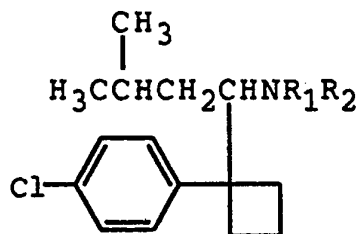




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(21) International Application Number: PCT/US95/01190 (22) International Filing Date: 3 February 1995 (03.02.95) (30) Priority Data: 08/190,924 3 February 1994 (03.02.94) US (60) Parent Application or Grant (63) Related by Continuation US 08/190,924 (CIP) Filed on 3 February 1994 (03.02.94) (71) Applicant (for all designated States except US): BOOTS PHARMACEUTICALS, INC. [US/US]; Tri-State International Center, Suite 200, Lincolnshire, IL 60069-4422 (US). (72) Inventor; and (75) Inventor/Applicant (for US only): VARGAS, Ramon [MX/US]; 2001 Manson Avenue, Metairie, LA 70001 (US). (74) Agents: MURRAY, Robert, B. et al.; Nikaido, Marmelstein, Murray & Oram, Metropolitan Square, Suite 330, G Street Lobby, 655 15th Street NW, Washington, DC 20005-5701 (US).		(81) Designated States: AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, JP, KE, KG, KP, KR, KZ, LK, LR, LT, LU, LV, MD, MG, MN, MW, MX, NL, NO, NZ, PL, PT, RO, RU, SD, SE, SI, SK, TJ, TT, UA, US, UZ, VN, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG), ARIPO patent (KE, MW, SD, SZ). Published <i>With international search report.</i> <i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>
(54) Title: IMPROVING GLUCOSE TOLERANCE (57) Abstract A compound of formula (I) or a pharmaceutically acceptable salt thereof in which R ₁ and R ₂ are independently H or methyl (for example <u>N,N</u> -dimethyl-1-[1-(4-chlorophenyl)cyclobutyl]-3-methylbutylamine hydrochloride optionally in the form of its monohydrate) is used for improving the glucose tolerance of humans having impaired glucose tolerance or non-insulin dependent diabetes mellitus.		



(I)

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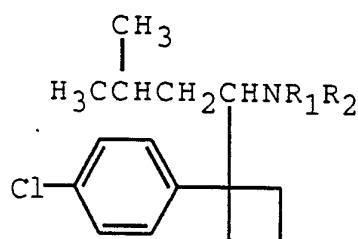
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IMPROVING GLUCOSE TOLERANCE

This invention relates to a method for improving the glucose tolerance of humans having Impaired Glucose Tolerance or Non-Insulin Dependent Diabetes Mellitus (NIDDM).

According to the present invention there is provided a method for improving the glucose tolerance of humans having Impaired Glucose Tolerance or Non-Insulin Dependent Diabetes Mellitus (NIDDM) in which a therapeutically effective amount of a compound of formula I



or pharmaceutically acceptable salts thereof in which R₁ and R₂ are independently H or methyl is administered in conjunction with a pharmaceutically acceptable diluent or carrier.

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.

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.

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.

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.

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 carboxymethylcellulose, 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.

- 5 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.

- 10 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
15 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
20 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
25 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
30 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
5 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
10 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
15 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
20 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.

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

The term "Impaired Glucose Tolerance" includes humans suffering from Diabetes Mellitus of the insulin
30 or non-insulin dependent type.

The term "glucose tolerance" includes glucose disposal in muscle tissue, and hepatic glucose output.

A deviation from normal glucose tolerance is indicative of Impaired Glucose Tolerance, or with more severe deviation, of Non-Insulin Dependent Diabetes Mellitus. Glucose tolerance can be quantified by reference to the
5 "area under the curve" relative to baseline in a glucose concentration against time course graph, by reference to the maximum glucose concentration (Cmax) in a glucose concentration against time course graph, or by reference to the fasting blood glucose concentration. A
10 significant increase in any of these from their normal values is indicative of a reduction in glucose tolerance. Humans having Impaired Glucose Tolerance or Non-Insulin Dependent Diabetes Mellitus show significant increases in these factors and so have reduced glucose
15 tolerance. In the management of Impaired Glucose Tolerance and Non-Insulin Dependent Diabetes Mellitus it is desirable to maintain as near to normal glucose tolerance as possible.

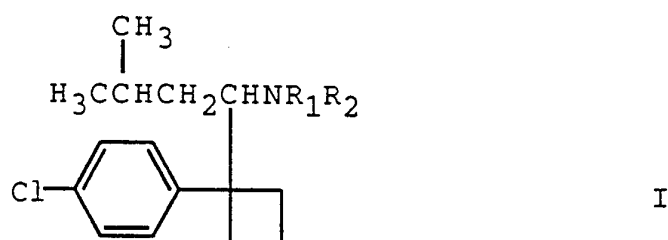
The ability of sibutramine hydrochloride to
20 increase (improve) the glucose tolerance of humans having Impaired Glucose Tolerance or Non-Insulin Dependent Diabetes Mellitus (NIDDM) is illustrated as follows.

In a clinically supervised trial in which obese,
25 non-insulin dependent diabetic volunteers were given 30 mg of sibutramine hydrochloride daily for four days, the glucose tolerance test indicated a greater reduction in the mean "area under the curve" relative to baseline for the glucose-time course for subjects given sibutramine
30 relative to that seen with subjects given placebo. This indicates that administration of sibutramine hydrochloride to humans having NIDDM would have utility for improving their glucose tolerance.

