Abstract:

Title: METHODS OF TREATING SCHIZOPHRENIA WITH PYRAZOLE DERIVATIVE INHIBITORS OF TGF - BETA

Embodiments of the invention relate to the treatment of schizophrenia in mammals. Embodiments of the invention include methods for treating schizophrenia and/or symptoms of schizophrenia and/or positive symptoms of schizophrenia in a psychotic disease as well as methods for preparing medicaments used in the treatment of mammalian schizophrenia. In one embodiment, methods of the invention comprise the inhibition of TGF-beta for the treatment of mammalian schizophrenia.
Methods of treating schizophrenia with pyrazole derivative inhibitors of TGF-beta

Field

Embodiments of the invention relate to the treatment of schizophrenia in mammals.

Background

Schizophrenia

Schizophrenia is a mental disorder marked by severe cognitive dysfunction and psychosis, estimated to affect greater than 1% of the population, with onset typically in late adolescence and early adulthood. There are three main symptom categories of schizophrenia: positive symptoms, which include delusions, hallucinations, and movement and thought disorders, such as disorganized speech and/or grossly disorganized or catatonic behavior; negative symptoms comprised of social disturbances, flat affect and deficits in expressing emotion and experiencing pleasure such as alogia and/or avolition; and cognitive symptoms, which affect attention span, working memory and other intellectual functions and may include one or more of disorganized thinking, slow thinking, difficulty understanding, poor concentration, poor memory, difficulty expressing thoughts and difficulty integrating thoughts, feelings and behavior. Together, these symptoms have a severe impact on the quality of life for the schizophrenic patient, and contribute to a higher rate of substance abuse and suicide, factors contributing to a life expectancy of fifteen years less than the norm.

The positive symptoms of schizophrenia may also be present in other psychotic diseases, for example, bipolar disorder, delusional disorder, psychotic depression, Tourette syndrome, autism spectrum disorder, OCD, dementia and Alzheimer's disease. Antipsychotics used to treat these symptoms of schizophrenia may also used to treat these symptoms in the other psychotic diseases.

Schizophrenia is a clear unmet medical need, of great import to general public health. Finding effective treatments for this disease has been difficult because both the disease course and cause are highly complex, comprising any number of poorly understood genetic and environmental interactions. Currently, schizophrenia is managed using second-generation, or "atypical", anti-psychotic agents. These dopamine receptor antagonists target serotonin receptors to a greater extent
than their predecessors, and may target other receptors such as histamine and NMDA receptors. They are more effective at treating positive symptoms, but are not effective against negative or cognitive deficit symptoms. Thus, there is an urgent need for new classes of schizophrenia drugs.

**LY-2157299 and related pyrrole derivative TGF-beta inhibitors**

Eli Lilly & Co. is developing a series of TGF-beta inhibitors, including 4-[2-(6-Methyl-pyridin-2-yl)-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl]phenol and 4-[2-(6-Methyl-pyridin-2-yl)-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl]-quinoline-6-carboxylic acid amide, also known as "LY-2157299", for the potential treatment of inflammation, cancer and atherosclerosis. In January 2006, phase I trials had commenced for cancer indications with LY-2157299.

![Structural Formula I](image)

wherein

![R3](image)

is a four, five or six membered saturated ring and X is C, O or S:

R1 is unsubstituted or substituted phenyl; unsubstituted or substituted pyridine; unsubstituted or substituted pyridine N-oxide; unsubstituted or substituted quinoline; unsubstituted or substituted quinoline N-oxide; unsubstituted or substituted naphthyridine; unsubstituted or substituted pyrazine; furyl; unsubstituted or substituted thiazolyl; unsubstituted or substituted imidazolyl; unsubstituted or substituted pyrazolyl; or unsubstituted or substituted thiophenyl;

wherein the substitution may be one or more of the following: (Cl-C6)alkyl, (C2-C6)alkenyl, (C2-C6)alkynyl, (Cl-C6)alkoxy, (C2-C6)alkenlyoxy, (C2-C6)alkynlyoxy, (Cl-C6)alkynlyhio, (Cl-C6)alkylsulphinyl, (Cl-C6)alkylsulphonyl, (Cl-C6)alkylamino, di-[(Cl-C6)alkyl]amino, (Cl-C6)alkoxycarbonyl, N—(Cl-
C6)alkylcarbamoyl, N,N-di-[(Cl-C6)alkyl] carbamoyl, (C2-C6)alkanoyl, (C2-
C6)alkanoyloxy, (C2-C6)alkanoylamino, N—(C 1-C6)alkyl-(C2-C6)alkanoylamino, 
(C3-C6)alkenoylamino, N—(C 1-C6)alkyl-(C3-C6)alkenoylamino, (C3-
C6)alkynoylamino, N—(C 1-C6)alkyl-(C3-C6)alkynoylamino, N—(Cl-
C6)alkylsulphamoyl, N,N-di-[(Cl-C6)alkyl]sulphamoyl, (Cl-
C6)alkanesulphonylamino, N—(C 1-C6)alkyl-(C1-C6)alkanesulphonylamino, 
carboxamide, ethylene, thiophenyl, aminophenyl, trifluoromethyl, halo, 
trifluoromethoxy, hydroxymethyl, N-pyrrolidino, N-morpholino, phenylthio, (Cl-
C4)dialkylaminomethyl, methoxyphenyl, amino, hydroxy, carboxyl, phenyl, and 
arylalky;

R2 is unsubstituted or substituted quinoline; unsubstituted or substituted quinoline N-oxide; 
unsubstituted or substituted phenyl; unsubstituted or substituted naphthalene; unsubstituted 
or substituted pyridine; unsubstituted or substituted pyridine N-oxide; unsubstituted or 
substituted quinazoline; unsubstituted or substituted cinnoline; unsubstituted or substituted 
benzodioxole; unsubstituted or substituted benzodioxane; unsubstituted or substituted 
pyrimidine; unsubstituted or substituted benzothiophene; or unsubstituted or substituted 
phenanthroline;

wherein the substitution may independently be one or more of the following:
hydrogen, (Cl-C6)alkyl, (C2-C6)alkenyl, (C2-C6)alkynyl, (Cl-C6)alkylhalide, (Cl-
C6)alkoxy, (C2-C6)alkenylxy, (C2-C6)alkynlyoxy, (Cl-C6)alkylthio, (Cl-
C6)alkylsulphinyl, (Cl-C6)alkylsulphonyl, (Cl-C6)alkylamino, di-[(Cl-
C6)alkyl]amino, (Cl-C6)alkoxy carbonyl, N—(C 1-C6)alkylcarbamoyl, N,N-di-[(Cl-
C6)alkyl]carbamoyl, aminoxy, N—(Cl-C6)alkyl aminoxy, N,N-di-[(Cl-
C6)alkyl]aminoxy, (C2-C6)alkanoyl, (C2-C6)alkanoyloxy, (C2-C6)alkanoylamino, 
N—(C 1-C6)alkyl-(C2-C6)alkanoylamino, (C3-C6)alkenoylamino, N—(C 1-C6)alkyl-
(C3-C6)alkenoylamino, (C3-C6)alkynoylamino, N—(C 1-C6)alkyl-(C3-
C6)alkynoylamino, sulphamoyl, N—(Cl-C6)alkylsulphamoyl, N,N-di-[(Cl-
C6)alkyl]sulphamoyl, (C1-C6)alkanesulphonylamino, N—(C 1-C6)alkyl-(C 1-
C6)alkanesulphonylamino, carboxamide, ethylene, phenyl, thiophenyl, aminophenyl, 
phenylthio, halo, cyano, pyridinyl, aryalkyl, hydroxy, N-pyrrolidino, N-morpholino, 
carboxyl, [5-phenyl-1,2,4-oxadiazole-3-yl]methoxy, 6-methyl-pyridazin-3-yloxy, (5-
oxo-2-pyrrolidinyl)methoxy, 2-(4,5-dihydro-IH-imidazolyl), N,N-
dialkylcarbamoyloxy, 1-hydroxy-1-methylethyl, 4-fluorophenyl, 3,4-
methylenedioxyphenyl, trifluoromethyl, trifluoromethoxy,
or a group of the formula

\[
\begin{align*}
\text{R}_{10} & \quad \text{X}_1 \quad \text{(CH}_2\text{)}_n\text{C(\text{CH}_2)_mQ}_1 \\
\text{R}_{16} & \quad \text{Q}_5
\end{align*}
\]

wherein: \(\text{X}_1\) is \(\text{O}, \text{N}, \text{S}, \text{SO}_2, \text{NR}_{13}, \text{C(O)}, \) or bond; \(\text{Q}_1\) is hydrogen, phenyl, 5-
(2,2-difluoro-1,3-benzodioxolyl), \(\text{C(O)Q}_5\), or pyridyl when \(m\) and \(n\) are
independently 0-2, except when one is 0 the other cannot be 0; \(\text{Q}_5\) is \(\text{OR}_{11},\)
\(\text{NR}_{11}\text{R}_{12}\), halo, \(\text{N-morpholino}, \text{N-piperazino-N'R}_{13}, \text{N-imidazolyl}, \text{N-}
\text{pyrazolyl}, \text{N-triazolyl}, \text{N-(4-piperidinylpiperidine)}, \text{SO}_2\text{R}_{14}, \text{SOR}_{14},\)
\(\text{NHSO}_2\text{R}_{15}\), acetamido, \(\text{N-phthalimido}, \text{N-oxazolidino}, \text{N-imidazolino}, \text{N-}
\text{benzoxazolidino}, \text{N-pyrolidinonyl}, \text{N(N'-methylbenzimidazolino)}, \text{N,N-di(Cl-}
\text{C4)alkylamino(Cl-C4)alkoxy}, \text{N-benzimidazolino}; \) when \(m\) and \(n\) are
independently 0-2, but one or the other of \(m\) or \(n\) is not 0; \(\text{Q}_5\) is hydroxy,
methoxy, amino, diethylamino, dimethylamino; \(\text{R}_{10}\) is hydrogen, halo, \(\text{Cl-}
\text{C6)alkyl}; \(\text{R}_{11}\) and \(\text{R}_{12}\) are independently hydrogen, \(\text{Cl-C6)alkyl}, \(\text{Cl-}
\text{C6)alkoxy}, \text{arylalkyl}, \text{C3-C8)cycloalkyl}, \text{C3-C8)cycloalkylmethyl}, \text{4-(N-}
\text{methylpiperidinyl)}, \text{pyridyl}, or \(\text{R}_{11}\) and \(\text{R}_{10}\) can be taken together to form a 4,
5, 6, or 7 membered ring, or \(\text{R}_{11}\) and \(\text{R}_{12}\) can be taken together to form a 3, 4,
5, 6, or 7 membered ring; \(\text{R}_{13}\) is hydrogen, \(\text{Cl-C6)alkyl}, \text{2-methoxyphenyl},
2-pyridimidinyl; \(\text{R}_{14}\) is 2-pyrimidinyl, \(\text{N-methyl-2-imidazolyl}, \text{4-}
chlorophenyl, 2-pyridylmethyl; \(\text{R}_{15}\) is \(\text{Cl-C6)alkyl}, \text{N-methyl-4-imidazolyl};\)
\(\text{R}_{16}\) is hydrogen, halo, arylalkyl, aryl,
or a group of the formula
wherein: $Q_2$ is hydrogen, 4-imidazolyl, or $\text{C}(0)NR_4R_5$ when $o$ and $p$ are independently 0-2; $Q_2$ is $\text{OR}_4R_5$, or $\text{N-morpholino}$, when $o$ and $p$ are independently 0-2, but one or the other of $o$ or $p$ is not 0; $R_{20}$ is hydrogen, or (Cl-C6)alkyl; $R_{21}$ is hydrogen, (Cl-C6)alkyl, or $R_2$, and $R_{20}$ can be taken together to form a 4, 5, 6, or 7 membered ring; $R_{22}$ is hydrogen, (Cl-C6)alkyl, arylalkyl, aryl, or $R_2$, and $R_{22}$ can be taken together to be a 3, 4, 5, 6, 7 membered ring; $R_{23}$ is hydrogen or (Cl-C6)alkyl; $R_{24}$ is hydrogen, (Cl-C6)alkyl, or $R_{24}$ and $R_{25}$ can be taken together to form a 3, 4, 5, 6, or 7 membered ring; or $R_{24}$ and $R_{25}$ can be taken together to form a 6 or 7 membered ring; $R_{25}$ is hydrogen, (Cl-C6)alkyl, or acetyl, or a group of the formula

\[
 \begin{array}{c}
 \text{o} \\
 \hline \\
 \text{CNR}_3R_4 \\
 \\text{R}_3R_4 \\
 \end{array}
\]

wherein: $R_{30}$ is hydrogen, or (Cl-C6)alkyl; $R_{31}$ is hydrogen, (Cl-C6)alkyl, 2-pyridyl, pyridylmethyl, amino, or hydroxy, or a group of the formula

\[
 \begin{array}{c}
 \text{—NR}_{32}R_{33} \\
 \end{array}
\]

wherein: $R_{32}$ and $R_{33}$ are each independently hydrogen, (Cl-C6)alkyl, acetyl, (Cl-C4)alkylsulphonyl, or $R_{32}$ and $R_{33}$ can be taken together to form a 4, 5, 6, or 7 membered ring, or a group of the formula
wherein: $X_i$ is $\text{CH}_2$, O, or N; $q_i$ is 2-3 except when $Q_i$ is a bond, $q_i$ is 0-3; $Q_i$ is $\text{NR}_3\text{R}_7$, or $\text{OR}_3\text{R}_8$, and $R_{35}$ is hydrogen, or $R_{35}$ and $Q_3$ can be taken together to form a 5 membered ring; $R_{36}$, $R_{37}$, and $R_{38}$ are each independently hydrogen, or (Cl-C6)alkyl, 
or a group of the formula

![Formula](image)

wherein: $X_3$ is cyano, carboxamide, $\text{N,N-dimethylcarboxamide}$, $\text{N,N-dimethylthiocarboxamide}$, $\text{N,N-dimethylaminomethyl}$, 4-methylpiperazinylmethyl or carboxylate, 
or a group of the formula

![Formula](image)

wherein: $Q_6$ is $\text{N}_1\text{R}_{41}\text{R}_{42}$; $r$ is 2-3; $R_{40}$ is hydrogen, or (Cl-C6)alkyl; $R_{41}$, and $R_{42}$ are hydrogen, (Cl-C6)alkyl, or $R_{41}$, and $R_{42}$ can be taken together to form a 6 or 7 membered ring, 
or a group of the formula

![Formula](image)

wherein: $Q_7$ is hydroxy, methoxy, dimethylamino, or N-piperidinyl;
with the proviso that when one of R1 or R2 is unsubstituted or substituted phenyl, then the other cannot be unsubstituted or substituted phenyl or thiophen-2-yl; and with the proviso that when R2 is quinolin-4-yl, substitution at the quinoline 7-position cannot include an aryl, heteroaryl, fused aryl, or fused heteroaryl;

k is 1-8; \(R_3\) is one or more of the following: hydrogen; \((\text{Cl-C}4)\text{alkyl}\); \((\text{Cl-C}4)\text{alkylhydroxy}\); hydroxy; \(\text{N,N-di(Cl-C}4)\text{alkylamino(Cl-C}4)\text{alkoxy}\); benzyl oxymethyl; phenyloxymethyl; oxo; carboxyl; \((\text{Cl-C}4)\text{alkylaryl}\); benzyloxy; acetoxy; amino\((\text{Cl-C}4)\text{alkyl}\); \((\text{C}2-\text{C}4)\text{alkenyl}\); halo; \(-\text{O}-\text{(Cl-C}4)\text{alkyl}\); chlorophenethyl; acetonitrile; unsubstituted or substituted phenyl; wherein the substitution may be one or more of the following: \((\text{Cl-C}6)\text{alkoxy}, \text{ halo, carboxy, or } (\text{Cl-C}6)\text{alkoxycarbonyl}\);

and the pharmaceutically acceptable salts, esters and prodrugs thereof.

US Patent 7,087,626 further discloses subgenuses of TGF-beta antagonists useful for treating cancer, of structural Formulas II, III and IV, as defined below.

Formula II
is a five or six membered saturated ring with the proviso that the ring is a fully saturated carbon ring;

R1 is defined as in Formula I;

R2' is hydrogen; (Cl-C6)alkyl; (Cl-C6)alkylthio; (Cl-C6)alkoxy; halo; thiophenyl; aminophenyl; N-pyrrolidino; N-morpholino;

R6' and R7' are independently one or more of the following: hydrogen, (Cl-C6)alkyl, (C2-C6)alkenyl, (C2-C6)alkynyl, (Cl-C6)alkylhalide, (Cl-C6)alkoxy, (C2-C6)alkenyloxy, (C2-C6)alkynoxy, (Cl-C6)alkylthio, (Cl-C6)alkylsulphinyl, (Cl-C6)alkylsulphonyl, (Cl-C6)alkylamino, di-[(Cl-C6)alkyl]amino, (Cl-C6)alkoxy carbonyl, N—(C 1-C6)alkyl carbamoyl, N,N-di-[(C 1-C6)alkyl]carbamoyl, aminooxy, N—(Cl-C6)alkyl aminooxy, N,N-di-[(Cl-C6)alkyl]aminooxy, (Cl-C6)alkanoyl, (C2-C6)alkanoyloxy, (C2-C6)alkanoylamino, N—(C 1-C6)alkyl-(C2-C6)alkanoyl amino, (C3-C6)alkanoyl amino, N—(Cl-C6)alkyl-(C3-C6)alkenoylamino, (C3-C6)alkynoylamino, N—(Cl-C6)alkyl-(C3-C6)alkynoylamino, sulphamoyl, N—(Cl-C6)alkylsulphamoyl, N,N-di-[(Cl-C6)alkyl] sulphamoyl, (Cl-C6)alkanesulphonylamino, N—(C 1-C6)alkyl-(C 1-C6)alkanesulphonylamino, carboxamide, ethylene, phenyl, aminophenyl, aminophenyl, phenylthio, halo, cyano, pyridinyl, arylalkyl, hydroxy, N-pyrrolidino, N-morpholino, carboxyl, [5-phenyl-1,2,4-oxadiazole-3-yl]methoxy, 6-methyl-pyridazin-3-yloxy, (5-oxo-2-pyrrolidinyl)methoxy, 2-(4,5-dihydro-lH-imidazolyl), N,N-dialkyl carbamoyloxy, 1-hydroxy-1-methylethyl, 4-fluorophenyl, 3,4-methylenedioxyphenyl, trifluoromethyl, trifluoromethoxy, or a group of the formula

\[
\begin{align*}
R_{10} & \\
X_1 & \quad (\text{CH}_2)_n \quad C(\text{CH}_2)_m Q_1 \\
R_{16} & 
\end{align*}
\]

wherein: \(X_1\) is O, N, S, S0 \(\_2\), NR \(\_3\), C(O), or bond, \(Q_1\) is hydrogen, phenyl, 5-(2,2-difluoro-1,3-benzodioxoyl), C(O)Q \(\_5\), or pyridyl when \(m\) and \(n\) are independently 0-2,
except when one is 0 the other cannot be 0; $Q_i$ is $\text{OR}_{11}^1, \text{NR}_{11}^1, \text{R}_{12}^1$, halo, N-morpholino, N-piperazino-N'R$_{13}^1$, N-imidazolyl, N-pyrazolyl, N-triazolyl, N-(4-piperidinyl)piperidine), S0$_2$R$_{14}^2$, SOR$_{14}^2$, NHSOF$_2$R$_{15}^2$, acetamido, N-phthalimido, N-oxazolidino, N-imidazolino, N-benzoxazolidino, N-pyridinonyl, N(4-methylbenzimidazolino), N,N-di(4-C4)alkylamino(4-C4)alkoxy, N-benzimidazolino; when m and n are independently 0-2, but one or the other of m or n is not 0; $Q_5$ is hydroxy, methoxy, amino, diethylamino, dimethylamino; $R_{10}$ is hydrogen, halo, (Cl-C6)alkyl; $R_{11}$ and $R_{12}$ are independently hydrogen, (Cl-C6)alkyl, (Cl-C6)alkoxy, arylalkyl, cycloalkyl, cycloalkylmethyl, 4-(N-methylpiperidinyl), pyridyl, or $R_{11}$ and $R_{12}$ can be taken together to form a 4, 5, 6, or 7 membered ring, or $R_{11}$ and $R_{12}$ can be taken together to form a 3, 4, 5, 6, or 7 membered ring; $R_{13}$ is hydrogen, (Cl-C6)alkyl, 2-methoxyphenyl; $R_{14}$ is 2-pyrimidinyl, N-methyl-2-imidazolyl, 4-chlorophenyl, 2-pyridylmethyl; $R_{15}$ is (C$_j$-C6)alkyl, N-methyl-4-imidazolyl; $R_{16}$ is hydrogen, halo, arylalkyl, aryl, or a group of the formula

$$\begin{align*}
\text{O} & \quad \text{R}_{21} \\
\text{CN} & \left(\text{CH}_2\right)_k \text{C} & \left(\text{CH}_2\right)_k \text{Q}_2 \\
\text{R}_{20} & \quad \text{R}_{22}
\end{align*}$$

wherein: $Q_2$ is hydrogen, 4-imidazolyl, or C(0)NR$_{24}^1$R$_{25}^1$ when o and p are independently 0-2; $Q_2$ is $\text{OR}_{23}^1, \text{NR}_{24}^1, \text{R}_{25}^1$, or N-morpholino, when o and p are independently 0-2, but one or the other of o or p is not 0; $R_{20}$ is hydrogen, or (Cl-C6)alkyl; $R_{21}$ is hydrogen, (Cl-C6)alkyl, or $R_{21}$ and $R_{20}$ can be taken together to form a 4, 5, 6, or 7 membered ring; $R_{22}$ is hydrogen, (Cl-C6)alkyl, arylalkyl, aryl, or $R_{21}$ and $R_{22}$ can be taken together to be a 3, 4, 5, 6, 7 membered ring; $R_{23}$ is hydrogen or (Cl-C6)alkyl; $R_{24}$ is hydrogen, (Cl-C6)alkyl, or $R_{24}$ and $R_{25}$ can be taken together
to form a 3, 4, 5, 6, or 7 membered ring, or \( R_{24} \) and \( R_{20} \) can be taken together to form a 6 or 7 membered ring; \( R_{25} \) is hydrogen, (Cl-C6)alkyl, or acetyl, or a group of the formula

\[
\text{O} \\
\text{CN} \ R_{31} \\
\text{R}_{30}
\]

wherein: \( R_{30} \) is hydrogen, or (Cl-C6)alkyl; \( R_{31} \) is hydrogen, (Cl-C6)alkyl, 2-pyridyl, pyridylmethyl, amino, or hydroxy, or a group of the formula

\[
-\text{NR}_{32} \ R_{33}
\]

wherein: \( R_{32} \) and \( R_{33} \) are each independently hydrogen, (Cl-C6)alkyl, acetyl, alkylsulphonyl, or \( R_{32} \) and \( R_{33} \) can be taken together to form a 4, 5, 6, or 7 membered ring, or a group of the formula

\[
\text{O} \\
\text{NCX}_{2}(\text{CH}_{2})_{q} \ Q_{3} \\
\text{R}_{35}
\]

wherein: \( X_{2} \) is CH\(_{2}\), O, or N; \( q \) is 2-3 except when \( Q_{3} \) is a bond, \( q \) is 0-3; \( Q_{3} \) is \( \text{NR}_{36} \ R_{37}, \text{OR}_{38}, \) or a bond; \( R_{35} \) is hydrogen, or \( R_{35} \) and \( Q_{3} \) (when \( Q_{3} \) is a bond) can be taken together to form a 5 membered ring; \( R_{36}, R_{37}, \) and \( R_{38} \) are each independently hydrogen, or (Cl-C6)alkyl, or a group of the formula
wherein: $X_i$ is cyano, carboxamide, $N,N$-dimethylcarboxamide, $N,N$-dimethylthiocarboxamide, $N,N$-dimethylaminomethyl, 4-methylpiperazin-yl-methyl or carboxylate,
or a group of the formula

$$
\begin{align*}
\text{O} & \quad \text{CN(CH}_2)_kQ_6 \\
\text{I} & \quad \text{R}_{40}
\end{align*}
$$

wherein: $Q_6$ is $NR_4R_{42}; r$ is 2-3; $R_{40}$ is hydrogen, or (Cl-C6)alkyl; $R_4$ and $R_{42}$ are hydrogen, (Cl-C6)alkyl, or $R_4$ and $R_{40}$ can be taken together to form a 6 or 7 membered ring,
or a group of the formula

$$
\begin{align*}
\text{O} & \quad \text{CQ}_7
\end{align*}
$$

wherein: $Q_7$ is hydroxy, methoxy, or N-piperidinyl;

$k$ is 1-8;

$R_3$ is one or more of the following: hydrogen; (Cl-C4)alkyl; (C1-C4) alkylhydroxy; hydroxy; N,N-di(Cl-C4)alkylamino(Cl-C4)alkoxy; benzyl oxymethyl; phenyloxymethyl; oxo; carboxyl; (Cl-C4)alkylaryl; benzyloxy; acetoxy; amino(Cl-C4)alkyl; (C2-C4)alkenyl; halo; —O—(Cl-C4)alkyl; chlorophenethyl; acetonitrile; phenyl; or an optionally substituted phenyl; wherein the substitution may be one or more of the following: (Cl-C6)alkoxy, halo, carboxy, or (Cl-C6)alkoxycarbonyl;

with the proviso that $R_7'$ cannot be aryl; heteroaryl; fused aryl; or fused heteroaryl,

and the pharmaceutically acceptable salts, esters and prodrugs thereof.
Formula III

wherein

\[(R_3)_k\]

is a five or six-membered saturated ring, with the proviso that the ring is a fully saturated carbon ring;

R1 is defined as in Formula I;

R3" is hydrogen, halo, trifluoromethyl;

R4" is hydrogen, halo, (C1-C6)alkyl, (C1-C6)alkoxy, hydroxy, (C1-C6)alkylsulphonyl;

k and R3 are defined as in Formula I;

and the pharmaceutically acceptable salts, esters and prodrugs thereof.

