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(54) Title: COMPOUNDS HAVING SEROTONIN 5-HT17 RECEPTOR ANTAGONIST ACTIVITY AND MUSCARINIC M4 RECEPTOR AGONIST ACTIVITY AND THEIR USE IN THE TREATMENT OF PSYCHOTIC DISORDERS

(57) Abstract: The present invention relates to novel treatments for schizophrenia, based on the concept of identifying agents capable of selectively binding to the serotonin 5-HT_7 and muscarinic M_4 receptors and the use of such compounds in treating schizophrenia. The present invention also relates to novel amidine compounds for treating schizophrenia, a method of manufacturing such compounds, pharmaceutical formulations comprising said compounds, as well as medical uses and methods of treatment using said compounds.

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COMPOUNDS HAVING SEROTONIN 5-HT17 RECEPTOR ANTAGONIST ACTIVITY AND MUSCARINIC M4 RECEPTOR AGONIST ACTIVITY AND THEIR USE IN THE TREATMENT OF PSYCHOTIC DISORDERS

Technical Field

The present invention relates to novel treatments for schizophrenia, based on the concept of identifying agents capable of selectively binding to the serotonin 5-HT_7 and muscarinic M_4 receptors and the use of such compounds in treating schizophrenia. The present invention also relates to novel amidine compounds for treating schizophrenia, a method of manufacturing such compounds, pharmaceutical formulations comprising said compounds, as well as medical uses and methods of treatment using said compounds.

Background Art

The antipsychotic drugs (APDs) currently used in the treatment of schizophrenia are less than optimal in many respects, showing a lack of efficacy against some of the symptoms of schizophrenia and a significant tendency to produce unpleasant side-effects. While all APDs are effective against the positive symptoms of schizophrenia in the majority of patients, they are all less than completely effective against the negative symptoms and cognitive deficits of the disease, with many APDs showing virtually no efficacy against these symptoms. Negative symptoms include loss of emotional responsiveness, lack of motivation and social withdrawal. Cognitive deficits include deficits in working memory, attention and executive function. In addition, in a significant proportion of patients, the positive symptoms which include hallucinations and delusions do not respond to conventional antipsychotic drugs. All current APDs share the common property of affinity and antagonist action at D_2 dopamine receptors (Seeman, 2001). This is thought to

underly their activity against the positive symptoms, but unfortunately is responsible also for unpleasant side-effects such as parkinsonian motor deficits and hyperprolactinaemia.

It is widely accepted that clozapine shows the most favourable therapeutic profile of current antipsychotic drugs used in the treatment of schizophrenia. While all APDs, including clozapine, are effective to some degree against the positive symptoms of schizophrenia, clozapine is more effective than other APDs against the negative symptoms and cognitive deficits of the disease, and is also effective in many patients who do not respond to conventional APDs. However, despite its high clinical efficacy, clozapine exhibits relatively low occupancy of D_2 dopamine receptors. In common with most APDs, clozapine binds to many different neurotransmitter receptors implicated in psychosis.

Muscarinic M_4 receptors (Eglen, 2001) are located in brain regions that have been implicated in psychosis, including the prefrontal cortex, and are present in the specific neurones which are compromised in the post-mortem prefrontal cortex tissue from schizophrenic patients. While most APDs either have no affinity for the M_4 receptor or act as antagonists, there is some evidence that M_4 agonists may show APD-like activity in some tests. This is consistent with evidence that the levels of M_4 receptors may be reduced in prefrontal cortex from schizophrenic patients as compared to normal controls (Crook et al., 2001). In addition, serotonin 5-HT_7 receptors (Vanhoenacker et al., 2000) are strikingly localised to thalamic nuclei. Some of the more effective atypical APDs have significant 5-HT_7 affinity as part of their complex pharmacological profile.

There is a need for effective APDs which are able to ameliorate both positive and negative symptoms and the cognitive deficits of schizophrenia and/or bipolar disorder without significant D_2 affinity.

Disclosure of Invention

Therefore it is a first object of the present invention to obviate and/or mitigate the deficiencies associated with current antipsychotic drug treatments.

It is a second object of the present invention to provide a novel pharmaceutical agent which combines serotonin 5-HT_7 receptor antagonist activity and muscarinic M_4 receptor agonist activity for use in the treatment of schizophrenia and/or bipolar disorder.

It is a third object of the present invention to provide the abovementioned pharmaceutical agents which additionally possess relatively low or negligible dopaminergic D_2 affinity which are useful as antipsychotic agents useful for the treatment of schizophrenia and/or bipolar disorder.

It is a fourth object of the present invention to provide an agent which represents a novel class of antipsychotic drug, useful for the treatment of schizophrenia and/or bipolar disorder.

It is fifth object of the present invention to provide an agent according to the third object which additionally possess relatively low or negligible dopaminergic D_2 affinity which represents a novel class of antipsychotic drug, useful for the treatment of schizophrenia and/or bipolar disorder.

It is a sixth object of the present invention to provide at least one novel amidine compound which possesses serotonin 5-HT_7 receptor antagonist activity and/or muscarinic M_4 receptor agonist activity.

It is a seventh object of the present invention to provide at least one novel amidine compound which additionally possesses relatively low or negligible dopaminergic D_2 affinity.

It is an eighth object of the present invention to provide a pharmaceutical composition comprising said agents for the treatment of schizophrenia and/or bipolar disorder.

A further object of the present invention is to provide a method for identifying an agent as defined above.

The present inventors have hypothesised that the favourable therapeutic profile of clozapine might be based on its 5-HT_7 antagonist activity and muscarinic M_4 agonist activity with low occupancy of D_2 dopamine receptors. According to this hypothesis, an agent possessing 5-HT_7 antagonist activity and substantial muscarinic M_4 agonist activity, yet without significant D_2 dopamine affinity, is postulated to show antipsychotic efficacy against both positive and negative symptoms and cognitive deficits. Such an agent may show an improved therapeutic profile relative to existing APDs, in terms of improved clinical efficacy and reduced side effect profile.

We therefore hypothesised that the combination of these two unusual properties - 5-HT_7 antagonist activity and muscarinic M_4 agonist activity - might act to restore disturbed function in the brains of schizophrenic patients. Furthermore, we hypothesised that 5-HT_7 antagonist activity and muscarinic M_4 agonist activity alone, in the absence of D2 antagonist activity, might be sufficient to bestow effective APD activity on such a pharmacological agent. According to this hypothesis, a compound possessing 5-HT_7 antagonist activity and

substantial muscarinic M_4 agonist activity, yet without significant D2 dopamine antagonist activity, would show antipsychotic efficacy against both positive and negative symptoms. Such a compound would be predicted to show an improved therapeutic profile relative to existing APDs, in terms of improved clinical efficacy and reduced side effect profile.

Furthermore, schizophrenic patients show marked deficits in cognitive tests, particularly those that are prefrontal cortex dependent, and this is thought to contribute to their inability to lead a relatively normal life. Since there is evidence that M_4 muscarinic agonists should act as cognitive enhancers (Jerusalinsky et al., 1998), a drug with substantial M_4 agonist activity should also be effective against the cognitive impairment characteristic of the disease.

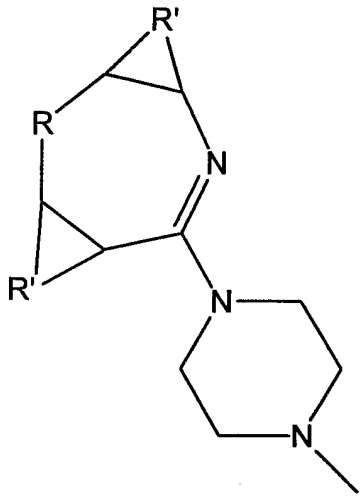
Hence, the present inventors sought to demonstrate that potential therapeutic efficacy from a pharmacological agent combining selectivity versus other receptors with serotonin 5-HT_7 antagonist activity and muscarinic M_4 agonist activity - hereinafter termed a "serominic" compound.

Thus, in a first aspect of the present invention there is provided a pharmaceutical agent having serotonin 5-HT_7 receptor antagonist activity and muscarinic M_4 receptor agonist activity, for use in treating psychotic conditions such as schizophrenia and/or bipolar disorder, wherein the agent does not include compounds having a chemical structure falling within the following definition, namely:

bisarylazepines substituted at the azepine ring portion by a 4-methyl piperazinyl, wherein the aryl moieties are fused to the azepine ring and wherein aryl is phenyl, substituted phenyl, thienyl or substituted

thienyl; including optional replacement of an azepine ring carbon atom with a nitrogen atom, or substitution of said ring carbon atom.

The compounds not encompassed by the present invention are represented by the following general formula:



wherein R represents substituted or unsubstituted C or N and each R' together with the carbon to which it is bonded independently represents phenyl, substituted phenyl, thienyl or substituted thienyl.

The above disclaimer is intended to exclude in particular any accidental anticipation by the compounds clozapine, fluperlipine, tenilapine and olanzapine. These compounds are four known antipsychotic drugs which display M_4 agonism and 5-HT_7 antagonism as part of their wide spectrum of pharmacological actions. Thus, the compounds also show affinity for a large number of receptors, such as adrenergic α_1, α_2; histaminergic H_1, H_2, H_3; dopaminergic D_1, D_2, D_3, D_4, D_5; muscarinic cholinergic M_1, M_2, M_3, M_4, M_5; serotonergic 5-HT_{1A}, 5-HT_{2A}, 5-HT_{2B}, 5-HT_{2C}, 5-HT_3, 5-HT_6, 5-HT_7. As such there is no suggestion in the art that the activities towards the M_4 and 5-HT_7 receptors alone or together are significant or for that

matter that the compounds are selective in their action i.e. do not act on many diverse receptors. Moreover, only the four compounds mentioned above out of the large number of atypical antipsychotic drugs show a very weak agonist activity at muscarinic M_4 receptors. While it has been suggested that M_4 agonists or 5-HT_7 antagonists individually may have some therapeutic efficacy against the positive symptoms of schizophrenia, based on results in animal models (Bymaster et al., 1998; Shannon et al., 1999a,b; Pouzet et al., 2002), M_4 agonists or 5-HT_7 antagonists individually have failed to show activity in animal models predictive of efficacy against the negative symptoms of schizophrenia (Bymaster et al., 1998; Pouzet et al., 2002). In view of the very large number of receptors potentially linked to the treatment of schizophrenia, which would include adrenergic α_1, α_2; histaminergic H_1, H_2, H_3; dopaminergic D_1, D_3, D_4, D_5; muscarinic cholinergic M_1, M_2, M_3, M_4, M_5; and serotonergic 5-HT_{1A}, 5-HT_{2A}, 5-HT_{2B}, 5-HT_{2C}, 5-HT_3, 5-HT_6, 5-HT_7 receptors, in addition to D_2 receptors, there is no suggestion in the art that the specific combination of activities just towards the M_4 and 5-HT_7 receptors is significant for the treatment of schizophrenia. Since most clinically useful atypical antipsychotic drugs do not show M_4 agonist activity it is likely that the skilled artisan would not generally believe this property to be important clinically. It has never before been suggested, or demonstrated, that combining the properties of M_4 agonism and 5-HT_7 antagonism, in the absence of any other pharmacological activity, would give activity against all the range of symptoms of schizophrenia.

As used herein the term agonist refers to a ligand that, upon binding to said receptor, triggers activation of a chemical signalling cascade that results in a

definable change in the behaviour or physical or biological state of a cell (including partial agonists which cause detectable but sub-maximal activation of signalling cascades) and the term antagonist refers to a molecule that, by virtue of binding to said receptor, is able to block the cell-activating influence of an agonist to said receptor, and which itself does not result in substantial activation of the cell.

The pharmaceutical agent may comprise a mixture of at least two compounds, wherein at least one of said compounds possesses serotonin 5-HT_7 receptor antagonist activity and wherein at least one of said compounds possess muscarinic M_4 receptor agonist activity.

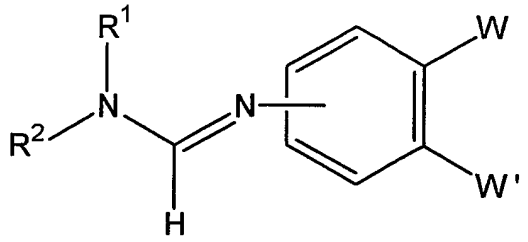
Alternatively, the pharmaceutical agent may comprise a compound which possess both serotonin 5-HT_7 receptor antagonist activity and muscarinic M_4 receptor agonist activity, hereinafter termed a serominic compound.

Preferably the pharmaceutical agent additionally has a low or substantially no dopaminergic D_2 receptor affinity.

A low dopaminergic D_2 receptor affinity may be, for example, a minimum of at least 5 fold less than the affinity at the muscarinic M_4 and/or serotonin 5-HT_7 receptors.

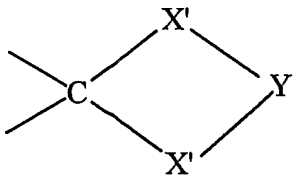
More preferably the dopaminergic D_2 receptor affinity is at least 5 fold, preferably at least 10 or 20 fold or at least 50 fold less than the affinity at the muscarinic M_4 and/or serotonin 5-HT_7 receptors.

In a second aspect of the present invention there is provided a compound represented by formula (I):



(I)

wherein R^1 and R^2 independently are a hydrogen atom, a substituted or unsubstituted straight chain or branched chain C_{1-6} alkyl group or C_{1-6} alkoxy group, a substituted or unsubstituted C_{3-8} cycloalkyl group or a C_{3-8} cycloalkoxy group, or an aralkyl group, or R^1 and R^2 form, together with the nitrogen atom to which they are bonded, a cyclic amine; W and W' form, together with the benzene ring to which they are bonded, a fused five-membered, six-membered or seven-membered saturated carbocyclic ring being independently unsubstituted, substituted or fully substituted at each carbon atom of the ring by a group $-X-R^{13}$ wherein X is O, S, SO or SO_2 and R^{13} is a hydrogen atom, a C_{1-6} alkyl group, an acyl group, or an aroyl group or two of said $-X-R^{13}$ groups, together with the carbon atom in the ring to which they are both bonded, form a C=O group, a C=S group or the following group:



wherein both of X' are O or S and Y is a C_{1-3} alkylene group.

The cyclic amine may be substituted by a halogen atom, a C_{1-6} alkyl group or a C_{1-6} alkoxy group. Alternatively or additionally, the cyclic amine may be fused with a benzene ring. Said benzene ring may be

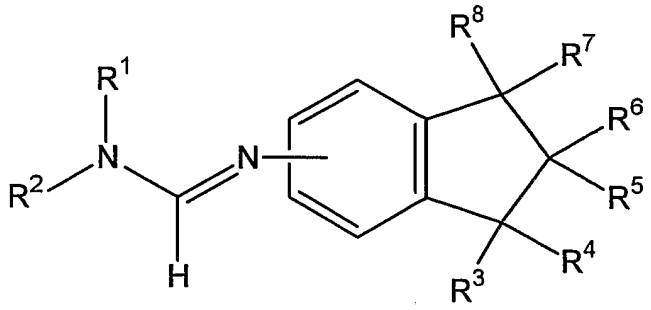
substituted by one or two halogen atoms, C_{1-6} alkyl groups or C_{1-6} alkoxy groups.

The term "substituted" as used herein when in association with the saturated carbocyclic ring refers to one hydrogen atom of a carbon atom of the ring being replaced by a substituent, whereas the term "fully substituted" refers to both of the hydrogen atoms of a carbon atom of the ring being replaced by substituents.

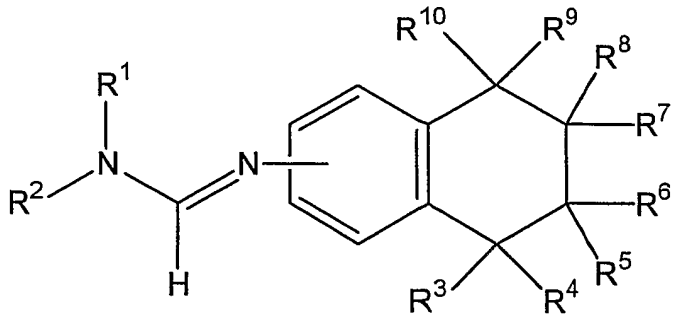
The present inventors hypothesised that exemplary compounds may contain the following features:

- a framework that contains an N^+ or a latent N^+
- a 5-HT_7 responsive group, which would typically be an aromatic system possibly with alkoxy substituents
- an M_4 responsive group.

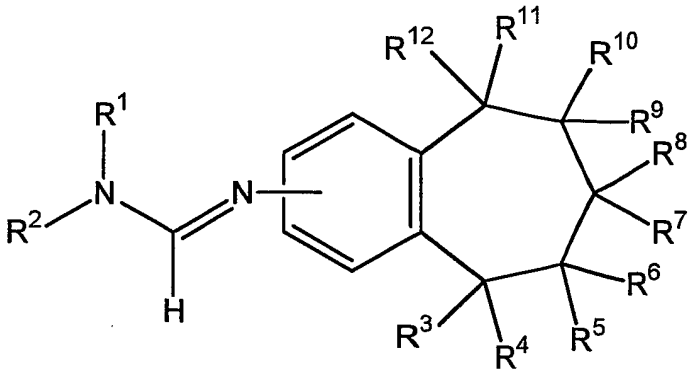
Further compounds of the second aspect of the present invention are represented by the following formulae (II), (III) and (IV) which fall within general formula (I):



(II)



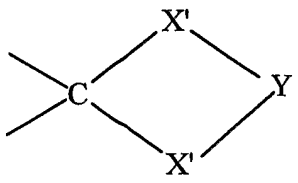
(III)



(IV)

In formulae (II), (III) and (IV), R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11} and R^{12} are independently a hydrogen atom or the group $-X-R^{13}$ wherein X is O, S, SO or SO_2 and R^{13} is a hydrogen atom, a C_{1-6} alkyl group, an acyl group, or an aroyl group.

Alternatively, R^3 and R^4, R^5 and R^6, R^7 and R^8, R^9 and R^{10}, and R^{11} and R^{12} together with the carbon atom in the ring to which they are both bonded, form a C=O group, a C=S group or the following group:



wherein both of X' are O or S and Y is a C_{1-3} alkylene group.

