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UREA AND AMIDE DERIVATIVES AND THEIR USE IN THE CONTROL OF CELL MEMBRANE POTASSIUM CHANNELS

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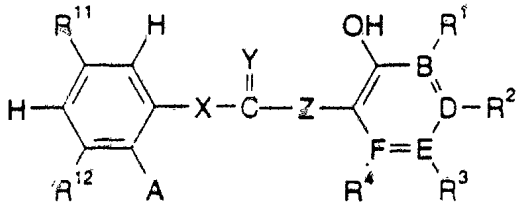
(56) Prior Art Documents
US 5011837
US 3935263
US 3935262

(57)

It is an object of the present invention to provide novel urea compounds which are useful in the treatment of disorders or diseases of a living animal body, including a human, and especially in the treatment of disorders or diseases which can be treated by opening cell membrane potassium channels of such a living animal body.

Claim

1. A compound having the formula



or a pharmaceutically acceptable salt thereof,

wherein

X and Z each independently are NH or CH_2, at least one of X and Z being NH;

.../2

Y is O, S, NCN, or NH;

B,D,E and F each independently are C or N, at least three of B, D, E, and F being C;

R^1 and R^4 each independently are hydrogen, halogen, CF_3, COOH, COO-alkyl, COO-aryl, CO-amino, CN, alkyl, alkoxy, hydroxy, nitro, hydroxymethyl, sulphamoyl, amino, aryloxy, alkylcarbonyl, arylcarbonyl, arylcarbonyloxy, alkylcarbonyloxy;

R^2 is hydrogen, CF_3, COOH, COO-alkyl, COO-aryl, CO-amino, CN, alkoxy, hydroxy, hydroxymethyl, sulphamoyl, aryloxy, alkylcarbonyl, arylcarbonyl, arylcarbonyloxy, alkylcarbonyloxy;

R^3 is hydrogen, halogen, COOH, COO-alkyl, COO-aryl, CO-amino, CN, alkoxy, hydroxy, nitro, hydroxymethyl, sulphamoyl, amino, aryloxy, alkylcarbonyl, arylcarbonyl, arylcarbonyloxy, alkylcarbonyloxy, or

R^2 and R^3 or R^3 and R^4 together with the carbon atoms to which they are attached form an additional fused carbocyclic ring which may be fully or partially unsaturated;

at least one of R^{11} and R^{12} is halogen, OCF_3, CF_3, COOH, COO-alkyl, COO-aryl, CO-amino, CN, alkyl, alkoxy, hydroxy, nitro, hydroxymethyl, sulphamoyl, amino, aryloxy, alkylcarbonyl, arylcarbonyl, arylcarbonyloxy, alkylcarbonyloxy and the other of R^{11} and R^{12} is hydrogen, halogen, OCF_3, CF_3, COOH, COO-alkyl, COO-aryl, CO-amino, CN, alkyl, alkoxy, hydroxy, nitro, hydroxymethyl, sulphamoyl, amino, aryloxy, alkylcarbonyl, arylcarbonyl, arylcarbonyloxy, alkylcarbonyloxy;

A is hydrogen or together with R^{12} and the carbon atoms to which they are attached form an additional fused carbocyclic ring which may be fully or partially unsaturated;

provided that the compound is not N-(3-chlorophenyl)-2-hydroxy-phenylacetic amide.

UREA AND AMIDE DERIVATIVES AND THEIR USE IN THE CONTROL OF CELL MEMBRANE POTASSIUM CHANNELS

The present invention relates to novel urea derivatives, a method of preparing the same, a method of treatment with the novel urea derivatives, and to pharmaceutical com-positions comprising the same.

Object of the Invention

It is an object of the present invention to provide novel urea compounds which are useful in the treatment of disorders or diseases of a living animal body, including a human, and especially in the treatment of disorders or diseases which can be treated by opening cell membrane potassium channels of s ch a living animal body.

Another object of the present invention is to provide a method of treating disorders or diseases of a living animal body, including a human, which disorders or diseases are responsive to opening of potassium channels and ch comprises administering to such a living animal body in need thereof a compound of the invention.

A third object of the present invention is to provide novel pharmaceutical compositions for the treatment of disorders or diseases of a living animal body, including a human, which disorders or diseases are responsive to the opening of potassium channels.

Other objects will be apparent to the person skilled in the art hereinafter.

Background of the Invention

European patent application Publication No 477 819 discloses that certain compounds are openers of BK channels.

It is generally well known that opening of potassium (K+) channels leads to a hyperpolarization and relaxation of cells. The presently known K+ channel openers (e.g. cromakalim and pinacidil) exert their effect primarily by interaction with the K+ channel subtype K_{ATP}. These compounds have a high affinity for vascular smooth muscle cells and are thus mostly vasodilators. Recent studies indicate, however, that K+ channel openers hyperpolarizing neuronal cells also have anticonvulsive and antiischemic effects in the central nervous system (the CNS), European Journal of Pharmacology 167, 181-183 (1989), Neuroscience Letters 115, 195-200 (1990), Neuroscience 37(1), 55-60 (1990), The Journal of Pharmacology and Experimental Therapeutics 251(1), 98-104 (1989). Furthermore recent studies demonstrate that potassium channel openers acting on airways smooth muscle (tracheal smooth muscle) cells will have anti-asthmatic effects (Williams et al., The Lancet 336, 334-336 (1990)).

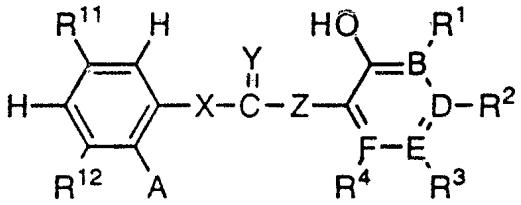
There exist other K+ channel sybtypes than K_{ATP}, and one such subtype is the BK channel, also called the maxi-K channel or large-conductance Ca^{2+} dependent K+ channel. The BK channel is present in many cells including most central and peripheral nerve cells, striated muscle cells, smooth muscle cells of the airways, the vasculature, the gastrointestinal tract and bladder, in endo- and exocrine glands including pancreatic ß-cells and in kidney tubules (R. Latorre et al., Annu. Rev. Physiol. 51, 385 (1989)).

A scorpion toxin peptide, charybdotoxin, which blocks the BK channel fairly specific has been used to demonstrate that the BK channel plays an important role as a relaxing negative feed-back when the cells in these tissues become highly active or spastic (J.E. Brayden and M.T. Nelson, Science 256, 532 (1992); T.R. Jones et al., J. Pharmacol. Exp. Ther. 255, 697 (1990); R. Robiteille and M.P. Charlton, J. Neurosci. 12, 297 (1992); G. Suarez-Kurtz et al., J. Pharmacol. Exp. Ther. 259, (1991)).

Summary of the Invention

The invention then, inter alia, comprises the following, alone or in combination:

A compound having the formula



or a pharmaceutically acceptable salt thereof,
wherein
X and Z each independently are NH or CH2, at least one of X and Z being NH;

Y is O, S, NCN, or NH;

B,D,E and F each independently are C or N, at least three of B, D, E, and F being C;

R^1 and R^4 each independently are hydrogen, halogen, CF_3, COOH, COO-alkyl, COO-aryl, CO-amino, CN, alkyl, alkoxy, hydroxy, nitro, hydroxymethyl, sulphamoyl, amino, aryloxy, alkylcarbonyl, arylcarbonyl, arylcarbonyloxy, alkylcarbonyloxy;

R^2 is hydrogen, CF_3, COOH, COO-alkyl, COO-aryl, CO-amino, CN, alkoxy, hydroxy, hydroxymethyl, sulphamoyl, aryloxy, alkylcarbonyl, arylcarbonyl, arylcarbonyloxy, alkylcarbonyloxy;

R^3 is hydrogen, halogen, COOH, COO-alkyl, COO-aryl, CO-amino, CN, alkoxy, hydroxy, nitro, hydroxymethyl, sulphamoyl, amino, aryloxy, alkylcarbonyl, arylcarbonyl, arylcarbonyloxy, alkylcarbonyloxy; or

R^2 and R^3 or R^3 and R^4 together with the carbon atoms to which they are attached form an additional fused carbocyclic ring which may be fully or partially unsaturated;

at least one of R^{11} and R^{12} is halogen, OCF_3, CF_3, COOH, COO-alkyl, COO-aryl, CO-amino, CN, alkyl, alkoxy, hydroxy, nitro, hydroxymethyl, sulphamoyl, amino, aryloxy, alkylcarbonyl, arylcarbonyl, arylcarbonyloxy, alkylcarbonyloxy and the other of R^{11} and R^{12} is hydrogen, halogen, OCF_3, CF_3, COOH, COO-alkyl, COO-aryl, CO-amino, CN, alkyl, alkoxy, hydroxy, nitro, hydroxymethyl, sulphamoyl, amino, aryloxy, alkylcarbonyl, arylcarbonyl, arylcarbonyloxy, alkylcarbonyloxy;

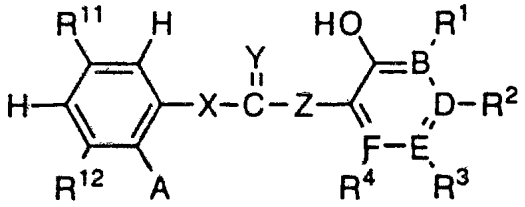
A is hydrogen or together with R^{12} and the carbon atoms to which they are attached form an additional fused carbocyclic ring which may be fully or partially unsaturated, and

a compound as above which is
N-(2-hydroxy-5-chlorophenyl)-3-(trifluoromethyl)phenylacetic amide,
N-(3-(trifluoromethoxy)phenyl)-N'-(2-hydroxy-5-chlorophenyl) urea,
N-(3-(trifluoromethyl)phenyl)-N'-(2-hydroxyphenyl) urea,
N-(3-(trifluoromethyl)phenyl)-N'-(2-hydroxy-6-nitrophenyl) urea,
N-(3-(trifluoromethyl)phenyl)-2-hydroxy-5-chlorophenylacetic amide,
N-(3-(trifluoromethyl)phenyl)-N'-(2-hydroxy-5-chlorophenyl) thiourea,
N-(3-(trifluoromethyl)phenyl)-N'-(2-hydroxy-5-methoxycarbonylphenyl) urea,
N-(3-(trifluoromethyl)phenyl)-N'-(2-hydroxy-4-methoxycarbonyl-5-chlorophenyl) urea,
N-(3-(trifluoromethyl)phenyl)-N'-(2-hydroxy-4-methoxcarbonylphenyl) urea,
N-(3-(trifluoromethyl)phenyl)-N'-(2-hydroxy-4-chlorophenyl) urea,
N-(3-(trifluoromethyl)phenyl)-N'-(2-hydroxy-6-methoxy-3-pyridyl) urea,
N-(3-(trifluoromethyl)phenyl)-N'-(2-hydroxy-5-chloro-3-pyridyl) urea,
N-(3-(trifluoromethyl)phenyl)-N'-(2-hydroxy-3-nitrophenyl) urea,
N-(3-(trifluoromethyl)phenyl)-N'-(2-hydroxy-4-methoxyphenyl) urea,
N-(3-(trifluoromethyl)phenyl)-N'-(2, 4-dihydroxyphenyl) urea,

N-(3-(trifluoromethyl)phenyl)-N'-(2-hydroxy-5-nitrophenyl) urea,
N-(3-(trifluoromethyl)phenyl)-N'-(3-hydroxy-2-naphthyl) urea,
N-(3-(trifluoromethyl)phenyl)-N'-(3-hydroxy-2-pyridyl) urea,
N-(3-(trifluoromethyl)phenyl)-N'-(2-hydroxy-1-naphthyl) urea,
N-(3-(trifluoromethyl)phenyl)-N'-(2-hydroxy-5-chlorophenyl) urea,
N-(3-(trifluoromethyl)phenyl)-N'-(2-hydroxy-5-methoxyphenyl) urea,
N-(3-(trifluoromethyl)phenyl)-N'-(2-hydroxy-4-(phenylamino)phenyl) urea,
N-(3-(trifluoromethyl)phenyl)-N'-(2, 5-dihydroxyphenyl) urea,
N-(3-benzoylphenyl)-N'-(2-hydroxy-5-chlorophenyl) urea,
N-(3-carbamoylphenyl)-N'-(2-hydroxy-5-chlorophenyl) urea,
N-(3-carboxyphenyl)-N'-(2-hydroxy-5-chlorophenyl) urea,
N-(3-hydroxyphenyl)-N'-(2-hydroxy-5-chlorophenyl) urea,
N-(3-methoxycarbonylphenyl)-N'-(2-hydroxy-5-chlorophenyl) urea,
N-(3-methylphenyl)-N'-(2-hydroxy-5-chlorophenyl) urea, or
N-(3-nitrophenyl)-N'-(2-hydroxy-5-chlorophenyl) urea,
or a pharmaceutically acceptable salt thereof, and

a pharmaceutical composition comprising a therapeutically effective amount of a compound as any above together with at least one pharmaceutically acceptable carrier, and

a method of treating a disorder or disease of a living animal body, including a human, which disorder or disease is responsive to opening of potassium channels and which comprises administering to such a living animal body, including a human in need thereof an effective amount of a compound having the formula



or a pharmaceutically acceptable salt thereof,
wherein
X and Z each independently are NH or CH2, at least one of X and Z being NH;

Y is O, S, NCN, or NH;

B,D,E and F each independently are C or N, at least three of B, D, E, and F being C;

R^1 and R^4 each independently are hydrogen, halogen, CF_3, COOH, COO-alkyl, COO-aryl, CO-amino, CN, alkyl, alkoxy, hydroxy, nitro, hydroxymethyl, sulphamoyl, amino, aryloxy, alkylcarbonyl, arylcarbonyl, arylcarbonyloxy, alkylcarbonyloxy;

