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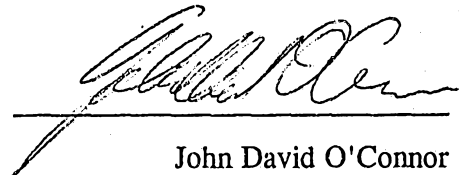
I, John David O'Connor, of 31 Market Street, Sydney, New South Wales, 2000, Australia, Patent Attorney for the Applicant/Nominated Person in respect of Application No. 61132/94 state the following:-

The Applicant/Nominated Person has entitlement from the actual inventors as follows:-

The Applicant/Nominated Person is the assignee of the actual inventors.

- : The Applicant/Nominated Person is the applicant of the applications listed in the Declaration under Article 8 of the PCT.
- : The basic applications listed on the Declaration under Article 8 of the PCT are the first applications made in a Convention country in respect of the invention.

Dated 25 August 1995


John David O'Connor

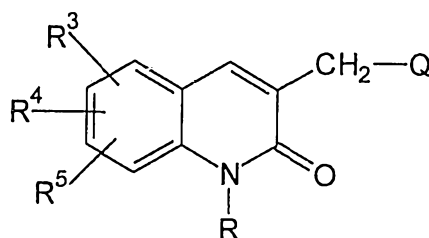


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QUINOLONE DERIVATIVES AS DOPAMINE D4 LIGANDS
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- (57) Claim

1. A method for the treatment and/or prevention of psychotic disorders, which comprises administering to a patient in need of such treatment an effective amount of a compound of formula I, or a pharmaceutically acceptable salt thereof

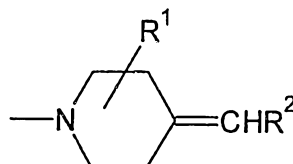
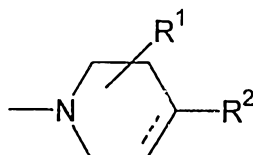


(I)

wherein

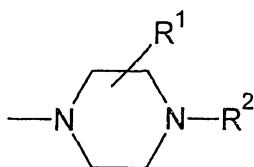
R represents hydrogen or C₁₋₆ alkyl;

Q represents a moiety of formula Qa, Qb, Qc or Qd:

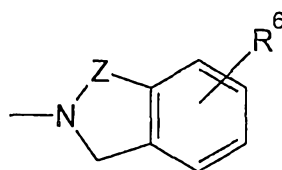


(Qa)

(Qb)



(Qc)



(Qd)

in which the broken line represents an optional chemical bond;

R^1 represents hydrogen, or an optionally substituted (as herein defined) C_{1-6} alkyl, C_{1-6} alkoxy, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl, aryl(C_{1-6})alkyl, aryl(C_{1-6}) alkoxy, aryl (C_{2-6})alkenyl, aryl (C_{2-6})alkynyl, C_{3-7} heterocycloalkyl (C_{1-6})alkyl, heteroaryl, heteroaryl (C_{1-6})alkyl, heteroaryl (C_{2-6})alkenyl or heteroaryl (C_{2-6})alkynyl group;

R^2 represents an optionally substituted (as herein defined) C_{1-6} alkyl, C_{1-6} alkoxy, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl, aryl(C_{1-6})alkyl, aryl(C_{1-6})alkoxy, aryl(C_{2-6})alkenyl, aryl(C_{2-6})alkynyl, C_{3-7} heterocycloalkyl (C_{1-6})alkyl, heteroaryl, heteroaryl(C_{1-6})alkyl, heteroaryl(C_{2-6})alkenyl or heteroaryl (C_{2-6}) alkynyl group;

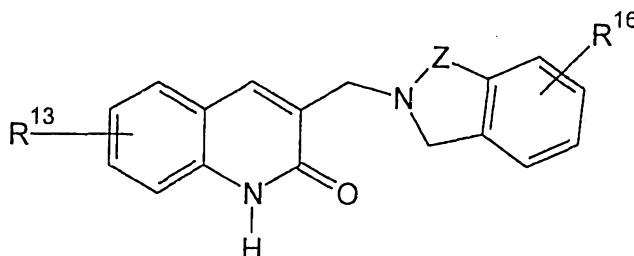
R^3 , R^4 and R^5 independently represent hydrogen, hydrocarbon (as herein defined), a heterocyclic group (as herein defined), halogen, cyano, trifluoromethyl, nitro, $-OR^a$, $-SR^a$, $-SOR^a$, $-SO_2R^a$, $-SO_2NR^aR^b$, $-NR^aR^b$, $-NR^aCOR^b$, $-NR^aCO_2R^b$, $-COR^a$, $-CO_2R^a$ or $-CONR^aR^b$;

Z represents $-CH_2-$ or $-CH_2CH_2-$;

R^6 represents hydrogen, C_{1-6} alkyl, C_{1-6} alkoxy, aryl, aryl(C_{1-6})alkyl or halogen; and

R^a and R^b independently represent hydrogen, hydrocarbon (as herein defined) or a heterocyclic group (as herein defined).

6. A compound of formula IIB, or a salt thereof:



(IIB)

wherein

Z represents $-CH_2-$ or $-CH_2CH_2-$;

R^{13} is as defined in claim 2; and

R^{16} represents hydrogen, C_{1-6} alkyl, C_{1-6} alkoxy, aryl, aryl (C_{1-6})alkyl or halogen.

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II

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(21) International Application Number: PCT/GB94/00383 (22) International Filing Date: 25 February 1994 (25.02.94) (30) Priority Data: 9304525.0 5 March 1993 (05.03.93) GB 9316261.8 5 August 1993 (05.08.93) GB (71) Applicant (for all designated States except US): MERCK SHARP & DOHME LIMITED [GB/GB]; Hertford Road, Hoddesdon, Hertfordshire EN11 9BU (GB). (72) Inventors; and (75) Inventors/Applicants (for US only): KULAGOWSKI, Janusz, Jozef [GB/GB]; Terlings Park, Eastwick Road, Harlow, Essex CM20 2QR (GB). LEESON, Paul, David [GB/GB]; Terlings Park, Eastwick Road, Harlow, Essex CM20 2QR (GB). MAWER, Ian, Michael [GB/GB]; Terlings Park, Eastwick Road, Harlow, Essex CM20 2QR (GB). (74) Agent: THOMPSON, John; Merck & Co., Inc., Terlings Park, Eastwick Road, Harlow, Essex CM20 2QR (GB).		(81) Designated States: AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, ES, FI, GB, HU, JP, KP, KR, KZ, LK, LU, LV, MG, MN, MW, NL, NO, NZ, PL, PT, RO, RU, SD, SE, SK, UA, US, UZ, VN, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG). Published With international search report. 679042	
(54) Title: QUINOLONE DERIVATIVES AS DOPAMINE D4 LIGANDS			
(57) Abstract A class of chemical compounds comprising a 2(1H)-quinolone moiety and a substituted heterocyclic moiety, linked via the 3-position of the 2(1H)-quinolone moiety by a methylene group, are antagonists of dopamine receptor subtypes within the brain, having a selective affinity for the dopamine D ₄ receptor subtype over other dopamine receptor subtypes, and are accordingly of benefit in the treatment and/or prevention of psychotic disorders such as schizophrenia whilst manifesting fewer side-effects than those associated with classical neuroleptic drugs.			

