamine;
(-)-1-[1-(4-chlorophenyl)cyclobutyl]-3-methylbutylamine;
(+)-N-{1-[1-(4-chlorophenyl)cyclobutyl]-3-methylbutyl}-N-N-dimethylamine;
(-)-N-{1-[1-(4-chlorophenyl)cyclobutyl]-3-methylbutyl}-N-N-dimethylamine;

or a pharmaceutically acceptable salt thereof.

The hydrochloride salts are preferred in each case, but the free bases and other pharmaceutically acceptable salts are also suitable.

The compound of formula I may be administered in any of the known pharmaceutical dosage forms. The amount of the compound to be administered will depend on a number of factors including the age of the patient, the severity of the condition and the past medical history of the patient and always lies within the sound discretion of the administering physician but it is generally envisaged that the dosage of the compound to be administered will be in the range 0.1 to 50 mg preferably 1 to 30 mg per day given in one or more doses.

Oral dosage forms are the preferred compositions for use in the present invention and these are the known pharmaceutical forms for such administration, for example tablets, capsules, granules, syrups and aqueous or oil suspensions. The excipients used in the preparation of these compositions are the excipients known in the pharmacist's art. Tablets may be prepared from a mixture of the active compound with fillers, for example calcium phosphate; disintegrating agents, for example maize starch; lubricating agents, for example magnesium stearate; binders, for example microcrystalline cellulose or polyvinylpyrrolidone and other optional ingredients known in the art to permit tableting the mixture by

known methods. The tablets may, if desired, be coated using known methods and excipients which may include enteric coating using for example hydroxypropylmethylcellulose phthalate. The tablets may be formulated in a manner known to those skilled in the art so as to give a sustained release of the compounds of the present invention. Such tablets may, if desired, be provided with enteric coatings by known methods, for example by the use of cellulose acetate phthalate. Similarly, capsules, for example hard or soft gelatin capsules, containing the active compound with or without added excipients, may be prepared by known methods and, if desired, provided with enteric coatings in a known manner. The contents of the capsule may be formulated using known methods so as to give sustained release of the active compound. The tablets and capsules may conveniently each contain 1 to 50 mg of the active compound, preferably 10 mg or 15 mg.

Other dosage forms for oral administration include, for example, aqueous suspensions containing the active compound in an aqueous medium in the presence of a non-toxic suspending agent such as sodium carboxy-methylcellulose, and oily suspensions containing a compound of the present invention in a suitable vegetable oil, for example arachis oil. The active compound may be formulated into granules with or without additional excipients. The granules may be ingested directly by the patient or they may be added to a suitable liquid carrier (for example, water) before ingestion. The granules may contain disintegrants, eg an effervescent couple formed from an acid and a carbonate or bicarbonate salt to facilitate dispersion in the liquid medium.

The therapeutically active compounds of formula I may be formulated into a composition which the patient retains in his mouth so that the active compound is administered through the mucosa of the mouth.

Dosage forms suitable for rectal administration are the known pharmaceutical forms for such administration, for example, suppositories with cocoa butter or polyethylene glycol bases.

Dosage forms suitable for parenteral administration are the known pharmaceutical forms for such administration, for example sterile suspensions or sterile solutions in a suitable solvent.

Dosage forms for topical administration may comprise a matrix in which the pharmacologically active compounds of the present invention are dispersed so that the compounds are held in contact with the skin in order to administer the compounds transdermally. A suitable transdermal composition may be prepared by mixing the pharmaceutically active compound with a topical vehicle, such as a mineral oil, petrolatum and/or a wax, e.g. paraffin wax or beeswax, together with a potential transdermal accelerant such as dimethyl sulphoxide or propylene glycol. Alternatively the active compounds may be dispersed in a pharmaceutically acceptable cream, gel or ointment base. The amount of active compound contained in a topical formulation should be such that a therapeutically effective amount of the compound is delivered during the period of time for which the topical formulation is intended to be on the skin.

The therapeutically active compound of formula I may be formulated into a composition which is dispersed as an aerosol into the patients oral or nasal cavity. Such aerosols may be administered from a pump pack or from a pressurised pack containing a volatile propellant.

