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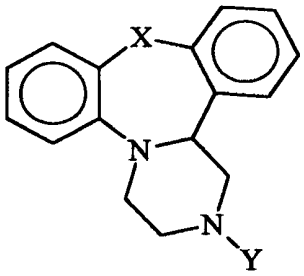
(54) Title: RESOLUTION OF OPTICALLY–ACTIVE COMPOUNDS

(57) Abstract

Methods for the separation of enantiomers of mianserin or mianserin–like compounds by using (+)– or (–)–di–p–toluoyl–(L) or (D)–tartaric acid. Also claimed are optically pure (+)– or (–)– mianserin–like compounds and pharmaceutical preparations containing these compounds. Additionally methods for treating disturbances of 5–hydroxytrytamine metabolism and histamine metabolism, and treating conditions such as depression, hypertension, congestive heart failure, migraine, anxiety, schizophrenia, gastrointestinal disturbances, diarrhoea, asthma or allergic conditions is also claimed. The mianserin–like compound has formula (1) wherein X = CH_2, O, S or NR^4, and Y = H, CN or (2); Z = O, S or NR^2.



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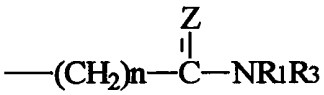

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RESOLUTION OF OPTICALLY-ACTIVE COMPOUNDS

TECHNICAL FIELD

This invention relates to methods for separation of enantiomers of heterocyclic organic compounds, and in particular to methods for separation of enantiomers of mianserin and related compounds.

BACKGROUND ART

The formation of racemic mixtures of enantiomers (optical isomers) during the synthesis of pharmacologically-active agents is a significant problem in the pharmaceutical industry. It is well known in the art that in many cases there is differential activity between the two enantiomers, and that in some cases deleterious side-effects are associated with one optical isomer but not with the other.

Because of the complex molecular structure of organic compounds which have pharmacological activity, it is extremely common for pharmaceutically-useful agents to comprise one or more chiral centres. The complex structure of such molecules also means that their synthesis involves many steps, and consequently where chiral centres are present the compounds are usually prepared in the form of racemic mixtures. The pharmacological activity is mediated by the binding of the pharmacological agent to a target site, which may be extracellular or intracellular. The 3-dimensional interaction between the pharmaceutical agent and its target site results in the pharmacological action, either by stimulating a biological activity, or by blocking a biological activity which is mediated by the target site. The more accurate the 3-dimensional fit between the pharmacological agent and its target site, the more potent will be the pharmacological activity which results, and the

lower the likelihood of unwanted side-effects.

Because 3-dimensional interaction is crucial, it is not unexpected that individual enantiomeric forms of a chiral compound show different pharmacological activities, differences in metabolic behaviour and different spectra of undesirable side-effects. A notorious example of one enantiomer having a much higher specific activity while the other enantiomer is predominantly, if not solely, responsible for side-effects is thalidomide.

It is therefore highly desirable to ensure as far as possible that the end-products of synthesis of pharmaceutical compounds are in the enantiomerically pure form. Regulatory authorities responsible for reviewing efficacy and safety data and for approving pharmaceutical agents for clinical use are increasingly emphasising the need for enantiomeric purity.

Therefore there is a great need in the art for reliable and efficient methods for separation of optical isomers of useful pharmaceutical compounds. However, it is not possible to predict which will be the most suitable method for any given compound, or, even if a given method is successful in resolving the optical isomers of a family of compounds, whether the yield and purity of the compounds thus resolved will be sufficient to make the method commercially applicable.

Mianserin, (±)-1,2,3,4,10,14b-hexahydro-2-methyldibenzo[c,f]pyrazino[1,2-α]azepine is an anti-depressant drug marketed under the name of Tolvin by Organon. Its synthesis was originally described in US Patent No.3534041 by Organon, and derivatives of mianserin are disclosed in British Patents No. 1498632 and No. 1498633.

Normianserin (Chemical Abstracts No. 71936-92-0), also known as desmethylmianserin, has similar pharmacological activity to that of mianserin but is less potent (Pinder, 1985; Doggrell, 1985; Przegalinski et al, 1986).

A related class of dibenzo-pyrazino-azepines was disclosed in U.S. Patent No. 3,701,778 (van der Burg). These compounds were selected to have anti-inflammatory, anti-serotonergic, anti-histamine and cardiovascular effects, while certain intermediates in their preparation were also pharmacologically active. The compounds included oxazepines, thiazepines and diazepines, and a variety of synthetic routes for obtaining the desired products was set forth.

Mianserin and the closely related compound normianserin are serotonin antagonists, and in addition to their anti-depressant activity have anti-histamine activity, and therefore are useful in the treatment of allergies. Synthetic methods for production of mianserin and normianserin result in a racemic mixture. There is now a significant body of evidence in the literature to suggest that the (+) enantiomer of mianserin is either the active component of such mixtures, or has higher activity than the (-) enantiomer as a result of preferential binding to cell membranes.

In International Patent Application No. PCT/AU88/00095, the disclosure of which is incorporated herein by reference, we described the synthesis of novel derivatives of mianserin and normianserin which had excellent anti-histamine activity, but did not penetrate the blood-brain barrier, and consequently were non-sedating. One particularly preferred compound, 2-carboxamidino-1,2,3,4,10,14b-hexahydrodibenzo [c,f] pyrazino-[1,2-α] azepine, was designated FCC-5. This

compound blocks mediator release during allergic reactions, with additional potent anti-histamine reactions at H1 receptors. These effects were specific to peripheral tissues; no central effects would be detected. As in the case of mianserin and normianserin, the synthesis described in this earlier application resulted in production of a racemic mixture.

A variety of anti-histamine agents is available which do not cross the blood-brain barrier, and consequently are non-sedating, for example terfenadine (Seldane; Hoechst Marion Roussel), astemizole (Hismanal; Janssen Pharmaceutica) and loratadine (Claritin; Schering Corporation). However, recently some of these agents have been found to be associated with serious heart abnormalities. For example there have been reports that terfenadine interacts with certain anti-fungal drugs and antibiotics to cause life-threatening abnormalities of cardiac ventricular rhythm, as a result of inhibition by the anti-fungal agent or antibiotic of conversion of terfenadine to its active metabolite, terfenadine carboxylate (fexofenadine). Astemizole requires approximately a week to become effective, and therefore patients frequently exceed the recommended dose. This can result in abnormal heart rhythms or even cardiac arrest. Moreover, astemizole also interacts with certain anti-fungal agents and antibiotics in a similar manner to terfenadine, resulting in increased blood levels of atemizol. Elevated blood levels of loratadine can also result from such interactions, but so far no adverse cardiac effects have been reported. Thus there is a also a considerable need in the art for further non-sedating anti-histamine agents. Of the agents of this type which are currently in clinical use, only terfenadine and its metabolite fexofenadine, marketed under the name Allegra by Hoechst Marion Roussel, are chiral compounds, and both of these are marketed as racemates. However, a method for

separation of the enantiomers of terfenadine is described in International patent publication No. WO95/31436 by Merrell Dow Pharmaceuticals Inc.