Formula IV

wherein

\[(R_3)_k\]
is a five or six membered saturated ring, with the proviso that the ring is a fully
saturated carbon ring;
R6 may be one or more of the following: hydrogen, (Cl-C6)alkyl, (C2-C6)alkenyl,
(C2-C6)alkynyl, (Cl-C6)alkoxy, (C2-C6)alkenlyoxy, (C2-C6)alkynlyoxy, (Cl-
C6)alkylthio, (Cl-C6)alkylsulphinyl, (Cl-C6)alkylsulphonyl, (Cl-C6)alkylamino, di-
[(Cl-C6)alkyl]amino, (Cl-C6)alkoxycarbonyl, N—(C1-C6)alkylcarbamoyl, N,N-di-
[(Cl-C6)alkyl]carbamoyl, (C2-C6)alkanoyl, (C2-C6)alkanoyloxy, (C2-
C6)alkanoylamino, N—(C1-C6)alkyl-(C2-C6)alkanoylamino, (C3-C6)alkenylamino,
N—(C1-C6)alkyl-(C3-C6)alkenylamino, (C3-C6)alkynylamino, N—(C1-C6)alkyl-
(C3-C6)alkynylamino, N—(Cl-C6)alkyl sulphamoyl, N,N-di-[(Cl-
C6)alkyl]sulphamoyl, (C1-C6)alkanesulphonylamino, N—(C1-C6)alkyl-(C1-
C6)alkanesulphonylamino, carboxamide, ethylene, thiophenyl, aminophenyl,
trifluoromethyl, halo, trifluoromethoxy, hydroxymethyl, N-pyrrolidino, N-morpholino,
phenylthio, dialkylaminomethyl, methoxyphenyl, amino, hydroxy, carboxyl, phenyl,
arylalky;
R2" is unsubstituted or substituted quinoline-8-yl; unsubstituted or substituted
quinoline-6-yl; unsubstituted or substituted 1-naphthyl; unsubstituted or substituted 2-
naphthyl; unsubstituted or substituted 3,4-methylenedioxyphenyl; unsubstituted or
substituted 3,4-ethylenedioxyphenyl; unsubstituted or substituted benzothiophen-2-yl;
wherein the substitution may independently be one or more of the following:
(C1-C6)alkyl, (C2-C6)alkenyl, (C2-C6)alkynyl, (Cl-C6)alkylhalide, (Cl-
C6)alkoxy, (C2-C6)alkenlyoxy, (C2-C6)alkynlyoxy, (Cl-C6)alkylthio, (Cl-
C6)alkylsulphinyl, (Cl-C6)alkylsulphonyl, (Cl-C6)alkylamino, di-[(Cl-
C6)alkyl]amino, (Cl-C6)alkoxycarbonyl, N—(Cl-C6)alkylcarbamoyl, N,N-di-
[(Cl-C6)alkyl]carbamoyl, aminoxy, N—(Cl-C6)alkyl aminoxy, N,N-di-
[(Cl-C6)alkyl]aminoxy, (C2-C6)alkanoyl, (C2-C6)alkanoyloxy, (C2-
C6)alkanoylamino, N—(Cl-C6)alkyl-(C2-C6)alkanoylamino, (C3-
C6)alkenylamino, N—(Cl-C6)alkyl-(C3-C6)alkenylamino, (C3-
C6)alkynylamino, N—(Cl-C6)alkyl-(C3-C6)alkynylamino, sulphamoyl, N—
(Cl-C6)alkylsulphamoyl, N,N-di-[(Cl-C6)alkyl] sulphamoyl, (Cl-
C6)alkanesulphonylamino, N—(C1-C6)alkyl-(C1-C6)alkanesulphonylamino,
carboxamide, ethylene, phenyl, thiophenyl, aminophenyl, phenylthio, halo, cyano, pyridinyl, aarylalkyl, hydroxy, N-pyrrolidino, N-morpholino, carboxyl,
[5-phenyl-1,2,4-oxadiazole-3-yl]methoxy, 6-methyl-pyridazin-3-yloxy, (5-oxo-2-pyrolidinyl) methoxy, 2-(4,5-dihydro-1H-imidazolyl), N,N-dialkylcarbamoyloxy, 1-hydroxy-1-methylethyl, 4-fluorophenyl, 3,4-methylenedioxyphenyl, trifluoromethyl, trifluoromethoxy, or a group of the formula

\[
\begin{array}{c}
\text{R}_{10} \\
\text{X}_1 (\text{CH}_2)_\text{i} \text{C(\text{CH}_2)_\text{m}Q_1} \\
\text{R}_{16}
\end{array}
\]

wherein: \(X_1\) is O, N, S, S\(\text{O}_2\), N(R)\(_{13}\), C(O), or bond; \(Q_1\) is hydrogen, phenyl, 5-(2,2-difluoro-1,3-benzodioxolyl), C(0)\(Q_5\), or pyridyl when \(m\) and \(n\) are independently 0-2, except when one is 0 the other cannot be 0; \(Q_1\) is OR\(_{11}\), NR\(_{11}\)\(_{12}\), halo, N-morpholino, N-piperazino-N'R\(_{13}\), N-imidazolyl, N-pyrrozolyl, N-triazolyl, N-(4-piperidinylpiperidine), S\(\text{O}_2\)\(_{14}\), SOR\(_{14}\), NHSO\(_{2}\)\(_{15}\), acetamido, N-phthalimido, N-oxazolidino, N-imidazolino, N-benzoazolidino, N-pyrididinonyl, N(N'-methylbenzimidazolino), N,N-di(Cl-C4)alkylamino(Cl-C4)alkoxy, N-benzimidazolino; when \(m\) and \(n\) are independently 0-2, but one or the other of \(m\) or \(n\) is not 0; \(Q_3\) is hydroxy, methoxy, amino, diethylamino, dimethylamino; \(R_{10}\) is hydrogen, halo, (C\(_j\)-C6)alkyl; \(R_{11}\) and \(R_{12}\) are independently hydrogen, (Cl-C6)alkyl, (Cl-C6)alkoxy, arylalkyl, cycloalkyl, cycloalkylmethyl, 4-N-methylpiperidinyl), pyridyl, or \(R_{11}\) and \(R_{10}\) can be taken together to form a 4, 5, 6, or 7 membered ring, or \(R_{11}\) and \(R_{12}\) can be taken together to form a 3, 4, 5, 6, or 7 membered ring; \(R_{13}\) is hydrogen, (Cl-C6)alkyl, 2-methoxyphenyl; \(R_{14}\) is 2-pyrimidinyl, N-methyl-2-imidazolyl, 4-chlorophenyl, 2-pyridylmethyl; \(R_{15}\) is (Cl-C6)alkyl, N-methyl-4-imidazolyl; \(R_{16}\) is hydrogen, halo, arylalkyl, aryl, or a group of the formula
wherein: $Q_2$ is hydrogen, 4-imidazolyl, or C(0)NR$_{24}$R$_{25}$ when $o$ and $p$ are independently 0-2; $Q_2$ is OR$_{23}$NR$_{24}$R$_{25}$, or N-morpholino, when $o$ and $p$ are independently 0-2, but one or the other of $o$ or $p$ is not 0; R$_{20}$ is hydrogen, or (Cl-C6)alkyl; R$_{21}$ is hydrogen, (Cl-C6)alkyl, or R$_{21}$ and R$_{20}$ can be taken together to form a 4, 5, 6, or 7 membered ring; R$_{22}$ is hydrogen, (Cl-C6)alkyl, arylalkyl, aryl, or R$_{21}$ and R$_{22}$ can be taken together to be a 3, 4, 5, 6, 7 membered ring; R$_{23}$ is hydrogen or (C$_1$-C6)alkyl; R$_{24}$ is hydrogen, (Cl-C6)alkyl, or R$_{24}$ and R$_{25}$ can be taken together to form a 3, 4, 5, 6, or 7 membered ring, or R$_{24}$ and R$_{20}$ can be taken together to form a 6 or 7 membered ring; R$_{25}$ is hydrogen, (Cl-C6)alkyl, or acetyl, or a group of the formula

$$\begin{array}{c}
O \\
\hline
\hline
\hline
\hline
CNR_{31} \\
\hline
R_{30}
\end{array}$$

wherein: R$_{30}$ is hydrogen, or (Cl-C6)alkyl; R$_{31}$ is hydrogen, (Cl-C6)alkyl, 2-pyridyl, pyridylmethyl, amino, or hydroxy, or a group of the formula

$$-NR_{32}R_{33}$$

wherein: R$_{32}$ and R$_{33}$ are each independently hydrogen, (Cl-C6)alkyl, acetyl, alkysulphonyl, or R$_{32}$ and R$_{33}$ can be taken together to form a 4, 5, 6, or 7 membered ring, or a group of the formula
wherein: $X_i$ is $\text{CH}_2$, O, or N; $q$ is 2-3 except when $Q_i$ is a bond, $q$ is 0-3; $Q_i$ is $\text{NR}_{36}R_{37}$, $\text{OR}_{38}$, or a bond; $R_{35}$ is hydrogen, or $R_{35}$ and $Q_3$ (when $Q_3$ is a bond) can be taken together to form a 5 membered ring; $R_{36}$, $R_{37}$, and $R_{38}$ are each independently hydrogen, or (Cl-C6)alkyl, or a group of the formula

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wherein: $X_3$ is cyano, carboxamide, $\text{N},\text{N}$-dimethylcarboxamide, $\text{N},\text{N}$-dimethylthiocarboxamide, $\text{N},\text{N}$-dimethylaminomethyl, 4-methylpiperazine-1ylmethyl or carboxylate, or a group of the formula

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wherein: $Q_6$ is $\text{NR}_{41}R_{42}$; $r$ is 2-3; $R_{40}$ is hydrogen, or (Cl-C6)alkyl; $R_{41}$ and $R_{42}$ are hydrogen, (Cl-C6)alkyl, or $R_{41}$ and $R_{40}$ can be taken together to form a 6 or 7 membered ring, or a group of the formula

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wherein: \( Q_i \) is hydroxy, methoxy, dimethylamino, or N-piperidinyl;

\( k \) is 1-8;

\( R_3 \) is hydrogen;

and the pharmaceutically acceptable salts, esters and prodrugs thereof.

The disclosure of such compounds and methods for making such compounds as described in US Patent 7,087,626 is incorporated by reference herein in its entirety. US Patent 7,087,626 further discloses pharmaceutically acceptable salts, such as acid addition salts, solvates, hydrates and esters of such compounds, as well as pharmaceutical compositions of such compounds.

**Preclinical data**

LY-2157299 possessed good activity and selectivity over p38 MAP kinase, with IC50 values of 0.047, 0.022, 0.105 and 4.3 microM against TGF-beta kinase domain, p3TP lux, NIH3T3 cell proliferation and p38 MAP kinase, respectively.

HUVEC cells were cultured in the presence or absence of TGFalpha, VEGF or bFGF, with varying concentrations of LY-2157299; TGFalpha signaling was found to be inhibited and TGFalpha exposed HUVEC cells proliferated. LY-2157299 was also found to stimulate VEGF or bFGF HUVEC migration. In an in vitro angiogenesis co-culture model, in which HUVEC cells form cord structures on dermal fibroblast feeder layers, TGFalpha inhibited cord formation in a dose-dependent fashion. LY-2157299 potentiated angiogenesis. The compound was also tested in vivo against a variety of cancer models, including the 3T1 breast cancer syngeneic model and the U87MG and A549 xenograft models. In all models, the tumor-bearing mice received LY-2157299 (75 mg/kg po bid) for 3 or 5 days. LY-2157299 increased the vessel density in all tumor models and also inhibited tumor growth and prolonged survival in the syngeneic 4T1 breast cancer model.

**Clinical data**

A phase I trial in the US and Europe was initiated by Eli Lilly in January 2006 in 49 patients with cancers of the breast, prostate and kidney, lymphoma and myeloma. Primary endpoints would be safety and tolerability, with pharmacokinetic and pharmacodynamic parameters as secondary endpoints. In December 2006, Lilly reported that the drug was still in phase I development. At that
time, the drug was being evaluated as a monotherapy and a combination therapy in patients with brain, prostate, breast and lung cancers.

**Summary**

According to the present invention, schizophrenia and/or symptoms of schizophrenia and/or positive symptoms of schizophrenia in mammals is treated by the administration of a therapeutically effective amount of a TGF-beta antagonist of Formulas I, II, III or IV or a pharmaceutically acceptable salt, ester or prodrug thereof.

Compounds of Formulas I, II, III and IV may be made using synthetic methods known in the art. Methods of making such compounds are described in US Patent 7,087,626, which description is incorporated by reference herein in its entirety.

An embodiment of the invention is a composition for the treatment of schizophrenia and/or symptoms of schizophrenia and/or positive symptoms of schizophrenia comprising at least one compound of Formulas I, II, III or IV or a salt, ester, hydrate, solvate, prodrug or polymorph thereof, incorporated in a pharmaceutically acceptable adjuvant, excipient, diluent or carrier composition.

An embodiment of the invention is a method of treating schizophrenia and/or symptoms of schizophrenia and/or positive symptoms of schizophrenia in a mammal in need of such treatment comprising administering a therapeutically effective amount of a compound selected from the group consisting of 4-[2-(6-Methyl-pyridin-2-yl)-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl]phenol, 4-[2-(6-Methyl-pyridin-2-yl)-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl]-quinoline-6-carboxylic acid amide and pharmaceutically acceptable salts, hydrates, solvates, prodrugs, and polymorphs thereof.

Another embodiment of the invention comprises compositions used for treating schizophrenia and/or symptoms of schizophrenia and/or positive symptoms of schizophrenia comprising at least one compound selected from the group consisting of 4-[2-(6-Methyl-pyridin-2-yl)-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl]phenol, 4-[2-(6-Methyl-pyridin-2-yl)-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl]-quinoline-6-carboxylic acid amide and salts, esters, hydrates, solvates, prodrugs, and polymorphs thereof, incorporated in a pharmaceutically acceptable adjuvant, excipient, diluent, or carrier composition.
Description of the Figures

Figure 1 shows the reversal of PCP-induced pre-pulse-inhibition deficit in a rat model of schizophrenia by 100 mg/kg of 4-[2-(6-Methyl-pyridin-2-yl)-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl]phenol (labeled as "Test Compound"), with a pre-pulse inhibition tone of 81 dB.

Figure 2 shows the reversal of PCP-induced pre-pulse-inhibition deficit in a rat model of schizophrenia by 20 mg/kg of 4-[2-(6-Methyl-pyridin-2-yl)-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl]-quinoline-6-carboxylic acid amide (labeled as "LY-2157299"), with a pre-pulse inhibition tone of 69 dB.

Figure 3 shows the reversal of PCP-induced pre-pulse-inhibition deficit in a rat model of schizophrenia by 20 mg/kg of 4-[2-(6-Methyl-pyridin-2-yl)-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl]-quinoline-6-carboxylic acid amide (labeled as "LY-2157299"), with a pre-pulse inhibition tone of 73 dB.

Detailed Description

Embodiments of the invention provide methods for treating schizophrenia and/or symptoms of schizophrenia with compounds of Formula I, Formula II, Formula III or Formula IV. Symptoms of schizophrenia are well-documented by the literature and diagnostic authorities on schizophrenia and include delusions; hallucinations; movement and thought disorders, such as disorganized speech and/or grossly disorganized or catatonic behavior; social disturbances; flat affect; deficits in expressing emotion and experiencing pleasure such as alogia and/or avolition; disorganized thinking, slow thinking; difficulty understanding; poor concentration; poor memory; difficulty expressing thoughts; and difficulty integrating thoughts, feelings and behavior.

Embodiments of the invention also provide methods for treating positive symptoms of schizophrenia in other psychotic diseases, for example, bipolar disorder, delusional disorder, psychotic depression, Tourette syndrome, autism spectrum disorder, OCD, dementia and Alzheimer's disease, with one or more compounds of Formula I, Formula II, Formula III or Formula IV and pharmaceutically acceptable salts, esters and prodrugs thereof.

Embodiments of the invention provide methods for treating schizophrenia and/or symptoms of schizophrenia and/or positive symptoms of schizophrenia in other psychotic diseases, by
administering to a subject in need of such treatment a therapeutically effective amount of a compound that modulates TGF-beta activity or expression. A particular embodiment of the invention provides a method of treating schizophrenia and/or symptoms of schizophrenia and/or positive symptoms of schizophrenia in other psychotic diseases by administering to a mammal in need of such treatment a therapeutically effective amount of a TGF-beta antagonist.

According to embodiments of the invention, a therapeutically effective amount of a compound of Formula I, Formula II, Formula III or Formula IV that modulates TGF-beta activity or expression is administered to a subject to treat schizophrenia and/or symptoms of schizophrenia and/or positive symptoms of schizophrenia in other psychotic diseases. A compound useful in carrying out therapeutic method embodiments of the invention is advantageously formulated in a pharmaceutical composition in combination with a pharmaceutically acceptable carrier. The amount of compound in the pharmaceutical composition depends on the desired dosage and route of administration. In one embodiment, suitable dose ranges of the active ingredient are from about 0.01 mg/kg to about 1500 mg/kg of body weight taken at necessary intervals (e.g., daily, every 12 hours, etc.), although it will, of course, readily be understood that the amount of the compound actually to be administered will be determined by a physician, in the light of all the relevant circumstances including the condition to be treated, the choice of compound to be administered and the choice of route of administration. In another embodiment, a suitable dosage range of the active ingredient is from about 0.2 mg/kg to about 150 mg/kg of body weight taken at necessary intervals. In another embodiment, a suitable dosage range of the active ingredient is from about 3 mg/kg to about 15 mg/kg of body weight taken at necessary intervals.

In one embodiment, the dosage and administration are such that TGF-beta activity or expression is only partially modulated so as to avoid any unacceptably deleterious effects.

The compositions of the present invention are therapeutically effective amounts of the TGF-β antagonists noted above. The composition may be formulated with common excipients, diluents or carriers, and compressed into tablets, or formulated elixirs or solutions for convenient oral administration or administered by intramuscular or intravenous routes. The compounds can be administered transdermally.

The method of treating a human patient according to the present invention includes
administration of the TGF-β antagonists of Formula I. The TGF-β antagonists of Formula I are formulated into formulations which may be administered by the oral and rectal routes, topically, parenterally, e.g., by injection, by subcutaneous depot and by continuous or discontinuous intra-arterial infusion, in the form of, for example, tablets, lozenges, sublingual tablets, sachets, cachets, elixirs, gels, suspensions, aerosols, ointments, for example, containing from 1 to 10% by weight of the active compound in a suitable base, soft and hard gelatin capsules, suppositories, injectable solutions and suspensions in physiologically acceptable media, and sterile packaged powders adsorbed onto a support material for making injectable solutions. Advantageously for this purpose, compositions of Formula I may be provided in dosage unit form, preferably each dosage unit containing from about 5 to about 1000 mg (from about 5 to 100 mg in the case of parenteral or inhalation administration, and from about 25 to 1000 mg in the case of oral or rectal administration) the compounds.

The method of treating a human patient according to the present invention includes administration of the TGF-β antagonists of Formula II. The TGF-β antagonists of Formula II are formulated into formulations which may be administered by the oral and rectal routes, topically, parenterally, e.g., by injection, by subcutaneous depot and by continuous or discontinuous intra-arterial infusion, in the form of, for example, tablets, lozenges, sublingual tablets, sachets, cachets, elixirs, gels, suspensions, aerosols, ointments, for example, containing from 1 to 10% by weight of the active compound in a suitable base, soft and hard gelatin capsules, suppositories, injectable solutions and suspensions in physiologically acceptable media, and sterile packaged powders adsorbed onto a support material for making injectable solutions. Advantageously for this purpose, compositions of Formula II may be provided in dosage unit form, preferably each dosage unit containing from about 5 to about 1000 mg (from about 5 to 100 mg in the case of parenteral or inhalation administration, and from about 25 to 1000 mg in the case of oral or rectal administration) the compounds.