The therapeutically active compounds of formula I used in the method of the present invention may also be administered by continuous infusion either from an external source, for example by intravenous infusion or from a source of the compound placed within the body. Internal sources include implanted reservoirs containing the compound to be infused which is continuously released for example by osmosis and implants which may be (a) liquid such as an oily suspension of the compound to be infused for example in the form of a very sparingly water-soluble derivative such as a dodecanoate salt or a lipophilic ester or (b) solid in the form of an implanted support, for example of a synthetic resin

or waxy material, for the compound to be infused. The support may be a single body containing all the compound or a series of several bodies each containing part of the compound to be delivered. The amount of active compound present in an internal source should be such that a therapeutically effective amount of the compound is delivered over a long period of time.

In some formulations it may be beneficial to use the compounds of the present invention in the form of particles of very small size, for example as obtained by fluid energy milling.

In the compositions of the present invention the active compound may, if desired, be associated with other compatible pharmacologically active ingredients.

The invention further provides the use of compounds of formula I in the manufacture of a medicament for treating sleeping disorders including sleep apnoea and snoring . Preferably the sleeping disorder is sleep apnoea.

In another aspect, the invention further provides a pharmaceutical composition for treating sleeping disorders including sleep apnoea and snoring comprising a compound of formula I in conjunction with a pharmaceutically acceptable diluent or carrier. Preferably the sleeping disorder is sleep apnoea.

The efficacy of compounds of formula I in treating sleep apnoea was demonstrated by the data presented below and a clinical trial in a relevant population set.

Monoamine reuptake inhibitors have been used to treat certain of the disorders described in the present invention. However, these compounds are known to suffer from a number of disadvantages. Firstly such compounds are not effective in all patients. Secondly where the compounds are effective they may not provide a complete cure of the disorder. Thirdly, there are many

undesirable side-effects known with this type of compound. Such side-effects include nausea, sexual dysfunction, light headedness, somnolence, sweating, tremor, dry mouth, asthenia, insomnia, diarrhoea, headache, vomiting, anxiety, drowsiness, dizziness, fever, rash or allergic reactions, arthralgia, myalgia, convulsions, hypomania and mania.

Sibutramine (Formula I, $R_1 = CH_3$, $R_2 = CH_3$) has a pharmacological profile which is unique amongst monoamine reuptake inhibitors. Through its pharmacologically active metabolites, (metabolite 1, $R_1 = H$, $R_2 = CH_3$ in Formula I and metabolite 2, $R_1 = H$, $R_2 = H$ in Formula I) sibutramine inhibits the reuptake of all three monoamines differentiating it from serotonin (5-HT)-selective reuptake inhibitors, e.g. fluoxetine, noradenaline-selective reuptake inhibitors, e.g. desipramine, dopamine-selective reuptake inhibitors, e.g. bupropion, and serotonin-noradenaline reuptake inhibitors, e.g. venlafaxine (Table 1). It is this unique combination of pharmacological actions which renders sibutramine, and the other compounds of formula I, efficacious in the treatment of sleep apnoea. The assays below were performed in a similar manner to those described in WO98/41528.

TABLE 1

Comparison of the *in vitro* monoamine reuptake inhibition profiles of Examples 1 and 2, and various reference monoamine reuptake inhibitors in rat brain tissue

	Ki (nM)		
	[^{3}H]Noradenaline	[^{3}H]5-HT	[^{3}H]Dopamine
Example 1	3	18	24
Example 2	5	26	31
Bupropion	2590	18312	409

Desipramine	2	200	4853
Fluoxetine	320	11	2025
Venlafaxine	196	26	2594

The results are the means of ≥3 separate determinations

Example 1 $R_1 = H, R_2 = CH_3$ in Formula I

Example 2 $R_1 = H, R_2 = H$ in Formula I

Clinical Trial

Study design: An open explorative study with 5 volunteer patients suffering from clinically relevant obesity (BMI>30) and sleep apnoea was performed. All patients (3 f, 2 m) were treated with sibutramine 10 or15 mg/kg daily over a period of 6 to 14 weeks. No other control treatment was applied.