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QUINOLONE DERIVATIVES AS DOPAMINE D4 LIGANDS

5 This invention relates to the use of a
particular class of heteroaromatic compounds. More
particularly, the invention is concerned with the use of
substituted 2(1H)-quinolone derivatives which are
antagonists of dopamine receptor subtypes within the
brain and are therefore of benefit in the treatment
10 and/or prevention of psychotic disorders such as
schizophrenia.

The "dopamine hypothesis" of schizophrenia
predicts an increased activity of dopamine
neurotransmission in the disease. The hypothesis is
15 supported by early observations that drugs, such as
amphetamine, with dopamine agonist or dopamine-releasing
properties are capable of eliciting a psychosis
indistinguishable from acute paranoid schizophrenia.

Schizophrenia is a disorder which is
20 conventionally treated with drugs known as neuroleptics.
In the majority of cases, the symptoms of schizophrenia
can be treated successfully with so-called "classical"
neuroleptic agents such as haloperidol. Classical
neuroleptics generally are antagonists at dopamine D₂
25 receptors. The fact that classical neuroleptic drugs
have an action on dopamine receptors in the brain thus
lends credence to the "dopamine hypothesis" of
schizophrenia.

Molecular biological techniques have revealed
30 the existence of several subtypes of the dopamine
receptor. The dopamine D₁ receptor subtype has been
shown to occur in at least two discrete forms. Two forms
of the D₂ receptor subtype, and at least one form of the
D₃ receptor subtype, have also been discovered. More
35 recently, the D₄ (Van Tol et al., Nature (London), 1991,

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350, 610) and D₅ (Sunahara *et al.*, *Nature* (London), 1991, 350, 614) receptor subtypes have been described.

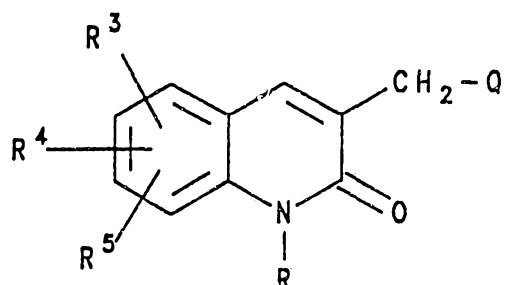
Notwithstanding their beneficial antipsychotic effects, classical neuroleptic agents such as haloperidol
5 are frequently responsible for eliciting acute extrapyramidal symptoms and neuroendocrine disturbances. These side-effects, which clearly detract from the clinical desirability of classical neuroleptics, are believed to be attributable to D₂ receptor blockade in
10 the striatal region of the brain. It is considered (Van Tol *et al.*, *supra*) that compounds which can interact selectively with the dopamine D₄ receptor subtype, whilst having a less-pronounced action at the D₂ subtype, might be free from, or at any rate less prone to, the side-
15 effects associated with classical neuroleptics, whilst at the same time maintaining a beneficial level of antipsychotic activity.

The compounds of use in the present invention, being antagonists of dopamine receptor subtypes within
20 the brain, are accordingly of benefit in the treatment and/or prevention of psychotic disorders such as schizophrenia. Moreover, the compounds of use in the invention have a selective affinity for the dopamine D₄ receptor subtype over other dopamine receptor subtypes,
25 in particular the D₂ subtype, and can therefore be expected to manifest fewer side-effects than those associated with classical neuroleptic drugs.

JP-A-64-63518 and HU-A-T/54348 variously describe certain 2(1H)-quinolone derivatives which are
30 stated to have anti-arrhythmic activity. There is, however, no suggestion in either of these publications that the compounds described therein would be of any benefit in the treatment and/or prevention of psychotic disorders such as schizophrenia, still less that in doing
35 so they might be expected to manifest fewer side effects than those exhibited by classical neuroleptic agents.

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The present invention accordingly provides the use of a compound of formula I, or a pharmaceutically acceptable salt thereof or a prodrug thereof:



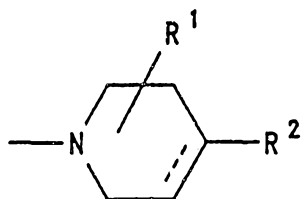
(I)

15 wherein

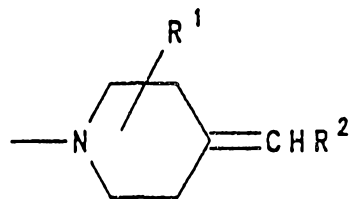
R represents hydrogen or C₁₋₆ alkyl;

Q represents a moiety of formula Qa, Qb, Qc or

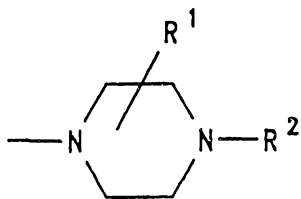
Qd:



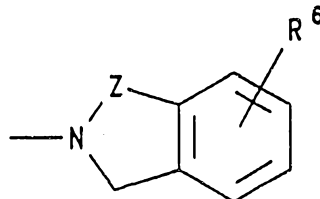
(Q a)



(Q b)



(Q c)



(Q d)

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in which the broken line represents an optional chemical bond;

5 R^1 represents hydrogen, or an optionally substituted C_{1-6} alkyl, C_{1-6} alkoxy, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl, aryl(C_{1-6})alkyl, aryl(C_{1-6})alkoxy, aryl(C_{2-6})alkenyl, aryl(C_{2-6})alkynyl, C_{3-7} heterocycloalkyl(C_{1-6})alkyl, heteroaryl, heteroaryl(C_{1-6})alkyl, heteroaryl(C_{2-6})alkenyl or heteroaryl(C_{2-6})alkynyl group;

10 R^2 represents an optionally substituted C_{1-6} alkyl, C_{1-6} alkoxy, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl, aryl(C_{1-6})alkyl, aryl(C_{1-6})alkoxy, aryl(C_{2-6})alkenyl, aryl(C_{2-6})alkynyl, C_{3-7} heterocycloalkyl(C_{1-6})alkyl, heteroaryl, heteroaryl(C_{1-6})alkyl, heteroaryl(C_{2-6})alkenyl or heteroaryl(C_{2-6})alkynyl group;

15 R^3 , R^4 and R^5 independently represent hydrogen, hydrocarbon, a heterocyclic group, halogen, cyano, trifluoromethyl, nitro, $-OR^a$, $-SR^a$, $-SOR^a$, $-SO_2R^a$, $-SO_2NR^aR^b$, $-NR^aR^b$, $-NR^aCOR^b$, $-NR^aCO_2R^b$, $-COR^a$, $-CO_2R^a$ or $-CONR^aR^b$;

20 Z represents $-CH_2-$ or $-CH_2CH_2-$;

R^6 represents hydrogen, C_{1-6} alkyl, C_{1-6} alkoxy, aryl, aryl(C_{1-6})alkyl or halogen; and

25 R^a and R^b independently represent hydrogen, hydrocarbon or a heterocyclic group; for the manufacture of a medicament for the treatment and/or prevention of psychotic disorders such as schizophrenia.

