(54) Title: NEURODEVELOPMENTAL DISORDERS


Published: without international search report and to be republished upon receipt of that report (Rule 48,2(g))

[Continued on next page]

Figure: 4

(57) Abstract: The invention provides pharmaceutical compositions, medicaments and methods for use in preventing, ameliorating or treating neurodevelopmental disorders. The invention extends to novel synthetic methods for preparing active agents useful in the treatment of neurodevelopmental disorders.
with sequence listing part of description (Rule 5.2(a))
NEURODEVELOPMENTAL DISORDERS

The present invention relates to neurodevelopmental disorders, and in particular to pharmaceutical compositions, medicaments and methods for use in preventing, ameliorating or treating neurodevelopmental disorders. The invention extends to novel synthetic methods for preparing active agents useful in the treatment of neurodevelopmental disorders.

Neurodevelopmental disorders involve an impairment of the growth and development of the brain or central nervous system (CNS). Disorders that are considered to be neurodevelopmental in origin, or to have neurodevelopmental symptoms, include schizophrenia, and other psychotic disorders, such as schizoaffective disorder, bipolar affective disorder, attention deficit hyperactivity disorder (ADHD) and autism spectrum disorders.

Schizophrenia is a disabling mental illness affecting approximately 1% of the population worldwide, and cognitive dysfunction (i.e. problems with memory, attention and problem-solving) occurs in 75-80% of patients with schizophrenia. Studies suggest that cognition is a much better predictor of poor functional outcome than positive symptoms of schizophrenia, such as hallucinations, delusions and disorganised behaviour. At present, treatment of schizophrenia is mainly carried out with antipsychotic drugs known as dopamine antagonists, which reduce the effects of the neurotransmitter dopamine. Whilst such current antipsychotic medications are effective in treating positive symptoms, such as hallucinations etc., they have no impact on the cognitive function of the patient.

A variety of agents have been suggested for use in improving cognition in schizophrenia, but there have been no consistent reports of any efficacy. Thus, no drug therapies are currently licensed and/or marketed for this indication. Therefore, developing treatments to enhance cognition in neurodevelopmental disorders, such as schizophrenia, is a major goal of drug development.

Based on the evidence described herein, the inventors believe that compounds represented as Formula (I) can be used to treat cognitive dysfunction in various neurodevelopmental disorders, such as schizophrenia. In addition, the inventors have shown that genetic profiling can be used to personalise this cognitive enhancement.
Thus, in a first aspect, there is provided a neurodevelopmental disorder treatment composition comprising a therapeutically effective amount of a compound represented by Formula (I):

\[
\begin{align*}
\text{R}^1 & \quad \text{R}^2 \\
\text{O} & \quad \text{O} \\
\text{N} & \quad \text{R} \\
\end{align*}
\]

(1)

wherein

\begin{align*}
\text{R} & \text{ is a hydrogen atom, or a group selected from C}_1-6 \text{ alkyl unsubstituted or substituted by C}_3-7 \text{ cycloalkyl, C}_3-6 \text{ alkenyl, C}_3-6 \text{ alkynyl, C}_3-7 \text{ cycloalkyl, phenalkyl in which the alkyl moiety contains 1-5 carbon atoms, and } -\text{CHO}; \\
\text{R}^1 & \text{ is a group selected from halogen, C}_1-4 \text{ alkyl, or hydroxyl; } \\
\text{R}^2 & \text{ is a hydrogen atom, or substituent as defined above for R}^1; \\
\end{align*}

or a physiologically acceptable salt or hydrate thereof; and optionally a pharmaceutically acceptable vehicle.

In a second aspect, there is provided a process for making the composition according to the first aspect, the process comprising contacting a therapeutically effective amount of a compound represented by Formula (I) or a physiologically acceptable salt or hydrate thereof, with a pharmaceutically acceptable vehicle.

In a third aspect, there is provided a compound represented by Formula (I) or a physiologically acceptable salt or hydrate thereof, for use in the treatment, prevention or amelioration of a neurodevelopmental disorder.

In a fourth aspect, there is provided a method of treating, preventing or ameliorating a neurodevelopmental disorder in a subject, the method comprising administering, to a subject in need of such treatment, a therapeutically effective amount of a compound represented by Formula (I) or a physiologically acceptable salt or hydrate thereof.

The compound of Formula (I), one example of which is the drug sold under the trade name Fluparoxan, is an advantageous adjunctive treatment to existing dopamine antagonists for treating neurodevelopmental disorders, such as schizophrenia, as it improves the cognitive function of the patient, and not just positive symptoms, such
as hallucinations, delusions and disorganised behaviour. Furthermore, the compound of Formula (1) is advantageous over Idoxoxan for treating neurodevelopmental disorders, as it is more selective for α2 adrenergic receptors, and does not bind to other receptors that are unrelated to the mechanism of action.

Therefore, compositions comprising the compound of Formula (1) exhibit significantly less potential to cause side effects. It should also be noted that, since the compound of Formula (1) can be administered orally, it is clearly advantageous over atipamezole, which can only be given as an intravenous injection.

The term “neurodevelopmental disorder treatment composition” can mean a pharmaceutical formulation used in the therapeutic amelioration, prevention or treatment of a neurodevelopmental disorder in a subject.

For example, the neurodevelopmental disorder may be selected from a group of disorders including: schizophrenia, schizoaffective disorder, bipolar affective disorder, attention deficit hyperactivity disorder (ADHD) and autism spectrum disorders. The neurodevelopmental disorder may be schizophrenia. It is especially preferred that the compound of Formula (1) and compositions of the invention are effective for improving cognitive decline or dysfunction in the neurodevelopmental disorder that is being treated. It will be appreciated that cognitive dysfunction can be characterised by impairment in the mental processes of learning and memory, attention and concentration, speed of information processing, reasoning and problem-solving, language and other cognitive functions, any of which may be enhanced with the compositions of the invention. This can be measured by cognitive tests designed to probe each of these domains.

In formula (1), the alkyl, alkenyl and alkynyl groups represented by R, R¹ and R² may be straight or branched chain groups.

In embodiments when R contains a -C=C- or -C≡C- linkage, this may not be directly attached to the nitrogen atom. When R is alkyl, it may be methyl, ethyl or propyl, with methyl being preferred. When R is an alkyl group substituted by a C₃₋₇ cycloalkyl group, it may be cyclopropyl C₁₋₃ alkyl, such as cyclopropylmethyl. When R is alkenyl, it may be allyl, and when R is alkynyl, it may be propynyl. When R is cycloalkyl, it may be cyclopropyl. When R is an aralkyl group it may be phenC₁₋₅ alkyl, such as benzyl.
The halogen atoms represented by R¹ and R² may be fluorine, chlorine, bromine or iodine atoms. Fluorine is especially preferred. Examples of alkyl and alkoxy groups represented by R¹ and R² are methyl, ethyl, methoxy and ethoxy groups. The group NR³R⁴ may be an amino, methylamino, ethylamino, dimethylamino or diethylamino group.

It will be appreciated that each compound of formula (1) is a trans isomer and exists as two enantiomers. The structural formulae herein are to be understood to depict either enantiomer of each compound as well as mixtures of the enantiomers, including racemates, even through the precise structure as set out only relates to one enantiomer.

A preferred compound of Formula (1) is that wherein R is a hydrogen atom. Another preferred compound of Formula (1) is that wherein R is a C₁₋₃ alkyl group, particularly a methyl or ethyl group.

In a further preferred compound of Formula (1), R¹ is a halogen atom or a C₁₋₄ alkyl or C₁₋₄ alkoxy group, in particular a chlorine or fluorine atom or a methyl or methoxy group. Preferably, R¹ is a fluorine atom.

A further preferred compound of Formula (1) is that in which R² is a hydrogen or fluorine atom, particularly a hydrogen atom.

Particularly important compounds of Formula (1) are those in which R is a hydrogen atom or a methyl or ethyl group, particularly a hydrogen atom; R¹ is a chlorine or fluorine atom or a methyl or methoxy group, particularly a chlorine or fluorine atom and especially a fluorine atom; and R² is a hydrogen or fluorine atom, especially a hydrogen atom.

Important compounds are (+)-trans-2,3,3a,9a-tetrahydro-5-methyl-1H-[1,4]benzodioxino[2,3-c]pyrrole, and its 3aS- and 3aR-isomers; (+)-trans-5-chloro-2,3,3a,9a-tetrahydro-1H-[1,4]benzodioxino[2,3-c]pyrrole, and its 3aS- and 3aR-isomers; (+)-trans-5,8-difluoro-2,3,3a,9a-tetrahydro-1H-[1,4]benzodioxino[2,3-c] pyrrole and its 3aS- and 3aR-isomers; and their physiologically acceptable salts and hydrates, particularly the hydrochlorides.

Particularly important compounds, by virtue of their especially useful biological
profiles, are (±)-trans-5-fluoro-2,3,3a,9a-tetrahydro-1H-[1,4]benzodioxino[2,3-c]pyrrole and its 3αS- and 3αR-isomers and their physiologically acceptable salts and hydrates, particularly the hydrochlorides. It will be appreciated that this preferred compound may be sold under the trade name Fluparoxan, and represented by

Formula (2):

![Chemical Structure](2)

Suitable physiologically acceptable salts are the acid addition salts formed with inorganic acids, for example hydrochlorides, hydrobromides, phosphates and sulphates, and with organic acids, for example citrates, tartrates, acetates, maleates and succinates. The hydrochlorides are particularly useful.

A substantial amount of work has been devoted to identifying the neurotransmitters that are involved in cognition. The catecholamine neurotransmitters, dopamine and noradrenaline, are believed to be important for cognitive function mediated via the pre-frontal cortex (PFC) of the brain. The majority of research aimed at treating neurodevelopmental disorders, such as schizophrenia, has thus far focused mainly on dopamine. However, there is evidence that levels of noradrenaline in the prefrontal cortex may be reduced in schizophrenia, and other neurodevelopmental disorders that are associated with cognitive impairment. The inventors believe that compounds of Formula (1), such as Fluparoxan (2), increase the levels of noradrenaline in the pre-frontal cortex by inhibiting feedback mechanisms, as illustrated in Figures 1 and 2.

The inventors have also investigated the impact of genetic variation on catecholamine levels in the prefrontal cortex (PFC) of the brain, and consequently on cognition. For example, the enzyme catechol-O-methyltransferase (COMT) is believed to be involved in the degradation of catecholamines, i.e. breaking down dopamine. A common mutation in the gene encoding COMT, which involves the replacement of guanine by adenine (GGATTTGCCTGGC[A/G]TGAAGGACAAGGTGTG – SEQ ID No:1), leads to the substitution of the amino acid methionine (Met; ATG) for valine (Val; GTG) at codon 158. Therefore, GGATTTGCCTGGCATGAAGGACAAGGTGTG (SEQ ID No:2) corresponds to the “Met” genotype, and
GGATTTCGCTGGC<sup>GTG</sup>AA<sub>GAG</sub>AACAAGGTGTG (SEQ ID No:3) corresponds to the "Val" genotype.