R^2 is hydrogen, halogen, CF_3, COOH, COO-alkyl, COO-aryl, CO-amino, CN, alkyl, alkoxy, hydroxy, nitro, hydroxymethyl, sulphamoyl, amino, aryloxy, alkylcarbonyl, arylcarbonyl, arylcarbonyloxy, alkylcarbonyloxy;

R^3 is hydrogen, halogen, CF_3, COOH, COO-alkyl, COO-aryl, CO-amino, CN, alkyl, alkoxy, hydroxy, nitro, hydroxymethyl, sulphamoyl, amino, aryloxy, alkylcarbonyl, arylcarbonyl, arylcarbonyloxy, alkylcarbonyloxy; or

R^2 and R^3 or R^3 and R^4 together with the carbon atoms to which they are attached form an additional fused carbocyclic ring which may be fully or partially unsaturated;

at least one of R^{11} and R^{12} is halogen, OCF_3, CF_3, COOH, COO-alkyl, COO-aryl, CO-amino, CN, alkyl, alkoxy, hydroxy, nitro, hydroxymethyl, sulphamoyl, amino, aryloxy, alkylcarbonyl, arylcarbonyl, arylcarbonyloxy, alkylcarbonyloxy and the other of R^{11} and R^{12} is hydrogen, halogen, OCF_3, CF_3, COOH, COO-alkyl, COO-aryl, CO-amino, CN, alkyl, alkoxy, hydroxy, nitro, hydroxymethyl, sulphamoyl, amino, aryloxy, alkylcarbonyl, arylcarbonyl, arylcarbonyloxy, alkylcarbonyloxy;

A is hydrogen or together with R^{12} and the carbon atoms to which they are attached form an additional fused carbocyclic ring which may be fully or partially unsaturated, and

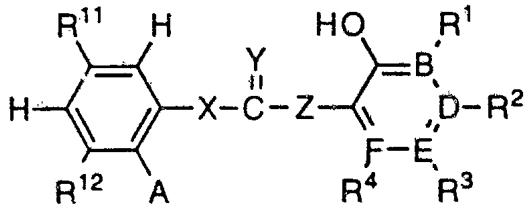
the method as above wherein arterial hypertension, coronary artery spasms, asthma, irritable bowl syndrome, spastic bladder, ischemia, psychosis, or convulsions are treated, and

the method as any above wherein the compound is administered in the form of a pharmaceutical composition thereof, in which it is present together with a pharmaceutically acceptable carrier or diluent, and

the method as any above wherein
N-(1-naphthyl)-N'-(2-hydroxy-5-(trifluoromethyl)phenyl) urea,
N-(2-hydroxy-5-chlorophenyl)-3-(trifluoromethyl)phenylacetic amide,
N-(3, 5-dichlorophenyl)-N'-(2-hydroxy-5-(trifluoromethyl)phenyl) urea,
N-(3-(trifluoromethoxy)phenyl)-N'-(2-hydroxy-5-chlorophenyl) urea,
N-(3-(trifluoromethyl)phenyl)-N'-(2-hydroxyphenyl) urea,
N-(3-(trifluoromethyl)phenyl)-N'-(2-hydroxy-6-nitrophenyl) urea,
N-(3-(trifluoromethyl)phenyl)-N'-(2-hydroxy-5-(trifluoromethyl)phenyl) thiourea,
N-(3-(trifluoromethyl)phenyl)-2-hydroxy-5-chlorophenylacetic amide,
N-(3-(trifluoromethyl)phenyl)-N'-(2-hydroxy-5-chlorophenyl) thiourea,
N-(3-(trifluoromethyl)phenyl)-N'-(2-hydroxy-5-methoxycarbonylphenyl) urea,
N-(3-(trifluoromethyl)phenyl)-N'-(2-hydroxy-4-nitro-5-carboxyphenyl) urea,
N-(3-(trifluoromethyl)phenyl)-N'-(2-hydroxy-4-nitro-5-methoxycarbonylphenyl) urea,
N-(3-(trifluoromethyl)phenyl)-N'-(2-hydroxy-4-methoxycarbonyl-5-chlorophenyl) urea,
N-(3-(trifluoromethyl)phenyl)-N'-(2-hydroxy-4-methoxcarbonylphenyl) urea,
N-(3-(trifluoromethyl)phenyl)-N'-(2-hydroxy-4-chlorophenyl) urea,
N-(3-(trifluoromethyl)phenyl)-N'-(2-hydroxy-6-methoxy-3-pyridyl) urea,
N-(3-(trifluoromethyl)phenyl)-N'-(2-hydroxy-5-chloro-3-pyridyl) urea,
N-(3-(trifluoromethyl)phenyl)-N'-(2-hydroxy-3-nitrophenyl) urea,

N-(3-(trifluoromethyl)phenyl)-N'-(2-hydroxy-5-chloro-4-nitrophenyl) urea,
N-(3-(trifluoromethyl)phenyl)-N'-(2-hydroxy-4-methoxyphenyl) urea,
N-(3-(trifluoromethyl)phenyl)-N'-(2, 4-dihydroxyphenyl) urea,
N-(3-(trifluoromethyl)phenyl)-N'-(2-hydroxy-5-methoxy-4-nitrophenyl) urea,
N-(3-(trifluoromethyl)phenyl)-N'-(2-hydroxy-5-nitrophenyl) urea,
N-(3-(trifluoromethyl)phenyl)-N'-(3-hydroxy-2-naphthyl) urea,
N-(3-(trifluoromethyl)phenyl)-N'-(3-hydroxy-2-pyridyl) urea,
N-(3-(trifluoromethyl)phenyl)-N'-(2-hydroxy-1-naphthyl) urea,
N-(3-(trifluoromethyl)phenyl)-N'-(2-hydroxy-5-chlorophenyl) urea,
N-(3-(trifluoromethyl)phenyl)-N'-(2-hydroxy-5-tert-butylphenyl) urea,
N-(3-(trifluoromethyl)phenyl)-N'-(2-hydroxy-5-methoxyphenyl) urea,
N-(3-(trifluoromethyl)phenyl)-N'-(2-hydroxy-4-nitrophenyl) urea,
N-(3-(trifluoromethyl)phenyl)-N'-(2-hydroxy-5-(trifluoromethyl)phenyl) urea,
N-(3-(trifluoromethyl)phenyl)-N'-(2-hydroxy-4-aminophenyl) urea,
N-(3-(trifluoromethyl)phenyl)-N'-(2-hydroxy-4-(phenylamino)phenyl) urea,
N-(3-(trifluoromethyl)phenyl)-N'-(2, 5-dihydroxyphenyl) urea,
N-(3-benzoyl)-N'-(2-hydroxy-5-chlorophenyl) urea,
N-(3-carbamoylphenyl)-N'-(2-hydroxy-5-chlorophenyl) urea,
N-(3-carboxyphenyl)-N'-(2-hydroxy-5-chlorophenyl) urea,
N-(3-hydroxyphenyl)-N'-(2-hydroxy-5-chlorophenyl) urea,
N-(3-methoxycarbonylphenyl)-N'-(2-hydroxy-5-chlorophenyl) urea,
N-(3-methylphenyl)-N'-(2-hydroxy-5-chlorophenyl) urea, or
N-(3-nitrophenyl)-N'-(2-hydroxy-5-chlorophenyl) urea, is employed, and

the use of a compound having the formula



or a pharmaceutically acceptable salt thereof,

wherein
X and Z each independently are NH or CH2, at least one of X and Z being NH;

Y is O, S, NCN, or NH;

B,D,E and F each independently are C or N, at least three of B, D, E, and F being C;

R^1 and R^4 each independently are hydrogen, halogen, CF_3, COOH, COO-alkyl, COO-aryl, CO-amino, CN, alkyl, alkoxy, hydroxy, nitro, hydroxymethyl, sulphamoyl, amino, aryloxy, alkylcarbonyl, arylcarbonyl, arylcarbonyloxy, alkylcarbonyloxy;

R^2 is hydrogen, halogen, CF_3, COOH, COO-alkyl, COO-aryl, CO-amino, CN, alkyl, alkoxy, hydroxy, nitro, hydroxymethyl, sulphamoyl, amino, aryloxy, alkylcarbonyl, arylcarbonyl, arylcarbonyloxy, alkylcarbonyloxy;

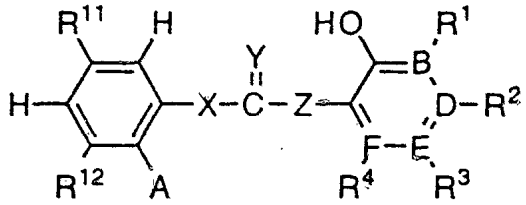
R^3 is hydrogen, halogen, CF_3, COOH, COO-alkyl, COO-aryl, CO-amino, CN, alkyl, alkoxy, hydroxy, nitro, hydroxymethyl, sulphamoyl, amino, aryloxy, alkylcarbonyl, arylcarbonyl, arylcarbonyloxy, alkylcarbonyloxy; or

R^2 and R^3 or R^3 and R^4 together with the carbon atoms to which they are attached form an additional fused carbocyclic ring which may be fully or partially unsaturated;

at least one of R^{11} and R^{12} is halogen, OCF_3, CF_3, COOH, COO-alkyl, COO-aryl, CO-amino, CN, alkyl, alkoxy, hydroxy, nitro, hydroxymethyl, sulphamoyl, amino, aryloxy, alkylcarbonyl, arylcarbonyl, arylcarbonyloxy, alkylcarbonyloxy and the other of R^{11} and R^{12} is hydrogen, halogen, OCF_3, CF_3, COOH, COO-alkyl, COO-aryl, CO-amino, CN, alkyl, alkoxy, hydroxy, nitro, hydroxymethyl, sulphamoyl, amino, aryloxy, alkylcarbonyl, arylcarbonyl, arylcarbonyloxy, alkylcarbonyloxy;

A is hydrogen or together with R^{12} and the carbon atoms to which they are attached form an additional fused carbocyclic ring which may be fully or partially unsaturated, for the manufacture of a medicament for the treatment of a disorder or disease of a living animal body, including a human, which disorder or disease is responsive to opening of potassium channels, and

the use of a compound having the formula



or a pharmaceutically acceptable salt thereof,
wherein
X and Z each independently are NH or CH2, at least one of X and Z being NH;

Y is O, S, NCN, or NH;

B,D,E and F each independently are C or N, at least three of B, D, E, and F being C;

R^1 and R^4 each independently are hydrogen, halogen, CF_3, COOH, COO-alkyl, COO-aryl, CO-amino, CN, alkyl, alkoxy, hydroxy, nitro, hydroxymethyl, sulphamoyl, amino, aryloxy, alkylcarbonyl, arylcarbonyl, arylcarbonyloxy, alkylcarbonyloxy;

R^2 is hydrogen, halogen, CF_3, COOH, COO-alkyl, COO-aryl, CO-amino, CN, alkyl, alkoxy, hydroxy, nitro, hydroxymethyl, sulphamoyl, amino, aryloxy, alkylcarbonyl, arylcarbonyl, arylcarbonyloxy, alkylcarbonyloxy;

R^3 is hydrogen, halogen, CF_3, COOH, COO-alkyl, COO-aryl, CO-amino, CN, alkyl, alkoxy, hydroxy, nitro, hydroxymethyl, sulphamoyl, amino, aryloxy, alkylcarbonyl, arylcarbonyl, arylcarbonyloxy, alkylcarbonyloxy; or

R^2 and R^3 or R^3 and R^4 together with the carbon atoms to which they are attached form an additional fused carbocyclic ring which may be fully or partially unsaturated;

at least one of R^{11} and R^{12} is halogen, OCF_3, CF_3, COOH, COO-alkyl, COO-aryl, CO-amino, CN, alkyl, alkoxy, hydroxy, nitro, hydroxymethyl, sulphamoyl, amino, aryloxy, alkylcarbonyl, arylcarbonyl, arylcarbonyloxy, alkylcarbonyloxy and the other of R^{11} and R^{12} is hydrogen, halogen, OCF_3, CF_3, COOH, COO-alkyl, COO-aryl, CO-amino, CN, alkyl, alkoxy, hydroxy, nitro, hydroxymethyl, sulphamoyl, amino, aryloxy, alkylcarbonyl, arylcarbonyl, arylcarbonyloxy, alkylcarbonyloxy;

A is hydrogen or together with R^{12} and the carbon atoms to which they are attached form an additional fused carbocyclic ring which may be fully or partially unsaturated, for the manufacture of a medicament for the treatment of arterial hypertension, coronary artery spasms, asthma, irritable bowl syndrome, spastic bladder, ischemia, psychosis, or convulsions, and

the use as above wherein the compound employed is
N-(1-naphthyl)-N'-(2-hydroxy-5-(trifluoromethyl)phenyl) urea,
N-(2-hydroxy-5-chlorophenyl)-3-(trifluoromethyl)phenylacetic amide,
N-(3, 5-dichlorophenyl)-N'-(2-hydroxy-5-(trifluoromethyl)phenyl) urea,
N-(3-(trifluoromethoxy)phenyl)-N'-(2-hydroxy-5-chlorophenyl) urea,
N-(3-(trifluoromethyl)phenyl)-N'-(2-hydroxyphenyl) urea,
N-(3-(trifluoromethyl)phenyl)-N'-(2-hydroxy-6-nitrophenyl) urea,
N-(3-(trifluoromethyl)phenyl)-N'-(2-hydroxy-5-(trifluoromethyl)phenyl) thiourea,
N-(3-(trifluoromethyl)phenyl)-2-hydroxy-5-chlorophenylacetic amide,
N-(3-(trifluoromethyl)phenyl)-N'-(2-hydroxy-5-chlorophenyl) thiourea,
N-(3-(trifluoromethyl)phenyl)-N'-(2-hydroxy-5-methoxycarbonylphenyl) urea,
N-(3-(trifluoromethyl)phenyl)-N'-(2-hydroxy-4-nitro-5-carboxyphenyl) urea,

N-(3-(trifluoromethyl)phenyl)-N'-(2-hydroxy-4-nitro-5-methoxycarbonylphenyl) urea,