Separation of the enantiomers of mianserin by chromatography on microcrystalline cellulose triacetate, or by capillary electrophoresis using cyclodextrin buffer modifiers has been reported (Blaschke, 1986; Chankvetadze, 1995). However, neither of these methods is suitable for large-scale production of purified enantiomers. More traditional methods of enantiomeric resolution require differential crystallisation of salts formed between the desired compound and a chirally-pure reagent, such as (+)-tartaric acid or (-)-tartaric acid. Although such methods are extremely well-known, going back to the days of the original discovery of optical isomerism by Louis Pasteur, they are frequently of very poor efficiency, and it cannot confidently be predicted whether a given chirally-pure reagent will be effective in any particular desired system. For example, although salts of di-p-toluoyl tartaric acid are known in the art to provide more efficient resolution of enantiomers in a number of cases, the use of these salts is not by any means always successful.

We have now surprisingly found that by a significant modification of the conditions of crystallisation, we are able to prepare optically-pure enantiomers of mianserin in excellent yield, using a simple protocol which is readily amenable to scale up. This method is applicable to preparation of optically-pure enantiomers of related compounds, such as FCC-5, which are synthesized using mianserin as starting material.

DISCLOSURE OF THE INVENTION

According to a first aspect of the present

invention there is provided a method for the preparation of a substantially optically pure (+)-mianserin, comprising the steps of:

(i) exposing a solution of mianserin containing a mixture of (+) and (-) enantiomers to (-)-di-p-toluoyl-L-tartaric acid under conditions which permit formation of a (-)-di-p-toluoyl-L-tartrate salt of mianserin and crystallisation of the (-)-di-p-toluoyl-L-tartrate salt;

(ii) allowing substantially optically pure crystals of the (-)-di-p-toluoyl-L-tartrate salt to form;

(iii) subjecting the substantially optically pure crystals of the (-)-di-p-toluoyl-L-tartrate salt to basification to give substantially optically pure (+)-mianserin; and

(iv) isolating the substantially optically pure (+)-mianserin.

It will be appreciated that formation of a crystalline salt of mianserin from (-)-di-p-toluoyl-L-tartaric acid involves a change in sign and the salt formed actually has an $[\alpha]_D$ of +42°, but for the sake of clarity the salt formed by reaction of mianserin with (-)-di-p-toluoyl-L-tartaric acid is referred to throughout the specification as the (-)-di-p-toluoyl-L-tartrate salt of mianserin or simply as (-)-di-p-toluoyl-L-tartrate salt since the optical rotation of such a salt cannot be predicted prior to its isolation. Reaction of (-)-di-p-toluoyl-L-tartrate salt with a base yields (+)-mianserin, which has an $[\alpha]_D$ of +439.4°.

According to a second aspect of the present invention there is provided a method for the preparation of a substantially optically pure (-)-mianserin, comprising

the steps of:

(i) exposing a solution of mianserin containing a mixture of (+) and (-) enantiomers to (+)-di-p-toluoyl-D-tartaric acid under conditions which permit formation of a (+)-di-p-toluoyl-D-tartrate salt of mianserin and crystallisation of the (+)-di-p-toluoyl-D-tartrate salt;

(ii) allowing substantially optically pure crystals of the (+)-di-p-toluoyl-D-tartrate salt to form;

(iii) subjecting the substantially optically pure crystals of the (+)-di-p-toluoyl-D-tartrate salt to basification to give substantially optically pure (-)-mianserin; and

(iv) isolating the substantially optically pure (-)-mianserin.

It will be appreciated that the formation of a crystalline salt of mianserin from (+)-di-p-toluoyl-D-tartaric acid involves a change in sign and the salt formed actually has a negative optical rotation, and yields (-)-mianserin with an $[\alpha]_D$ of -423° when reacted with a base. However, for the sake of clarity the salt formed by reaction of mianserin with (+)-di-p-toluoyl-D-tartaric acid is referred to throughout the specification as the (+)-di-p-toluoyl-D-tartrate salt of mianserin, or simply as the (+)-di-p-toluoyl-D-tartrate salt.

Preferably the initial crystallisation step in either is performed using a ratio of mianserin to (-)-di-p-toluoyl-L-tartaric acid or (+)-di-p-toluoyl-D-tartaric acid (as appropriate) of 1:2-2.2.

Preferably the crystallisation steps are performed using hot absolute ethanol as solvent.

In a preferred embodiment of the invention a method wherein the mother liquor remaining after the substantially optically pure crystals of the (-)-di-p-toluoyl-L-tartrate or (+)-di-p-toluoyl-D-tartrate salt form is subjected to treatment to isolate (+)-mianserin or (-)-mianserin, respectively. Treatment of the mother liquor typically involves a molar ratio of mianserin to the tartaric acid enantiomer of about 1:1.1.

More particularly the treatment to isolate (-)-mianserin comprises the steps of:

(i) exposing the mother liquor to (+)-di-p-toluoyl-D-tartaric acid under conditions which permit formation of a (+)-di-p-toluoyl-D-tartrate salt of mianserin and crystallisation of the (+)-di-p-toluoyl-D-tartrate salt;

(ii) allowing substantially optically pure crystals of the (+)-di-p-toluoyl-D-tartrate salt to form;

(iii) subjecting the substantially optically pure crystals of the (+)-di-p-toluoyl-D-tartrate salt to basification to give substantially optically pure (-)-mianserin; and

(iv) isolating the substantially optically pure (-)-mianserin.