At each occurrence in formulae (I), (II), (III) and (IV) examples of C_{1-6} alkyl groups are methyl, ethyl, propyl, isopropyl, butyl, tert-butyl, pentyl and hexyl.

Examples of aralkyl groups are benzyl, phenylethyl, chlorobenzyl, methylbenzyl, and methoxybenzyl.

Examples of halogen atoms are chlorine, bromine, fluorine and iodine.

Examples of C_{1-6} alkoxy groups are methoxy, ethoxy, propoxy, butoxy, pentyloxy and hexyloxy.

An example of an acyl group is a C_{2-6} alkanoyl group for example an acetyl, propionyl, butyryl, pentanoyl or hexanoyl.

Examples of aroyl groups are benzoyl, phenylacetyl, chlorobenzoyl, methylbenzoyl, methoxybenzoyl, dichlorobenzoyl, dimethylbenzoyl or dimethoxybenzoyl.

Examples of C_{1-3} alkylene groups are methylene, ethylene, propylene or trimethylene.

Examples of C_{3-8} cycloalkyl groups are cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl or cycloctyl optionally substituted by one or more substituents selected from the group consisting of a halogen atom, a C_{1-6} alkyl group and C_{1-6} alkoxy group.

Examples of C_{3-8} cycloalkoxy groups are cyclopropyloxy, cyclobutyloxy, cyclopentyloxy, cyclohexyloxy, cycloheptyloxy or cycloctyloxy optionally substituted by one or more substituents selected from the group consisting of a halogen atom, a C_{1-6} alkyl group and C_{1-6} alkoxy group.

Preferred compounds, although not exclusively, are those represented by the above formulae when R^1 and R^2 form together with the nitrogen atom to which they are bonded, a four-membered, five-membered or six-membered cylic amine.

The six-membered cyclic amine is preferably fused with a benzene ring, typically at carbon atoms 4a and 8a (according to isoquinoline numbering nomenclature).

The said benzene ring may also be substituted at any two adjacent carbon atoms.

Preferably said substitution is with a C_{1-6} alkoxy group which is preferably a methoxy group.

Alternatively, R^1 and R^2 may both be a C_{1-6} alkyl group.

Preferably the alkyl group is a methyl group.

In a further embodiment, R^1 may be an aralkyl group, preferably a benzyl group and R^2 may be a C_{1-6} alkyl group, preferably a methyl group.

The five-membered, six-membered or seven-membered saturated (except at the ring fusion) carbocyclic ring is typically substituted by a hydroxyl or an O-acyl group.

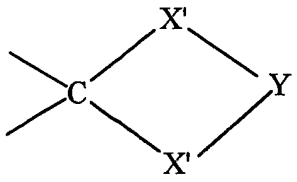
Preferably the acyl part of the O-acyl group is a C_{2-6} alkanoyl group such as an acetyl group or a propionyl group.

Typically the substitution is at carbon number 5 of the seven-membered benzocycloheptyl ring systems and carbon number 1 of the five-membered indanyl and six-membered tetrahydronaphthalenyl ring systems.

Alternatively, the five-membered, six-membered or seven-membered saturated carbocyclic ring may be substituted with an O-aroyl group in which the aroyl part is typically a benzoyl group. The benzene ring of the benzoyl group may be further substituted with halogen atoms such as chlorine atoms. Typically two chlorine atoms are present, preferably at positions 3 and 4 of the benzene ring.

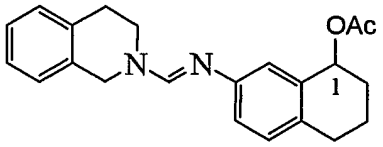
The carbocyclic ring may instead be substituted with a thiol group or a thio group such as a C_{1-6} alkylthio group. A typical group is a butylthio group.

Alternatively the carbocyclic ring may be substituted by the group $-X-R^{13}$ when it forms the group:

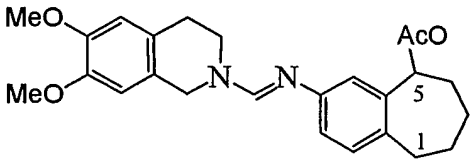


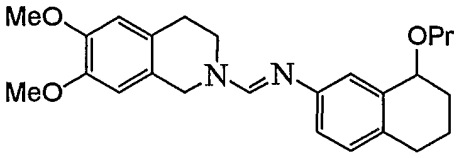
Preferably X^1 is S and Y is a C_2 alkylene group i.e. an ethylene group.

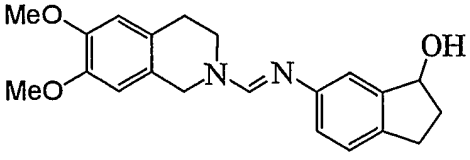
Examples of preferred compounds of the present invention are represented by the following formulae, some of which are named and ring positions numbered to indicate placement of substituents as used herein within the structural formulae.

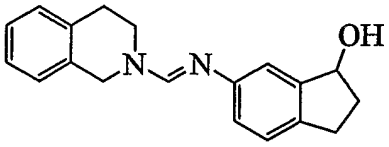


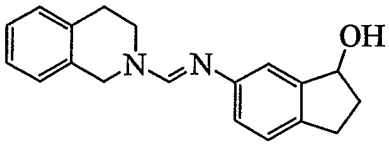
Acetic acid 7-[(3,4-dihydro-1*H*-isoquinolin-2-yl methylene)-amino]-1,2,3,4-tetrahydronaphthalen-1-yl ester



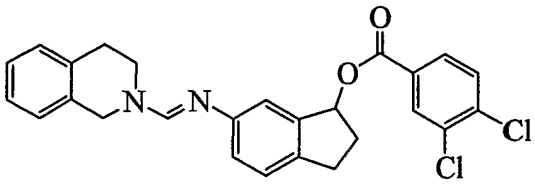


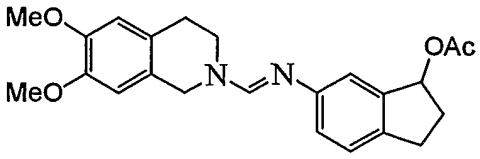


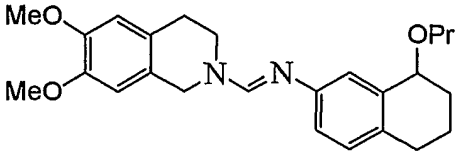


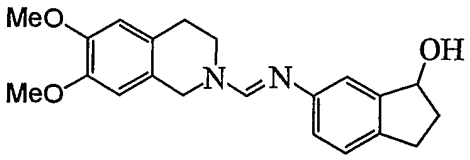


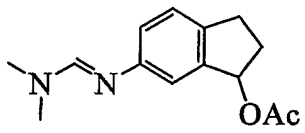
6-[(3,4-dihydro-1*H*-isoquinolin-2-ylmethylene)-amino]-indan-1-ol

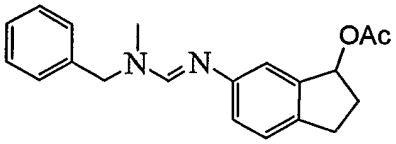


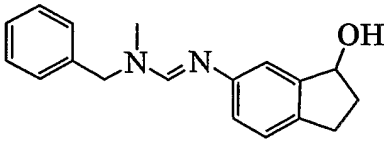


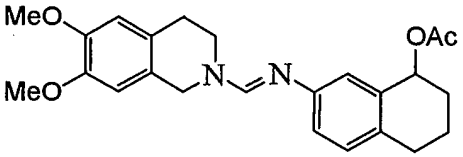




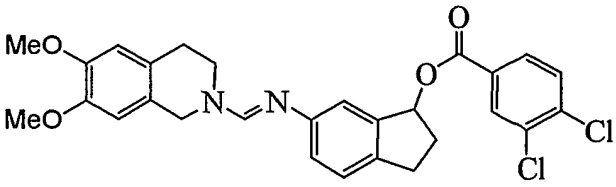


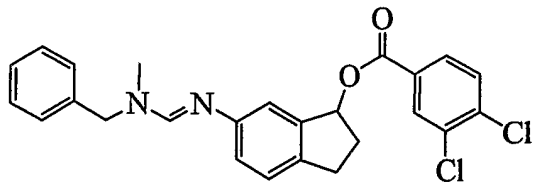


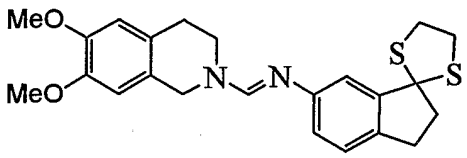


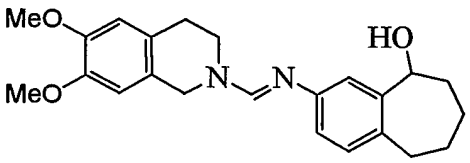


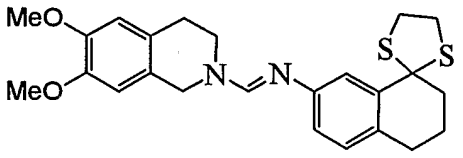
Acetic acid 6-[(3,4-dihydro-1*H*-isoquinolin-2-yl methylene)-amino]-indan-1-yl ester

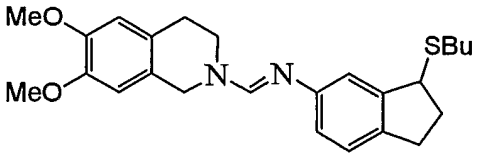












Preferably the said compounds according to any of the formulae (I), (II), (III) or (IV) possess serotonin 5-HT_7 receptor antagonist activity and/or muscarinic M_4 receptor agonist activity.

Preferably the compounds additionally have a low or substantially no dopaminergic D_2 receptor affinity.

A low dopaminergic D_2 receptor affinity may be, for example, a D_2 receptor affinity having a minimum of at least 5 fold less than the affinity for the muscarinic M_4 and/or serotonin 5-HT_7 receptors.

More preferably the dopaminergic D_2 receptor affinity is a D_2 receptor affinity is at least 10 or 20 fold or at least 50 fold less than the affinity for the muscarinic M_4 and/or serotonin 5-HT_7 receptors.

For the avoidance of doubt the compounds of the present invention may be provided as pharmaceutically acceptable salts, solvates inclusive of hydrates or derivatives such as esters.

It is understood that the present invention extends to each of the stereoisomers of the compounds of formulae (I), (II), (III) and (IV) as well as the racemates.

According to a third aspect of the present invention, the amidine compounds represented by formulae (I), (II), (III) and (IV) may be prepared by:

(i) providing an aromatic amine compound;

(ii) providing a formamide compound; and

(iii) coupling the aromatic amine with the formamide to give said amidine compound.

The formamide may be made by condensing an amine with an anhydride derived from formic acid.

The aromatic amine may be produced by reduction of an aromatic nitro compound, which can be prepared by nitration of an arene.

The compounds of formulae (I), (II), (III) and (IV) and their pharmaceutically acceptable salts and/or hydrates can be prepared according to the following procedure for the coupling of amine and formamide,

hydrolysis of ester and, if necessary, preparation of salt and/or hydrate form of amidine:

(1) To a solution of formamide (2.0eq.) in dry dichloromethane (5mL/mmol of amine) under nitrogen at room temperature was added phosphorus oxychloride (2.0eq.) dropwise. The solution was stirred at room temperature for 30min. The resulting solution was transferred to a flask containing amine (1.0eq) via a cannula under nitrogen and the reaction continued at room temperature for 2 to 3h. The mixture was diluted with dichloromethane and washed with sodium hydroxide solution (2M), dried over magnesium sulfate, filtered and concentrated. Purification by flash chromatography with suitable eluent afforded the corresponding amidine (base form). Yields ranged from 40 to 60%.

(2) The hydrolysis of some of the coupling product (acetate esters) was performed by dissolving samples in methanol containing a catalytic amount of potassium carbonate at room temperature. The reaction was followed by TLC. The solvent was removed and the residue was dissolved in dichloromethane, washed with water, dried over magnesium sulfate, filtered and concentrated. Purification by flash chromatography gave alcohols.

(3) The salt form of the amidine was made by dissolving the amidine free base sample in dichloromethane and washing with, for example hydrochloric acid (2M), and drying over magnesium sulfate. Filtration and concentration afforded the corresponding salt form of amidine.

Emerging evidence suggests that schizophrenia results from dysfunction of specific neural circuits in

the brain. There is pathological evidence for dysfunction of cells in the prefrontal cortex in schizophrenic patients, along with clear indications from brain imaging studies that the prefrontal cortex is hypofunctional. The prefrontal cortex is a key part of the corticolimbothalamic circuit, which connects it both directly and indirectly to the midline thalamic nuclei. Dysfunction of this circuit in schizophrenia is consistent with the concept that the symptoms of schizophrenia are due to perturbation of midline thalamic function. Without wishing to be bound by theory, the present inventors therefore hypothesised that a pharmacological agent able to restore disturbed thalamic and prefrontal cortex function may effectively treat the symptoms of schizophrenia.

Muscarinic M_4 receptors (Eglen, 2001) are located in brain regions that have been implicated in psychosis, including the prefrontal cortex, and are present in the specific neurones which are compromised in the post-mortem prefrontal cortex tissue from schizophrenic patients. While most APDs either have no affinity for the M_4 receptor or act as antagonists, there is some evidence that M_4 agonists may show APD-like activity in some tests. This is consistent with evidence that the levels of M_4 receptors may be reduced in prefrontal cortex from schizophrenic patients as compared to normal controls (Crook et al., 2001). In addition, serotonin 5-HT_7 receptors (Vanhoenacker et al., 2000) are strikingly localised to thalamic nuclei. Some of the more effective atypical APDs have significant 5-HT_7 affinity as part of their complex pharmacological profile.

The present inventors therefore considered it possible that the combination of the two unusual properties - 5-HT_7 antagonist activity and muscarinic M_4

agonist activity - might act to restore disturbed function in the brains of schizophrenic patients. Furthermore, they hypothesise that 5-HT_7 antagonist activity and muscarinic M_4 agonist activity, in the absence of D_2 affinity might be sufficient to bestow effective APD activity on such a pharmacological agent. According to this hypothesis, an agent possessing 5-HT_7 antagonist activity and substantial muscarinic M_4 agonist activity, yet without significant D_2 dopamine affinity, is postulated to show antipsychotic efficacy against both positive and negative symptoms and cognitive deficits. Such an agent may show an improved therapeutic profile relative to existing APDs, in terms of improved clinical efficacy and reduced side effect profile.

The present inventors have observed that some existing agents used in the treatment of schizophrenia have affinity for 5-HT_7 and M_4 receptors, as well as many other receptors. There is however no suggestion in the art that the activity of the agents is due to a combination of their affinity and/or activity on the 5-HT_7 and M_4 receptors. These agents fall under the general grouping of bisorylazepines and in order to avoid any accidental anticipation by these compounds, such compounds are not encompassed by the present invention.

In addition, schizophrenic patients show marked deficits in cognitive tests, and this is thought to contribute to their inability to lead a relatively normal life. Since there is evidence that M_4muscarinic agonists should act as cognitive enhancers (Jerusalinsky et al., 1998), a drug with substantial M_4 agonist activity may also be effective against the cognitive impairment characteristic of the disease.

Hence, the present inventors sought to demonstrate the potential therapeutic efficacy of a pharmacological agent combining selectivity versus other receptors with serotonin 5-HT_7 antagonist activity and muscarinic M_4 agonist activity.

The compounds with properties according to the present invention may be provided as pharmaceutical formulations wherein the compound or compounds is/are admixed with a pharmaceutically acceptable carrier (e.g. binder, corrective, corrigent, disintegrator, emulsion, excipient), diluent or solibilizer to give a pharmaceutical composition by a conventional manner, which is formulated into, for example, a tablet, capsule, granule, powder, syrup, suspension, solution, injection, infusion, deposit agent, suppository. Administration may be for example orally or parenterally.

When the tablets are used for oral administration, typically used carriers include sucrose, lactose, mannitol, maltitol, dextran, corn starch, typical lublicants such as magnesium stearate, preservatives such as paraben, sorbin, antioxidants such as ascorbic acid, α-tocopherol, cystein, disintegrators or binders. When administered orally as capsules, effective diluents include lactose and dry corn starch. A liquid for oral use includes syrup, suspension, solution and emulsion, which may contain a typical inert diluent used in this field, such as water. In addition, sweeteners or flavors may be contained.

In the case of parenteral administration such as subcutaneous injection, intraveneous injection, intramuscular injection, intraperitoneal injection or infusion, the pH of the active ingredient solution may be appropriately adequately adjusted, bufferized or sterilized. Examples of usable vehicle or solvent

include distilled water, Ringer water and isotonic brine. For intraveneous use, the total concentration of solute is adjusted to make the solution isotonic.

Suppositories may be prepared by admixing the compounds of the present invention with a suitable nonirritative excipient such as those that are solid at normal temperature but become liquid at the temperature in the intestine and melt in rectum, such as cocoa butter and polyethylene glycols to release the active ingredient.

The dose can be determined depending on age, body weight, administration time, administration method, combination of drugs, the level of condition for which a patient is undergoing therapy, and other factors. While the daily dose may vary depending on the conditions and body weight of patients, the species of active ingredient, and administration route, in the case of oral use, the daily dose is about 0.1 mg-100 mg/person/day, preferably 0.5 mg-30 mg/person/day. In the case of parenteral use, the daily dose is desirably 0.1 mg-50 mg/person/day, preferably 0.1 mg-30 mg/person/day for subsutaneous injection, intraveneous injection, intramuscular injection and intrarectal administration.

Accordingly the agents and compounds according to the first and second aspects of the present invention, may be used in a method for treating psychotic disorders, for example schizophrenia for example the positive and/or negative symptoms of schizophrenia, and/or the cognitive deficits of schizophrenia, and/or bipolar disorder.

The present invention accordingly provides agents with properties according to the present invention and compounds represented by formulae (I), (II), (III) and (IV) for use in medicine or therapy.

According to a fourth aspect of the present invention, there is provided use of the agents with properties according to the present invention and compounds represented by formulae (I), (II), (III) and (IV) for the preparation of a medicament for the treatment of psychotic disorders, for example, schizophrenia e.g. the positive and/or negative symptoms of schizophrenia and/or the cognitive deficits of schizophrenia, and/or bipolar disorder.