In another clinically supervised trial in which obese, non-insulin dependent diabetic volunteers were given 15 mg of sibutramine hydrochloride daily for 12 weeks, the glucose tolerance test indicated a greater
5 reduction in the mean maximum glucose concentration (Cmax) for the glucose-time course for subjects given sibutramine relative to that seen with subjects given placebo. This indicates that administration of
10 sibutramine hydrochloride to humans having NIDDM would have utility for improving their glucose tolerance.

Claims

1. A method of improving the glucose tolerance of humans having Impaired Glucose Tolerance or Non-Insulin Dependent Diabetes Mellitus which comprises
5 administering to a human in need thereof a therapeutically effective amount of a compound of formula I

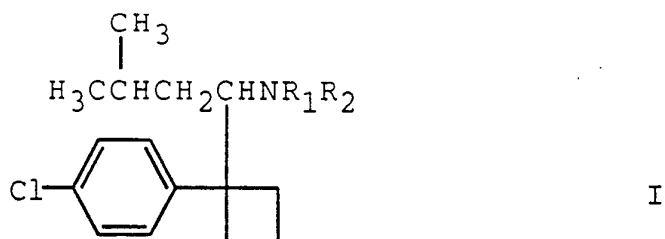


- or pharmaceutically acceptable salts thereof in which R_1 and R_2 are independently H or methyl in conjunction with
10 a pharmaceutically acceptable diluent or carrier.

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

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

4. The use of a compound of formula I



or a pharmaceutically acceptable salt thereof in which R_1 and R_2 are independently H or methyl in the manufacture of a medicament for improving the glucose tolerance of humans having Impaired Glucose Tolerance or

5 Non-Insulin Dependent Diabetes Mellitus.

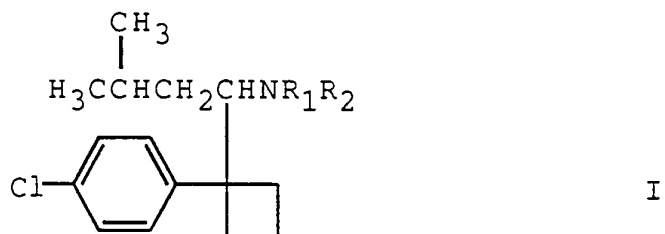
5. The use of N,N-dimethyl-1-[1-(4-chlorophenyl)-cyclobutyl]-3-methylbutylamine hydrochloride in the manufacture of a medicament for improving the glucose tolerance of humans having Impaired Glucose Tolerance or

10 Non-Insulin Dependent Diabetes Mellitus.

6. The use of N,N-dimethyl-1-[1-(4-chlorophenyl)-cyclobutyl]-3-methylbutylamine hydrochloride monohydrate in the manufacture of a medicament for improving the glucose tolerance of humans having Impaired Glucose

15 Tolerance or Non-Insulin Dependent Diabetes Mellitus.

7. The use of a compound of formula I



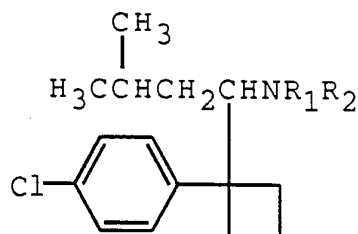
or a pharmaceutically acceptable salt thereof in which R_1 and R_2 are independently H or methyl for improving

the glucose tolerance of humans having Impaired Glucose Tolerance or Non-Insulin Dependent Diabetes Mellitus.

8. The use of N,N-dimethyl-1-[1-(4-chlorophenyl)-cyclobutyl]-3-methylbutylamine hydrochloride for
5 improving the glucose tolerance of humans having Impaired Glucose Tolerance or Non-Insulin Dependent Diabetes Mellitus.

9. The use of N,N-dimethyl-1-[1-(4-chlorophenyl)-cyclobutyl]-3-methylbutylamine hydrochloride mono-
10 hydrate for improving the glucose tolerance of humans having Impaired Glucose Tolerance or Non-Insulin Dependent Diabetes Mellitus.

10. A pharmaceutical composition for improving the glucose tolerance of humans having Impaired Glucose
15 Tolerance or Non-Insulin Dependent Diabetes Mellitus comprising a therapeutically effective amount of a compound of formula I



I

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

11. A pharmaceutical composition for improving the glucose tolerance of humans having Impaired Glucose Tolerance or Non-Insulin Dependent Diabetes Mellitus comprising a therapeutically effective amount of N,N-
25 dimethyl-1-[1-(4-chlorophenyl)cyclo-butyl]-3-

methylbutylamine hydrochloride in conjunction with a pharmaceutically acceptable diluent or carrier.

12. A pharmaceutical composition for improving the glucose tolerance of humans having Impaired Glucose
5 Tolerance or Non-Insulin Dependent Diabetes Mellitus comprising a therapeutically effective amount of N,N-dimethyl-1-[1-(4-chlorophenyl)cyclo-butyl]-3-methylbutylamine hydrochloride monohydrate in
10 conjunction with a pharmaceutically acceptable diluent or carrier.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US95/01190

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :A61K 31/135

US CL :514/646

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/646

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US, A, 4,939,175 (UKAI ET AL.) 03 July 1990, see entire document.	10-12

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

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