The method of treating a human patient according to the present invention includes administration of the TGF-β antagonists of Formula III. The TGF-β antagonists of Formula III are formulated into formulations which may be administered by the oral and rectal routes, topically, parenterally, e.g., by injection, by subcutaneous depot and by continuous or discontinuous intra-arterial infusion, in the form of, for example, tablets, lozenges, sublingual tablets, sachets, cachets, elixirs, gels, suspensions, aerosols, ointments, for example, containing from 1 to 10% by weight of
the active compound in a suitable base, soft and hard gelatin capsules, suppositories, injectable solutions and suspensions in physiologically acceptable media, and sterile packaged powders adsorbed onto a support material for making injectable solutions. Advantageously for this purpose, compositions of Formula III may be provided in dosage unit form, preferably each dosage unit containing from about 5 to about 1000 mg (from about 5 to 100 mg in the case of parenteral or inhalation administration, and from about 25 to 1000 mg in the case of oral or rectal administration) the compounds.

The method of treating a human patient according to the present invention includes administration of the TGF-β antagonists of Formula IV. The TGF-β antagonists of Formula IV are formulated into formulations which may be administered by the oral and rectal routes, topically, parenterally, e.g., by injection, by subcutaneous depot and by continuous or discontinuous intra-arterial infusion, in the form of, for example, tablets, lozenges, sublingual tablets, sachets, cachets, elixirs, gels, suspensions, aerosols, ointments, for example, containing from 1 to 10% by weight of the active compound in a suitable base, soft and hard gelatin capsules, suppositories, injectable solutions and suspensions in physiologically acceptable media, and sterile packaged powders adsorbed onto a support material for making injectable solutions. Advantageously for this purpose, compositions of Formula IV may be provided in dosage unit form, preferably each dosage unit containing from about 5 to about 1000 mg (from about 5 to 100 mg in the case of parenteral or inhalation administration, and from about 25 to 1000 mg in the case of oral or rectal administration) the compounds.

The formulations useful for separate administration of the TGF-β antagonists will normally consist of at least one compound selected from the compounds specified herein mixed with a carrier, or diluted by a carrier, or enclosed or encapsulated by an ingestible carrier in the form of a capsule, sachet, cachet, paper or other container or by a disposable container such as an ampoule. A carrier or diluent may be a solid, semi-solid or liquid material which serves as a vehicle, excipient or medium for the active therapeutic substance. Some examples of the diluents or carrier which may be employed in the pharmaceutical compositions of the present invention are lactose, dextrose, sucrose, sorbitol, mannitol, propylene glycol, liquid paraffin, white soft paraffin, kaolin, fumed silicon dioxide, microcrystalline cellulose, calcium silicate, silica, polyvinylpyrrolidone, cetostearyl alcohol, starch, modified starches, gum acacia, calcium phosphate, cocoa butter, ethoxylated esters, oil of theobroma, arachis oil, alginates, tragacanth, gelatin, syrup, methyl cellulose, polyoxyethylene
sorbitan monolaurate, ethyl lactate, methyl and propyl hydroxybenzoate, sorbitan trioleate, sorbitan sesquioleate and oleyl alcohol and propellants such as trichloromonofluoromethane, dichlorodifluoromethane and dichlorotetrafluoroethane. In the case of tablets, a lubricant may be incorporated to prevent sticking and binding of the powdered ingredients in the dies and on the punch of the tableting machine. For such purpose there may be employed for instance aluminum, magnesium or calcium stearates, talc or mineral oil.

Pharmaceutical forms of the present invention include capsules, tablets, suppositories, injectable solutions, creams and ointments. Additional forms are formulations for inhalation application, such as an aerosol, for injection, and for oral ingestion.

In another embodiment, the therapeutic agent is delivered in a controlled release manner. For example, a therapeutic agent can be administered using intravenous infusion with a continuous pump, or in a polymer matrix such as poly-lactic/glutamic acid (PLGA), or in a pellet containing a mixture of cholesterol and the active ingredient, or by subcutaneous implantation, or by transdermal patch.

Embodiments of the invention provide methods for treating schizophrenia and/or symptoms of schizophrenia and/or positive symptoms of schizophrenia in other psychotic diseases in a subject in need of such treatment by antagonizing TGF-beta by administering a therapeutically effective amount of at least one compound selected from the group consisting of:

a) 6-Bromo-4-(2-pyridin-2-yl)-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl)-quinoline,
b) 3-Pyridin-4-yl-2-pyridin-2-yl-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazole,
c) 2-(6-Methyl-pyridin-2-yl)-3-p-tolyl-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazole,
d) 4-[3-(6-Methyl-pyridin-2-yl)-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-2-yl]-quinoline,
e) 2-(6-Methyl-pyridin-2-yl)-3-naphthalen-1-yl-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazole,
f) 2-(6-Methyl-pyridin-2-yl)-3-pyridin-3-yl-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazole,
g) 3-(4-Fluoro-naphthalen-l-yl)-2-(6-methyl-pyridin-2-yl)-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazole,
h) 3-(3,4-Difluoro-phenyl)-2-(6-methyl-pyridin-2-yl)-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazole,
i) 1-[2-(4-Methanesulfonyl-phenyl)- 1-(6-methyl-pyridin-2-yl)-ethyldeneamino]-pyrrolidin-2-one,
j) 7-Methoxy-4-(2-pyridin-2-yl)-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl)-quinoline,
k) 7-Benzylxoy-6-methoxy-4-(2-pyridin-2-yl)-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl)-quinoline,
li) 6-(2-Pyridin-2-yl)-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl)-quinoline,
m) 6-[2-(6-Methyl-pyridin-2-yl)-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl]-quinoline,
n) 3-Naphthalen-2-yl-2-pyridin-2-yl-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazole,
o) 2-(6-Methyl-pyridin-2-yl)-3-naphthalen-2-yl-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazole,
p) 3-(4-Fluoro-phenyl)-2-(6-trifluoromethylpyridin-2-yl)-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazole,
q) 4-(Quinolin-4-yl)-3-(5-fluoropyridin-2-yl)-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazole,
r) 4-(7-Bromoquinolin-4-yl)-3-(pyridin-2-yl)-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazole,
s) (Quinolin-4-yl)-3-(2,4-difluorophenyl)-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazole,
t) 4-(2-Pyrazin-2-yl)-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl]-quinoline,
u) 4-(5-Methyl-2-pyridin-2-yl)-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl]-quinoline,
v) 6-Bromo-4-[2-(6-methyl-pyridin-2-yl)-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl]-quinoline,
w) 4-[2-(6-Methyl-pyridin-2-yl)5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl]-6-trifluoromethylquinoline,
x) 3-(3-Chloro-4-fluoro-phenyl)-2-(6-methyl-pyridin-2-yl)-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazole,
y) 3-(2-Chloro-4-fluoro-phenyl)-2-(6-methyl-pyridin-2-yl)-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazole,
z) 3-(4-Fluoro-3-trifluoromethyl-phenyl)-2-(6-methyl-pyridin-2-yl)-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazole,
aa) 2-(6-Methyl-pyridin-2-yl)-3-(2,4,5-trifluorophenyl)-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazole,
bb) 8-Fluoro-4-[2-(6-methyl-pyridin-2-yl)-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl]-quinoline,
cc) 7-Bromo-4-[2-(6-methyl-pyridin-2-yl)-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl]-quinoline,
dd) 4-[2-(6-Methyl-pyridin-2-yl)-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl]-6-trifluoromethoxyquinoline,
ee) 4-[2-(6-Methyl-pyridin-2-yl)-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl]-7-trifluoromethylquinoline,
ff) 7-Methoxy-4-[2-(6-methyl-pyridin-2-yl)-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl]-quinoline,
gg) 3-(2-Chloro-pyridin-4-yl)-2-pyridin-2-yl-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazole,
hh) [2-(6-Methyl-pyridin-2-yl)-3-quinolin-4-yl]-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-6-yl]-methanol,
ii) [3-(7-Bromo-quinolin-4-yl)-2-(6-methyl-pyridin-2-yl)-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-6-yl]-methanol,
jj) 4-[2-(6-Chloro-pyridin-2-yl)-5-(4-fluorophenyl)-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl]-quinoline,
kk) 4-[2-(6-Ethoxy-pyridin-2-yl)-5-(4-fluorophenyl)-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl]-quinoline,
11) (S)-4-[6-Benzylxoxymethyl-2-(6-methyl-pyridin-2-yl)-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl]-7-chloro-quinoline,
mm) (S)-4-[6-Benzylxoxymethyl-2-(6-chloro-pyridin-2-yl)-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-1-3-yl]-quinoline,
nn) 4-[2-(6-Methyl-pyridin-2-yl)-3-quinolin-4-yl-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-5-yi ]-benzoic acid ethyl ester,
oo) 3-(4-Fluoro-phenyl)-5,5-dimethyl-2-(6-methyl-pyridin-2-yl)-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazole,
pp) (R)-6-Benzylxoxymethyl-3-(4-fluoro-phenyl)-2-(6-methyl-pyridin-2-yl)-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazole,
qq) 5-(4-Chloro-phenyl)-3-(4-fluoro-phenyl)-2-(6-methyl-pyridin-2-yl)-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazole,
rr) 4-[2-(3-Trifluoromethyl-phenyl)-4,5,6,7-tetrahydro-pyrazolo[1,5-a]pyridin-3-yl]-quinolinm^ ,
s) 4-[2-(4-Trifluoromethyl-phenyl)4,5,6,7-tetrahydro-pyrazolo[1,5-a]pyridin-3-yl]-quinoline,
tt) 4-[2-(4-Chloro-phenyl)-4,5,6,7-tetrahydro-pyrazolo[1,5-a]pyridin-3-yl]-quinoline,
uu) 4-[2-(3-Chloro-phenyl)-4,5,6,7-tetrahydro-pyrazolo[1,5-a]pyridin-3-y]-quinoline,
w ) 4-[2-(3-Fluoro-5-trifluoromethyl-phenyl)-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl]-quinolinm^ ,
ww) 4-[2-(3-Fluoro-5-trifluoromethyl-phenyl)-4,5,6,7-tetrahydro-pyrazolo[1,5-a]pyridin-3-yl]-quinoline,
xx) 4-(2-Phenyl-4,5,6,7-tetrahydro-pyrazolo[1,5-a]pyridin-3-yl]-quinoline,
yy) 4-(2-Pyridin-2-yl-4,5,6,7-tetrahydro-pyrazolo[1,5-a]pyridin-3-yl)-[1,10]phenanthroline,
zz) 4-[2-(4-Fluoro-phenyl)-4,5,6,7-tetrahydro-pyrazolo[1,5-a]pyridin-3-yl]-quinoline,
aaa) 4-[2-(3-Trifluoromethoxy-phenyl)-4,5,6,7-tetrahydro-pyrazolo[1,5-a]pyridin-3-yl]-quinolinm^ ,
bbb) 4-[2-(2-Fluoro-phenyl)-4,5,6,7-tetrahydro-pyrazolo[1,5-a]pyridin-3-yl]-quinoline,
ccc) 4-(2-Quinolin-2-yl-4,5,6,7-tetrahydro-pyrazolo[1,5-a]pyridin-3-yl]-quinoline,
ddd) 4-[2-(4-Ethyl-pyridin-2-yl)-4,5,6,7-tetrahydro-pyrazolo[1,5-a]pyridin-3-yl]-quinoline,
ee) 4-(2-Quinolin-2-yl-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl)-quinoline,
fff) 2-(3-Quinolin-4-yl-4,5,6,7-tetrahydro-pyrazolo[1,5-a]pyridin-2-yl)-[1,8]naphthyridine,
ggg) 4-[5-(4-Fluoro-phenyl)-2-pyridin-2-yl-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl]-quinoline,
hhh) 4-(6-Hydroxymethyl-2-pyridin-2-yl-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl)-quinoline,
iii) 4-(3-Pyridin-2-yl-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-2-yl)-quinoline,
jjj) 4-(4-Methyl-2-pyridin-2-yl-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl)-quinoline,
kkk) 4-(5-Benzyl-2-pyridin-2-yl-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl)-quinoline,
111) 4-(5-Phenethyl-2-pyridin-2-yl-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl)-quinoline,

mmm) 4-(5-Phenyl-2-pyridin-2-yl-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl)-quinoline,

nnn) 4-[2-(3-Trifluoromethylphenyl)-5,6-dihydropyrrolo[1,2-b]pyrazol-3-yl]-quinoline,

ooo) 4-[2-(4-Trifluoromethylphenyl)-5,6-dihydropyrrolo[1,2-b]pyrazol-3-yl]-quinoline,

ppp) 4-(2-Phenyl-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl)-quinoline,

qqq) 2-Chloro-4-(2-pyridin-2-yl-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl)-quinoline,

rrr) 6,8-Dimethoxy-4-[2-(6-methylpyridin-2-yl)-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl]-quinoline,

sss) 4-[2-(6-Bromo-pyridin-2-yl)-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl]-quinoline,

ttt) 6,8-Dimethoxy-4-[2-pyridin-2-yl-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl]-quinoline,

uuu) 3-(4-Fluorophenyl)-2-pyridin-2-yl-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazole,

vv) 3-(4-Methoxyphenyl)-2-pyridin-2-yl-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazole,

www) 3-(4-Fluorophenyl)-2-(6-methylpyridin-2-yl)-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazole,

xxx) 3-(4-Methoxyphenyl)-2-(6-methylpyridin-2-yl)-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazole,

yyy) 4-(2-Thiophen-2-yl-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl)quinoline,

zzz) 4-[2-(6-Propylpyridin-2-yl)-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl]-quinoline,

aaaa) 4-[2-(6-Isopropylpyridin-2-yl)-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl]quinoline,

bbbb) 4-[2-(6-Ethyl-pyridin-2-yl)-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl]quinoline,

cccc) 4-[2-(6-Methyl-pyridin-2-yl)-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl]quinoline

dddd) 4-[2-(3-Fluorophenyl)-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl]quinoline,

eeee) 4-[2-(2-Fluoro-phenyl)-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl]-quinoline,

ffff) 4-[2-(4-Fluorophenyl)-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl]-quinoline,

gggg) 4-[2-(3-Trifluoromethoxy-phenyl)-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl]-quinolm^ 

hhhh) 4-[2-(4-Chloro-pyridin-2-yl)-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl]-quinoline,

iii) 4-[2-(4-Fluoro-3-trifluoromethyl-phenyl)-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl]-quinoline,

jjj) 4-[2-(2-Fluoro-3-trifluoromethyl-phenyl)-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl]-quinoline,

kkkk) 4-[5-(3-Methoxy-phenyl)-2-pyridin-2-yl-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl]-quinoline,

1111) 4-[2-(4-Fluoro-3-trifluoromethyl-phenyl)-5-(3-methoxy-phenyl)-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl]-quinoline,

mmmm) 4-(7-Chloro-quinolin-4-yl)-3-(6-methylpyridin-2-yl)-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazole,
nnnn) 4-(7-Ethoxyquinolin-4-yl)-3-(6-methylpyridin-2-yl)-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazole, 
oooo) 6-(3-Quinolin-4-yl)-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-2-yl)-pyridine-2-carboxylic acid hydrochloride, 
pppp) 6,7-Difluoro-4-[2-(6-methyl-pyridin-2-yl)-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl]-quinoline, 
qqqq) 6,7-Dimethoxy-4-[2-(6-methyl-pyridin-2-yl)-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl]-quinoline, 
rhhh) 3-Benzol[1,3]dioxol-5-yl-2-(6-methyl-pyridin-2-yl)-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazole, 
ssss) 6-(4-Fluoro-phenyl)-4-[2-(6-methyl-pyridin-2-yl)-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl]-quinoline, 
tttt) 6-Benzo[1,3]dioxol-5-yl-4-[2-(6-methyl-pyridin-2-yl)-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl]-quinoline, 
uuuu) 4-[2-(6-Methyl-pyridin-2-yl)-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl]-6-thiophen-2-yl-quinoline, 
vww) 4-[2-(6-Methyl-pyridin-2-yl)-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl]-6-phenyl-quinoline, 
wwww) 8-[2-(6-Methyl-pyridin-2-yl)-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl]-quinoline, 
xxxx) 3-Benzol[b]thiophen-2-yl-2-(6-methyl-pyridin-2-yl)-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazole, 
yyyy) 4-(2-Pyridin-2-yl-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl]-quinoline-6-carboxylic acid methyl ester, 
zzzz) 4-[2-(6-Methyl-pyridin-2-yl)-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl]-quinoline-6-carboxylic acid methyl ester, 
aaaa) 4-[2-(6-Methyl-pyridin-2-yl)-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl]-quinoline-7-carboxylic acid methyl ester, 
bbbbb) 4-[2-Pyridin-2-yl-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl]-quinoline-7-carboxylic acid methyl ester, 
cccccc) 2-Pyridin-2-yl-3-quinolin-4-yl-pyrazolo[5,1-c]morpholine, 
ddddd) 2-Pyridin-2-yl-3-quinolin-4-yl-pyrazolo[5,1-c]morpholin-4-one, 
eeeeee) Dimethyl- {3-[4-(2-pyridin-2-yl-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl)-quinolin-7-yloxy]-propyl} -amine, 
fffff) {3-[6-Methoxy-4-(2-pyridin-2-yl-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl)-quinolin-7-yloxy]-propyl} -dimethyl-amine, 
ggggg) Cyclopropylmethyl-propyl-{3-[4-(2-pyridin-2-yl-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl)-quinolin-7-yloxy]-propyl} -amine,
hhhhh) Diethyl-{3-[4-(2-pyridin-2-yl-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl)-quinolin-7-yloxy]propyl} -amine,

iiiiii) Ethyl-methyl-{3-[4-(2-pyridin-2-yl-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl)-quinolin-7-yloxy]propyl} -amine,

jjjjjj) 3-[4-(2-Pyridin-2-yl-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl)-quinolin-7-yloxy]-propylamine,

kkkkkk) 7-[3-(4-Methyl-piperazin-1-yl)-propoxy]-4-(2-pyridin-2-yl-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl)-quinoline,

lllllll) Benzyl-methyl-{3-[4-(2-pyridin-2-yl-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl)-quinolin-7-yloxy]propyl} -amine,

mmmmmm) 7-(3-Piperidin-1-yl-propoxy)-4-(2-pyridin-2-yl-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl)-quinoline,

nnnnnn) 4-(2-Pyridin-2-yl-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl)-7-(3-pyrrolidin-1-yl-propoxy)-quinoline,

oooooo) 7-(3-Azepan-1-yl-propoxy)-4-(2-pyridin-2-yl-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl)-quinoline,

pppppp) 7-(3-Imidazol-1-yl-propoxy)-4-(2-pyridin-2-yl-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl)-quinoline,

qqqqqq) 7-(3-Pyrazol-1-yl-propoxy)-4-(2-pyridin-2-yl-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl)-quinoline,

rrrrrr) 1'-(3-[4-(2-Pyridin-2-yl-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl)-quinolin-7-yloxy]-propyl) -[1,4']bipiperidinyl,

ssssss) Cyclopropyl-(1-methyl-piperidin-4-yl)-{3-[4-(2-pyridin-2-yl-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl)-quinolin-7-yloxy]-propyl}-amine,

ttttttt) 4-(2-Pyridin-2-yl-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl)-7-(3-[1,2,3]triazol-1-yl-propoxy)-quinoline,

uuuuuu) Dimethyl-(3-[4-[2-(6-methyl-pyridin-2-yl)-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl]-quinolin-7-yloxy]propyl)-amine,

vww) Diethyl-(3-[4-[2-(6-methyl-pyridin-2-yl)-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl]-quinolin-7-yloxy]-propyl)-amine,

wwwww) Cyclopropylmethyl-(3-[4-[2-(6-methyl-pyridin-2-yl)-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl]-quinolin-7-yloxy]-propyl)-amine,

xxxxxx) Ethyl-methyl-(3-[4-[2-(6-methyl-pyridin-2-yl)-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl]-quinolin-7-yloxy]propyl)-propyl-amin,
quinolin-7-yloxy)-propyl)-amine,

yyyyy) Dimethyl- [2-(4-(2-pyridin-2-y1-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-y1)-quinolin-7-yloxy)-ethyl] -amine,

zzzzz) Diethyl- [2-(4-(2-pyridin-2-y1-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl)-quinolin-7-yloxy)-ethyl] -amine,

aaaaa) 7-(2-Piperidin-1-y1-ethoxy)-4-(2-pyridin-2-y1-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl)-quinoline,

bbbbbb) Ethyl-methyl-[2-(4-(2-pyridin-2-y1-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl)-quinolin-7-yloxy]-ethyl] -amine,

cccccc) 4-(2-Pyridin-2-y1-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl)-7-(2-pyroridin-1-y1-ethoxy)-quinoline,

dddddd) 7-{[2-(4-Methyl-piperazin-1-y1)-ethoxy]-4-(2-pyridin-2-y1-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl)-quinoline,

eeeeee) Dimethyl- [3-[1-oxo-4-(2-pyridin-2-y1-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl)-quinolin-7-yloxy]-propyl] -amine,

fffffff) 7-Methylsulfanyl-4-(2-pyridin-2-y1-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl)-quinoline,

gggggg) 7-Ethylsulfanyl-4-(2-pyridin-2-y1-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl)-quinoline,

hhhhhh) 6-Methylsulfanyl-4-(2-pyridin-2-y1-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl)-quinoline,

iiiiii) 7-Benzylsulfanyl-4-(2-pyridin-2-y1-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl)-quinoline,

jjjjjj) 3-[4-(2-Pyridin-2-y1-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl)-quinolin-7-y1sulfanyl]-propan-1-ol,

kklckkk) Dimethyl- [2-(4-(2-pyridin-2-y1-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl)-quinolin-7-yloxy]-ethyl] -amine,

11111) Dimethyl-[6-(3-quinolin-4-y1-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl)-pyridin-2-yl-methyl] amine,

mmmmmm) 7-(2-Proproxy-ethoxy)-4-(2-pyridin-2-y1-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl)-quinoline,

nnnnn) N,N-Dimethyl-N’-[4-(2-pyridin-2-y1-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl)-pyridin-2-yl]-ethane-1,2-diamine,

oooooo) N,N-Dimethyl-N’-[4-(2-pyridin-2-y1-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl)-pyridin-2-yl]-propane-1,3-diamine,

pppppp) 3-{3-[4-(2-Pyridin-2-y1-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl)-quinolin-7-yloxy]-propyl} -oxazolidin-2-one,
1-\{3-\{4-(2-Pyridin-2-yl-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl)-quinolin-7-yloxy\}propyl\}imidazolidin-2-one,

3-\{3-\{4-(2-Pyridin-2-yl-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl)-quinolin-7-yloxy\}propyl\}3H-benzoaxazol-2-one,

Dimethyl-\{2-\{2-(6-methyl-pyridin-2-yl)-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl\}pyridin-2-ylsulfanyl\}-ethyl-amine,

4-(2-Pyridin-2-yl-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl)-2-pyrrolidin-1-yl-quinoline,

2-Phenylsulfanyl-4-(2-pyridin-2-yl-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl)-quinoline,

2-Morpholin-4-yl-4-(2-pyridin-2-yl-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl)-quinoline,

2-Ethylsulfanyl-4-(2-pyridin-2-yl-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl)-quinoline,

Phenyl-\{4-(2-pyridin-2-yl-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl)-quinolin-2-yl\}amine,

2-Methoxy-4-(2-pyridin-2-yl-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl)-quinoline,