According to a fifth aspect of the present invention, there is provided a method of identifying an agent having the properties according to the present invention comprising the steps of:

a) providing an agent to be tested;

b) subjecting said agent to one or more test procedures to identify 5-HT_7 receptor antagonist activity and muscarinic M_4 receptor agonist activity of said agent;

wherein the desired agent is considered to have been identified when said agent provides a 5-HT_7 receptor antagonist activity and a muscarinic M_4 receptor agonist activity.

Desirably, the method further includes the step of subjecting the agent to a test procedure to identify low dopaminergic D_2 receptor affinity.

More preferably the agent is generally more selective than existing antischizophrenic and/or anti-bipolar disorder drugs. That is the agent has less affinity for other receptors than existing antischizophrenic and/or anti-bipolar disorder drugs.

Thus, the method may further comprise the step of subjecting the agent to a procedure to detect affinity for other receptors namely adrenergic α_1, α_2; histaminergic H_1, H_2, H_3; dopaminergic D_1, D_2, D_3, D_4, D_5;

muscarinic cholinergic M_1, M_2, M_3, M_4, M_5; serotoneric 5-HT_{1A}, 5-HT_{2A}, 5-HT_{2B}, 5-HT_{2C}, 5-HT_3, 5-HT_6, 5-HT_7 and selecting agents which display affinity for less than 75% of said receptors, preferably less then 50% of said receptors.

The present invention will now be described by way of example with reference to the following experimental section and drawings in which:

Figure 1 is a representation of a full treatment paradigm of chronic PCP rat model with PTAC ((5R,6R)6-(3-propylthio-1,2,5-thiadiazol-4-yl)-1 azabicyclo(3.2.1)octane) and SB258741 (R-(+)-1-(toluene-3-sulfonyl)-2-[2-(4-methylpiperidin-1-yl)ethyl]pyrrolidine, CNS Drug Rev., 2002 Spring; 8(1):90-100);

Figure 2 shows the effect of haloperidol (Hal), clozapine (cloz) or the experimental serominic combination - PTAC + SB258741 (PTAC/SB) - on chronic PCP-induced hypofrontality;

Figure 3 relates to the reticular thalamic metabolic activity and shows the effect of haloperidol (Hal), clozapine (cloz) or the experimental serominic combination - PTAC + SB258741 (PTAC/SB) - on chronic PCP-induced hypoactivity;

Figure 4 relates to the auditory structure metabolic activity and shows the effect of haloperidol (Hal), clozapine (cloz) or the experimental serominic combination - PTAC + SB258741 (PTAC/SB) - on chronic PCP-induced hypoactivity.

Figure 5 - Effects of PTAC alone on apomorphine-induced deficits in PPI in rats. Values represent mean ± SEM. ##$p<0.01$ compared to Vehicle+APO group and PTAC treated groups (Dunnett's test). n=7.PPI (average) means

that PPI collapsed across all three prepulse intensities (73,75 and 80dB).

Figure 6 - Effects of SB258741 alone on apomorphine-induced deficits in PPI in rats. Values represent mean± SEM. ##p<0.01 compared to Vehicle+Vehicle group (t-test). There are no significant difference between Vehicle+APO group and SB258741 treated groups (Dunnett's test). n=7.

Figure 7 - Synergisitic effect of PTAC and SB258741 on apomorphine-induced deficits in PPI in rats. Values represent mean±SEM. ##p<0.01 compared to Vehicle+Vehicle+Vehicle group (t-test). **p<0.01 compared to Vehicle+Vehicle+APO group (t-test). n=7.

Figure 8 shows the modulation of PACAP-induced stimulation of cAMP by the compound 32.

Example 1 gives the various methods and results of testing for compound efficacy in the treatment of schizophrenia;

Example 2 gives the various methods and results of screening for binding affinity of the compounds of the present invention and in vivo testing;

Example 3 describes several examples for the preparation of the compounds of the present invention.

Example 1

In vivo activity:

To test the hypothesis that a serominic compound would show efficacy in the treatment of schizophrenia, we exploited our recent discovery of an animal model of schizophrenia that mimics the neurochemical and metabolic dysfunction in the brains of patients with schizophrenia (Cochran et al., 2003).

Schizophrenic patients show reduced metabolic activity in the prefrontal cortex, auditory system and hippocampus, along with reduced levels of expression of

parvalbumin within inhibitory interneurones of the prefrontal cortex. The hypometabolism in the prefrontal cortex is not restored to normal by typical APDs, or by atypical APDs such as clozapine, although the hypometabolism in the auditory system is thought to be improved by both typical and atypical APDs (Schroeder et al., 1994; Andreasen et al., 1992 and Potkin et al., 1994). We have previously reported (Cochran et al., 2003) that these deficits observed in schizophrenic patients are reproduced in rats treated chronically with phencyclidine (PCP) – a drug known to cause schizophrenic symptoms when administered chronically in humans. We have also observed that, in parallel with the clinical observations, the prefrontal cortex hypometabolism in PCP-treated rats is not attenuated by the representative atypical and typical antipsychotic drugs clozapine or haloperidol (Cochran et al., 2003), whereas the hypometabolism in the auditory system is restored towards normal levels by both haloperidol and clozapine. Thus evidence that a serominic compound could restore the prefrontal cortex hypometabolism in PCP-treated rats towards normal levels would indicate that a serominic compound would be more effective than currently available antipsychotic drugs for the treatment of schizophrenia. (5R,6R)6-(3-propylthio -1,2,5-thiadiazol-4-yl)-1-azabicyclo(3.2.1)octane.

When the M_4 muscarinic partial agonist (PTAC) (Calbiochem Biochemicals) was administered chronically in combination with the 5-HT_7 antagonist SB258741, the drug combination was found to attenuate the hypometabolism in the prefrontal cortex, and thus demonstrate efficacy superior not only to haloperidol, but also to clozapine. A similar effect was observed in the reticular thalamus, which is a brain region functionally connected with the

prefrontal cortex and involved in the regulation of its activity. In addition, the hypometabolism in the auditory system was also restored to normal by the M_4 agonist/5-HT_7 antagonist combination. Thus, the combination of M_4 agonist/5-HT_7 antagonist appears to exert profound antipsychotic activity, as assessed by these markers, in the absence of any D_2 affinity.

Experimental procedure

Male hooded Long Evans rats (180-220g) were randomly allocated to one of the following treatment groups: vehicle/vehicle, PCP/vehicle, and PCP/SB258741+PTAC. The first drug (PCP or vehicle) was administered by i.p injection and the second drug combination (SB258741 + PTAC) was delivered via osmotic minipump which was implanted under halothane anaesthetic on day 8 of the YRING PCP model. See WO01/75440. The doses of drug used were 2.58mg/kg PCP, vehicle (sterile saline), 0.1mg/kg/day PTAC together with SB258741 20mg/kg/day. The full treatment paradigm of the chronic PCP model is shown in Figure 1.

On the day of the 2-DG procedure, the animals were prepared according to the method of Crane and Porrino, (1989). The brains were sectioned and exposed to X-ray film and LCGU measurements were calculated using the MCID 5 densitometry system. The results were analysed using a one way ANOVA followed by LSD post hoc test where appropriate for each discrete brain region. Statistical significance was defined as $p<0.05$.

The rats treated chronically with the M_4 agonist/5-HT_7 antagonist combination did not show any overt evidence of side-effects.

LCGU within cortical regions

The effect of PTAC and SB258741 (the serominic combination) on LCGU within cortical brain regions is shown in table 1.1. The only non-auditory cortical brain region which showed a significant metabolic hypofunction induced by PCP was in the prefrontal cortex. Within the prelimbic region of the prefrontal cortex, a significant decrease in LCGU following chronic PCP compared to controls was observed in layer I (19%) and layers II and III (25%). Layers V&VI was just outside statistical significance. When SB258741+PTAC were administered in conjunction with PCP they reversed the PCP-induced hypofunction back to control levels (see table 1.1). The medial orbital cortex also displayed a significant decrease in LCGU following chronic PCP treatment compared to control animals within layer I (16%), layers II&III (19%) and layers V and VI (16%). No other cortical brain region showed any significant alterations in LCGU following any combination of drug treatment.

LCGU within auditory structures

Table 1.2 shows the effect of the serominic combination given in combination with the YRING PCP Model on LCGU in auditory brain structures. PCP treatment induced a metabolic hypofunction within a few structures of the auditory system. Within the ventral lateral lemniscus, the ventral cochlear nucleus and the primary auditory cortex chronic PCP treatment significantly reduced LCGU (26%, 21% and 25% respectively). In all these three auditory structures the serominic combination reversed the PCP-induced hypofunction

LCGU within thalamic nuclei

The effect of the serominic given in combination with the YRING PCP Model on LCGU within thalamic brain regions is shown in table 1.3. The only thalamic nuclei which displayed a metabolic hypofunction with PCP was the reticular thalamus. Within the dorsal region of the reticular thalamus LCGU was significantly decreased by 25% and in the ventral reticular thalamus the PCP-induced decrease was 21%. In both regions of the reticular thalamus the serominic combination completely reversed the PCP-induced hypofunction.

	LCGU (µmol/100g/min)		
	Vehicle	PCP	
	vehicle	Vehicle	Serominic Combination
MO1	113±4	95±3*	98±4*
MO2	118±7	95±6*	112±5#
MO3	111±8	93±3*	102±5
vO1	135±8	153±8	163±3
vO2	165±8	168±12	158±10
vO3	155±8	151±9	147±8
lO1	153±7	150±11	162±5
lO2	158±8	155±10	138±7
lO3	148±6	138±7	138±7
PrL1	129±1	105±5*	124±4#
PrL2	144±6	108±4*	145±2#
PrL3	148±7	128±8	143±7
IL1	97±5	98±6	100±5
IL2	99±5	102±7	99±5
IL3	96±5	96±7	97±6

M1	143±9	128±7	132±6
M2	124±9	117±4	119±2
Cg1	127±8	123±5	124±6
Cg2	138±8	135±6	132±4
Cg3	117±7	119±6	108±3
Pir	153±7	137±7	139±6
I	92±6	86±7	84±5
RS1	117±7	116±11	119±2
RS2	116±7	120±11	120±5
RS3	103±7	110±11	107±4
Ent1	79±6	81±4	83±5
Ent2	73±5	77±4	73±5
Ent3	69±4	72±5	63±8

Table 1.1 The effect of chronic SB258741+PTAC treatment on chronic PCP induced changes in LCGU within cortical region. All data expressed as mean LCGU (µmol/100g/min) ± SEM (n=5-7). * signifies $p<0.05$ compared to vehicle-vehicle treated animals, # signifies $p<0.05$ compared to PCP-vehicle treated animals. The abbreviations used in the table are listed hereinafter.

	LCGU (µmol/100g/min)		
	Vehicle	PCP	
	Vehicle	Vehicle	Serominic
AudCx1	177±7	133±4*	164±8#
AudCx2	140±16	123±3	131±6
VisCx1	147±6	129±11	133±9
VisCx2	129±8	115±8	117±9

ILL	113±6	94±6	110±6
DLL	105±4	87±3	112±5
VLL	121±7	95±4*	114±5#
VCP	129±8	95±4*	124±5#

Table 1.2 The effect of chronic SB258741+PTAC treatment on chronic PCP induced changes in LCGU within auditory structures. All data expressed as mean LCGU (µmol/100g/min) ± SEM (n=5-7). * signifies $p<0.05$ compared to vehicle-vehicle treated animals, # signifies $p<0.05$ compared to PCP-vehicle treated animals. Appendix 1 details the abbreviations used in the table.

	LCGU (µmol/100g/min)		
	Vehicle	PCP	
	Vehicle	Vehicle	Serominic
AV	161±8	145±10	148±3
AM	144±8	138±8	139±5
Rt dorsal	107±6	80±5*	109±2#
Rt ventral	115±7	91±5*	120±2#
G	155±9	142±11	140±5
Re	107±8	118±7	115±4
Rh	106±3	102±6	110±3
VL	119±4	121±11	116±3
VM	137±10	137±13	134±4
PV	87±5	88±6	83±2
MD	133±10	131±8	133±4

CM	117±6	110±6	113±2
CL	122±8	129±10	127±2
IM	108±4	109±6	112±4

Table 1.3 The effect of chronic SB258741+PTAC treatment on chronic PCP induced changes in LCGU within thalamic nuclei. All data expressed as mean LCGU (μmol/100g/min) ±SEM (n=5-7). * signifies $p<0.05$ compared to vehicle-vehicle treated animals, # signifies $p<0.05$ compared to PCP-vehicle treated animals. Appendix 1 details the abbreviations used in the table.

This study has shown that the chronic PCP-induced metabolic hypofunction in the prelimbic region of the prefrontal cortex is completely reversed back to control levels when administered with chronic PCP and the serominic combination. This is of great interest as we have shown previously (Cochran et al., 2003) that both clozapine and haloperidol failed to reverse this PCP-induced metabolic hypofunction in the prelimbic region of the prefrontal cortex.

Local glucose utilisation was measured in the prelimbic area of the prefrontal cortex after chronic treatment with PCP alone or with the antipsychotic drugs. Note that the reduced metabolic activity caused by PCP (*$p<0.05$ vs control) is restored to normal values by the serominic combination (#$p<0.05$ vs PCP alone) but not by haloperidol or clozapine.

Thus, the combination of M_4 agonist/5-HT_7 antagonist appears to exert profound antipsychotic activity, as assessed by these markers, in the absence of any D_2

antagonist activity. This provides dramatic evidence that an agent with serominic properties is likely to be - markedly superior to any of the currently-available antipsychotic agents.

This inability of haloperidol and clozapine to modulate the hypofrontality is consistent with data from clinical studies where similar results are obtained in medicated and unmediated patients (Schroeder et al., 1994; Andreasen et al., 1992 and Potkin et al., 1994). The prefrontal cortex is involved in working memory, attention and cognitive flexibility and has been implicated in the cognitive dysfunction observed in schizophrenic patients. Also this hypofunction has been correlated to the intensity of negative and cognitive dysfunction of schizophrenia (Wolkin et al., 1992: Schroder et al., 1995). There is conflicting evidence that clozapine and other new atypical antipsychotics are effective in treating these symptoms of the disease, but it is generally accepted that the negative symptoms and cognitive impairments seen in schizophrenia have proved very difficult to treat to date (Goldberg et al., 1993). In this study we have shown that the serominic combination can reverse the PCP-induced hypofunction in the prefrontal cortex.

In the reticular nucleus of the thalamus the PCP-induced metabolic hypofunction is restored to control levels when the serominic combination is administered (Fig 3). Previously we have shown that both clozapine and haloperidol failed to reverse the PCP-induced hypofunction in the reticular nucleus of the thalamus (Cochran et al., 2003).

Local glucose utilisation was measured in the ventral reticular thalamic nucleus after chronic treatment with PCP alone or with the antipsychotic drugs.

Note that the reduced metabolic activity caused by PCP (*p<0.05 vs control) is restored to normal values by the serominic combination (#p<0.05 vs PCP alone) but not by haloperidol or clozapine.

The mechanism by which serominic is reversing the PCP-induced metabolic hypofunction in the reticular thalamus is postulated to be through a 5-HT_7 receptor mediated mechanism since 5-HT_7 receptors are concentrated in thalamic areas.

The fact that the serominic combination can reverse the PCP-induced hypofunction in the dorsal and ventral parts of the reticular thalamus is again of much interest as it suggests that the serominic may be beneficial in treating the positive symptom of the disease (poor filtering of irrelevant information) and also indirectly in treating the negative symptoms and cognitive deficits as the reticular thalamus has reciprocal projections to the prefrontal cortex. Once again, the serominic combination shows superior efficacy to current APDs.

. In selected auditory brain structures (ventral lateral lemniscus, ventral cochlear nucleus and in the primary auditory cortex) chronic PCP treatment caused a significant hypofunction. Previously, we reported that both clozapine and haloperidol reversed the PCP-induced hypofunction in these auditory structures (Cochran et al., 2003), consistent with their efficacy against positive symptoms such as auditory hallucinations. This study shows that the serominic is also effective in reversing the metabolic hypofunction within these auditory structures.

Local glucose utilisation was measured in the ventral lateral lemniscus after chronic treatment with PCP alone or with the antipsychotic drugs. Note that the reduced metabolic activity caused by PCP (*p<0.05 vs

control) is restored to normal values by clozapine or the serominic combination (#p<0.05 vs PCP alone) but haloperidol only partially restores the hypofunction. Similar effects were observed in the auditory cortex and other auditory structures.

Decreased metabolism of the temporal lobe (auditory cortex and hippocampus) have been directly correlated with the positive symptoms of the disease (Buchsbaum et al, 1996; Klemm et al., 1996). Therefore this study shows that the serominic is effective in reversing the metabolic hypofunction within these auditory structures, which are associated with hallucinations (positive symptom of the disease). Therefore it appears that a serominic agent will behave in a similar way to clozapine and haloperidol in ameliorating the positive symptoms of the disease.

These results imply that a serominic may be beneficial in treating both the negative symptoms and cognitive impairment which to date have proved very difficult to treat, as well as being effective in treating the positive symptoms of the disease.

The startle reaction to a strong acoustic stimulus is reduced by the prior presentation of a weak stimulus. This reduction, termed prepulse inhibition (PPI), has been used as a measure of sensorimotor gating and significantly diminished in schizophrenic patients (Braff et al., 1978). In rats, the disruption of PPI by apomorphine is reversed by the administration of antipsychotics with potency correlating well with clinically effective dosages of each drug. Thus, the disruption of PPI by apomorphine is a valid animal model for some aspects of schizophrenia (Swerdlow et al., 1994).

Methods

Male Wistar rats (Japan SLC Inc., Shizuoka, Japan) were used. They were housed in a light, humidity and temperature controlled environment maintained on a 12-hour/12-hour light/dark schedule (light on at 7 am) with food and water provided ad libitum. Four startle chambers (SR-LAB, San Diego Instruments, San Diego, CA) were placed in a sound-attenuated room. Each chamber consisted of Plexiglas cylinder 8.8 cm in diameter resting on a 12.7 x 20.3 cm Plexiglas stand. Acoustic stimuli and background noise were presented via a Supertweeter mounted 24 cm above the Plexiglas cylinder. Startle magnitude was detected and recorded by a microcomputer and interface assembly (San Diego Instruments) as transduced cylinder movement via a piezoelectric device mounted below the Plexiglas stand.

