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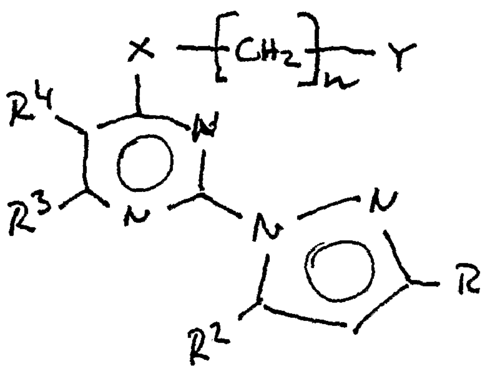
(54) Title: PYRAZOLYL-PYRIMIDINES AS POTASSIUM CHANNEL MODULATING AGENTS AND THEIR MEDICAL USE



(I)

(57) Abstract: This invention relates to novel potassium channel modulating agents of formul (I) with the definitions of R1-R4, X, Y and n according to claiml, and their use in the preparation of pharmaceutical compositions. Moreover the invention is directed to pharmaceutical compositions useful for the treatment or alleviation of diseases or disorders associated with the activity of potassiu channels, in particular respiratory diseases, epilepsy, convulsions, vascular spasms, coronary artery spasms, renal disorders, polycystic kidney disease, bladder spasms, urinary incontinence, bladder outflow obstruction, irritable bowel syndrome, gastrointestinal dysfunction, secretory diarrhoea, ischaemia, cerebral ischaemia, ischaemic heart disease, angina pectoris, coronary heart disease, traumatic brain injury, psychosis, schizophrenia, anxiety, depression, dementia, memory and attention deficits, Alzheimer's disease, dysmenorrhea, narcolepsy, Reynaud's disease, intermittent claudication, Sjorgren's syndrome, migraine, arrhythmia, hypertension, absence seizures, myotonic muscle dystrophia, xerostomi, diabetes type II, hyperinsulinemia, premature labour, baldness, cancer, immune suppression or pain.

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PYRAZOLYL-PYRIMIDINES AS POTASSIUM CHANNEL MODULATING AGENTS AND THEIR MEDICAL USE

TECHNICAL FIELD

This invention relates to novel potassium channel modulating agents, and their use in the preparation of pharmaceutical compositions.

Moreover the invention is directed to pharmaceutical compositions useful for the treatment or alleviation of diseases or disorders associated with the activity of potassium channels, in particular respiratory diseases, epilepsy, convulsions, seizures, absence seizures, vascular spasms, coronary artery spasms, renal disorders, polycystic kidney disease, bladder spasms, urinary incontinence, bladder outflow obstruction, erectile dysfunction, gastrointestinal dysfunction, secretory diarrhoea, ischaemia, cerebral ischaemia, ischaemic heart disease, angina pectoris, coronary heart disease, ataxia, traumatic brain injury, Parkinson's disease, bipolar disorder, psychosis, schizophrenia, anxiety, depression, mood disorders, dementia, memory and attention deficits, Alzheimer’s disease, amyotrophic lateral sclerosis (ALS), dysmenorrhea, narcolepsy, Reynaud’s disease, intermittent claudication, Sjorgren’s syndrome, arrhythmia, hypertension, myotonic muscle dystrophia, spasticity, xerostomi, diabetes type II, hyperinsulinemia, premature labour, baldness, cancer, irritable bowel syndrome, immune suppression, migraine or pain.

BACKGROUND ART

Ion channels are transmembrane proteins, which catalyse the transport of inorganic ions across cell membranes. The ion channels participate in processes as diverse as the generation and timing of action potentials, synaptic transmissions, secretion of hormones, contraction of muscles, etc.

All mammalian cells express potassium (K^+) channels in their cell membranes, and the channels play a dominant role in the regulation of the membrane potential. In nerve and muscle cells they regulate the frequency and form of the action potential, the release of neurotransmitters, and the degree of broncho- and vasodilation.

From a molecular point of view, the K^+ channels represent the largest and most diverse group of ion channels. For an overview they can be divided into five large subfamilies: Voltage-activated K^+ channels (K_v), long QT related K^+ channels (KvLQT), inward rectifiers (K_{IR}), two-pore K^+ channels (K_{TP}), and calcium-activated K^+ channels (K_{ca}).

The latter group, the Ca^{2+}-activated K^+ channels, consists of three well-defined subtypes: SK channels, IK channels and BK channels. SK, IK and BK refer to the single-channel conductance (Small, Intermediate and Big conductance K channel). The SK, IK, and BK channels exhibit differences in e.g. voltage- and calcium-sensitivity, pharmacology, distribution and function.

SK channels are present in many central neurons and ganglia, where their primary function is to hyperpolarize nerve cells following one or several action potentials, in order to prevent long trains of epileptogenic activity to occur. The SK channels are also present in several peripheral cells including skeletal muscle, gland cells, liver cells, and T-lymphocytes. The significance of SK channels in normal skeletal muscle is not clear, but their number is significantly increased in denervated muscle, and the large number of SK channels in the muscle of patients with myotonic muscle dystrophia, suggest a role in the pathogenesis of the disease.

Studies indicate that K^+ channels may be a therapeutic target in the treatment of a number of diseases including asthma, cystic fibrosis, chronic obstructive pulmonary disease and rhinorrhea, convulsions, vascular spasms, coronary artery spasms, renal disorders, polycystic kidney disease, bladder spasms, urinary incontinence, bladder outflow obstruction, irritable bowel syndrome, gastrointestinal dysfunction, secretory diarrhoea, ischaemia, cerebral ischaemia, ischaemic heart disease, angina pectoris, coronary heart disease, traumatic brain injury, psychosis, anxiety, depression, dementia, memory and attention deficits, Alzheimer’s disease, dysmenorrhea, narcolepsy, Reynaud’s disease, intermittent claudication, Sjorgren’s syndrome, migraine, arrhythmia, hypertension, absence seizures, myotonic muscle dystrophia, xerostomi, diabetes type II, hyperinsulinemia, premature labour, baldness, cancer and immune suppression.

US 6,559,307 describes an improved process for preparing substituted pyrimidines. The pyrazolyl-pyrimidine derivatives of the present invention are not disclosed and their activity as potassium channel modulators certainly not suggested.

WO 97/19065 describes substituted 2-anilinopyrimidines useful as protein kinase inhibitors. The pyrazolyl-pyrimidine derivatives of the present invention are not disclosed and their activity as potassium channel modulators certainly not suggested.

WO 2001/29009 describes 4,5-disubstituted anilinopyrimidines useful as protein kinase inhibitors. The pyrazolyl-pyrimidine derivatives of the present invention are not disclosed and their activity as potassium channel modulators certainly not suggested.

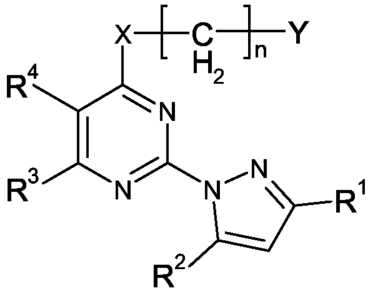
WO 2003/075828 describes various compounds useful for the treatment of cancer including compounds of formulas VI, VII and XI. The pyrazolyl-pyrimidine derivatives of the present invention are not disclosed and their activity as potassium channel modulators certainly not suggested.

SUMMARY OF THE INVENTION

The present invention resides in the provision of novel chemical compounds capable of selectively modulating SK channels, or subtypes of SK channels.

Moreover the invention is directed to pharmaceutical compositions useful for the treatment or alleviation of diseases or disorders associated with the activity of potassium channels, including diseases or conditions like respiratory diseases, epilepsy, convulsions, seizures, absence seizures, vascular spasms, coronary artery spasms, renal disorders, polycystic kidney disease, bladder spasms, urinary incontinence, bladder outflow obstruction, erectile dysfunction, gastrointestinal dysfunction, secretory diarrhoea, ischaemia, cerebral ischaemia, ischaemic heart disease, angina pectoris, coronary heart disease, ataxia, traumatic brain injury, Parkinson's disease, bipolar disorder, psychosis, schizophrenia, anxiety, depression, mood disorders, dementia, memory and attention deficits, Alzheimer's disease, amyotrophic lateral sclerosis (ALS), dysmenorrhea, narcolepsy, Reynaud's disease, intermittent claudication, Sjorgren's syndrome, arrhythmia, hypertension, myotonic muscle dystrophia, spasticity, xerostomi, diabetes type II, hyperinsulinemia, premature labour, baldness, cancer, irritable bowel syndrome, immune suppression, migraine or pain.