2-Ethylsulfanyl-4-(2-pyridin-2-yl-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl)-quinoline,

Phenyl-\{6-(3-quinolin-4-yl-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-2-yl)-pyridin-2-yl\}amine,

4-\{2-(6-Phenylsulfanyl-pyridin-2-yl)-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl\}quinoline,

4-\{2-(6-Morpholin-4-yl-pyridin-2-yl)-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl\}quinoline,

4-\{2-(6-Methoxy-pyridin-2-yl)-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl\}quinoline,

4-\{2-(6-Pyrrolidin-1-yl-pyridin-2-yl)-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl\}quinoline,

4-\{2-(6-Methoxy-pyridin-2-yl)-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl\}quinoline,

7-(3-Chloro-propoxy)-4-(2-pyridin-2-yl-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl)-quinoline,

7-(3-Fluoro-propoxy)-4-(2-pyridin-2-yl-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl)-quinoline,

7-(3-Chloro-propoxy)-4-(2-pyridin-2-yl-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl)-quinoline,

7-(3-Chloro-propoxy)-4-(2-pyridin-2-yl-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl)-quinoline,
quinoline,

7-(3-Chloro-propoxy)-6-methoxy-4-(2-pyridyl)-quinoline,

7-(3-Chloro-propoxy)-4-[2-(6-methyl-pyridin-2-yl)-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl]-quinoline,

N,N-Diethyl-2-[4-(2-pyridin-2-yl-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl)-quinolin-7-yloxy]-acetamide,

Dimethyl-[4-[4-(2-pyridin-2-yl-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl)-quinolin-7-yloxy]-butyl]-amine,

1-[3-[7-(2-Chloro-ethoxy)-quinolin-4-yl]-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-2-yl]-propenyl-methylene-amine,

N,N-Diethyl-2-[4-(2-pyridin-2-yl-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl)-quinolin-7-yloxy]-acetamide,

Dimethyl-[4-[4-(2-pyridin-2-yl-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl)-quinolin-7-yloxy]-butyl]-amine,
acetamide,

7-(5-Phenyl-[1,2,4]oxadiazol-3-ylmethoxy)-4-(2-pyridin-2-yl-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl)-quinoline,

7-(2,2-Difluoro-benzo[1,3]dioxol-5-ylmethoxy)-4-(2-pyridin-2-yl-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl)-quinoline,

7-[2-((2S)-Methyl-pyrrolidin-2-yl)-ethoxy]-4-(2-pyridin-2-yl-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl)-quinoline,

5-[4-(2-Pyridin-2-yl-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl)-quinolin-7-yloxymethyl]-pyrrolidin-2-one,

4-(6-Phenoxymethyl-2-pyridin-2-yl-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl)-quinoline,

4-(6-Methylene-2-pyridin-2-yl-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl)-quinoline,

3-(4-Fluoro-phenyl)-6-methylene-2-(6-methyl-pyridin-2-yl)-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazole,

7-(l-Methyl-piperidin-2-ylmethoxy)-4-(2-pyridin-2-yl-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl)-quinoline hydrochloride,

7-(l-Methyl-pyrrolidin-2-ylmethoxy)-4-(2-pyridin-2-yl-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl)-quinoline hydrochloride,

4-[2-(6-Methyl-1-oxy-pyridin-2-yl)-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl]-quinoline 1-oxide,

4-[2-(6-Methyl-pyridin-2-yl)-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl]-quinoline 1-oxide,

4-[2-(6-Methyl-1-oxy-pyridin-2-yl)-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl]-quinoline 1-oxide,

7-(3-Chloro-propoxy)-4-(2-pyridin-2-yl-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl)-quinoline 1-oxide,

7-Methanesulfonyl-4-(2-pyridin-2-yl-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl)-quinoline,

3-(4-Fluoro-phenyl)-2-(6-methyl-1-oxy-pyridin-2-yl)-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazole,

4-(Quinolin-N-oxide-4-yl)-3-(6-methylpyridin-2-yl)-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazole,

6-Methanesulfonyl-4-(2-pyridin-2-yl-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl)-
quinoline,

7-Ethanesulfonyl-4-(2-pyridin-2-yl-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl)-quinoline,
4-(2-Pyridin-2-yl-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl)-7-[3-(pyrimidine-2-sulfonyl)-propoxy]-quinoline,

7-[3-(1-Methyl-1H-imidazole-2-sulfonyl)-propoxy]-4-(2-pyridin-2-yl-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl)-quinoline,

7-[3-(4-Chloro-benzenesulfonyl)-propoxy]-4-(2-pyridin-2-yl-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl)-quinoline,

4-(2-Pyridin-2-yl-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl)-7-[3-(pyridin-2-ylmethanesulfonyl)-propoxy]-quinoline,

4-(2-Pyridin-2-yl-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl)-7-[3-(pyridin-2-ylmethanesulfonyl)-propoxy]-quinoline,

4-(2-Pyridin-2-yl-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl)-7-vinyl-quinoline,

4-[2-(6-Methyl-pyridin-2-yl)-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl]-quinolin-7-carboxylic acid,

4-[2-(6-Methyl-pyridin-2-yl)-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl]-quinolin-7-carboxylic acid,
4-(2-(6-Methyl-pyridin-2-yl)-3-quinolin-4-yl)-5,6-dihydro-4H-pyrrolo[1,2-b]pyr
yl]-benzoic acid,

4-(2-Pyridin-2-yl-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl)-quinoline-7-carboxylic acid cyclopentylamide,

4-(2-Pyridin-2-yl-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl)-quinoline-7-carboxylic acid (2-morpholin-4-yl-ethyl)-amide,

4-(2-Pyridin-2-yl-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl)-quinoline-7-carboxylic acid [2-(1H-imidazol-4-yl)-ethyl] -amide,

4-(2-Pyridin-2-yl-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl)-quinoline-7-carboxylic acid (2-methylamino-ethyl)-amide,

4-(2-Pyridin-2-yl-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl)-quinoline-7-carboxylic acid (3-methylamino-propyl)-amide,

4-(2-Pyridin-2-yl-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl)-quinoline-7-carboxylic acid (2-dimethylamino-ethyl)-amide,

(4-Methyl-piperazin-1-yl)-[4-(2-pyridin-2-yl-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl)-quinolin-7-yl]-methanone,

4-(2-Pyridin-2-yl-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl)-quinoline-7-carboxylic acid cyclobutylamide,

4-(2-Pyridin-2-yl-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl)-quinoline-7-carboxylic acid cyclopropylamide,

4-(2-Pyridin-2-yl-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl)-quinoline-7-carboxylic acid (1-ethyl-propyl)-amide,

4-(2-Pyridin-2-yl-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl)-quinoline-7-carboxylic acid ethyl amide,

4-(2-Pyridin-2-yl-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl)-quinoline-7-carboxylic acid isobutyl-amide,

4-(2-Pyridin-2-yl-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl)-quinoline-7-carboxylic acid tert-butylamide,

4-(2-Pyridin-2-yl-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl)-quinoline-7-carboxylic acid isopropylamide,

4-(2-Pyridin-2-yl-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl)-quinoline-7-carboxylic acid propylamide,

4-(2-Pyridin-2-yl-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl)-quinoline-7-carboxylic acid isopropylamide,
acid(2-methyl-butyl)-amide,

4-(2-Pyridin-2-yl-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl)-quinoline-7-carboxylic acid((2S)-2-methyl-butyl)-amide,

ccccccccc 4-(2-Pyridin-2-yl-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl)-quinoline-7-carboxylic acid(2S)-sec-butylamide,

dddddddddd 4-(2-Pyridin-2-yl-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl)-quinoline-7-carboxylic acid(2R)-sec-butylamide,

eeeeeeeeee 4-(2-Pyridin-2-yl-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl)-quinoline-7-carboxylic acid((1R)-1,2-dimethyl-propyl)-amide,

fffffffff 4-(2-Pyridin-2-yl-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl)-quinoline-7-carboxylic acid(pyridin-4-ylmethyl)-amide,

ggggggggg 4-(2-Pyridin-2-yl-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl)-quinoline-7-carboxylic acid(pyridin-3-ylmethyl)-amide,

hhhhhhhhh 4-(2-Pyridin-2-yl-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl)-quinoline-7-carboxylic acid(pyridin-2-ylmethyl)-amide,

iiiiiiiiii 6-(3-Quinolin-4-yl-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-2-yl)-pyridine-2-carboxylic acid

iiiiiiiiii i-(4-Methyl-piperazin-1-yl)-2-[4-(2-pyridin-2-yl-5,6-dihydro-4H-pyrrolo[1,2-b]pyra

kkkkkkkkkkk N-(2-dimethylamino-ethyl)-2-[4-(2-pyridin-2-yl-5,6-dihydro-4H-pyrrolo[1,2-

lllllllllll N-(2-dimethylamino-ethyl)-N-m^ thyl-2-[4-(2-pyridin-2-yl-5,6-dihydro-4H-pyrrolo[1,2-

mmmmmmmmmm N,N-Dimethyl-3-[4-(2-pyridin-2-yl-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-

nnnnnnnnnn 4-(2-Pyridin-2-yl-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl)-quinoline-7-carboxylic acid

oooonoooooo 4-(2-Pyridin-2-yl-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl)-quinoline-7-carboxylic acid(2-dimethylamino-ethyl)-methyl-amide,

pppppppppp 4-(2-Pyridin-2-yl-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl)-quinoline-7-carboxylic acid(3-dimethylamino-propyl)-methyl-amide,

qqqqqqqqqqq 4-(2-Pyridin-2-yl-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl)-quinoline-7-carboxylic acid dimethylamide,
4-(2-Pyridin-2-yl-5,6-dihydro-4H-pyrrolo[1,2-H]pyrazol-3-yl)-quinoline-7-carboxylic acid methylamide,
4-(2-Pyridin-2-yl-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl)-quinoline-7-carboxylic acid pyridin-2-ylamide,
N-(2,2-Dimethylamino-ethyl)-N-methyl-3-{442-(6-methyl-pyrid in-2-yl)-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl]-quinolin-7-yl} -propionamide,
2-(6-Methyl-pyridin-2-yl)-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl-quinoline-6-carboxylic acid(2-dimethylamino-ethyl)-amide,
4-[2-(6-Methyl-pyridin-2-yl)-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl]-quinoline-6-carboxylic acid(3-dimethylamino-propyl)-amide,
1-[2-(Quinolin-4-yl)-l-(6-methyl-pyridin-2-yl)-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl]quinoline-7-carboxylic acid N,N-dimethylaminoethylamide,
4-[2-(6-Methylpyridin-2-yl)-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl]quinoline-7-carboxylic acid(2-piperidin-1-yl-ethyl)amide,
N-(2-Dimethylamino-ethyl)-3-{4-[2-(6-methyl-pyridin-2-yl)-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl]-quinolin-7-yl} -propionamide,
4-(2-Pyridin-2-yl-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl)-quinoline-6-carboxylic acid(2-morpholin-4-yl-ethyl)-amide,
N-(2-Dimethylamino-ethyl)-3-{4-[2-(6-methyl-pyridin-2-yl)-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl]-quinolin-7-yl} -propionamide,
4-(2-Pyridin-2-yl-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl)-quinoline-6-carboxylic acid(3-pyrrolidin-1-yl-propyl)-amide,
4-(2-Pyridin-2-yl-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl)-quinoline-6-carboxylic acid(3-morpholin-4-yl-propyl)-amide,
acid hydrazide,

iiiiiiiiii) 4-(2-Pyridin-2-yl-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl)-quinoline-6-carboxylic acid amide,

iii) 4-(2-Pyridin-2-yl-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl)-quinoline-6-carboxylic acid(3-methylamino-propyl)-amide,

kkkkkkkkkkk) 4-(2-Pyridin-2-yl-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl)-quinoline-6-carboxylic acid amide,

llllllllllllll) 4-(2-Pyridin-2-yl-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl)-quinoline-6-carboxylic acid(2-hydroxy-ethyl)-amide,

mmmmmmmmmmm) 4-(2-Pyridin-2-yl-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl)-quinoline-7-carboxylic acid hydrazide,

nnnnnnnnnnnn) 4-(2-Pyridin-2-yl-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl)-quinoline-7-carboxylic acid hydroxyamide,

oooooonooooo) 4-(2-Pyridin-2-yl-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl)-quinoline-7-carboxylic acid(2-amino-ethyl)-amide,

pppppppppppp) 4-(2-Pyridin-2-yl-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl)-quinoline-7-carboxylic acid(2-hydroxy-ethyl)-amide,

qqqqqqqqqqqqq) 4-(2-Pyridin-2-yl-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl)-quinoline-7-sulfonic acid amide,

rrrrrrrrrrrr) 4-(2-Pyridin-2-yl-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl)-quinoline-7-sulfonic acid methylamide,

ssssssssssssss) 4-(2-Pyridin-2-yl-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl)-quinoline-7-sulfonic acid dimethylamide,

ttttttttttttttt) 4-(2-Pyridin-2-yl-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl)-quinoline-7-sulfonic acid(3-dimethylamino-propyl)-amide,

uuuuuuuuuuuuu) 4-(2-Pyridin-2-yl-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl)-quinoline-7-sulfonic acid diethylamide,

wwwwwwwwww) 4-(2-Pyridin-2-yl-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl)-quinoline-7-sulfonic acid(2-piperidin-1-yl-ethyl)-amide,

wwwwwwwwwwww) 4-(2-Pyridin-2-yl-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl)-quinoline-7-sulfonic acid(2-hydroxy-ethyl)-amide,

xxxxxxxxxxxxxx) 4-(2-Pyridin-2-yl-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl)-quinolin-7-ylamine,

yyyyyyyyyyyy) 2-Dimethylamino-N-[4-(2-pyridin-2-yl-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol]-3-yl]-
quinolin-7-yl]acetamide,

3-Dimethylamino-N-[4-(2-pyridin-2-yl-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl]-
quinolin-7-yl]propionamide,

N-[4-(2-Pyridin-2-yl-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl]-quinolin-7-yl]-
methanesulfonamide,

N-[4-(2-Pyridin-2-yl-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl]-quinolin-7-yl]-
acetamide,

4-(2-Pyridin-2-yl-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl]-quinoline-7-carboxylic
acid(2-acetylamino-ethyl)-amide,

N-[3-[4-(2-Pyridin-2-yl-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl]-quinolin-7-yloxy]-propyl]-methanesulfonamide,

1-methyl-1H-imidazole-4-sulfonic acid {3-[4-(2-pyridin-2-yl-5,6-dihydro-4H-
pyrrolo[1,2-b]pyrazol-3-yl]-quinolin-7-yloxy]-propyl} -amide,

1-(2-Dimethylamino-ethyl)-3-[4-(2-pyridin-2-yl-5,6-dihydro-4H-pyrrolo[1,2-b]
pyrazol-3-yl]-quinolin-7-y1]-urea,

1-(3-Dimethylamino-propyl)-3-[4-(2-pyridin-2-yl-5,6-dihydro-4H-pyrrolo[1,2-
pyrazol-3-yl]-quinolin-7-yl]-urea,

1-(2-Hydroxy-ethyl)-3-[4-(2-pyridin-2-yl-5,6-dihydro-4H-pyrrolo[1,2-b]
pyrazol-3-yl]-quinolin-7-yl]-urea,

[4-(2-Pyridin-2-yl-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl]-quinolin-7-yl]-carbamic
acid methyl ester,

[4-(2-Pyridin-2-yl-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl]-quinolin-7-yl]-carbamic
acid 2-hydroxy-ethyl ester,

[4-(2-Pyridin-2-yl-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl]-quinolin-7-yl]-carbamic
acid 2-methoxy-ethyl ester,

L,3-Bis-[4-(2-pyridin-2-yl-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl]-quinolin-7-yl]-urea,

Dimethyl-carbamic acid 4-(2-pyridin-2-yl-5,6-dihydro-4H-pyrrolo[1,2-
pyrazol-3-yl]-quinolin-7-yl ester,

7-Bromo-2-isopropyl-4-(2-pyridin-2-yl-5,6-dihydro-4H-pyrrolo[1,2-b]
pyrazol-3-yl]-quinoline,

2-[4-(6-Methyl-pyridin-2-yl)-5,6-dihydro-4H-pyrrolo[1,2-b]
pyrazol-3-yl]-quinolin-6-y1] -propan-2-ol,

7-(3-Chloro-propylsulfanyl)-4-(2-pyridin-2-yl-5,6-dihydro-4H-pyrrolo[1,2-
b|pyrazol-3-yl)-quinoline,

7-Bromo-4-(4-chloro-2-pyridin-2-yl-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl)-quinoline,

8-Chloro-4-(2-pyridin-2-yl-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl)-quinolin-7-ol,

3-(7-Bromo-quinolin-4-yl)-2-pyridin-2-yl-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-4-ol,

7-Bromo-4-(4-methoxy-2-pyridin-2-yl-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl)-quinoline,

3-(7-Bromo-quinolin-4-yl)-2-pyridin-2-yl-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-4-yl]-methyl-amine,

3-(7-Bromo-quinolin-4-yl)-2-pyridin-2-yl-5,6-dihydro-pyrrolo[1,2-b]pyrazol-4-one,

3-[4-(2-Pyridin-2-yl-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl)-quinolin-7-yloxy]-benzamide,

N,N-Dimethyl-3-[4-(2-pyridin-2-yl-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl)-quinolin-7-yloxy]-thiobenzamide,

Dimethyl- [3-[4-(2-pyridin-2-yl-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl)-quinolin-7-yloxy]-benzyl] -amine,

4-[2-(6-Methyl-pyridin-2-yl)-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl]-IH-quinolin-2-one,

4-(2-Pyridin-2-yl-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl)-quinolin-7-ol,

4-[2-(6-Methyl-pyridin-2-yl)-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl]-quinolin-7-ol,

6-Methoxy-4-(2-pyridin-2-yl-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl)-quinolin-7-ol,

3-[4-[2-(6-Methyl-pyridin-2-yl)-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl]-quinolin-7-yi]-propionic acid methyl ester,

4-(6-Methyl-2-pyridin-2-yl-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl)-quinoline,

3-[4-[2-(6-Methyl-pyridin-2-yl)-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl]-quinolin-6-yl]-propionic acid methyl ester,

7-Amino-4-[2-(6-Methyl-pyridin-2-yl)-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl]-quinoline,

N,N-Dimethyl-3-[4-[2-(6-methyl-pyridin-2-yl)-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl]-quinol

40
yl]-quinolin-7-yl]-propionamide,

N-[3-[4-(2-Pyridin-2-yl-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl]-quinolin-7-yloxy]-propyl] -acetamide,

N-Acetyl-N-[2-(6-methyl-pyridin-2-yl)-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl]-quinolin-7-yl] -acetamide,

2-Pyridin-2-yl-3-quinolin-4-yl-pyrazolo[1,5-a]pyridin-7-ol,

7-Acetoxy-2-pyridin-2-yl-3-quinolin-4-yl-pyrazolo[1,5-a]pyridine,

Methyl- {3-[4-(2-pyridin-2-yl-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl]-quinolin-7-yloxy]-propyl}-amine,

7-(Piperidin-4-yloxy)-4-(2-pyridin-2-yl-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl)-quinoline,

4-[2-(6-Methyl-pyridin-2-yl)-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl]-quinoline-7-carboxylic acid(2-amino-1,1-dimethyl-ethyl)-amide,

6-[3-(4-Fluoro-phenyl)-5,6-dihydro-4H-pyrrolo[1,2-b]pyridin-2-yl]-methanol,

7-Methyl-pyrrolidin-3-ylmethoxy]-4-(2-pyridin-2-yl-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl)-quinoline,

4-[2-(6-Methyl-pyridin-2-yl)-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl]-quinoline-7-carboxylic acid(2-dimethylamino-1,1-dimethyl-ethyl)-amide,

(S)-[3-(4-Fluoro-phenyl)-2-(6-methyl-pyridin-2-yl)-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-6-yl]-methanol,

(R)-[3-(4-Fluoro-phenyl)-2-(6-methyl-pyridin-2-yl)-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-6-yl]-methanol,

(S)-[3-(4-Fluoro-phenyl)-2-(6-methyl-pyridin-2-yl)-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-6-yl]-acetonitrile,

(R)-[3-(4-Fluoro-phenyl)-2-(6-methyl-pyridin-2-yl)-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-6-yl]-acetonitrile,

4-(3-Pyridin-2-yl-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-2-yl)-quinoline,

4-(6-Pyridin-2-yl-2,3-dihydro-pyrazolo[5,1-b]oxazol-7-yl)-quinoline,
3-[4-(2-Pyridin-2-yl)-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl]-quinolin-7-yl]-oxazolidin-2-one,

1-[4-(2-Pyridin-2-yl)-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl]-quinolin-7-yl]-imidazolidin-2-one,

4-(2-Pyridin-2-yl)-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl]-(pyridin-4-ylmethoxy)-quinoline,

2-(2-Pyridin-2-yl)-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl]-7-(3-pyridin-3-yl-propoxy)-quinoline,

7-(4,5-Dihydro-1H-imidazol-2-yl)-4-(2-pyridin-2-yl)-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl]-quinoline (Enantiomer A),

4-(5-(4-Fluoro-phenyl)-2-(6-methyl-pyridin-2-yl)-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl]-quinoline (Enantiomer B),

2-Pyridin-2-yl-3-quinolin-4-yl-pyrazolo[5,1-c]morpholine,

4-[2-(6-Vinyl-pyridin-2-yl)-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl]-quinoline,

3-[4-(2-Methoxy-phenyl)-piperazin-1-yl]-propoxy]-4-(2-pyridin-2-yl-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl]-quinoline,

3-(442-(3-[4-(2-Methoxy-phenyl)-piperazin-1-yl]-propoxy})-4-(2-pyridin-2-yl-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl]-quinoline,

Pyridin-2-yl-[3-[4-(2-pyridin-2-yl)-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl]-quinolin-7-yloxy]-propyl]-amine,

4-[2-(6-Methyl-phenyl)-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl]-quinoline-7-carboxylic acid(2-dimethylamino-1-methyl-ethyl)-amide,

4-[2-(6-Methyl-phenyl)-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl]-quinoline-7-carboxylic acid amide,

4-(2-Pyridin-2-yl)-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl]-quinoline-7-carboxylic acid(3-dimethylamino-propyl)-amide,
4-(2-(6-Methyl-pyridin-2-yl)-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl)-quinoline-7-carboxylic acid(2-dimethylamino-ethyl)-methyl-amide,
N,N-Dimethyl-3-{4-(2-(6-methyl-pyridin-2-yl)-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl]-quinolin-7-yl]-acrylamide,
4-(2-Pyridin-2-yl-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl]-quinoline-l-oxide,
7-Benzylxy-4-(2-(6-methyl-pyridin-2-yl)-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl]-quinoline,
4-(2-Chloro-6-dihydro-4H-pyrrolo-pyridin-2-yl)-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl]-quinoline,
6-(3-Quinolin-4-yl-5,6-dihydro-4H-pyrrolo[1,2-db]pyrazol-2-yl)pyridine-2-carboxylic acid methyl ester,
4-(7-Chloroquinolin-4-yl)-3-(pyridin-2-yl)-5,6-dihydro-4H-pyrrolo[1,2-db]pyrazole,
3-(442<6-Methyl-pyridin-2-yl)-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl]-quinolin-6-yl] -acrylic acid methyl ester,
4-[2-(2-Methyl-thiazol-4-yl)-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl]-quinoline,
3-(4-Fluoro-phenyl)-2-(2-methyl-thiazol-4-yl)-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazole,
4-[2-(2-Methyl-2H-pyrazol-3-yl)-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl]-quinoline,
4-(2-Thiazol-2-yl-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl]-quinoline,
4-(1-Methyl-1H-imidazol-2-yl)-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazole,
6,7-Dichloro-4-(2-(6-methyl-pyridin-2-yl)-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl]-quinoline,
(S)-6-Benzylxymethyl-3-(4-fluoro-phenyl)-2-(6-methyl-pyridin-2-yl)-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazole,
N,N-Dimethyl-3-{4-(2-(6-methyl-pyridin-2-yl)-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl]-quinolin-7-yl]-acrylamide; and the pharmaceutically acceptable salts, esters and prodrugs thereof.
Another embodiment of the invention comprises compositions used for treating schizophrenia and/or symptoms of schizophrenia and/or positive symptoms of schizophrenia in other psychotic diseases, comprising at least one compound selected from the group consisting of 4-[2-(6-Methyl-pyridin-2-yl)-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl]phenol; 4-[2-(6-Methylpyridin-2-yl)-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl]-quinoline-6-carboxylic acid amide; and salts, esters, hydrates, solvates, prodrugs, and polymorphs thereof incorporated in a pharmaceutically acceptable adjuvant, diluent, or carrier composition.