For use in medicine, the salts of the compounds of formula I will be pharmaceutically acceptable salts. Other salts may, however, be useful in the preparation of the compounds of use in the invention or of their pharmaceutically acceptable salts. Suitable pharmaceutically acceptable salts of the compounds of use in this invention include acid addition salts which may, for example, be formed by mixing a solution of the

- 5 -

compound of use in the invention with a solution of a pharmaceutically acceptable acid such as hydrochloric acid, sulphuric acid, fumaric acid, maleic acid, succinic acid, acetic acid, benzoic acid, oxalic acid, citric acid, tartaric acid, carbonic acid or phosphoric acid. Furthermore, where the compounds of use in the invention carry an acidic moiety, suitable pharmaceutically acceptable salts thereof may include alkali metal salts, e.g. sodium or potassium salts; alkaline earth metal salts, e.g. calcium or magnesium salts; and salts formed with suitable organic ligands, e.g. quaternary ammonium salts.

The term "hydrocarbon" as used herein includes straight-chained, branched and cyclic groups containing up to 18 carbon atoms, suitably up to 15 carbon atoms, and conveniently up to 12 carbon atoms. Suitable hydrocarbon groups include C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₇ cycloalkyl, C₃₋₇ cycloalkyl(C₁₋₆)alkyl, aryl, aryl(C₁₋₆)alkyl, aryl(C₂₋₆)alkenyl and aryl(C₂₋₆)alkynyl.

The expression "a heterocyclic group" as used herein includes cyclic groups containing up to 18 carbon atoms and at least one heteroatom preferably selected from oxygen, nitrogen and sulphur. The heterocyclic group suitably contains up to 15 carbon atoms and conveniently up to 12 carbon atoms, and is preferably linked through carbon. Examples of suitable heterocyclic groups include C₃₋₇ heterocycloalkyl, C₃₋₇ heterocycloalkyl(C₁₋₆)alkyl, heteroaryl, heteroaryl(C₁₋₆)alkyl, heteroaryl(C₂₋₆)alkenyl and heteroaryl(C₂₋₆)alkynyl groups.

Suitable alkyl groups within the scope of the term "hydrocarbon" and within the definition of the substituents R, R¹, R² and R⁶ include straight-chained and branched alkyl groups containing from 1 to 6 carbon atoms. Typical examples include methyl and ethyl groups,

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and straight-chained or branched propyl and butyl groups. Particular alkyl groups are methyl, ethyl, n-propyl, isopropyl and t-butyl.

5 Suitable alkenyl groups within the scope of the term "hydrocarbon" and within the definition of the substituents R^1 and R^2 include straight-chained and branched alkenyl groups containing from 2 to 6 carbon atoms. Typical examples include vinyl and allyl groups.

10 Suitable alkynyl groups within the scope of the term "hydrocarbon" and within the definition of the substituents R^1 and R^2 include straight-chained and branched alkynyl groups containing from 2 to 6 carbon atoms. Typical examples include ethynyl and propargyl groups.

15 Suitable cycloalkyl groups include groups containing from 3 to 7 carbon atoms. Particular cycloalkyl groups are cyclopropyl and cyclohexyl.

20 Particular aryl groups within the scope of the term "hydrocarbon" and within the definition of the substituents R^1 , R^2 and R^6 include phenyl and naphthyl.

 Particular aryl(C_{1-6})alkyl groups within the scope of the term "hydrocarbon" and within the definition of the substituents R^1 , R^2 and R^6 include benzyl, naphthylmethyl, phenethyl and phenylpropyl.

25 A particular aryl(C_{2-6})alkenyl group within the scope of the term "hydrocarbon" and within the definition of the substituents R^1 and R^2 is phenylethenyl.

30 Suitable heterocycloalkyl groups include azetidiny, pyrrolidyl, piperidyl, piperazinyl, morpholinyl and tetrahydrofuryl groups.

 A particular C_{3-7} heterocycloalkyl(C_{1-6})alkyl group within the scope of the expression "a heterocyclic group" and within the definition of the substituents R^1 and R^2 is tetrahydrofurylethyl.

35 Suitable heteroaryl groups within the scope of the expression "a heterocyclic group" and within the

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definition of the substituents R^1 and R^2 include pyridyl, quinolyl, isoquinolyl, pyridazinyl, pyrimidinyl, pyrazinyl, pyranyl, furyl, benzofuryl, dibenzofuryl, thienyl, benzthienyl, indolyl, indazolyl, imidazolyl, benzimidazolyl, oxadiazolyl and thiadiazolyl groups.

Particular heteroaryl(C_{1-6})alkyl groups within the scope of the expression "a heterocyclic group" and within the definition of the substituents R^1 and R^2 include thienylmethyl, pyridylmethyl, pyrimidinylmethyl and pyrazinylmethyl.

The hydrocarbon and heterocyclic groups, as well as the substituents R^1 and R^2 , may in turn be optionally substituted by one or more groups selected from C_{1-6} alkyl, adamantyl, phenyl, aryl(C_{1-6})alkyl, halogen, C_{1-6} haloalkyl, C_{1-6} aminoalkyl, trifluoromethyl, hydroxy, C_{1-6} alkoxy, aryloxy, keto, C_{1-3} alkylenedioxy, nitro, cyano, carboxy, C_{2-6} alkoxycarbonyl, C_{2-6} alkoxycarbonyl(C_{1-6})alkyl, C_{2-6} alkylcarbonyloxy, arylcarbonyloxy, C_{2-6} alkylcarbonyl, arylcarbonyl, C_{1-6} alkylthio, C_{1-6} alkylsulphinyl, C_{1-6} alkylsulphonyl, arylsulphonyl, trifluoromethanesulphonyloxy, $-NR^V R^W$, $-NR^V COR^W$, $-NR^V CO_2 R^W$, $-NR^V SO_2 R^W$, $-CH_2 NR^V SO_2 R^W$, $-NH CONR^V R^W$, $-PO(OR^V)(OR^W)$, $-CONR^V R^W$, $-SO_2 NR^V R^W$ and $-CH_2 SO_2 NR^V R^W$, in which R^V and R^W independently represent hydrogen, C_{1-6} alkyl, aryl or aryl(C_{1-6})alkyl.

The term "halogen" as used herein includes fluorine, chlorine, bromine and iodine, especially chlorine.