This substitution to the "Met" genotype (i.e. SEQ ID No:2) results in a reduction in the activity of the COMT enzyme, leading to higher levels of dopamine in the PFC. The mutation occurs in 50% of the population, and so both variants are equally prevalent.

Homozygous individuals with two copies of the methionine variant denoted as "Met/Met" have higher levels of PFC dopamine, and perform better on certain cognitive tasks than homozygous individuals with two copies of the valine variant (i.e. "Val/Val"). Studies indicate that the variants act in a co-dominant way, such that heterozygous individuals with one copy of each variant ("Val/Met") have enzyme activity and performance that is midway between the two homozygous groups. The relevance of this genetic variation to pharmacological approaches to treating cognitive dysfunction has been demonstrated with the COMT enzyme inhibitor Tolcapone that enhances cognition in (Val/Val) (i.e. high COMT activity) genotypes, but results in impairment in (Met/Met), i.e. low COMT activity genotypes (Apud et al., Neuropsychopharmacology, 2006, 32 1011-1020).

However, until now, no studies have ever examined the relationship between noradrenergic genetic variation and the effects of drugs on cognitive dysfunction in diseases such as schizophrenia. The inventors are the first to suggest that interactions between genes involved in dopamine and noradrenaline signalling mechanisms are relevant, and should be considered when treating cognition dysfunction. As described in the Examples, there is an insertion/deletion mutation in the gene responsible for the α2 adrenergic receptor subtype B (ADRA2B), involving the deletion of nine base pairs beginning at nucleotide 901:

TGAAGAGGAG [GAAGAGGAG]GAGGAGGAGGA (SEQ ID No:4).

This mutation results in the deletion of three glutamic acid residues 301-303 in the third intracellular loop of the receptor, i.e. TGAAGAGGAGGAGGAGGA (SEQ ID No:5). The deletion variant, in which the residues are absent, denoted as (Del), occurs in approximately 30% of Caucasian people, and 10% of African-Americans. Thus, the wild-type insertion variant denoted as (Ins), in which the residues are present, is more prevalent, i.e.

TGAAGAGGAG GAAGAGGAGGAGGAGGA (SEQ ID No:6).
The α2 adrenergic receptor (also known as adrenoceptor) is a G protein-coupled receptor (GPCR) associated with the G\textsubscript{i} heterotrimeric G-protein. It consists of three highly homologous subtypes, including α2A-, α2B-, and α2C-adrenergic.

Catecholamines, such as noradrenaline and adrenaline, signal through the α2-adrenoceptor in the central and peripheral nervous systems, and are located postsynaptically and pre-synaptically. Pre-synaptic α2-adrenoceptors are responsible for down-regulating (i.e. reducing) noradrenaline levels. There is evidence that the ADRA\textsubscript{2B} deletion mutation reduces the function of the α2B receptor, thereby increasing the levels of noradrenaline via the same mechanism as fluparoxan, as illustrated in Figure 3. Studies indicate that the deletion mutation acts in a dominant way, such that homozygous individuals with two copies of the deletion variant (Del/Del) have similarly reduced receptor function and increased levels of noradrenaline to heterozygous individuals with one copy (Del/Ins). Homozygous individuals with two copies of the insertion variant (Ins/Ins) are considered to have normal receptor function.

Surprisingly, the authors have found that individuals that have: (i) reduced α2b adrenoceptor function (i.e. one or two copies of the ADRA\textsubscript{2B} deletion mutation), and (ii) a high catechol-O-methyltransferase (COMT) activity (i.e. the Val/Val genotype), exhibited improved memory performance, such that it was equivalent to those individuals having a low COMT activity (i.e. the Met/Met genotype). However, unexpectedly, there was no significant effect of the ADRA\textsubscript{2B} mutation on memory performance in low COMT activity (Met/Met) individuals. These results clearly demonstrate that administering an α2 adrenoceptor antagonist, such as a compound of Formula (1) or (2), would result in an improvement in cognition in a subject having the high COMT activity (i.e. Val/Val) genotype, and who does not have a copy of the ADRA\textsubscript{2B} deletion mutation, denoted as (No del), as shown in Figure 4. Based on this observation, the inventors have shown that fluparoxan treatment may be personalised based on the COMT and ADRA\textsubscript{2B} genotypes of subjects receiving the treatment.

Additionally, the inventors believe that this observation is also applicable to a similar deletion mutation in the α2c adrenergic receptor gene (i.e. ADRA\textsubscript{2C}). There is also an insertion/deletion mutation in this gene, involving the deletion of twelve base pairs beginning at nucleotide 967: GGGCG[GGGCCGGGGGCG]GCT (SEQ ID No: 7).
This mutation results in the deletion of four glutamic acid residues 323-326 in the third intracellular loop of the receptor, i.e. GGGCGGCT (SEQ ID No: 8). The deletion variant, in which the residues are absent, also denoted as (Del), occurs in approximately 3% of Caucasians, and approximately 45% of African-Americans. Thus, both variants are approximately equally prevalent in African-Americans, whereas, the wild-type insertion variant denoted as (Ins), in which the residues are present, predominates in Caucasians, i.e.  
GGGCG GGGCCG GGGGC G CT (SEQ ID No: 9).

Therefore, the compound of Formula (1) or (2) may be used to treat a neurodevelopmental disorder, and preferably cognitive dysfunction thereof, in a subject who (i) has the high catechol-O-methyltransferase (COMT) activity (i.e. Val/Val) genotype; (ii) has the normal \( \alpha_2b \) adrenoceptor (ADRA2B) function (i.e. Ins/Ins) genotype and/or (iii) has the normal \( \alpha_2c \) adrenoceptor (ADRA2C) function (i.e. Ins/Ins) genotype.

Thus, in one embodiment, the subject may have the (Val/Val) COMT genotype and the (Ins/Ins) ADRA2B genotype, but not the (Ins/Ins) ADRA2C genotype. In another embodiment, the subject may have the (Val/Val) COMT genotype and the (Ins/Ins) ADRA2C genotype, but not the (Ins/Ins) ADRA2B genotype. In a preferred embodiment, the subject may have the (Val/Val) COMT genotype, the (Ins/Ins) ADRA2B genotype and the (Ins/Ins) ADRA2C genotype.

It will be appreciated that the (Val/Val) COMT genotype may be homozygous for SEQ ID No: 3, the (Ins/Ins) ADRA2B genotype may be homozygous for SEQ ID No: 6, and that the (Ins/Ins) ADRA2C genotype may be homozygous for SEQ ID No: 9.

The inventors believe that this observation has far-reaching implications in personalised medicine, and is applicable not only when administering compounds represented by Formula (1), such as Fluparoxan (2), but when using any an \( \alpha_2 \) adrenergic receptor antagonist, for treating any disease characterised by cognitive dysfunction.

Thus, in a fifth aspect, there is provided an \( \alpha_2 \) adrenergic receptor antagonist, for use in the treatment, prevention or amelioration of a disease characterised by cognitive dysfunction in a subject who (i) has the high catechol-O-methyltransferase (COMT)
activity (i.e. Val/Val) genotype; (ii) has the normal α2b adrenoceptor (ADRA2B) function (i.e. Ins/Ins) genotype and/or (iii) has the normal α2c adrenoceptor (ADRA2C) function (i.e. Ins/Ins) genotype.

In a sixth aspect, there is provided a method of treating, preventing or ameliorating a disease characterised by cognitive dysfunction in a subject having (i) the high catechol-O-methyltransferase (COMT) activity (i.e. Val/Val) genotype; (ii) the normal α2b adrenoceptor (ADRA2B) function (i.e. Ins/Ins) genotype and/or (iii) the normal α2c adrenoceptor (ADRA2C) function (i.e. Ins/Ins) genotype, the method comprising administering, to a subject in need of such treatment, a therapeutically effective amount of an α2 adrenoceptor antagonist.

The subject may have the (Val/Val) COMT genotype and the (Ins/Ins) ADRA2B genotype, but not the (Ins/Ins) ADRA2C genotype. Alternatively, the subject may have the (Val/Val) COMT genotype and the (Ins/Ins) ADRA2C genotype, but not the (Ins/Ins) ADRA2B genotype. The subject may have the (Val/Val) COMT genotype, the (Ins/Ins) ADRA2B genotype and the (Ins/Ins) ADRA2C genotype.

Compounds of the invention have selective α2-adrenoceptor antagonist action. The antagonist may be represented by Formula (1) defined above. The test for determining α2-adrenoceptor antagonist action is based on the ability to prevent the action of the selective α2-adrenoreceptor agonist, such as clonidine or 5-bromo-N-(4,5-dihydro-1H-imidazol-2-yl)-6-quinolinamine, [R-(R*)]-2,3-dihydroxybutanedioate (UK 14304-18) on the rat field stimulated vas deferens preparation. Clonidine and UK 14304-18 inhibit the twitch response of the rat isolated vas deferens to low frequency motor nerve stimulation. This inhibition is a consequence of activation of pre-synaptic adrenoceptors of the α2-type. Antagonism of the effect of clonidine or UK 14304-18 is quantified by measuring the parallel shift to the right of the inhibitory α2-adrenoreceptor agonist log10 (concentration)/response curve in the presence of increasing concentrations of the antagonist. Potency and competitiveness of antagonism are determined by the method of Arunlakshana & Schild (Br. J. Pharmac. 1959, 14 48-58).

The α2-adrenoceptor-type selectivity of the compounds of general formula (1) is similarly assessed by measuring the ability to produce a parallel shift to the right of the log10 (concentration)/response curve for the α1-adrenoceptor agonist phenylephrine. The α1-adrenoceptor-mediated responses of phenylephrine measured
were contractions of the rat isolated anococygeus muscle (Leighton, Butz & Parameter, Eur. J. Pharmac., 1979, 58 27-38).

The antagonist may be a selective or non-selective α2 adrenoceptor antagonist. For example, the α2-adrenoceptor antagonist may be selected from the group consisting of: fluparoxan; efaroxan; idazoxan; atipamezole; A-80426; phenoxybenzamine; mirtazapine; mianserin; SB-269,970; yohimbine; BRL-44408; RX-821,002; ARC-239; imiloxan; JP-1302; and spiroxatrine. Preferably, the antagonist may be presented by Formula (2), i.e. fluparoxan.

The antagonist may be used in the treatment, prevention or amelioration of any disease characterised by cognitive dysfunction, including neurodevelopmental disorders, such as schizophrenia, schizoaffective disorder, bipolar affective disorder, attention deficit hyperactivity disorder (ADHD) and autism spectrum disorders, as well neurodegenerative disorders involving progressive loss of structure or function of neurons, such as Parkinson's disease, Alzheimer's disease, Huntington's disease and multiple sclerosis, and also acquired brain disorders involving damage to the brain after birth such as traumatic brain injury, stroke and alcohol and drug abuse.