One day before drug testing, all rats were exposed to a "matching" startle session. Data from this session were used to assign rats to balanced groups according to their startle responses. On the drug testing day, rats were treated with vehicle (sterile saline) or drug (PTAC and/or SB258741) subcutaneously 25 minutes prior to apomorphine (0.5 mg/kg, s.c.) treatments. Immediately after apomorphine treatments, rats were placed into the startle chamber and a test session was started. Each session was approximately 20 minutes and consisted of 5 minutes of 70-dB background followed by five trial types, PULSE ALONE trial: a 120-dB 50 ms noise burst, PREPULSE trials which consisted of 20 ms noise bursts 3, 5, 10 dB above 70-dB background noise followed 100 ms later by a 120-dB 40 ms noise burst, NOSTIM trial: 100 ms of response was recorded during periods where no stimulus was presented. Each trial presented in pseudorandom order every 15 seconds for a total 60 trials (12 trials

each). The percentage PPI was defined as 100 - [(startle amplitude on PREPULSE trial/startle amplitude on PULSE ALONE trial) x 100].

Results

Apomorphine (0.5 mg/kg, s.c.) significantly reduced the PPI (Fig. 1,2,3). Neither PTAC nor SB25871 alone affect the disruption induced by apomorphine (Fig. 1 and 2, respectively). PTAC combined with SB25871 restored the apomorphine-induced disruption of PPI (Fig. 3).

The agents with properties according to the present invention are useful as a novel type of antipsychotic agent which are effective for both the positive and negative symptoms of schizophrenia, and which may cause less side effects of extrapyramidal motor disorder and the like and which may cause less serious side effects such as agranulocytosis and the like.

Example 2

The compounds of the present invention were screened for binding affinity using membranes containing stably expressed human M_4 muscarinic receptors or human 5-HT_7 receptors.

M_4 assay:

Total volume 200µl/well. Membrane concentration - human M_4 membranes (NEN) - 8µg/ml; ^{3}H-NMS 0.25nM; Sample conc. 10nM-300µM; Atropine Displacement Curve - 0.3nM-1µM.

The plates are incubated at 20^{0}C for 60 minutes in the dark to avoid any photo degradation. Membranes are harvested by rapid filtration using a vacuum manifold under 700mbar pressure. The plates are washed 3 times

with 200ul per well of ice-cold wash buffer. Plates are dried at 40°C for 1 hour, 100µl scintillation fluid is added to each well and cpm determined using a Microbeta scintillation counter.

5-HT_7 assay:

Total volume 200µl/well. Membrane concentration - human 5-HT_7 membrane (purchased from Euroscreen) - 6µg/ml;^{3}H-5CT 0.5nM; Sample conc. 10nM-300µM; 8OH-DPAT Displacement Curve - 1nM-3µM. The plates are incubated at 20°C for 120 minutes in the dark to avoid any photo degradation. Membranes are harvested by rapid filtration using a vacuum manifold under 700mbar pressure. The plates are washed 3 times with 200ul/well of ice-cold wash buffer. Plates are dried at 40°C for 1 hour (Higher CPMs are obtained when the filters are dried) 100µl scintillation fluid is added to each well and cpm determined using a Microbeta scintillation counter.

D_2 assay:

Total volume 200µl/well. Membrane concentration - human D_2 membrane (purchased from Euroscreen) - 10µg/ml;^{3}H-spiperone 0.5nM; Sample conc. 10nM-300µM; Haloperidol Displacement Curve - 1nM-10µM. The plates are incubated at 25°C for 60 minutes in the dark to avoid any photo degradation.

Membranes are harvested by rapid filtration using a vacuum manifold under 700mbar pressure. The plates are washed 3 times with 200ul/well of ice-cold wash buffer. Plates are dried at 40°C for 1 hour (Higher CPMs are obtained when the filters are dried). 100µl scintillation fluid is added to each well and cpm determined using a Microbeta scintillation counter.

The following are examples showing data for Compounds 32 and 34

Compound	Ki ($5\text{-}HT_7$) (μM)	Ki (M_4) (μM)	Ki (D_2) (μM)
Compound 32	0.4	0.32	>300
Compound 34	2.7	2.8	>300

Efficacy (cAMP): Homogenate assay for c-AMP production

Methods:

N1E-115 cells were harvested by scraping and placed in Ribolyser tubes on dry ice. Ice cold buffer (0.5ml) containing 50mM Tris HCl, 0.4 mM EDTA and 0.4 mM EGTA (pH 7.4) was added to the tubes. The tubes were then placed in a Ribolyser and shaken at 4g for 20sec. The homogenate was then transferred to eppendorf tubes and was then centrifuged at 19,700g for 30 min at 4°C. The pellet was resuspended in ice cold 50mM Tris HCl (pH7.4) at a concentration of 50mg ml^{-1} wet weight of tissue. The homogenate was stored in aliquots at-70°C. Protein concentrations of the homogenates were determined using a Bio-Rad protein determination kit. The assay was carried out in a final assay volume of 120μl containing 50mM Tris HCl (pH7.4), 5 mM $MgCl_2$ 50 μM GTP, 200 μM ATP, 120 μM sucrose, 0.4 mM EDTA, 0.4 mM EGTA, 200 μM ascorbic acid, 20 μM papaverine, 200 μM rolipram, 10 μM vinpocetine, 10mM phosphocreatinine, 0.4mM DTT, 100nM WAY 100635, 1 μM propranolol, 36 μg bacitracin, 4.8U creatine phosphokinase, 3.6 KIU aprotinin. Homogenate ($1mgml^{-1}$) was preincubated with the test compound in ice cold assay buffer for 10 min. PACAP (0.1nM) was then added to the tubes. The tubes were then incubated at 30°C for 20 min

and then at 99°C for 5 min. Levels of c-AMP in the tubes were measured using the Amersham Pharmacia Biotech Biotrak c-AMP enzymeimmunoassay kit.

Results:

Mouse N1E-115 cells express a pure population of M_4 muscarinic receptors, negatively coupled to c-AMP levels. Known muscarinic agonists with activity at M_4 receptors, including oxotremorine and acetylcholine, showed the ability to reduce c-AMP levels.
Compounds of this series also showed similar agonist activity: an example is shown for **32** in Figure 1.

Compound 32 was able to reduce cAMP levels, and the effect was blocked by the muscarinic antagonist atropine.

In vivo activity:

To test the hypothesis that these compounds would show efficacy in the treatment of schizophrenia, we tested their inhibitory effect on a standard test for antipsychotic activity - amphetamine-induced hyper-activity in rats.

Methods

Male Long Evans rats (190-280 g) in each group of five were used.

Amphetamine (1.0mg/kg i.p.) was dissolved in saline, and test compounds were dissolved or suspended in 0.5 % hydroxypropylmethylcellulose (HPMC) solution. All the test compounds were injected intraperitoneally in a volume of 0.1 ml / 100 g, and control rats were treated with the respective vehicle.

The plastic open-field box (40×40×40(H) cm) was used to measure the locomotor activity of rats. The locomotor activity was expressed as the number of line crossings marked on the floor of the test box at 20 cm square. Individual rats were placed in the test box just after the injection of amphetamine, and were allowed to habituate there for 10 min. The line crossings were counted over 15 min thereafter. The behavioural observation was conducted on two rats simultaneously using two test boxes.

Test compounds were pretreated 30 min before the injection of amphetamine.

Results

Compound **32** suppressed the hyperactivity in a dose-dependent manner, of which ED50 value was estimated as 8.1 (95% confidence limits; 4.4-15) mg/kg,i.p. (Table 2).

Table 2 Effect of Compound **32** on amphetamine-induced hyperactivity in rats

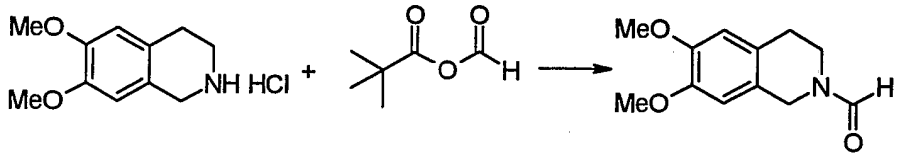
Dose (mg/kg,i.p.)	Line Crossings (mean±S.E.)
0 (amphetamine control)	111.6 ± 6.4
1	98.8 ± 7.3
3	89.6 ± 13.3
10	45.6 ± 8.3**

The compounds of formula **(I)** of the present invention are useful as a novel type of the antipsychotic agents which are effective for both the positive and negative symptoms of schizophrenia, which causes less side effects of extrapyramidal motor disorder and the

like and which causes less serious side effects such as agranulocytosis and the like.

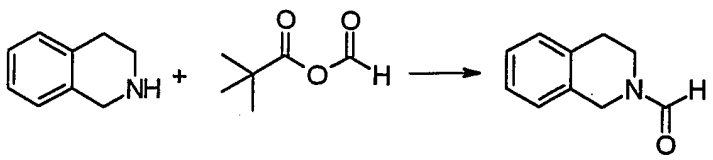
Example 3

The following are some examples for the preparation of the compounds of the present invention:



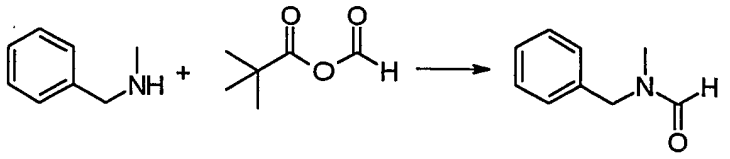
1

Trimethylacetic formic anhydride (5.3g, 40.77mmol) (E. J. Vlietstra *et al.*, *Journal of the Royal Netherlands Chemical Society*, **101**/12, *1982*, 460-462) was added to a solution of 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline hydrochloride (9.36g, 40.77mmol) in dry dichloromethane (40mL) cooled in an ice-water bath under nitrogen atmosphere, followed, dropwise, by dry triethylamine (4.95g, 58.924mmol). The mixture was stirred at room temperature for 1h and was then diluted with dichloromethane, washed with dilute hydrochloric acid (2M), saturated sodium bicarbonate, the organic phase was dried over $MgSO_4$, filtered and concentrated. Purification by flash chromatography (pure EtOAc to dichloromethane/MeOH 95/5) afforded compound **1** (8.29g, 92%) as a white solid consisting of two rotamers (major:minor ratio ca. 2:1) in ^{1}HNMR spectrum (all *J* values are quoted in Hertz). ^{1}H NMR ($CDCl_3$, 400MHz): 2.78-2.85 (2H, m), 3.63 (major) and 3.78 (minor) [2H, 2 x t, *J* 5.9 (major) and 6.1 (minor)], 3.86 (6H, s), 4.48 (minor) and 4.61 (major) (2H, 2 x s), 6.58-6.63 (2H, m, ArH), 8.26 (minor) and 8.19 (major) (1H, 2 x s).



2

Trimethylacetic formic anhydride (3.12g, 23.79mmol) was added dropwise to a solution of 1,2,3,4-tetrahydroisoquinoline (2.9g, 21.79mmol) in chloroform (20mL) cooled in an ice-water bath under nitrogen atmosphere. The mixture was stirred at room temperature for 1h and then diluted with dichloromethane, washed with dilute hydrochloric acid (2M), saturated sodium bicarbonate, the organic phase was dried over $MgSO_4$, filtered and concentrated. Purification by flash chromatography (pure EtOAc to dichlormethane/MeOH 95/5) afforded compound **2** (2.98g, 85%) as a pale yellow oil, consisting of two isomers (major:minor ratio, *ca.* 1.5:1) in ^1H NMR spectrum ($CDCl_3$, 400MHz) ^1H NMR: 2.86-2.93(2H, m, $ArCH_2$), 3.65 (major) and 3.79 (minor) [2H, 2 x t, *J* 5.9 (major), 6.1 (minor) CH_2N], 4.54 (minor) and 4.69 (major) (2H, 2 x s, $ArCH_2N$), 7.09-7.23 (4H, m, ArH), 8.20 (major) and 8.25 (minor) (1H, s, CHO).



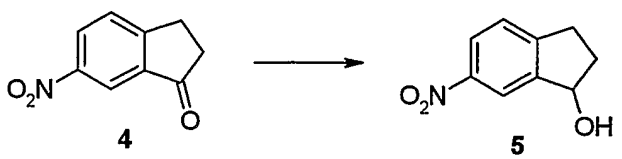
3

Trimethylacetic formic anhydride (3.55g, 27.27mmol) was added dropwise to a solution of *N*-methylbenzylamine (3.0g, 24.79mmol) in dry dichloromethane (20mL) cooled in an ice-water bath under nitrogen atmosphere. The mixture was stirred at room temperature for 1h and then diluted with dichloromethane, washed with dilute hydrochloric

acid (2M), saturated sodium bicarbonate, the organic phase was dried over $MgSO_4$, filtered and concentrated. Purification by flash chromatography (pure EtOAc to dichloromethane/MeOH, 95/5) afforded compound **3** (3.1g, 84%) as a pale yellow oil, consisting of two rotamers (major:minor ratio *ca.* 1.2/1) in ^1H NMR spectrum. ^1HNMR ($CDCl_3$, 400MHz): 2.84 (major) and 2.90 (minor) (3H, 2 x s, NMe), 4.45 (major) and 4.85 (minor) (2H, 2 x s, NCH_2), 7.25-7.45 (5H, m, ArH), 8.22 (minor) and 8.34 (major) (1H, 2 x s, CHO).

Preparation of compound 4

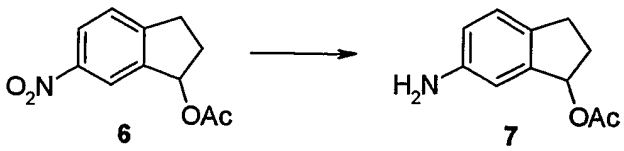
A solution of potassium nitrate (50.5g, 0.5mol) in H_2SO_4 (200mL) was added, via a dropping funnel, to a solution of 1-indanone (60g, 0.454mol) in concentrated sulfuric acid (500mL) cooled in an ice-water bath at a speed to maintain an internal temperature below 15°C. After stirring at 0°C for 1h, the reaction mixture was poured into crushed ice and stirred for 30 min. The solid was filtered, washed with water, and air-dried. Purification by flash chromatography (toluene/EtOAc, 95/5) gave compound **4** (43.5g, 54%) as a pale yellow solid. ^1H NMR ($CDCl_3$, 400MHz): 2.81-2.85 (2H, m, CH_2), 3.28 (2H, t, *J* 6.1, CH_2), 7.67 (1H, d, *J* 8.4, ArH), 8.45 (1H, d, *J* 8.4, ArH), 8.56 (1H, s, ArH).



A solution of **4** (2.7g, 15.254mmol) in MeOH (50mL) was cooled in an ice-water bath and sodium borohydride (580mg, 15.254mmol) was added in three portions. The

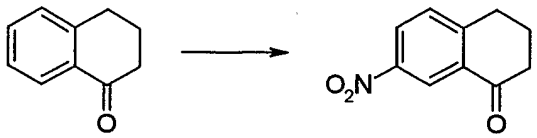
reaction was continued at room temperature for 30 min, quenched by adding hydrochloric acid (2M, 30mL). Most of the methanol was removed by rotavapor, the residue was diluted with water, extracted with dichloromethane, the organic phase was dried over $MgSO_4$, filtered and concentrated to provide crude alcohol **5** as a brown solid. The product was used in the next reaction without further purification. ^1H NMR ($CDCl_3$, 400MHz): 2.00-2.08 (1H, m, CH_2), 2.44 (1H, broad, OH), 2.56-2.63 (1H, m, CH_2), 2.85-2.94 (1H, m, CH_2), 3.08-3.16 (1H, m, CH_2), 5.30-5.31 (1H, m, CHO), 7.36 (1H, d, *J* 8.3, ArH), 8.11 (1H, dd, *J* 8.3, 2.0, ArH), 8.22 (1H, d, *J* 2.0, ArH).

To the solution of crude **5** in pyridine (20mL) under nitrogen was added acetic anhydride (6mL) at 0°C and the mixture was stirred at room temperature overnight. The mixture was poured into water, extracted with diethyl ether, the organic phase was washed with hydrochloric acid (2M), dried over $MgSO_4$, filtered and concentrated. Purification by flash chromatography (petroleum ether/EtOAc, 75/25) gave compound **6** (3.23g, 95% for two steps) as a slightly yellow oil. ^1H NMR ($CDCl_3$, 400MHz): 2.10 (3H, s, Ac), 2.14-2.23 (1H, m, CH_2), 2.57-2.66 (1H, m, CH_2), 2.93-3.01 (1H, m, CH_2), 3.14-3.23 (1H, m, CH_2), 6.19-6.23(1H, m, CHO), 7.41 (1H, d, *J* 8.3Hz, ArH), 8.18 (1H, d, *J* 8.3Hz, ArH), 8.24 (1H, s, ArH).



6 7

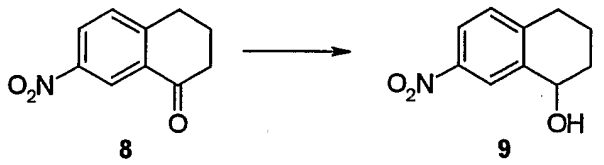
A solution of **6** (1.0g, 4.52mmol) in MeOH (10mL) was subjected to hydrogenation at atmospheric pressure with Pd/C as catalyst. The reaction was followed carefully by TLC and was stopped when most of the starting material was consumed. The mixture was filtered through kieselguhr and was concentrated. Purification by flash chromatography (petroleum ether/EtOAc, 60/40) gave compound **7** (460mg, 53%) as a pale brown oil. ^{1}H NMR ($CDCl_3$, 400MHz): 2.01-2.11 (4H, m, Ac + CH_2), 2.41-2.51 (1H, m, CH_2), 2.72-2.79 (1H, m, CH_2), 2.95-3.03 (1H, m, CH_2), 3.71 (2H, broad, NH_2), 6.11-6.14 (1H, m, ArCH), 6.62 (1H, dd, *J* 8.4, 2.2, ArH), 5.75 (1H, d, *J* 2.2, ArH), 7.04 (1H, d, *J* 8.4, ArH).