The present invention includes within its scope the use of prodrugs of the compounds of formula I above. In general, such prodrugs will be functional derivatives of the compounds of formula I which are readily convertible in vivo into the required compound of formula I. Conventional procedures for the selection and preparation of suitable prodrug derivatives are

described, for example, in "Design of Prodrugs", ed. H. Bundgaard, Elsevier, 1985.

Where the compounds of use in the invention have at least one asymmetric centre, they may accordingly exist as enantiomers. Where the compounds of use in the invention possess two or more asymmetric centres, they may additionally exist as diastereoisomers. It is to be understood that the use of all such isomers and mixtures thereof is encompassed within the scope of the present invention.

Suitably, the substituent R represents hydrogen or methyl, especially hydrogen.

Suitably, the substituent R¹ represents hydrogen.

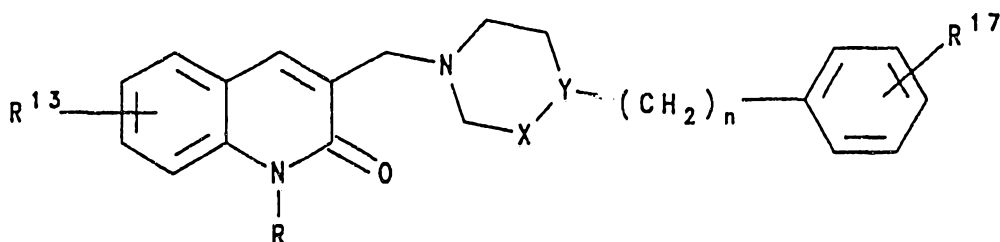
Suitable values for the substituent R² include C₁₋₆ alkyl, phenyl, halophenyl, C₁₋₆ alkylphenyl, C₁₋₆ alkoxyphenyl, nitrophenyl, benzyl, halobenzyl, phenethyl and phenylethenyl. Particular values of R² include methyl, ethyl, n-propyl, isopropyl, phenyl, chlorophenyl, ethylphenyl, methoxyphenyl, nitrophenyl, benzyl, chlorobenzyl, phenethyl and phenylethenyl.

Suitable values for the substituents R³, R⁴ and R⁵ include hydrogen, halogen, cyano, nitro, trifluoromethyl, amino, C₁₋₆ alkylamino, di(C₁₋₆)alkylamino, C₁₋₆ alkyl, C₁₋₆ alkoxy, aryl(C₁₋₆)alkoxy and C₂₋₆ alkylcarbonyl. Particular values include hydrogen, fluoro, chloro, methyl, methoxy and benzyloxy.

Particular values of R⁶ include hydrogen, phenyl, chloro and bromo.

A particular sub-class of compounds of use in the invention is represented by the compounds of formula IIA, and pharmaceutically acceptable salts thereof and prodrugs thereof:

- 9 -



(IIIA)

wherein

R is as defined with reference to formula I
above;

n is zero, 1, 2 or 3;

15 -X-Y- represents -CH₂-CH-, -CH=C- or -CH₂-N-;

and

R¹³ and R¹⁷ independently represent hydrogen,
halogen, cyano, nitro, trifluoromethyl, amino, C₁₋₆
alkylamino, di(C₁₋₆)alkylamino, C₁₋₆ alkyl, C₁₋₆ alkoxy,
20 aryl(C₁₋₆)alkoxy or C₂₋₆ alkylcarbonyl.

Particular values of R¹³ include hydrogen,
fluoro, chloro, methyl, ethyl, methoxy and benzyloxy.

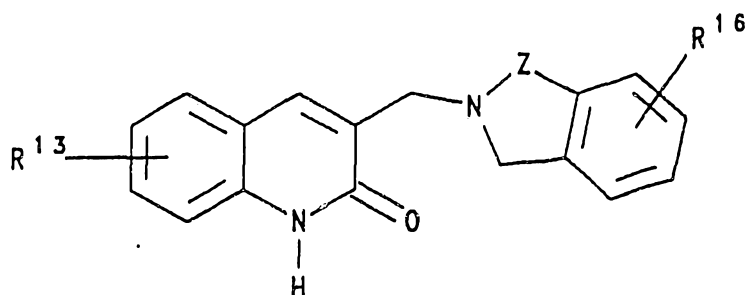
Particular values of R¹⁷ include hydrogen,
chloro, methoxy and nitro.

25 Another sub-class of compounds of use in the
invention is represented by the compounds of formula IIB,
and pharmaceutically acceptable salts thereof and
prodrugs thereof:

30

35

- 10 -



(IIB)

wherein

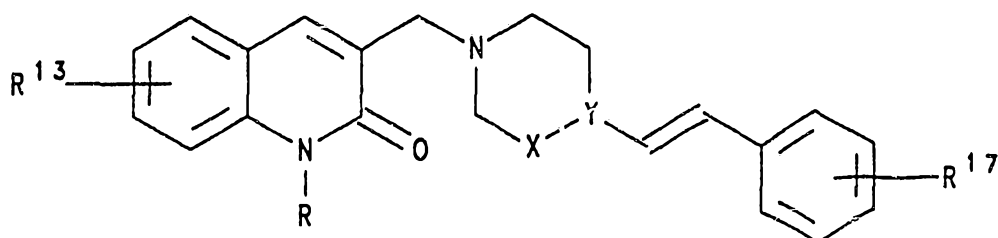
Z represents $-\text{CH}_2-$ or $-\text{CH}_2\text{CH}_2-$;

R^{13} is as defined with reference to formula IIA above; and

15 R^{16} represents hydrogen, C_{1-6} alkyl, C_{1-6} alkoxy, aryl, aryl(C_{1-6})alkyl or halogen.

Particular values of R^{16} include hydrogen, phenyl, chloro and bromo, especially hydrogen.

20 A further sub-class of compounds of use in the invention is represented by the compounds of formula IIC, and pharmaceutically acceptable salts thereof and prodrugs thereof:



(IIC)

wherein

35 R is as defined with reference to formula I above; and

- 11 -

X, Y, R¹³ and R¹⁷ are as defined with reference to formula IIA above.

Specific compounds of use in the present invention include:

- 5 3-(4-phenylpiperazin-1-ylmethyl)-2(1H)-quinolone;
and pharmaceutically acceptable salts thereof and prodrugs thereof.