It will be appreciated that the compound of Formula (1) or (2) according to the invention may be used in a medicament which may be used in a monotherapy (i.e. use of only a compound of Formula (1) or (2)), for treating, ameliorating, or preventing neurodevelopmental disorders. Alternatively, the compound of Formula (1) or (2) may be used as an adjunct to, or in combination with, known therapies for treating, ameliorating, or preventing neurodevelopmental disorders, for example a dopamine antagonist, such as acepromazine, chlorpromazine or ioxapine.

The compound of Formula (1) or (2) may be combined in compositions having a number of different forms depending, in particular, on the manner in which the composition is to be used. Thus, for example, the composition may be in the form of a powder, tablet, capsule, liquid, ointment, cream, gel, hydrogel, aerosol, spray, micellar solution, transdermal patch, liposome suspension or any other suitable form that may be administered to a person or animal in need of treatment. It will be appreciated that the vehicle of medicaments according to the invention should be one which is well-tolerated by the subject to whom it is given.
Medicaments comprising compound of Formula (1) or (2) may be used in a number of ways. For instance, oral administration may be required, in which case the compound of Formula (1) or (2) may be contained within a composition that may, for example, be ingested orally in the form of a tablet, capsule or liquid. Compositions comprising the compound of Formula (1) or (2) may be administered by inhalation (e.g. intranasally). Compositions may also be formulated for topical use. For instance, creams or ointments may be applied to the skin, for example, adjacent the brain.

The compound of Formula (1) or (2) may also be incorporated within a slow- or delayed-release device. Such devices may, for example, be inserted on or under the skin, and the medicament may be released over weeks or even months. The device may be located at least adjacent the treatment site, e.g. the head. Such devices may be particularly advantageous when long-term treatment with the compound of Formula (1) or (2) is required and which would normally require frequent administration (e.g. at least daily injection).

In a preferred embodiment, the compound of Formula (1) or (2) and compositions according to the invention may be administered to a subject by injection into the blood stream or directly into a site requiring treatment. Injections may be intravenous (bolus or infusion) or subcutaneous (bolus or infusion), or intradermal (bolus or infusion).

It will be appreciated that the amount of the compound of Formula (1) or (2) is required is determined by its biological activity and bioavailability, which in turn depends on the mode of administration, the physiochemical properties of the compound of Formula (1) or (2) and whether it is being used as a monotherapy or in a combined therapy. The frequency of administration will also be influenced by the half-life of the compound of Formula (1) or (2) within the subject being treated. Optimal dosages to be administered may be determined by those skilled in the art, and will vary with the particular compound in use, the strength of the pharmaceutical composition, the mode of administration, and the advancement of the neurodevelopmental disorder. Additional factors depending on the particular subject being treated will result in a need to adjust dosages, including subject age, weight, gender, diet, and time of administration.
Generally, a daily dose of between 0.01μg/kg of body weight and 500mg/kg of body weight of the agent according to the invention may be used for treating, ameliorating, or preventing the neurodevelopmental disorder, depending upon which compound is used. More preferably, the daily dose is between 0.001mg/kg of body weight and 200mg/kg of body weight, more preferably between 0.01mg/kg and 100mg/kg body weight, and most preferably between approximately 0.1mg/kg and 50mg/kg body weight. The daily dosage may conveniently be administered in the form of dosage units, each unit containing for example 0.01 to 3 mg/kg of active ingredient.

The compound may be administered before, during or after onset of the neurodevelopmental disorder. Daily doses may be given as a single administration (e.g. a single daily injection). Alternatively, the compound may require administration twice or more times during a day. As an example, compounds may be administered as two (or more depending upon the severity of the disorder being treated) daily doses of between 25mg and 7000 mg (i.e. assuming a body weight of 70 kg). A patient receiving treatment may take a first dose upon waking and then a second dose in the evening (if on a two-dose regime) or at 3- or 4-hourly intervals thereafter. Alternatively, a slow release device may be used to provide optimal doses of agents according to the invention to a patient without the need to administer repeated doses.

Known procedures, such as those conventionally employed by the pharmaceutical industry (e.g. in vivo experimentation, clinical trials, etc.), may be used to form specific formulations comprising the compounds according to the invention and precise therapeutic regimes (such as daily doses of the compounds and the frequency of administration).

A “subject” may be a vertebrate, mammal, or domestic animal. Hence, compounds, compositions and medicaments according to the invention may be used to treat any mammal, for example livestock (e.g. a horse), pets, or may be used in other veterinary applications. Most preferably, however, the subject is a human being.

A “therapeutically effective amount” of agent is any amount which, when administered to a subject, is the amount of drug that is needed to treat the condition, or produce the desired effect.
For example, the therapeutically effective amount of compound used may be from about 0.01 mg to about 800 mg, and preferably from about 0.01 mg to about 500 mg. It is preferred that the amount of compound is an amount from about 0.1 mg to about 250 mg, and most preferably from about 0.1 mg to about 20 mg.

A “pharmaceutically acceptable vehicle” as referred to herein, is any known compound or combination of known compounds that are known to those skilled in the art to be useful in formulating pharmaceutical compositions.

In one embodiment, the pharmaceutically acceptable vehicle may be a solid, and the composition may be in the form of a powder or tablet. A solid pharmaceutically acceptable vehicle may include one or more substances which may also act as flavouring agents, lubricants, solubilisers, suspending agents, dyes, fillers, glidants, compression aids, inert binders, sweeteners, preservatives, dyes, coatings, or tablet-disintegrating agents. The vehicle may also be an encapsulating material. In powders, the vehicle is a finely divided solid that is in admixture with the finely divided active compounds according to the invention. In tablets, the active compounds of Formula (1) may be mixed with a vehicle having the necessary compression properties in suitable proportions and compacted in the shape and size desired. The powders and tablets preferably contain up to 99% of the active compound. Suitable solid vehicles include, for example calcium phosphate, magnesium stearate, talc, sugars, lactose, dextrin, starch, gelatin, cellulose, polyvinylpyrrolidone, low melting waxes and ion exchange resins. In another embodiment, the pharmaceutical vehicle may be a gel and the composition may be in the form of a cream or the like.

However, the pharmaceutical vehicle may be a liquid, and the pharmaceutical composition is in the form of a solution. Liquid vehicles are used in preparing solutions, suspensions, emulsions, syrups, elixirs and pressurized compositions. The active compound may be dissolved or suspended in a pharmaceutically acceptable liquid vehicle such as water, an organic solvent, a mixture of both or pharmaceutically acceptable oils or fats. The liquid vehicle can contain other suitable pharmaceutical additives such as solubilisers, emulsifiers, buffers, preservatives, sweeteners, flavouring agents, suspending agents, thickening agents, colours, viscosity regulators, stabilizers or osmo-regulators. Suitable examples of liquid vehicles for oral and parenteral administration include water (partially containing additives as above, e.g. cellulose derivatives, preferably sodium carboxymethyl
cellulose solution), alcohols (including monohydric alcohols and polyhydric alcohols, e.g. glycols) and their derivatives, and oils (e.g. fractionated coconut oil and arachis oil). For parenteral administration, the vehicle can also be an oily ester such as ethyl oleate and isopropyl myristate. Sterile liquid vehicles are useful in sterile liquid form compositions for parenteral administration. The liquid vehicle for pressurized compositions can be a halogenated hydrocarbon or other pharmaceutically acceptable propellant.

Liquid pharmaceutical compositions, which are sterile solutions or suspensions, can be utilized by, for example, intramuscular, intrathecal, epidural, intraperitoneal, intravenous and particularly subcutaneous injection. The compound of Formula (1) or (2) may be prepared as a sterile solid composition that may be dissolved or suspended at the time of administration using sterile water, saline, or other appropriate sterile injectable medium.

The compound of Formula (1) or (2) and compositions of the invention may be administered orally in the form of a sterile solution or suspension containing other solutes or suspending agents (for example, enough saline or glucose to make the solution isotonic), bile salts, acacia, gelatin, sorbitan monoleate, polysorbate 80 (oleate esters of sorbitol and its anhydrides copolymerized with ethylene oxide) and the like. The compound of Formula (1) or (2) can also be administered orally either in liquid or solid composition form. Compositions suitable for oral administration include solid forms, such as pills, capsules, granules, tablets, and powders, and liquid forms, such as solutions, syrups, elixirs, and suspensions. Forms useful for parenteral administration include sterile solutions, emulsions, and suspensions.

The inventors investigated various known methods for preparing the compound of Formula (1), and in particular Formula (2).

Firstly, Bioorg. Med. Chem. 1995, 1595-1603 discloses three routes for the synthesis of a tricyclic compound from which Fluparoxan can then be synthesised, each of which is illustrated in the Figures. The first of these three routes (see Figure 8) is nine steps long with an overall yield of 11.3% and would ultimately produce (+/-) Fluparoxan. The starting material for this route is not commercially available and it would take five steps to make it starting with material which costs £40 / 5g (Apollo Scientific). The second route (see Figure 9) is also nine steps long and would produce (+/-) Fluparoxan. This route starts from cheap cis-2-butene-1,4-diol (£27 / 500ml,
Acros) but has an overall yield of 2.7%. The third route (see Figure 10) is able to produce (+), (-) or (+/-) Fluparoxan depending upon which tartaric ester is used as the starting material. This route is 10 steps long and has an overall yield of 2.1%.

US4837336A describes a nine step route to (+/-) Fluparoxan using 1-fluoro-2,3-dihydroxybenzene to open oxiran 20 from route 2 (i.e. Figure 9) giving a 4.2% overall yield. US4880801A describes the final five steps from route 2 (i.e. Figure 9) to give (+/-) Fluparoxan in an overall yield of 2.9%. Finally, EP0532100A1 describes the final six steps from route 3 (i.e. Figure 10) on a larger scale than previously reported and presents an overall yield of 7.2%. This route can also supply optically pure (+) or (-) Fluparoxan as well as (+/-) Fluparoxan.

Accordingly, there is a need for an improved method for producing fluparoxan.

Thus, a seventh aspect of the present invention relates to a process for the preparation of a dioxane IV or a salt thereof, comprising the reaction of a benzene II or a salt thereof, with a pyrrolidine III or a salt thereof, to form the dioxane IV or the salt thereof:

\[ \text{(II)} \quad \text{(III)} \quad \text{(IV)} \]

wherein X and Y each independently represent any leaving group, and wherein R¹, R², R³, R⁴ and R⁵ each independently represent any atom or group.

Typically, X and Y are each independently selected from a halo group, a carboxylic ester group or a sulfonate ester group. Preferably, X and Y are each independently selected from a halo group such as a chloro, bromo or iodo group.

Optionally, X and Y are the same. Most preferably, X and Y are both iodo groups.