Methods: Patients willing to lose weight who had obtained prescriptions for Reductil® (Knoll) from their doctor were asked to take part in this voluntary observational study. All patients were willing to change dietary habits during treatment, and to perform at least moderate physical training (twice a week at least half an hour). Patients were interviewed pre and post treatment, and their partners asked for their observations on snoring behaviour. The patients were asked for their own rating of severity of daytime sleepiness, and their partners for objective observations about frequency and heaviness of snoring as well as for their observations about apnoea signs.

Results: Mean BMI was 34 before treatment, and 29 at end of treatment. In each case weight loss occurred under treatment, at mean 14 kg (=14.6%; span from –7% to –22%). All patients were slight to heavy snorers before the treatment period (mean score 2,2 at a scale 0-3), and 4 of 5 patients were reported to disturb sleep companions significantly. All patients were reported to stop breathing during night sleep by their sleep companions. All patients

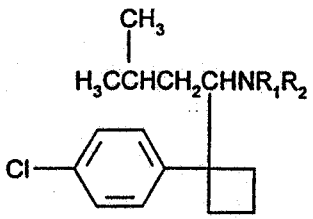
reported moderate to severe daytime sleepiness (mean score 2 at a scale 0-3). After treatment the snoring had reduced to a scale mean of 1, as observed by sleep companions. The patients reported that their sleepiness scale reduced from 2,0 to 0,6. Subjectively all felt better, and 4 out of 5 had clearly reduced daytime sleepiness. The arousal index AI improved from a mean of 23,5 to 10,0. This is a mean decrease of -57% (span from –25% to –67%). 3 out of 5 patients reported that the ease of breathing with closed mouth had improved under sibutramine treatment, while this was not observed by 2 patients.

The beneficial effects of the compounds of the present invention at doses of 15 mg and 20 mg daily may also be confirmed in a double-blind, randomised, placebo-controlled clinical trial using questionnaires or by recording Holter ecgs with a Rozin/GeTeMed tape recorder device for 24 to 36 hours pre and post treatment period, using IEC-I type tapes. The ecg data may be computer-processed to study arousals.

In a clinical study with 150 patients suffering from clincally relevant obesity, many of them with serious sleep apnoea problems, a subset of 36 patients was arbitrarily selected for computer supported arousal/apnoea recognition. Two consecutive nights were recorded at week-1(pre-treatment) and week-12 of treatment, and the number of arousals per hour of sleep time was evaluated. The results prove that there is a clinically significant effect in the reduction of number of arousals for treatment with Sibutramine 20 mg daily. Compared to placebo this is significant at a 5%-level (p=0.0227). In some patients with clearly excessive daytime sleepiness, the signs of sleepiness were clearly reduced."

Claims

1. A method of treating sleeping disorders including sleep apnoea and snoring comprising administering to a human in need thereof a therapeutically effective amount of a compound of formula I



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including enantiomers and pharmaceutically acceptable salts thereof in which R_1 and R_2 are independently H or methyl, in conjunction with a pharmaceutically acceptable diluent or carrier.

2. A method as claimed in claim 1 wherein the sleeping disorder is sleep apnoea.

3. A method as claimed in either claim 1 or claim 2 wherein the compound of formula I is N,N-dimethyl-1-[1-(4-chlorophenyl)cyclobutyl]-3-methylbutylamine hydrochloride.

4. A method as claimed in claim 3 wherein the compound of formula I is N,N-dimethyl-1-[1-(4-chlorophenyl)cyclobutyl]-3-methylbutylamine hydrochloride in the form of its monohydrate.

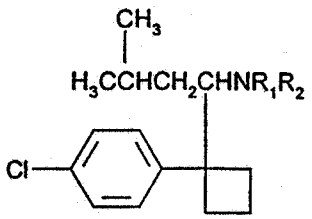
5. A method as claimed in either claim 1 or claim 2 in which the compound is selected from:

(+)-N-[1-[1-(4-chlorophenyl)cyclobutyl]-3-methylbutyl]-N-methylamine;
(-)-N-[1-[1-(4-chlorophenyl)cyclobutyl-3-methylbutyl]-N-methylamine;
(+)-1-[1-(4-chlorophenyl)cyclobutyl]-3-methylbutylamine;

(-)-1-[1-(4-chlorophenyl)cyclobutyl]-3-methylbutylamine;
(+)-N-{1-[1-(4-chlorophenyl)cyclobutyl]-3-methylbutyl}-N-N-dimethylamine;
(-)-N-{1-[1-(4-chlorophenyl)cyclobutyl]-3-methylbutyl}-N-N-dimethylamine;

or a pharmaceutically acceptable salt thereof.