Accordingly, in its first aspect, the invention provides novel pyrazolyl-pyrimidine derivatives of Formula I



(I)

an isomer or a mixture of its isomers, an N-oxide thereof, a prodrug thereof, or a pharmaceutically acceptable salt thereof, wherein

n is 0, 1, 2 or 3;

X represents O, S or NR'; wherein R' represents hydrogen, alkyl, cycloalkyl or cycloalkyl-alkyl; or, when n is 0 and X is NR', R' together with Y and together with the nitrogen to which they are attached form a heterocyclic ring, which heterocyclic ring is optionally substituted one or two times with substituents selected from the group consisting of alkyl and phenyl;

Y represents alkyl, cycloalkyl, alkyl-cycloalkyl, amino-alkyl, alkyl-amino, alkyl-amino-alkyl, hydroxy-alkyl, alkoxy-alkyl, alkenyl, phenyl, benzyl, naphthyl, 1,2,3,4-tetrahydro-naphthyl, indenyl, 1,2-dihydro-indenyl, furanyl, thienyl, pyranyl, tetrahydro-pyran-4-yl, pyridinyl, indolinyl or quinolinyl, which phenyl, benzyl, naphthyl, 1,2,3,4-tetrahydro-naphthyl, indenyl, 1,2-dihydro-indenyl, furanyl, thienyl, pyranyl, 2,3,5,6-tetrahydro-4*H*-pyran-4-yl, pyridinyl, indolinyl and quinolinyl groups may optionally be substituted one or more times with substituents selected from the group consisting of alkyl, amino-alkyl, alkyl-amino, alkyl-amino-alkyl, hydroxy-alkyl, alkoxy-alkyl, cycloalkyl, cycloalkyl-alkyl, alkenyl, halo, haloalkyl, hydroxy, alkoxy, methylenedioxy, haloalkoxy, cyano, nitro, amino, phenyl and morpholinyl; or, when n is 0 and X is NR', Y together with R' and together with the nitrogen to which they are attached form a heterocyclic ring, which heterocyclic ring is optionally substituted one or two times with substituents selected from the group consisting of alkyl and phenyl; and

R^1, R^2, R^3 and R^4, independently of each other, represent hydrogen, alkyl, cycloalkyl, cycloalkyl-alkyl, cycloalkyl, cycloalkyl-alkyl, halo, haloalkyl, hydroxy, alkoxy, alkoxy-carbonyl, haloalkoxy, cyano, nitro and/or amino.

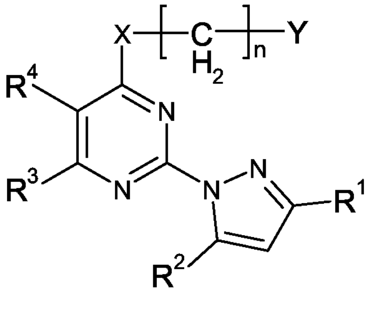
In another aspect, the invention provides pharmaceutical compositions comprising an effective amount of a chemical compound of the invention.

In further aspects the invention relates to the use of a chemical compound of the invention for the manufacture of a medicament for the treatment or alleviation of diseases or disorders associated with the activity of potassium channels, and to method of treatment or alleviation of disorders or conditions responsive to modulation of potassium channels.

DETAILED DISCLOSURE OF THE INVENTION

Potassium Channel Modulating Agents

In its first aspect, the invention provides novel pyrazolyl-pyrimidine derivatives of Formula I



(I)

an isomer or a mixture of its isomers, an N-oxide thereof, a prodrug thereof, or a pharmaceutically acceptable salt thereof, wherein

n is 0, 1, 2 or 3;

X represents O, S or NR'; wherein R' represents hydrogen, alkyl, cycloalkyl or cycloalkyl-alkyl; or, when n is 0 and X is NR', R' together with Y and together with the nitrogen to which they are attached form a heterocyclic ring, which heterocyclic ring is optionally substituted one or two times with substituents selected from the group consisting of alkyl and phenyl;

Y represents alkyl, cycloalkyl, alkyl-cycloalkyl, amino-alkyl, alkyl-amino, alkyl-amino-alkyl, hydroxy-alkyl, alkoxy-alkyl, alkenyl, phenyl, benzyl, naphthyl, 1,2,3,4-tetrahydro-naphthyl, indenyl, 1,2-dihydro-indenyl, furanyl, thienyl, pyranyl, tetrahydro-pyran-4-yl, pyridinyl, indolinyl or quinolinyl, which phenyl, benzyl, naphthyl, 1,2,3,4-tetrahydro-naphthyl, indenyl, 1,2-dihydro-indenyl, furanyl, thienyl, pyranyl, 2,3,5,6-tetrahydro-4*H*-pyran-4-yl, pyridinyl, indolinyl and quinolinyl groups may optionally be substituted one or more times with substituents selected from the group consisting of alkyl, amino-alkyl, alkyl-amino, alkyl-amino-alkyl, hydroxy-alkyl, alkoxy-alkyl, cycloalkyl, cycloalkyl-alkyl, alkenyl, halo, haloalkyl, hydroxy, alkoxy, methylenedioxy, haloalkoxy, cyano, nitro, amino, phenyl and morpholinyl; or, when n is 0 and X is NR', Y together with R' and together with the nitrogen to which they are attached form a heterocyclic ring, which heterocyclic ring is optionally substituted one or two times with substituents selected from the group consisting of alkyl and phenyl; and

R^1, R^2, R^3 and R^4, independently of each other, represent hydrogen, alkyl, cycloalkyl, cycloalkyl-alkyl, cycloalkyl, cycloalkyl-alkyl, halo, haloalkyl, hydroxy, alkoxy, alkoxy-carbonyl, haloalkoxy, cyano, nitro and/or amino;

provided, however, that the pyrazolyl-pyrimidine derivative is not

Methyl-[2-(3,5-dimethyl-pyrazol-1-yl)-6-methyl-pyrimidin-4-yl]-amine;

Cyclohexyl-[2-(3,5-dimethyl-pyrazol-1-yl)-6-methyl-pyrimidin-4-yl]-amine;

Phenyl-[2-(3,5-Dimethyl-pyrazol-1-yl)-6-methyl-pyrimidin-4-yl]-amine;

[2-(3,5-Dimethyl-pyrazol-1-yl)-6-methyl-pyrimidin-4-yl]-(4-chloro-phenyl)-amine;

[2-(3,5-Dimethyl-pyrazol-1-yl)-6-methyl-pyrimidin-4-yl]-(4-methyl-phenyl)-amine;

[2-(3,5-Dimethyl-pyrazol-1-yl)-6-methyl-pyrimidin-4-yl]-(4-n-butyl-phenyl)-amine;

[2-(3,5-Dimethyl-pyrazol-1-yl)-5-ethyl-6-methyl-pyrimidin-4-yl]-(4-n-butyl-phenyl)-amine;

[2-(3,5-Dimethyl-pyrazol-1-yl)-6-methyl-pyrimidin-4-yl]-(4-methoxy-phenyl)-amine;

[2-(3,5-Dimethyl-pyrazol-1-yl)-6-methyl-pyrimidin-4-yl]-(4-ethoxy-phenyl)-amine;

[2-(3,5-Dimethyl-pyrazol-1-yl)-6-methyl-pyrimidin-4-yl]-(2-trifluoromethyl-phenyl)-amine;

[2-(3,5-Dimethyl-pyrazol-1-yl)-6-methyl-pyrimidin-4-yl]-(3-trifluoromethyl-phenyl)-amine;

[2-(3,5-Dimethyl-pyrazol-1-yl)-6-methyl-pyrimidin-4-yl]-(4-ethoxy-phenyl)-amine;

[2-(3,5-Dimethyl-pyrazol-1-yl)-6-methyl-pyrimidin-4-yl]-(3-trifluoromethyl-phenyl)-amine;

Phenyl-[2-(3,5-Dimethyl-pyrazol-1-yl)-5-ethyl-6-methyl-pyrimidin-4-yl]-amine;

2-[2-(3,5-Dimethyl-pyrazol-1-yl)-6-methyl-pyrimidin-4-yl-amino]-ethanol;

4-Cyclohexylamino-2-(3,5-dimethyl-pyrazol-1-yl)-pyrimidine-5-carboxylic acid ethyl ester;

2-(3,5-Dimethyl-pyrazol-1-yl)-4-methyl-6-(4-methyl-piperidin-1-yl)-pyrimidine;

2-(3,5-Dimethyl-pyrazol-1-yl)-4-methyl-6-(4-phenyl-piperazin-1-yl)-pyrimidine;

4-[2-(3,5-Dimethyl-pyrazol-1-yl)-6-methyl-pyrimidin-4-yl]-morpholine; or

2,4-Bis-(3,5-dimethyl-pyrazol-1-yl)-6-methyl-pyrimidine.