Typically, R¹, R³, R⁴ and R⁵ are each independently selected from hydrogen, halogen or a hydrocarbyl group, wherein each hydrocarbyl group independently is a...
substituted or unsubstituted, straight-chain, branched or cyclic alkyl, alkenyl, alkynyl, acyl, aryl, arylalkyl, arylalkenyl, alkylaryl, alkenylaryl or alkynylaryl group which optionally includes one or more heteroatoms in its carbon skeleton, and wherein any two or more of R₁, R₂, R₃, R⁴ and R⁵ together with the atom or atoms to which they are attached may form a cyclic hydrocarbyl group which may optionally be substituted and which may optionally include one or more heteroatoms N, O or S in its carbon skeleton.

For the purposes of the present invention, an “alkyl” group is defined as a monovalent saturated hydrocarbon, which may be straight-chained or branched, or be or include cyclic groups. An alkyl group may optionally include one or more heteroatoms N, O or S in its carbon skeleton. Examples of alkyl groups are methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, t-butyl and n-pentyl groups. Preferably an alkyl group is straight-chained or branched and does not include any heteroatoms in its carbon skeleton. Preferably an alkyl group is a C₁-C₁₂ alkyl group, which is defined as an alkyl group containing from 1 to 12 carbon atoms. More preferably an alkyl group is a C₁-C₆ alkyl group, which is defined as an alkyl group containing from 1 to 6 carbon atoms. An “alkylene” group is similarly defined as a divalent alkyl group.

An “alkenyl” group is defined as a monovalent hydrocarbon, which comprises at least one carbon-carbon double bond, which may be straight-chained or branched, or be or include cyclic groups. An alkenyl group may optionally include one or more heteroatoms N, O or S in its carbon skeleton. Examples of alkenyl groups are vinyl, allyl, but-1-enyl and but-2-enyl groups. Preferably an alkenyl group is straight-chained or branched and does not include any heteroatoms in its carbon skeleton. Preferably an alkenyl group is a C₂-C₁₂ alkenyl group, which is defined as an alkenyl group containing from 2 to 12 carbon atoms. More preferably an alkenyl group is a C₂-C₆ alkenyl group, which is defined as an alkenyl group containing from 2 to 6 carbon atoms. An “alkenylen” group is similarly defined as a divalent alkenyl group.

An “alkynyl” group is defined as a monovalent hydrocarbon, which comprises at least one carbon-carbon triple bond, which may be straight-chained or branched, or be or include cyclic groups. An alkynyl group may optionally include one or more heteroatoms N, O or S in its carbon skeleton. Examples of alkynyl groups are ethynyl, propargyl, but-1-ynyl and but-2-ynyl groups. Preferably an alkynyl group is straight-chained or branched and does not include any heteroatoms in its carbon skeleton. Preferably an alkynyl group is a C₂-C₁₂ alkynyl group, which is defined as an
alkynyl group containing from 2 to 12 carbon atoms. More preferably an alkynyl group is a C_2-C_6 alkynyl group, which is defined as an alkynyl group containing from 2 to 6 carbon atoms. An “alkynylene” group is similarly defined as a divalent alkynyl group.

An “aryl” group is defined as a monovalent aromatic hydrocarbon. An aryl group may optionally include one or more heteroatoms N, O or S in its carbon skeleton. Examples of aryl groups are phenyl, naphthyl, anthracenyl and phenanthrenyl groups. Preferably an aryl group does not include any heteroatoms in its carbon skeleton. Preferably an aryl group is a C_4-C_14 aryl group, which is defined as an aryl group containing from 4 to 14 carbon atoms. More preferably an aryl group is a C_5-C_10 aryl group, which is defined as an aryl group containing from 6 to 10 carbon atoms.

An “acyl” group is defined as a -CHO, -CO-alkyl, -CO-alkenyl, -CO-alkynyl, -CO-aryl, -CO-arylalkyl, -CO-arylalkenyl, -CO-arylalkynyl, -CO-alkylaryl, -CO-alkenylaryl or -CO-alkynylaryl group.

For the purposes of the present invention, where a combination of groups is referred to as one moiety, for example, arylalkyl, arylalkenyl, arylalkynyl, alkylaryl, alkenylaryl or alkynylaryl, the last mentioned group contains the atom by which the moiety is attached to the rest of the molecule. A typical example of an arylalkyl group is benzyl.

For the purposes of this invention, an optionally substituted alkyl, alkenyl, aryl, arylalkyl, arylalkenyl, arylalkynyl, alkylaryl, alkenylaryl, alkynylaryl or hydrocarbyl group may be substituted with one or more of -F, -Cl, -Br, -I, -CF_3, -CCl_3, -CBr_3, -Cl_3, -OH, -SH, -NH_2, -CN, -NO_2, -N_3, -COOH, -R^α-O-R^β, -R^α-S-R^β, -R^α-SO-R^β, -R^α-SO_2-R^β, -R^α-SO_2-OR^β, -R^α-O-SO_2-R^β, -R^α-O-SO_2-OR^β, -R^α-O-SO_2-N(R^β)_2, -R^α-NR^β-SO_2-R^β, -R^α-O-SO_2-OR^β, -R^α-O-SO_2-N(R^β)_2, -R^α-NR^β-SO_2-OR^β, -R^α-NR^β-SO_2-N(R^β)_2, -R^α-N(R^β)_2, -R^α-NH_2, -R^α-PR^β_2, -R^α-Si(R^β)_3, -R^α-CO-R^β, -R^α-CO-OR^β, -R^α-O-CO-R^β, -R^α-O-CO-OR^β, -R^α-OCO-N(R^β)_2, -R^α-NR^β-CO-R^β, -R^α-O-CO-OR^β, -R^α-OCO-N(R^β)_2, -R^α-NR^β-CO-OR^β, -R^α-OCO-N(R^β)_2, -R^α-NR^β-CS-R^β, -R^α-CS-R^β, -R^α-CS-OR^β, -R^α-O-CS-R^β, -R^α-CS-N(R^β)_2, -R^α-NR^β-CS-R^β, -R^α-NR^β-CS-OR^β, -R^α-NR^β-CS-N(R^β)_2, -R^β, a bridging substituent such as =O, =S or =NR^β. In this context, -R^α- is independently a chemical bond, a C_1-C_10 alkylene, C_1-C_10 alkenylene or C_1-C_10 alkynylene group. -R^β is independently hydrogen, unsubstituted C_1-C_6 alkyl or unsubstituted C_5-C_10 aryl.
Optional substituent(s) are preferably taken into account when calculating the total number of carbon atoms in the parent group substituted with the optional substituent(s). Preferably an optionally substituted alkyl, alkenyl, alkynyl, aryl, arylalkyl, arylalkenyl, arylalkynyl, alkylaryl, alkenylaryl or alkynylaryl group is not substituted with a bridging substituent. Preferably an optionally substituted alkyl, alkenyl, alkynyl, aryl, arylalkyl, arylalkenyl, arylalkynyl, alkylaryl, alkenylaryl or alkynylaryl group is not substituted with a π-bonded substituent. Preferably a substituted group comprises 1, 2 or 3 substituents, more preferably 1 or 2 substituents, and even more preferably 1 substituent.


Preferably, \( R^1 \) is hydrogen or a halo, hydroxyl, \( C_1-C_4 \) alkyl or \( C_1-C_4 \) alkoxy group. More preferably, \( R^1 \) is a halo group such as a fluoro, chloro, bromo or iodo group. Most preferably \( R^1 \) is a fluoro group.

Preferably, \( R^2 \) is hydrogen or a halo, hydroxyl, \( C_1-C_4 \) alkyl or \( C_1-C_4 \) alkoxy group. Most preferably \( R^2 \) is hydrogen.

In a preferred embodiment, \( R^1 \) is a halo group and \( R^2 \) is hydrogen. Most preferably, \( R^1 \) is a fluoro group and \( R^2 \) is hydrogen.

Preferably, \( R^3 \) and \( R^4 \) are each independently selected from hydrogen or a hydroxyl protecting group. Suitable protecting groups for protecting hydroxyl groups are known in the art, for example from “Protective Groups in Organic Synthesis” by T.W. Greene and P.G.M. Wuts (Wiley-Interscience, 4th edition, 2006). Typical hydroxyl protecting groups include silyl, acetyl, acyl, acetal, ketal, benzyl, benzoyl and tetrahydropyranyl groups.

More preferably, \( R^3 \) and \( R^4 \) are each independently selected from hydrogen or a base-labile hydroxyl protecting group such as an acetyl or other acyl group. Most preferably, \( R^3 \) and \( R^4 \) are both hydrogen.
Preferably, R₅ is selected from hydrogen or a nitrogen protecting group. Suitable nitrogen protecting groups are known in the art, for example from "Protective Groups in Organic Synthesis" by T.W. Greene and P.G.M. Wuts (Wiley-Interscience, 4th edition, 2006).

More preferably, R₅ is a nitrogen protecting group. Suitable nitrogen protecting groups include alkoxy carbonyl groups such as benzyloxy carbonyl (Z), t-butoxy carbonyl (Boc), 2-(4-biphenylyl)-isopropoxy carbonyl (Bpoc) and 9-fluorenylmethoxy carbonyl (Fmoc) groups; trityl groups; acyl groups such as acetyl and benzoyl groups; arylalkyl groups such as benzyl, p-methoxybenzyl (PMB) and 3,4-dimethoxybenzyl (DMPM) groups; sulphenyl groups such as 2-nitrophenyl sulphenyl (Nps) groups; and sulphonyl groups such as tosyl groups.

More preferably still, R₅ is a nitrogen protecting group that may be removed by catalytic hydrogenation, such as a benzyloxy carbonyl (Z), 2-(4-biphenylyl)-isopropoxy carbonyl (Bpoc), 9-fluorenylmethoxy carbonyl (Fmoc), trityl, benzyl, p-methoxy benzyl (PMB) or 3,4-dimethoxy benzyl (DMPM) group. Most preferably, R₅ is a benzyl group.

In a preferred embodiment of the seventh aspect of the present invention, where R₅ and one or both of R³ and R⁴ are protecting groups, the R₅ protecting group is orthogonal to the R³ and/or the R⁴ protecting groups.

In a particularly preferred embodiment of the seventh aspect of the present invention, X and Y are both iodo groups, R¹ is a fluoro group, R², R³ and R⁴ are hydrogen, and R₅ is a benzyl group.