Likewise, the treatment to isolate (+)-mianserin comprises the steps of:

(i) exposing the mother liquor to (-)-di-p-toluoyl-L-tartaric acid under conditions which permit formation of a (-)-di-p-toluoyl-L-tartrate salt of mianserin and crystallisation of the (-)-di-p-toluoyl-L-

tartrate salt;

(ii) allowing substantially optically pure crystals of the (-)-di-p-toluoyl-L-tartrate salt to form;

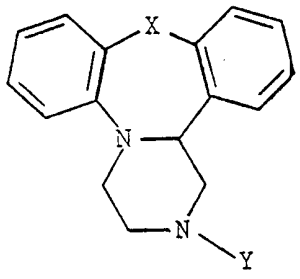
(iii) subjecting the substantially optically pure crystals of the (-)-di-p-toluoyl-L-tartrate salt to basification to give substantially optically pure (+)-mianserin; and

(iv) isolating the substantially optically pure (+)-mianserin.

Preferably the basification step is performed using 10% sodium hydroxide. The final purification step may suitably be performed by extraction with ethyl acetate.

The method is also applicable to the preparation of mianserin-like compounds in optically pure form.

As used throughout the specification and claims, a mianserin-like compound is a compound prepared from mianserin as a precursor. Thus a purified enantiomer of mianserin prepared by the method of the invention may be used as starting material for preparation of a substantially pure (+) or (-) enantiomer, as appropriate, of a mianserin-like compound. Typically, the mianserin-like compound is selected from the group consisting of compounds of general formula I:



(I)

wherein X = CH_2, O, S or NR^4, and

Y = H, CN or $-(CH_2)_n-C(=Z).NR^1R^3$

where R^1 = H, lower alkyl or an aryloxyalkyl group wherein the aryl group is optionally substituted by alkyl, alkoxy, halogen or alkyl substituted by halogen, and n is an integer between 0 and 5, and

Z = O, S or NR^2

wherein R^2 = H, lower alkyl, hydroxy, amino, cyano, or acyl, or R^1 and R^2 may together form a ring such that Y is a heterocyclic group,

R^3 = H or lower alkyl, and

R^4 = H, lower alkyl, or lower acyl.

According to a third aspect of the present invention there is provided a method for the preparation of a substantially optically pure (+)- or (-)-mianserin-like compound, comprising the steps of:

(i) providing substantially optically pure (+)- or (-)-mianserin;

(ii) converting the substantially optically pure (+)- or (-)-mianserin into a substantially optically pure (+)- or (-)-mianserin-like compound; and

(iii) isolating the substantially optically pure (+)- or (-)-mianserin-like compound.

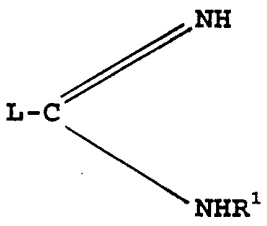
Where Y is CN the substantially optically pure (+)- or (-)-mianserin can be converted to (+) or (-) 2-cyanonormianserin by reaction with a cyanogen halide, preferably cyanogen bromide. Typically this reaction is conducted in dry benzene under an atmosphere of nitrogen. The product may be extracted with a 1:1 mixture of benzene and ether.

It will be appreciated that (+) or (-)-2-cyanonormianserin can be converted to (+)- or (-)-2-carboxamidino-1,2,3,4,10,14b-hexahydrodibenzo [c,f] pyrazino-[1,2-α] azepine by reaction with an alkylhaloaluminium amide. Typically the alkylhaloaluminium amide is methylchloroaluminium amide generated *in situ* from trimethylaluminium and ammonium chloride.

It will also be appreciated that (+) or (-)-2-cyanonormianserin can be converted to (+)- or (-)-normianserin, where necessary, and (+)- or (-)-mianserin-like compounds of the general formula I are prepared by:

(a) reacting normianserin with a compound of formula R^1NHCN where R^1 is H, lower alkyl or an aryloxyalkyl group wherein the aryl group is optionally substituted by alkyl, alkoxy, halogen, or alkyl substituted by halogen,

(b) reacting normianserin with a compound of formula



where R^1 is as defined above, and L is a leaving group selected from the group consisting of CH_3O, CH_3S, CH_3SO_2, SO_3H, and 3,5-dimethylpyrazol-1-yl,

(c) reacting 2-cyanonormaianserin with H_2S to form a compound of a formula I in which Z is S, then reacting said compound with R^1R^3NH,

(d) reacting normianserin with ethyl isocyanate

or ethyl isothiocyanate,

(e) reacting cyanonormianserin with a p-toluene sulphonate to form an imidazolinyl compound, and optionally oxidizing the imidazolinyl compound to produce an imidazolyl compound,

(f) reacting N-cyanonormianserin with H_2S as in step (c), reacting the thus-formed product with methyl iodide in a second step, and reacting the product of the second step with R^1R^3NH,

(g) reacting N-cyanonormianserin with methanol under acid conditions, and reacting the thus-formed product with R^1R^3NH,

(h) reacting N-cyanonormianserin with sodamide or with a metallated residue, or

(i) where X is CH_2, reacting normianserin under nucleophilic conditions with a compound selected from the group consisting of S,S-dimethyl N-cyanodiothioiminocarbonate, 2-chloroacetamide, cyanamide, acrylamide, and 3-bromopropyl-1-cyanide,

to produce the said compound of formula I.

According to a fourth aspect of the present invention there is provided a substantially optically pure (+)- or (-)-mianserin-like compound. Preferably the mianserin-like compound is FCC-5. More preferably, the compound is the (-)-enantiomer of FCC-5.

According to a fifth aspect of the present invention there is provided a pharmaceutical composition comprising (+)- or (-)-mianserin or a (+)- or (-)-mianserin-like compound and a pharmaceutically acceptable

carrier.

According to a sixth aspect of the present invention there is provided a method for the treatment of disturbances of 5-hydroxytryptamine metabolism and/or histamine metabolism in a mammal, comprising the step of administering to a mammal suffering from such disturbance a pharmacologically effective amount of a substantially optically pure (+)- or (-)-mianserin-like compound.

According to a seventh aspect of the present invention there is provided the use of a substantially optically pure (+) or (-)-mianserin-like compound in the treatment of disturbances of 5-hydroxytryptamine metabolism and/or histamine metabolism.

According to an eighth aspect of the present invention there is provided use of a substantially optically pure (+) or (-)-mianserin-like compound in the preparation of a medicament for the treatment of disturbances of 5-hydroxytryptamine metabolism and/or histamine metabolism.

Throughout this specification and the claims, the words "comprise", "comprises" and "comprising" are used in a non-exclusive sense.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 shows the time course for the onset and recovery during washing of the antihistaminic effect of 10 nM FCC-5 (+ and - isomers) or mepyramine (15 min contact, from time = 0 min) in the guinea pig ileum.