8

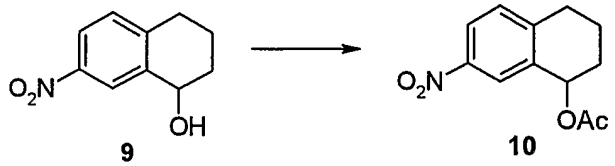
Concentrated sulfuric acid (60 ml) was cooled to 0°C in an ice bath. α-Tetralone (8g, 54.7 mmol) was added with stirring, then potassium nitrate (6g, 59.3 mmol, 1.08 equiv.) dissolved in concentrated sulfuric acid (18 ml) was added dropwise via a dropping funnel, making sure that the temperature of the solution did not rise above 15°C. After addition, the solution was stirred for 1 h and then poured into crushed ice. The precipitate was filtered and washed with distilled water and then left to dry. Recrystallisation from a ethanol/water (1:1)

yielded **8** as a slightly yellow solid (8.5 g, 81%), m.p. 104-106°C; I.R. (film)/cm^{-1} 1675, 1500, 1340; ^1H NMR (400 MHz, $CDCl_3$) 2.18-2.25 (2H, m, CH_2), 2.75 (2H, t, *J* 6.8, CH_2), 3.10 (2H, t, *J* 6.1, CH_2), 7.45 (1H, d, *J* 8.4, ArH), 8.30 (1H, dd, *J* 2.4, 8.4, ArH), 8.86 (1H, d, *J* 2.4, ArH).



8 **9**

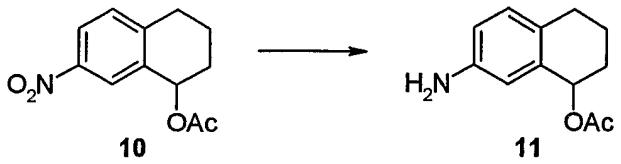
Sodium borohydride (6.95g, 183.9 mmol) was added to a solution of 3,4-dihydro-7-nitro-1(2*H*)-naphthalenone (8g, 41.8 mmol) in ethanol (240 ml) at 0°C. After the vigorous reaction subsided, the cooling bath was removed and the solution was then stirred for a further 10 min. Hydrochloric acid (2M) was then added and the crude reaction mixture was then extracted with ethyl acetate. Column chromatography on silica gel eluting with petroleum ether : ethyl acetate 4:1 gave alcohol **9** as a pale green solid (7.9 g, 98%), m.p. 107-109°C; I.R. (film)/cm^{-1} 3500; ^1H NMR (400 MHz, $CDCl_3$) 1.73-2.26 (4H, m, 2 x CH_2), 2.29 (1H, bs, OH), 2.78-2.91 (2H, m, CH_2), 4.78 (1H, m, CH), 7.17-7.26 (1H, d, *J* 8.4, ArH), 7.92-8.12 (1H, dd, *J* 2.4, 8.4, ArH), 8.30 (1H, d, *J* 2.4, ArH).



9 **10**

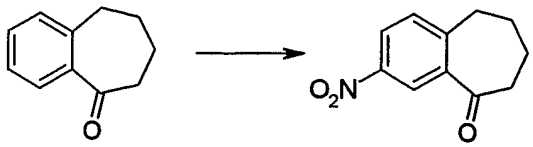
An excess of acetic anhydride (2.4 ml) was added to a solution of 7-nitro-1,2,3,4-tetrahydronaphthalen-1-ol **9** (0.45g, 2.33 mmol.) in pyridine (3.2 ml). The reaction

mixture was stirred for 16 h at room temperature and then worked up to give the crude acetate **10**. Column chromatography on silica gel eluting with petroleum ether: ethyl acetate 5:1 gave pure acetate **10** as a slightly yellow oil (0.46g, 84%); ^{1}H NMR (400 MHz, $CDCl_3$) 1.84-2.10 (4H, m, 2 x CH_2), 2.13 (3H, s, CH_3), 2.80-3.00 (2H, m, CH_2), 6.00 (1H, t, *J* 4.8, CH), 7.28 (1H, d, *J* 8.4, ArH), 8.07 (1H, dd, *J* 2.4, 8.4, ArH), 8.16 (1H, d, *J* 2.4, ArH).



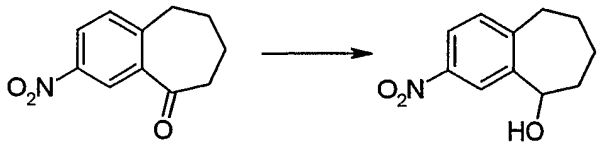
10 **11**

Copper (II) acetylacetonate (94 mg, 0.36 mmol) was dissolved in ethanol (70 ml) and sodium borohydride (68 mg, 1.79 mmol) was added under nitrogen. The reaction mixture was further stirred for 1 h at which time a black precipitate was formed. At this time ethanol (74 ml) and acetate **10** (0.42 g, 1.79 mmol) were added followed by sodium borohydride (135 mg, 3.58 mmol). The reaction was stirred for a further 2h. Then water was added and the solvent was removed *in vacuo*. After this, the mixture was diluted with diethyl ether and washed with brine, the ether layer was dried over anhydrous sodium sulfate, filtered and the solvent was removed *in vacuo*. Column chromatography on silica gel eluting with petroleum ether: ethyl acetate 2:1 gave amine **11** as a yellow oil (0.36g, 98%); ^{1}H NMR (400 MHz, $CDCl_3$) 1.74-1.97 (4H, m, 2 x CH_2), 2.09 (3H, s, CH_3), 2.59-2.78 (2H, m, CH_2), 3.57 (2H, bs, NH_2), 5.91 (1H, t, *J* 4.4, CH), 6.60 (2H, m, ArH), 6.93 (1H, d, *J* 7.7, ArH).



12

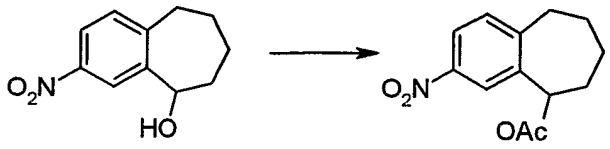
Concentrated sulfuric acid (55 ml) was cooled to 0°C in an ice bath. 1-Benzosuberone (8 g, 49.9 mmol) was added with stirring, then potassium nitrate (5.55g, 54.9 mmol) dissolved in concentrated sulfuric acid (15 ml) was added dropwise via a dropping funnel, making sure that the temperature of the solution did not rise above 15°C. After addition, the solution was stirred for 1 h and then poured into crushed ice. The precipitate was filtered and washed with distilled water and then left to dry. Recrystallisation from ethanol/water 1:1 yielded nitro derivative **12** as a pale yellow solid (7.98 g, 78%), m.p. 91-93°C (lit. m.p. 92-93°C); ^{13}C NMR (100.61 MHz, $CDCl_3$) 25.1 (t), 31.5 (t), 32.1 (t), 38.9 (t), 123.6 (d), 127.9 (d), 129.1 (d), 138.2 (s), 145.6 (s), 146.1 (s), 197.6 (s).



12 13

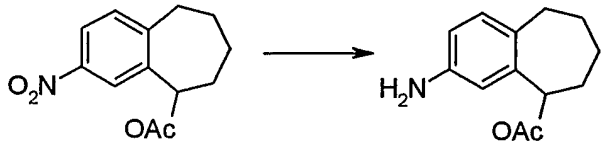
Sodium borohydride (4.9g, 130.2 mmol) was added to a solution of nitroderivative **12** (6.1g, 29.6 mmol) in ethanol (160 ml) at 0°C. After the vigorous reaction subsided, the cooling bath was removed and the solution was then stirred for a further 10 min. Hydrochloric acid (2M) was then added and the crude reaction mixture was then extracted with ethyl acetate. Column chromatography on silica gel eluting with petroleum ether : ethyl

acetate 5:1 gave alcohol **13** as a pale yellow solid (6.0 g, 98%), m.p. 115-117°C; ^{1}H NMR (400 MHz, $CDCl_3$) 1.61-1.93 (3H, m, CH_2), 2.05-2.13 (3H, m, CH_2), 2.78 (1H, m, CH_2), 3.04 (1H, m, CH_2), 5.02 (1H, m, CH), 7.25 (1H, d, *J* 8.8, ArH), 8.03 (1H, dd, *J* 2.3, 8.8, ArH), 8.42 (1H, d, *J* 2.3, ArH).



13 **14**

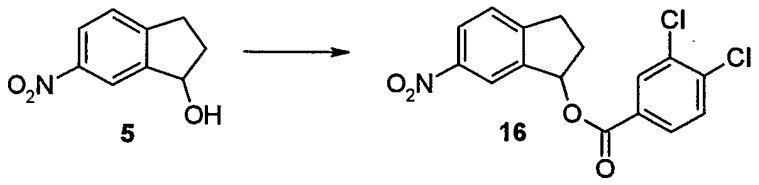
An excess of acetic anhydride (9 ml) was added to a solution of alcohol **13** (1.5g, 7.2 mmol) in pyridine (15 ml). The reaction mixture was stirred for 16 h at room temperature and then extracted, evaporated filtered and dried to give the crude acetate. Column chromatography on silica gel eluting with petroleum ether: ethyl acetate 6:1 gave pure the acetate **14** as a colourless oil (1.69g, 94%); ^{1}H NMR (400 MHz, $CDCl_3$) 1.62-1.80 (2H, m, CH_2), 1.89-2.09 (4H, m, 2 x CH_2), 2.18 (3H, s, CH_3), 2.73 (1H, m, CH_2), 2.97 (1H, m, CH_2), 5.96 (1H, t, *J* 7.7, CH), 7.28 (1H, d, *J* 8.8, ArH), 8.09 (1H, dd, *J* 2.3, 8.8, ArH), 8.48 (1H, d, *J* 2.3, ArH).



14 **15**

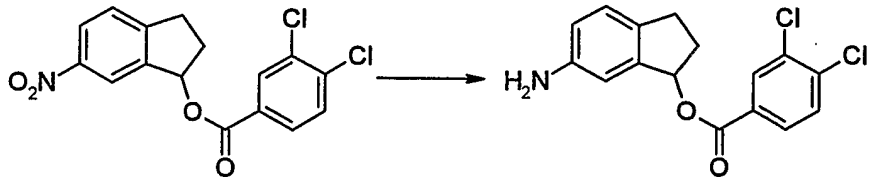
Copper (II)acetylacetonate (440 mg, 1.68 mmol) was dissolved in ethanol (300 ml) and sodium borohydride (319.3 mg, 8.4 mmol) was added under nitrogen. The reaction mixture was further stirred for 1h at which time

a black precipitate had formed. Ethanol (350 ml) and acetate ester **14** (2.1 g, 8.4 mmol) were added, followed by sodium borohydride (638.7 mg, 16.8 mmol). The reaction was stirred for a further 2h. Then water was added and the solvent was removed *in vacuo*. After this, the residue was dissolved in diethyl ether and washed with brine, dried over anhydrous sodium sulfate, filtered and the solvent was removed *in vacuo*. Column chromatography on silica gel eluting with petroleum ether: ethyl acetate 2:1 gave amine **15** as a yellow solid (1.77g, 96%), m.p. 84-86°C; ^{1}H NMR (400 MHz, $CDCl_3$) 1.52-1.65 (1H, m, CH_2), 1.68-1.79 (1H, m, CH_2), 1.80-1.99 (4H, m, 2 x CH_2), 2.15 (3H, s, CH_3), 2.62-2.69 (1H, m, CH_2), 2.82-2.88 (1H, m, CH_2), 5.84 (1H, t, *J* 7.7, CH), 6.49 (1H, dd, *J* 2.5, 7.9, ArH), 6.68 (1H, d, *J* 2.5, ArH), 6.90 (1H, d, *J* 7.9, ArH).



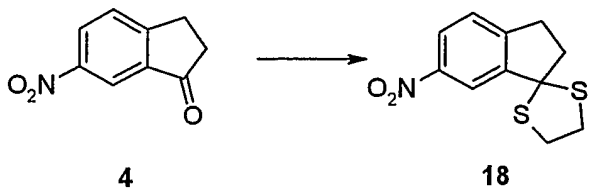
3,4-Dichlorobenzoyl chloride (3.1g, 14.8mmol) was added to a solution of crude **5** (2.4g, 13.4mmol) in pyridine (10mL) under nitrogen at 0°C, and the mixture was stirred at room temperature overnight before being poured into water, and then extracted with dichloromethane. The organic phase was washed with hydrochloric acid (2M), dried over magnesium sulfate, filtered and concentrated. Purification by flash chromatography (petroleum ether/ethyl acetate, 85/15) gave compound **16** (3.78g, 80%) as a white solid. ^{1}H NMR ($CDCl_3$, 400MHz): 2.31-2.39 (1H, m, CH_2), 2.70-2.79 (1H, m, CH_2), 3.02-3.10 (1H, m, CH_2), 3.24-3.33 (1H, m, CH_2),

6.45-6.48 (1H, m, CHO), 7.47 (1H, d, *J* 8.3, ArH), 7.53 (1H, d, *J* 8.3, ArH), 7.87 (1H, dd, *J*, 8.3, 2.0, ArH), 8.10 (1H, d, *J*, 2.0, ArH), 8.22 (1H, dd, *J*, 8.3, 2.0, ArH), 8.33 (1H, d, *J*, 2.0, ArH).



16 **17**

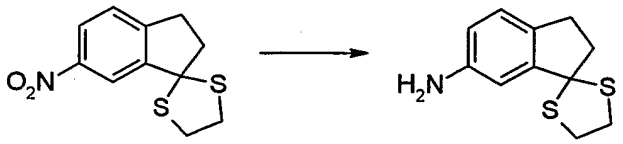
A solution of **16** (2.0g, 5.68mmol) in ethyl acetate (10mL) was subjected to hydrogenation at atmospheric pressure with Pd/C as catalyst. The reaction was followed carefully by TLC and was stopped when most of the starting material was consumed. The mixture was filtered through kieselguhr and was concentrated. Purification by flash chromatography (petroleum ether/ethyl acetate, 70/30) gave amine **17** (823mg, 45%) as a pale brown solid. ^{1}H NMR ($CDCl_3$, 400MHz): 2.17-2.25 (1H, m, CH_2), 2.55-2.64 (1H, m, CH_2), 2.81-2.92 (1H, m, CH_2), 2.05-3.12 (1H, m, CH_2), 3.66 (2H, broad, NH_2), 6.34-6.50 (1H, m, CHO), 6.69 (1H, dd, *J* 8.0, 2.0, ArH), 6.81 (1H, d, *J* 2.0, ArH), 7.10 (1H, d, *J* 8.0, ArH), 7.50 (1H, d, *J*, 8.4, ArH), 7.87 (1H, dd, *J*, 8.4, 1.9, ArH), 8.10 (1H, d, *J*, 1.9, ArH).



4 **18**

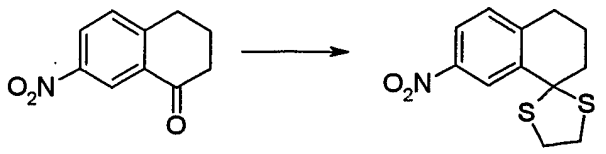
To a solution of **4** (2.40g, 13.56mmol) in dry DCM (20mL) under nitrogen atmosphere was added 1, 2-

ethanedithiol (1.915g, 20.34mmol, 1.71mL) and $BF_3.OEt_2$ (1.92g, 13.56mmol, 1.67mL). The mixture was stirred at room temperature for 2 hours and was diluted with DCM (50mL) washed with aqueous NaOH (10%), dried over $MgSO_4$, filtered and concentrated to give **18** as a yellow oil (3.26g, 95%), which was used in next reaction without purification. ^1H NMR ($CDCl_3$, 400MHz): 2.76 (2H, t, *J* 6.75, CH_2), 3.05 (2H, t, *J* 6.75, CH_2), 3.44-3.51 (2H, m, CH_2), 3.55-3.62 (2H, m, CH_2), 7.31 (1H, d, *J* 8.28, ArH), 8.08 (1H, dd, *J* 8.28, 2.19, ArH), 8.35 (1H, d, *J* 2.19, ArH).



18 **19**

A solution of **18** (500mg, 1.976mmol) and $SnCl_2.2H_2O$ (2.23g, 9.88mmol) in MeOH (15mL) was refluxed for 4 hours and then stirred at room temperature overnight. The mixture was quenched by adding saturated aqueous $NaHCO_3$ (30mL) carefully, extracted with ethyl acetate (50mL), the organic phase was dried over $MgSO_4$, filtered and concentrated. Purification by flash chromatography (petroleum ether/EtOAc 75/25) gave compound **19** as a yellow oil (315mg, 71%). ^1H NMR ($CDCl_3$, 400MHz): 2.64 (2H, t, *J* 6.55, CH_2), 2.84 (2H, t, *J* 6.55, CH_2), 3.38-3.41 (2H, m, CH_2), 3.46-3.55 (2H, m, CH_2), 3.65 (2H, broad, NH_2), 6.54 (1H, dd, *J* 7.97, 2.07, ArH), 6.89 (1H, d, *J* 2.07, ArH), 6.95 (1H, d, *J* 7.97, ArH).



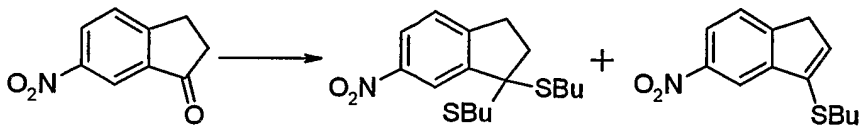
8 20

To a solution of **8** (1.0g, 5.235mmol) in dry DCM (10mL) was added 1,2-ethanedithiol (740mg, 7.853mmol, 0.66mL) and $BF_3.OEt_2$ (1.113g, 7.853mmol, 0.96mL) under nitrogen atmosphere. The mixture was stirred at room temperature overnight, diluted with DCM (50mL), washed with 2N NaOH, dried over $MgSO_4$, filtered and concentrated. Compound **20** was obtained as slightly yellow solid (1.4g, 100%) and was used without purification in next reaction. ^1H NMR ($CDCl_3$, 400MHz): 2.02-2.08 (2H, m, CH_2), 2.40-2.43 (2H, m, CH_2), 2.87 (2H, t, *J* 6.38, CH_2), 3.47-3.54 (2H, m, CH_2), 3.62-3.70 (2H, m, CH_2), 7.14 (1H, d, *J* 8.49, ArH), 7.93 (1H, dd, *J* 8.49, 2.40, ArH), 8.80 (1H, d, *J* 2.40, ArH).