The -OR³ and -OR⁴ groups of the pyrrolidine III may be cis- or trans-. Preferably the -OR³ and -OR⁴ groups of the pyrrolidine III are trans-. Most preferably, the pyrrolidine III or the salt thereof is a compound of formula IIIa or a salt thereof:
Alternatively, the pyrrolidine III or the salt thereof may be a compound of formula IIIb or a salt thereof:

\[ 
\text{IIIb} \]  

Where the pyrrolidine III or the salt thereof is a compound of formula IIIa or the salt thereof, it is preferred that the dioxane IV or the salt thereof is a compound of formula IVa or a salt thereof:

\[ 
\text{IVa} \]  

Similarly, where the pyrrolidine III or the salt thereof is a compound of formula IIIb or the salt thereof, it is preferred that the dioxane IV or the salt thereof is a compound of formula IVb or a salt thereof:

\[ 
\text{IVb} \]  

The process of the seventh aspect of the present invention may use racemic mixtures of the cis- or trans- isomers of the pyrrolidine III or salts thereof, or enantiomerically enriched or substantially enantiomerically pure isomers of the cis- or trans-pyrrolidine III or salts thereof, such as the trans-pyrrolidines IIIa and IIIb. For the purposes of this invention, a “substantially enantiomerically pure” isomer of a compound comprises less than 5% of other isomers of the same compound,
preferably less than 3%, more preferably less than 2%, more preferably less than 1%, and most preferably less than 0.5%.

Preferably, the reaction of the seventh aspect of the present invention occurs with retention of stereochemistry in the pyrrolidine ring.

Typically, where racemic mixtures of the cis- or trans- isomers of the pyrrolidine III or salts thereof are used, the dioxane IV or the salt thereof is also racemic. Likewise, where enantiomerically enriched or substantially enantiomerically pure isomers of the cis- or trans-pyrrolidine III or salts thereof are used, the dioxane IV or the salt thereof is also enantiomerically enriched or substantially enantiomerically pure.

In one embodiment of the seventh aspect of the present invention, the reaction is performed in the presence of a copper catalyst. Preferably, the reaction is performed in the presence of a copper (I) catalyst. More preferably, the reaction is performed in the presence of a copper (I) halide such as CuI.

Where the reaction is performed in the presence of a copper catalyst, optionally a bidentate ligand is also present.

As used herein, the term ‘ligand’ refers to any ion or molecule capable of donating and/or sharing electrons. Preferably the ligands are anionic ligands or neutral donor ligands. A ‘bidentate ligand’ refers to a ligand capable of binding to a central metal atom such as Cu via two donor groups.

Suitable bidentate ligands include 2,2-bipyridine, 3,4,7,8-tetramethyl-1,10-phenanthroline, (MeCOCHCOME); H₂NCH₂CH₂NH₂ and H₂NCH₂CO₂-. A preferred bidentate ligand is 3,4,7,8-tetramethyl-1,10-phenanthroline.

The reaction may also be performed in the presence of a base. The base may be an organic base such as an amine, or an inorganic base such as ammonia, a hydroxide, a carbonate or a bicarbonate. Preferably the base is a carbonate or a bicarbonate. More preferably the base is a metal or ammonium carbonate, such as sodium carbonate, potassium carbonate, caesium carbonate or ammonium carbonate. Most preferably the base is caesium carbonate.
In any embodiment of the seventh aspect of the present invention, the reaction may be performed in a non-polar solvent or a dipolar aprotic solvent, or a mixture thereof. More preferably the reaction is performed in a non-polar solvent. Exemplary non-polar solvents include alkanes and cycloalkanes such as n-hexane, cyclohexane or n-heptane, aromatic hydrocarbons such as toluene or benzene, alkyl ethers and cycloalkyl ethers such as diethyl ether, tert-butyl methyl ether, tetrahydrofuran (THF) or 1,4-dioxane, and chlorohydrocarbons such as chloroform or dichloromethane (DCM). Preferably the non-polar solvent is an aromatic hydrocarbon, most preferably toluene.

Typically, the reaction is performed at a temperature of from about 0°C to about 200°C. Preferably, the reaction is performed at a temperature of from about 50°C to about 150°C. Most preferably, the reaction is performed at a temperature of about 110°C.

Optionally, the reaction is performed under reflux conditions.

Optionally, the reaction is performed under an inert atmosphere, such as under nitrogen or argon.

In a particularly preferred embodiment of the seventh aspect of the present invention, the reaction is performed in the presence of CuI, 3,4,7,8-tetramethyl-1,10-phenanthroline and caesium carbonate, in toluene at a temperature of about 110°C.

In a further embodiment of the seventh aspect of the present invention, the benzene \( \mathbf{II} \) or the salt thereof is prepared by the step of converting a precursor \( \mathbf{I} \) or a salt thereof into the benzene \( \mathbf{II} \) or the salt thereof:

\[
\begin{array}{c}
\text{(I)} \\
\begin{array}{c}
R^1 \\
R^2 \\
Y \\
\end{array} \\
\begin{array}{c}
R^1 \\
R^2 \\
X \\
\end{array} \\
\end{array}
\rightarrow
\begin{array}{c}
\text{(II)} \\
\begin{array}{c}
R^1 \\
R^2 \\
X \\
\end{array} \\
\begin{array}{c}
R^1 \\
R^2 \\
Y \\
\end{array} \\
\end{array}
\]
Typically, the conversion is performed in the presence of \( X_2 \) and a base, wherein \( X_2 \) is preferably \( \text{Cl}_2, \text{Br}_2 \) or \( \text{I}_2 \). Most preferably \( X_2 \) is \( \text{I}_2 \). Preferably, the base is a non-nucleophilic base, such as \( \text{NaH}, \text{KH}, \text{KOrBu}, 1,4\)-diazabicyclo[2,2,2]octane (DABCO), 1,8-diazabicyclo[5,4,0]undec-7-ene (DBU), \( N,N\)-diisopropylethylamine (DIPEA), lithium diisopropylamide (LDA), sodium bis(trimethylsilyl)amide (NaHMDS) or potassium bis(trimethylsilyl)amide (KHMD). Most preferably the base is lithium diisopropylamide (LDA).

The conversion of the precursor \( \mathbf{I} \) or the salt thereof into the benzene \( \mathbf{II} \) or the salt thereof is typically performed in a non-polar solvent or a dipolar aprotic solvent, or a mixture thereof. More preferably the conversion is performed in a non-polar solvent. Preferably the non-polar solvent is an alkyl or cycloalkyl ether, most preferably tetrahydrofuran (THF).

The conversion of the precursor \( \mathbf{I} \) or the salt thereof into the benzene \( \mathbf{II} \) or the salt thereof is typically performed at a temperature of from about -100°C to about 50°C. Preferably, the conversion is performed at a temperature of from about -80°C to about 0°C. Most preferably, the conversion is performed at a temperature of about -78°C.

Optionally, the conversion is performed under an inert atmosphere, such as under nitrogen or argon.

The pyrrolidines \( \mathbf{III}, \mathbf{IIIa} \) and \( \mathbf{IIIb} \) may optionally be prepared from tartaric acid, as described in US patent application no. US 2007/029076.

In one embodiment of the seventh aspect of the present invention, wherein \( R^5 \) is not hydrogen, the process further comprises the step of converting the dioxane \( \mathbf{IV} \) or the salt thereof into a tricyclic pyrrolidine \( \mathbf{V} \) or a salt thereof:

![Diagram](image-url)
Preferably, such a process comprises converting the dioxane IVa or the salt thereof into a tricyclic pyrrolidine Va or a salt thereof:

\[(\text{IVa}) \xrightarrow{\text{reaction}} (\text{Va})\]

Alternatively, such a process may comprise converting the dioxane IVb or the salt thereof into a tricyclic pyrrolidine Vb or a salt thereof:

\[(\text{IVb}) \xrightarrow{\text{reaction}} (\text{Vb})\]

Typically, where racemic mixtures of the cis- or trans- isomers of the dioxane IV or salts thereof are used, the tricyclic pyrrolidine V or the salt thereof is also racemic. Likewise, where enantiomerically enriched or substantially enantiomerically pure isomers of the cis- or trans-dioxane IV or salts thereof are used, the tricyclic pyrrolidine V or the salt thereof is also enantiomerically enriched or substantially enantiomerically pure.

Typically, where the dioxane IV, IVa or IVb or any salt thereof is converted into the tricyclic pyrrolidine V, Va or Vb or any salt thereof, R is a nitrogen protecting group that may be removed by catalytic hydrogenation, such as a benzyl group.

Accordingly, in a preferred embodiment of the seventh aspect of the present invention, the dioxane IV, IVa or IVb or the salt thereof is converted into the tricyclic pyrrolidine V, Va or Vb or the salt thereof by catalytic hydrogenation.
The catalyst used for the hydrogenation step may optionally be selected from a palladium, platinum, nickel, rhodium or ruthenium catalyst. Preferably the catalyst is a palladium catalyst such as palladium on carbon.

The catalytic hydrogenation may be performed under an atmosphere of hydrogen. Alternatively or in addition, the catalytic hydrogenation may be performed by catalytic transfer hydrogenation. Typically, the hydrogen source for the catalytic transfer hydrogenation is a reagent such as ammonium formate, cyclohexene, or a trialkysilane. Preferably, ammonium formate is used. Where the catalytic transfer hydrogenation is not performed under an atmosphere of hydrogen, preferably an inert atmosphere such as under nitrogen or argon is used.

Preferably, the catalytic hydrogenation step is performed in a polar protic solvent such as an alcohol. Preferably the alcohol is methanol, ethanol, 1-propanol, isopropanol, 1-butanol, 2-methyl-1-propanol, t-butanol, 1-pentanol, cyclopentanol, 1-hexanol, cyclohexanol, 1-heptanol, 1-octanol, or a mixture thereof. Most preferably the alcohol is methanol.

Typically the catalytic hydrogenation step is performed at a temperature of from about 0°C to about 100°C. Preferably, the catalytic hydrogenation step is performed at a temperature of from about 20°C to about 80°C. Most preferably, the catalytic hydrogenation step is performed at a temperature of about 65°C.

Optionally, the catalytic hydrogenation step is performed under reflux conditions.

In a preferred embodiment of the seventh aspect of the present invention, the process is for the preparation of fluparoxan, or a salt thereof.

Advantageously, the novel synthetic route devised by the inventors to synthesise fluparoxan is only three steps from commercially available starting materials and only five steps if it was necessary to synthesize 1-benzyl-3,4-pyrrolidinediol. Surprisingly, the inventors have been able to synthesize (+/-) Fluparoxan in 3 steps with an overall yield of 8.3% which is higher than the best reported yield in the Glaxo patents and in 6/7 fewer steps. This route can also supply optically pure (+) or (-) Fluparoxan. If the yields for the synthesis of 1-fluoro-2,3-diiodobenzene (Eur. J. Org. Chem. 2002, 3351-3358) and for the final hydrogenation (EP0532100A1) could be
repeated, then the overall yield for this route would be 16.8% without any further modification to double Ullmann type reaction.

An eighth aspect of the present invention relates to fluparoxan or a salt thereof, when prepared by a process of the seventh aspect of the present invention.

Further aspects of the present invention relate to dioxanes of formulae IV, IVa and IVb, to tricyclic pyrrolidines of formulae V, Va and Vb, and to salts thereof, when prepared by a process of the seventh aspect of the present invention.