N-(3-(trifluoromethyl)phenyl)-N'-(2-hydroxy-4-methoxycarbonyl-5-chlorophenyl) urea,

N-(3-(trifluoromethyl)phenyl)-N'-(2-hydroxy-4-methoxcarbonylphenyl) urea,

N-(3-(trifluoromethyl)phenyl)-N'-(2-hydroxy-4-chlorophenyl) urea,

N-(3-(trifluoromethyl)phenyl)-N'-(2-hydroxy-6-methoxy-3-pyridyl) urea,

N-(3-(trifluoromethyl)phenyl)-N'-(2-hydroxy-5-chloro-3-pyridyl) urea,

N-(3-(trifluoromethyl)phenyl)-N'-(2-hydroxy-3-nitrophenyl) urea,

N-(3-(trifluoromethyl)phenyl)-N'-(2-hydroxy-5-chloro-4-nitrophenyl) urea,

N-(3-(trifluoromethyl)phenyl)-N'-(2-hydroxy-4-methoxyphenyl) urea,

N-(3-(trifluoromethyl)phenyl)-N'-(2, 4-dihydroxyphenyl) urea,

N-(3-(trifluoromethyl)phenyl)-N'-(2-hydroxy-5-methoxy-4-nitrophenyl) urea,

N-(3-(trifluoromethyl)phenyl)-N'-(2-hydroxy-5-nitrophenyl) urea,

N-(3-(trifluoromethyl)phenyl)-N'-(3-hydroxy-2-naphthyl) urea,

N-(3-(trifluoromethyl)phenyl)-N'-(3-hydroxy-2-pyridyl) urea,

N-(3-(trifluoromethyl)phenyl)-N'-(2-hydroxy-1-naphthyl) urea,

N-(3-(trifluoromethyl)phenyl)-N'-(2-hydroxy-5-chlorophenyl) urea,

N-(3-(trifluoromethyl)phenyl)-N'-(2-hydroxy-5-tert-butylphenyl) urea,

N-(3-(trifluoromethyl)phenyl)-N'-(2-hydroxy-5-methoxyphenyl) urea,

N-(3-(trifluoromethyl)phenyl)-N'-(2-hydroxy-4-nitrophenyl) urea,

N-(3-(trifluoromethyl)phenyl)-N'-(2-hydroxy-5-(trifluoromethyl)phenyl) urea,

N-(3-(trifluoromethyl)phenyl)-N'-(2-hydroxy-4-aminophenyl) urea,

N-(3-(trifluoromethyl)phenyl)-N'-(2-hydroxy-4-(phenylamino)phenyl) urea,

N-(3-(trifluoromethyl)phenyl)-N'-(2, 5-dihydroxyphenyl) urea,

N-(3-benzoyl)-N'-(2-hydroxy-5-chlorophenyl) urea,

N-(3-carbamoylphenyl)-N'-(2-hydroxy-5-chlorophenyl) urea,

N-(3-carboxyphenyl)-N'-(2-hydroxy-5-chlorophenyl) urea,

N-(3-hydroxyphenyl)-N'-(2-hydroxy-5-chlorophenyl) urea,

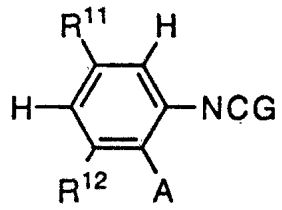
N-(3-methoxycarbonylphenyl)-N'-(2-hydroxy-5-chlorophenyl) urea,

N-(3-methylphenyl)-N'-(2-hydroxy-5-chlorophenyl) urea, or

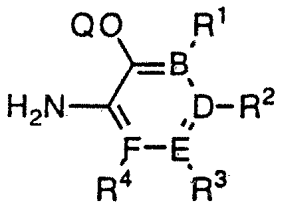
N-(3-nitrophenyl)-N'-(2-hydroxy-5-chlorophenyl) urea, and

a method of preparing a compound as first above, comprising the step of

a) reacting a compound having the formula

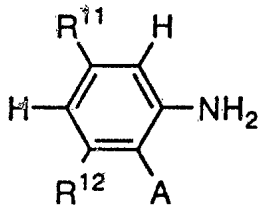


wherein A, R^{11} and R^{12} have the meanings set forth in claim 1, and G is O or S with a compound having the formula

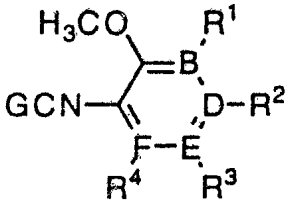


wherein B, D, E, F, R^1, R^2, R^3 and R^4 have the meanings set forth in claim 1 and Q is H or CH_3 as necessary, followed by deprotection with BBr_3 in case Q is CH_3, or

b) reacting a compound having the formula

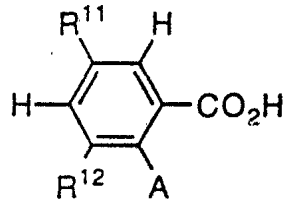


wherein A, R^{11} and R^{12} have the meanings set forth in claim 1, with a compound having the formula

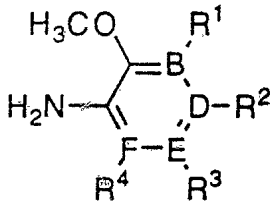


wherein B, D, E, F, R^1, R^2, R^3 and R^4 have the meanings set forth in claim 1, and G is O or S followed by deprotection with BBr_3, or

c) reacting a compound having the formula

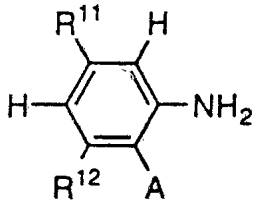


wherein A, R^{11} and R^{12} have the meanings set forth in claim 1 with a compound having the formula

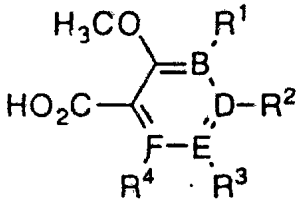


wherein B, D, E, F, R^1, R^2, R^3 and R^4 have the meanings set forth in claim 1, using dicyclohexylcarbodiimide as coupling agent followed by deprotection with BBr_3, or

d) reacting a compound having the formula

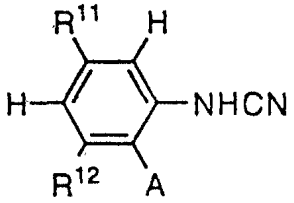


wherein A, R^{11} and R^{12} have the meanings set forth in claim 1 with a compound having the formula

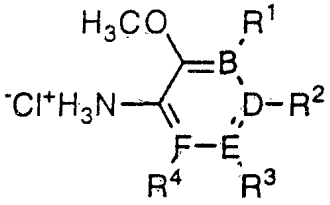


wherein B, D, E, F, R^1, R^2, R^3 and R^4 have the meanings set forth in claim 1 using dicyclohexylcarbodiimide as coupling agent followed by deprotection with BBr_3, or

e) reacting a compound having the formula

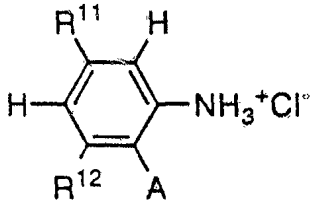


wherein A, R^{11} and R^{12} have the meanings set forth in claim 1 with a compound having the formula

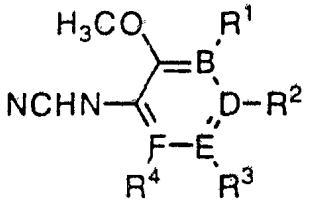


wherein B, D, E, F, R^1, R^2, R^3 and R^4 have the meanings set forth in claim 1 followed by deprotection with BBr_3, or

f) reacting a compound having the formula

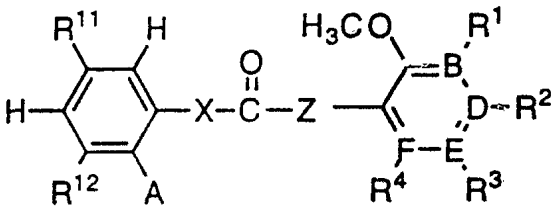


wherein A, R^{11} and R^{12} have the meanings set forth in claim 1 with a compound having the formula



wherein B, D, E, F, R^1, R^2, R^3 and R^4 have the meanings set forth in claim 1 followed by deprotection with BBr_3, or

g) reacting a compound having the formula



wherein X, Z, A, B, D, E, F, R^1, R^2, R^3, R^4, R^{11} and R^{12} have the meanings set forth in claim 1 with Lawesson's Reagent or P_2S_5 followed by deprotection with BBr_3, and

a method as above wherein
N-(2-hydroxy-5-chlorophenyl)-3-(trifluoromethyl)phenylacetic amide,
N-(3-(trifluoromethoxy)phenyl)-N'-(2-hydroxy-5-chlorophenyl) urea,
N-(3-(trifluoromethyl)phenyl)-N'-(2-hydroxyphenyl) urea,
N-(3-(trifluoromethyl)phenyl)-N'-(2-hydroxy-6-nitrophenyl) urea,
N-(3-(trifluoromethyl)phenyl)-2-hydroxy-5-chlorophenylacetic amide,
N-(3-(trifluoromethyl)phenyl)-N'-(2-hydroxy-5-chlorophenyl) thiourea,
N-(3-(trifluoromethyl)phenyl)-N'-(2-hydroxy-5-methoxycarbonylphenyl) urea,
N-(3-(trifluoromethyl)phenyl)-N'-(2-hydroxy-4-methoxycarbonyl-5-chlorophenyl) urea,
N-(3-(trifluoromethyl)phenyl)-N'-(2-hydroxy-4-methoxcarbonylphenyl) urea,
N-(3-(trifluoromethyl)phenyl)-N'-(2-hydroxy-4-chlorophenyl) urea,
N-(3-(trifluoromethyl)phenyl)-N'-(2-hydroxy-6-methoxy-3-pyridyl) urea,
N-(3-(trifluoromethyl)phenyl)-N'-(2-hydroxy-5-chloro-3-pyridyl) urea,
N-(3-(trifluoromethyl)phenyl)-N'-(2-hydroxy-3-nitrophenyl) urea,
N-(3-(trifluoromethyl)phenyl)-N'-(2-hydroxy-4-methoxyphenyl) urea,
N-(3-(trifluoromethyl)phenyl)-N'-(2, 4-dihydroxyphenyl) urea,
N-(3-(trifluoromethyl)phenyl)-N'-(2-hydroxy-5-nitrophenyl) urea,
N-(3-(trifluoromethyl)phenyl)-N'-(3-hydroxy-2-naphthyl) urea,

N-(3-(trifluoromethyl)phenyl)-N'-(3-hydroxy-2-pyridyl) urea,
N-(3-(trifluoromethyl)phenyl)-N'-(2-hydroxy-1-naphthyl) urea,
N-(3-(trifluoromethyl)phenyl)-N'-(2-hydroxy-5-chlorophenyl) urea,
N-(3-(trifluoromethyl)phenyl)-N'-(2-hydroxy-5-methoxyphenyl) urea,
N-(3-(trifluoromethyl)phenyl)-N'-(2, 5-dihydroxyphenyl) urea,
N-(3-benzoylphenyl)-N'-(2-hydroxy-5-chlorophenyl) urea,
N-(3-carbamoylphenyl)-N'-(2-hydroxy-5-chlorophenyl) urea,
N-(3-carboxyphenyl)-N'-(2-hydroxy-5-chlorophenyl) urea,
N-(3-hydroxyphenyl)-N'-(2-hydroxy-5-chlorophenyl) urea,
N-(3-methoxycarbonylphenyl)-N'-(2-hydroxy-5-chlorophenyl) urea,
N-(3-methylphenyl)-N'-(2-hydroxy-5-chlorophenyl) urea, or
N-(3-nitrophenyl)-N'-(2-hydroxy-5-chlorophenyl) urea, is prepared.

Halogen is fluorine, chlorine, bromine, or iodine.

Alkyl means a straight chained or branched chain of from one to six carbon atoms, cyclic alkyl of from three to seven carbon atoms, or cycloalkylalkyl, including but not limited to, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, t-butyl, pentyl, hexyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclopropylmethyl; methyl, ethyl, propyl and isopropyl are preferred groups.

Alkoxy means O-alkyl, wherein alkyl is as defined above.

Acyl means (C=O)-alkyl wherein alkyl is as defined above.

Amino means NH_2 or NH-alkyl, N-$(alkyl)_2$, NH-acyl, NH-phenyl or N$(acyl)_2$.

Sulphamoyl means SO_2-amino, wherein amino is as defined above.

Examples of pharmaceutically-acceptable addition salts include inorganic and organic acid addition salts such as the hydrochloride, hydrobromide, phosphate, nitrate, perchlorate, sulphate, citrate, lactate, tartrate, maleate, fumarate, mandelate, benzoate, ascorbate, cinnamate, benzenesulfonate,

methanesulfonate, stearate, succinate, glutamate, glycollate, toluene-p-sulphonate, formate, malonate, naphthalene-2-sulphonate, salicylate and the acetate. Such salts are formed by procedures well known in the art.

Other acids such as oxalic acid, while not in themselves pharmaceutically acceptable may be useful in the preparation of salts useful as intermediates in obtaining compounds of the invention and their pharmaceutically acceptable acid addition salts.

Further, the compounds of this invention may exist in unsolvated as well as in solvated forms with pharmaceutically acceptable solvents such as water, ethanol and the like. In general, the solvated forms are considered equivalent to the unsolvated forms for the purposes of this invention.

Some of the compounds of the present invention exist in (+) and (-) forms as well as in racemic forms. Racemic forms can be resolved into the optical antipodes by known methods, for example, by separation of diastereomeric salts thereof, with an optically active acid, and liberating the optically active amine compound by treatment with a base. Another method for resolving racemates into the optical antipodes is based upon chromatography on an optical active matrix. Racemic compounds of the present invention can thus be resolved into their optical antipodes, e.g., by fractional crystallization of d- or l- (tartrates, mandelates, or camphorsulphonate) salts for example.