6. The use of a compound of formula I



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including enantiomers and pharmaceutically acceptable salts thereof in which R_1 and R_2 are independently H or methyl, in the manufacture of a medicament for treating sleeping disorders including sleep apnoea and snoring.

7. The use as claimed in claim 6 in which the medicament is for treating sleep apnoea.

8. The use as claimed in claim 6 in which the compound of formula I is N,N-dimethyl-1-[1-(4-chlorophenyl)cyclobutyl]-3-methylbutylamine hydrochloride.

9. The use as claimed in claim 8 in which the compound of formula I is N,N-dimethyl-1-[1-(4-chlorophenyl)cyclobutyl]-3-methylbutylamine hydrochloride monohydrate.

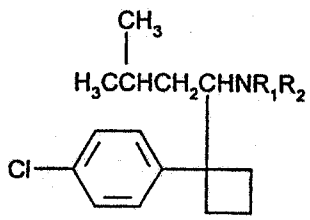
10. The use of a compound as claimed in claim 6 in which the compound is selected from:

(+)-N-[1-[1-(4-chlorophenyl)cyclobutyl]-3-methylbutyl}-N-methylamine;
(-)-N-{1-[1-(4-chlorophenyl)cyclobutyl-3-methylbutyl}-N-methylamine;

(+)-1-[1-(4-chlorophenyl)cyclobutyl]-3-methylbutylamine;
(-)-1-[1-(4-chlorophenyl)cyclobutyl]-3-methylbutylamine;
(+)-N-{1-[1-(4-chlorophenyl)cyclobutyl]-3-methylbutyl}-N-N-dimethylamine;
(-)-N-{1-[1-(4-chlorophenyl)cyclobutyl]-3-methylbutyl}-N-N-dimethylamine;

or a pharmaceutically acceptable salt thereof.

11. A pharmaceutical composition for treating treating sleeping disorders including sleep apnoea and snoring, comprising a therapeutically effective amount of a compound of formula I



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including enantiomers and pharmaceutically acceptable salts thereof in which R_1 and R_2 are independently H or methyl, in conjunction with a pharmaceutically acceptable diluent or carrier.

12. A pharmaceutical composition as claimed in claim 11 in which the sleeping disorder is sleep apnoea.

13. A pharmaceutical composition as claimed in either claim 11 or claim12 in which the compound of formula I is N,N-dimethyl-1-[1-(4-chlorophenyl)cyclobutyl]-3-methylbutylamine hydrochloride.

14. A pharmaceutical composition as claimed in claim 13 in which the compound of formula I is N,N-dimethyl-1-[1-(4-chlorophenyl)cyclobutyl]-3-methylbutylamine hydrochloride monohydrate.

15. A pharmaceutical composition as claimed in either claim 11 or claim 12 in which the compound of formula I is selected from:

(+)-N-[1-[1-(4-chlorophenyl)cyclobutyl]-3-methylbutyl}-N-methylamine;
(-)-N-{1-[1-(4-chlorophenyl)cyclobutyl-3-methylbutyl}-N-methylamine;
(+)-1-[1-(4-chlorophenyl)cyclobutyl]-3-methylbutylamine;
(-)-1-[1-(4-chlorophenyl)cyclobutyl]-3-methylbutylamine;
(+)-N-{1-[1-(4-chlorophenyl)cyclobutyl]-3-methylbutyl}-N-N-dimethylamine;
(-)-N-{1-[1-(4-chlorophenyl)cyclobutyl]-3-methylbutyl}-N-N-dimethylamine;

or a pharmaceutically acceptable salt thereof.