The compounds of the present invention can be used both, in their free base form and their acid addition salt form. For the purposes of this invention, a “salt” of a compound of the present invention is an acid addition salt. Acid addition salts are preferably pharmaceutically acceptable, non-toxic addition salts with suitable acids, including but not limited to inorganic acids such as hydrohalogenic acids (for example, hydrofluoric, hydrochloric, hydrobromic or hydroiodic acid) or other inorganic acids (for example, nitric, perchloric, sulphuric or phosphoric acid); or organic acids such as organic carboxylic acids (for example, propionic, butyric, glycolic, lactic, mandelic, citric, acetic, benzoic, salicylic, succinic, malic or hydroxysuccinic, tartaric, fumaric, maleic, hydroxymaleic, mucic or galactaric, gluconic, pantothentic or pamoic acid), organic sulphonic acids (for example, methanesulphonic, trifluoromethanesulphonic, ethanesulphonic, 2-hydroxyethanesulphonic, benzenesulphonic, toluene-p-sulphonic, naphthalene-2-sulphonic or camphorsulphonic acid) or amino acids (for example, ornithinic, glutamic or aspartic acid). The acid addition salt may be a mono- or di-acid addition salt. A preferred salt is a hydrohalogenic, sulphuric, phosphoric or organic acid addition salt. A more preferred salt is a hydrochloric acid addition salt.

In addition to pharmaceutically acceptable acid addition salts, other acid addition salts are included in the present invention, since they have potential to serve as intermediates in the purification or preparation of other, for example, pharmaceutically acceptable, acid addition salts, or are useful for identification, characterisation or purification of the free base.

It will be appreciated that the fluparoxan produced by the new method of the seventh aspect may be used for treating any condition which requires administration of an alpha 2 antagonist and not just neurodevelopmental disorders.
All of the features described herein (including any accompanying claims, abstract and drawings), and/or all of the steps of any method or process so disclosed, may be combined with any of the above aspects in any combination, except combinations where at least some of such features and/or steps are mutually exclusive.

For a better understanding of the invention, and to show how embodiments of the same may be carried into effect, reference will now be made, by way of example, to the accompanying diagrammatic drawings, in which:-

Figure 1 shows an illustrative view of neuronal feedback mechanisms reducing noradrenaline (NA) release mediated via the α2 adrenergic receptors;

Figure 2 shows an illustrative view of inhibition of neuronal feedback by fluparoxan blockade of α2 adrenergic receptors leading to increased noradrenaline (NA) release;

Figure 3 shows an illustrative view of inhibition of neuronal feedback by the deletion variant of the α2 adrenergic receptor subtype B leading to increased noradrenaline (NA) release;

Figure 4 shows a graphical illustration of the enhancing effect of the ADRA2B deletion on memory performance (Pr) in COMT Val/Val genotypes and the predicted effect of fluparoxan;

Figure 5 shows a graphical illustration of the enhancing effect of fluparoxan on memory performance (Discrimination index) in COMT Val-tg mice and control mice;

Figure 6 shows a graphical illustration of the dose-dependent enhancing effect of fluparoxan on memory performance in COMT Val-tg mice;

Figure 7 shows an embodiment of a reaction scheme for synthesising fluparoxan in accordance with the invention; and

Figures 8-10 show prior art reaction schemes for producing tricylic benzodioxinopyrroles.
Examples

Example 1 - Genetic Study
A deletion mutation in the gene responsible for the α2 adrenergic receptor subtype B (ADRA2B) occurs in approximately 1 in 3 people. There is evidence that this mutation reduces the function of the receptor, thereby increasing levels of noradrenaline via the same mechanism as fluparoxan, as illustrated in Figure 3. A preliminary study of memory performance was conducted in 97 healthy individuals (Gibbs, Naudts, Azevedo & David, Eur. Neuropsychopharmacology, 2010, 272-275).

The authors found that having one or two copies of the ADRA2B deletion variant improved memory performance in individuals with high catechol-O-methyltransferase (COMT) activity (i.e. Val/Val) such that it was equivalent to those with low COMT activity (Met/Met). However, surprisingly, there was no significant effect of the ADRA2B mutation on memory performance in low COMT activity (Met/Met) individuals. These results show that administering an α2 adrenoceptor antagonist, such as fluparoxan, would bring about an improvement in cognition in people with COMT Val/Val genotypes, and who do not have the ADRA2B deletion mutation, as shown in Figure 4.

Based on this observation, the inventors have shown that fluparoxan can be used to enhance cognition, for example in schizophrenia. In addition, the inventors have shown that fluparoxan treatment may be individualised based on COMT and ADRA2B genotypes.

Example 2 – Treatment of cognition impairment in schizophrenia
Fluparoxan was initially prepared using the materials and methods described in US 4,880,801. 400mg fluparoxan was then mixed with a pharmaceutically acceptable vehicle in order to prepare an oral dosage form, and administered to patients suffering from schizophrenia. Prior to treatment with fluparoxan, the patients were genotyped in relation to the COMT, ADRA2B and ADRA2C polymorphisms. The inventors found an improvement in cognitive function in the patients. This improvement was greatest in patients having the high catechol-O-methyltransferase (COMT) activity (i.e. Val/Val) genotype (i.e. SEQ ID No. 3), and having the normal α2b adrenoceptor (ADRA2B) function (i.e. Ins/Ins) genotype (i.e. SEQ ID No. 6), and the normal α2c adrenoceptor (ADRA2C) function (i.e. Ins/Ins) genotype (i.e. SEQ ID No. 9).
Example 3 – Administration of fluparoxan to transgenic mice with high catechol-O-methyltransferase (COMT) activity (i.e. Val/Val genotype)

The inventors examined the effect of fluparoxan on memory performance in transgenic mice overexpressing the high activity human catechol-o-methyltransferase (COMT) allele (COMT Val-tg) and control mice with low COMT activity using an Object Recognition Task. They administered either fluparoxan 1mg/kg or vehicle (saline) and found that fluparoxan significantly improved memory performance in all mice. However, surprisingly, this improvement was greater in the transgenic mice with high COMT activity compared to the control mice, as shown in Figure 5. The inventor then compared the effects of doses of 1mg/kg and 0.5mg/kg in the high COMT activity mice and found that the smaller dose of 0.5mg/kg resulted in an eight-fold increase in memory performance whilst the larger dose of 1mg/kg resulted in a sixty-fold increase in memory performance, as shown in Figure 6.

Based on these observations, the inventors have shown that fluparoxan can be used to enhance cognition. In addition, the inventors have shown that fluparoxan treatment may be individualised based on genetically determined COMT activity.

Example 4 – (+/-)-Fluparoxan Synthesis

The inventors have devised a novel process for synthesising fluparoxan, and the reaction scheme is summarised in Figure 7.

All reactions were conducted under an atmosphere of nitrogen unless otherwise stated. Reagents and anhydrous solvents were used as purchased.

Thin layer chromatography was performed on glass plates pre-coated with Merck silica gel 60 F_{254}. Visualisation was achieved with U.V. florescence (254 nm) or by staining with a potassium permanganate dip or phosphomolybdic acid dip.

Flash column chromatography was carried out using pre-packed columns filled with Merck silica gel 60 (40-63 μm) on an ISCO Combiflash RF or a Biotage Isolera Prime.

Proton nuclear magnetic resonance spectra were recorded at 500 MHz on a Varian VNMRS 500 MHz spectrometer (at 30 °C), using residual isotopic solvent (DMSO δ_H = 2.50 ppm) as an internal reference. Chemical shifts are quoted in parts per million (ppm). Coupling constants (J) are recorded in Hertz (Hz).
LCMS data was recorded on a Waters 2695 HPLC using a Waters 2487 UV detector and a Thermo LCQ ESI-MS. Samples were eluted through a Phenomenex Lunar 3μ C18 50 mm × 4.6 mm column, using water and acetonitrile acidified by 0.1% formic acid at 1 ml/min and detected at 254 nm. The gradient employed was:

<table>
<thead>
<tr>
<th>Time (minutes)</th>
<th>% Water + 0.1% formic acid</th>
<th>% MeCN + 0.1% formic acid</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.0</td>
<td>70</td>
<td>30</td>
</tr>
<tr>
<td>5.0</td>
<td>10</td>
<td>90</td>
</tr>
<tr>
<td>6.0</td>
<td>10</td>
<td>90</td>
</tr>
<tr>
<td>6.5</td>
<td>70</td>
<td>30</td>
</tr>
<tr>
<td>7.0</td>
<td>70</td>
<td>30</td>
</tr>
</tbody>
</table>

**Synthesis of compound 2**

Compound 2 was synthesised from commercially available compound 1 (£42 /100g, Apollo Scientific) using the route described in Eur. J. Org. Chem. 2002, 3351-3358.

In this paper, they describe the synthesis of 2 in a 92% yield. The reaction is run at -78°C and it should be possible to perform the deprotonation step at a higher temperature.

**Synthesis of compound 3**

This is the novel step in the synthesis of Fluparoxan. Currently, by using the 3,4,7,8-tetramethyl-1,10-phenanthroline ligand, which had previously been shown by Buchwald (J. Org. Chem. 2008, 73, 284-286) to couple single alkyl alcohols to aromatic halides, the inventors were able to synthesis 3 in a 20% yield. This reaction represents a new way to synthesis the benzo-1,4-dioxanopyrrole core of Fluparoxan and the first example of this double Ullmann type reaction. The coupling partner (S,S) or (R,R)-1-benzyl-3,4-pyrrolidinedioli is commercially available ((S,S) £240 /5g, Acros and (R,R) £360 /5g, Acros) but relatively expensive. However, the S,S-pyrrolidinedioli has been synthesised on large scale (US2007299076A1) by a 2-step procedure starting from inexpensive tartaric acid (L-(+)-tartaric acid £60 /2.5Kg, Acros).

**Synthesis of compound 4**

The inventors have achieved a 66% yield of 4 using an ammonium formate / palladium on carbon hydrogenation of the benzyl protecting group. This is
comparable to the 56-59% yield reported in the original (Bioorg. Med. Chem. 1995, 1595-1603) paper.

Example 5: 1-fluoro-2,3-diiodobenzene

![Chemical Structure](image)

1-Fluoro-2,3-diiodobenzene was prepared following a method described in Eur. J. Org. Chem. 2002, 3351-3358.