The compounds of the present invention may also be resolved by the formation of diastereomeric amides by reaction of the compounds of the present invention with an optically active activated carboxylic acid such as that derived from (+) or (-) phenylalanine, (+) or (-) phenylglycine, (+) or (-) camphanic acid or by the formation of diastereomeric carbamates by reaction of the compounds of the present invention with an optically active chloroformate or the like.

Additional methods for the resolvation of optical isomers, known to those skilled in the art may be used, and will be apparent to the average skilled in the art. Such methods include those discussed by J. Jaques, A. Collet, and S. Wilen in "Enantiomers, Racemates, and Resolutions", John Wiley and Sons, New York (1981).

Starting materials for the processes described in the present application are known or can be prepared by known processes from commercially available chemicals.

The products of the reactions described herein are isolated by conventional means such as extraction, crystallization, distillation, chromatography, and the like.

Biology

The compounds of the present invention are potent openers of the high conductance BK channel, and the ability of the compounds of the present invention to open the BK channel can be demonstrated in several ways.

All experiments were performed with patch-clamp technique (Hamill et al., Pflügers Arch. 391, 85-100 (1981)). The ion composition of the internal solution was (in mM) 140 KCl, 1 $CaCl_2$, 1 $MgCl_2$, 2 EGTA, 10 HEPES and the external solution contained 140 NaCl, 4 KCl, 2 $CaCl_2$, 1 $MgCl_2$ and 10 HEPES.

Whole Cell Recordings

The membrane currents of calf aortic smooth muscle cells were determined in whole-cell recordings using voltage clamp mode (HEKA EPC-9 patch-clamp amplifier). Administration of N-(3-(trifluoromethyl)phenyl)-N'-(2-hydroxy-5-chlorophenyl) urea to the bath at concentrations of 1-10 µM specifically activated BK currents, which were blockable by charybdotoxin, by increasing the outward

current by up to 10 times and shifting the activation curve by more than -60 mV towards negative membrane potentials.

A selective activation of BK currents was also found in cultured cortical neurons, cerebellar granule cells, PC12 cells and in human coronary atery smooth muscle cells. No effect was found on Na^+ currents or voltage-dependent K^+ currents (A type, delayed rectifier type) also present in the neuronal cells.

Single Channel Experiments

In inside-out patches of human coronary atery smooth muscle cell membrane single BK channels were activated by for example N-(3-(trifluoromethyl)phenyl)-N'-(2-hydroxy-5-chlorophenyl) urea (1-10μM). This compound increased the open probability of the BK channel with several hundred percent.

Likewise in cultured bovine aortic smooth muscle cells in which the BK channel is the predominant K^+ channel for example N-(3-(trifluoromethyl)phenyl)-N'-(2-hydroxy-5-chlorophenyl) urea (1 μM) significantly activated the BK channel. The BK channels were also activated by N-(3-(trifluoromethyl)phenyl)-N'-(2-hydroxy-5-chlorophenyl) urea and N-phenyl-N'-(2-hydroxy-5-chlorophenyl) urea at concentrations equal or greater than 3μM and by N-(3-(trifluoromethyl)phenyl)-N'-(2-hydroxy-5-(trifluoromethyl)phenyl) urea at concentrations greater than 10μM.

Guinea-Pig Ileum Experiment

The compound, N-(3-(trifluoromethyl)phenyl)-N'-(2-hydroxy-5-chlorophenyl) urea, has been studied for its ability to relax acetylcholine-contracted guinea-pig ileum. The smooth muscle cells of the ileum express many BK channels and the model predicts relaxing effects on the gastrointestinal or urogenital tracts. The above mentioned compound relaxes the ileum in a dose-dependent way (3-30 μM).

Method: Ileum from guinea-pigs are isolated and mounted in an isometric contraction chamber. It is bathed in a physiological Krebs solution at 98°F. The ileum is precontracted with increasing concentrations of acetylcholine (0.015-5.0 μM). The contractions are reversed by including the compound in the bathing solution.

Cocaine Experiment

The compound, N-(3-(trifluoromethyl)phenyl)-N'-(2-hydroxy-5-chlorophenyl) urea, has been studied in the cocaine motility test. Cocaine induces hypermotility due to an inhibition of dopamine reuptake. The test is recognized as a test predicting anti-psychotic activity. The above mentioned compound (10-30 mg/kg) antagonizes cocaine induced hypermotility according to the test procedure described below.

Method: Two female NMRI mice (20-25 g) are placed in each test box (normal transparent plexiglas cage, w, l, h = 21 x 39 x 19 cm) in the test room for at least 16 hours with food and water ad libitum before the test in order for the animals to habituate to the situation.The test compound is administered i.p. 15 min before saline or 25 mg/kg cocaine i.p. to 32 mice (16 boxes) per dose. Food and water are withdrawn, and the motility is measured as the number of interrupted infra-red photo-beams (8 per box placed 5 cm apart and 3 cm over the bottom of the cage) for the next 120 min.

These results also demonstrate that the compounds of the invention are potential anti-psychotics acting by a novel discovered mechanism.

Pharmaceutical Compositions

While it is possible that, for use in therapy, a compound of the invention may be administered as the raw chemical, then it is preferable to present the active ingredient as a pharmaceutical formulation.

The invention thus further provides a pharmaceutical formulation comprising a compound of the invention or a pharmaceutically acceptable salt or derivative thereof together with one or more pharmaceutically acceptable carriers therefore and, optionally, other therapeutic and/or prophylactic ingredients. The carrier(s) must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and not deleterious to the recipient thereof.

Pharmaceutical formulations include those suitable for oral, rectal, nasal, topical (including buccal and sub-lingual), vaginal or parenteral (including intramuscular, sub-cutaneous and intravenous) administration or in a form suitable for administration by inhalation or insufflation.

The compounds of the invention, together with a conventional adjuvant, carrier, or diluent, may thus be placed into the form of pharmaceutical compositions and unit dosages thereof, and in such form may be employed as solids, such as tablets or filled capsules, or liquids such as solutions, suspensions, emulsions, elixirs, or capsules filled with the same, all for oral use, in the form of suppositories for rectal administration; or in the form of sterile injectable solutions for parenteral (including subcutaneous) use. Such pharmaceutical compositions and unit dosage forms thereof may comprise conventional ingredients in conventional proportions, with or without additional active compounds or principles, and such unit dosage forms may contain any suitable effective amount of the active ingredient commensurate with the intended daily dosage range to be employed. Formulations containing ten (10) milligrams of active ingredient or, more broadly, 0.1 to one hundred (100) milligrams, per tablet, are accordingly suitable representative unit dosage forms.

The compounds of the present invention can be administrated in a wide variety of oral and parenteral dosage forms. It will be obvious to those skilled in the art that the following dosage forms may comprise as the active component, either a compound of the invention or a pharmaceutically acceptable salt of a compound of the invention.

For preparing pharmaceutical compositions from the compounds of the present invention, pharmaceutically acceptable carriers can be either solid or liquid. Solid form preparations include powders, tablets, pills, capsules, cachets, suppositories, and dispersible granules. A solid carrier can be one or more substances which may also act as diluents, flavouring agents, solubilizers, lubricants, suspending agents, binders, preservatives, tablet disintegrating agents, or an encapsulating material.

In powders, the carrier is a finely divided solid which is in a mixture with the finely divided active component.

In tablets, the active component is mixed with the carrier having the necessary binding capacity in suitable proportions and compacted in the shape and size desired.

The powders and tablets preferably contain from five or ten to about seventy percent of the active compound. Suitable carriers are magnesium carbonate, magnesium stearate, talc, sugar, lactose, pectin, dextrin, starch, gelatin, tragacanth, methylcellulose, sodium carboxymethylcellulose, a low melting vax, cocoa butter, and the like. The term "preparation" is intended to include the formulation of the active compound with encapsulating material as carrier providing a capsule in which the active component, with or without carriers, is surrounded by a carrier, which is thus in association with it. Similarly, cachets and lozenges are included. Tablets, powders, capsules, pills, cachets, and lozenges can be used as solid forms suitable for oral administration.

For preparing suppositories, a low melting vax, such as a mixture of fatty acid glycerides or cocoa butter, is first melted and the active component is dispersed homogeneously therein, as by stirring. The molten homogeneous mixture is then poured into convenient sized molds, allowed to cool, and thereby to solidify.

Formulations suitable for vaginal administration may be presented as pessaries, tampons, creams, gels, pastes, foams or sprays containing, in addition to the active ingredient, such carriers as are known in the art to be appropriate.

Liquid form preparations include solutions, suspensions, and emulsions, for example, water or water propylene glycol solutions. For example, parenteral injection liquid preparations can be formulated in solutions in aqueous polyethylene glycol solution.

The compounds according to the present invention may thus be formulated for parenteral administration (e.g. by injection, for example bolus injection or continuous infusion) and may be presented in unit dose form in ampoules, pre-filled syringes, small volume infusion or in multi-dose containers with an added preservative. The compositions may take such forms as suspensions, solutions, or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilising and/or dispersing agents. Alternatively, the active ingredient may be in powder form, obtained by aseptic isolation of sterile solid or by lyophilisation from solution, for constitution with a suitable vehicle, e.g. sterile, pyrogen-free water, before use.

Aqueous solutions suitable for oral use can be prepared by dissolving the active component in water and adding suitable colorants, flavours, stabilizing and thickening agents, as desired.

Aqueous suspensions suitable for oral use can be made by dispersing the finely divided active component in water with viscous material, such as natural or synthetic gums, resins, methylcellulose, sodium carboxymethylcellulose, and other well known suspending agents.

Also included are solid form preparations which are intended to be converted, shortly before use, to liquid form preparations for oral administration. Such liquid forms include solutions, suspensions, and emulsions. These preparations may contain, in addition to the active component, colorants, flavours, stabilizers,

buffers, artificial and natural sweeteners, dispersants, thickeners, solubilizing agents, and the like.

For topical administration to the epidermis the compounds according to the invention may be formulated as ointments, creams or lotions, or as a transdermal patch. Ointments and creams may, for example, be formulated with an aqueous or oily base with the addition of suitable thickening and/or gelling agents. Lotions may be formulated with an aqueous or oily base and, in general, will also contain one or more emulsifying agents, stabilizing agents, dispersing agents, suspending agents, thickening agents, or colouring agents.

Formulations suitable for topical administration in the mouth include lozenges comprising active agent in a flavoured base, usually sucrose and acacia or tragacanth; pastilles comprising the active ingredient in an inert base such as gelatin and glycerin or sucrose and acacia; and mouthwashes comprising the active ingredient in a suitable liquid carrier.

Solutions or suspensions are applied directly to the nasel cavity by conventional means, for example with a dropper, pipette or spray. The formulations may be provided in single or multidose form. In the latter case of a dropper or pipette this may be achieved by the patient administering an appropriate, predetermined volume of the solution of suspension. In the case of a spray this may be achieved for example by means of a metering atomizing spray pump.

Administration to the respiratory tract may also be achieved by means of an aerosol formulation in which the active ingredient is provided in a pressurized pack with a suitable propellant such as a chlorofluorocarbon (CFC) for example dichlorodifluoromethane, trichlorofluoromethane, or dichlorotetrafluoroethane, carbon dioxide or other suitable gas. The aerosol may conveniently also contain a surfactant such as lecithin. The dose of drug may be controlled by provision of a metered valve.

Alternatively the active ingredients may be provided in the form of a dry powder, for example a powder mix of the compound in a suitable powder base such as lactose, starch, starch derivatives such as hydroxypropylmethyl cellulose and polyvinylpyrrolidine (PVP). Conveniently the powder carrier will form a gel in the nasal cavity. The powder composition may be presented in unit dose form for example in capsules or cartridges of e.g. gelatin or blister packs from which the powder may be administered by means of an inhaler.

In formulations intended for administration to the respiratory tract, including intranasal formulations, the compound will generally have a small particle size for example of the order of 5 microns or less. Such a particle size may be obtained by means known in the art, for example by micronization.

When desired, formulations adapted to give sustained release of the active ingredient may be employed.

The pharmaceutical preparations are preferably in unit dosage forms. In such form, the preparation is subdivided into unit doses containing appropriate quantities of the active component. The unit dosage form can be a packaged preparation, the package containing discrete quantities of preparation, such as packeted tablets, capsules, and powders in vials or ampoules. Also, the unit dosage form can be a capsule, tablet, cachet, or lozenge itself, or it can be the appropriate number of any of these in packaged form.

Tablets or capsules for oral administration and liquids for intravenous administration are preferred compositions.

Method of Treating

The compounds of this invention are extremely useful in the treatment of disorders or diseases of mammals due to their potent potassium channel activating properties. These properties make the compounds of this invention extremely useful in the treatment of potassium channel dependent convulsions, potassium channel dependent asthma, potassium channel dependent arterial hypertension, potassium channel dependent coronary artery spasms, potassium channel dependent irritable bowl, potassium channel dependent spastic bladder, potassium channel dependent ischemia, and other disorders sensitive to potassium channel activating activity. The compounds of this invention may accordingly be administered to a subject, including a human, in need of treatment, alleviation, or elimination of an indication associated with the potassium channels. This includes especially convulsions and every form of epilepsia, asthma, hypertension, spastic bladder, irritable bowl, coronary artery spasms, aterial hypertension, psychosis and ischemia.

Suitable dosage range are 0.1-1000 milligrams daily, 10-500 milligrams daily, and especially 30-100 milligrams daily, dependent as usual upon the exact mode of administration, form in which administered, the indication toward which the administration is directed, the subject involved and the body weight of the subject involved, and further the preference and experience of the physician or veterinarian in charge.

The following examples will illustrate the invention further, however, they are not to be construed as limiting.