In a preferred embodiment the pyrazolyl-pyrimidine derivative of the invention is a compound of Formula I, wherein

n is 0, 1, 2 or 3;

X represents O, S or NR'; wherein R' represents hydrogen, alkyl, cycloalkyl or cycloalkyl-alkyl; or, when n is 0, R' together with Y and together with the nitrogen to which they are attached form a heterocyclic ring;

Y represents alkyl, amino-alkyl, alkyl-amino, alkyl-amino-alkyl, hydroxy-alkyl, alkoxy-alkyl, alkenyl, or a monocyclic or polycyclic, carbocyclic or heterocyclic group, which carbocyclic or heterocyclic groups may optionally be substituted one or more times with substituents selected from the group consisting of alkyl, amino-alkyl, alkyl-amino, alkyl-amino-alkyl, hydroxy-alkyl, alkoxy-alkyl, cycloalkyl, cycloalkyl-alkyl, alkenyl, halo, haloalkyl, hydroxy, alkoxy, haloalkoxy, cyano, nitro and amino; or, when n is 0, Y together with R' and together with the nitrogen to which they are attached form a heterocyclic ring; and

R^1, R^2 and R^3, independently of each other, represent hydrogen, alkyl, cycloalkyl, cycloalkyl-alkyl, cycloalkyl, cycloalkyl-alkyl, alkenyl, halo, haloalkyl, hydroxy, alkoxy, haloalkoxy, cyano, nitro and amino; and R^4 represents hydrogen.

In another preferred embodiment the pyrazolyl-pyrimidine derivative of the invention is a compound of Formula I, wherein n is 0, 1, 2 or 3.

In a more preferred embodiment n is 0 or 1.

In an even more preferred embodiment n is 0.

In a third preferred embodiment the pyrazolyl-pyrimidine derivative of the invention is a compound of Formula I, wherein X represents O, S or NR'; wherein R' represents hydrogen, alkyl, cycloalkyl or cycloalkyl-alkyl; or, when n is 0 and X is NR', R' together with Y and together with the nitrogen to which they are attached form a heterocyclic ring, which heterocyclic ring is optionally substituted one or two times with substituents selected from the group consisting of alkyl and phenyl.

In a more preferred embodiment X represents O, S or NR'; wherein R' represents hydrogen, alkyl, cycloalkyl or cycloalkyl-alkyl; or, when n is 0 and X is NR', R' together with Y and together with the nitrogen to which they are attached form a heterocyclic ring.

In a fourth preferred embodiment the pyrazolyl-pyrimidine derivative of the invention is a compound of Formula I, wherein X represents O, S or NR'; wherein R' represents hydrogen, alkyl, cycloalkyl or cycloalkyl-alkyl.

In a more preferred embodiment X represents NR'; wherein R' represents hydrogen, alkyl, cycloalkyl or cycloalkyl-alkyl.

In an even more preferred embodiment X represents NR'; wherein R' represents hydrogen or alkyl, in particular methyl or ethyl.

In a still more preferred embodiment X represents NR'; wherein R' represents hydrogen, methyl or ethyl.

In a yet more preferred embodiment X represents NR'; wherein R' represents hydrogen.

In a further more preferred embodiment X represents NR'; wherein R' represents methyl or ethyl.

In a fifth preferred embodiment the pyrazolyl-pyrimidine derivative of the invention is a compound of Formula I, wherein

n is 0;

X is NR'; and R' together with Y and together with the nitrogen to which they are attached form a heterocyclic ring, in particular pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl or pyrazolyl, which heterocyclic ring is optionally substituted one or two times with substituents selected from the group consisting of alkyl and phenyl.

In a more preferred embodiment

n is 0;

X represents NR'; and R' together with Y and together with the nitrogen to which they are attached form a pyrrolidinyl or piperidinyl ring.

In an even more preferred embodiment

n is 0;

X is NR'; and R' together with Y and together with the nitrogen to which they are attached form a piperidinyl, piperazinyl or pyrazolyl ring, which heterocyclic ring is optionally substituted one or two times with substituents selected from the group consisting of alkyl and phenyl.

In a still more preferred embodiment

n is 0;

X is NR'; and R' together with Y and together with the nitrogen to which they are attached form a piperidinyl, a 4-methyl-piperidinyl, a piperazinyl, a 4-phenyl-piperazinyl, a pyrazolyl or a 3,5-dimethyl-pyrazolyl ring.

In a yet more preferred embodiment

n is 0;

X is NR'; and R' together with Y and together with the nitrogen to which they are attached form a 4-methyl-piperidinyl, a 4-phenyl-piperazinyl or a 3,5-dimethyl-pyrazolyl ring.

In a sixth preferred embodiment the pyrazolyl-pyrimidine derivative of the invention is a compound of Formula I, wherein Y represents alkyl, cycloalkyl, alkyl-cycloalkyl, amino-alkyl, alkyl-amino, alkyl-amino-alkyl, hydroxy-alkyl, alkoxy-alkyl, alkenyl, phenyl, benzyl, naphthyl, 1,2,3,4-tetrahydro-naphthyl, indenyl, 1,2-dihydro-indenyl, furanyl, thienyl, pyranyl, tetrahydro-pyran-4-yl, pyridinyl, indolinyl or quinolinyl, which phenyl, benzyl, naphthyl, 1,2,3,4-tetrahydro-naphthyl, indenyl, 1,2-dihydro-indenyl, furanyl, thienyl, pyranyl, 2,3,5,6-tetrahydro-4*H*-pyran-4-yl, pyridinyl, indolinyl and quinolinyl groups may optionally be substituted one or more times with substituents selected from the group consisting of alkyl, amino-alkyl, alkyl-amino, alkyl-amino-alkyl, hydroxy-alkyl, alkoxy-alkyl, cycloalkyl, cycloalkyl-alkyl, alkenyl, halo, haloalkyl, hydroxy, alkoxy, methylenedioxy, haloalkoxy, cyano, nitro, amino, phenyl and morpholinyl.

In a seventh preferred embodiment the pyrazolyl-pyrimidine derivative of the invention is a compound of Formula I, wherein Y represents alkyl, amino-alkyl, alkyl-amino, alkyl-amino-alkyl, hydroxy-alkyl, alkoxy-alkyl, alkenyl, or a monocyclic or polycyclic, carbocyclic or heterocyclic group, which carbocyclic or heterocyclic groups may optionally be substituted one or more times with substituents selected from the group consisting of alkyl, amino-alkyl, alkyl-amino, alkyl-amino-alkyl, hydroxy-alkyl, alkoxy-alkyl, cycloalkyl, cycloalkyl-alkyl, alkenyl, halo, haloalkyl, hydroxy, alkoxy, haloalkoxy, cyano, nitro and amino; or, when n is 0 and X is NR', Y together with R' and together with the nitrogen to which they are attached form a heterocyclic ring.