**Experimental Results**

Prepulse inhibition of the acoustic startle response (PPI) is the reduction of the startle response to a sudden pulse of noise when it is preceded by a weak prepulse stimulus. The effect of the prepulse is considered as a form of sensorimotor gating and is common to many species, from mice to humans.

Deficits in PPI are commonly associated with schizophrenia, or positive symptoms of schizophrenia in other psychotic diseases, and can be reproducibly induced in laboratory animals by administration of psychotropic agents such as dopamine agonists (apomorphine), NMDA antagonists (phencyclidine) or even serotonin agonists. These deficits can be partially reversed by antipsychotic agents such as Clozapine and Risperidone. The effectiveness of a number of putative antipsychotic agents in animal models of PPI has been shown to correlate closely to their clinical effectiveness. Given their predictive value, animal models of PPI are now one of the most widely-used preclinical models for evaluating novel antipsychotic drugs.

**Methods:**

Male Sprague-Dawley rats weighing 210-250 g at time of experiment were used. Animals were housed in a temperature and humidity controlled environment and allowed free access to food and water prior to use.

The amplitude of the inherent startle response varies considerably from animal to animal. The gain of the platforms must be calibrated to ensure that the average startle waveform falls within the desired range. To this end, baseline studies were conducted before the full PPI protocol to allow the
calibration of the platforms to be fine-tuned to the startle waveform amplitude. This also allows the animals to become acclimatised to the testing equipment prior to drug administration.

Animals were placed in restraining holders and transferred to the designated chamber. Once all holders were securely fastened to the platform, the Baseline protocol was started. This consists of:

Acclimation Period: Animals were exposed to 5 minutes of 65 decibel (dB) background noise (white noise).

Block 1: 10 x startle stimulus alone (white noise, 120 dB, 40 ms)

Block 2: 6 x startle stimulus alone

6 x pre-pulse plus startle stimulus (pure tone, 16 dB above background noise, 20 ms) followed 100 ms later by the startle stimulus.

During this time, the amplitude of the startle responses was recorded. On completion of this protocol, the sensitivity of the equipment was re-calibrated where necessary by adjusting the gain settings.

The same group of rats was again subjected to the Baseline protocol described above. Again, on completion of this protocol, the sensitivity of the equipment was re-calibrated where necessary by adjusting the gain settings. The gain settings required for each rat were noted for use in the subsequent PPI protocol. These animals were then returned to their home cages for subsequent dosing with compound.

The study compounds were suspended from dry powder stocks in Vehicle (5% Tween 80/5% PEG/saline) and sonicated for 60 minutes at 37°C to generate suspensions suitable for oral dosing. Control rats received Vehicle by oral gavage. PCP was dissolved in sterile saline (0.9% NaCl).

Rats were dosed with either saline (0.9% NaCl) or 2.5 mg/kg PCP by intraperitoneal injection 15 minutes prior to PPI testing.

4-[2-(6-Methyl-pyridin-2-yl)-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl]phenol, 4-[2-(6-Methyl-pyridin-2-yl)-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl]-quinoline-6-carboxylic acid amide or Clozapine was administered orally by gavage 45 minutes before challenge with PCP or saline. 4-[2-(6-Methyl-pyridin-2-yl)-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl]phenol or 4-[2-(6-Methyl-pyridin-2-yl)-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl]-quinoline-6-carboxylic acid amide was
administered at 20 mg/kg and 100 mg/kg. Clozapine was administered at 5 mg/kg. Vehicle control rats received Vehicle (5% Tween 80/ 5% PEG/ saline) by oral gavage 45 minutes before challenge with PCP or saline.

Exactly 15 minutes after the injection of PCP or saline, the full PPI protocol was started. Animals were exposed to 5 minutes of 65 dB background noise (white noise) as an acclimation period, before the acoustic stimuli began.

- **Block 1:** 6 x startle stimulus alone (white noise, 120 dB, 40 ms)
- **Block 2:** 14 x startle stimulus
  - 8 x no pulse
  - 30 x pre-pulse (10 each of 4, 8, and 16 dB above the background noise) followed 100 ms later by the startle stimulus. This corresponds to intensities of 69, 73 and 81 dB, respectively. A total of 52 trials were presented to the animals in this block in a pseudo-random order with a variable interval of 8 to 23 seconds, averaging 15 s between trials.
- **Block 3:** 6 x startle stimulus alone

Pre-pulse inhibition was calculated from trials in Block 2 by the following formula:

\[
\%\text{PPI} = (100 \times \frac{\text{pulse alone score} - (\text{prepulse} + \text{pulse score})}{\text{pulse alone}})
\]

At the lowest prepulse intensity of 69 dB (4 dB above background noise), in this experiment, 4-[2-(6-Methyl-pyridin-2-yl)-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl]phenol did not have a noticeable effect on pre-pulse inhibition. When a prepulse intensity of 73 dB (8 dB above background noise) was used, there was a clear, dose-dependent effect seen with 4-[2-(6-Methyl-pyridin-2-yl)-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl]phenol, with the higher dose inducing a greater response. This effect, however, was not found to be statistically significant by one-way ANOVA statistics. When the prepulse intensity was increased to 81 dB (16 dB above background noise), the ability of 4-[2-(6-Methyl-pyridin-2-yl)-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl]phenol to attenuate the PCP-induced deficit in PPI was even more evident. See Figure 1. At a dose of 100 mg/kg, 4-[2-(6-Methyl-pyridin-2-yl)-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl]phenol significantly (p < 0.01) reversed the PCP-induced deficit in PPI.

At the lowest prepulse intensity of 69 dB (4 dB above background noise), in this experiment, 4-
[2-(6-Methyl-pyridin-2-yl)-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl]-quinoline-6-carboxylic acid amide significantly (p<0.05) reversed the PCP-induced deficit in PPI at the 20 mg/kg dose, but not at the 100 mg/kg dose. See Figure 2. When a prepulse intensity of 73 dB (8 dB above background noise) was used, 4-[2-(6-Methyl-pyridin-2-yl)-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl]-quinoline-6-carboxylic acid amide significantly (p<0.05) reversed the PCP-induced deficit in PPI at the 20 mg/kg dose, but not at the 100 mg/kg dose. See Figure 3. When the prepulse intensity was increased to 81 dB (16 dB above background noise), the ability of 4-[2-(6-Methyl-pyridin-2-yl)-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl]-quinoline-6-carboxylic acid amide to attenuate the PCP-induced deficit in PPI was not statistically significant at either dose.

In terms of startle magnitude, treatment of rats with PCP did not alter the actual magnitude of the startle responses. At the doses used, Clozapine, 4-[2-(6-Methyl-pyridin-2-yl)-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl]-quinoline-6-carboxylic acid amide and 4-[2-(6-Methylpyridin-2-yl)-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl]phenol did not alter the magnitude of the startle response compared to the positive control group.

**Definitions**

The term "therapeutically effective amount" as used in "a therapeutically effective amount of a compound of Formula I," for example, refers to an amount of a compound of the present invention that is capable of measurably alleviating, partially or completely, one or more symptoms of schizophrenia in that subject.

The general chemical terms used herein have their usual meanings. For example, as used herein, the term "C<sub>1</sub>-C<sub>4</sub> alkyl", alone or in combination, denotes a straight-chain or branched-chain C<sub>J</sub>-C<sub>4</sub> alkyl group consisting of carbon and hydrogen atoms, examples of which are methyl, ethyl, propyl, isopropyl, butyl, sec-butyl, tert-butyl, and the like. The term "C<sub>3</sub> -C<sub>6</sub> cycloalkyl" refers to cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl.

The term "C<sub>1</sub>-C<sub>4</sub> alkoxy", alone or in combination, denotes an alkyl group as defined earlier, which is attached via an oxygen atom, such as, for example, methoxy, ethoxy, propoxy, isopropoxy, butoxy, tert-butoxy, and the like.

The term "C<sub>J</sub>-C<sub>4</sub> alkylthio", alone or in combination, denotes an alkyl group as defined
earlier and is attached via a sulfur atom, and includes methylthio, ethylthio, isobutylthio, and the like.

As used herein, the term "halo" or "halogen" represents fluorine, chlorine, bromine, or iodine. The term "hydroxy," alone or in combination, represents an —OH moiety. The term "carboxy" or "carboxyl" refers to a carboxylic acid. The term "carboxamide" refers to a carbonyl substituted with an —NH₂ moiety. The term "oxo" refers to a carbonyl group.

As used herein, the term "aryl" represents a substituted or unsubstituted phenyl or naphthyl. Aryl may be optionally substituted with one or more groups independently selected from hydroxy, carboxy, C₁-C₆ alkoxy, C₁-C₆ alkyl, halogen, carboxamide, trifluoromethyl, hydroxymethyl, and hydroxy(C₁-C₆ alkyl).

The term "C₃-C₈ cycloalkyl" refers to cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and cyclooctyl. The term "optionally substituted C₃-C₈ cycloalkyl" refers to a C₃-C₈ cycloalkyl as defined herein unsubstituted or substituted with one or more groups independently selected from hydroxy, carboxy, C₁-6 alkoxy, C₁-6 alkyl, halogen, carboxamide, trifluoromethyl, hydroxymethyl, and hydroxy(C₁-C₆ alkyl).

As used herein, the term "C₁-C₆ alkyl" refers to straight or branched, monovalent, saturated aliphatic chains of 1 to 6 carbon atoms and includes, but is not limited to, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, t-butyl, pentyl, isopentyl, and hexyl. The term "C₁-C₆ alkyl" includes within its definition the terms "C₁-C₄ alkyl" and "C₁-C₃ alkyl."

"C₁-C₉ alkenyl" refers to a straight or branched, divalent, unsaturated aliphatic chain of 1 to 6 carbon atoms and includes, but is not limited to, methylenyl, ethylenyl, propylenyl, isopropylenyl, butylenyl, isobutylenyl, 1-butylenyl, pentylenyl, isopentenyl, hexylenyl.

"C₁-C₉ alkoxy carbonyl" represents a straight or branched C₁-C₉ alkoxy chain, as defined above, that is attached via the oxygen atom to a carbonyl moiety. Typical C₁-C₉ alkoxy carbonyl groups include methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, isopropoxycarbonyl, butoxycarbonyl, 1-butoxycarbonyl and the like.

The term "di(C₁-C₉ alkyl)amino" refers to a group of the formula:
wherein each R group independently represents a "$C_1-C_6$ alkyl" group, as defined above.

An "optionally substituted phenyl" is a phenyl ring that is unsubstituted or substituted with 1 to 5 substituents, or 1 to 3 substituents, for example: halo, $C_1-C_6$ alkyl, $C_1-C_6$ alkoxy, $C_1-C_6$ alkylamino, trifluoromethyl, nitro, and cyano.

An "optionally substituted benzyl" is a benzyl ring that is unsubstituted or substituted with 1 to 5 substituents, or 1 to 3 substituents, for example: halo, $C_1-C_6$ alkyl, $C_1-C_6$ alkoxy, trifluoromethyl, nitro, and cyano.

"Phenoxy carbonyl" refers to the group: phenyl-O—C(O)—. "Aryl" refers to an unsaturated aromatic carbocyclic group of 6 to 14 carbon atoms having a single ring (e.g., phenyl) or multiple condensed (fused) rings (e.g., naphthyl or anthracenyl).

Unless otherwise constrained by the definition for the aryl substituent, such aryl groups can optionally be substituted with 1 to 5 substituents, more preferably 1 to 3 substituents, selected from the group consisting of halo, hydroxy, acetyl, nitro, cyano, $C_1-C_6$ alkyl, $C_1-C_6$ alkoxy, phenyl, di($C_1-C_6$ alkyl)amino, trifluoromethyl, trifluoromethoxy, —S(0)$_m$—($C_1-C_6$ alkyl), and —S(0)$_m$—(phenyl), wherein m can be 0, 1, or 2.

"Arylalkyl" refers to aryl groups attached to alkyl groups, preferably having 1 to 6 carbon atoms in the alkyl moiety and 6 to 10 carbon atoms in the aryl moiety. Such arylalkyl groups are exemplified by benzyl, phenethyl, and the like.

Unless otherwise constrained by the definition for arylalkyl, such arylalkyl groups can be optionally substituted with 1 to 5 substituents, more preferably 1 to 3 substituents, selected from the group consisting of halo, hydroxy, nitro, cyano, $C_1-C_6$ alkyl, $C_1-C_6$ alkoxy, di(Cj-Cg alkyl)amino, trifluoromethyl, trifluoromethoxy, carbamoyl, pyrrolidinyl, —S(0)$_m$—($C_1-C_6$ alkyl), and —S(0)$_m$—(phenyl), wherein m can be 0, 1, or 2. The arylalkyl groups may be optionally substituted on the aryl moiety, the alkyl moiety, or both the aryl moiety and the alkyl moiety.

The term "heterocycle" represents an unsubstituted or substituted 5- to 7-membered monocyclic, or 7- to 11-membered bicyclic heterocyclic ring that is saturated or unsaturated and that
consists of carbon atoms and from one to five heteroatoms selected from the group consisting of nitrogen, oxygen or sulfur, and including a bicyclic group in which any of the above-defined heterocyclic rings is fused to a benzene ring to another heterocycle as defined above.

The term "heteroaryls" represents the above-defined heterocyclic rings that are fused to a benzene ring to another heterocycle as defined above.

Unless otherwise constrained by the definition for the heterocyclic substituent, such heterocycles can be optionally substituted with 1 to 8 substituents selected from the group consisting of halo, nitro, cyano, hydroxy, acetyl, C1-C6 alkyl, C1-C6 alkoxy, C3-C10 cycloalkyl, optionally substituted phenyl, phenethyl, phenoxy, phenoxycarbonyl, optionally substituted benzyl, 1,1-diphenylmethyl, oxo, C1-C6 alkoxy carbonyl, (C1-C6 alkoxy)C1-C6 alkyl-, trifluoromethyl, pyridyl, (pyrrolidinyl)C1-C6 alkyl-, and (pyridyl)C1-C6 alkyl-, di(C1-C6 alkyl)amino, trifluoromethyl, trifluoromethoxy, —S(0)m —(C1-C6 alkyl), and —S(0)m-(phenyl), wherein m can be 0, 1, or 2.

Examples of such heterocycles include azepinyl, azetidinyl, benzazepinyl, benzimidazolyl, benzoazolyl, benzodioxolyl, benzodioxanyl, benzopryranyl, benzothiazolyl, benzothienyl, dihydropyrazolooxazinyl, dihydropyrazolo oxazolyl, furyl, imidazolyl, imidazolinyl, imidazolidinyl, indoliny, indolyl, isoindoliny, isoquinolinyl, isothiazolidinyl, isothiazolyl, isoazolidinyl, isoxazolyl, morpholinyl, napthyridinyl, oxadiazolyl, oxazolyl, oxazolidinyl, phthalimidyl, piperazinyl, piperidinyl, pyrazinyl, pyridyl, pyrazinyl, pyrazolidinyl, pyrazolyl, pyridyl, pyrimidinyl, pyridazinyl, pyrrolidinyl, pyrrolopyrazolyl, pyrrolyl, quinazolinyl, quinolinyl, quinuclidinyl, tetrahydrofuryl, tetrahydropranyl, tetrahydroisoquinolinyl, tetrahydroquinolinyl, thiazolyl, thiazoliny, thiazolidinyl, thiadiazolyl, thienyl, thiomorpholinyl, triazolyl, and the like.

Preferred heterocycles include: benzodioxolyl, dihydropyrrolo pyrazolyl, pyridyl and quinolinyl.
We claim:

1. A method of treating schizophrenia, a symptom of schizophrenia or a positive symptom of schizophrenia in a psychotic disease, comprising administering a pharmaceutical composition to a mammal in need of such treatment, wherein the pharmaceutical composition comprises a therapeutically effective amount of a compound of structural formula I:

\[
\begin{align*}
\text{wherein} \\
(R_3)_2 & \\
\text{is a four, five or six membered saturated ring and } X \text{ is } C, O \text{ or } S; \\
R_1 & \text{ is un/substituted or substituted phenyl; un/substituted or substituted pyridine; un/substituted or substituted pyridine } N\text{-oxide; un/substituted or substituted quinoline; un/substituted or substituted quinoline } N\text{-oxide; un/substituted or substituted naphthyridine; un/substituted or substituted pyrazine; furyl; un/substituted or substituted thiazolyl; un/substituted or substituted imidazolyl; un/substituted or substituted pyrazolyl; or un/substituted or substituted thiophenyl; wherein the substitution is one or more group selected from the group consisting of:} \\
(\text{Cl-C6}) & \text{alkyl, (C2-C6)alkenyl, (C2-C6)alkynyl, (Cl-C6)alkoxy, (C2-C6)alkenloxy,} \\
(\text{C2-C6}) & \text{alkynloxy, (Cl-C6)alkylthio, (Cl-C6)alkylsulphinyl, (Cl-C6)alkylsulphonyl, (Cl-C6)alkylamino, di-[(Cl-C6)alkyl]amino, (Cl-C6)alkoxy carbonyl, } N—(\text{C1-C6}) & \text{alkylcarbamoyl, N,N-di-[(C1-C6)alkyl]carbamoyl,} \\
(\text{C2-C6}) & \text{alkanoyl, (C2-C6)alkanoyloxy, (C2-C6)alkanoylamino, N—(Cl-C6)alkyl-} \\
(\text{C2-C6}) & \text{alkanoylamino, (C3-C6)alkenoylamino, N—(C1-C6)alkyl-(C3-}
\end{align*}
\]
C6)alkenoylamino, (C3-C6)alkynoylamino, N—(Cl-C6)alkyl-(C3-
C6)alkenoylamino, N—(C 1-C6)alkylsulphamoyl, N,N-di-[\((C 1-C6)alkyl\)sulphamoyl, (C 1-C6)alkanesulphonylamino, N—(C 1-C6)alkyl-(C 1-C6)alkanesulphonylamino, carboxamide, ethylene, thiophenyl, aminophenyl, trifluoromethyl, halo, trifluoromethoxy, hydroxymethyl, N-pyrrolidino, N-morpholino, phenylthio, (C1-C4)dialkylaminomethyl, methoxyphenyl, amino, hydroxy, carboxyl, phenyl, and arylalky;