EXAMPLE 1

N-(3-(trifluoromethyl)phenyl)-N'-(2-hydroxy-5-nitrophenyl) urea

2-hydroxy-5-nitroaniline (1.25 g, 8.1 mmol) and 3-(trifluoromethyl)phenyl isocyanate (1.00 ml, 7.3 mmol) were added to toluene (50 ml). The reaction mixture was stirred at RT overnight, the product filtered off and recrystallized from methanol/water 8:1 (45 ml).
1.39 g (56%) of the title compound was isolated. M.p. 226°C (dec.).

The following compounds were prepared in a similar manner.

N-(3-(trifluoromethyl)phenyl)-N'-(2, 5-dimethoxyphenyl) urea,
N-(3-(trifluoromethyl)phenyl)-N'-(2-methoxy-5-(phenylamino)phenyl) urea,
N-(3-(trifluoromethyl)phenyl)-N'-(2-hydroxy-4-nitrophenyl) urea. M.p. 199-200°C,
N-(3-(trifluoromethyl)phenyl)-N'-(2-hydroxy-5-chlorophenyl) urea. M.p. 171-173°C,
N-(3-(trifluoromethyl)phenyl)-N'-(2-hydroxy-5-tert-butylphenyl) urea. M.p. 173-174°C,
N-(3-(trifluoromethyl)phenyl)-N'-(2-hydroxy-5-methoxyphenyl) urea. M.p. 153-154°C,
N-(3-(trifluoromethyl)phenyl)-N'-(2-methoxy-5-(trifluoromethyl)phenyl) urea. M.p. 192-194°C,
N-(3-(trifluoromethyl)phenyl)-N'-(3-hydroxy-2-naphthyl) urea. M.p. 184-188°C (dec.),
N-(3-(trifluoromethyl)phenyl)-N'-(3-hydroxyl-2-pyridyl) urea. M.p. 181-183°C,
N-(3-(trifluoromethyl)phenyl)-N'-(2-hydroxy-1-naphthyl) urea. M.p. 187-189°C (dec),
N-(3-(trifluoromethyl)phenyl)-N'-(2-methoxy-5-chlorophenyl) urea. M.p. 169-171°C,
N-(3-(trifluoromethyl)phenyl)-N'-(2-hydroxy-6-nitrophenyl) urea. M.p. 174-175°C,

N-(3-(trifluoromethyl)phenyl)-N'-(2-hydroxyphenyl) urea. M.p. 178-179°C,
N-(3-(trifluoromethyl)phenyl)-N'-(2, 5-dimethoxy-4-nitrophenyl) urea,
N-(3-(trifluoromethyl)phenyl)-N'-(2-hydroxy-4-methoxcarbonylphenyl) urea. M.p. 222-223°C,
N-(3-(trifluoromethyl)phenyl)-N'-(2-hydroxy-3-nitrophenyl) urea. M.p. 223-224°C,
N-(3-(trifluoromethyl)phenyl)-N'-(2, 6-dimethoxy-3-pyridyl) urea,
N-(3-(trifluoromethyl)phenyl)-N'-(2-hydroxy-5-chloro-3-pyridyl) urea. M.p. >310°C,
N-(3-(trifluoromethyl)phenyl)-N'-(2-hydroxy-4-chlorophenyl) urea. M.p. 173-174°C,
N-(3-(trifluoromethyl)phenyl)-N'-(2-methoxy-5-methoxycarbonyl-4-nitrophenyl) urea,
N-(3-(trifluoromethyl)phenyl)-N'-(2-hydroxy-5-chloro-4-nitrophenyl) urea. M.p. 201-203°C,
N-(3-(trifluoromethyl)phenyl)-N'-(2-hydroxy-4-methoxycarbonyl-5-chlorophenyl) urea. M.p. 173-174°C,
N-(3-(trifluoromethyl)phenyl)-N'-(2-methoxy-5-methoxycarbonylphenyl) urea,
N-(3-(trifluoromethyl)phenyl)-N'-(2-methoxy-4-nitro-5-carboxyphenyl) urea.

EXAMPLE 2

N-(3-(trifluoromethyl)phenyl)-N'-(2-hydroxy-4-aminophenyl) urea.

N-(3-(trifluoromethyl)phenyl)-N'-(2-hydroxy-4-nitrophenyl) urea (1.00 g, 2.9 mmol) was subjected to catalytic reduction in tetrahydrofuran (50 ml) using 5% palladium on carbon (0.20 g). The reaction mixture was filtered through a path of celite. Evaporation of the filtrate and subsequent recrystallization of the crude product from methanol/water 1:1 (50 ml) afforded the title compound. 0.68 g (75%) of the title compound was isolated. M.p. 200-202°C.

EXAMPLE 3

N-(1-naphthyl)-N'-(2-hydroxy-5-(trifluoromethyl)phenyl) urea.

2-hydroxy-5-(trifluoromethyl)aniline (0.12 g, 0.7 mmol) in toluene (3 ml) was added to a solution of alpha-naphthyl isocyanate (0.11 g, 0.7 mmol) in toluene (3 ml). The reaction was stirred at RT overnight and the product filtered off. 0.17 g (72%) of the title compound was isolated. M.p. 205-207°C.

EXAMPLE 4

N-(2-methoxy-5-chlorophenyl)-3-(trifluoromethyl)phenylacetic amide.

Dicyclohexylcarbodiimide (2.20 g, 10.7 mmol) was added to a solution of 3-(trifluoromethyl)phenylacetic acid (2.00 g, 9.8 mmol) and 5-chloro-2-methoxyaniline (1.55 g, 9.8 mmol) in dichloromethane (50 ml). The reaction was stirred at RT overnight. The reaction mixture was filtered and the filtrate evaporated to dryness. The residue was recrystallized from methanol/water 2:1 (30 ml). 2.05 g (61%) of the title compound was isolated.

The following compound was prepared in a similar manner.

N-(3-(trifluoromethyl)phenyl)-2-methoxy-5-chlorophenylacetic amide starting from 3-trifluoromethylphenylamine and 2-methoxy-5-chlorophenylacetic acid.

EXAMPLE 5

N-(3,5-dichlorophenyl)-N'-(2-methoxy-5-(trifluoromethyl)phenyl) urea

3,5-dichlorophenyl isocyanate (0.94 g, 5.0 mmol) in toluene (10 ml) was added to a solution of 2-methoxy-5-(trifluoromethyl)aniline (0.96 g, 5.0 mmol) in toluene (10 ml). The reaction was stirred at RT for 1 hour and the product filtered off. 1.20 g (63%) of the title compound was isolated.

EXAMPLE 6

N-(5,6,7,8-tetrahydro-1-naphthyl)-N'-(2-methoxy-5-(trifluoromethyl)phenyl) urea.

2-methoxy-5-(trifluoromethyl)phenyl carbamoylchloride (0.81 g, 3.2 mmol), 1-amino-5,6,7,8-tetrahydronaphtalene (445 µl, 3.2 mmol) and triethylamine (446 µl, 3.2 mmol) were added to chloroform (20 ml) and the resulting mixture was stirred at RT overnight. The reaction mixture was poured into water and extracted with ethyl acetate. The solvent was evaporated in vacuuo and the residue recrystallized from toluene (20 ml). 0.45 g of the title compound was isolated.

EXAMPLE 7

N-(3-(trifluoromethyl)phenyl)-N'-(2-methoxy-5-(trifluoromethyl)phenyl) thiourea.

3-(trifluoromethyl)phenyl isothiocyanate in toluene (0.76 ml, 5.0 mmol) was added to a solution of 2-methoxy-5-(trifluoromethyl)aniline in toluene (10 ml). The resulting reaction mixture was stirred at RT overnight and the product was subsequently filtered off. 1.00 g (51%) of the title compound was isolated.

The following compound was prepared in a similar manner.
N-(3-(trifluoromethyl)phenyl)-N'-(2-methoxy-5-chlorophenyl) thiourea.

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EXAMPLE 8

N-(3-methoxycarbonylphenyl)-N'-(2-methoxy-5-chlorophenyl) urea.

N-(3-carboxyphenyl)-N'-(2-methoxy-5-chlorophenyl) urea (3.00 g, 9.4 mmol) was suspended in methanol (100 ml). Concentrated sulfuric acid (1.0 ml) was added and the reaction was heated at reflux for 6 hours. The reaction mixture was poured into cold (0°C) water (600 ml). Filtration of the suspension afforded the crude product. The crude product was purified by column chromatography on silica using dichloromethane/ethyl acetate 19:1 as eluent. 2.35 g of the title compound was isolated.

EXAMPLE 9

1-(3-(trifluoromethyl)phenyl-3-(2-methoxy-5-chlorophenyl) guanidine.

A mixture of 3-(trifluoromethyl)phenylcyanamide (2.00 g, 10.7 mmol) and 5-chloro-2-methoxyaniline hydrochloride (2.30 g, 11.8 mmol) was suspended in acetonitrile (80 ml). The reaction was heated at reflux for four days. The solvent was evaporated in vacuo. The residue was redissolved in dichloromethane (100 ml) and washed with a saturated sodium bicarbonate solution. The crude product was purified by column chromatography on silica gel initially using dichloromethane as eluent followed by dichloromethane/methanol 9:1 as eluent. 2.27 g of the title compound was obtained as a dark oil which slowly crystallises.

EXAMPLE 10

N-(3-benzoylphenyl)-N'-(2-methoxy-5-chlorophenyl) urea.

A mixture of 5-chloro-2-methoxyphenyl isocyanate (1.00 g, 5.4 mmol) and 3-aminobenzophenone (1.29 g, 6.5 mmol) was stirred in toluene (20 ml) for two days. The reaction was filtered and the filter cake washed with toluene. 1.9 g of the title compound was isolated.

The following compounds were prepared in a similar manner.

N-(3-carbamoylphenyl)-N'-(2-methoxy-5-chlorophenyl) urea,
N-(3-(trifluoromethoxy)phenyl)-N'-(2-methoxy-5-chlorophenyl) urea,
N-(3-methylphenyl)-N'-(2-methoxy-5-chlorophenyl) urea,
N-(3-hydroxyphenyl)-N'-(2-methoxy-5-chlorophenyl) urea,
N-(3-nitrophenyl)-N'-(2-methoxy-5-chlorophenyl) urea, and
N-(3-carboxyphenyl)-N'-(2-methoxy-5-chlorophenyl) urea.

EXAMPLE 11

N-(3-(trifluoromethyl)phenyl)-N'-(2-hydroxy-5-(phenylamino)phenyl) urea

To a cold (0°C) suspension of N-(3-(trifluoromethyl)phenyl)-N'-(2-methoxy-5-(phenylamino)phenyl) urea (1.00 g, 2.5 mmol) in dichloromethane (50 ml), boron tribromide (0.48 ml, 5.1 mmol) was added. After the addition of boron tribromide the ice bath was removed and the reaction mixture was stirred for 3 hours at RT. The reaction was poured on ice (10 ml) and 1 M sodium bicarbonate (50 ml) was added. The aqueous phase was extracted with ethyl acetate (50 ml) and the organic phase dried over magnesium sulfate. 1.05 g crude product was obtained. The crude product was purified by column chromatography on silica gel using petroleum ether/ethyl acetate 1:1 as eluent. The partly purified product (0.61 g) was recrystallized from ethanol/water 1:1 (20 ml). 0.20 g (21%) of the title compound was isolated. M.p. 166-168°C.

The following compounds were prepared in a similar manner.

N-(3-(trifluoromethyl)phenyl)-N'-(2, 5-dihydroxyphenyl) urea, M.p. 165-168°C,
N-(3-(trifluoromethyl)phenyl)-N'-(2-hydroxy-5-(trifluoromethyl)phenyl) urea, M.p. 160-162°C,
N-(3-(trifluoromethyl)phenyl)-N'-(2-hydroxy-5-chlorobenzyl) urea, M.p. 56-66°C,
N-(3-(trifluoromethyl)phenyl)-N'-(2,3-dihydroxybenzyl) urea, M.p. 159-161°C,
N-(2-hydroxy-5-chlorophenyl)-3-(trifluoromethyl)phenylacetic amide, M.p. 148-153°C,
N-(3, 5-dichlorophenyl)-N'-(2-hydroxy-5-(trifluoromethyl)phenyl) urea, M.p. 202°C,
N-(5,6,7,8-tetrahydro-1-naphthyl)-N'-(2-hydroxy-5-(trifluoromethyl)phenyl) urea,
N-(3-(trifluoromethyl)phenyl)-N'-(2-hydroxy-5-(trifluoromethyl)phenyl) thiourea, M.p. 124-125°C,
N-(3-methylphenyl)-N'-(2-hydroxy-5-chlorophenyl) urea, M.p. 179-180°C,
N-(3-hydroxyphenyl)-N'-(2-hydroxy-5-chlorophenyl) urea,
N-(3-nitrophenyl)-N'-(2-hydroxy-5-chlorophenyl) urea, M.p. 194-196°C,
N-(3-carboxyphenyl)-N'-(2-hydroxy-5-chlorophenyl) urea, M.p. 216°C,
N-(3-benzoylphenyl)-N'-(2-hydroxy-5-chlorophenyl) urea, M.p. 205-206°C,
N-(3-carbamoylphenyl)-N'-(2-hydroxy-5-chlorophenyl) urea, M.p. 203-204°C,
N-(3-(trifluoromethoxy)phenyl)-N'-(2-hydroxy-5-chlorophenyl) urea, M.p. 158-159°C,
N-(3-(trifluoromethyl)phenyl)-N'-(2-hydroxy-5-methoxy-4-nitrophenyl) urea, M.p. 220-222°C,
N-(3-methoxycarbonylphenyl)-N'-(2-hydroxy-5-chlorophenyl) urea, M.p. 182°C,
N-(3-(trifluoromethyl)phenyl)-N'-(2, 4-dihydroxyphenyl) urea, M.p. 179-180°C,
N-(3-(trifluoromethyl)phenyl)-N'-(2-hydroxy-4-methoxyphenyl) urea, M.p. 176-177°C,
N-(3-(trifluoromethyl)phenyl)-N'-(2-hydroxy-6-methoxy-3-pyridyl) urea, M.p. 223-224°C,
N-(3-(trifluoromethyl)phenyl)-N'-(2-hydroxy-4-nitro-5-methoxycarbonylphenyl) urea, M.p. 201-202°C,

N-(3-(trifluoromethyl)phenyl)-N'-(2-hydroxy-5-methoxycarbonylphenyl) urea, M.p. 205-206°C,

N-(3-(trifluoromethyl)phenyl)-N'-(2-hydroxy-5-chlorophenyl) thiourea.