(•) Histamine (1 μM) time controls;

(■) after FCC-5 (- isomer) (10 nM);

(□) after FCC-5 (+ isomer) (10 nM);

(Δ) after mepyramine (10 nM).

The point represent mean values, and the bars indicate standard error of the mean, n = 4. *P<0.05, **P<0.01, compared with corresponding controls (ANOVA).

BEST MODE FOR CARRYING OUT THE INVENTION

The invention will now be described in detail by way of reference only to the following non-limiting examples, and to the figure.

Initially we attempted a conventional procedure using crystallisation with tartaric acid, but this proved to be unsuccessful. We then tried the chromatographic method of Blaschke et al (1986); although pure enantiomers were obtained, the yield was very low, and the method could not be scaled up. Initially attempts at crystallisation using di-p-toluoyl-tartaric acid were unsuccessful; however, by modifying the conditions we were able to produce both (+)- and (-)-mianserin in good yield and with an excellent degree of purity. The conditions which proved to be necessary are highly unusual conditions for achieving crystallisation. Although several attempts were made using more normal conditions, using a ratio of base to acid of 1:1 or 1:1.1, this gave no crystallisation.

Example 1 Classical Resolution with Tartaric Acid Salts

(+) Tartaric acid (0.30 g, 0.0019 mol) dissolved in hot absolute ethanol (5 ml) was added with stirring to a hot solution of racemic mianserin (0.5 g, 0.0018 mol) in absolute ethanol (10 ml). After being left to stand overnight at room temperature the salt separated as white crystals. The salt was fractionally recrystallised, and after three recrystallisations material with almost constant rotation of $[\alpha]_D$ +38.6° was obtained. The mother liquors yielded material of $[\alpha]_D$ -20°. Liberation of free

mianserin by base treatment of the salt with $[\alpha]_D$ +38.6° gave material with $[\alpha]_D$ +48.8°. These results showed that the enantiomeric purity of this material was very low. This method was thus not pursued any further.

Example 2 Chromatographic Resolution with Cellulose Triacetate

A commercial sample of cellulose triacetate was obtained, and the chromatographic separation as described by Blaschke et al (1986) was performed. Total separation was not achieved, even on a small scale, but samples of optically pure (+)-mianserin, $[\alpha]_D$ = + 417° (0.1, MeOH) and (-)-mianserin, $[\alpha]_D$ = -425° were obtained. Attempts to scale up the separation were unsuccessful, but $[\alpha]_D$ values for pure enantiomers were established by this method.

Example 3 Resolution with Di-p-Toluoyl Tartaric Acid Salts

(-)-Di-p-toluoyl-L-tartaric acid (1.62 g, 4.19 mmol) dissolved in hot absolute ethanol (2.5 ml) was added with stirring to a hot solution of racemic mianserin (1.0 g, 3.78 mmol) in absolute ethanol (5 ml).

The solution was allowed to stand overnight at room temperature. Since no crystallisation occurred even after concentrating the solution, an additional 1.1 equivalent (1.62 g) of the acid dissolved in hot absolute ethanol (2.5 ml) was added. The resulting solution was heated with stirring to evaporate some of the solvent. After being left to stand overnight at room temperature, the salt crystallised as white crystals.

The crystallisation was repeated six times with absolute ethanol to constant optical rotation, $[\alpha]_D$ = (+) 42° (0.43, MeOH was obtained); yield = 0.45 g.

The salt obtained was treated with a solution of 10% NaOH and extracted with ethyl acetate. The organic layer was dried over MgSO4 and concentrated to give (+)-mianserin $[\alpha]_D$ = 439.4° (0.49, MeOH), 0.16 g (22% yield).

The base obtained from the mother liquor (0.59 g, 2.26 mmol) was dissolved in absolute ethanol (3 ml) and was treated with a solution of (+)-di-p-toluoyl-D-tartaric acid (1.0 g, 2.48 mmol) in absolute ethanol (1.5 ml). The salt obtained after six crystallisations ($[\alpha]_D$ = -36° (0.33, MeOH), yield = 0.46 g) was treated as above to give (-)-mianserin, $[\alpha]_D$ = -423° (0.74, MeOH),0.14 g (19% yield).

Example 4 Preparation of (+) and (-) Isomers of 2-carboxamidino-1,2,3,4,10,14b-hexahydrodibenzo [c,f] pyrazino-[1,2-α] azepine (FCC-5)

(+) and (-) isomers of FCC-5 were prepared in two steps from (+) and (-) isomers of mianserin. Each isomer of mianserin was first converted to 2-cyanonormianserin (2-Cyano-1,2,3,4,10,14b-hexahydrodibenzo-[c,f]pyrazino[1,2-α]azepine) using cyanogen bromide in benzene. 2-cyanonormianserin was then converted to FCC-5 according to the method of Garigipati (Garigipati, 1990).

a) Preparation of (+) 2-cyanonormianserin

A solution of (+)-mianserin (0.40 g, 0.0015 mol) in anhydrous benzene (5 ml) was added slowly to a solution of cyanogen bromide (0.18 g, 0.0016 mol) in dry benzene in an atmosphere of nitrogen. After stirring for 24 hours at room temperature, the mixture was diluted with ether (10 ml) and washed with distilled water (10 ml). The separated aqueous layer was extracted with a mixture of benzene and ether (1:1, 10 ml). The combined organic

layers were dried over andydrous potassium carbonate. After removal of the solvents in vacuo, (+)-2-cyanonormianserin was obtained as a white solid, ($[\alpha]_D$ = + 337.4 (0.31, MeOH), 0.34 g (82% yield).

b) Preparation of (+)-FCC-5

A solution of (+)-2-cyanonormianserin (100 mg, 0.36 mmol) in dry benzene (2 ml) was added to a solution of methylchloroaluminum amide, generated in situ from trimethyl aluminium and ammonium chloride according to the standard Weinreb procedure (Weinreb, 1982). This solution was heated at 80°C for 24 hours. The reaction mixture was then cooled in an ice bath and the aluminium complex was decomposed by pouring the solution into a slurry of silica gel (2.5 g) in chloroform. The mixture was stirred for 10 min and the silica gel was filtered. The filter cake was further washed with methanol. After removal of the solvents in vacuo, the product was chromatographed on silica gel (CH2Cl2, MeOH. NH4OH, 90:10:1) to afford (+)-FCC-5, ($[\alpha]_D$ = +228.47 (0.46, MeOH), 0.09 g, 77% yield).

c) Preparation of (-)-FCC-5

(-)-Mianserin was converted to (-)-2-cyanonormianserin ($[\alpha]_D$ = -316 (0.33, MeOH) in 94% yield which was then converted to (-)-FCC-5 ($[\alpha]_D$ = -259 (0.48, MeOH)) in 87% yield according to the above procedure.