Example 6: (3aS,9aS)-2-benzyl-5-fluoro-2,3,3a,9a-tetrahydro-1H-[1,4]benzodioxinol2,3-c]pyrrole hydrochloride

![Chemical Structure](image)

A mixture of 1-fluoro-2,3-diiodobenzene (5.0 g, 14.4 mmol, Example A), (S,S)-1-benzyl-3,4-pyrrolidinediol (3.6 g, 18.7 mmol), 3,4,7,8-tetramethyl-1,10-phenanthroline (679 mg, 2.88 mmol) and caesium carbonate (9.36 g, 28.8 mmol) in toluene (75 ml) were degassed with nitrogen for 10 minutes. Copper (I) iodide (273 mg, 1.44 mmol) was then added and the reaction mixture was heated at 110°C for 24 hours. After cooling to room temperature the reaction mixture was filtered through kieselguhr. The filter cake was washed with EtOAc (3 x 50 ml) and the combined filtrate and washes were concentrated under reduced pressure. The residue was partially purified by flash column chromatography (50 g silica, 100% petrol ether to 20% EtOAc / petrol ether). Fractions containing product were concentrated under reduced pressure before being dissolved in MeOH (15 ml). 3M HCl in MeOH (15 ml) was then added and the resulting mixture was stirred for 10 minutes. The reaction mixture was again concentrated under reduced pressure and EtOAc (20 ml) was added. The suspension was sonicated for 15 minutes before being filtered to give the title compounds as an off-white solid (965 mg, 21% molar yield).
δ_H (500 MHz, DMSO) 11.85 (br s, 1H), 7.71 – 7.54 (m, 2H), 7.54 – 7.37 (m, 3H), 7.05 – 6.92 (m, 2H), 6.92 – 6.82 (m, 1H), 4.81 – 4.33 (m, 4H), 4.01 – 3.70 (m, 2H), 3.63 – 3.44 (m, 2H).

LCMS (ESI) retention time 1.36 min, m/z 286.17.

Example 7: (3aR,9aR)-2-benzyl-5-fluoro-2,3,3a,9a-tetrahydro-1H-[1,4]benzodioxino[2,3-c]pyrrole hydrochloride

A mixture of 1-fluoro-2,3-diodobenzene (6.9 g, 19.9 mmol, Example 5), (R,R)-1-benzyl-3,4-pyrroldinediol (5.0 g, 25.9 mmol), 3,4,7,8-tetramethyl-1,10-phenanthroline (941 mg, 3.98 mmol) and caesium carbonate (13.0 g, 39.8 mmol) in toluene (100 ml) were degassed with nitrogen for 10 minutes. Copper (I) iodide (379 mg, 2.00 mmol) was then added and the reaction mixture was heated at 110°C for 24 hours. After cooling to room temperature the reaction mixture was filtered through kieselguhr. The filter cake was washed with EtOAc (3 x 70 ml) and the combined filtrate and washes were concentrated under reduced pressure. The residue was partially purified by flash column chromatography (50 g silica, 100 % petrol ether to 20 % EtOAc / petrol ether). Fractions containing product were concentrated under reduced pressure before being dissolved in MeOH (20 ml). 3M HCl in MeOH (20 ml) was then added and the resulting mixture was stirred for 10 minutes. The reaction mixture was again concentrated under reduced pressure and EtOAc (20 ml) was added. The suspension was sonicated for 15 minutes before being filtered to give the title compounds as an off-white solid (1.44 g, 23% molar yield).

δ_H (500 MHz, DMSO) 11.93 (br s, 1H), 7.71 – 7.54 (m, 2H), 7.54 – 7.37 (m, 3H), 7.05 – 6.92 (m, 2H), 6.92 – 6.82 (m, 1H), 4.81 – 4.33 (m, 4H), 4.01 – 3.70 (m, 2H), 3.63 – 3.44 (m, 2H).

LCMS (ESI) retention time 1.38 min, m/z 286.17.
Example 8: (3aS,9aS)-5-fluoro-2,3,3a,9a-tetrahydro-1H-[1,4]benzodioxino[2,3-c]pyrrole hydrochloride

To a mixture of (3aS,9aS)-2-benzyl-5-fluoro-2,3,3a,9a-tetrahydro-1H-[1,4]benzodioxino[2,3-c]pyrrole hydrochloride (965 mg, 3.00 mmol, Example 6) and ammonium formate (945 mg, 15.00 mmol) in MeOH (60 ml) was added 5% palladium on carbon (319 mg, 0.15 mmol). The reaction mixture was heated under reflux for 4 hours before being allowed to cool to room temperature. The mixture was filtered through kieselguhr and the filter cake was washed with MeOH (3 x 15 ml). The combined filtrate and washings were concentrated under reduced pressure. The residue had EtOAc (20 ml) and saturated aqueous NaHCO₃ (10 ml) added. The mixture was stirred for 10 minutes before the phases were separated. The organic phase was washed with saturated aqueous NaHCO₃ (2 x 10 ml), then washed with brine (10 ml) and dried over MgSO₄, filtered and concentrated under reduced pressure. The residue was then acidified with 3M HCl in MeOH (10 ml) and concentrated under reduced pressure. The residue was recrystallised from hot MeOH to give the title compound as an off-white solid (442 mg, 64% molar yield).

δₜ (500 MHz, DMSO) 9.69 (br s, 2H), 7.00 – 6.92 (m, 2H), 6.91 – 6.84 (m, 1H), 4.49 – 4.36 (m, 2H), 3.86 – 3.74 (m, 2H), 3.34 – 3.23 (m, 2H).

LCMS (ESI) retention time 0.51 min, m/z 196.19.

Example 9: (3aR,9aR)-5-fluoro-2,3,3a,9a-tetrahydro-1H-[1,4]benzodioxino[2,3-c]pyrrole hydrochloride

To a mixture of (3aR,9aR)-2-benzyl-5-fluoro-2,3,3a,9a-tetrahydro-1H-[1,4]benzodioxino[2,3-c]pyrrole hydrochloride (1.44 g, 4.47 mmol, Example 7) and
ammonium formate (1.42 g, 22.38 mmol) in MeOH (90 ml) was added 5% palladium on carbon (480 mg, 0.22 mmol). The reaction mixture was heated under reflux for 4 hours before being allowed to cool to room temperature. The mixture was filtered through kieselguhr and the filter cake was washed with MeOH (3 x 25 ml). The combined filtrate and washings were concentrated under reduced pressure. The residue had EtOAc (30 ml) and saturated aqueous NaHCO₃ (15 ml) added. The mixture was stirred for 10 minutes before the phases were separated. The organic phase was washed with saturated aqueous NaHCO₃ (2 x 15 ml), then washed with brine (15 ml) and dried over MgSO₄, filtered and concentrated under reduced pressure. The residue was then acidified with 3M HCl in MeOH (15 ml) and concentrated under reduced pressure. The residue was recrystallised from hot MeOH to give the title compound as an off-white solid (687 mg, 66% molar yield).

δH (500 MHz, DMSO) 9.75 (br s, 2H), 7.00 – 6.92 (m, 2H), 6.91 – 6.84 (m, 1H), 4.49 – 4.36 (m, 2H), 3.86 – 3.74 (m, 2H), 3.34 – 3.23 (m, 2H).

LCMS (ESI) retention time 0.52 min, m/z 196.16.

Example 10: (+/-)-(trans)-5-fluoro-2,3,3a,9a-tetrahydro-1H-[1,4]benzodioxino[2,3-c]pyrrole hydrochloride

A solution of (3aS,9aS)-5-fluoro-2,3,3a,9a-tetrahydro-1H-[1,4]benzodioxino[2,3-c]pyrrole hydrochloride (75 mg, 0.323 mmol, Example 8) and (3aR,9aR)-5-fluoro-2,3,3a,9a-tetrahydro-1H-[1,4]benzodioxino[2,3-c]pyrrole hydrochloride (75 mg, 0.323 mmol) in MeOH (10 ml) was concentrated under reduced pressure to give the title compound as an off-white solid (150 mg).

δH (500 MHz, DMSO) 9.88 (br s, 2H), 7.00 – 6.92 (m, 2H), 6.91 – 6.84 (m, 1H), 4.49 – 4.36 (m, 2H), 3.86 – 3.74 (m, 2H), 3.34 – 3.23 (m, 2H).

LCMS (ESI) retention time 0.52 min, m/z 196.18.
Summary

The synthetic route devised by the inventors to synthesise Fluparoxan is only three steps from commercially available starting materials and only five steps if it is necessary to synthesize 1-benzyl-3,4-pyrrolidinediol. The inventors have been able to synthesize (+/-) Fluparoxan in three steps with an overall yield of 8.3% which is higher than the best reported yield in the Glaxo patents and in 6/7 fewer steps. This route can also supply optically pure (+) or (-) Fluparoxan. If the yields for the synthesis of 1-fluoro-2,3-diodobenzene (Eur. J. Org. Chem. 2002, 3351-3358) and for the final hydrogenation (EP0532100A1) could be repeated, then the overall yield for this route would be 16.8% without any further modification to double Ullmann type reaction.
Claims

1. A neurodevelopmental disorder treatment composition comprising a therapeutically effective amount of a compound represented by Formula (1):

![Chemical Structure]  

**Formula (1)**

wherein

- R is a hydrogen atom, or a group selected from C\(_{1-6}\) alkyl unsubstituted or substituted by C\(_{3-7}\) cycloalkyl, C\(_{3-6}\) alkenyl, C\(_{3-6}\) alkynyl, C\(_{3-7}\) cycloalkyl, phenalkyl in which the alkyl moiety contains 1-5 carbon atoms, and -CHO;
- R\(^{1}\) is a group selected from halogen, C\(_{1-4}\) alkyl, or hydroxyl;
- R\(^{2}\) is a hydrogen atom, or substituent as defined above for R\(^{1}\);

or a physiologically acceptable salt or hydrate thereof;

and optionally a pharmaceutically acceptable vehicle.

2. A composition according to claim 1, wherein the neurodevelopmental disorder is selected from a group of disorders including: schizophrenia, schizoaffective disorder, bipolar affective disorder, attention deficit hyperactivity disorder (ADHD) and autism spectrum disorder.

3. A composition according to either claim 1 or 2, wherein the neurodevelopmental disorder is schizophrenia.

4. A composition according to any preceding claim, wherein the compound is effective for improving cognitive decline or dysfunction in the neurodevelopmental disorder.

5. A composition according to any preceding claim, wherein R is a hydrogen atom.
6. A composition according to any one of claims 1-4, wherein R is a C_{1-3} alkyl group, particularly a methyl or ethyl group.

7. A composition according to any preceding claim, wherein R¹ is a halogen atom or a C_{1-4} alkyl or C_{1-4} alkoxy group.

8. A composition according to any preceding claim, wherein R² is a hydrogen or fluorine atom.

9. A composition according to any preceding claim, wherein R is a hydrogen atom or a methyl or ethyl group; R¹ is a chlorine or fluorine atom or a methyl group; and R² is a hydrogen or fluorine atom.

10. A composition according to any preceding claim, wherein the compound is selected from (±)-trans-2,3,3a,9a-tetrahydro-5-methyl-1H-[1,4]benzodioxino[2,3-c]pyrrole, and its 3aS- and 3aR-isomers; (±)-trans-5-chloro-2,3,3a,9a-tetrahydro-1H-[1,4]benzodioxino[2,3-c]pyrrole, and its 3aS- and 3aR-isomers; (±)-trans-5,8-difluoro-2,3,3a,9a-tetrahydro-1H-[1,4]benzodioxino[2,3-c] pyrrole and its 3aS- and 3aR-isomers.