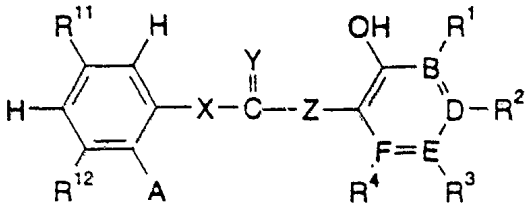
N-(3-(trifluoromethyl)phenyl)-N'-(2-hydroxy-4-nitro-5-carboxyphenyl) urea, M.p. 201-203°C,

1-(3-(trifluoromethyl)phenyl-3-(2-hydroxy-5-chlorophenyl) guanidine, M.p. 172-174°C, and

N-(3-(trifluoromethyl)phenyl)-2-hydroxy-5-chlorophenylacetic amide, M.p. 148-150°C.

We claim:

1. A compound having the formula



or a pharmaceutically acceptable salt thereof,

wherein

X and Z each independently are NH or CH_2, at least one of X and Z being NH;

Y is O, S, NCN, or NH;

B,D,E and F each independently are C or N, at least three of B, D, E, and F being C;

R^1 and R^4 each independently are hydrogen, halogen, CF_3, COOH, COO-alkyl, COO-aryl, CO-amino, CN, alkyl, alkoxy, hydroxy, nitro, hydroxymethyl, sulphamoyl, amino, aryloxy, alkylcarbonyl, arylcarbonyl, arylcarbonyloxy, alkylcarbonyloxy;

R^2 is hydrogen, CF_3, COOH, COO-alkyl, COO-aryl, CO-amino, CN, alkoxy, hydroxy, hydroxymethyl, sulphamoyl, aryloxy, alkylcarbonyl, arylcarbonyl, arylcarbonyloxy, alkylcarbonyloxy;

R^3 is hydrogen, halogen, COOH, COO-alkyl, COO-aryl, CO-amino, CN, alkoxy, hydroxy, nitro, hydroxymethyl, sulphamoyl, amino, aryloxy, alkylcarbonyl, arylcarbonyl, arylcarbonyloxy, alkylcarbonyloxy; or

R^2 and R^3 or R^3 and R^4 together with the carbon atoms to which they are attached form an additional fused carbocyclic ring which may be fully or partially unsaturated;

at least one of R^{11} and R^{12} is halogen, OCF_3, CF_3, COOH, COO-alkyl, COO-aryl,

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CO-amino, CN, alkyl, alkoxy, hydroxy, nitro, hydroxymethyl, sulphamoyl, amino, aryloxy, alkylcarbonyl, arylcarbonyl, arylcarbonyloxy, alkylcarbonyloxy and the other of R^{11} and R^{12} is hydrogen, halogen, OCF_3, CF_3, COOH, COO-alkyl, COO-aryl, CO-amino, CN, alkyl, alkoxy, hydroxy, nitro, hydroxymethyl, sulphamoyl, amino, aryloxy, alkylcarbonyl, arylcarbonyl, arylcarbonyloxy, alkylcarbonyloxy;

A is hydrogen or together with R^{12} and the carbon atoms to which they are attached form an additional fused carbocyclic ring which may be fully or partially unsaturated;

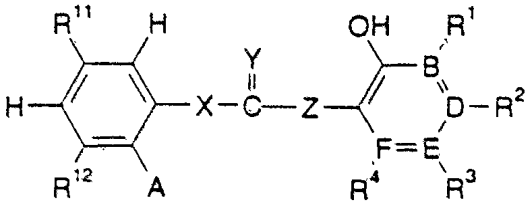
provided that the compound is not N-(3-chlorophenyl)-2-hydroxy-phenylacetic amide.

2. A compound of claim 1 which is
N-(2-hydroxy-5-chlorophenyl)-3-(trifluoromethyl)phenylacetic amide,
N-(3-(trifluoromethoxy)phenyl)-N'-(2-hydroxy-5-chlorophenyl) urea,
N-(3-(trifluoromethyl)phenyl)-N'-(2-hydroxyphenyl) urea,
N-(3-(trifluoromethyl)phenyl)-N'-(2-hydroxy-6-nitrophenyl) urea,
N-(3-(trifluoromethyl)phenyl)-2-hydroxy-5-chlorophenylacetic amide,
N-(3-(trifluoromethyl)phenyl)-N'-(2-hydroxy-5-chlorophenyl) thiourea,
N-(3-(trifluoromethyl)phenyl)-N'-(2-hydroxy-5-methoxycarbonylphenyl) urea,
N-(3-(trifluoromethyl)phenyl)-N'-(2-hydroxy-4-methoxycarbonyl-5-chlorophenyl) urea,
N-(3-(trifluoromethyl)phenyl)-N'-(2-hydroxy-4-methoxcarbonylphenyl) urea,
N-(3-(trifluoromethyl)phenyl)-N'-(2-hydroxy-4-chlorophenyl) urea,
N-(3-(trifluoromethyl)phenyl)-N'-(2-hydroxy-6-methoxy-3-pyridyl) urea,
N-(3-(trifluoromethyl)phenyl)-N'-(2-hydroxy-5-chloro-3-pyridyl) urea,
N-(3-(trifluoromethyl)phenyl)-N'-(2-hydroxy-3-nitrophenyl) urea,
N-(3-(trifluoromethyl)phenyl)-N'-(2-hydroxy-4-methoxyphenyl) urea,
N-(3-(trifluoromethyl)phenyl)-N'-(2, 4-dihydroxyphenyl) urea,
N-(3-(trifluoromethyl)phenyl)-N'-(2-hydroxy-5-nitrophenyl) urea,
N-(3-(trifluoromethyl)phenyl)-N'-(3-hydroxy-2-naphthyl) urea,
N-(3-(trifluoromethyl)phenyl)-N'-(3-hydroxy-2-pyridyl) urea,
N-(3-(trifluoromethyl)phenyl)-N'-(2-hydroxy-1-naphthyl) urea,
N-(3-(trifluoromethyl)phenyl)-N'-(2-hydroxy-5-chlorophenyl) urea,

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N-(3-(trifluoromethyl)phenyl)-N'-(2-hydroxy-5-methoxyphenyl) urea,
N-(3-(trifluoromethyl)phenyl)-N'-(2-hydroxy-4-(phenylamino)phenyl) urea,
N-(3-(trifluoromethyl)phenyl)-N'-(2, 5-dihydroxyphenyl) urea,
N-(3-benzoylphenyl)-N'-(2-hydroxy-5-chlorophenyl) urea,
N-(3-carbamoylphenyl)-N'-(2-hydroxy-5-chlorophenyl) urea,
N-(3-carboxyphenyl)-N'-(2-hydroxy-5-chlorophenyl) urea,
N-(3-hydroxyphenyl)-N'-(2-hydroxy-5-chlorophenyl) urea,
N-(3-methoxycarbonylphenyl)-N'-(2-hydroxy-5-chlorophenyl) urea,
N-(3-methylphenyl)-N'-(2-hydroxy-5-chlorophenyl) urea, or
N-(3-nitrophenyl)-N'-(2-hydroxy-5-chlorophenyl) urea,
or a pharmaceutically acceptable salt thereof.

3. A pharmaceutical composition comprising a therapeutically effective amount of a compound having the formula



or a pharmaceutically acceptable salt thereof,
wherein
X and Z each independently are NH or CH_2, at least one of X and Z being NH;

Y is O, S, NCN, or NH;

B,D,E and F each independently are C or N, at least three of B, D, E, and F being C;

R^1 and R^4 each independently are hydrogen, halogen, CF_3, COOH, COO-alkyl, COO-aryl, CO-amino, CN, alkyl, alkoxy, hydroxy, nitro, hydroxymethyl, sulphamoyl, amino, aryloxy, alkylcarbonyl, arylcarbonyl, arylcarbonyloxy, alkylcarbonyloxy;

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R^2 is hydrogen, CF_3, COOH, COO-alkyl, COO-aryl, CO-amino, CN, alkoxy, hydroxy, hydroxymethyl, sulphamoyl, aryloxy, alkylcarbonyl, arylcarbonyl, arylcarbonyloxy, alkylcarbonyloxy;

R^3 is hydrogen, halogen, COOH, COO-alkyl, COO-aryl, CO-amino, CN, alkoxy, hydroxy, nitro, hydroxymethyl, sulphamoyl, amino, aryloxy, alkylcarbonyl, arylcarbonyl, arylcarbonyloxy, alkylcarbonyloxy; or

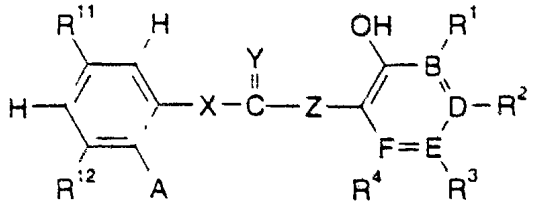
R^2 and R^3 or R^3 and R^4 together with the carbon atoms to which they are attached form an additional fused carbocyclic ring which may be fully or partially unsaturated;

at least one of R^{11} and R^{12} is halogen, OCF_3, CF_3, COOH, COO-alkyl, COO-aryl, CO-amino, CN, alkyl, alkoxy, hydroxy, nitro, hydroxymethyl, sulphamoyl, amino, aryloxy, alkylcarbonyl, arylcarbonyl, arylcarbonyloxy, alkylcarbonyloxy and the other of R^{11} and R^{12} is hydrogen, halogen, OCF_3, CF_3, COOH, COO-alkyl, COO-aryl, CO-amino, CN, alkyl, alkoxy, hydroxy, nitro, hydroxymethyl, sulphamoyl, amino, aryloxy, alkylcarbonyl, arylcarbonyl, arylcarbonyloxy, alkylcarbonyloxy;

A is hydrogen or together with R^{12} and the carbon atoms to which they are attached form an additional fused carbocyclic ring which may be fully or partially unsaturated;

together with at least one pharmaceutically acceptable carrier.

4. A method of treating a disorder or disease of a living animal body, including a human, which disorder or disease is responsive to opening of potassium channels and which comprises administering to such a living animal body, including a human in need thereof an effective amount of a compound having the formula



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or a pharmaceutically acceptable salt thereof,

wherein

X and Z each independently are NH or CH_2, at least one of X and Z being NH;

Y is O, S, NCN, or NH;

B,D,E and F each independently are C or N, at least three of B, D, E, and F being C;

R^1 and R^4 each independently are hydrogen, halogen, CF_3, COOH, COO-alkyl, COO-aryl, CO-amino, CN, alkyl, alkoxy, hydroxy, nitro, hydroxymethyl, sulphamoyl, amino, aryloxy, alkylcarbonyl, arylcarbonyl, arylcarbonyloxy, alkylcarbonyloxy;

R^2 is hydrogen, halogen, CF_3, COOH, COO-alkyl, COO-aryl, CO-amino, CN, alkyl, alkoxy, hydroxy, nitro, hydroxymethyl, sulphamoyl, amino, aryloxy, alkylcarbonyl, arylcarbonyl, arylcarbonyloxy, alkylcarbonyloxy;

R^3 is hydrogen, halogen, CF_3, COOH, COO-alkyl, COO-aryl, CO-amino, CN, alkyl, alkoxy, hydroxy, nitro, hydroxymethyl, sulphamoyl, amino, aryloxy, alkylcarbonyl, arylcarbonyl, arylcarbonyloxy, alkylcarbonyloxy; or

R^2 and R^3 or R^3 and R^4 together with the carbon atoms to which they are attached form an additional fused carbocyclic ring which may be fully or partially unsaturated;

at least one of R^{11} and R^{12} is halogen, OCF_3, CF_3, COOH, COO-alkyl, COO-aryl, CO-amino, CN, alkyl, alkoxy, hydroxy, nitro, hydroxymethyl, sulphamoyl, amino, aryloxy, alkylcarbonyl, arylcarbonyl, arylcarbonyloxy, alkylcarbonyloxy and the other of R^{11} and R^{12} is hydrogen, halogen, OCF_3, CF_3, COOH, COO-alkyl, COO-aryl, CO-amino, CN, alkyl, alkoxy, hydroxy, nitro, hydroxymethyl, sulphamoyl, amino, aryloxy, alkylcarbonyl, arylcarbonyl, arylcarbonyloxy, alkylcarbonyloxy;

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A is hydrogen or together with R^{12} and the carbon atoms to which they are attached form an additional fused carbocyclic ring which may be fully or partially unsaturated.

5. The method of claim 4 wherein arterial hypertension, coronary artery spasms, asthma, irritable bowl syndrome, spastic bladder, ischemia, psychosis, or convulsions are treated.

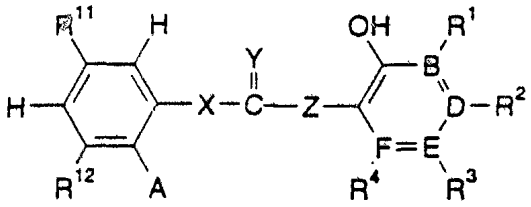
6. The method of claim 4 wherein the compound is administered in the form of a pharmaceutical composition thereof, in which it is present together with a pharmaceutically acceptable carrier or diluent.