Example 5 Pharmacological Effects of (+) and (-) Isomers of FCC-5

In order to evaluate the pharmacological activity of the (+) and (-) isomers of FCC-5, the effect of the two isomers on the response of guinea pig ileum to histamine

was compared. The known anti-histamine compound mepyramine maleate was used as positive control. The time course of the anti-histaminic effects of the FCC-5 isomers and mepyramine the response of guinea pig ileum to histamine was examined.

The (+) and (-) isomers of FCC-5 were prepared as described in Example 4. Other compounds used were histamine diphosphate and mepyramine maleate (Sigma, MO, USA). Saline (NaCl, 0.9% w/v) was used as the vehicle for all drugs. FCC-5 was dissolved in saline at a concentration of 1 mM, and the solution was sonicated and slightly warmed to aid solubility. Concentrations of the test compounds are expressed as molar concentrations.

Guinea pigs were killed instantly by exposure to halothane and exsanguination. An approximate 2 cm length of ileum was removed and mounted in a 15 mL organ bath containing Krebs solution of the following composition (mM): NaCl 97.0, KCl 3.0, CaCl2 1.89, MgSo4 1.0, KH2PO4 1.2, NaHCO3 24.4 and D-glucose 5.5, bubbled with 95% O2 - 5% Co2. The tissue was equilibrated for 45-60 min under 0.5 g resting tension before drugs were administered.

The time course of the onset of action of drugs and persistence of their effects after removal by washing was examined. After equilibration in Krebs solution at 37°C, three control submaximal contractile responses of the ilea to histamine (1 μM, producing responses 60-90% of maximum) were obtained every 10 min for 30 min, leaving the histamine in contact with the tissue for 45-90 s. The bathing solution was then changed to Krebs solution containing 10 nM of either FCC-5 or mepyramine (H1 receptor antagonist). A response to the same concentration of histamine was obtained 15 min later. The bathing solution was changed back to Krebs solution free from the antagonist, and responses to histamine were again

determined every 10 min for the following 1 h, with further washing. Responses to histamine in the absence or presence of FCC-5 or mepyramine were expressed as a percentage of the initial control responses. Parallel experiments in which the tissue did not receive any antagonist were performed in order to monitor any time-dependent changes in agonist sensitivity. Grass force-displacement transducers (FT03) and polygraph (79E) were used to record contractions of all isolated tissues.

Figure 1 shows the time course for the recovery during washing of the antagonism of histamine by both FCC-5 isomers and mepyramine (15 min contact time). The response of the ileum to histamine was significantly antagonised in the presence of either isomer of FCC-5 (10 nM), after 15 min contact (ANOVA, $P<0.05$). However, in the presence of FCC-5 (-)-isomer (10 nM) there was no subsequent recovery of the response to histamine, despite continued washing every 15 min of the tissue with antagonist-free Krebs solution, for a total of 1 h. In contrast, in the presence of the FCC-5 (+)-isomer (10 nM) or mepyramine, the responses to histamine, which were also attenuated after 15 min contact to each antagonist, recovered quickly over a period of 30 min, after the bathing solution was switched to antagonist-free Krebs solution. The rank order for the duration of the antihistaminic effect on the guinea pig ileum was FCC-5 (-)-isomer >> FCC-5 (+)-isomer =mepyramine. There were no significant time-dependent changes of submaximal responses to histamine.

The antihistaminic properties of the isomers of FCC-5 have been demonstrated in vitro for the first time. Both isomers of FCC-5 produced potent antagonism of contractile responses to histamine in the isolated guinea pig ileum, an effect mediated by H1 receptors. A distinguishing characteristic of the antihistaminic effect of FCC-5 (-)-isomer in the isolated ileum was the

relatively rapid onset of this effect, within 15 min, and the subsequent lack of return of responses to histamine following washing of the tissue to remove the antagonist. In contrast, the effect of FCC-5 (+)-isomer or mepyramine could be fully reversed with washing. The rank order of the duration of antihistaminic effect was FCC-5 (-)-isomer >> FCC-5 (+)-isomer = mepyramine.

These results suggest that the FCC-5 (-)-isomer produces a non-competitive type of antagonism or a specific antihistaminic effect with slow dissociation of FCC-5 (-)-isomer from its H1 binding sites. On the other hand, FCC-5 (+)-isomer acts more like a competitive H1 receptor antagonist, similarly to mepyramine. The present data support our previous findings with racemic FCC-5, which also showed powerful and long-lasting antihistamine properties in vitro and in vivo, particularly in the guinea pig respiratory system. Our results with FCC-5 (-)-isomer suggest that this compound is a nonsedating antihistamine which has significant therapeutic potential for the treatment of allergic disease.

It will be apparent to the person skilled in the art that while the invention has been described in some detail for the purposes of clarity and understanding, various modifications and alterations to the embodiments and methods described herein may be made without departing from the scope of the inventive concept disclosed in this specification.

INDUSTRIAL APPLICABILITY

The purified enantiomers provided by the method of the invention are useful in the treatment of disturbances of 5-hydroxytryptamine and/or histamine metabolism in a mammal, hence they are useful as non-sedating anti-histamines for the treatment of asthma or an

allergic condition and in the treatment of conditions such as depression, hypertension, congestive heart failure, migraine, anxiety, schizophrenia, gastrointestinal disturbances, diarrhoea and emesis.

References cited herein are listed below, and are incorporated herein by this reference.

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CLAIMS

1. A method for the preparation of a substantially optically pure (+)-mianserin, comprising the steps of:

(i) exposing a solution of mianserin containing a mixture of (+) and (-) enantiomers to (-)-di-p-toluoyl-L-tartaric acid under conditions which permit formation of a (-)-di-p-toluoyl-L-tartrate salt of mianserin and crystallisation of the (-)-di-p-toluoyl-L-tartrate salt;

(ii) allowing substantially optically pure crystals of the (-)-di-p-toluoyl-L-tartrate salt to form;

(iii) subjecting the substantially optically pure crystals of the (-)-di-p-toluoyl-L-tartrate salt to basification to give substantially optically pure (+)-mianserin; and

(iv) isolating the substantially optically pure (+)-mianserin.