Certain compounds falling within the definition of formula I above are novel. Particular sub-classes of
10 novel compounds in accordance with the present invention comprise the compounds of formula IIB and IIC as defined above; the compounds of formula IIA as defined above wherein n is zero and -X-Y- represents -CH=C-; the compounds of formula IIA as defined above wherein n is
15 zero, -X-Y- represents -CH₂-N- and R is other than hydrogen; and salts and prodrugs thereof. The invention further provides a novel compound selected from the following:

- 20 3-[4-(4-chlorophenyl)piperazin-1-ylmethyl]-2(1H)-quinolone;
3-[4-(4-methoxyphenyl)piperazin-1-ylmethyl]-2(1H)-quinolone;
3-(1,2,3,4-tetrahydroisoquinolin-2-ylmethyl)-2(1H)-quinolone;
25 3-(4-phenyl-1,2,3,6-tetrahydropyrid-1-ylmethyl)-2(1H)-quinolone;
3-[4-(2-phenylethyl)-1,2,3,6-tetrahydropyrid-1-ylmethyl]-2(1H)-quinolone;
3-(4-benzyl-1,2,3,6-tetrahydropyrid-1-ylmethyl)-2(1H)-
30 quinolone;
1-methyl-3-(4-phenylpiperazin-1-ylmethyl)-2(1H)-quinolone;
3-[4-(2-phenylethenyl)-1,2,3,6-tetrahydropyrid-1-ylmethyl]-2(1H)-quinolone;
35 and salts and prodrugs thereof.

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The invention also provides pharmaceutical compositions comprising one or more of the novel compounds according to the invention in association with a pharmaceutically acceptable carrier. Preferably these compositions are in unit dosage forms such as tablets, pills, capsules, powders, granules, sterile parenteral solutions or suspensions, metered aerosol or liquid sprays, drops, ampoules, auto-injector devices or suppositories; for oral, parenteral, intranasal, sublingual or rectal administration, or for administration by inhalation or insufflation. Alternatively, the compositions may be presented in a form suitable for once-weekly or once-monthly administration; for example, an insoluble salt of the active compound, such as the decanoate salt, may be adapted to provide a depot preparation for intramuscular injection. For preparing solid compositions such as tablets, the principal active ingredient is mixed with a pharmaceutical carrier, e.g. conventional tableting ingredients such as corn starch, lactose, sucrose, sorbitol, talc, stearic acid, magnesium stearate, dicalcium phosphate or gums, and other pharmaceutical diluents, e.g. water, to form a solid preformulation composition containing a homogeneous mixture of a compound of the present invention, or a pharmaceutically acceptable salt thereof. When referring to these preformulation compositions as homogeneous, it is meant that the active ingredient is dispersed evenly throughout the composition so that the composition may be readily subdivided into equally effective unit dosage forms such as tablets, pills and capsules. This solid preformulation composition is then subdivided into unit dosage forms of the type described above containing from 0.1 to about 500 mg of the active ingredient of the present invention. The tablets or pills of the novel composition can be coated or otherwise compounded to

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provide a dosage form affording the advantage of prolonged action. For example, the tablet or pill can comprise an inner dosage and an outer dosage component, the latter being in the form of an envelope
5 over the former. The two components can be separated by an enteric layer which serves to resist disintegration in the stomach and permits the inner component to pass intact into the duodenum or to be delayed in release. A variety of materials can be used for such enteric layers
10 or coatings, such materials including a number of polymeric acids and mixtures of polymeric acids with such materials as shellac, cetyl alcohol and cellulose acetate.

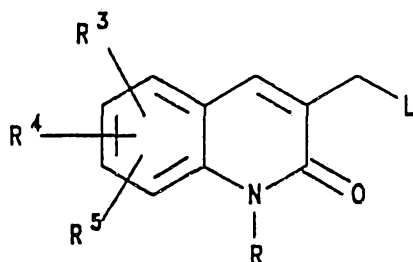
The liquid forms in which the novel
15 compositions of the present invention may be incorporated for administration orally or by injection include aqueous solutions, suitably flavoured syrups, aqueous or oil suspensions, and flavoured emulsions with edible oils such as cottonseed oil, sesame oil, coconut oil or peanut
20 oil, as well as elixirs and similar pharmaceutical vehicles. Suitable dispersing or suspending agents for aqueous suspensions include synthetic and natural gums such as tragacanth, acacia, alginate, dextran, sodium carboxymethylcellulose, methylcellulose, polyvinyl-
25 pyrrolidone or gelatin.

In the treatment of schizophrenia, a suitable dosage level is about 0.01 to 250 mg/kg per day, preferably about 0.05 to 100 mg/kg per day, and especially about 0.05 to 5 mg/kg per day. The compounds
30 may be administered on a regimen of 1 to 4 times per day.

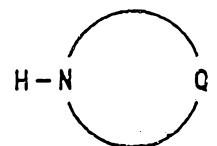
The compounds of formula I above, including the novel compounds according to the present invention, may be prepared by a process which comprises reacting a compound of formula III with a compound of formula IV:

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(III)



(IV)

wherein R, R³, R⁴ and R⁵ are as defined above, Q¹ represents the residue of a moiety of formula Qa to Qd as defined above, and L represents a suitable leaving group.

15 The leaving group L is suitably a halogen atom, e.g. chlorine or bromine.

 The reaction is conveniently carried out by stirring the reactants under basic conditions in a suitable solvent, for example potassium carbonate in N,N-dimethylformamide, or triethylamine in tetrahydrofuran or acetonitrile.

20 Where they are not commercially available, the starting materials of formula III and IV may be prepared by procedures analogous to those described in the accompanying Examples, or by standard methods well known from the art.

 It will be appreciated that any compound of formula I initially obtained from any of the above processes may, where appropriate, subsequently be elaborated into a further desired compound of formula I using techniques known from the art. For example, a compound of formula I wherein R is hydrogen initially obtained may be converted into a compound of formula I wherein R represents C₁₋₆ alkyl by standard alkylation techniques, such as by treatment with an alkyl iodide, e.g. methyl iodide, typically under basic conditions,

35

- 15 -

e.g. sodium hydride in dimethylformamide, or triethylamine in acetonitrile.

Where the above-described processes for the preparation of the compounds of use in the invention give rise to mixtures of stereoisomers, these isomers may be separated by conventional techniques such as preparative chromatography. The compounds may be prepared in racemic form, or individual enantiomers may be prepared either by enantiospecific synthesis or by resolution. The compounds may, for example, be resolved into their component enantiomers by standard techniques such as preparative HPLC, or the formation of diastereomeric pairs by salt formation with an optically active acid, such as (-)-di-p-toluoyl-d-tartaric acid and/or (+)-di-p-toluoyl-l-tartaric acid, followed by fractional crystallization and regeneration of the free base. The compounds may also be resolved by formation of diastereomeric esters or amides, followed by chromatographic separation and removal of the chiral auxiliary.

During any of the above synthetic sequences it may be necessary and/or desirable to protect sensitive or reactive groups on any of the molecules concerned. This may be achieved by means of conventional protecting groups, such as those described in Protective Groups in Organic Chemistry, ed. J.F.W. McOmie, Plenum Press, 1973; and T.W. Greene & P.G.M. Wuts, Protective Groups in Organic Synthesis, John Wiley & Sons, 1991. The protecting groups may be removed at a convenient subsequent stage using methods known from the art.

The following Examples illustrate the preparation of compounds according to the invention.

The compounds useful in this invention potentially inhibit [³H]-spiperone binding to human dopamine D₄ receptor subtypes expressed in clonal cell lines.