11. A composition according to any preceding claim, wherein the compound is selected from (±)-trans-5-fluoro-2,3,3a,9a-tetrahydro-1H-[1,4]benzodioxino[2,3-c]pyrrole and its 3aS- and 3aR-isomers and their physiologically acceptable salts and hydrates, particularly the hydrochlorides.

12. A composition according to any preceding claim, wherein the compound is represented by Formula (2):

```
F
O
O
\ \NH
```

(2)

13. A composition according to any preceding claim, wherein the compound is used to treat a neurodevelopmental disorder in a subject who (i) has the high catechol-O-methyltransferase (COMT) activity (i.e. Val/Val) genotype; (ii) has the
normal α2b adrenoceptor (ADRA2B) function (i.e. Ins/Ins) genotype and/or (iii) has the normal α2c adrenoceptor (ADRA2C) function (i.e. Ins/Ins) genotype.

14. A process for making the composition according to any one of claims 1-13, the process comprising contacting a therapeutically effective amount of a compound represented by Formula (I) or a physiologically acceptable salt or hydrate thereof, with a pharmaceutically acceptable vehicle.

15. A compound represented by Formula (I) or a physiologically acceptable salt or hydrate thereof, for use in the treatment, prevention or amelioration of a neurodevelopmental disorder.

16. A compound, for use according to claim 15, wherein the compound is defined as in any one of claims 1-13.

17. An α2 adrenergic receptor antagonist, for use in the treatment, prevention or amelioration of a disease characterised by cognitive dysfunction in a subject who (i) has the high catechol-O-methyltransferase (COMT) activity (i.e. Val/Val) genotype; (ii) has the normal α2b adrenoceptor (ADRA2B) function (i.e. Ins/Ins) genotype and/or (iii) has the normal α2c adrenoceptor (ADRA2C) function (i.e. Ins/Ins) genotype.

18. An antagonist according to claim 17, wherein the subject has the (Val/Val) COMT genotype and the (Ins/Ins) ADRA2B genotype, but not the (Ins/Ins) ADRA2C genotype.

19. An antagonist according to claim 17, wherein the subject has the (Val/Val) COMT genotype and the (Ins/Ins) ADRA2C genotype, but not the (Ins/Ins) ADRA2B genotype.

20. An antagonist according to claim 17, wherein the subject has the (Val/Val) COMT genotype, the (Ins/Ins) ADRA2B genotype and the (Ins/Ins) ADRA2C genotype.

21. An antagonist according to any one of claims 17-20, wherein the antagonist is a selective or non-selective α2 adrenoceptor antagonist.
22. An antagonist according to any one of claims 17-21, wherein the α2-adrenoceptor antagonist is selected from the group consisting of: fluvoxamine; efavirenz; idoxyn; atipamezole; A-80426; phenoxybenzamine; mirtazapine; mianserin; SB-269,970; yohimbine; BRL-44408; RX-821,002; ARC-239; imiloxyan; JP-1302; and spiroxatrine.

23. An antagonist according to any one of claims 17-22, wherein the antagonist is represented by Formula (1) defined in any one of claims 1-13.

24. An antagonist according to any one of claims 17-23, wherein the antagonist is used in the treatment, prevention or amelioration of any disease characterised by cognitive dysfunction, including neurodevelopmental disorders, such as schizophrenia, schizoaffective disorder, bipolar affective disorder, attention deficit hyperactivity disorder (ADHD) and autism spectrum disorders; neurodegenerative disorders involving progressive loss of structure or function of neurons, such as Parkinson’s disease, Alzheimer’s disease, Huntington’s disease and multiple sclerosis; and acquired brain disorders involving damage to the brain after birth, such as traumatic brain injury, stroke and alcohol and drug abuse.

25. A method of treating, preventing or ameliorating a neurodevelopmental disorder in a subject, the method comprising administering, to a subject in need of such treatment, a therapeutically effective amount of a compound represented by Formula (1) or a physiologically acceptable salt or hydrate thereof.

26. A method of treating, preventing or ameliorating a disease characterised by cognitive dysfunction in a subject having (i) the high catechol-O-methyltransferase (COMT) activity (i.e. Val/Val) genotype; (ii) the normal α2b adrenoceptor (ADRA2B) function (i.e. Ins/Ins) genotype and/or (iii) the normal α2c adrenoceptor (ADRA2C) function (i.e. Ins/Ins) genotype, the method comprising administering, to a subject in need of such treatment, a therapeutically effective amount of an α2 adrenoceptor antagonist.

27. A composition according to claim 13, an antagonist according to any one of claims 17-24, or a method according to either claim 25 or 26, wherein the (Val/Val) COMT genotype is homozygous for SEQ ID No: 3, the (Ins/Ins) ADRA2B genotype is homozygous for SEQ ID No: 6 and the (Ins/Ins) ADRA2C genotype is homozygous for SEQ ID No: 9.
28. A process for the preparation of a dioxane IV or a salt thereof, comprising the reaction of a benzene II or a salt thereof, with a pyrrolidine III or a salt thereof, to form the dioxane IV or the salt thereof:

wherein X and Y each independently represent any leaving group, and wherein R¹, R², R³, R⁴ and R⁵ each independently represent any atom or group.

29. A process according to claim 28, wherein X and Y are both iodo groups.

30. A process according to claim 28 or claim 29, wherein R¹ is a fluoro group and R² is hydrogen.

31. A process according to any one of claims 28 to 30, wherein R² and R³ are both hydrogen.

32. A process according to any one of claims 28 to 31, wherein R⁵ is a benzyl group.

33. A process according to any one of claims 28 to 32, wherein the pyrrolidine III or the salt thereof is a compound of formula IIIa or a salt thereof:

34. A process according to any one of claims 28 to 33, wherein the reaction is performed in the presence of CuI.
35. A process according to claim 34, wherein the reaction is performed in the presence of CuI and 3,4,7,8-tetramethyl-1,10-phanthraline.

36. A process according to any one of claims 28 to 35, wherein the reaction is performed in the presence of a base such as caesium carbonate.

37. A process according to any one of claims 28 to 36, wherein the benzene II or the salt thereof is prepared by the step of converting a precursor I or a salt thereof into the benzene II or the salt thereof:

\[ \text{R}^1 \quad \text{R}^2 \quad \text{R}^3 \quad \text{Y} \quad \rightarrow \quad \text{R}^1 \quad \text{X} \quad \text{R}^2 \quad \text{Y} \]

38. A process according to claim 37, wherein the conversion is performed in the presence of \( X_2 \) and a base.

39. A process according to claim 38, wherein the conversion is performed in the presence of \( I_2 \) and lithium diisopropylamide (LDA).

40. A process according to any one of claims 28 to 39, wherein \( R^5 \) is not hydrogen and the process further comprises the step of converting the dioxane IV or the salt thereof into a tricyclic pyrrolidine V or a salt thereof:

\[ \text{R}^1 \quad \text{R}^2 \quad \text{O} \quad \text{N} \quad \text{R}^5 \quad \rightarrow \quad \text{R}^1 \quad \text{R}^2 \quad \text{O} \quad \text{NH} \quad \text{R}^5 \]
41. A process according to claim 40, wherein the dioxane IV or the salt thereof is converted into the tricyclic pyrrolidine V or the salt thereof by catalytic hydrogenation.

42. A process according to any one of claims 28 to 41, wherein the process is for the preparation of fluparoxan, or a salt thereof.

43. Fluparoxan or a salt thereof, when prepared by a process according to any one of claims 28 to 42.
Figure: 7

1. LDA, I₂, THF, -78°C, 60%;
2. trans-1-benzyl-3,4-pyrrolidinediol, 3,4,7,8-tetramethyl-1,10-phenanthroline, Cul, Cs₂CO₃, Toluene, 110°C, 21%;
3. 5% Pd/C, HCO₂NH₄, MeOH, reflux, 66%.

Figure: 8

a) LDA/CO₂; b) HCl/EtOH; c) H₂/Pd on C/EtOH; d) Na₂CO₃/EtOH; e) LAH/THF;
   f) MsCl/NB₃/DCM; g) (1) PhCH₂NH₂, (2) HCl/Et₂O; h) H₂/Pd on C/MeOH.
Figure: 9

\[
\begin{align*}
\text{HO} & \xrightarrow{a} \text{OCH}_2\text{Ph} \quad \text{(19)} \\
\text{OCH}_2\text{Ph} & \xrightarrow{b} \text{OCH}_2\text{Ph} \quad \text{(20)} \\
\text{(a)} & \xrightarrow{c} \text{OCH}_2\text{Ph} \quad \text{(23)} \\
\text{HO} & \xrightarrow{d} \text{OCH}_2\text{Ph} \quad \text{(21)} \\
\text{OCH}_2\text{Ph} & \xrightarrow{e} \text{OCH}_2\text{Ph} \quad \text{(22)} \\
\text{HO} & \xrightarrow{f} \text{NH.HCl} \quad \text{(18)}
\end{align*}
\]

a) NaH/iPrCH$_2$Cl/DMF; b) m-CPBA/DCM; c) 2N-HCl/H$_2$O/DMSO; d) TsCl/Py; e) Catechol/CS$_2$/CO$_2$/MeCN; f) H$_2$/Pd on C/EOH

Scheme 2.

Figure: 10

\[
\begin{align*}
\text{HO} & \xrightarrow{a} \text{O}_2\text{CO}_2\text{Et} \quad \text{(24)} \\
\text{O}_2\text{CO}_2\text{Et} & \xrightarrow{b} \text{OH} \quad \text{(25)} \\
\text{HO} & \xrightarrow{c} \text{O}_2\text{CO}_2\text{Et} \quad \text{(26)} \\
\text{O}_2\text{CO}_2\text{Et} & \xrightarrow{d} \text{OH} \quad \text{(27)} \\
\text{OH} & \xrightarrow{e} \text{OCH}_2\text{Ph} \quad \text{(29)} \\
\text{OCH}_2\text{Ph} & \xrightarrow{f} \text{OH} \quad \text{(28)} \\
\text{OH} & \xrightarrow{g} \text{OCH}_2\text{Ph} \quad \text{(30)} \\
\text{OCH}_2\text{Ph} & \xrightarrow{h} \text{OH} \quad \text{(31)} \\
\text{OH} & \xrightarrow{i} \text{NH.HCl} \quad \text{(33)} \\
\text{OCH}_2\text{Ph} & \xrightarrow{j} \text{OH} \quad \text{(32)}
\end{align*}
\]

a) Me$_3$CO/H$^+$; b) LAH/THF; c) NaH/iPrCH$_2$Br/THF; d) HCl/MeOH; e) TsCl/Py; f) Catechol/CS$_2$/MeCN; g) H$_2$/Pd on C/EOH

Scheme 1.