In a more preferred embodiment Y represents alkyl, in particular methyl, ethyl, propyl, butyl or pentyl; cycloalkyl, in particular cyclopropyl, cyclopentyl, cyclohexyl, cycloheptyl or cyclooctyl; alkyl-cycloalkyl, in particular methyl-cyclohexyl or t-butyl-cyclohexyl; hydroxy-alkyl, in particular hydroxyl-methyl, 2-hydroxy-ethyl or 3-hydroxy-propyl; alkenyl, in particular propenyl; phenyl, benzyl, or naphthyl, which phenyl, benzyl and naphthyl groups may optionally be substituted one or two times with substituents selected from the group consisting of alkyl, in particular methyl; halo, in particular fluoro, chloro, bromo or iodo; haloalkyl, in particular trifluoromethyl; and alkoxy, in particular methoxy.

In an even more preferred embodiment Y represents methyl, ethyl, propyl, butyl, pentyl, cyclopropyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, methyl-cyclohexyl, t-butyl-cyclohexyl, hydroxyl-methyl, 2-hydroxy-ethyl, 3-hydroxy-propyl, phenyl, benzyl, or naphthyl, which phenyl, benzyl and naphthyl groups may optionally be substituted one or two times with substituents selected from the group consisting of methyl, fluoro, chloro, trifluoromethyl and methoxy.

In a still more preferred embodiment Y represents alkyl, alkenyl or cycloalkyl.

In a yet more preferred embodiment Y represents phenyl, benzyl, or naphthyl, which phenyl, benzyl and naphthyl groups may optionally be substituted one or two times with substituents selected from the group consisting of methyl, fluoro, chloro, trifluoromethyl and methoxy.

In a further more preferred embodiment Y represents phenyl or benzyl, which phenyl and benzyl groups may optionally be substituted one or two times with substituents selected from the group consisting of methyl, fluoro, chloro, trifluoromethyl and methoxy.

In a still further more preferred embodiment Y represents naphthyl.

In a still further more preferred embodiment Y represents a monocyclic or polycyclic carbocyclic group selected from phenyl, naphthyl or 1,2,3,4-tetrahydronaphthyl; or a monocyclic or polycyclic heterocyclic group selected from pyrrolidinyl, piperidinyl, furanyl, thienyl and pyrrolyl; which phenyl, naphthyl, 1,2,3,4-tetrahydronaphthyl, pyrrolidinyl, piperidinyl, furanyl, thienyl and pyrrolyl groups may optionally be substituted one or more times with substituents selected from the group consisting of alkyl, amino-alkyl, alkyl-amino, alkyl-amino-alkyl, hydroxy-alkyl, alkoxy-alkyl, cycloalkyl, cycloalkyl-alkyl, alkenyl, halo, haloalkyl, hydroxy, alkoxy, haloalkoxy, cyano, nitro and amino.

In an eight preferred embodiment the pyrazolyl-pyrimidine derivative of the invention is a compound of Formula I, wherein R^1, R^2, R^3 and R^4, independently of each other, represent hydrogen, alkyl, cycloalkyl, cycloalkyl-alkyl, cycloalkyl, cycloalkyl-alkyl, halo, haloalkyl, hydroxy, alkoxy, alkoxy-carbonyl, haloalkoxy, cyano, nitro and/or amino.

In a more preferred embodiment

R^1 and R^2, independently of each other, represent hydrogen or alkyl, in particular methyl, ethyl or propyl; and

R^3 and R^4, independently of each other, represent hydrogen; alkyl, in particular methyl, ethyl or propyl; halo, in particular fluoro, chloro, bromo or iodo; haloalkyl, in particular trifluoromethyl; alkoxy-carbonyl, in particular methoxy-carbonyl or ethoxy-carbonyl; and/or cyano.

In an even more preferred embodiment

R^1 and R^2, independently of each other, represent alkyl, in particular methyl, ethyl or propyl; and

R^3 and R^4, independently of each other, represent hydrogen; alkyl, in particular methyl, ethyl or propyl; halo, in particular fluoro, chloro, bromo or iodo;

haloalkyl, in particular trilfuoromethyl; alkoxy-carbonyl, in particular methoxy-carbonyl or ethoxy-carbonyl; and/or cyano.

In a still more preferred embodiment

R^1 and R^2, independently of each other, represent methyl, ethyl or propyl; and

R^3 and R^4, independently of each other, represent hydrogen; alkyl, in particular methyl, ethyl or propyl; halo, in particular fluoro, chloro, bromo or iodo; haloalkyl, in particular trifluoromethyl; alkoxy-carbonyl, in particular methoxy-carbonyl or ethoxy-carbonyl; and/or cyano.

In a yet more preferred embodiment

R^1 and R^2 represent methyl; and

R^3 and R^4, independently of each other, represent hydrogen; alkyl, in particular methyl, ethyl or propyl; halo, in particular fluoro, chloro, bromo or iodo; haloalkyl, in particular trifluoromethyl; alkoxy-carbonyl, in particular methoxy-carbonyl or ethoxy-carbonyl; and/or cyano.

In a further more preferred embodiment

R^1 and R^2 represent methyl;

R^3 represents hydrogen or alkyl, in particular methyl, ethyl or propyl; and

R^4 represents hydrogen; alkyl, in particular methyl, ethyl or propyl; halo, in particular fluoro, chloro, bromo or iodo; alkoxy-carbonyl, in particular methoxy-carbonyl or ethoxy-carbonyl; and/or cyano.

In a still further more preferred embodiment

R^1 and R^2 represent methyl;

R^3 represents hydrogen, methyl, ethyl or propyl; and

R^4 represents hydrogen, methyl, ethyl, propyl, chloro, bromo, ethoxy-carbonyl and/or cyano.

In a ninth preferred embodiment the pyrazolyl-pyrimidine derivative of the invention is a compound of Formula I, wherein R^1, R^2 and R^3, independently of each other, represent hydrogen, alkyl, cycloalkyl, cycloalkyl-alkyl, cycloalkyl, cycloalkyl-alkyl, alkenyl, halo, haloalkyl, hydroxy, alkoxy, haloalkoxy, cyano, nitro and amino, and R^4 represents hydrogen.

In a more preferred embodiment R^1, R^2 and R^3, independently of each other, represent alkyl, cycloalkyl or cycloalkyl-alkyl, and R^4 represents hydrogen.

In a tenth preferred embodiment the pyrazolyl-pyrimidine derivative of the invention is a compound of Formula I, wherein

n is 0;

X is NH;

Y represents alkyl, in particular methyl, ethyl, propyl, butyl or pentyl; cycloalkyl, in particular cyclopropyl, cyclopentyl, cyclohexyl, cycloheptyl or cyclooctyl;

alkyl-cycloalkyl, in particular methyl-cyclohexyl or t-butyl-cyclohexyl; hydroxy-alkyl, in particular hydroxyl-methyl, 2-hydroxy-ethyl or 3-hydroxy-propyl; phenyl, benzyl or naphthyl;

R^1 and R^2 represent methyl;

R^3 represents hydrogen, methyl, ethyl or propyl; and

R^4 represents hydrogen, methyl, ethyl, propyl, chloro, bromo, ethoxy-carbonyl and/or cyano.

In an eleventh preferred embodiment the pyrazolyl-pyrimidine derivative of the invention is a compound of Formula I, wherein

n is 0;

X represents NR'; wherein R' represents hydrogen, methyl, ethyl or propyl;

Y represents alkyl, cycloalkyl, cycloalkyl-alkyl, or alkenyl, piperidinyl or phenyl, which phenyl may optionally be substituted one or two times with halo or trifluoromethyl; and

R^1, R^2 and R^3, independently of each other, represent methyl, ethyl or propyl, and R^4 represents hydrogen.

In a twelfth preferred embodiment the pyrazolyl-pyrimidine derivative of the invention is a compound of Formula I, wherein

n is 0;

X represents NR'; and R' together with Y and together with the nitrogen to which they are attached form a pyrrolidinyl or piperidinyl ring; and

R^1, R^2 and R^3, independently of each other, represent methyl, ethyl or propyl, and R^4 represents hydrogen.

In a thirteenth preferred embodiment the pyrazolyl-pyrimidine derivative of the invention is a compound of Formula I, wherein

n is 1; and

X represents NR'; wherein R' represents hydrogen, methyl, ethyl or propyl;

Y represents furanyl, thienyl or phenyl, which phenyl may optionally be substituted one or two times with halo or trifluoromethyl; and

R^1, R^2 and R^3, independently of each other, represent methyl, ethyl or propyl, and R^4 represents hydrogen.