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[³H]-Spiperone Binding Studies

Clonal cell lines expressing the human dopamine D₄ receptor subtype were harvested in PBS and then lysed in 10 mM Tris-HCl pH 7.4 buffer containing 5 mM MgSO₄ for 20 min on ice. Membranes were centrifuged at 50,000g for 15 min at 4°C and the resulting pellets resuspended in assay buffer (50 mM Tris-HCl pH 7.4 containing 5 mM EDTA, 1.5 mM CaCl₂, 5 mM MgCl₂, 5 mM KCl, 120 mM NaCl, and 0.1% ascorbic acid) at 20 mg/ml wet weight. Incubations were carried out for 60 min at room temperature (22°C) in the presence of 0.05-2 nM [³H]-spiperone or 0.2 nM for displacement studies and were initiated by addition of 20-100 µg protein in a final assay volume of 0.5 ml. The incubation was terminated by rapid filtration over GF/B filters presoaked in 0.3% PEI and washed with 10 ml ice-cold 50 mM Tris-HCl, pH 7.4. Specific binding was determined by 10 µM apomorphine and radioactivity determined by counting in a LKB beta counter. Binding parameters were determined by non-linear least squares regression analysis, from which the inhibition constant K_i could be calculated for each test compound.

The compounds of the accompanying Examples were tested in the above assay, and all were found to possess a K_i value for displacement of [³H]-spiperone from the human dopamine D₄ receptor subtype of below 1.5 µM.

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EXAMPLE 13-(4-Phenylpiperazin-1-yl)methylquinolin-2(1H)-one

3-Bromomethylquinolin-2(1H)-one (480mg, 2mmol),
(prepared according to the method of M. Uchida *et al*, Chem.
5 Pharm. Bull., 1985, 33, 3775), 1-phenylpiperazine (324mg,
2mmol), and triethylamine (303mg, 3mmol) were combined in
dry tetrahydrofuran (20ml) and the mixture stirred under reflux
for 3h. The residue remaining on removal of solvent was
suspended in water and the suspension filtered, the collected
10 solid washed with water and methanol, dried and recrystallised
from dioxan to give the product as a buff powder (391mg), m.p.
260°C (dec.); (Found: C, 75.07; H, 6.82; N, 12.95. $C_{20}H_{21}N_3O$
requires C, 75.21; H, 6.63; N, 13.16%); δ_H (DMSO- d_6) 2.60-2.63
(4H, m, 2 x piperazinyl CH_2), 3.17-3.19 (4H, m, 2 x piperazinyl
15 CH_2), 3.47 (2H, s, CH_2NR_2), 6.77 (1H, t, J 7.2Hz, 4'-H), 6.93 (2H,
d, J 8.0Hz, 2', 6'-H), 7.15-7.23 (3H, m, 6-H and 3', 5'-H), 7.31
(1H, d, J 8.1Hz, 5-H), 7.46 (1H, t, J 8.3Hz, 7-H), 7.69 (1H, d, J
7.2Hz, 8-H), 7.90 (1H, s, 4-H), and 11.79 (1H, br s, NH); m/z
(CI^+ , NH_3) 320 ($M+1$)⁺.

20

Similarly prepared were:

EXAMPLE 23-(4-[4-Methoxyphenyl]piperazin-1-yl)methylquinolin-2(1H)-one

25 M.p. 263-266°C (dioxan/ H_2O); (Found: C, 71.74; H, 6.72; N,
11.55. $C_{21}H_{23}N_3O_2 \cdot 0.1H_2O$ requires C, 71.81; H, 6.66; N, 11.96%);
 δ_H (DMSO- d_6) 2.61 (4H, br s, 2 x piperazinyl CH_2), 3.06 (4H, br s,
2 x piperazinyl CH_2), 3.46 (2H, s, CH_2NR_2), 3.68 (3H, s, OCH_3),

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6.81 (2H, d, J 9.2Hz, ArH), 6.89 (2H, d, J 9.2Hz, ArH), 7.16 (1H, t, J 8.0Hz, ArH), 7.30 (1H, d, J 8.0Hz, ArH), 7.45 (1H, t, J 8.3Hz, ArH), 7.68 (1H, d, J 6.9Hz, ArH), 7.88 (1H, s, 4-H), and 11.76 (1H, br s, NH); m/z (CI⁺, NH₃) 350 (M+1)⁺.

5

EXAMPLE 3

3-(1,2,3,4-Tetrahydro^{iso}quinolin-2-yl)methylquinolin-2(1H)-one
^

M.p. 196-199°C (dioxan); (Found: C, 77.52; H, 6.35; N, 9.37. C₁₉H₁₈N₂O.0.25H₂O requires C, 77.39; H, 6.32; N, 9.50%); δ_H (DMSO-d₆) 2.74-2.77 (2H, m, -CH₂), 2.86-2.89 (2H, m, -CH₂), 3.57 (2H, s, 3-CH₂NR₂), 3.66 (2H, s, R₂NCH₂Ar), 7.03-7.18 (5H, m, ArH), 7.31 (1H, d, J 8.3Hz, 5-H), 7.46 (1H, ddd, J 9.5, 8.4, 1.5Hz, 7-H), 7.68 (1H, d, J 7.8Hz, 8-H), 7.92 (1H, s 4-H), and 11.80 (1H, br s, NH); m/z (CI⁺, NH₃) 291 (M+1)⁺.

15

EXAMPLE 4

3-(4-[4-Chlorophenyl]piperazin-1-yl)methyl-1H-quinolin-2-one

M.p. 256-259°C (dioxan/H₂O); (Found: C, 68.09; H, 5.61; N, 11.91; C₂₀H₂₀ClN₃O requires C, 67.87; H, 5.70; N, 11.88%); δ_H (DMSO-d₆) 2.59-2.61 (4H, m, piperazinyl H), 3.16-3.19 (4H, m, piperazinyl H), 3.46 (2H, s, NCH₂ Ar), 6.94 (2H, d, J 9.1Hz, ArH), 7.14-7.24 (3H, m, ArH), 7.31 (1H, d, J 8.2Hz, ArH), 7.46 (1H, t, J 8.1Hz, ArH), 7.68 (1H, d, J 7.0Hz, ArH), 7.88 (1H, s, ArH), and 11.77 (1H, br s, NH); m/z (CI⁺, NH₃) 354 (M+1)⁺.

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EXAMPLE 53-(4-Phenyl-1,2,3,6-tetrahydropyridin-1-yl)methyl-2(1H)-quinolone

5

M.p. 213-216°C (dioxan/H₂O); (Found: C, 80.26; H, 6.58; N, 9.03. C₂₁H₂₀N₂O requires C, 79.72; H, 6.37; N, 8.85%). δ_H (DMSO-d₆) 2.54 (2H, br s, tetrahydropyridinyl 3-CH₂), 2.73 (2H, t, J 5.5Hz, tetrahydropyridinyl 2-CH₂), 3.20 (2H, br s, tetrahydropyridinyl 6-CH₂), 3.52 (2H, s, NCH₂Ar), 6.19 (1H, br s, tetrahydropyridinyl 5-CH), 7.16 (1H, t, J 7.0Hz, ArH), 7.24 (1H, t, J 7.3Hz, ArH), 7.29-7.35 (3H, m, ArH), 7.43-7.48 (3H, m, ArH), 7.69 (1H, d, J 6.4Hz, 8-H), 7.90 (1H, s, 4-H), and 11.78 (1H, br s, NH); m/z (CI⁺, NH₃) 317 (M+1)⁺.