R2 is unsubstituted or substituted quinoline; unsubstituted or substituted quinoline N-oxide; unsubstituted or substituted phenyl; unsubstituted or substituted naphthalene; unsubstituted or substituted pyridine; unsubstituted or substituted pyridine N-oxide; unsubstituted or substituted quinazoline; unsubstituted or substituted cinnoline; unsubstituted or substituted benzodioxole; unsubstituted or substituted benzodioxane; unsubstituted or substituted pyrimidine; unsubstituted or substituted benzothiophene; or unsubstituted or substituted phenanthrene;

wherein is one or more group selected from the group consisting of: hydrogen, (Cl-
C6)alkyl, (C2-C6)alkenyl, (C2-C6)alkynyl, (Cl-C6)alkylhalide, (Cl-C6)alkoxy, (C2-
C6)alkenyl, (C2-C6)alkynyl, (Cl-C6)alkylthio, (Cl-C6)alkylsulphinyl, (Cl-
C6)alkylsulphonyl, di-[(Cl-C6)alkyl]amino, (Cl-
C6)alkoxy, (C1-C6)alkylcarbamoyl, N,N-di-[\((C 1-C6)alkyl\)carbamoyl, aminoxy, N—(Cl-C6)alkyl aminoxy, N,N-di-[\((C 1-C6)alkyl\)aminoxy, (C2-
C6)alkanoyl, (C2-C6)alkanoyloxy, (C2-C6)alkanoylamino, N—(C 1-C6)alkyl-(C2-
C6)alkanoylamino, (C3-C6)alkenoylamino, N—(Cl-C6)alkyl-(C3-
C6)alkenoylamino, (C3-C6)alkynoylamino, sulphamoyl, N—(Cl-C6)alkylsulphamoyl, N,N-di-[\((Cl-
C6)alkyl\)sulphamoyl, (C 1-C6)alkanesulphonylamino, N—(C 1-C6)alkyl-(C 1-
C6)alkanesulphonylamino, carboxamide, ethylene, phenyl, thiophenyl, aminophenyl, phenylthio, halo, cyano, pyridinyl, arylalkyl, hydroxy, N-pyrrolidino, N-morpholino, carboxyl, [5-phenyl-1,2,4-oxadiazole-3-yl]methoxy, 6-methyl-pyridazin-3-yloxy, (5-
oxo-2-pyrrolidinyl) methoxy, 2-(4,5-dihydro-lH-imidazolyl), N,N-
dialkylcarbamoyloxy, 1-hydroxy-1-methylethyl, 4-fluorophenyl, 3,4-
methylenedioxyphenyl, trifluoromethyl, trifluoromethoxy,
a group of the formula

\[
\begin{array}{c}
\text{\(R_{16}\)} \\
\text{\(\text{X}_1\)} \\
\text{\((\text{CH}_2)_n\text{C(\text{CH}_2)_m\text{Q}_1}\)} \\
\end{array}
\]

wherein: \(\text{X}_1\) is O, N, S, S\(_2\), NR\(_{13}\), C(O), or bond; \(\text{Q}_1\) is hydrogen, phenyl, 5-(2,2-difluoro-1,3-benzodioxolyl), C(0)Q\(_5\), or pyridyl when \(m\) and \(n\) are independently 0-2, except when one is 0 the other cannot be 0; \(\text{Q}_1\) is OR\(_{11}\), NR\(_{11}\)R\(_{12}\), halo, N-morpholino, N-piperazino-N'R\(_{13}\), N-imidazolyl, N-pyrazolyl, N-triazolyl, N-(4-piperidinylpiperidine), S\(_2\)R\(_{14}\), SOR\(_{14}\), NHSO\(_2\)R\(_{15}\), acetamido, N-phthalimido, N-oxazolidino, N-imidazolino, N-benzoazolidino, N-pyrididinonyl, N(N'-methylbenzimidazolino), N,N-di(Cl-C4)alkylamino(Cl-C4)alkoxy, N-benzimidazolino; when \(m\) and \(n\) are independently 0-2, but one or the other of \(m\) or \(n\) is not 0; \(\text{Q}_5\) is hydroxy, methoxy, amino, diethylamino, dimethylamino; \(\text{R}_{10}\) is hydrogen, halo, (Cl-C6)alkyl; \(\text{R}_{11}\) and \(\text{R}_{12}\) are independently hydrogen, (Cl-C6)alkyl, (Cl-C6)alkoxy, arylalkyl, (C3-C8)cycloalkyl, (C3-C8)cycloalkylmethyl, 4-(N-methylpiperidinyl), pyridyl, or \(\text{R}_{11}\) and \(\text{R}_{10}\) can be taken together to form a 4, 5, 6, or 7 membered ring, or \(\text{R}_{11}\) and \(\text{R}_{12}\) can be taken together to form a 3, 4, 5, 6, or 7 membered ring; \(\text{R}_{13}\) is hydrogen, (Cl-C6)alkyl, 2-methoxyphenyl, 2-pyridimidinyl; \(\text{R}_{14}\) is 2-pyrimidinyl, N-methyl-2-imidazolyl, 4-chlorophenyl, 2-pyridylmethyl; \(\text{R}_{15}\) is (Cl-C6)alkyl, N-methyl-4-imidazolyl; \(\text{R}_{16}\) is hydrogen, halo, arylalkyl, aryl,
wherein: Q2 is hydrogen, 4-imidazolyl, or C(0)NR24 R25 when o and p are independently 0-2; Q2 is OR23, NR24 R25, or N-morpholino, when o and p are independently 0-2, but one or the other of o or p is not 0; R20 is hydrogen, or (Cl-C6)alkyl; R21 is hydrogen, (Cl-C6)alkyl, or R, and R20 can be taken together to form a 4, 5, 6, or 7 membered ring; R22 is hydrogen, (Cl-C6)alkyl, arylalkyl, aryl, or R, and R22 can be taken together to be a 3, 4, 5, 6, 7 membered ring; R23 is hydrogen or (Cl-C6)alkyl; R24 is hydrogen, (Cl-C6)alkyl, or R24 and R25 can be taken together to form a 3, 4, 5, 6, or 7 membered ring, or R24 and R20 can be taken together to form a 6 or 7 membered ring; R25 is hydrogen, (Cl-C6)alkyl, or acetyl, a group of the formula

\[
\begin{align*}
\text{CNR}_31 \\
\text{R}_{30}
\end{align*}
\]

wherein: R30 is hydrogen, or (Cl-C6)alkyl; R31 is hydrogen, (Cl-C6)alkyl, 2-pyridyl, pyridylmethyl, amino, or hydroxy, a group of the formula

\[
-\text{NR}_{32} R_{33}
\]

wherein: R32 and R33 are each independently hydrogen, (Cl-C6)alkyl, acetyl, (Cl-C4)alkysulphonyl, or R32 and R33 can be taken together to form a 4, 5, 6, or 7 membered ring, a group of the formula
wherein: $X_i$ is $\text{CH}_2$, $O$, or $N$; $q_i$ is 2-3 except when $Q_i$ is a bond, $q_i$ is 0-3; $Q_i$ is $NR_{36}R_{37}$, or $OR_{36}$, and $R_{35}$ is hydrogen, or $R_{35}$ and $Q_3$ can be taken together to form a 5 membered ring; $R_{36}$, $R_{37}$, and $R_{38}$ are each independently hydrogen, or (Cl-C6)alkyl, a group of the formula

![Chemical structure 1](image)

wherein: $X_3$ is cyano, carboxamide, $\text{NN}$-dimethylcarboxamide, $\text{NN}$-dimethylthiocarboxamide, $\text{NN}$-dimethylaminomethyl, 4-methylpiperazin-1yl-methyl or carboxylate, a group of the formula

![Chemical structure 2](image)

wherein: $Q_6$ is $N_1R_{41}R_{42}$; $r$ is 2-3; $R_{40}$ is hydrogen, or (Cl-C6)alkyl; $R_{41}$, and $R_{42}$ are hydrogen, (Cl-C6)alkyl, or $R_{41}$ and $R_{42}$ can be taken together to form a 6 or 7 membered ring, a group of the formula

![Chemical structure 3](image)

wherein: $Q_7$ is hydroxy, methoxy, dimethylamino, or N-piperidinyl;
with the proviso that when one of R1 or R2 is unsubstituted or substituted phenyl, then the other cannot be unsubstituted or substituted phenyl or thiophen-2-yl; and with the proviso that when R2 is quinolin-4-yl, substitution at the quinoline 7-position cannot include an aryl, heteroaryl, fused aryl, or fused heteroaryl;

k is 1-8;

R₃ is one or more of the following: hydrogen; (Cl-C₄)alkyl; (Cl-C₄)alkylhydroxy; hydroxy; N,N-di(Cl-C₄)alkylamino(Cl-C₄)alkoxy; benzyl oxymethyl; phenyloxymethyl; oxo; carboxyl; (Cl-C₄)alkylaryl; benzylox; acetoxy; amino(Cl-C₄)alkyl; (C₂-C₄)alkenyl; halo; —O—(Cl-C₄)alkyl; chlorophenethyl; acetonitrile; unsubstituted or substituted phenyl; wherein the substitution may be one or more of the following: (Cl-C₆)alkoxy, halo, carboxy, or (Cl-C₆)alkoxycarbonyl;

and pharmaceutically acceptable salts and esters thereof.

2. The method of treating schizophrenia, a symptom of schizophrenia or a positive symptom of schizophrenia in a psychotic disease according to Claim 1, wherein the pharmaceutical composition comprises a therapeutically effective amount of a compound of structural formula II:
is a five or six membered saturated ring with the proviso that the ring is a fully saturated carbon ring;

R1 is defined as in structural formula I;

R2' is hydrogen; (Cl-C6)alkyl; (Cl-C6)alkythio; (Cl-C6)alkoxy; halo; thiophenyl; aminophenyl; N-pyrrolidino; N-morpholino;

R6' and R7' are independently selected from the group consisting of: hydrogen, (Cl-C6)alkyl, (C2-C6)alkenyl, (C2-C6)alkynyl, (Cl-C6)alkylhalide, (Cl-C6)alkoxy, (C2-C6)alkenyloxy, (C2-C6)alkynloxy, (Cl-C6)alkythio, (Cl-C6)alkylsulphinyl, (Cl-C6)alkylsulphonyl, (Cl-C6)alkylamino, di-[(Cl-C6)alkyl]amino, (Cl-C6)alkoxycarbonyl, N—(C 1-C6)alkyl carbamoyl, N,N-di-[(C 1-C6)alkyl] carbamoyl, aminooxy, N—(Cl-C6)alkyl aminooxy, N,N-di-[(Cl-C6)alkyl] aminooxy, (C2-C6)alkanoyl, (C2-C6)alkanoxyloxy, (C2-C6)alkanoylamino, N—(C 1-C6)alkyl-(C2-C6)alkanoyl amino, (C3-C6)alkanoyl amino, N—(Cl-C6)alkyl-(C3-C6)alkenoylamino, (C3-C6)alkynoylamino, N—(C1-C6)alkyl-(C3-C6)alkynoylamino, sulphamoyl, N—(Cl-C6)alkyl sulphamoyl, N,N-di-[(Cl-C6)alkyl] sulphamoyl, (Cl-C6)alkanesulphonylamino, N—(C 1-C6)alkyl-(C 1-C6)alkanesulphonylamino, carboxamide, ethylene, phenyl, thiophenyl, aminophenyl, phenylthio, halo, cyano, pyridinyl, arylalkyl, hydroxy, N-pyrrolidino, N-morpholino, carboxyl, [5-phenyl-1,2,4-oxadiazole-3-yl]methoxy, 6-methyl-pyridazin-3-ylmethoxy, (5-oxo-2-pyrrolidinyl)methoxy, 2-(4,5-dihydro-lH-imidazolyl), N,N-dialkylcarbamoyloxy, 1-hydroxy-1-methylethyl, 4-fluorophenyl, 3,4-methylenedioxyphenyl, trifluoromethyl, trifluoromethoxy,
a group of the formula

\[
- X, \quad (C^{\gamma})_n^\gamma C(C^{\gamma})_m^\gamma Q_1^\gamma \quad \text{or bond,}
\]

wherein: X, is O, N, S, S0^2, NR^2, C(O), or bond, Q_1 is hydrogen, phenyl, 5-(2,2-difluoro-1,3-benzodioxoyl), C(0)Q_5, or pyridyl when m and n are independently 0-2, except when one is 0 the other cannot be 0; Q_1 is OR, NR^1, R^12, halo, N-
morpholino, N-piperazino-N'R, N-imidazolyl, N-pyrazolyl, N-triazolyl, N-(4-piperidinylpiperidine), S0_2R_14, SOR_14, NHSO_2R_15, acetamido, N-phthalimido, N-oxazolidino, N-imidazolino, N-benzoxazolidino, N-pyrolidinonyl, N(N'-methylbenzimidazolino), N,N-di(Cl-C4)alkylamino(Cl-C4)alkoxy, N-benzimidazolino; when m and n are independently 0-2, but one or the other of m or n is not 0; Q_5 is hydroxy, methoxy, amino, diethylamino, dimethylamino; R_10 is hydrogen, halo, (Cl-C6)alkyl; R_{11} and R_{12} are independently hydrogen, (Cl-C6)alkyl, (Cl-C6)alkoxy, arylalkyl, cycloalkyl, cycloalkylmethyl, 4-(N-methylpiperidinyl), pyridyl, or R_{11} and R_{10} can be taken together to form a 4, 5, 6, or 7 membered ring, or R_{11} and R_{12} can be taken together to form a 3, 4, 5, 6, or 7 membered ring; R_{13} is hydrogen, (Cl-C6)alkyl, 2-methoxyphenyl; R_{14} is 2-pyrimidinyl, N-methyl-2-imidazolyl, 4-chlorophenyl, 2-pyridylmethyl; R_{15} is (C_j-C6)alkyl, N-methyl-4-imidazolyl; R_{16} is hydrogen, halo, arylalkyl, aryl, a group of the formula

\[
\begin{array}{c}
\text{O} \\
\text{CN(CH}_2)_n\text{C(CH}_2)_m\text{Q}_2 \\
\text{R}_21 \\
\text{R}_20 \\
\text{R}_22
\end{array}
\]

wherein: Q_2 is hydrogen, 4-imidazolyl, or C(0)NR_24R_25 when o and p are independently 0-2; Q_2 is OR_23, NR_24R_25, or N-morpholino, when o and p are independently 0-2, but one or the other of o or p is not 0; R_{20} is hydrogen, or (Cl-C6)alkyl; R_{21} is hydrogen, (Cl-C6)alkyl, or R_{21} and R_{20} can be taken together to form a 4, 5, 6, or 7 membered ring; R_{22} is hydrogen, (Cl-C6)alkyl, arylalkyl, aryl, or R_{21} and R_{22} can be taken together to be a 3, 4, 5, 6, 7 membered ring; R_{23} is hydrogen or (Cl-C6)alkyl; R_{24} is hydrogen, (Cl-C6)alkyl, or R_{24} and R_{25} can be taken together to form a 3, 4, 5, 6, or 7 membered ring, or R_{24} and R_{20} can be taken together to form a 6 or 7 membered ring; R_{25} is hydrogen, (Cl-C6)alkyl, or acetyl,
a group of the formula

\[
\text{O} \begin{array}{c}
\text{CN} \\
\text{R}_{31} \\
\hline
\text{R}_{30}
\end{array}
\]

wherein: \( R_{30} \) is hydrogen, or (Cl-C6)alkyl; \( R_{31} \) is hydrogen, (Cl-C6)alkyl, 2-pyridyl, pyridylmethyl, amino, or hydroxy,

a group of the formula

\[
\begin{array}{c}
\text{NR}_{32} \\
\text{R}_{33}
\end{array}
\]

wherein: \( R_{32} \) and \( R_{33} \) are each independently hydrogen, (Cl-C6)alkyl, acetyl, alkylsulphonyl, or \( R_{32} \) and \( R_{33} \) can be taken together to form a 4, 5, 6, or 7 membered ring,

a group of the formula

\[
\text{O} \begin{array}{c}
\text{NCX} \\
\text{Q}_3
\end{array}
\]

wherein: \( X_2 \) is CH\(_2\), O, or N; \( q \) is 2-3 except when \( Q_3 \) is a bond, \( q \) is 0-3; \( Q_3 \) is \( NR_{36}R_{37} \), OR\(_{38}\), or a bond; \( R_{35} \) is hydrogen, or \( R_{35} \) and \( Q_3 \) (when \( Q_3 \) is a bond) can be taken together to form a 5 membered ring; \( R_{36} \), \( R_{37} \), and \( R_{38} \) are each independently hydrogen, or (Cl-C6)alkyl,

a group of the formula

\[
\text{O} \begin{array}{c}
\text{X}_3
\end{array}
\]

wherein: \( X_3 \) is cyano, carboxamide, N,N-dimethylcarboxamide, N,N-dimethylthiocarboxamide, N,N-dimethylaminomethyl, 4-methylpiperazin-yl-methyl or carboxylate,
a group of the formula

\[
\begin{array}{c}
\text{O} \\
\text{CN(CH}_2)_6\text{Q}_6 \\
\text{R}_40
\end{array}
\]

wherein: \(Q_6\) is \(NR_4_1R_4_2\); \(r\) is 2-3; \(R_40\) is hydrogen, or \((\text{Cl-C6})\text{alkyl}\); \(R_4_1\) and \(R_4_2\) are hydrogen, \((\text{Cl-C6})\text{alkyl}\), or \(R_4_1\) and \(R_4_0\) can be taken together to form a 6 or 7 membered ring,
a group of the formula

\[
\begin{array}{c}
\text{O} \\
\text{CQ}_7
\end{array}
\]

wherein: \(Q_7\) is hydroxy, methoxy, or \(\text{N-piperidinyl}\);
\(k\) is 1-8;
\(R_3\) is one or more of the following: hydrogen; \((\text{Cl-C4})\text{alkyl}\); \((\text{C1-C4})\text{alkylhydroxy}\); hydroxy; \(\text{N,N-di(Cl-C4)alkylamino(Cl-C4)alkoxy}\); benzyl oxymethyl; phenyloxymethyl; oxo; carboxyl; \((\text{Cl-C4})\text{alkylaryl}\); benzyloxy; acetoxy; amino\((\text{Cl-C4})\text{alkyl}\); \((\text{C2-C4})\text{alkenyl}\); halo; \(\text{O}--(\text{Cl-C4})\text{alkyl}\); chlorophenethyl; acetonitrile; phenyl; or an optionally substituted phenyl; wherein the substitution may be one or more of the following: \((\text{Cl-C6})\text{alkoxy}\), halo, carboxy, or \((\text{Cl-C6})\text{alkoxycarbonyl}\); with the proviso that \(R_7'\) cannot be aryl; heteroaryl; fused aryl; or fused heteroaryl,
and the pharmaceutically acceptable salts and esters thereof.

3. The method of treating schizophrenia, a symptom of schizophrenia or a positive symptom of schizophrenia in a psychotic disease according to Claim 1, wherein the pharmaceutical composition comprises a therapeutically effective amount of a compound of structural formula III:
is a five or six-membered saturated ring, with the proviso that the ring is a fully saturated carbon ring;

R1 is is defined as in structural formula I;
R3" is hydrogen, halo, thirfluoromethyl;
R4" is hydrogen, halo, (Ci-C6)alkyl, (Ci-C6)alkoxy, hydroxy, (Ci-C6)alkylsulphonyl;

k and R3 are defined as in structural formula I; and the pharmaceutically acceptable salts and esters thereof.

4. The method of treating schizophrenia, a symptom of schizophrenia or a positive symptom of schizophrenia in a psychotic disease according to Claim 1, wherein the pharmaceutical composition comprises a therapeutically effective amount of a compound of structural formula IV:
is a five or six membered saturated ring, with the proviso that the ring is a fully saturated carbon ring; 
R6 may be one or more of the following: hydrogen, (Cl-C6)alkyl, (C2-C6)alkenyl, (C2-C6)alkynyl, (Cl-C6)alkoxy, (C2-C6)alkenylthio, (Cl-C6)alkylsulphinyl, (Cl-C6)alkylsulphonyl, (Cl-C6)alkylamino, di-[(Cl-C6)alkyl]amino, (Cl-C6)alkoxycarbonyl, N—(Cl-C6)alkylcarbamoyl, N,N-di[(Cl-C6)alkyl]carbamoyl, (C2-C6)alkanoyl, (C2-C6)alkanoyloxy, (C2-C6)alkanoylamino, N—(C1-C6)alkyl-(C2-C6)alkanoylamino, (C3-C6)alkenoylamino, N—(C1-C6)alkyl-(C3-C6)alkenoylamino, (C3-C6)alkynoylamino, N—(C1-C6)alkyl-(C3-C6)alkynoylamino, N—(Cl-C6)alkyl sulphanoylamino, N,N-di-[(Cl-C6)alkyl]sulphamoylamino, (C1-C6)alkanesulphonylamino, carboxamide, ethylene, thiophenyl, aminophenyl, trifluoromethyl, halo, trifluoromethoxy, hydroxymethyl, N-pyrrolidino, N-morpholino, phenylthio, dialkylaminomethyl, methoxyphenyl, amino, hydroxy, carboxyl, phenyl, arylalky;
R2" is unsubstituted or substituted quinoline-8-yl; unsubstituted or substituted quinoline-6-yl; unsubstituted or substituted 1-naphthyl; unsubstituted or substituted 2-naphthyl; unsubstituted or substituted 3,4-methylenedioxyphenyl; unsubstituted or substituted 3,4-ethylenedioxyphenyl; unsubstituted or substituted benzothiophen-2-yl;
wherein the substitution may independently be one or more of the following: (Cl-C6)alkyl, (C2-C6)alkenyl, (C2-C6)alkynyl, (Cl-C6)alkylhalide, (Cl-C6)alkoxy, (C2-C6)alkenyloxy, (C2-C6)alkynylthio, (Cl-C6)alkylthio, (Cl-C6)alkylsulfinyl, (Cl-C6)alkylsulfonyl, (Cl-C6)alkylamino, di-[(Cl-C6)alkyl]amino, (Cl-C6)alkoxycarbonyl, N—(Cl-C6)alkylcarbamoyl, N,N-di[(Cl-C6)alkyl]carbamoyl, (C2-C6)alkanoyl, (C2-C6)alkanoyloxy, (C2-C6)alkanoylamino, N—(C1-C6)alkyl-(C2-C6)alkanoylamino, (C3-C6)alkenoylamino, N—(C1-C6)alkyl-(C3-C6)alkenoylamino, (C3-C6)alkynoylamino, N—(C1-C6)alkyl-(C3-C6)alkynoylamino, N—(Cl-C6)alkyl sulphanoylamino, N,N-di-[(Cl-C6)alkyl]sulphamoylamino, (C1-C6)alkanesulphonylamino, carboxamide, ethylene, thiophenyl, aminophenyl, trifluoromethyl, halo, trifluoromethoxy, hydroxymethyl, N-pyrrolidino, N-morpholino, phenylthio, dialkylaminomethyl, methoxyphenyl, amino, hydroxy, carboxyl, phenyl, arylalky;
alkylsulphinyl, (Cl-C6)alkylsulphonyl, (Cl-C6)alkylamino, di-[(Cl-C6)alkyl]amino, (Cl-C6)alkoxycarbonyl, N—(Cl-C6)alkylcarbamoyl, N,N-di[(Cl-C6)alkyl]aminooxy, (C2-C6)alkanoyl, (C2-C6)alkanoyloxy, (C2-C6)alkanoylamino, N—(Cl-C6)alkyl-(C2-C6)alkanoylamino, (C3-C6)alkenoylamino, N—(Cl-C6)alkyl-(C3-C6)alkenoylamino, (C3-C6)alkynoylamino, N—(Cl-C6)alkyl-(C3-C6)alkynoylamino, sulphamoyl, —(Cl-C6)alkylsulphamoyl, N,N-di-[(Cl-C6)alkyl]sulphamoyl, (Cl-C6)alkanesulphonylamino, —(C1-C6)alkyl-(C1-C6)alkanesulphonylamino, carboxamide, ethylene, phenyl, thiophenyl, aminophenyl, phenylthio, halo, cyano, pyridinyl, arylalkyl, hydroxy, N-pyrrolidino, N-morpholino, carboxyl, [5-phenyl-1,2,4-oxadiazole-3-yl]methoxy, 6-methyl-pyridazin-3-yl oxygen, (5-oxo-2-pyrolidinyl)methoxy, 2-(4,5-dihydro-1H-imidazolyl), N,N-dialkylcarbamoyloxy, 1-hydroxy-1-methylethyl, 4-fluorophenyl, 3,4-methylenedioxyphenyl, trifluoromethyl, trifluoromethoxy,

\[
\begin{align*}
\text{X} & \text{H} \quad \text{C} \quad (\text{CH}_2)_n \quad \text{C} \quad (C^3) \quad \text{m} \quad \text{Q}_1 \\
\end{align*}
\]

a group of the formula

\[
\begin{align*}
\text{R}_{10} \\
\end{align*}
\]

wherein: X \text{is} O, N, S, S0_2, NR_{13}, C(O), or bond; Q_1 is hydrogen, phenyl, 5-(2,2-difluoro-1,3-benzodioxolyl), C(0)Q_5, or pyridyl when m and n are independently 0-2, except when one is 0 the other cannot be 0; Q_1 is OR_{11}, NR_{11}, R_{12}, halo, N-morpholino, N-piperazino-N'NR_{13}, N-imidazolino, N-pyrrozalino, N-triazolino, N-(4-piperidinylpiperidine), S0_2R_{14}, SOR_{14}, NHSO_2R_{15}, acetamido, N-phthalimido, N-oxazolidino, N-imidazolino, N-benoxazolidino, N-pyrolinonilly, N(N'-methylbenzimidazolino), N,N-di(Cl-C4)alkylamino(Cl-C4)alkoxy, N-benzimidazolino; when m and n are independently 0-2, but one or the other of m or n is not 0; Q_5 is hydroxy, methoxy, amino, diethylamino, dimethylamino; R_{10} is hydrogen, halo, (C_1-C6)alkyl; R_{11} and R_{12} are independently hydrogen, (Cl-
C6)alkyl, (Cl-C6)alkoxy, arylalkyl, cycloalkyl, cycloalkylmethyl, 4-N-methylpiperidinyl, pyridyl, or R_{11} and R_{10} can be taken together to form a 4, 5, 6, or 7 membered ring, or R_{11} and R_{12} can be taken together to form a 3, 4, 5, 6, or 7 membered ring; R_{13} is hydrogen, (Cl-C6)alkyl, 2-methoxyphenyl; R_{14} is 2-pyrimidinyl, N-methyl-2-imidazolyl, 4-chlorophenyl, 2-pyridylmethyl; R_{15} is (Cl-C6)alkyl, N-methyl-4-imidazolyl; R_{16} is hydrogen, halo, arylalkyl, aryl, a group of the formula

\[
\begin{array}{c}
\text{O} \quad R_{21} \\
\hline
\text{CN(CH}_2\text{)}_6\text{C(CH}_2\text{)}_pQ_2 \\
\hline
R_{20} \quad 1 \quad R_{22}
\end{array}
\]

wherein: Q_2 is hydrogen, 4-imidazolyl, or C(0)NR_{23}R_{25} when o and p are independently 0-2; Q_2 is OR_{23}, NR_{23}R_{25}, or N-morpholino, when o and p are independently 0-2, but one or the other of o or p is not 0; R_{20} is hydrogen, or (Cl-C6)alkyl; R_{21} is hydrogen, (Cl-C6)alkyl, or R_{21} and R_{20} can be taken together to form a 4, 5, 6, or 7 membered ring; R_{22} is hydrogen, (Cl-C6)alkyl, arylalkyl, aryl, or R_{21} and R_{22} can be taken together to be a 3, 4, 5, 6, 7 membered ring; R_{23} is hydrogen or (C_1-C6)alkyl; R_{24} is hydrogen, (Cl-C6)alkyl, or R_{24} and R_{25} can be taken together to form a 3, 4, 5, 6, or 7 membered ring, or R_{24} and R_{20} can be taken together to form a 6 or 7 membered ring; R_{25} is hydrogen, (Cl-C6)alkyl, or acetyl, a group of the formula

\[
\begin{array}{c}
p \\
\hline
\text{C|R}_\text{31} \\
R_{30}
\end{array}
\]

wherein: R_{30} is hydrogen, or (Cl-C6)alkyl; R_{31} is hydrogen, (Cl-C6)alkyl, 2-pyridyl, pyridylmethyl, amino, or hydroxy,