20 21

A suspension of **20** (1.4g, 5.235mmol) and $SnCl_2.2H_2O$ in MeOH (30mL) was refluxed under nitrogen atmosphere for 4 hours. The mixture was cooled to room temperature and poured into 100mL of saturated $NaHCO_3$, the mixture was extracted with EtOAc, dried over $MgSO_4$, filtered and concentrated. Purification by flash chromatography afforded compound **21** as a slightly yellow oil (1.0g, 80%). ^1H NMR ($CDCl_3$, 400MHz): 1.62-2.00 (2H, m, CH_2), 2.30-2.39 (2H, m, CH_2), 2.70 (2H, t, *J* 6.41, CH_2), 3.30-3.34 (2H, m,

CH_2), 3.38-3.61 (4H, m, CH_2 + NH_2), 6.51 (1H, dd, *J* 8.12, 2.28, ArH), 6.80 (1H, d, *J* 2.48, ArH), 7.29 (1H, d, *J* 8.12, ArH).

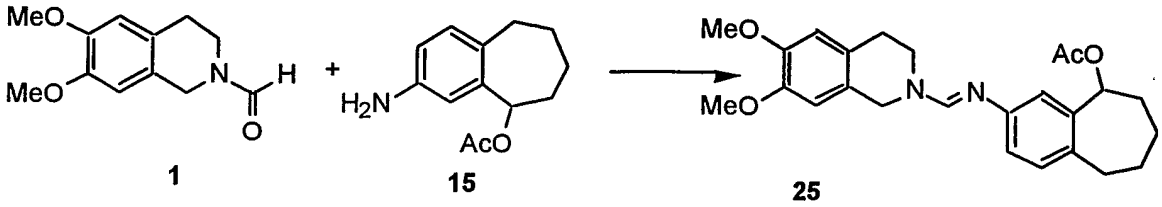


4 **22** **23**

To a solution of **4** (1.0g, 5.65mmol) in chloroform (10mL) under nitrogen atmosphere at room temperature was added n-butanethiol (1.27g, 14.124mmol, 1.513mL) and chlorotrimethylsilane (1.534g, 14.124mmol, 1.805mL). The mixture was stirred at room temperature overnight and was diluted with DCM (20mL), washed with 2N NaOH, dried over $MgSO_4$, filtered and concentrated. Purification by column (petro-leum ether/ether 95/5) gave compound **22** (slightly yellow oil, 1.27g, 77%) and **23** (yellow solid, 290mg, 20%). ^{1}HNMR for **22**: ^{1}H NMR ($CDCl_3$, 400MHz): 0.89 (6H, t, *J* 7.28, CH_3). 1.32-1.43 (4H, m, CH_2), 1.45-1.61 (4H, m, CH_2), 2.46-2.53 (2H, m, CH_2), 2.59-2.67 (4H, m, CH_2), 3.10 (2H, t, *J* 6.92, CH_2), 7.38 (1H, d, *J* 8.06, ArH), 8.11-8.14 (2H, m, ArH). ^{1}HNMR for **23**: ^{1}H NMR ($CDCl_3$, 400MHz): 0.97 (3H, t, *J* 7.35, CH_3). 1.46-1.57 (2H, m, CH_2), 1.71-1.78 (2H, m, CH_2), 3.00 (2H, t, *J* 7.33, CH_2), 3.56 (2H, d, *J* 2.29, CH_2), 6.35 (1H, t, *J* 2.29, CH), 7.56 (1H, d, *J* 8.14, ArH), 8.14 (1H, dd, *J* 8.14, 2.11, ArH), 8.22 (1H, d, *J* 2.11, ArH).

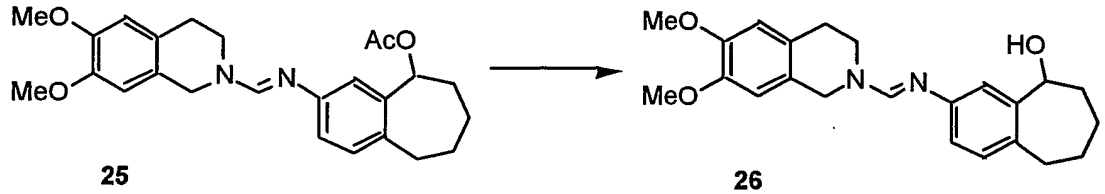
23 **24**

A solution of **23** (40mg, 0.16mmol) in EtOAc (10mL) was subjected to hydrogenation at atmospheric pressure with Pd/C as catalyst overnight. After filtration, the solvent was removed to give a residue (20mg), that was used in the coupling reaction without further purification.



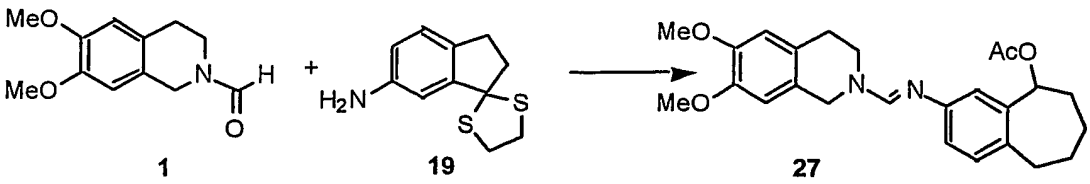
1 **15** **25**

25 m.p. 160°C [decomp.]; (Found: MH^+ 423.2276, $C_{25}H_{30}N_2O_4$ requires *MH* 423.2284); *m/z* (EI) 423 ($[M+H]^+$, 5%), 362 (65), 192 (48), 177 (50), 115 (60), 44 (85), 43 (100).



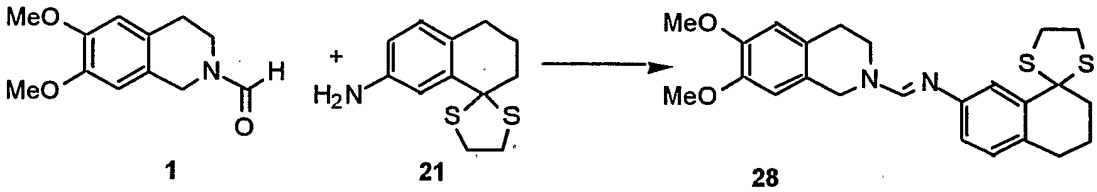
25 **26**

26 ^1H NMR ($CDCl_3$, 400MHz): 1.35-1.43 (1H, m, CH_2), 1.68-1.80 (3H, m, CH_2), 1.90-2.05 (2H, m, CH_2), 2.24 (1H, broad OH), 2.61-2.86 (4H, m, CH_2), 3.68 (2H, broad, NCH_2), 3.85 (3H, s, CH_3), 3.86 (3H, s, CH_3), 4.63 (2H, broad, NCH_2), 4.85-4.88 (1H, m, OCH), 6.63 (1H, s, ArH), 6.64 (1H, s, ArH), 6.76 (1H, dd, *J* 7.81, 1.83 ArH), 6.97 (1H, d, *J* 7.81, ArH), 7.07 (1H, d, *J* 1.83, ArH), 7.70 (1H, s, N=CH). MS: $C_{23}H_{28}N_2O_3$, M+H, calculated 381.2178, found 381.2178



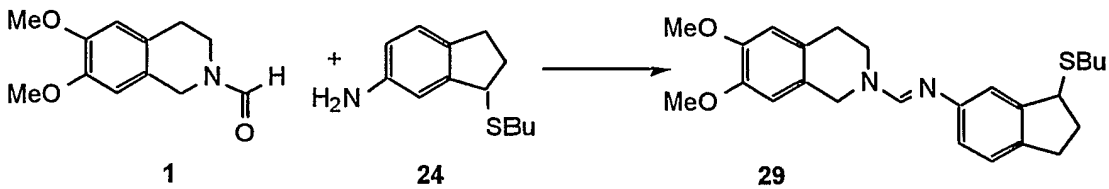
1 19 27

27 ^{1}H NMR ($CDCl_3$, 400MHz): 2.69 (2H, t, *J* 6.58, CH_2), 2.86 (2H, t, *J* 5.69, CH_2), 2.92 (2H, t, *J* 6.58, CH_2), 3.40-3.46 (2H, m, CH_2), 3.50-3.56 (2H, m, CH_2), 3.68 (2H, broad, NCH_2), 3.86 (3H, s, CH_3), 3.87 (3H, s, CH_3), 4.66 (2H, broad, NCH_2), 6.64 (1H, s, ArH), 6.65 (1H, s, ArH), 6.87 (1H, dd, *J* 7.95, 1.89 ArH), 7.08 (1H, d, *J* 7.95, ArH), 7.17 (1H, d, *J* 1.89, ArH), 7.71 (1H, s, N=CH). MS: $C_{23}H_{26}N_2O_2S_2$, M+H, calculated 427.1514, found 427.1514



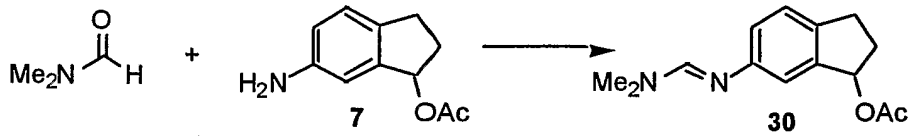
1 21 28

28 ^{1}H NMR ($CDCl_3$, 400MHz): 2.69 (2H, t, *J* 6.58, CH_2), 1.97-2.02 (2H, m, CH_2), 2.37-2.40 (2H, m, CH_2), 2.76 (2H, t, *J* 5.91, CH_2), 2.85 (2H, t, *J* 5.66, CH_2), 3.40-3.48 (2H, m, CH_2), 3.68 (2H, broad, NCH_2), 3.85 (3H, s, CH_3), 3.87 (3H, s, CH_3), 4.65 (2H, broad, NCH_2), 6.63 (1H, s, ArH), 6.64 (1H, s, ArH), 6.78 (1H, dd, *J* 8.09, 2.12 ArH), 6.90 (1H, d, *J* 8.09, ArH), 7.55 (1H, d, *J* 2.12, ArH), 7.67 (1H, s, N=CH). MS: $C_{24}H_{28}N_2O_2S_2$, M+H, calculated 441.1670, found 441.1662.

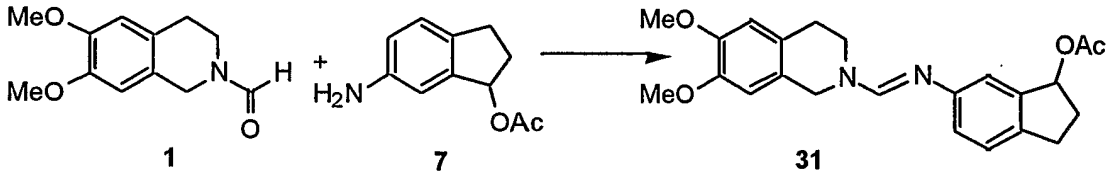


1 24 29

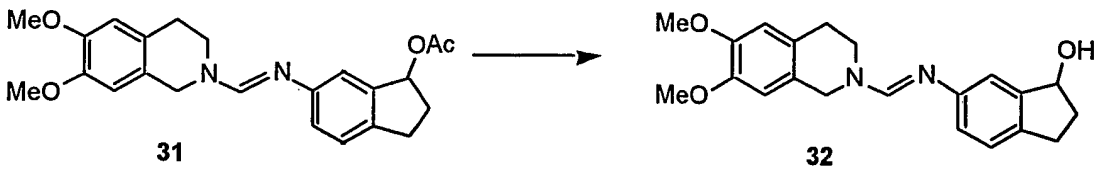
29 ^{1}H NMR ($CDCl_3$, 400MHz): 0.92 (3H, t, *J* 7.33, CH_3), 1.38-1.46 (2H, m, CH_2), 1.56-1.64 (2H, m, CH_2), 2.11-2.19 (1H, m, CH_2), 2.49-2.60 (3H, m, CH_2), 2.78-2.88 (3H, m, CH_2), 2.98-3.05 (1H, m, CH_2), 3.68 (2H, broad, NCH_2), 3.86 (3H, s, CH_3), 3.87 (3H, s, CH_3), 4.29 (1H, dd, *J* 7.35, 5.35, SCH), 4.65 (2H, broad, NCH_2), 6.64 (1H, s, ArH), 6.65 (1H, s, ArH), 6.84 (1H, dd, *J* 7.92, 1.75 ArH), 6.97 (1H, d, *J* 1.75, ArH), 7.11 (1H, d, *J* 7.92, ArH), 7.69 (1H, s, N=CH).



30 ^{1}H NMR ($CDCl_3$, 400MHz): 2.03-2.14 (4H, m, Ac + CH_2), 2.44-2.53 (1H, m, CH_2), 2.76-2.87 (1H, m, CH_2), 2.94-3.07 (7H, m, NMe_2 + CH_2), 6.12-6.17 (1H, m, CHO), 6.90 (1H, dd, *J*, 7.9, 1.7Hz, ArH), 6.97 (1H, d, *J*, 1.7Hz, ArH). 7.13 (1H, 7.9Hz, ArH), 7.51 (1H, s, CH=N).



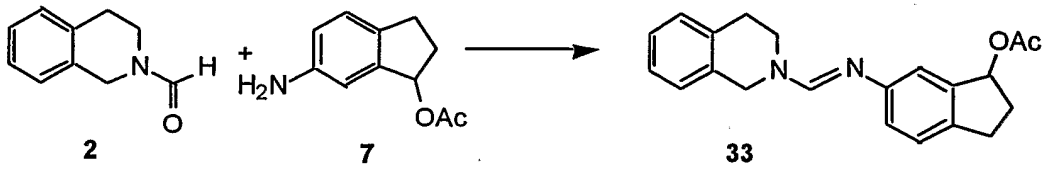
31 ^{1}H NMR ($CDCl_3$, 400MHz): 2.01-2.13 (4H, m, Ac + CH_2), 2.46-2.55 (1H, m, CH_2), 2.79-2.88 (3H, m, CH_2), 3.02-3.10 (1H, m, CH_2), 3.67 (2H, broad, CH_2), 3.86 (3H, s), 3.87 (3H, s), 4.66 (2H, broad, CH_2), 6.17-6.20 (1H, m, CHO), 6.64 (1H, s, ArH), 6.65 (1H, m, ArH), 6.95 (1H, d, *J*, 8.0Hz, ArH), 7.01 (1H, s, ArH), 7.16 (1H, d, *J*, 8.0Hz, ArH), 7.69 (1H, s, CH=N).



31 32

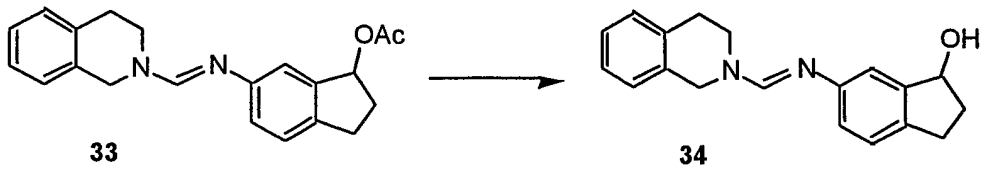
32 ^{1}H NMR ($CDCl_3$, 400MHz): 1.90-1.98 (1H, m), 2.17 (1H, broad), 2.44-2.52 (1H, m), 2.72-2.77 (1H, m), 2.84-2.87 (2H, m), 2.95-3.02 (1H, m), 3.70 (2H, broad), 3.85 (3H, s), 3.87 (3H, s), 4.65 (2H, broad), 5.19 (1H, t, *J*, 6.1, CHO), 6.63 (1H, s, ArH), 6.64 (1H, s, ArH), 6.90 (1H, d, *J*, 7.9, ArH), 7.02 (1H, s, ArH), 7.12 (1H, d, *J*, 7.9, ArH), 7.69 (1H, CH=N).

MS: $C_{21}H_{24}N_2O_3$, M+H, calculated 353.1865, found 353.1859



2 7 33

33 ^{1}H NMR $CDCl_3$, 400MHz): 2.15-2.23 (4H, m, Ac + CH_2), 2.55-2.64 (1H, m, CH_2), 2.88-2.96 (1H, m, CH_2), 3.01-3.02 (2H, m, CH_2), 3.10-3.19 (1H, m, CH_2), 3.79 (2H, broad, CH_2), 4.82 (2H, broad, CH_2), 6.26-6.29 (1H, m, CHO), 7.05 (1H, d, *J*, 7.9, ArH), 7.12 (1H, s, ArH), 7.25-7.35 (5H, m, ArH), 7.79 (1H, s, CH=N).

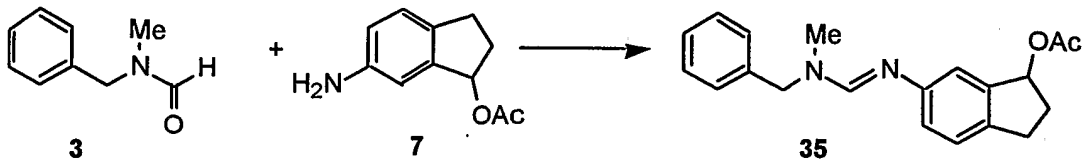


33 34

34 ^{1}H NMR ($CDCl_3$, 400MHz): 1.91-2.00 (1H, m), 2.44-2.52 (1H, m), 2.72-2.80 (2H, m), 2.93-3.03 (3H, m), 3.69 (2H, broad), 4.70 (2H, broad), 5.20 (1H, t, *J*, 6.2, CHO),

6.92 (1H, d, *J*, 7.9Hz, ArH), 7.05 (1H, m, ArH), 7.13-7.28 (5H, m, ArH), 7.70 (1H, s, CH=N).