10

15

EXAMPLE 63-(4-Phenylethyl-1,2,3,6-tetrahydropyridin-1-yl)methyl-2-(1H)-quinolone

20

M.p. 177-179°C (MeOH/H₂O); (Found: C, 79.31; H, 6.99; N, 8.05. C₂₃H₂₄N₂O. 0.15H₂O requires C, 79.56; H, 7.05; N, 8.07%); δ_H (DMSO-d₆) 2.11 (2H, br s, tetrahydropyridinyl 3-CH₂), 2.23 (2H, t, J 7.6Hz, PhCH₂CH₂), 2.55 (2H, t, J 5.6Hz, tetrahydropyridinyl 2-CH₂), 2.67-2.73 (2H, m, tetrahydropyridinyl 6-CH₂), 3.44 (2H, s, NCH₂Ar), 5.40 (1H, br s, tetrahydropyridinyl 5-CH), 7.14-7.30 (7H, m, ArH), 7.45 (1H, t, J 7.0Hz, ArH), 7.68 (1H, d, J 7.2Hz, 8-H), 7.84 (1H, s, 4-H), and 11.76 (1H, br s, NH); m/z (CI⁺, NH₃) 345 (M+1)⁺.

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- 20 -

EXAMPLE 73-(4-Benzyl-1,2,3,6-tetrahydropyridin-1-yl)methyl-2(1H)-quinolone

5

M.p. 155-158°C (DMF/H₂O); (Found: C, 79.77; H, 6.77; N, 8.53. C₂₂H₂₂N₂O requires C, 79.97; H, 6.71; N, 8.48%); δ_H (DMSO-d₆) 1.99 (2H, br s, tetrahydropyridinyl 3-CH₂), 2.53 (2H, br s, tetrahydropyridinyl 2-CH₂), 2.89 (2H, br s, tetrahydropyridinyl 6-CH₂), 3.27 (2H, s, PhCH₂), 3.43 (2H, s, NCH₂Ar), 5.42 (1H, br s, tetrahydropyridinyl 5-CH), 7.12-7.21 (4H, m, ArH), 7.27-7.31 (3H, m, ArH), 7.44 (1H, t, J 7.1Hz, ArH), 7.67 (1H, d, J 7.0Hz, 8-H), 7.82 (1H, s, 4-H), and 11.75 (1H, br s, NH); m/z (CI⁺, NH₃) 331 (M+1)⁺.

10

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EXAMPLE 8(E)-3-(4-[2-Phenylethenyl]-1,2,3,6-tetrahydropyridin-1-yl)methyl-2(1H)-quinolone

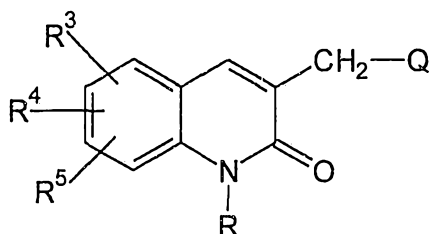
20

M.p. 258-260°C (DMF); (Found: C, 80.47; H, 6.44; N, 8.21. C₂₃H₂₂N₂O requires C, 80.67; H, 6.48; N, 8.18%); δ_H (DMSO-d₆) 2.39 (2H, br s, tetrahydropyridinyl CH₂), 2.68 (2H, t, J 5.6Hz, tetrahydropyridinyl CH₂), 3.17 (2H, br s, tetrahydropyridinyl CH₂), 3.51 (2H, s, ArCH₂N), 5.94 (1H, br s, tetrahydropyridinyl 5-H), 6.50 (1H, d, J 16.2Hz, CH=CH), 6.92 (1H, d, J 16.2Hz, CH=CH), 7.14-7.23 (2H, m, ArH), 7.29-7.35 (3H, m, ArH), 7.43-7.49 (3H, m, ArH), 7.70 (1H, d, J 7.9Hz, ArH), 7.89 (1H, s, 4-H), and 11.78 (1H, br s, NH); m/z (CI⁺, NH₃) 343 (M+1)⁺.

25

The claims defining the invention are as follows:

1. A method for the treatment and/or prevention of psychotic disorders, which comprises administering to a patient in need of such treatment an effective amount of a compound of formula I, or a pharmaceutically acceptable salt thereof



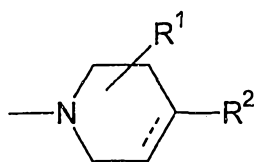
(I)

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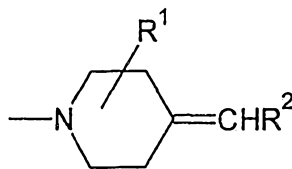
wherein

R represents hydrogen or C₁₋₆ alkyl;

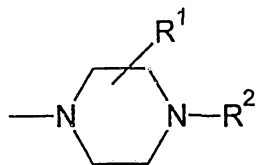
Q represents a moiety of formula Qa, Qb, Qc or Qd:



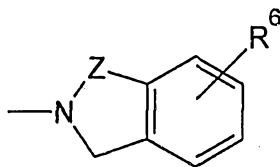
(Qa)



(Qb)



(Qc)



(Qd)

10 in which the broken line represents an optional chemical bond;

R¹ represents hydrogen, or an optionally substituted (as herein defined) C₁₋₆ alkyl, C₁₋₆ alkoxy, C₂₋₆ alkenyl, C₂₋₆ alkynyl, aryl, aryl(C₁₋₆)alkyl, aryl(C₁₋₆) alkoxy, aryl (C₂₋₆)alkenyl, aryl (C₂₋₆)alkynyl, C₃₋₇ heterocycloalkyl (C₁₋₆)alkyl, heteroaryl, heteroaryl (C₁₋₆)alkyl, heteroaryl (C₂₋₆)alkenyl or heteroaryl (C₂₋₆)alkynyl group;

15

R² represents an optionally substituted (as herein defined) C₁₋₆ alkyl, C₁₋₆ alkoxy, C₂₋₆ alkenyl, C₂₋₆ alkynyl, aryl, aryl(C₁₋₆)alkyl, aryl(C₁₋₆)alkoxy, aryl(C₂₋₆)alkenyl, aryl(C₂₋₆)alkynyl, C₃₋₇ heterocycloalkyl (C₁₋₆)alkyl, heteroaryl, heteroaryl(C₁₋₆)alkyl, heteroaryl(C₂₋₆)alkenyl or heteroaryl (C₂₋₆) alkynyl group;