64
a group of the formula
\[ \text{NR}_3^2 \text{R}_3^3 \]
wherein: \( \text{R}_3^2 \) and \( \text{R}_3^3 \) are each independently hydrogen, \((\text{Cl-C6})\)alkyl, acetyl, alkylsulphonyl, or \( \text{R}_3^2 \) and \( \text{R}_3^3 \) can be taken together to form a 4, 5, 6, or 7 membered ring,
a group of the formula
\[
\begin{array}{c}
| \\
\text{O} \\
\text{NCX}_2(\text{CH}_2)_q\text{Q}_3 \\
\text{R}_3^5 \\
\end{array}
\]
wherein: \( X_2 \) is \( \text{CH}_2, \text{O}, \text{or N}; \) \( q \) is 2-3 except when \( \text{Q}_3 \) is a bond, \( q \) is 0-3; \( \text{Q}_3 \) is \( \text{NR}_3^6 \text{R}_3^{37}, \text{OR}_3^{38}, \text{or a bond}; \) \( \text{R}_3^5 \) is hydrogen, or \( \text{R}_3^5 \) and \( \text{Q}_3 \) (when \( \text{Q}_3 \) is a bond) can be taken together to form a 5 membered ring; \( \text{R}_3^{36}, \text{R}_3^{37}, \text{and R}_3^{38} \) are each independently hydrogen, or \((\text{Cl-C6})\)alkyl,
a group of the formula
\[
\begin{array}{c}
\text{O} \\
\text{X}_3 \\
\end{array}
\]
wherein: \( \text{X}_3 \) is cyano, carboxamide, \( \text{N, N-dimethylcarboxamide, N, N-dimethylthiocarboxamide, N, N-dimethylaminomethyl, 4-methylpiperazin- lyl-methyl or carboxylate,} \)
a group of the formula
\[
\begin{array}{c}
\text{O} \\
\text{CN(\text{CH}_2)_r\text{Q}_6} \\
\text{R}_4^0 \\
\end{array}
\]
wherein: \( \text{Q}_6 \) is \( \text{NR}_4^1 \text{R}_4^{42}; \) \( r \) is 2-3; \( \text{R}_4^0 \) is hydrogen, or \((\text{Cl-C6})\)alkyl; \( \text{R}_4^1 \) and \( \text{R}_4^2 \) are
hydrogen, (Cl-C6)alkyl, or R_{41} and R_{40} can be taken together to form a 6 or 7 membered ring,
a group of the formula

\[
\begin{align*}
\text{(CQ)}_7
\end{align*}
\]

wherein: Q is hydroxy, methoxy, dimethylamino, or N-piperidinyl;

k is 1-8;

R_{3} is hydrogen;

and the pharmaceutically acceptable salts and esters thereof.

5. The method of treating schizophrenia, a symptom of schizophrenia or a positive symptom of schizophrenia in a psychotic disease according to Claim 3, wherein the compound is selected from the group consisting of 4-[2-(6-Methyl-pyridin-2-yl)-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl]phenol; and pharmaceutically acceptable salts and esters thereof.

6. The method of treating schizophrenia, a symptom of schizophrenia or a positive symptom of schizophrenia in a psychotic disease according to Claim 2, wherein the compound is selected from the group consisting of 4-[2-(6-Methyl-pyridin-2-yl)-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl]-quinoline-6-carboxylic acid amide; and pharmaceutically acceptable salts and esters thereof.

7. The method of treating schizophrenia, a symptom of schizophrenia or a positive symptom of schizophrenia in a psychotic disease according to Claim 1, wherein the pharmaceutical composition further comprises at least one pharmaceutically acceptable additive selected from the group consisting of adjuvant, excipient, diluent, and carrier.

8. The method of treating schizophrenia, a symptom of schizophrenia or a positive symptom of schizophrenia in a psychotic disease according to Claim 2, wherein the pharmaceutical composition further comprises at least one pharmaceutically acceptable additive selected from the group consisting of adjuvant, excipient, diluent, and carrier.
9. The method of treating schizophrenia, a symptom of schizophrenia or a positive symptom of schizophrenia in a psychotic disease according to Claim 3, wherein the pharmaceutical composition further comprises at least one pharmaceutically acceptable additive selected from the group consisting of adjuvant, excipient, diluent, and carrier.

10. The method of treating schizophrenia, a symptom of schizophrenia or a positive symptom of schizophrenia in a psychotic disease according to Claim 4, wherein the pharmaceutical composition further comprises at least one pharmaceutically acceptable additive selected from the group consisting of adjuvant, excipient, diluent, and carrier.

11. The method of treating schizophrenia, a symptom of schizophrenia or a positive symptom of schizophrenia in a psychotic disease according to Claim 5, wherein the pharmaceutical composition further comprises at least one pharmaceutically acceptable additive selected from the group consisting of adjuvant, excipient, diluent, and carrier.

12. The method of treating schizophrenia, a symptom of schizophrenia or a positive symptom of schizophrenia in a psychotic disease according to Claim 6, wherein the pharmaceutical composition further comprises at least one pharmaceutically acceptable additive selected from the group consisting of adjuvant, excipient, diluent, and carrier.

13. The method of treating schizophrenia, a symptom of schizophrenia or a positive symptom of schizophrenia in a psychotic disease according to Claim 1, wherein the mammal is a human.

14. The method of treating schizophrenia, a symptom of schizophrenia or a positive symptom of schizophrenia in a psychotic disease according to Claim 2, wherein the mammal is a human.

15. The method of treating schizophrenia, a symptom of schizophrenia or a positive symptom of schizophrenia in a psychotic disease according to Claim 3, wherein the mammal is a human.

16. The method of treating schizophrenia, a symptom of schizophrenia or a positive symptom of schizophrenia in a psychotic disease according to Claim 4, wherein the mammal is a human.
17. The method of treating schizophrenia, a symptom of schizophrenia or a positive symptom of schizophrenia in a psychotic disease according to Claim 5, wherein the mammal is a human.

18. The method of treating schizophrenia, a symptom of schizophrenia or a positive symptom of schizophrenia in a psychotic disease according to Claim 6, wherein the mammal is a human.

19. The method of treating a positive symptom of schizophrenia in a psychotic disease according to Claim 1, wherein the disease is bipolar disorder, delusional disorder, psychotic depression, Tourette syndrome, autism spectrum disorder, OCD, dementia or Alzheimer's disease.

20. The method of treating a positive symptom of schizophrenia in a psychotic disease according to Claim 2, wherein the disease is bipolar disorder, delusional disorder, psychotic depression, Tourette syndrome, autism spectrum disorder, OCD, dementia or Alzheimer's disease.

21. The method of treating a positive symptom of schizophrenia in a psychotic disease according to Claim 3, wherein the disease is bipolar disorder, delusional disorder, psychotic depression, Tourette syndrome, autism spectrum disorder, OCD, dementia or Alzheimer's disease.

22. The method of treating a positive symptom of schizophrenia in a psychotic disease according to Claim 4, wherein the disease is bipolar disorder, delusional disorder, psychotic depression, Tourette syndrome, autism spectrum disorder, OCD, dementia or Alzheimer's disease.

23. The method of treating a positive symptom of schizophrenia in a psychotic disease according to Claim 5, wherein the disease is bipolar disorder, delusional disorder, psychotic depression, Tourette syndrome, autism spectrum disorder, OCD, dementia or Alzheimer's disease.

24. The method of treating a positive symptom of schizophrenia in a psychotic disease according to Claim 6, wherein the disease is bipolar disorder, delusional disorder, psychotic depression, Tourette syndrome, autism spectrum disorder, OCD, dementia or Alzheimer's disease.
25. The method of treating a positive symptom of schizophrenia in a psychotic disease according to Claim 1, wherein the positive symptom is at least one selected from the group consisting of delusions, hallucinations, and movement and thought disorders.

26. The method of treating a positive symptom of schizophrenia in a psychotic disease according to Claim 25, wherein the thought disorder is selected from the group consisting of disorganized speech, grossly disorganized behavior and catatonic behavior.

27. The method of treating a positive symptom of schizophrenia in a psychotic disease according to Claim 2, wherein the positive symptom is at least one selected from the group consisting of delusions, hallucinations, and movement and thought disorders.

28. The method of treating a positive symptom of schizophrenia in a psychotic disease according to Claim 27, wherein the thought disorder is selected from the group consisting of disorganized speech, grossly disorganized behavior and catatonic behavior.

29. The method of treating a positive symptom of schizophrenia in a psychotic disease according to Claim 3, wherein the positive symptom is at least one selected from the group consisting of delusions, hallucinations, and movement and thought disorders.

30. The method of treating a positive symptom of schizophrenia in a psychotic disease according to Claim 29, wherein the thought disorder is selected from the group consisting of disorganized speech, grossly disorganized behavior and catatonic behavior.

31. The method of treating a positive symptom of schizophrenia in a psychotic disease according to Claim 4, wherein the positive symptom is at least one selected from the group consisting of delusions, hallucinations, and movement and thought disorders.

32. The method of treating a positive symptom of schizophrenia in a psychotic disease according to Claim 31, wherein the thought disorder is selected from the group consisting of disorganized speech, grossly disorganized behavior and catatonic behavior.
33. The method of treating a positive symptom of schizophrenia in a psychotic disease according to Claim 5, wherein the positive symptom is at least one selected from the group consisting of delusions, hallucinations, and movement and thought disorders.

34. The method of treating a positive symptom of schizophrenia in a psychotic disease according to Claim 33, wherein the thought disorder is selected from the group consisting of disorganized speech, grossly disorganized behavior and catatonic behavior.

35. The method of treating a positive symptom of schizophrenia in a psychotic disease according to Claim 6, wherein the positive symptom is at least one selected from the group consisting of delusions, hallucinations, and movement and thought disorders.

36. The method of treating a positive symptom of schizophrenia in a psychotic disease according to Claim 35, wherein the thought disorder is selected from the group consisting of disorganized speech, grossly disorganized behavior and catatonic behavior.

37. A compound of structural formula I:

Diagram of structural formula I:

wherein

Diagram of structural formula I:

is a four, five or six membered saturated ring and X is C, O or S;
R1 is unsubstituted or substituted phenyl; unsubstituted or substituted pyridine; unsubstituted or substituted quinoline; unsubstituted or substituted quinoline N-oxide; unsubstituted or substituted naphthalene; unsubstituted or substituted pyridine; unsubstituted or substituted pyrazine; unsubstituted or substituted thiazolyl; unsubstituted or substituted imidazolyl; unsubstituted or substituted pyrazolyl; or unsubstituted or substituted thiophenyl; wherein the substitution is one or more group selected from the group consisting of: (Cl-C6)alkyl, (C2-C6)alkenyl, (C2-C6)alkynyl, (Cl-C6)alkoxy, (C2-C6)alkenylcoxy, (C2-C6)alkynylcoxy, (Cl-C6)alkylsulphoxy, (Cl-C6)alkylthio, (Cl-C6)alkylsulphinyl, (Cl-C6)alkylsulphonyl, (Cl-C6)alkoxy carbonyl, N—[Cl-C6]alkylcarbamoyl, N,N-di-[Cl-C6]alkylcarbamoyl, (C2-C6)alkanoyl, (C2-C6)alkanoyloxy, (C2-C6)alkanoylamino, N—[(Cl-C6)alkyl](C3-C6)alkanoylamino, (C3-C6)alkenoylamino, N—[(Cl-C6)alkyl](C3-C6)alkenoylamino, (Cl-C6)alkynoylamino, N—[(Cl-C6)alkylsulphamoyl, N,N-di-[Cl-C6]alkylsulphamoyl, (Cl-C6)alkanesulphonylamino, (C1-C6)alkanesulphonylamino, carboxamide, ethylene, thiophenyl, aminophenyl, trifluoromethyl, halo, trifluoromethoxy, hydroxymethyl, N-pyrrolidino, N-morpholino, phenylthio, (Cl-C4)dialkylaminomethyl, methoxyphenyl, amino, hydroxy, carboxyl, phenyl, and arylalky;

R2 is unsubstituted or substituted quinoline; unsubstituted or substituted quinoline N-oxide; unsubstituted or substituted phenyl; unsubstituted or substituted naphthalene; unsubstituted or substituted pyridine; unsubstituted or substituted pyridine N-oxide; unsubstituted or substituted quinazoline; unsubstituted or substituted cinnoline; unsubstituted or substituted benzodioxole; unsubstituted or substituted benzodioxane; unsubstituted or substituted pyrimidine; unsubstituted or substituted benzothiophene; or unsubstituted or substituted phenanthroline;

wherein is one or more group selected from the group consisting of: hydrogen, (Cl-C6)alkyl, (C2-C6)alkenyl, (C2-C6)alkynyl, (Cl-C6)alkylhalide, (Cl-C6)alkoxy, (C2-C6)alkenyloxy, (C2-C6)alkynylcoxy, (Cl-C6)alkylthio, (Cl-C6)alkylsulphinyl, (Cl-C6)alkylsulphonyl, (Cl-C6)alkylamino, di-[(Cl-C6)alkyl]amino, (Cl-C6)alkoxy carbonyl, N—[Cl-C6]alkylcarbamoyl, N,N-di-[Cl-C6]alkylcarbamoyl, (Cl-C6)alkanoyl, (Cl-C6)alkanoyloxy, (Cl-C6)alkanoylamino, N—[(Cl-C6)alkylsulphamoyl, N,N-di-[Cl-C6]alkylsulphamoyl, (Cl-C6)alkanesulphonylamino, (C1-C6)alkanesulphonylamino, carboxamide, ethylene, thiophenyl, aminophenyl, trifluoromethyl, halo, trifluoromethoxy, hydroxymethyl, N-pyrrolidino, N-morpholino, phenylthio, (Cl-C4)dialkylaminomethyl, methoxyphenyl, amino, hydroxy, carboxyl, phenyl, and arylalky;
C6)alkanoyl, (C2-C6)alkanoyloxy, (C2-C6)alkanoylamino, N—(C1-C6)alkyl-(C2-C6)alkanoylamino, (C3-C6)alkenoylamino, — (C1-C6)alkyl-(C3-C6)alkenoylamino, (C3-C6)alkynoylamino, — (C1-C6)alkyl-(C3-C6)alkynoylamino, sulphamoyl, — (C1-C6)alkylsulphamoyl, N,N-di-[(C1-C6)alkyl]sulphamoyl, (C3-C6)alkanesulphonylamino, — (C1-C6)alkyl-(C3-C6)alkanesulphonylamino, carboxamide, ethylene, phenyl, thiophenyl, aminophenyl, phenylthio, halo, cyano, pyridinyl, arylalkyl, hydroxy, N-pyrrolidino, N-morpholino, carboxyl, [5-phenyl-1,2,4-oxadiazole-3-yl]methoxy, 6-methyl-pyridazin-3-yloxy, (5-oxo-2-pyrrolidinyl)methoxy, 2-(4,5-dihydro-1H-imidazolyl), N,N-dialkylcarbamoyloxy, 1-hydroxy-1-methylethyl, 4-fluorophenyl, 3,4-methylenedioxyphenyl, trifluoromethyl, trifluoromethoxy,

a group of the formula

\[ \begin{array}{c}
    R_{10} \\
    \downarrow \\
    X_j \quad (\text{CH}_2)_n \quad C(\text{CH}_2)_m \quad Q_1 \\
    \downarrow \\
    R_{16}
\end{array} \]

wherein: \( X_j \) is O, N, S, S0,2, NR13, C(O), or bond; \( Q_1 \) is hydrogen, phenyl, 5-(2,2-difluoro-1,3-benzodioxolyl), C(O)Q5, or pyridyl when m and n are independently 0-2, except when one is 0 the other cannot be 0; \( Q_1 \) is OR11, NR11, R12, halo, N-morpholino, N-piperazino-NR13, N-imidazolyl, N-pyrazolyl, N-triazolyl, N-(4-piperidinylpiperidine), S02R14, SOR14, NHS02R15, acetamido, N-phthalimido, N-oxazolidino, N-imidazolin, N-benzoaxazolidino, N-pyridinonyl, N(N'-methylbenzimidazolino), N,N-di(1-C6)alkylmino(Cl-C4)alkoxy, N-benzimidazolino; when m and n are independently 0-2, but one or the other of m or n is not 0; \( Q_5 \) is hydroxy, methoxy, amino, diethylamino, dimethylamino; \( R_{10} \) is hydrogen, halo, (Cl-C6)alkyl; \( R_{11} \) and \( R_{12} \) are independently hydrogen, (Cl-C6)alkyl, (Cl-C6)alkoxy, arylalkyl, (C3-C8)cycloalkyl, (C3-C8)cycloalkylmethyl, 4-(N-
methylpiperidinyl), pyridyl, or $R_{1j}$ and $R_{10}$ can be taken together to form a 4, 5, 6, or 7 membered ring, or $R_{1j}$ and $R_{12}$ can be taken together to form a 3, 4, 5, 6, or 7 membered ring; $R_{13}$ is hydrogen, (Cl-C6)alkyl, 2-methoxyphenyl, 2-pyrimidinyl; $R_{14}$ is 2-pyridimidyln, N-methyl-2-imidazolyl, 4-chlorophenyl, 2-pyridylmethyl; $R_{15}$ is (Cl-C6)alkyl, N-methyl-4-imidazolyl; $R_{16}$ is hydrogen, halo, arylalkyl, aryl, a group of the formula

$$\begin{align*}
\text{Q}_2 & \text{O} \\
& \text{CN}(\text{CH}_2)_QR_{21} \\
& \text{R}_{20} \quad \text{R}_{22}
\end{align*}$$

wherein: $Q_2$ is hydrogen, 4-imidazolyl, or C(0)NR$_{24}$R$_{25}$ when o and p are independently 0-2; $Q_2$ is OR$_{23}$, NR$_{24}$R$_{25}$, or N-morpholino, when o and p are independently 0-2, but one or the other of o or p is not 0; $R_{20}$ is hydrogen, or (Cl-C6)alkyl; $R_{21}$ is hydrogen, (Cl-C6)alkyl, arylalkyl, aryl, or $R_2$, and $R_{20}$ can be taken together to form a 4, 5, 6, or 7 membered ring; $R_{22}$ is hydrogen, (Cl-C6)alkyl, arylalkyl, aryl, or $R_2$, and $R_{22}$ can be taken together to form a 3, 4, 5, 6, 7 membered ring; $R_{23}$ is hydrogen or (Cl-C6)alkyl; $R_{24}$ is hydrogen, (Cl-C6)alkyl, or $R_{24}$ and $R_{25}$ can be taken together to form a 3, 4, 5, 6, or 7 membered ring, or $R_{24}$ and $R_{20}$ can be taken together to form a 6 or 7 membered ring; $R_{25}$ is hydrogen, (Cl-C6)alkyl, or acetyl, a group of the formula

$$\begin{align*}
\text{O} \\
\text{CNR}_{31} \\
\text{R}_{30}
\end{align*}$$
wherein: \( R_{3q} \) is hydrogen, or \((\text{Cl-C6})\text{alkyl}\); \( R_{31} \) is hydrogen, \((\text{Cl-C6})\text{alkyl}\), 2-pyridyl, pyridylmethyl, amino, or hydroxy,
a group of the formula

\[
-\text{NR}_{32}R_{33}
\]

wherein: \( R_{32} \) and \( R_{33} \) are each independently hydrogen, \((\text{Cl-C6})\text{alkyl}\), acetyl, 
\((\text{Cl-C4})\text{alkylsulphonyl}\), or \( R_{32} \) and \( R_{33} \) can be taken together to form a 4, 5, 6, or 7 membered ring,
a group of the formula

\[
\text{O} \\
\text{NCX}_2(\text{CH}_2)_qQ_3 \\
\text{R}_{35}
\]

wherein: \( X_2 \) is \( \text{CH}_2 \), O, or N; \( q \) is 2-3 except when \( Q_3 \) is a bond, \( q \) is 0-3; \( Q_3 \)
is \( \text{NR}_{36}R_{37} \), or \( \text{OR}_{38} \), and \( R_{35} \) is hydrogen, or \( R_{35} \) and \( Q_3 \) can be taken
together to form a 5 membered ring; \( R_{36}, R_{37}, \) and \( R_{38} \) are each independently hydrogen, or \((\text{Cl-C6})\text{alkyl}\),
a group of the formula

\[
\text{X}_3
\]

wherein: \( X_3 \) is cyano, carboxamide, \( \text{N,N-dimethylcarboxamide}\), \( \text{N,N-dimethylthiocarboxamide}\), \( \text{N,N-dimethylaminomethyl}\), 4-methylpiperazin-\( \text{N-1y1\text{-methyl or carboxylate}\),
a group of the formula

\[
\text{O} \\
\text{CN(\text{CH}_2)_3Q}_6 \\
\text{R}_{40}
\]
wherein: $Q_6$ is $N_j R_{41} R_{42}$; $r$ is 2-3; $R_{40}$ is hydrogen, or (Cl-C6)alkyl; $R_{41}$, and $R_{42}$ are hydrogen, (Cl-C6)alkyl, or $R_{41}$, and $R_{40}$ can be taken together to form a 6 or 7 membered ring,

a group of the formula

![Chemical Structure](image)

wherein: $Q_7$ is hydroxy, methoxy, dimethylamino, or N-piperidinyl;

with the proviso that when one of $R_1$ or $R_2$ is unsubstituted or substituted phenyl, then the other cannot be unsubstituted or substituted phenyl or thiophen-2-yl; and with the proviso that when $R_2$ is quinolin-4-yl, substitution at the quinoline 7-position cannot include an aryl, heteroaryl, fused aryl, or fused heteroaryl;