2. A method according to claim 1 wherein the mixture of (+) and (-)enantiomers of mianserin is exposed to (-)-di-p-toluoyl-L-tartaric acid in a molar ratio of 1:2 to 1:2.2.

3. A method according to claim 1 or claim 2 wherein the (-)-di-p-toluoyl-L-tartrate salt is repeatedly crystallised until crystals of the (-)-di-p-toluoyl-L-tartrate salt show constant optical rotation.

4. A method according to any one of claims 1 to 3 wherein the mixture of (+) and (-)enantiomers of mianserin is exposed to (-)-di-p-toluoyl-L-tartaric acid in hot absolute ethanol.

5. A method according to claim 4 wherein the (-)-di-p-toluoyl-L-tartrate salt is repeatedly crystallised in absolute ethanol.

6. A method according to any one of claims 1 to 5 wherein the mother liquor remaining after the substantially optically pure crystals of the (-)-di-p-toluoyl-L-tartrate salt form is subjected to treatment to isolate (-)-mianserin.

7. A method according to claim 6 wherein the treatment to isolate (-)-mianserin comprises the steps of:

(i) exposing the mother liquor to (+)-di-p-toluoyl-D-tartaric acid under conditions which permit formation of a (+)-di-p-toluoyl-D-tartrate salt of mianserin and crystallisation of the (+)-di-p-toluoyl-D-tartrate salt;

(ii) allowing substantially optically pure crystals of the (+)-di-p-toluoyl-D-tartrate salt to form;

(iii) subjecting the substantially optically pure crystals of the (+)-di-p-toluoyl-D-tartrate salt to basification to give substantially optically pure (-)-mianserin; and

(iv) isolating the substantially optically pure (-)-mianserin.

8. A method according to claim 7 wherein mianserin in the mother liquor is exposed to (+)-di-p-toluoyl-D-tartaric acid in molar ratio of about 1:1.1.

9. A method according to claim 7 or claim 8 wherein the mother liquor is an ethanolic solution.

10. A method according to claim 9 wherein the (+)-di-p-toluoyl-D-tartrate salt is repeatedly crystallised until crystals of the (+)-di-p-toluoyl-D-tartrate salt show constant optical rotation.

11. A method according to claim 10 wherein the (+)-di-p-toluoyl-D-tartrate salt is repeatedly crystallised in absolute ethanol.

12. A method according to any one of claims 1 to 11 wherein basification of substantially optically pure (+)- or (-)-mianserin is performed using 10% sodium hydroxide.

13. A method according to any one of claims 1 to 12 wherein substantially optically pure (+)- or (-)-mianserin is isolated by extraction with ethyl acetate.

14. A method for the preparation of a substantially optically pure (-)-mianserin, comprising the steps of:

(i) exposing a solution of mianserin containing a mixture of (+) and (-) enantiomers to (+)-di-p-toluoyl-D-tartaric acid under conditions which permit formation of a (+)-di-p-toluoyl-D-tartrate salt of mianserin and crystallisation of the (+)-di-p-toluoyl-D-tartrate salt;

(ii) allowing substantially optically pure crystals of the (+)-di-p-toluoyl-D-tartrate salt to form;

(iii) subjecting the substantially optically pure crystals of the (+)-di-p-toluoyl-D-tartrate salt to basification to give substantially optically pure (-)-mianserin; and

(iv) isolating the substantially optically pure (-)-mianserin.

15. A method according to claim 14 wherein the mixture of (+) and (-)enantiomers of mianserin is exposed to (+)-di-p-toluoyl-D-tartaric acid in a molar ratio of 1:2 to 1:2.2.

16. A method according to claim 14 or claim 15 wherein the (+)-di-p-toluoyl-D-tartrate salt is repeatedly crystallised until crystals of the (+)-di-p-toluoyl-D-tartrate salt show constant optical rotation.

17. A method according to any one of claims 14 to 16 wherein the mixture of (+) and (-) enantiomers of mianserin is exposed to (+)-di-p-toluoyl-L-tartaric acid in hot absolute ethanol.

18. A method according to claim 17 wherein the (+)-di-p-toluoyl-D-tartrate salt is repeatedly crystallised in absolute ethanol.

19. A method according to any one of claims 14 to 18 wherein the mother liquor remaining after the substantially optically pure crystals of the (+)-di-p-toluoyl-D-tartrate salt form is subjected to treatment to isolate (+)-mianserin.

20. A method according to claim 19 wherein the treatment to isolate (+)-mianserin comprises the steps of:

(i) exposing the mother liquor to (-)-di-p-toluoyl-L-tartaric acid under conditions which permit formation of a (-)-di-p-toluoyl-L-tartrate salt of mianserin and crystallisation of the (-)-di-p-toluoyl-L-tartrate salt;

(ii) allowing substantially optically pure crystals of the (-)-di-p-toluoyl-L-tartrate salt to form;

(iii) subjecting the substantially optically pure crystals of the (-)-di-p-toluoyl-L-tartrate salt to basification to give substantially optically pure (+)-mianserin; and

(iv) isolating the substantially optically pure (+)-mianserin.

21. A method according to claim 20 wherein mianserin in the mother liquor is exposed to (-)-di-p-toluoyl-L-tartaric acid in a molar ratio of about 1:1.1.

22. A method according to claim 20 or claim 21 wherein the mother liquor is an ethanolic solution.

23. A method according to claim 22 wherein the (-)-di-p-toluoyl-L-tartrate salt is repeatedly crystallised until crystals of the (-)-di-p-toluoyl-L-tartrate salt show constant optical rotation.

24. A method according to claim 23 wherein the (-)-di-p-toluoyl-L-tartrate salt is repeatedly crystallised in absolute ethanol.

25. A method according to claim 14 to 24 wherein basification of substantially optically pure (+)- or (-)-mianserin is performed using 10% sodium hydroxide.

26. A method according to any one of claims 14 to 25 wherein substantially optically pure (+)- or (-)-mianserin is isolated by extraction with ethyl acetate.

27. A method for the preparation of a substantially optically pure (+)- or (-)-mianserin-like compound, comprising the steps of:

(i) providing substantially optically pure (+)-

or (-)-mianserin;

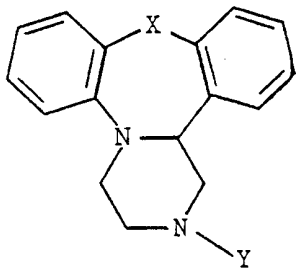
(ii) converting the substantially optically pure (+)- or (-)-mianserin into a substantially optically pure (+)- or (-)-mianserin-like compound; and

(iii) isolating the substantially optically pure (+)- or (-)-mianserin-like compound.