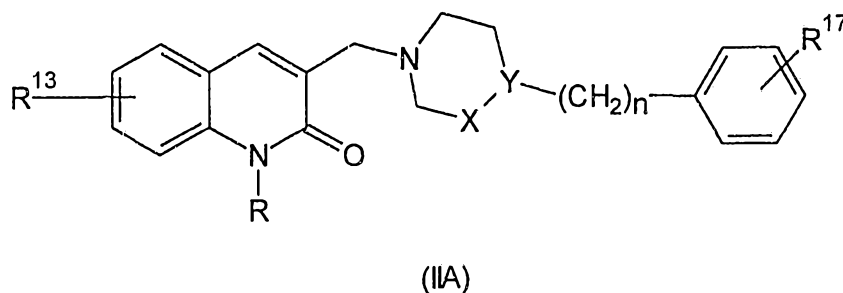
R^3 , R^4 and R^5 independently represent hydrogen, hydrocarbon (as herein defined), a heterocyclic group (as herein defined), halogen, cyano, trifluoromethyl, nitro, $-OR^a$, $-SR^a$, $-SOR^a$, $-SO_2R^a$, $-SO_2NR^aR^b$, $-NR^aR^b$, $-NR^aCOR^b$, $-NR^aCO_2R^b$, $-COR^a$, $-CO_2R^a$ or $-CONR^aR^b$;

5 Z represents $-CH_2-$ or $-CH_2CH_2-$;

R^6 represents hydrogen, C_{1-6} alkyl, C_{1-6} alkoxy, aryl, aryl(C_{1-6})alkyl or halogen; and

R^a and R^b independently represent hydrogen, hydrocarbon (as herein defined) or a heterocyclic group (as herein defined).

10 2. The method as claimed in claim 1 wherein the compound administered is represented by formula IIA, and pharmaceutically acceptable salts thereof.



wherein

R is as defined in claim 1;

15 n is zero, 1, 2 or 3;

-X-Y-represents $-CH_2-CH-$, $-CH=C-$ or $-CH_2-N-$;

and

R^{13} and R^{17} independently represent hydrogen, halogen, cyano, nitro, trifluoromethyl, amino, C_{1-6} alkylamino, di(C_{1-6})alkylamino, C_{1-6} alkyl, C_{1-6} alkoxy, 20 aryl (C_{1-6})alkoxy or C_{2-6} alkylcarbonyl.

3. The method as claimed in claim 1 wherein the compound administered is selected from:

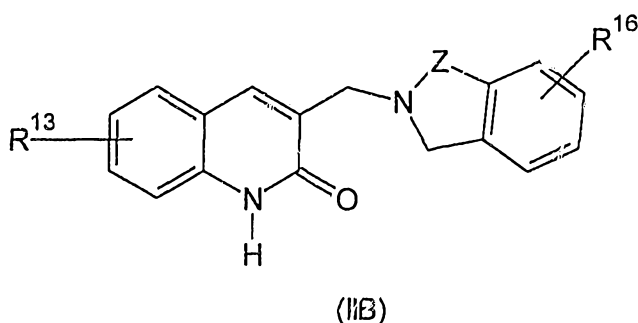
3-(4-phenylpiperazin-1-ylmethyl)-2(1H)-quinolone;
and pharmaceutically acceptable salts thereof.

25 4. A compound of formula IIA as defined in claim 2 wherein n is zero and -X-Y-represents $-CH=C-$, and salts thereof.

5. A compound of formula IIA as defined in claim 2 wherein n is zero, -X-Y-represents $-CH_2-N-$ and R represents C_{1-6} alkyl, and salts thereof.

6. A compound of formula IIB, or a salt thereof:





wherein

Z represents $-\text{CH}_2-$ or $-\text{CH}_2\text{CH}_2-$;

R^{13} is as defined in claim 2; and

5 R^{16} represents hydrogen, C_{1-6} alkyl, C_{1-6} alkoxy, a μ , aryl (C_{1-6})alkyl or halogen.

7. A compound selected from:

- 3-[4-(4-chlorophenyl)piperazin-1-ylmethyl]-2(1H)-quinolone;
- 3-[4-(4-methoxyphenyl)piperazin-1-ylmethyl]-2(1H)-quinolone;
- 3-(1,2,3,4-tetrahydroisoquinolin-2-ylmethyl)-2(1H)-quinolone;
- 10 3-(4-phenyl-1,2,3,6-tetrahydropyrid-1-ylmethyl)-2(1H)-quinolone;
- 3-[4-(2-phenylethyl)-1,2,3,6-tetrahydropyrid-1-ylmethyl]-2(1H)-quinolone;
- 3-(4-benzyl-1,2,3,6-tetrahydropyrid-1-ylmethyl)-2(1H)-quinolone;
- 1-methyl-3-(4-phenylpiperazin-1-ylmethyl)-2(1H)-quinoline;
- 3-[4-(2-phenylethenyl)-1,2,3,6-tetrahydropyrid-1-ylmethyl]-2(1H)-quinolone;

15 and salts thereof.

8. A pharmaceutical composition comprising a compound as claimed in any one of claims 4 to 7 in association with a pharmaceutically acceptable carrier.

9. A method for the treatment and/or prevention of psychotic disorders which comprises administering to a patient in need of such treatment an effective amount of a
20 compound as claimed in any one of claims 4 to 7 or the composition of claim 8.

10. A substituted 2(1H)-quinolone derivative, substantially as hereinbefore described with reference to any one of the Examples.

11. A process for the preparation of a substituted 2(1H)-quinolone derivative, substantially as hereinbefore described with reference to any one of the Examples.

25

Dated 2 April, 1997
Merck Sharp & Dohme Limited

Patent Attorneys for the Applicant/Nominated Person
SPRUSON & FERGUSON



INTERNATIONAL SEARCH REPORT

International application No.
PCT/GB 94/00383A. CLASSIFICATION OF SUBJECT MATTER
IPC 5 C07D215/22 A61K31/47 C07D401/06

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 5 C07D A61K

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)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP,A,0 364 327 (SYNTHELABO) 18 April 1990 * page 14, line 22-24; page 15, line 19-22; claims * -----	1

☐ Further documents are listed in the continuation of box C.☒ 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

10 May 1994

Date of mailing of the international search report

19. 05. 94

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Authorized officer

Van Bijlen, H

INTERNATIONAL SEARCH REPORT

International application No.

PCT/GB94/00383

Box I Observations where certain claims were found unsearchable (Continuation of item 1 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. ☐ Claims Nos.: 15
because they relate to subject matter not required to be searched by this Authority, namely:
Although claim 15 is directed to a method of treatment of (diagnostic method practised on) 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 II Observations where unity of invention is lacking (Continuation of item 2 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

Information on patent family members

International application No.

PCT/GB 94/00383

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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		AU-B- 619349	23-01-92
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		JP-A- 2157267	18-06-90
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