MS: $C_{19}H_{20}N_2O$, M+H, calculated 293.1654, found 293.1651

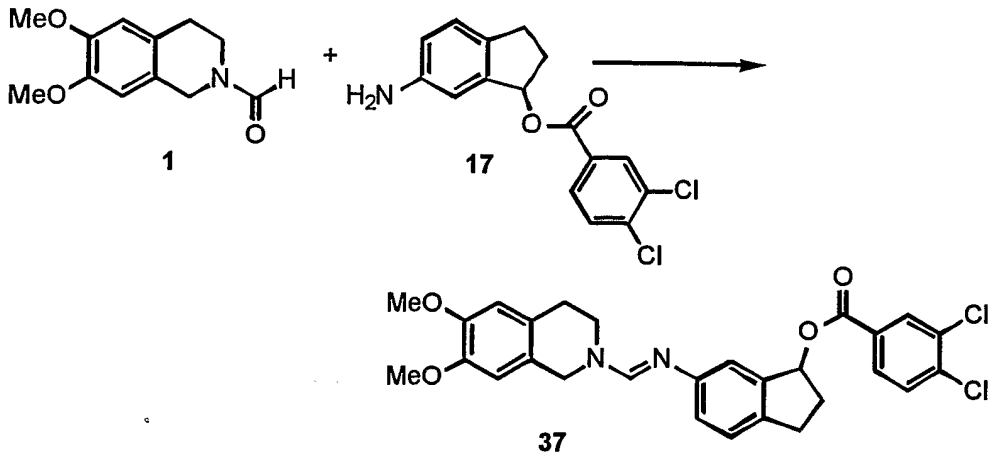


3 7 35

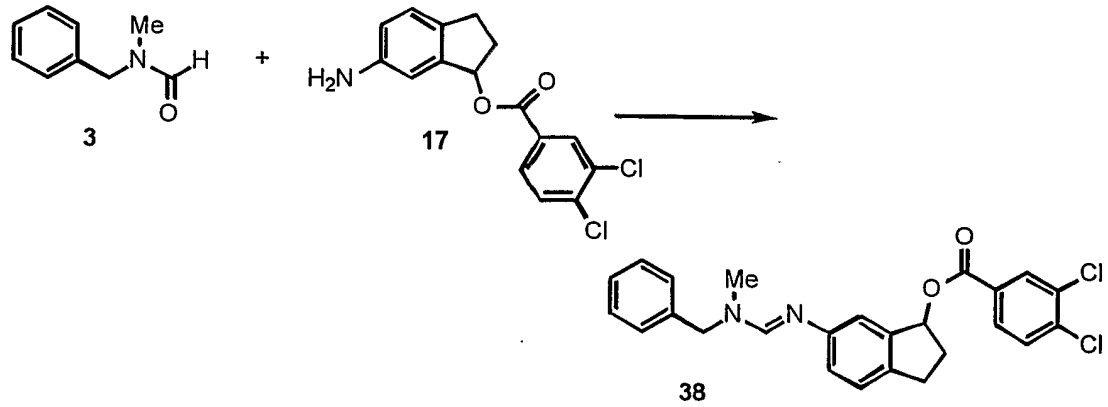
35 ^{1}H NMR ($CDCl_3$, 400MHz): 2.10-2.22 (4H, m, Ac + CH_2), 2.55-2.64 (1H, m, CH_2), 2.88-2.95 (1H, m, CH_2), 3.03 (3H, s, NMe), 3.11-3.18 (1H, m, CH_2), 4.50 (2H, broad, CH_2), 6.26-6.29 (1H, m, CHO), 7.06 (1H, d, *J*, 7.9, ArH), 7.14 (1H, s, ArH), 7.26 (1H, d, *J*, 7.9, ArH), 7.34-7.46 (5H, m, ArH), 7.83 (1H, broad, CH=N). MS: $C_{20}H_{22}N_2O_2$, M+H, calculated 323.1759, found 323.1765.

35 36

36 ^{1}H NMR ($CDCl_3$, 400MHz): 1.90-1.99 (1H, m, CH_2), 2.30 (1H, broad, OH), 2.44-2.53 (1H, m, CH_2), 2.72-2.80 (1H, m, CH_2), 2.95-3.11 (4H, m, NMe + CH_2), 4.50 (2H, broad, CH_2), 5.13-5.25 (1H, m, CHO), 6.92-6.94 (1H, m, ArH), 7.05 (1H, s, ArH), 7.13-7.16 (1H, m, ArH), 7.27-7.39 (5H, m, ArH), 7.76 (1H, broad, CH=N). MS: $C_{18}H_{20}N_2O$, M+H, calculated 281.1654, found 281.1648.

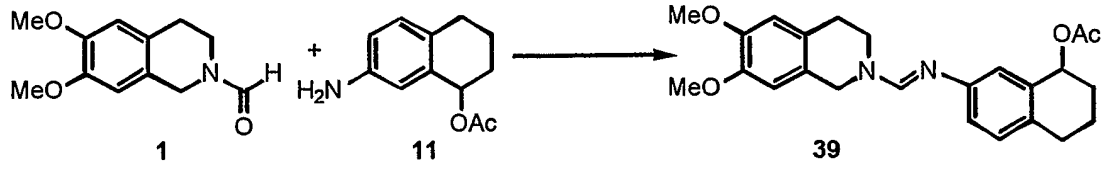


37 ^{1}H NMR ($CDCl_3$, 400MHz): 2.19-2.28 (1H, m, CH_2), 2.58-2.67 (1H, m, CH_2), 2.84-2.94 (3H, m, CH_2), 3.10-3.18 (1H, m, CH_2), 3.64 (2H, broad, CH_2), 3.85 (3H, s, OMe), 3.86 (3H, s, OMe), 4.68 (2H, broad, CH_2), 6.40-6.43 (1H, m, CHO), 6.62 (2H, s, ArH), 6.98 (1H, dd, *J*, 7.7, 1.6Hz, ArH), 7.08 (1H, d, *J*, 1.6, ArH), 7.19 (1H, d, *J*, 7.7, ArH), 7.48 (1H, d, *J*, 8.3, ArH), 7.69 (1H, s, CH=N), 7.86 (1H, dd, *J*, 8.3, 1.9Hz, ArH), 8.10 (1H, d, *J*, 1.9, ArH).



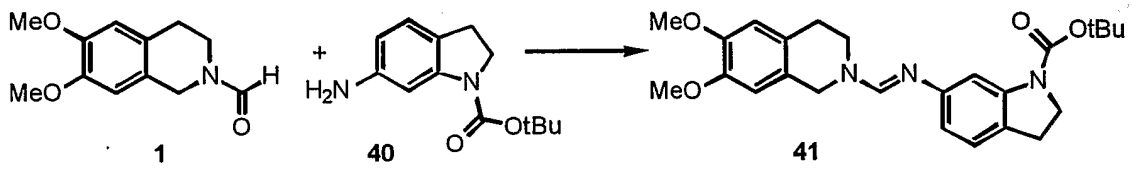
38 ^{1}H NMR ($CDCl_3$, 400MHz): 2.27-2.34 (1H, m, CH_2), 2.65-2.74 (1H, m, CH_2), 2.93-3.00 (4H, m, NMe + CH_2), 3.18-3.25 (1H, m, CH_2), 4.50 (2H, broad, CH_2), 6.48-6.51 (1H, m, CHO), 7.06 (1H, dd, *J*, 8.0, 1.8, ArH), 7.17 (1H, d, *J*, 1.8, ArH), 7.27-7.43 (6H, m, ArH), 7.54-7.56 (1H,

m, ArH), 7.81 (1H, broad, CH=N), 7.93 (1H, dd, *J*, 8.4, 1.9, ArH), 8.18 (1H, d, *J*, 1.9, ArH).



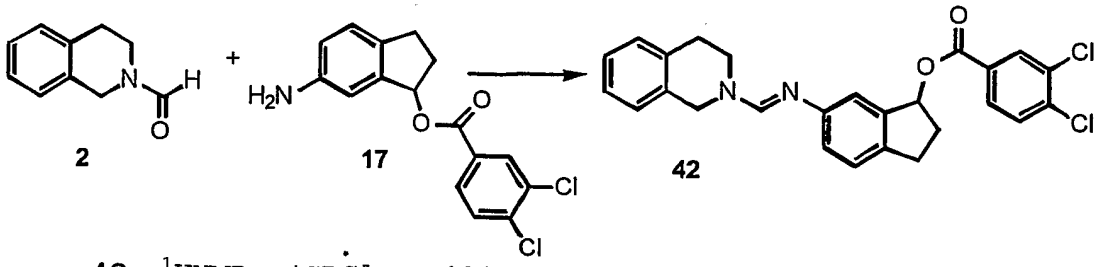
1 11 39

39 ^{1}H NMR ($CDCl_3$, 400MHz): 1.78-1.95 (4H, m, CH_2), 2.06 (3H, s, Ac), 2.65-2.85 (4H, m, CH_2), 3.61 (2H, broad, CH_2), 3.83-3.84 (6H, m, OMe), 4.66 (2H, broad, CH_2), 5.96 (1H, m, CHO), 6.61 (2H, s, ArH), 6.87-6.88 (2H, m, ArH), 7.00-7.03 (1H, m, ArH), 7.65 (1H, s, CH=N).



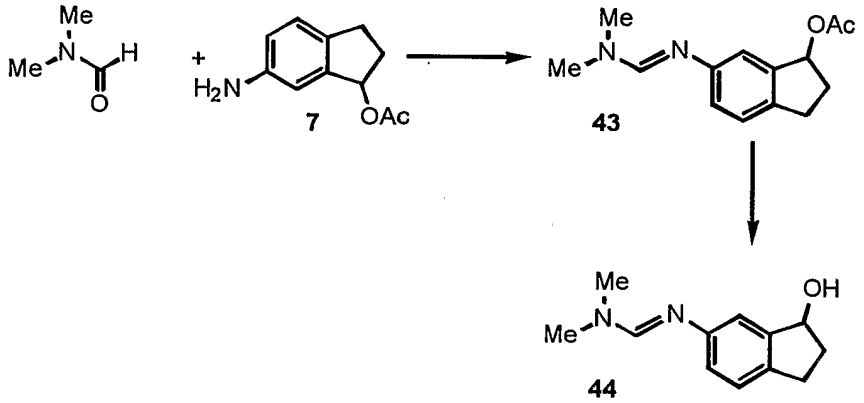
1 40 41

41 ^{1}HNMR (DMSO, 400MHz): 1.51 (9H, s, $C(CH_3)_3$), 2.92-3.08 (4H, m, $ArCH_2$), 3.75-3.76 (6H, m, OMe), 3.93-3.98 (4H, m, NCH_2), 4.86-4.90 (2H, m, $ArCH_2N$), 6.69 (1H, s, ArH), 6.81-6.89 (2H, m, ArH), 7.01-7.10 (1H, m, ArH), 7.25-7.28 (1H, m, ArH), 8.32 (1H, s, NCH=N), 8.82 (1H, broad, NH).



42 ^{1}HNMR ($CDCl_3$, 400MHz): 2.26-2.39 (2H, m, CH_2), 2.65-2.74 (1H, m, CH_2), 2.94-3.02 (2H, m, CH_2), 3.17-3.25 (1H, m, CH_2), 4.70 (2H, broad, CH_2N), 4.82 (2H, broad, $ArCH_2N$), 6.44-6.50 (1H, m, OCH), 7.04-7.05 (1H, m, ArH), 7.06-7.07 (1H, m, ArH), 7.14-7.38 (5H, m, ArH), 7.55-7.60 (1H, m, ArH), 7.76 (1H, s, NCH=N), 7.90-7.94 (1H, m, ArH), 8.15-8.17 (1H, m, ArH).

44 ^{1}HNMR ($CDCl_3$, 400MHz): 1.90-1.98 (1H, m, CH_2),



2.41-2.52 (1H, m, CH_2), 2.67-2.79 (1H, m, CH_2), 2.95-3.01 (7H, m, NCH_3 + CH_2), 5.19 (1H, t, *J* 6.05Hz), 6.86-6.88 (1H, m, ArH), 6.99-7.00 (1H, m, ArH), 7.11-7.13 (1H, m, ArH), 7.51-7.52 (1H, s, NCH=N). ^{13}CNMR ($CDCl_3$, 100MHz): 29.37 (CH_2), 36.34 (CH_2), 76.72 (CH), 116.44 (CH), 122.10 (CH), 125.39 (CH), 137.41 (C), 146.24 (C), 151.26 (C), 153.71 (CH).

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Each of the following references is specifically incorporated herein by reference. In addition, one skilled in the art can rely on the contents of these references to make and use embodiments of this invention.

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Abbreviations

The abbreviations used in this specification are those used within the article Brain in Stereotaxic Coordinates (Paxinos and Watson, 1998).

1, layer I of cortex

2, layers II & III of cortex

3, layers V & VI of cortex

AM, anteromedial thalamus

Au1, primary auditory cortex

V, anteroventral thalamus

Cg (Cg1,-Cg3), anterior cingulate cortex

CM, centromedial thalamic nucleus
DLL, dorsal nucleus of the lateral lemniscus
Ent, entorhinal cortex
Ge, gelatinous nucleus of the thalamus
I, insular cortex
IL, infralimbic cortex
IM, intramedial thalamic nucleus
lO, lateral orbital cortex
M1 & M2, primary and secondary motor cortex
MD, mediodorsal thalamic nucleus
MG, medial geniculates
mO, medial orbital cortex
P, parietal cortex
Pir, piriform cortex
PrL, prelimbic region of the medial prefrontal cortex
PV, paraventriclular thalamic nucleus
Re, nucleus reuniens of the thalamus
Rh, rhomboid nucleus of the thalamus
RSG, retrosplenial cortex
Rt, reticular nucleus of the thalamus (d = dorsal part; v = ventral part)
V2, secondary visual cortex
VCP, ventral cochlear nucleus, posterior
VL, ventrolateral thalamic nucleus
VLL, ventral nucleus of the secondary auditory cortex
VM, ventromedial thalamic nucleus
vO, ventral orbital cortex

CLAIMS

1. A pharmaceutical agent having serotonin 5-HT_7 receptor antagonist activity and muscarinic M_4 receptor agonist activity, for use in treating psychotic conditions, the agent does not include compounds having a chemical structure falling within the following definition, namely:

bisarylazepines substituted at the azepine ring portion by a 4-methyl piperazinyl, wherein the aryl moieties are fused to the azepine ring and wherein aryl is phenyl, substituted phenyl, thienyl or substituted thienyl; including optional replacement of an azepine ring carbon atom with a nitrogen atom, or substitution of said ring carbon atom.

2. The pharmaceutical agent according to claim 1 wherein the psychotic condition is schizophrenia and/or bipolar disorder.

3. The pharmaceutical agent according to claim 1 or claim 2 which comprises a mixture of at least two compounds, wherein at least one of said compounds possess serotonin 5-HT_7 receptor antagonist activity and wherein at least one of said compounds possess muscarinic M_4 receptor agonist activity.

4. The pharmaceutical agent according to claim 1 or claim 2 which comprises a compound which possess both serotonin 5-HT_7 receptor antagonist activity and muscarinic M_4 receptor agonist activity.

5. The pharmaceutical agent according to any one of claims 1 to 4 which additionally has a low or substantially no dopaminergic D_2 receptor affinity.

6. The pharmaceutical agent according to claim 5 wherein said dopaminergic D_2 receptor affinity is a minimum of at least 5 fold less than the affinity at the muscarinic M_4 and/or serotonin 5-HT_7 receptors.

7. The pharmaceutical agent according to claim 6 wherein said dopaminergic D_2 receptor affinity is at least 50 fold less than the affinity at the muscarinic M_4 and/or serotonin 5-HT_7 receptors.

8. A pharmaceutical agent according to any one of claims 1 to 7 for use in therapy.

9. A pharmaceutical formulation comprising a pharmaceutical agent according to any one of claims 1 to 7 together with a pharmaceutically acceptable carrier therefor.

10. Use of a pharmaceutical agent according to any one of claims 1 to 7 for the preparation of a medicament for the treatment or prophylaxis of schizophrenia and/or bipolar disorder.

11. A method of treating psychotic conditions in a patient in need thereof, comprising administering to the patient an effective amount of a pharmaceutical agent according to any one of claims 1 to 7.

12. A method of identifying an agent having the properties according to the present invention comprising the steps of:

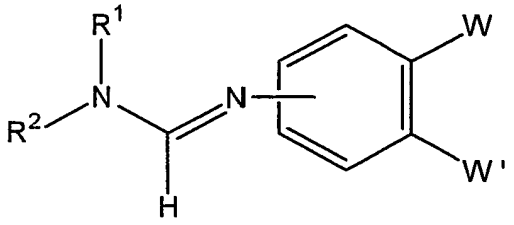
a) providing an agent to be tested;

b) subjecting said agent to one or more test procedures to identify 5-HT_7 receptor antagonist activity and muscarinic M_4 receptor agonist activity of said agent;

wherein the desired agent is considered to have been identified when said agent provides a 5-HT_7 receptor antagonist activity and a muscarinic M_4 receptor agonist activity.

13. The method according to claim 12 further comprising the step of subjecting the agent to a test procedure to identify low dopaminergic D_2 receptor affinity.

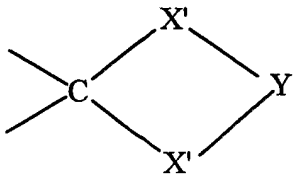
14. A compound represented by formula (I):



(I)

where R^1 and R^2 independently are a hydrogen atom, a substituted or unsubstituted straight chain or branched chain C_{1-6} alkyl group or C_{1-6} alkoxy group, a substituted or unsubstituted C_{3-8} cycloalkyl group or a C_{3-8} cycloalkoxy group, or an aralkyl group, or R^1 and R^2 form, together with the nitrogen atom to which they are bonded, a cyclic amine; W and W' form, together with the benzene ring to which they are bonded, a fused five-membered, six-membered or seven-membered saturated carbocylic ring being independently unsubstituted, substituted or fully

substituted at each carbon atom of the ring by a group -X-R^{13} where X is O, S, SO or SO_2 and R^{13} is a hydrogen atom, a C_{1-6} alkyl group, an acyl group, or an aroyl group or two of said -X-R^{13} groups, together with the carbon atom in the ring to which they are both bonded, form a C=S group or the following group:



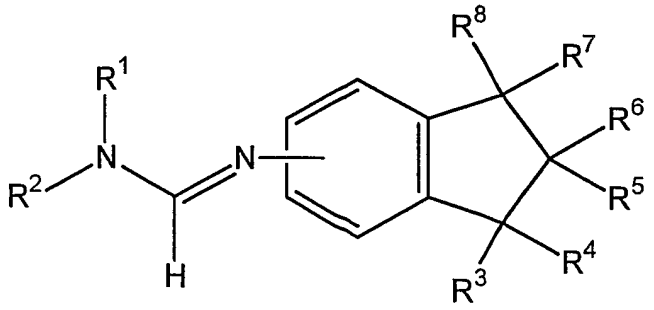
where both of X' are O or S and Y is a C_{1-3} alkylene group.