In a fourteenth preferred embodiment the pyrazolyl-pyrimidine derivative of the invention is a compound of Formula I, wherein

n is 0;

X is NH;

Y represents phenyl or benzyl, which phenyl and benzyl groups may optionally be substituted one or two times with substituents selected from the group consisting of alkyl, in particular methyl; halo, in particular fluoro, chloro, bromo or iodo; haloalkyl, in particular trifluoromethyl; and alkoxy, in particular methoxy;

R^1 and R^2 represent methyl;

R^3 represents hydrogen, methyl, ethyl or propyl; and

R^4 represents hydrogen, methyl, ethyl, propyl, chloro, bromo, ethoxycarbonyl or cyano.

In a more preferred embodiment

n is 0;

X is NH;

Y represents phenyl or benzyl, which phenyl and benzyl groups may optionally be substituted one or two times with substituents selected from the group consisting of methyl, chloro, trifluoromethyl and methoxy;

R^1 and R^2 represent methyl;

R^3 represents hydrogen, methyl, ethyl or propyl; and

R^4 represents hydrogen, methyl, ethyl, propyl, chloro, bromo, ethoxycarbonyl or cyano.

In a most preferred embodiment the pyrazolyl-pyrimidine derivative of the invention is

Benzyl-[2-(3,5-dimethyl-pyrazol-1-yl)-6-methyl-pyrimidin-4-yl]-amine;

Cyclopentyl-[2-(3,5-dimethyl-pyrazol-1-yl)-6-methyl-pyrimidin-4-yl]-amine;

[2-(3,5-Dimethyl-pyrazol-1-yl)-6-methyl-pyrimidin-4-yl]-diethyl-amine;

[2-(3,5-Dimethyl-pyrazol-1-yl)-6-methyl-pyrimidin-4-yl]-phenyl-amine;

[2-(3,5-Dimethyl-pyrazol-1-yl)-6-methyl-pyrimidin-4-yl]-*p*-tolyl-amine;

(3,4-Dichloro-phenyl)-[2-(3,5-dimethyl-pyrazol-1-yl)-6-methyl-pyrimidin-4-yl]-amine;

[2-(3,5-Dimethyl-pyrazol-1-yl)-6-methyl-pyrimidin-4-yl]-naphthalen-2-yl-amine;

[2-(3,5-Dimethyl-pyrazol-1-yl)-pyrimidin-4-yl]-(3-trifluoromethyl-phenyl)-amine;

Cyclohexyl-[2-(3,5-dimethyl-pyrazol-1-yl)-pyrimidin-4-yl]-amine;

[5-Chloro-2-(3,5-dimethyl-pyrazol-1-yl)-pyrimidin-4-yl]-cyclohexyl-amine;

(4-Chloro-phenyl)-[2-(3,5-dimethyl-pyrazol-1-yl)-pyrimidin-4-yl]-amine;

[5-Bromo-2-(3,5-dimethyl-pyrazol-1-yl)-pyrimidin-4-yl]-(4-chloro-phenyl)-amine;

[2-(3,5-Dimethyl-pyrazol-1-yl)-pyrimidin-4-yl]-p-tolyl-amine;

(4-Chloro-phenyl)-[2-(3,5-dimethyl-pyrazol-1-yl)-5-methyl-pyrimidin-4-yl]-amine;

[5-Bromo-2-(3,5-dimethyl-pyrazol-1-yl)-pyrimidin-4-yl]-cyclohexyl-amine; or

[5-Chloro-2-(3,5-dimethyl-pyrazol-1-yl)-pyrimidin-4-yl]-(4-chloro-phenyl)-amine;

or a pharmaceutically acceptable salt thereof.

Any combination of two or more of the embodiments described herein is considered within the scope of the present invention.

Definition of Substituents

In the context of this invention halo represents fluoro, chloro, bromo or iodo. Thus a trihalomethyl group represents e.g. a trifluoromethyl group, a trichloromethyl group, and similar trihalo-substituted methyl groups.

In the context of this invention a haloalkyl group designates an alkyl group as defined herein, which alkyl group is substituted one or more times with halo. Preferred haloalkyl groups of the invention include trihalomethyl, preferably trifluoromethyl.

In the context of this invention an alkyl group designates a univalent saturated, straight or branched hydrocarbon chain. The hydrocarbon chain preferably contain of from one to eighteen carbon atoms (C_{1-18}-alkyl), more preferred of from one to six carbon atoms (C_{1-6}-alkyl; lower alkyl), including pentyl, isopentyl, neopentyl, tertiary pentyl, hexyl and isohexyl. In a preferred embodiment alkyl represents a C_{1-4}-alkyl group, including butyl, isobutyl, secondary butyl, and tertiary butyl. In a preferred embodiment of this invention alkyl represents a C_{1-3}-alkyl group, which may in particular be methyl, ethyl, propyl or isopropyl.

In the context of this invention a hydroxy-alkyl group designates an alkyl group as defined above, which hydroxy-alkyl group is substituted with one or more hydroxy groups. Examples of preferred hydroxy-alkyl groups of the invention include 2-hydroxy-ethyl, 3-hydroxy-propyl, 4-hydroxy-butyl, 5-hydroxy-pentyl and 6-hydroxy-hexyl.

In the context of this invention an alkenyl group designates a carbon chain containing one or more double bonds, including di-enes, tri-enes and poly-enes. In a preferred embodiment the alkenyl group of the invention comprises of from two to eight carbon atoms (C_{2-8}-alkenyl), more preferred of from two to six carbon atoms (C_{2-6}-alkenyl), including at least one double bond. In a most preferred embodiment the alkenyl group of the invention is ethenyl; 1- or 2-propenyl; 1-, 2- or 3-butenyl, or 1,3-butenyl; 1-, 2-, 3-, 4- or 5-hexenyl, or 1,3-hexenyl, or 1,3,5-hexenyl; 1-, 2-, 3-, 4-, 5-, 6-, or 7-octenyl, or 1,3-octenyl, or 1,3,5-octenyl, or 1,3,5,7-octenyl.

In the context of this invention a cycloalkyl group designates a cyclic alkyl group, preferably containing of from three to ten carbon atoms (C_{3-10}-cycloalkyl), preferably of from three to eight carbon atoms (C_{3-8}-cycloalkyl), including cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and cyclooctyl.

In the context of this invention a cycloalkyl-alkyl group designates a cycloalkyl group as defined above, which cycloalkyl group is substituted on an alkyl group as also defined above. Examples of preferred cycloalkyl-alkyl groups of the invention include cyclopropylmethyl and cyclopropylethyl.

In the context of this invention an alkoxy group designates an "alkyl-O-" group, wherein alkyl is as defined above.

In the context of this invention a haloalkoxy group designates an alkoxy group as defined herein, which alkoxy group is substituted one or more times with halo. Preferred haloalkoxy groups of the invention include trihalomethoxy, preferably trifluoromethoxy.

In the context of this invention an amino group may be a primary ($-NH_2$), secondary (-NH-alkyl), or tertiary ($-N(alkyl)_2$) amino group, i.e. it may be substituted once or twice with an alkyl group as defined above.

In the context of this invention a mono- or poly-cyclic carbocyclic group designates a mono- or polycyclic hydrocarbon group, which group may in particular be an aromatic hydrocarbon group, i.e. a mono- or polycyclic aryl group, or a saturated hydrocarbon group, or a partially saturated hydrocarbon group. Preferred poly-carbocyclic group are the bicyclic carbocyclic groups.

In the context of this invention a monocyclic or polycyclic, carbocyclic group designates a monocyclic or polycyclic hydrocarbon group. Examples of preferred carbocyclic groups of the invention include cycloalkyl, phenyl, naphthyl, indenyl, azulenyl, anthracenyl, and fluorenyl. Most preferred carbocyclic groups of the invention include phenyl, naphthyl and 1,2,3,4-tetrahydro-naphthyl.