7. The method of claim 4 wherein
N-(1-naphthyl)-N'-(2-hydroxy-5-(trifluoromethyl)phenyl) urea,
N-(2-hydroxy-5-chlorophenyl)-3-(trifluoromethyl)phenylacetic amide,
N-(3, 5-dichlorophenyl)-N'-(2-hydroxy-5-(trifluoromethyl)phenyl) urea,
N-(3-(trifluoromethoxy)phenyl)-N'-(2-hydroxy-5-chlorophenyl) urea,
N-(3-(trifluoromethyl)phenyl)-N'-(2-hydroxyphenyl) urea,
N-(3-(trifluoromethyl)phenyl)-N'-(2-hydroxy-6-nitrophenyl) urea,
N-(3-(trifluoromethyl)phenyl)-N'-(2-hydroxy-5-(trifluoromethyl)phenyl) thiourea,
N-(3-(trifluoromethyl)phenyl)-2-hydroxy-5-chlorophenylacetic amide,
N-(3-(trifluoromethyl)phenyl)-N'-(2-hydroxy-5-chlorophenyl) thiourea,
N-(3-(trifluoromethyl)phenyl)-N'-(2-hydroxy-5-methoxycarbonylphenyl) urea,
N-(3-(trifluoromethyl)phenyl)-N'-(2-hydroxy-4-nitro-5-carboxyphenyl) urea,
N-(3-(trifluoromethyl)phenyl)-N'-(2-hydroxy-4-nitro-5-methoxycarbonylphenyl) urea,
N-(3-(trifluoromethyl)phenyl)-N'-(2-hydroxy-4-methoxycarbonyl-5-chlorophenyl) urea,
N-(3-(trifluoromethyl)phenyl)-N'-(2-hydroxy-4-methoxcarbonylphenyl) urea,
N-(3-(trifluoromethyl)phenyl)-N'-(2-hydroxy-4-chlorophenyl) urea,
N-(3-(trifluoromethyl)phenyl)-N'-(2-hydroxy-6-methoxy-3-pyridyl) urea,
N-(3-(trifluoromethyl)phenyl)-N'-(2-hydroxy-5-chloro-3-pyridyl) urea,
N-(3-(trifluoromethyl)phenyl)-N'-(2-hydroxy-3-nitrophenyl) urea,
N-(3-(trifluoromethyl)phenyl)-N'-(2-hydroxy-5-chloro-4-nitrophenyl) urea,
N-(3-(trifluoromethyl)phenyl)-N'-(2-hydroxy-4-methoxyphenyl) urea,

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N-(3-(trifluoromethyl)phenyl)-N'-(2, 4-dihydroxyphenyl) urea,
N-(3-(trifluoromethyl)phenyl)-N'-(2-hydroxy-5-methoxy-4-nitrophenyl) urea,
N-(3-(trifluoromethyl)phenyl)-N'-(2-hydroxy-5-nitrophenyl) urea,
N-(3-(trifluoromethyl)phenyl)-N'-(3-hydroxy-2-naphthyl) urea,
N-(3-(trifluoromethyl)phenyl)-N'-(3-hydroxy-2-pyridyl) urea,
N-(3-(trifluoromethyl)phenyl)-N'-(2-hydroxy-1-naphthyl) urea,
N-(3-(trifluoromethyl)phenyl)-N'-(2-hydroxy-5-chlorophenyl) urea,
N-(3-(trifluoromethyl)phenyl)-N'-(2-hydroxy-5-tert-butylphenyl) urea,
N-(3-(trifluoromethyl)phenyl)-N'-(2-hydroxy-5-methoxyphenyl) urea,
N-(3-(trifluoromethyl)phenyl)-N'-(2-hydroxy-4-nitrophenyl) urea,
N-(3-(trifluoromethyl)phenyl)-N'-(2-hydroxy-5-(trifluoromethyl)phenyl) urea,
N-(3-(trifluoromethyl)phenyl)-N'-(2-hydroxy-4-aminophenyl) urea,
N-(3-(trifluoromethyl)phenyl)-N'-(2-hydroxy-4-(phenylamino)phenyl) urea,
N-(3-(trifluoromethyl)phenyl)-N'-(2, 5-dihydroxyphenyl) urea,
N-(3-benzoyl)-N'-(2-hydroxy-5-chlorophenyl) urea,
N-(3-carbamoylphenyl)-N'-(2-hydroxy-5-chlorophenyl) urea,
N-(3-carboxyphenyl)-N'-(2-hydroxy-5-chlorophenyl) urea,
N-(3-hydroxyphenyl)-N'-(2-hydroxy-5-chlorophenyl) urea,
N-(3-methoxycarbonylphenyl)-N'-(2-hydroxy-5-chlorophenyl) urea,
N-(3-methylphenyl)-N'-(2-hydroxy-5-chlorophenyl) urea, or
N-(3-nitrophenyl)-N'-(2-hydroxy-5-chlorophenyl) urea, is employed.

8. ~~The use of a~~ A compound having the formula



or a pharmaceutically acceptable salt thereof,

wherein

X and Z each independently are NH or CH_2, at least one of X and Z being NH;

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Y is O, S, NCN, or NH;

B,D,E and F each independently are C or N, at least three of B, D, E, and F being C;

R^1 and R^4 each independently are hydrogen, halogen, CF_3, COOH, COO-alkyl, COO-aryl, CO-amino, CN, alkyl, alkoxy, hydroxy, nitro, hydroxymethyl, sulphamoyl, amino, aryloxy, alkylcarbonyl, arylcarbonyl, arylcarbonyloxy, alkylcarbonyloxy;

R^2 is hydrogen, halogen, CF_3, COOH, COO-alkyl, COO-aryl, CO-amino, CN, alkyl, alkoxy, hydroxy, nitro, hydroxymethyl, sulphamoyl, amino, aryloxy, alkylcarbonyl, arylcarbonyl, arylcarbonyloxy, alkylcarbonyloxy;

R^3 is hydrogen, halogen, CF_3, COOH, COO-alkyl, COO-aryl, CO-amino, CN, alkyl, alkoxy, hydroxy, nitro, hydroxymethyl, sulphamoyl, amino, aryloxy, alkylcarbonyl, arylcarbonyl, arylcarbonyloxy, alkylcarbonyloxy; or

R^2 and R^3 or R^3 and R^4 together with the carbon atoms to which they are attached form an additional fused carbocyclic ring which may be fully or partially unsaturated;

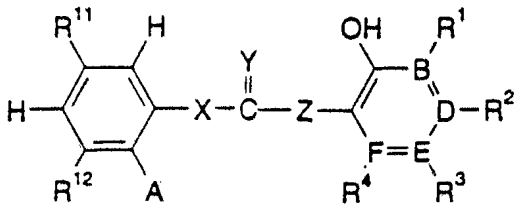
at least one of R^{11} and R^{12} is halogen, OCF_3, CF_3, COOH, COO-alkyl, COO-aryl, CO-amino, CN, alkyl, alkoxy, hydroxy, nitro, hydroxymethyl, sulphamoyl, amino, aryloxy, alkylcarbonyl, arylcarbonyl, arylcarbonyloxy, alkylcarbonyloxy and the other of R^{11} and R^{12} is hydrogen, halogen, OCF_3, CF_3, COOH, COO-alkyl, COO-aryl, CO-amino, CN, alkyl, alkoxy, hydroxy, nitro, hydroxymethyl, sulphamoyl, amino, aryloxy, alkylcarbonyl, arylcarbonyl, arylcarbonyloxy, alkylcarbonyloxy;

A is hydrogen or together with R^{12} and the carbon atoms to which they are attached form an additional fused carbocyclic ring which may be fully or partially unsaturated,

~~for the~~ manufacture of a medicament suitable for the treatment of a disorder or disease of a living animal body, including a human, which disorder or disease is responsive to opening of potassium channels.

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9. ~~The use of a~~ A compound having the formula



or a pharmaceutically acceptable salt thereof,

wherein

X and Z each independently are NH or CH_2, at least one of X and Z being NH;

Y is O, S, NCN, or NH;

B,D,E and F each independently are C or N, at least three of B, D, E, and F being C;

R^1 and R^4 each independently are hydrogen, halogen, CF_3, COOH, COO-alkyl, COO-aryl, CO-amino, CN, alkyl, alkoxy, hydroxy, nitro, hydroxymethyl, sulphamoyl, amino, aryloxy, alkylcarbonyl, arylcarbonyl, arylcarbonyloxy, alkylcarbonyloxy;

R^2 is hydrogen, halogen, CF_3, COOH, COO-alkyl, COO-aryl, CO-amino, CN, alkyl, alkoxy, hydroxy, nitro, hydroxymethyl, sulphamoyl, amino, aryloxy, alkylcarbonyl, arylcarbonyl, arylcarbonyloxy, alkylcarbonyloxy;

R^3 is hydrogen, halogen, CF_3, COOH, COO-alkyl, COO-aryl, CO-amino, CN, alkyl, alkoxy, hydroxy, nitro, hydroxymethyl, sulphamoyl, amino, aryloxy, alkylcarbonyl, arylcarbonyl, arylcarbonyloxy, alkylcarbonyloxy; or

R^2 and R^3 or R^3 and R^4 together with the carbon atoms to which they are attached form an additional fused carbocyclic ring which may be fully or partially unsaturated;

AUSTRALIAN PATENT OFFICE 13

at least one of R^{11} and R^{12} is halogen, OCF_3, CF_3, COOH, COO-alkyl, COO-aryl, CO-amino, CN, alkyl, alkoxy, hydroxy, nitro, hydroxymethyl, sulphamoyl, amino, aryloxy, alkylcarbonyl, arylcarbonyl, arylcarbonyloxy, alkylcarbonyloxy and the other of R^{11} and R^{12} is hydrogen, halogen, OCF_3, CF_3, COOH, COO-alkyl, COO-aryl, CO-amino, CN, alkyl, alkoxy, hydroxy, nitro, hydroxymethyl, sulphamoyl, amino, aryloxy, alkylcarbonyl, arylcarbonyl, arylcarbonyloxy, alkylcarbonyloxy;

A is hydrogen or together with R^{12} and the carbon atoms to which they are attached form an additional fused carbocyclic ring which may be fully or partially unsaturated, ~~for the~~ when used in the manufacture of a medicament for the treatment of arterial hypertension, coronary artery spasms, asthma, irritable bowl syndrome, spastic bladder, ischemia, psychosis, or convulsions.

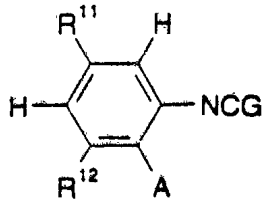
10. The use according to claim 8 wherein the compound employed is
N-(1-naphthyl)-N'-(2-hydroxy-5-(trifluoromethyl)phenyl) urea,
N-(2-hydroxy-5-chlorophenyl)-3-(trifluoromethyl)phenylacetic amide,
N-(3, 5-dichlorophenyl)-N'-(2-hydroxy-5-(trifluoromethyl)phenyl) urea,
N-(3-(trifluoromethoxy)phenyl)-N'-(2-hydroxy-5-chlorophenyl) urea,
N-(3-(trifluoromethyl)phenyl)-N'-(2-hydroxyphenyl) urea,
N-(3-(trifluoromethyl)phenyl)-N'-(2-hydroxy-6-nitrophenyl) urea,
N-(3-(trifluoromethyl)phenyl)-N'-(2-hydroxy-5-(trifluoromethyl)phenyl) thiourea,
N-(3-(trifluoromethyl)phenyl)-2-hydroxy-5-chlorophenylacetic amide,
N-(3-(trifluoromethyl)phenyl)-N'-(2-hydroxy-5-chlorophenyl) thiourea,
N-(3-(trifluoromethyl)phenyl)-N'-(2-hydroxy-5-methoxycarbonylphenyl) urea,
N-(3-(trifluoromethyl)phenyl)-N'-(2-hydroxy-4-nitro-5-carboxyphenyl) urea,
N-(3-(trifluoromethyl)phenyl)-N'-(2-hydroxy-4-nitro-5-methoxycarbonylphenyl) urea,
N-(3-(trifluoromethyl)phenyl)-N'-(2-hydroxy-4-methoxycarbonyl-5-chlorophenyl) urea,
N-(3-(trifluoromethyl)phenyl)-N'-(2-hydroxy-4-methoxcarbonylphenyl) urea,
N-(3-(trifluoromethyl)phenyl)-N'-(2-hydroxy-4-chlorophenyl) urea,
N-(3-(trifluoromethyl)phenyl)-N'-(2-hydroxy-6-methoxy-3-pyridyl) urea,
N-(3-(trifluoromethyl)phenyl)-N'-(2-hydroxy-5-chloro-3-pyridyl) urea,

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N-(3-(trifluoromethyl)phenyl)-N'-(2-hydroxy-3-nitrophenyl) urea,
N-(3-(trifluoromethyl)phenyl)-N'-(2-hydroxy-5-chloro-4-nitrophenyl) urea,
N-(3-(trifluoromethyl)phenyl)-N'-(2-hydroxy-4-methoxyphenyl) urea,
N-(3-(trifluoromethyl)phenyl)-N'-(2, 4-dihydroxyphenyl) urea,
N-(3-(trifluoromethyl)phenyl)-N'-(2-hydroxy-5-methoxy-4-nitrophenyl) urea,
N-(3-(trifluoromethyl)phenyl)-N'-(2-hydroxy-5-nitrophenyl) urea,
N-(3-(trifluoromethyl)phenyl)-N'-(3-hydroxy-2-naphthyl) urea,
N-(3-(trifluoromethyl)phenyl)-N'-(3-hydroxy-2-pyridyl) urea,
N-(3-(trifluoromethyl)phenyl)-N'-(2-hydroxy-1-naphthyl) urea,
3-(trifluoromethyl)phenyl)-N'-(2-hydroxy-5-chlorophenyl) urea,
N-(3-(trifluoromethyl)phenyl)-N'-(2-hydroxy-5-tert-butylphenyl) urea,
N-(3-(trifluoromethyl)phenyl)-N'-(2-hydroxy-5-methoxyphenyl) urea,
N-(3-(trifluoromethyl)phenyl)-N'-(2-hydroxy-4-nitrophenyl) urea,
N-(3-(trifluoromethyl)phenyl)-N'-(2-hydroxy-5-(trifluoromethyl)phenyl) urea,
N-(3-(trifluoromethyl)phenyl)-N'-(2-hydroxy-4-aminophenyl) urea,
N-(3-(trifluoromethyl)phenyl)-N'-(2-hydroxy-4-(phenylamino)phenyl) urea,
N-(3-(trifluoromethyl)phenyl)-N'-(2, 5-dihydroxyphenyl) urea,
N-(3-benzoyl)-N'-(2-hydroxy-5-chlorophenyl) urea,
N-(3-carbamoylphenyl)-N'-(2-hydroxy-5-chlorophenyl) urea,
N-(3-carboxyphenyl)-N'-(2-hydroxy-5-chlorophenyl) urea,
N-(3-hydroxyphenyl)-N'-(2-hydroxy-5-chlorophenyl) urea,
N-(3-methoxycarbonylphenyl)-N'-(2-hydroxy-5-chlorophenyl) urea,
N-(3-methylphenyl)-N'-(2-hydroxy-5-chlorophenyl) urea, or
N-(3-nitrophenyl)-N'-(2-hydroxy-5-chlorophenyl) urea.