28. A method according to claim 27, comprising the steps of:

(i) providing substantially optically pure (+)- or (-)-mianserin;

(ii) converting the substantially optically pure (+)- or (-)-mianserin into a substantially optically pure (+)- or (-)-mianserin-like compound selected from the group consisting of the (+) or (-) enantiomers of compounds of the general formula I



(I)

wherein X = CH_2, O, S or NR^4, and

Y = H, CN or $-(CH_2)_n-C(=Z).NR^1R^3$

where R^1 = H, lower alkyl or an aryloxyalkyl group wherein the aryl group is optionally substituted by alkyl, alkoxy, halogen, or alkyl substituted by halogen, and n is an integer between 0 and 5, and

Z = O, S or NR^2

wherein R^2 = H, lower alkyl, hydroxy, amino, cyano, or acyl, or R^1 and R^2 may together form a ring such

that Y is a heterocyclic group,

R^3 = H or lower alkyl, and

R^4 = H, lower alkyl, or lower acyl; and

(iii) isolating the substantially optically pure (+)- or (-)-mianserin-like compound.

29. A method according to claim 28 wherein Y is CN and the substantially optically pure (+)- or (-)-mianserin is converted to (+)- or (-)-2-cyanonormianserin by reaction with a cyanogen halide.

30. A method according to claim 29 wherein the cyanogen halide is cyanogen bromide.

31. A method according to claim 30 wherein the reaction is conducted in dry benzene in an atmosphere of nitrogen.

32. A method according to claim 31 wherein (+)- or (-)-2-cyanonormianserin is isolated by extraction with a 1:1 mixture of benzene and ether.

33. A method according to any one of claims 29 to 32 wherein (+) or (-) 2-cyanonormianserin is converted to (+)- or (-)-2-carboxamidino-1,2,3,4,10,14b-hexahydrodibenzo [c,f] pyrazino-[1,2-α] azepine by reaction with an alkylhaloaluminium amide.

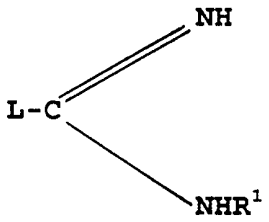
34. A method according to claim 33 wherein the alkylhaloaluminium amide is methylchloroaluminium amide generated *in situ* from trimethylaluminium and ammonium chloride.

35. A method according to any one of claims 29 to 32 wherein (+)- or (-)-2-cyanonormianserin is converted to (+)- or (-)-normianserin, where necessary, and (+)- or (-)-

mianserin-like compounds of the general formula I are prepared by:

(a) reacting normianserin with a compound of formula R^1NHCN where R^1 is H, lower alkyl or an aryloxyalkyl group wherein the aryl group is optionally substituted by alkyl, alkoxy, halogen, or alkyl substituted by halogen,

(b) reacting normianserin with a compound of formula



where R^1 is as defined above, and L is a leaving group selected from the group consisting of CH_3O, CH_3S, CH_3SO_2, SO_3H, and 3,5-dimethylpyrazol-1-yl,

(c) reacting 2-cyanonormaianserin with H_2S to form a compound of a formula I in which Z is S, then reacting said compound with R^1R^3NH,

(d) reacting normianserin with ethyl isocyanate or ethyl isothiocyanate,

(e) reacting cyanonormianserin with a p-toluene sulphonate to form an imidazolinyl compound, and optionally oxidizing the imidazolinyl compound to produce an imidazolyl compound,

(f) reacting N-cyanonormianserin with H_2S as in step (c), reacting the thus-formed product with methyl iodide in a second step, and reacting the product of the

second step with R^1R^3NH,

(g) reacting N-cyanonormianserin with methanol under acid conditions, and reacting the thus-formed product with R^1R^3NH,

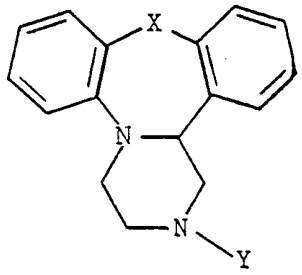
(h) reacting N-cyanonormianserin with sodamide or with a metallated residue, or

(i) where X is CH_2, reacting normianserin under nucleophilic conditions with a compound selected from the group consisting of S,S-dimethyl N-cyanodiothioiminocarbonate, 2-chloroacetamide, cyanamide, acrylamide, and 3-bromopropyl-1-cyanide,

to produce the said compound of formula I.

36. A substantially optically pure (+)- or (-)-mianserin-like compound.

37. A substantially optically pure (+)- or (-)-mianserin-like compound according to claim 36 selected from the group consisting of compounds of general formula I



(I)

wherein X = CH_2, O, S or NR^4, and

Y = H, CN or $-(CH_2)_n-C(=Z).NR^1R^3$

where R^1 = H, lower alkyl or an aryloxyalkyl group wherein the aryl group is optionally substituted by

alkyl, alkoxy, halogen or alkyl substituted by halogen, and n is an integer between 0 and 5, and

Z = O, S or NR^2

wherein R^2 = H, lower alkyl, hydroxy, amino, cyano, or acyl, or R^1 and R^2 may together form a ring such that Y is a heterocyclic group,

R^3 = H or lower alkyl, and

R^4 = H, lower alkyl, or lower acyl.

38. (+) 2-cyanonormianserin.

39. (-) 2-cyanonormianserin.

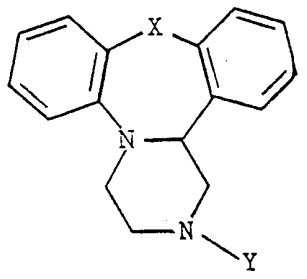
40. (+) 2-carboxamidino-1,2,3,4,10,14b-hexahydrodibenzo [c,f] pyrazino-[1,2-α] azepine.

41. (-) 2-carboxamidino-1,2,3,4,10,14b-hexahydrodibenzo [c,f] pyrazino-[1,2-α] azepine.

42. A pharmaceutical composition comprising (+)- or (-)-mianserin or a (+)- or (-)-mianserin-like compound and a pharmaceutically acceptable carrier.

43. A pharmaceutical composition according to claim 42 comprising (+)-mianserin and a pharmaceutically acceptable carrier.