In the context of this invention a monocyclic or polycyclic, heterocyclic group designates a mono- or polycyclic group, which group holds one or more heteroatoms in its ring structure. Preferred heteroatoms include nitrogen (N), oxygen (O), and sulphur (S). One or more of the ring structures may in particular be aromatic (i.e. a heteroaryl), saturated or partially saturated. Preferred heterocyclic monocyclic groups of the invention include 5- and 6 membered heterocyclic monocyclic groups. Preferred poly-heterocyclic groups of the invention are the bicyclic heterocyclic groups.

Examples of preferred heterocyclic monocyclic groups of the invention include pyrrolidinyl, in particular pyrrolidin-1-yl, pyrrolidin-2-yl, and pyrrolidin-3-yl; piperidinyl, in particular piperidin-1-yl, piperidin-2-yl, piperidin-3-yl and piperidin-4-yl; furanyl, in particular furan-2-yl and furan-3-yl; thienyl, in particular thien-2-yl and thien-3-yl; and pyrrolyl, in particular pyrrol-1-yl, pyrrol-2-yl and pyrrol-3-yl.

Isomers

It will be appreciated by those skilled in the art that the compounds of the present invention may exist in different stereoisomeric forms, including enantiomers, diastereomers, as well as geometric isomers (cis-trans isomers). The invention includes all such isomers and any mixtures thereof including racemic mixtures.

Racemic forms can be resolved into the optical antipodes by known methods and techniques. One way of separating the enantiomeric compounds (including enantiomeric intermediates) is by use of an optically active amine, and liberating the diastereomeric, resolved salt by treatment with an acid. 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 crystallisation of D- or L- (tartrates, mandelates, or camphorsulphonate) salts for example.

The chemical compounds of the present invention may also be resolved by the formation of diastereomeric amides by reaction of the chemical 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 chemical compound of the present invention with an optically active chloroformate or the like.

Additional methods for the resolving the optical isomers are known in the art. Such methods include those described by *Jaques J, Collet A, & Wilen S* in "Enantiomers, Racemates, and Resolutions", John Wiley and Sons, New York (1981).

Optical active compounds can also be prepared from optical active starting materials or intermediates.

Pharmaceutically Acceptable Salts

The chemical compound of the invention may be provided in any form suitable for the intended administration. Suitable forms include pharmaceutically (i.e. physiologically) acceptable salts, and pre- or prodrug forms of the chemical compound of the invention.

Examples of pharmaceutically acceptable addition salts include, without limitation, the non-toxic inorganic and organic acid addition salts such as the hydrochloride derived from hydrochloric acid, the hydrobromide derived from hydrobromic acid, the nitrate derived from nitric acid, the perchlorate derived from perchloric acid, the phosphate derived from phosphoric acid, the sulphate derived from sulphuric acid, the formate derived from formic acid, the acetate derived from acetic acid, the aconate derived from aconitic acid, the ascorbate derived from ascorbic acid, the benzenesulfonate derived from benzensulfonic acid, the benzoate derived from benzoic acid, the cinnamate derived from cinnamic acid, the citrate derived from citric acid, the embonate derived from embonic acid, the enantate derived from enanthic acid, the fumarate derived from fumaric acid, the glutamate derived from glutamic acid, the glycolate derived from glycolic acid, the lactate derived from lactic acid, the maleate derived from maleic acid, the malonate derived from malonic acid, the mandelate derived from mandelic acid, the methanesulfonate derived from methane sulphonic acid, the naphthalene-2-sulphonate derived from naphtalene-2-sulphonic acid, the phthalate derived from phthalic acid, the salicylate derived from salicylic acid, the sorbate derived from sorbic acid, the stearate derived from stearic acid, the succinate derived from succinic acid, the tartrate derived from tartaric acid, the toluene-p-sulphonate derived from p-toluene sulphonic acid, and the like. Such salts may be formed by procedures well known and described in the art.

Other acids such as oxalic acid, which may not be considered pharmaceutically acceptable, may be useful in the preparation of salts useful as intermediates in obtaining a chemical compound of the invention and its pharmaceutically acceptable acid addition salt.

Metal salts of a chemical compound of the invention include alkali metal salts, such as the sodium salt of a chemical compound of the invention containing a carboxy group.

In the context of this invention the “onium salts” of N-containing compounds are also contemplated as pharmaceutically acceptable salts. Preferred “onium salts” include the alkyl-onium salts, the cycloalkyl-onium salts, and the cycloalkylalkyl-onium salts.

The chemical compound of the invention may be provided in dissoluble or indissoluble forms together with pharmaceutically acceptable solvents such as water, ethanol, and the like. Dissoluble forms may also include hydrated forms such as the monohydrate, the dihydrate, the hemihydrate, the trihydrate, the tetrahydrate, and the like. In general, the dissoluble forms are considered equivalent to indissoluble forms for the purposes of this invention.

Methods of Preparation

The chemical compounds of the invention may be prepared by conventional methods of chemical synthesis, e.g. those described in the working examples. The starting materials for the processes described in the present application are known or may readily be prepared by conventional methods from commercially available chemicals.

The end products of the reactions described herein may be isolated by conventional techniques, e.g. by extraction, crystallisation, distillation, chromatography, etc.

Biological Activity

The chemical compounds of the invention have been subjected to *in vitro* experiments and found particularly useful as potassium channel modulating agents. More particularly the compounds of the invention are capable of selectively modulating SK1, SK2 and/or SK3 channels.

Therefore, in another aspect, the invention relates to the use of a chemical compound of the invention for the manufacture of medicaments, which medicament may be useful for the treatment or alleviation of a disease or a disorder associated with the activity of potassium channels, in particular SK channels, more particularly SK1, SK2 and/or SK3 channels.

In a preferred embodiment, the disease or a disorder associated with the activity of potassium channels is a respiratory disease, epilepsy, convulsions, seizures, absence seizures, vascular spasms, coronary artery spasms, renal disorders, polycystic kidney disease, bladder spasms, urinary incontinence, bladder outflow obstruction, erectile dysfunction, gastrointestinal dysfunction, secretory diarrhoea, ischaemia, cerebral ischaemia, ischaemic heart disease, angina pectoris, coronary heart disease, ataxia, traumatic brain injury, Parkinson's disease, bipolar disorder, psychosis, schizophrenia, anxiety, depression, mood disorders, dementia, memory and attention deficits, Alzheimer’s disease, amyotrophic lateral sclerosis (ALS), dysmenorrhea, narcolepsy, Reynaud’s disease, intermittent claudication, Sjorgren’s syndrome, arrhythmia, hypertension, myotonic muscle dystrophia, spasticity, xerostomi, diabetes type II, hyperinsulinemia, premature labour, baldness, cancer, irritable bowel syndrome, immune suppression, migraine or pain.

In a more preferred embodiment the disease or a disorder associated with the activity of potassium channels is a respiratory disease, urinary incontinence, erectile dysfunction, anxiety, epilepsy, psychosis, schizophrenia, amyotrophic lateral sclerosis (ALS) or pain.

In another preferred embodiment the disease or a disorder associated with the activity of potassium channels is a respiratory disease, in particular asthma, cystic fibrosis, chronic obstructive pulmonary disease (COPD) or rhinorrhea.

In a third preferred embodiment the disease or a disorder associated with the activity of potassium channels is urinary incontinence.

In a fourth preferred embodiment the disease or a disorder associated with the activity of potassium channels is epilepsy, seizures, absence seizures or convulsions.

In a fifth preferred embodiment the disease or a disorder associated with the activity of potassium channels is a respiratory disease, in particular asthma, cystic fibrosis, chronic obstructive pulmonary disease (COPD) or rhinorrhea.

The compounds tested all showed a biological activity in the micromolar and sub-micromolar range, i.e. of from below 1 to above 100 μM. Preferred compounds of the invention show a biological activity determined as described herein in the in the sub-micromolar and micromolar range, i.e. of from below 0.1 to about 10 μM.