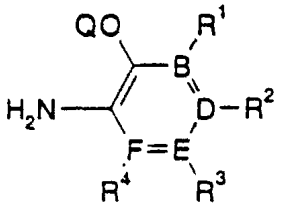
11. A method of preparing a compound of claim 1, comprising the step of

a) reacting a compound having the formula



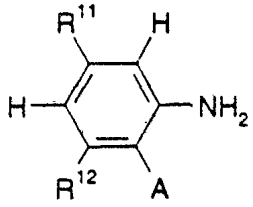
AUSTRALIAN PATENT OFFICE

wherein A, R^{11} and R^{12} have the meanings set forth in claim 1, and G is O or S with a compound having the formula

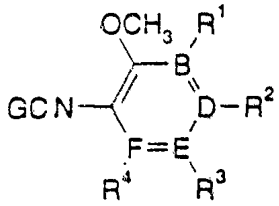


wherein B, D, E, F, R^1, R^2, R^3 and R^4 have the meanings set forth in claim 1 and Q is H or CH_3 as necessary, followed by deprotection with BBr_3 in case Q is CH_3, or

b) reacting a compound having the formula



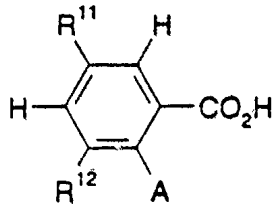
wherein A, R^{11} and R^{12} have the meanings set forth in claim 1, with a compound having the formula



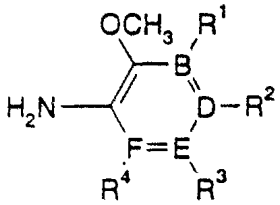
wherein B, D, E, F, R^1, R^2, R^3 and R^4 have the meanings set forth in claim 1, and G is O or S followed by deprotection with BBr_3, or

c) reacting a compound having the formula

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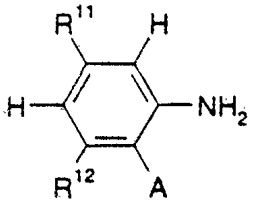


wherein A, R^{11} and R^{12} have the meanings set forth in claim 1 with a compound having the formula

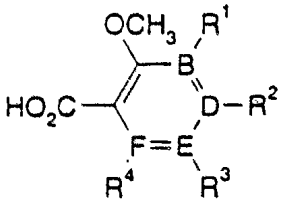


wherein B, D, E, F, R^1, R^2, R^3 and R^4 have the meanings set forth in claim 1, using dicyclohexylcarbodiimide as coupling agent followed by deprotection with BBr_3, or

d) reacting a compound having the formula



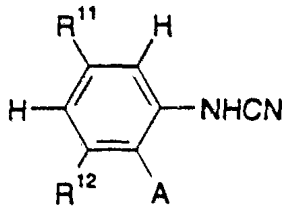
wherein A, R^{11} and R^{12} have the meanings set forth in claim 1 with a compound having the formula



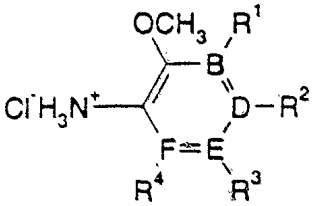
wherein B, D, E, F, R^1, R^2, R^3 and R^4 have the meanings set forth in claim 1 using dicyclohexylcarbodiimide as coupling agent followed by deprotection with BBr_3, or

e) reacting a compound having the formula

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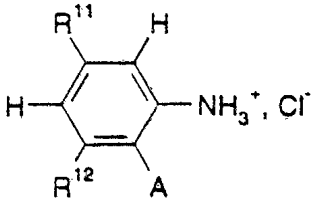


wherein A, R^{11} and R^{12} have the meanings set forth in claim 1 with a compound having the formula

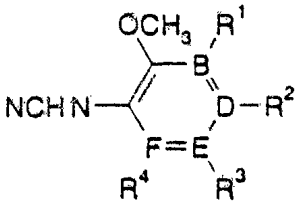


wherein B, D, E, F, R^1, R^2, R^3 and R^4 have the meanings set forth in claim 1 followed by deprotection with BBr_3, or

f) reacting a compound having the formula



wherein A, R^{11} and R^{12} have the meanings set forth in claim 1 with a compound having the formula

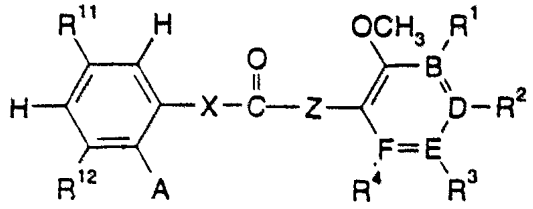


wherein B, D, E, F, R^1, R^2, R^3 and R^4 have the meanings set forth in claim 1 followed by deprotection with BBr_3, or

g) reacting a compound having the formula

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wherein X, Z, A, B, D, E, F, R^1, R^2, R^3, R^4, R^{11} and R^{12} have the meanings set forth in claim 1 with Lawesson's Reagent or P_2S_5 followed by deprotection with BBr_3.

12. A method according to claim 11 wherein

N-(2-hydroxy-5-chlorophenyl)-3-(trifluoromethyl)phenylacetic amide,

N-(3-(trifluoromethoxy)phenyl)-N'-(2-hydroxy-5-chlorophenyl) urea,

N-(3-(trifluoromethyl)phenyl)-N'-(2-hydroxyphenyl) urea,

N-(3-(trifluoromethyl)phenyl)-N'-(2-hydroxy-6-nitrophenyl) urea,

N-(3-(trifluoromethyl)phenyl)-2-hydroxy-5-chlorophenylacetic amide,

N-(3-(trifluoromethyl)phenyl)-N'-(2-hydroxy-5-chlorophenyl) thiourea,

N-(3-(trifluoromethyl)phenyl)-N'-(2-hydroxy-5-methoxycarbonylphenyl) urea,

N-(3-(trifluoromethyl)phenyl)-N'-(2-hydroxy-4-methoxycarbonyl-5-chlorophenyl) urea,

N-(3-(trifluoromethyl)phenyl)-N'-(2-hydroxy-4-methoxcarbonylphenyl) urea,

N-(3-(trifluoromethyl)phenyl)-N'-(2-hydroxy-4-chlorophenyl) urea,

N-(3-(trifluoromethyl)phenyl)-N'-(2-hydroxy-6-methoxy-3-pyridyl) urea,

N-(3-(trifluoromethyl)phenyl)-N'-(2-hydroxy-5-chloro-3-pyridyl) urea,

N-(3-(trifluoromethyl)phenyl)-N'-(2-hydroxy-3-nitrophenyl) urea,

N-(3-(trifluoromethyl)phenyl)-N'-(2-hydroxy-4-methoxyphenyl) urea,

N-(3-(trifluoromethyl)phenyl)-N'-(2, 4-dihydroxyphenyl) urea,

N-(3-(trifluoromethyl)phenyl)-N'-(2-hydroxy-5-nitrophenyl) urea,

N-(3-(trifluoromethyl)phenyl)-N'-(3-hydroxy-2-naphthyl) urea,

N-(3-(trifluoromethyl)phenyl)-N'-(3-hydroxy-2-pyridyl) urea,

N-(3-(trifluoromethyl)phenyl)-N'-(2-hydroxy-1-naphthyl) urea,

N-(3-(trifluoromethyl)phenyl)-N'-(2-hydroxy-5-chlorophenyl) urea,

N-(3-(trifluoromethyl)phenyl)-N'-(2-hydroxy-5-methoxyphenyl) urea,

N-(3-(trifluoromethyl)phenyl)-N'-(2, 5-dihydroxyphenyl) urea,

N-(3-benzoylphenyl)-N'-(2-hydroxy-5-chlorophenyl) urea,

N-(3-carbamoylphenyl)-N'-(2-hydroxy-5-chlorophenyl) urea,

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N-(3-carboxyphenyl)-N'-(2-hydroxy-5-chlorophenyl) urea,

N-(3-hydroxyphenyl)-N'-(2-hydroxy-5-chlorophenyl) urea,

N-(3-methoxycarbonylphenyl)-N'-(2-hydroxy-5-chlorophenyl) urea,

N-(3-methylphenyl)-N'-(2-hydroxy-5-chlorophenyl) urea, or

N-(3-nitrophenyl)-N'-(2-hydroxy-5-chlorophenyl) urea, is prepared.

AUSTRALIAN PATENT OFFICE

INTERNATIONAL SEARCH REPORT

Inte onal Application No
PCT/EP 94/01008

A. CLASSIFICATION OF SUBJECT MATTER
IPC 5 C07C233/29 C07C235/38 C07C275/34 C07D213/36 C07D213/63
C07D213/75 A61K31/165

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 5 C07C C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	JOURNAL OF PHARMACEUTICAL SCIENCES vol. 73, no. 12 , December 1984 pages 1871 - 1873 OMAR, A.-M. M.E. ET AL. 'Synthesis and Evaluation of Novel N-Substituted N'-(3-Hydroxy-17-oxoestra-1,3,5(10)-trien-2- and -4-yl)thiourea Derivatives for Binding to the Estrogen Receptor and Cytotoxic Activity on MCF-7 Cells' Compounds VI and IX see page 1872; figure 1 --- -/--	1,3,11

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

[X] Patent family members are listed in annex.

* Special categories of cited documents :

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

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

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

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

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

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

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

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

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
2 August 1994	18. 08. 94

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

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	CHEM. PHARM. BULL. vol. 21, no. 4 , 1973 pages 721 - 728 YAMANA, T. ET AL. 'Stabilization of Drugs. I. The Quantitative Prediction of the pH-Dependency of Amide and Anilide Hydrolyses by Neighboring Hydroxyl Groups' Compound 8 (p. 724)	1,11
X	DE,A,22 60 203 (EASTMAN KODAK CO.) 20 June 1973 Compounds II, VI; example 2	1,11
X	US,A,3 935 262 (LESTINA, G.J. ET AL.) 27 January 1976 Compounds III, X	1,11
Y	EP,A,0 354 553 (E.R. SQUIBB & SONS, INC.) 14 February 1990 see the whole document	1-12
Y	EP,A,0 477 819 (NEUROSEARCH A/S) 1 April 1992 see the whole document	1-12
A	US,A,3 331 874 (STECKER, A.C.) 18 July 1967	1
A	DE,A,19 12 553 (CIBA, AG) 9 October 1969	1,3

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 94/ 01008

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 4-7
because they relate to subject matter not required to be searched by this Authority, namely:
Claims 4-7 are directed to a method of treatment of the animal/human body. The search, which has nevertheless been carried out, was based on the alledged effects of the compounds.

2. [X] Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
Claims searched completely :2,7,10,12
Claims searched incompletely:1,3-6,8,9,11
See annex sheet.

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

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

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

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

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

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

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

Remark on Protest

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

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

FURTHER INFORMATION CONTINUED FROM PCT/ISA/210

Given the very high number of alternatives covered by the general formula of claim 1, a meaningful search was not possible in a reasonable amount of time. Therefore, and on the basis of the examples, the search was limited to compounds of the general formula wherein D and E cannot be N, and wherein only one of R11 and R12 is not H.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Inte ional Application No
PCT/EP 94/01008

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
DE-A-2260203	20-06-73	BE-A-	792599	12-06-73
		CA-A-	996119	31-08-76
		FR-A,B	2162660	20-07-73
		GB-A-	1417586	10-12-75
		JP-A-	48066441	12-09-73
		US-A-	3935262	27-01-76
		US-A-	3935263	27-01-76
US-A-3935262	27-01-76	BE-A-	792599	12-06-73
		CA-A-	996119	31-08-76
		DE-A-	2260203	20-06-73
		FR-A,B	2162660	20-07-73
		GB-A-	1417586	10-12-75
		JP-A-	48066441	12-09-73
		US-A-	3935263	27-01-76
EP-A-0354553	14-02-90	AU-B-	620424	20-02-92
		AU-A-	3895989	15-02-90
		AU-B-	640844	02-09-93
		AU-A-	9007591	13-02-92
		JP-A-	2091057	30-03-90
		US-A-	5011837	30-04-91
		US-A-	5278169	11-01-94
EP-A-0477819	01-04-92	AU-B-	635440	18-03-93
		AU-A-	8276791	26-03-92
		CA-A-	2052041	25-03-92
		JP-A-	4305568	28-10-92
		PT-A-	99032	30-11-93
		US-A-	5200422	06-04-93
US-A-3331874		FR-A-	1372475	
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DE-A-1912553	09-10-69	BE-A-	730185	22-09-69
		FR-A-	2004393	21-11-69
		GB-A-	1233125	26-05-71
		NL-A-	6904320	23-09-69
		SE-B-	370866	04-11-74
		US-A-	3689550	05-09-72