44. A pharmaceutical composition according to claim 42 wherein the (+)- or (-)-mianserin-like compound is selected from the group consisting of compounds of the general formula I



(I)

wherein X = CH_2, O, S or NR^4, and

Y = H, CN or $-(CH_2)_n-C(=Z).NR^1R^3$

where R^1 = H, lower alkyl or an aryloxyalkyl group wherein the aryl group is optionally substituted by alkyl, alkoxy, halogen or alkyl substituted by halogen, and n is an integer between 0 and 5, and

Z = O, S or NR^2

wherein R^2 = H, lower alkyl, hydroxy, amino, cyano, or acyl, or R^1 and R^2 may together form a ring such that Y is a heterocyclic group,

R^3 = H or lower alkyl, and

R^4 = H, lower alkyl, or lower acyl.

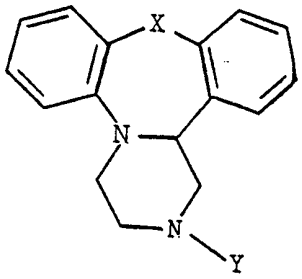
45. A pharmaceutical composition according to claim 44 wherein the compound of general formula I is (-)2-carboxamidino-1,2,3,4,10,14b-hexahydrodibenzo [c,f] pyrazino-[1,2-α] azepine.

46. A method for the treatment of disturbances of 5-hydroxytryptamine metabolism and/or histamine metabolism in a mammal, comprising the step of administering to a mammal suffering from such disturbance a pharmacologically effective amount of a substantially optically pure (+) or (-)-mianserin-like compound.

47. A method according to claim 46, for treatment of a condition selected from the group consisting of depression, hypertension, congestive heart failure, migraine, anxiety, schizophrenia, gastrointestinal disturbances, diarrhoea and emesis.

48. A method according to claim 46 for treatment of asthma or an allergic condition.

49. A method according to any one of claims 46 to 48 wherein the (+) or (-)-mianserin-like compound is selected from the group consisting of the (+) or (-) enantiomer of compounds of general formula I:



(I)

wherein X = CH_2, O, S or NR^4, and

Y = H, CN or $-(CH_2)_n-C(=Z).NR^1R^3$

where R^1 = H, lower alkyl or an aryloxyalkyl group wherein the aryl group is optionally substituted by alkyl, alkoxy, halogen or alkyl substituted by halogen, and n is an integer between 0 and 5, and

Z = O, S or NR^2

wherein R^2 = H, lower alkyl, hydroxy, amino, cyano, or acyl, or R^1 and R^2 may together form a ring such that Y is a heterocyclic group,

R^3 = H or lower alkyl, and

R^4 = H, lower alkyl, or lower acyl.

50. A method according to claim 14 wherein the (+) or (-)-mianserin-like compound is (-) 2-carboxamidino-1,2,3,4,10,14b-hexahydrodibenzo [c,f] pyrazino-[1,2-α] azepine.

51. Use of a substantially optically pure (+) or (-)-mianserin-like compound in the treatment of disturbances of 5-hydroxytryptamine metabolism and/or histamine metabolism.

52. Use of a substantially optically pure (+) or (-)-mianserin-like compound in the preparation of a medicament for the treatment of disturbances of 5-hydroxytryptamine metabolism and/or histamine metabolism.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/AU 98/00807

A. CLASSIFICATION OF SUBJECT MATTER

Int Cl[6]: C07D 487/04, 498/04, 513/04, A61K 31/55

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)

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)
STN Substructure search
STN Keyword search (Terms: mianserin and (?tartrate or ?tartaric)).

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X Y	WO 88/07997 (MONASH UNIVERSITY) 20 October 1988 Page 3 lines 19-21, page 6 lines 5-7 Whole document	36-37, 40-41 1-52
Y	**VOGEL'S Textbook of Practical Organic Chemistry**, 5th Ed, Section 5.19 Resolution of Racemates, pages 809-810, Experiment 5.219 page 812-813	1-52
X	EP B 421823 (SANKYO COMPANY LIMITED) 10 April 1991, See whole document, especially Method B (page 34) and Formula (I) (page 2).	1-37 42-44 46-49 51-52

[X] Further documents are listed in the continuation of Box C

[X] See patent family annex

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
18 NOVEMBER 1998	24 NOV 1998

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/AU 98/00807

C (Continuation). **DOCUMENTS CONSIDERED TO BE RELEVANT**

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	**Chemical Abstract 124: 176146** "Optical Resolution of nitrogen-containing cyclic compound" and JP,A, 07-247286 (SANKYO CO LTD) 26 September 1995 See Abstract	1-26, 36-37
X	**The Journal of Pharmacology and Experimental Therapeutics**, Vol. 278, No, pages 21-30, "Identification of Human Cytochrome P450 Isoforms Involved in the Stereoselective Metabolism of Mianserin Enantiomers". E. Koyama et al. See whole document, especially page 22, column 2, lines 4-6	36-37, 42-44, 46-47, 49, 51-52
X	**Acta psychiatr. Scand., 1985:72 (Suppl. 320);** 1-9 "Adrenoreceptor interactions of the enantiomers and metabolites of mianserin: are they responsible for the antidepressant effect?, R.M. Pinder. See whole document, especially Figure 1, page 2, page 3 column 1 lines 2-11	36,42-43, 46-47 51-52
X	**Bull. Chem. Soc. Jpn., 69, 3581-3590 (1996)** "Facile Optical Resolution of a Dibenzopyrazinoazepine Derivative and the Nature of Molecular Recognition of Amines by Chiral 2.3-Di-O-(arylcarbonyl) tartaric acids". H. Tomori et al. See whole document, particularly page 3581 column 1 lines 19-24, page 3588, column 1 lines 15-16, page 3589 column 1 lines 19 - column 2 line 10.	1-26, 36-37
A	AU B 39757/68 (423307) (NV ORGANON.) 8 January 1970 Whole document	1-52
A	AU B 18387/67 (415312) (N.V. ORGANON) 5 September 1968 Whole document	1-52

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/AU 98/00807

This Annex lists the known "A" publication level patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent Document Cited in Search Report		Patent Family Member					
WO	8807997	AU	15904/88	CA	1336773	EP	379483
		US	5049637	JP	2503670		
EP	421823	CA	2026925	EP	505014	US	5362725
		US	5461051	US	5476848	JP	3279383
		JP	8019130				
							END OF ANNEX