Pharmaceutical Compositions

In yet another aspect the invention provides novel pharmaceutical compositions comprising a therapeutically effective amount of the chemical compound of the invention, including the following compounds:

Benzyl-[2-(3,5-dimethyl-pyrazol-1-yl)-6-methyl-pyrimidin-4-yl]-amine;

Cyclopentyl-[2-(3,5-dimethyl-pyrazol-1-yl)-6-methyl-pyrimidin-4-yl]-amine;

[2-(3,5-Dimethyl-pyrazol-1-yl)-6-methyl-pyrimidin-4-yl]-diethyl-amine;

[2-(3,5-Dimethyl-pyrazol-1-yl)-6-methyl-pyrimidin-4-yl]-phenyl-amine;

[2-(3,5-Dimethyl-pyrazol-1-yl)-6-methyl-pyrimidin-4-yl]-*p*-tolyl-amine;

(3,4-Dichloro-phenyl)-[2-(3,5-dimethyl-pyrazol-1-yl)-6-methyl-pyrimidin-4-yl]-amine;

[2-(3,5-Dimethyl-pyrazol-1-yl)-6-methyl-pyrimidin-4-yl]-naphthalen-2-yl-amine;

[2-(3,5-Dimethyl-pyrazol-1-yl)-pyrimidin-4-yl]-(3-trifluoromethyl-phenyl)-amine;

Cyclohexyl-[2-(3,5-dimethyl-pyrazol-1-yl)-pyrimidin-4-yl]-amine;

[5-Chloro-2-(3,5-dimethyl-pyrazol-1-yl)-pyrimidin-4-yl]-cyclohexyl-amine;

(4-Chloro-phenyl)-[2-(3,5-dimethyl-pyrazol-1-yl)-pyrimidin-4-yl]-amine;

[5-Bromo-2-(3,5-dimethyl-pyrazol-1-yl)-pyrimidin-4-yl]-(4-chloro-phenyl)-amine;

[2-(3,5-Dimethyl-pyrazol-1-yl)-pyrimidin-4-yl]-p-tolyl-amine;

(4-Chloro-phenyl)-[2-(3,5-dimethyl-pyrazol-1-yl)-5-methyl-pyrimidin-4-yl]-amine;

[5-Bromo-2-(3,5-dimethyl-pyrazol-1-yl)-pyrimidin-4-yl]-cyclohexyl-amine;

[5-Chloro-2-(3,5-dimethyl-pyrazol-1-yl)-pyrimidin-4-yl]-(4-chloro-phenyl)-amine;

Methyl-[2-(3,5-dimethyl-pyrazol-1-yl)-6-methyl-pyrimidin-4-yl]-amine;

Cyclohexyl-[2-(3,5-dimethyl-pyrazol-1-yl)-6-methyl-pyrimidin-4-yl]-amine;

Phenyl-[2-(3,5-Dimethyl-pyrazol-1-yl)-6-methyl-pyrimidin-4-yl]-amine;

[2-(3,5-Dimethyl-pyrazol-1-yl)-6-methyl-pyrimidin-4-yl]-(4-chloro-phenyl)-amine;

[2-(3,5-Dimethyl-pyrazol-1-yl)-6-methyl-pyrimidin-4-yl]-(4-methyl-phenyl)-amine;

[2-(3,5-Dimethyl-pyrazol-1-yl)-6-methyl-pyrimidin-4-yl]-(4-n-butyl-phenyl)-amine;

[2-(3,5-Dimethyl-pyrazol-1-yl)-5-ethyl-6-methyl-pyrimidin-4-yl]-(4-n-butyl-phenyl)-amine;

[2-(3,5-Dimethyl-pyrazol-1-yl)-6-methyl-pyrimidin-4-yl]-(4-methoxy-phenyl)-amine;

[2-(3,5-Dimethyl-pyrazol-1-yl)-6-methyl-pyrimidin-4-yl]-(4-ethoxy-phenyl)-amine;

[2-(3,5-Dimethyl-pyrazol-1-yl)-6-methyl-pyrimidin-4-yl]-(2-trifluoromethyl-phenyl)-amine;

[2-(3,5-Dimethyl-pyrazol-1-yl)-6-methyl-pyrimidin-4-yl]-(3-trifluoromethyl-phenyl)-amine;

[2-(3,5-Dimethyl-pyrazol-1-yl)-6-methyl-pyrimidin-4-yl]-(4-ethoxy-phenyl)-amine;

[2-(3,5-Dimethyl-pyrazol-1-yl)-6-methyl-pyrimidin-4-yl]-(3-trifluoromethyl-phenyl)-amine;

Phenyl-[2-(3,5-Dimethyl-pyrazol-1-yl)-5-ethyl-6-methyl-pyrimidin-4-yl]-amine;

2-[2-(3,5-Dimethyl-pyrazol-1-yl)-6-methyl-pyrimidin-4-yl-amino]-ethanol;

4-Cyclohexylamino-2-(3,5-dimethyl-pyrazol-1-yl)-pyrimidine-5-carboxylic acid ethyl ester;

2-(3,5-Dimethyl-pyrazol-1-yl)-4-methyl-6-(4-methyl-piperidin-1-yl)-pyrimidine;

2-(3,5-Dimethyl-pyrazol-1-yl)-4-methyl-6-(4-phenyl-piperazin-1-yl)-pyrimidine;

4-[2-(3,5-Dimethyl-pyrazol-1-yl)-6-methyl-pyrimidin-4-yl]-morpholine; and

2,4-Bis-(3,5-dimethyl-pyrazol-1-yl)-6-methyl-pyrimidine.

In a preferred embodiment the pharmaceutical composition of the invention comprises a therapeutically-effective amount of a pyrazolyl-pyrimidine derivative as described above, or a pharmaceutically-acceptable addition salt thereof, together with at least one pharmaceutically-acceptable carrier or diluent.

While a chemical compound of the invention for use in therapy may be administered in the form of the raw chemical compound, it is preferred to introduce the active ingredient, optionally in the form of a physiologically acceptable salt, or in the form of a prodrug, in a pharmaceutical composition together with one or more adjuvants, excipients, carriers and/or diluents.

In a preferred embodiment, the invention provides pharmaceutical compositions comprising the chemical 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 compositions of the invention may be those suitable for oral, rectal, bronchial, nasal, topical (including buccal and sub-lingual), transdermal, vaginal or parenteral (including cutaneous, subcutaneous, intramuscular, intraperitoneal, intravenous, intraarterial, intracerebral, intraocular injection or infusion) administration, or those in a form suitable for administration by inhalation or insufflation, including powders and liquid aerosol administration, or by sustained release systems. Suitable examples of sustained release systems include semipermeable matrices of solid hydrophobic polymers containing the compound of the invention, which matrices may be in form of shaped articles, e.g. films or microcapsules.

The chemical compound 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. Such forms include solids, and in particular tablets, filled capsules, powder and pellet forms, and liquids, in particular aqueous or non-aqueous solutions, suspensions, emulsions, elixirs, and capsules filled with the same, all for oral use, suppositories for rectal administration, and sterile injectable solutions for parenteral 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.

The chemical compound of the present invention can be administered 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 chemical compound of the invention or a pharmaceutically acceptable salt of a chemical compound of the invention.

For preparing pharmaceutical compositions from a chemical compound 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 that 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 wax, 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 wax, such as a mixture of fatty acid glyceride or cocoa butter, is first melted and the active component is dispersed homogeneously therein, as by stirring. The molten homogenous mixture is then poured into convenient sized moulds, allowed to cool, and thereby to solidify.

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

The chemical compound 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 formulation 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 lyophilization 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, stabilising 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, or other well known suspending agents.

Also included are solid form preparations, intended for conversion 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, stabilisers, buffers, artificial and natural sweeteners, dispersants, thickeners, solubilizing agents, and the like

For topical administration to the epidermis the chemical compound 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 will in general also contain one or more emulsifying agents, stabilising agents, dispersing agents, suspending agents, thickening agents, or colouring agents.

Compositions suitable for topical administration in the mouth include lozenges comprising the 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 glycerine or sucrose and acacia; and mouthwashes comprising the active ingredient in a suitable liquid carrier.

Solutions or suspensions are applied directly to the nasal cavity by conventional means, for example with a dropper, pipette or spray. The compositions may be provided in single or multi-dose form.

Administration to the respiratory tract may also be achieved by means of an aerosol formulation in which the active ingredient is provided in a pressurised 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 polyvinylpyrrolidone (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 compositions intended for administration to the respiratory tract, including intranasal compositions, 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, compositions 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 packaged 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 and continuous infusion are preferred compositions.