$k$ is 1-8;

$R_3$ is one or more of the following: hydrogen; (Cl-C4)alkyl; (Cl-C4)alkylhydroxy; hydroxy; N,N-di(Cl-C4)alkylamino(Cl-C4)alkoxy; benzyl oxymethyl; phenyloxymethyl; oxo; carboxyl; (Cl-C4)alkylaryl; benzyloxy; acetoxy; amino(Cl-C4)alkyl; (C2-C4)alkenyl; halo; $—O—$(Cl-C4)alkyl; chlorophenethyl; acetonitrile; unsubstituted or substituted phenyl;

wherein the substitution may be one or more of the following: (Cl-C6)alkoxy, halo, carboxy, or (Cl-C6)alkoxycarbonyl;

or pharmaceutically acceptable salts and esters thereof,

for use in the treatment of schizophrenia or a symptom of schizophrenia or a positive symptom of schizophrenia in a psychotic disease.
38. The compound of Claim 37 for use in the treatment of schizophrenia or a symptom of schizophrenia or a positive symptom of schizophrenia in a psychotic disease, wherein the pharmaceutical composition comprises a therapeutically effective amount of a compound of structural formula II:

![Structural formula](image)

is a five or six membered saturated ring with the proviso that the ring is a fully saturated carbon ring;

R1 is defined as in structural formula I;

R2' is hydrogen; (Cl-C6)alkyl; (Cl-C6)alkylthio; (Cl-C6)alkoxy; halo; thiophenyl; aminophenyl; N-pyrrolidino; N-morpholino;

R6' and R7' are independently selected from the group consisting of: hydrogen, (Cl-C6)alkyl, (C2-C6)alkenyl, (C2-C6)alkynyl, (Cl-C6)alkylhalide, (Cl-C6)alkoxy, (C2-C6)alkenyloxy, (C2-C6)alkynloxy, (Cl-C6)alkylthio, (Cl-C6)alkylsulphinyl, (Cl-C6)alkylsulphonyl, (Cl-C6)alkylamino, di-[(Cl-C6)alkyl]amino, (Cl-C6)alkoxy carbonyl, N—(C 1-C6)alkyl carbamoyl, N,N-di-[(C 1-C6)alkyl] carbamoyl, aminooxy, N—(Cl-C6)alkyl aminooxy, N,N-di-[(Cl-C6)alkyl] aminooxy, (C2-C6)alkanoyl, (C2-C6)alkanoyloxy, (C2-C6)alkanoylamino, N—(C 1-C6)alkyl-(C2-C6) alkanoylamino, (C3-C6) alkanoyl amino, N—(Cl-C6) alkyl-(C3-C6) alkenoylamino,
(C3-C6)alkynoylamino, N—(Cl-C6)alkyl-(C3-C6)alkynoylamino, sulphamoyl, N—(Cl-C6)alkylsulphamoyl, N,N-di-[{(Cl-C6)alkyl}] sulphamoyl, (Cl-C6)alkanesulphonylamino, N—(C1-C6)alkyl-(C1-C6)alkanesulphonylamino, carboxamide, ethylene, phenyl, thiophenyl, aminophenyl, phenylthio, halo, cyano, pyridinyl, arylalkyl, hydroxy, N-pyrrolidino, N-morpholino, carboxyl, [5-phenyl-1,2,4-oxadiazole-3-yl]methoxy, 6-methyl-pyridazin-3-yl]methoxy, (5-oxo-2-pyrrolidinyl)methoxy, 2-(4,5-dihydro-1H-imidazolyl), N,N-dialkylcarbamoyloxy, 1-hydroxy-1-methylethyl, 4-fluorophenyl, 3,4-methylenedioxyphenyl, trifluoromethyl, trifluoromethoxy, a group of the formula

```
R_{10}
\downarrow
X_1\downarrow\,(CH_2)_n\text{C}(CH_2)_mQ_1
\downarrow
R_{16}
```

wherein: $X_1$ is O, N, S, S0$_2$, NR$_{13}$, C(O), or bond, $Q_1$ is hydrogen, phenyl, 5-(2,2-difluoro-1,3-benzodioxolyl), C(0)Q$_5$, or pyridyl when m and n are independently 0-2, except when one is 0 the other cannot be 0; $Q_j$ is OR$_{1 j}$, NR$_{11}$R$_{12}$, halo, N-morpholino, N-piperazino-N'R$_{13}$, N-imidazolyl, N-pyrazolyl, N-triazolyl, N-(4-piperidinylpiperidine), S0$_2$R$_{14}$, SOR$_{14}$, NHSO$_2$R$_{15}$, acetamido, N-phthalimido, N-oxazolidino, N-imidazolino, N-benzoazolidino, N-pyridinononyl, N(N'-methylbenzimidazolino), N,N-di(Cl-C4)alkylamino(Cl-C4)alkoxy, N-benzimidazolino; when m and n are independently 0-2, but one or the other of m or n is not 0; $Q_5$ is hydroxy, methoxy, amino, diethylamino, dimethylamino; $R_{10}$ is hydrogen, halo, (Cl-C6)alkyl; $R_{11}$ and $R_{12}$ are independently hydrogen, (Cl-C6)alkyl, (Cl-C6)alkoxy, aryalkyl, cycloalkyl, cycloalkylmethyl, 4-(N-methylpiperidinyl), pyridyl, or $R_{11}$ and $R_{10}$ can be taken together to form a 4, 5, 6, or 7 membered ring, or $R_{1 j}$ and $R_{12}$ can be taken together to form a 3, 4, 5, 6, or 7 membered ring; $R_{13}$ is hydrogen, (Cl-C6)alkyl, 2-methoxyphenyl; $R_{14}$ is 2-pyrimidinyl, N-methyl-2-imidazolyl, 4-chlorophenyl, 2-pyridylmethyl; $R_{15}$ is (C$_j$-
C6)alkyl, N-methyl-4-imidazolyl; R_{16} is hydrogen, halo, arylalkyl, aryl,
a group of the formula

\[
\begin{array}{c}
O \\
\hline
\hline
CN(CH_2)_nC(CH_2)_pQ_2 \\
\hline
R_{20} \\
R_{22}
\end{array}
\]

wherein: Q_2 is hydrogen, 4-imidazolyl, or C(0)NR_{24}R_{25} when o and p are
independently 0-2; Q_2 is OR_{23}, NR_{24}R_{25}, or N-morpholino, when o and p are
independently 0-2, but one or the other of o or p is not 0; R_{20} is hydrogen, or (Cl-C6)alkyl; R_{21} is hydrogen, (Cl-C6)alkyl, or R_{21} and R_{20} can be taken together to
form a 4, 5, 6, or 7 membered ring; R_{22} is hydrogen, (Cl-C6)alkyl, arylalkyl, aryl, or
R_{21} and R_{22} can be taken together to be a 3, 4, 5, 6, 7 membered ring; R_{23} is hydrogen
or (Cl-C6)alkyl; R_{24} is hydrogen, (Cl-C6)alkyl, or R_{24} and R_{25} can be taken together
to form a 3, 4, 5, 6, or 7 membered ring, or R_{24} and R_{20} can be taken together to form
a 6 or 7 membered ring; R_{25} is hydrogen, (Cl-C6)alkyl, or acetyl,
a group of the formula

\[
\begin{array}{c}
p \\
\hline
\hline
CNR_{31} \\
R_{30}
\end{array}
\]

wherein: R_{30} is hydrogen, or (Cl-C6)alkyl; R_{31} is hydrogen, (Cl-C6)alkyl, 2-pyridyl,
pyridylmethylyl, amino, or hydroxy,
a group of the formula

\[\text{NR}_{32}R_{33}\]

wherein: R_{32} and R_{33} are each independently hydrogen, (Cl-C6)alkyl, acetyl,
alkylsulphonyl, or R_{32} and R_{33} can be taken together to form a 4, 5, 6, or 7 membered
ring,
a group of the formula

![Chemical Structure]

wherein: $X_2$ is CH$_2$, O, or N; $q$ is 2-3 except when $Q_3$ is a bond, $q$ is 0-3; $Q_3$ is \text{NR}_3\text{R}_7, \text{OR}_8, or a bond; $R_{35}$ is hydrogen, or $R_{35}$ and $Q_3$ (when $Q_3$ is a bond) can be taken together to form a 5 membered ring; $R_{36}$, $R_{37}$, and $R_{38}$ are each independently hydrogen, or (Cl-C6)alkyl,

a group of the formula

![Chemical Structure]

wherein: $X_3$ is cyano, carboxamide, N,N-dimethylcarboxamide, N,N-dimethylthiocarboxamide, N,N-dimethylaminomethyl, 4-methylpiperazin-yl-methyl or carboxylate,

a group of the formula

![Chemical Structure]

wherein: $Q_6$ is NR$_{41}$R$_{42}$; $r$ is 2-3; $R_{40}$ is hydrogen, or (Cl-C6)alkyl; $R_{41}$ and $R_{42}$ are hydrogen, (Cl-C6)alkyl, or $R_{41}$ and $R_{40}$ can be taken together to form a 6 or 7 membered ring,

a group of the formula
wherein: Q is hydroxy, methoxy, or N-piperidinyl;
k is 1-8;
R₃ is one or more of the following: hydrogen; (Cl-C4)alkyl; (C1-C4) alkylhydroxy; hydroxy; N,N-di(Cl-C4)alkylamino(Cl-C4)alkoxy; benzyl oxymethyl; phenyloxymethyl; oxo; carboxyl; (Cl-C4)alkylaryl; benzyl; acetoxy; amino(Cl-C4)alkyl; (C2-C4)alkenyl; halo; —O—(Cl-C4)alkyl; chlorophenethyl; acetonitrile; phenyl; or an optionally substituted phenyl; wherein the substitution may be one or more of the following: (Cl-C6)alkoxy, halo, carboxy, or (Cl-C6)alkoxycarbonyl; with the proviso that R₇ cannot be aryl; heteroaryl; fused aryl; or fused heteroaryl, or pharmaceutically acceptable salts and esters thereof.

39. The compound of Claim 37 for use in the treatment of schizophrenia or a symptom of schizophrenia or a positive symptom of schizophrenia in a psychotic disease, wherein the pharmaceutical composition comprises a therapeutically effective amount of a compound of structural formula III:
is a five or six-membered saturated ring, with the proviso that the ring is a fully saturated carbon ring;

R1 is is defined as in structural formula I;
R3" is hydrogen, halo, thirfluoromethyl;
R4" is hydrogen, halo, (C1-C6)alkyl, (C1-C6)alkoxy, hydroxy, (C1-C6)alkylsulphonyl;
k and R3 are defined as in structural formula I;
or the pharmaceutically acceptable salts and esters thereof.

40. The compound of Claim 37 for use in the treatment of schizophrenia or a symptom of schizophrenia or a positive symptom of schizophrenia in a psychotic disease, wherein the pharmaceutical composition comprises a therapeutically effective amount of a compound of structural formula IV:

![Structural Formula IV](image)

wherein

![Dotted Diagram](image)

is a five or six membered saturated ring, with the proviso that the ring is a fully saturated carbon ring;
R6 may be one or more of the following: hydrogen, (C1-C6)alkyl, (C2-C6)alkenyl, (C2-C6)alkynyl, (C1-C6)alkoxy, (C2-C6)alkenlyoxy, (C2-C6)alkynlyoxy, (C1-C6)alkylthio, (C1-C6)alkylsulphinyl, (C1-C6)alkylsulphonyl, (C1-C6)alkylamino, di-[(C1-C6)alkyl]amino, (C1-C6)alkoxy carbonyl, N—(C1-C6)alkylcarbamoyl, N,N-di-[(C1-C6)alkyl]carbamoyl, (C2-C6)alkanoyl, (C2-C6)alkanoyloxy, (C2-C6)alkanoylamino, N—(C1-C6)alkyl-(C2-C6)alkanoylamino, (C3-C6)alkenoylamino, N—(C1-C6)alkyl-(C3-C6)alkenoylamino, (C3-C6)alkynoylamino, N—(C1-C6)alkyl-(C3-C6)alkynoylamino, (C3-C6)alkynoylamino, N—(C1-C6)alkyl-
(C3-C6)alkynoylamino, N—(Cl-C6)alkyl sulphamoyl, N,N-di-[(Cl-C6)alkyl]sulphamoyl, (C 1-C6)alkanesulphonylamino, N—(C 1-C6)alkyl-(C1-C6)alkanesulphonylamino, carboxamide, ethylene, thiophenyl, aminophenyl, trifluoromethyl, halo, trifluoromethoxy, hydroxymethyl, N-pyrrolidino, N-morpholino, phenylthio, dialkylaminomethyl, methoxyphenyl, amino, hydroxy, carboxyl, phenyl, aryalkyl; 
R2” is unsubstituted or substituted quinoline-8-yl; unsubstituted or substituted quinoline-6-yl; unsubstituted or substituted 1-naphthyl; unsubstituted or substituted 2-naphthyl; unsubstituted or substituted 3,4-methylenedioxyphenyl; unsubstituted or substituted 3,4-ethylenedioxyphenyl; unsubstituted or substituted benzothiophen-2-yl; wherein the substitution may independently be one or more of the following: (Cl-C6)alkyl, (Cl-C6)alkenyl, (Cl-C6)alkynyl, (Cl-C6)alkylhalide, (Cl-C6)alkoxy, (Cl-C6)alkenyloxy, (Cl-C6)alkynyloxy, (Cl-C6)alkylthio, (Cl-C6)alkylsulphinyl, (Cl-C6)alkylsulphonyl, (Cl-C6)alkylamino, di-[(Cl-C6)alkyl]amino, (Cl-C6)alkoxycarbonyl, N—(Cl-C6)alkylcarbamoyl, N,N-di-[(Cl-C6)alkyl]carbamoyl, aminooxy, N—(Cl-C6)alkyl aminooxy, N,N-di-[(Cl-C6)alkyl]aminooxy, (C2-C6)alkanoyl, (C2-C6)alkanoyloxy, (C2-C6)alkanoylamino, N—(C2-C6)alkyl-(C2-C6)alkanoylamino, (C3-C6)alkenoylamino, N—(Cl-C6)alkyl-(C3-C6)alkenoylamino, sulphamoyl, N—(Cl-C6)alkylsulphamoyl, N,N-di-[(Cl-C6)alkyl] sulphamoyl, (Cl-C6)alkanesulphonylamino, N—(C 1-C6)alkyl-(C1-C6)alkanesulphonylamino, carboxamide, ethylene, phenyl, thiophenyl, aminophenyl, phenylthio, halo, cyano, pyridinyl, aryalkyl, hydroxy, N-pyrrolidino, N-morpholino, carboxyl, [5-phenyl-1,2,4-oxadiazole-3-yl]methoxy, 6-methyl-pyridazin-3-yloxy, (5-oxo-2-pyrrolidinyl)methoxy, 2-(4,5-dihydro-lH-imidazolyl), N,N-dialkylcarbamoyloxy, 1-hydroxy-1-methylethyl, 4-fluorophenyl, 3,4-methylenedioxyphenyl, trifluoromethyl, trifluoromethoxy, a group of the formula
wherein: $X_1$ is O, N, S, S$_2$, NR, C(O), or bond; $Q_1$ is hydrogen, phenyl, 5-(2,2-difluorol,3-benzodioxolyl), C(0)Q$_5$, or pyridyl when m and n are independently 0-2, except when one is 0 the other cannot be 0; $Q_1$ is OR$_{11}$, NR$_{12}$, halo, N-morpholino, N-piperazino-N'R$_{13}$, N-imidazolyl, N-pyrazolyl, N-triazolyl, N-(4-piperidinylpiperidine), SO$_2$R$_{14}$, SOR$_{14}$, NHSO$_2$R$_{15}$, acetamido, N-phthalimido, N-oxazolidino, N-imidazolino, N-benzoazolidino, N-pyridinononyl, N(N'-methylbenzimidazolino), N,N-di(Cl-C4)alkylamino(Cl-C4)alkoxy, N-benzimidazolino; when m and n are independently 0-2, but one or the other of m or n is not 0; $Q_5$ is hydroxy, methoxy, amino, diethylamino, dimethylamino; R$_{10}$ is hydrogen, halo, (C$_1$-C6)alkyl; R$_{11}$ and R$_{12}$ are independently hydrogen, (Cl-C6)alkyl, (Cl-C6)alkoxy, arylalkyl, cycloalkyl, cycloalkylmethyl, 4-N-methylpiperidinyln, pyridyl, or R$_{11}$ and R$_{10}$ can be taken together to form a 4, 5, 6, or 7 membered ring, or R$_{11}$ and R$_{12}$ can be taken together to form a 3, 4, 5, 6, or 7 membered ring; R$_{13}$ is hydrogen, (Cl-C6)alkyl, 2-methoxyphenyl; R$_{14}$ is 2-pyrimidinyl, N-methyl-2-imidazolyl, 4-chlorophenyl, 2-pyridylmethyl; R$_{15}$ is (Cl-C6)alkyl, N-methyl-4-imidazolyl; R$_{16}$ is hydrogen, halo, arylalkyl, aryl, a group of the formula

$$\begin{align*}
\text{CN} & \left(\text{CH}_2\right)_6\text{C} & (\text{CH}_2)_p\text{Q}_2 \\
\text{R}_{20} & & \text{R}_{22} \\
\text{R}_{21} & \text{Q}_2
\end{align*}$$

wherein: $Q_2$ is hydrogen, 4-imidazolyl, or C(0)NR$_{24}$R$_{25}$ when o and p are independently 0-2; $Q_2$ is OR$_{23}$, NR$_{24}$R$_{25}$, or N-morpholino, when o and p are
independently 0-2, but one or the other of o or p is not 0; R20 is hydrogen, or (Cl-C6)alkyl; R21 is hydrogen, (Cl-C6)alkyl, or R21 and R20 can be taken together to form a 4, 5, 6, or 7 membered ring; R22 is hydrogen, (Cl-C6)alkyl, arylalkyl, aryl, or R21 and R22 can be taken together to be a 3, 4, 5, 6, 7 membered ring; R23 is hydrogen or (Cl-C6)alkyl; R24 is hydrogen, (Cl-C6)alkyl, or R24 and R25 can be taken together to form a 3, 4, 5, 6, or 7 membered ring, or R24 and R20 can be taken together to form a 6 or 7 membered ring; R25 is hydrogen, (Cl-C6)alkyl, or acetyl,
a group of the formula

$$\begin{align*}
\text{O} \\
\text{CNR}_{31} \\
\text{R}_{36}
\end{align*}$$

wherein: R30 is hydrogen, or (Cl-C6)alkyl; R31 is hydrogen, (Cl-C6)alkyl, 2-pyridyl, pyridylmethyl, amino, or hydroxy,
a group of the formula

$$\text{—NR}_{32}R_{33}$$

wherein: R32 and R33 are each independently hydrogen, (Cl-C6)alkyl, acetyl, alkylsulphonyl, or R32 and R33 can be taken together to form a 4, 5, 6, or 7 membered ring,
a group of the formula

$$\begin{align*}
\text{O} \\
\text{NCX}_2(CH_2)_qQ_3 \\
\text{R}_{35}
\end{align*}$$

wherein: X2 is CH2, O, or N; q is 2-3 except when Q3 is a bond, q is 0-3; Q3 is NR36R37, OR38, or a bond; R35 is hydrogen, or R35 and Q3 (when Q3 is a bond) can be taken together to form a 5 membered ring; R36, R37, and R38 are each independently hydrogen, or (Cl-C6)alkyl,
a group of the formula

![Chemical Structure](image)

wherein: $X_3$ is cyano, carboxamide, $N,N$-dimethylcarboxamide, $N,N$-dimethylthiocarboxamide, $N,N$-dimethylaminomethyl, 4-methylpiperazin-yl-methyl or carboxylate,

a group of the formula

![Chemical Structure](image)

wherein: $Q_6$ is $NR_4R_4^2$; $r$ is 2-3; $R_{40}$ is hydrogen, or (Cl-C6)alkyl; $R_{41}$ and $R_{42}$ are hydrogen, (Cl-C6)alkyl, or $R_{41}$ and $R_{42}$ can be taken together to form a 6 or 7 membered ring,

a group of the formula

![Chemical Structure](image)

wherein: $Q_7$ is hydroxy, methoxy, dimethylamino, or N-piperidinyl;

$k$ is 1-8;

$R_3$ is hydrogen;

or the pharmaceutically acceptable salts and esters thereof.

41. The compound of Claim 39 for use in the treatment of schizophrenia or a symptom of schizophrenia or a positive symptom of schizophrenia in a psychotic disease, wherein the compound
is selected from the group consisting of 4-[2-(6-Methyl-pyridin-2-yl)-5,6-dihydro-4H-pyrrolo[1,2-
b]pyrazol-3-yl]phenol; and pharmaceutically acceptable salts and esters thereof.

42. The compound of Claim 38 for use in the treatment of schizophrenia or a symptom of schizophrenia or a positive symptom of schizophrenia in a psychotic disease, wherein the compound is selected from the group consisting of 4-[2-(6-Methyl-pyridin-2-yl)-5,6-dihydro-4H-pyrrolo[1,2-
b]pyrazol-3-yl]-quinoline-6-carboxylic acid amide; and pharmaceutically acceptable salts and esters thereof.
% Pre-pulse Inhibition, 81 dB

Neg control

Post (PCP) control

Clozapine

Test compound, 20 mg/kg

Test compound, 100 mg/kg

*** = p < 0.01, **** = p < 0.001 vs. positive (PCP) control. Dunnett's post-hoc test.

Reversal of PCP-induced PPI deficit

Fig. 1
Fig. 2

LY-2157299: Reversal of PCP-induced PPI deficit; 69 dB pre-pulse tone

% Pre-pulse inhibition, 69 dB

-30
-20
-10
0
10
20
30
40
50
60

mg/kg

ly-2157299, 20
ly-2157299, 100

Clorazapate, 5

Neg control

Pos (PCP) control

mg/kg

* = p < 0.05 vs. positive (PCP) control Dunnet's post-hoc test

*
FIG. 3
LY-2157299: Reversal of Pcp-induced PPI deficit, 73 dB pre-pulse tone

= p < 0.05 vs. positive (p<sub>p</sub>) control Dunnet's post-hoc test
INTERNATIONAL SEARCH REPORT

International application No
PCT/US2012/032446

A. CLASSIFICATION OF SUBJECT MATTER

C07D471/04  C07D487/04  C07D498/04  C07D513/04
A61K31/4188  A61P25/18

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols):
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 practicable, search terms used):
EPO-Internal, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

<table>
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<th>Category</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
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Further documents are listed in the continuation of Box C. See patent family annex.

Date of the actual completion of the international search 5 June 2012

Date of mailing of the international search report 12/06/2012

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Authorized officer
Fanni, Stefano
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