15. A compound according to claim 14, wherein said cyclic amine is substituted by a halogen atom, a C_{1-6} alkyl group or a C_{1-6} alkoxy group.

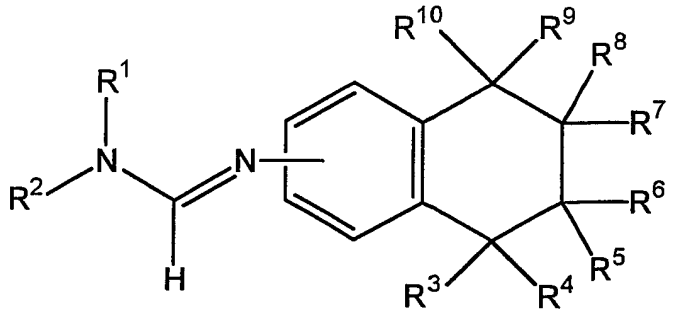
16. A compound according to claim 14 or claim 15 wherein said cyclic amine is fused with a benzene ring.

17. A compound according to claim 16 wherein said benzene ring is substituted by one or two halogen atoms, C_{1-6} alkyl groups or C_{1-6} alkoxy groups.

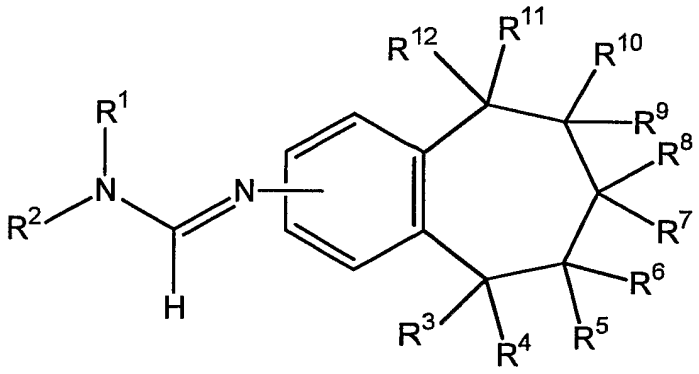
18. A compound according to claim 14 represented by the following formulae (II), (III) and (IV):



(II)



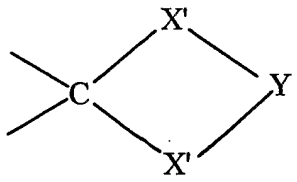
(III)



(IV)

wherein R^1 and R^2 independently are a hydrogen atom, a substituted or unsubstituted straight chain or branched chain C_{1-6} alkyl group or C_{1-6} alkoxy group, a substituted or unsubstituted C_{1-6} cycloalkyl group or a C_{1-6} cycloalkoxy group, or an aralkyl group, or R^1 and R^2 form, together with the nitrogen atom to which they are bonded, a cyclic amine; R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, and R^{12} are independently a hydrogen atom or the group $-X-R^{13}$ wherein X is O, S, SO or SO_2 and R^{13} is a hydrogen atom, a C_{1-6} alkyl group, an acyl group, or an aroyl group.

19. A compound according to claim 16 wherein R^3 and R^4, R^5 and R^6, R^7 and R^8, R^9 and R^{10}, and/or R^{11} and R^{12} together with the carbon atom in the ring to which they are both bonded, form a C=S group or the following group:



wherein both of X' are O or S and Y is a C_{1-3} alkylene group.

20. A compound according to claim 18 or claim 19 wherein R^1 and R^2 form together with the nitrogen atom to which they are bonded, a four-membered, five-membered or six-membered cyclic amine.

21. A compound according to claim 20 wherein said six-membered cyclic amine is fused with a benzene ring.

22. A compound according to claim 18 wherein R^1 and R^2 are a C_{1-6} alkyl group.

23. A compound according to any one of claims 14 to 22 which possesses serotonin 5-HT_7 receptor antagonist activity and/or muscarinic M_4 receptor agonist activity.

24. A compound according to claim 23 which additionally has a low or substantially no dopaminergic D_2 receptor affinity.

25. A compound according to any one of claims 14 to 24 for use in therapy.

26. A pharmaceutical formulation comprising a compound according to any one of claims 14 to 24 admixed with a pharmaceutically acceptable carrier.

27. Use of a compound according to any one of claims 14 to 24 for the preparation of a medicament for the treatment or prophylaxis of schizophrenia and/or bipolar disorder.

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28. A method of treating psychotic conditions in a patient in need thereof, comprising administering to the patient an effective amount of a compound according to any one of claims 14 to 24.

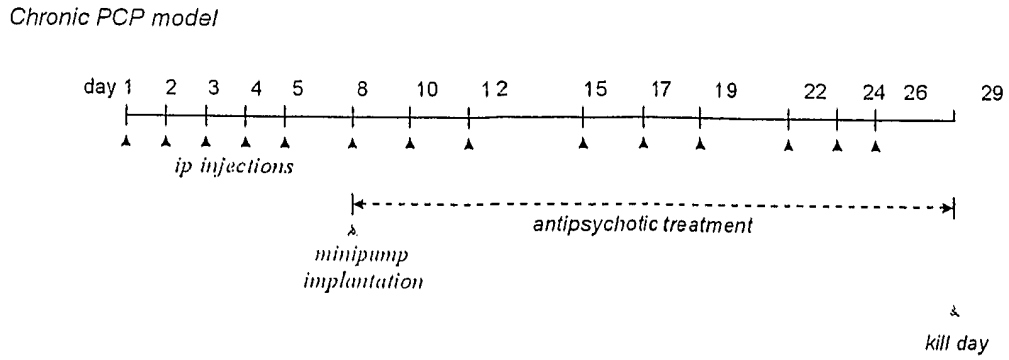

Figure 1

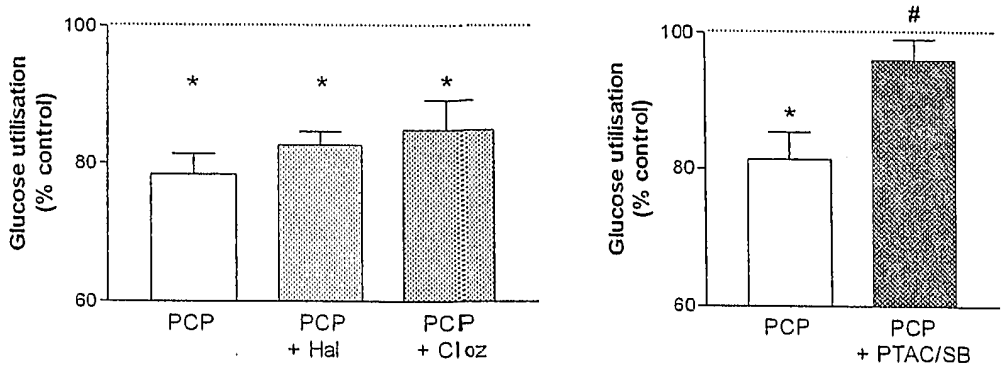

Figure 2

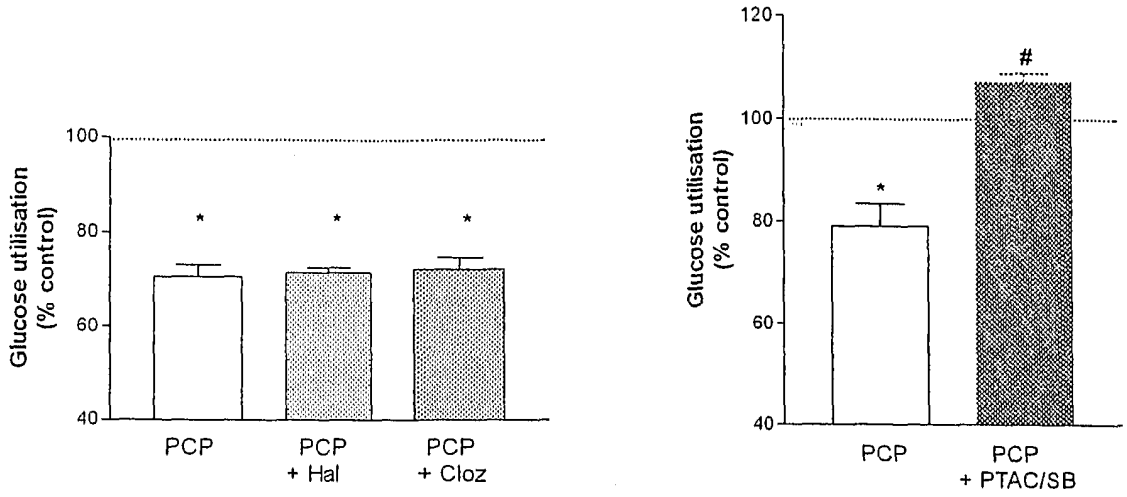

Figure 3

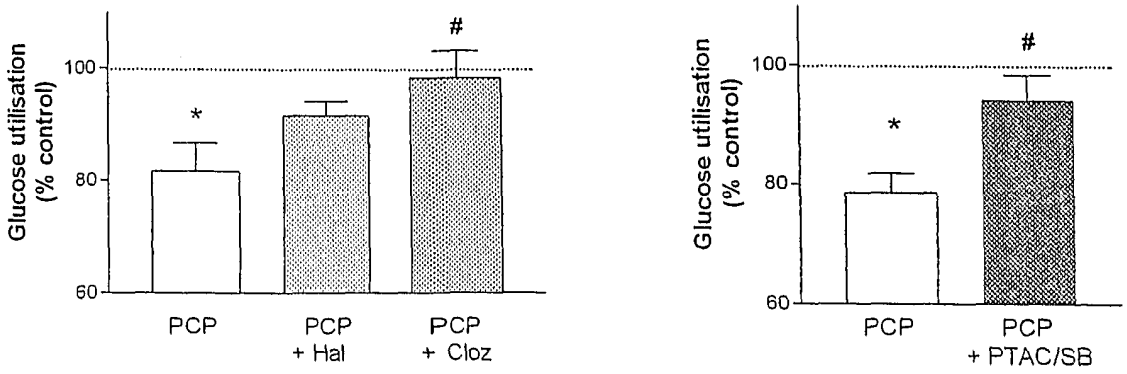

Figure 4

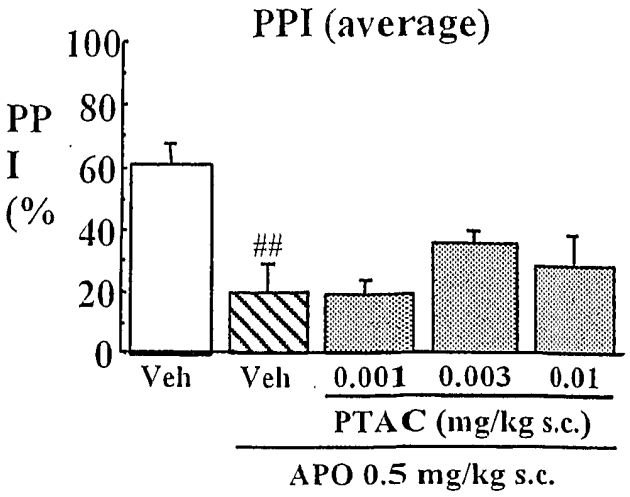

Figure 5

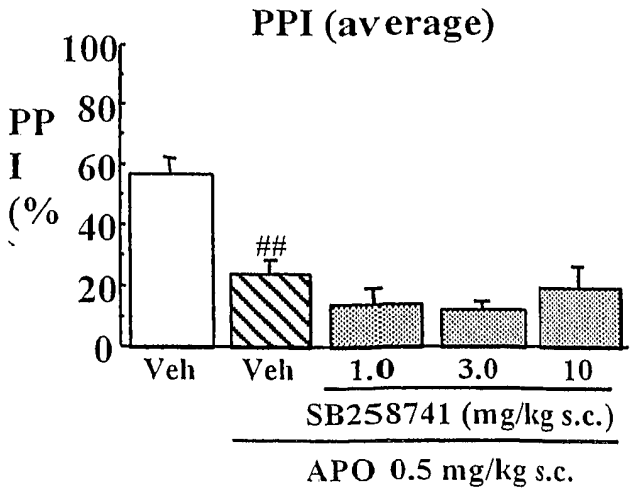

Figure 6

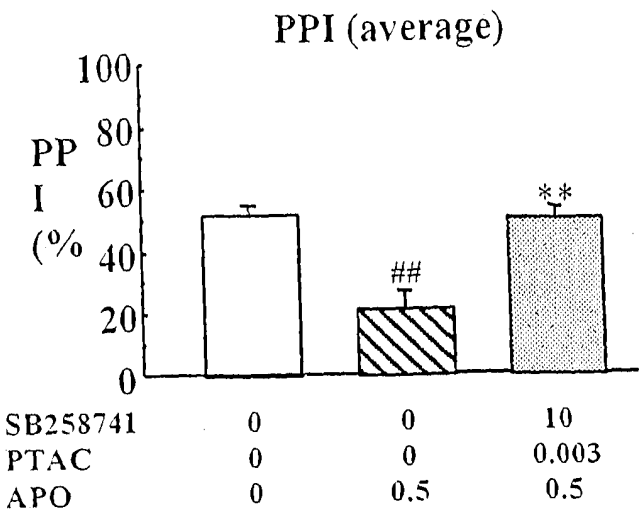

Figure 7

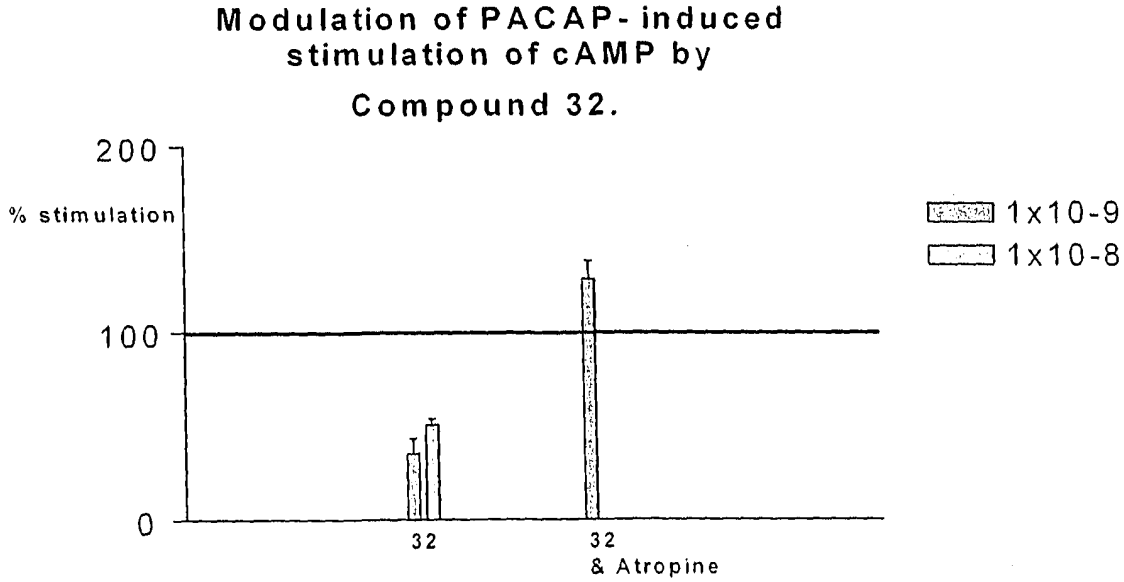

Figure 8

INTERNATIONAL SEARCH REPORT

International Application No
GB2004/001367

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/155 C07C257/12 A61P25/18

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)
IPC 7 A61K C07C A61P

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 practical, search terms used)
EPO-Internal, WPI Data, PAJ, BIOSIS, EMBASE, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 99/04778 A (HUGHES PHILIP FLOYD ; STASZAK MICHAEL ALEXANDER (US); WARD JOHN STANLE) 4 February 1999 (1999-02-04) page 59-65: examples 1-75, 77-105; page 73-81: examples 118-123, 125-127, 129-134	1,2, 4-11,14, 23-28
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X	US 3 539 631 A (PALLOS LASZLO ET AL) 10 November 1970 (1970-11-10) example 12	14,18, 23,24
	-/--	

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

[X] Patent family members are listed in 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 document 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
8 July 2004	27/07/2004

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Borst, M

Form PCT/ISA/210 (second sheet) (January 2004)

INTERNATIONAL SEARCH REPORT

ional Application No
GB2004/001367

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DATABASE REGISTRY CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; 12 April 1986 (1986-04-12), CHEMICAL ABSTRACTS: "RN 101398-76-9" XP002287521 abstract	14,18, 22-24
X	EP 0 011 182 A (BAYER AG) 28 May 1980 (1980-05-28) page 6, line 12-13	14,18, 23,24
A	BYMASTER FRANK P ET AL: "Unexpected antipsychotic-like activity with the muscarinic receptor ligand (5R,6R)6-(3-propylthio-1,2,5,-thiadiazol-4 -yl)-1-azabicyclo(3. 2.1)octane" EUROPEAN JOURNAL OF PHARMACOLOGY, vol. 356, no. 2-3, 4 September 1998 (1998-09-04), pages 109-119, XP002287518 ISSN: 0014-2999 cited in the application page 117-118, paragraph entitled "4. Discussion"	1-28
A	COCHRAN S M ET AL: "Induction of differential patterns of local cerebral glucose metabolism and immediate-early genes by acute clozapine and haloperidol." NEUROPHARMACOLOGY, vol. 43, no. 3, September 2002 (2002-09), pages 394-407, XP002287519 ISSN: 0028-3908 page 403, right hand column	1-28
A	POUZET B ET AL: "Effects of the 5-HT7 receptor antagonist SB-258741 in animal models for schizophrenia" PHARMACOLOGY BIOCHEMISTRY AND BEHAVIOR, vol. 71, no. 4, April 2002 (2002-04), pages 655-665, XP002287520 ISSN: 0091-3057 cited in the application page 663-664, paragraph entitled "4. Discussion"	1-28

INTERNATIONAL SEARCH REPORT

national application No.
PCT/GB2004/001367

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Rule 39.1(iv) PCT - Method for treatment of the human or animal body by therapy:Although claims 11 and 28 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

:ional Application No
'GB2004/001367

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