Further details on techniques for formulation and administration may be found in the latest edition of Remington's Pharmaceutical Sciences (Maack Publishing Co., Easton, PA).

A therapeutically effective dose refers to that amount of active ingredient which ameliorates the symptoms or condition. Therapeutic efficacy and toxicity, e.g. ED_{50} and LD_{50}, may be determined by standard pharmacological procedures in cell cultures or experimental animals. The dose ratio between therapeutic and toxic effects is the therapeutic index and may be expressed by the ratio LD_{50}/ED_{50}. Pharmaceutical compositions exhibiting large therapeutic indexes are preferred.

The dose administered must of course be carefully adjusted to the age, weight and condition of the individual being treated, as well as the route of administration, dosage form and regimen, and the result desired, and the exact dosage should of course be determined by the practitioner.

The actual dosage depend on the nature and severity of the disease being treated and the route of administration, and is within the discretion of the physician, and may be varied by titration of the dosage to the particular circumstances of this invention to produce the desired therapeutic effect. However, it is presently contemplated that pharmaceutical compositions containing of from about 0.1 to about 500 mg of active ingredient per individual dose, preferably of from about 1 to about 100 mg, most preferred of from about 1 to about 10 mg, are suitable for therapeutic treatments.

The active ingredient may be administered in one or several doses per day. A satisfactory result can, in certain instances, be obtained at a dosage as low as 0.1 µg/kg i.v. and 1 µg/kg p.o. The upper limit of the dosage range is presently considered to be about 10 mg/kg i.v. and 100 mg/kg p.o. Preferred ranges are from about 0.1 µg/kg to about 10 mg/kg/day i.v., and from about 1 µg/kg to about 100 mg/kg/day p.o.

Methods of Therapy

In another aspect the invention provides a method for the prevention, treatment or alleviation of a disease or a disorder or a condition of a living animal body, including a human, which disease, disorder or condition is responsive to modulation of potassium channels, in particular SK channels, and which method comprises comprising administering to such a living animal body, including a human, in need thereof a therapeutically-effective amount of a compound of the invention.

The preferred indications contemplated according to the invention are those stated above.

It is at present contemplated that suitable dosage ranges are 0.1 to 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.

A satisfactory result can, in certain instances, be obtained at a dosage as low as 0.005 mg/kg i.v. and 0.01 mg/kg p.o. The upper limit of the dosage range is about 10 mg/kg i.v. and 100 mg/kg p.o. Preferred ranges are from about 0.001 to about 1 mg/kg i.v. and from about 0.1 to about 10 mg/kg p.o.

EXAMPLES

The invention is further illustrated with reference to the following examples, which are not intended to be in any way limiting to the scope of the invention as claimed.

Example 1

Preparatory Example

Method A

Benzyl-[2-(3,5-dimethyl-pyrazol-1-yl)-6-methyl-pyrimidin-4-yl]-amine (Compound A1)

2,4-Dichloro-6-methylpyrimidine (528 mg; 3.24 mmol) was dissolved in acetonitrile (10 mL). Benzylamine (382 mg; 3.56 mmol) and triethylamine (2.26 mL; 16.2 mmol) were added. The mixture was stirred at room temperature over-night. Filtration and evaporation gave a yellow oil, which was dissolved in dichloromethane and washed three times with water. Drying ($MgSO_4$), filtration and evaporation followed by column chromatography in heptane/ethyl acetate gave 470 mg (61%) of benzyl-(2-chloro-6-methyl-pyrimidin-4-yl)-amine.

Benzyl-(2-chloro-6-methyl-pyrimidin-4-yl)-amine (460 mg; 2.01 mmol) was dissolved in acetonitrile (5 mL) and 3,5-dimethylpyrazole (290 mg; 3.02 mmol) was added. The mixture was heated in a microwave oven at 170°C for 20 minutes. Evaporation followed by extraction between dichloromethane and sodium hydroxide 1M, drying ($MgSO_4$), filtration and evaporation gave a yellow crystalline compound. Recrystallisation in heptane/ethyl acetate gave benzyl-[2-(3,5-dimethyl-pyrazol-1-yl)-6-methyl-pyrimidin-4-yl]-amine (180 mg; 31%) as a yellow crystalline compound. Mp. 135.9-137.3°C.

Cyclohexyl-[2-(3,5-dimethyl-pyrazol-1-yl)-6-methyl-pyrimidin-4-yl]-amine (Compound A2)

Is prepared according to Method A from 2,4-dichloro-6-methylpyrimidine, cyclohexylamine and 3,5-dimethylpyrazole. Mp. 145.0-146.7°C.

Cyclopentyl-[2-(3,5-dimethyl-pyrazol-1-yl)-6-methyl-pyrimidin-4-yl]-amine, hydrochloride (Compound A3)

Was prepared according to Method A from 2,4-dichloro-6-methylpyrimidine, cyclopentylamine and 3,5-dimethylpyrazole, but instead of extraction the product precipitated and was filtered of as the hydrochloride. Mp. 111.9-127.7°C.

[2-(3,5-Dimethyl-pyrazol-1-yl)-6-methyl-pyrimidin-4-yl]-diethyl-amine, fumerate (Compound A4)

Was prepared according to Method A from 2,4-dichloro-6-methylpyrimidine, diethylamine and 3,5-dimethylpyrazole. Instead of recrystallisation, fumaric acid (0,0775 M in ether/methanol 9:1) was added and the compound isolated as the fumaric acid salt. Mp. 120.5°C.

Cyclohexyl-[2-(3,5-dimethyl-pyrazol-1-yl)-pyrimidin-4-yl]-amine (Compound A5)

Was prepared according to Method A from 2,4-dichloropyrimidine, cyclohexylamine and 3,5-dimethylpyrazole. Mp 144.5-146.7°C;

[5-Chloro-2-(3,5-dimethyl-pyrazol-1-yl)-pyrimidin-4-yl]-cyclohexyl-amine (Compound A6)

Was prepared according to Method A from 2,4,5-trichloropyrimidine, cyclohexylamine and 3,5-dimethylpyrazole. Mp 90.0-99.0°C;

[5-Bromo-2-(3,5-dimethyl-pyrazol-1-yl)-pyrimidin-4-yl]-cyclohexyl-amine (Compound A7)

Was prepared according to Method A from 5-bromo-2,4-dichloropyrimidine, cyclohexylamine and 3,5-dimethylpyrazole LC-ESI-HRMS of [M+H]+ shows 350.0972 Da. Calc. 350.098033 Da, dev. -2.4 ppm

Method B

[2-(3,5-Dimethyl-pyrazol-1-yl)-6-methyl-pyrimidin-4-yl]-*p*-tolyl-amine (Compound B1)

2,4-Dichloro-6-methylpyrimidine (600 mg, 2.7 mmol) was dissolved in acetonitrile (4 mL). *p*-Toluidine (470 mg, 4.42 mmol) and triethylamine (0.65 mL, 5.52 mmol) were added. The mixture was shaken in a sealed vial on a sand bath at 60°C for 12 h..

Evaporation followed by column chromatography (ethylacetate:hexane) gave (2-chloro-6-methyl-pyrimidine-4-yl)-*p*-tolyl-amine (400 mg, 63%).

(2-Chloro-6-methyl-pyrimidine-4-yl)-*p*-tolyl-amine (400 mg, 1.7 mmol) was dissolved in acetonitrile (4 mL) and 3,5-dimethylpyrazole (181 mg, 1.88 mmol) was added. The mixture was heated in a microwave oven at 130°C for 30 min. The mixture was concentrated and the residue basified with sodium hydrogencarbonate, extracted with chloroform dried over anhydrouos sodium sulfate filtated and evaporated. The crude product was purified by column chromatography (ethylacetate/hexane) to give [2-(3,5-Dimethyl-pyrazol-1-yl)-6-methyl-pyrimidin-4-yl]-*p*-tolyl-amine (200 mg, 40%) Mp. 135.1-137.5°C.

The following compounds are prepared in analogy herewith:

[2-(3,5-Dimethyl-pyrazol-1-yl)-6-methyl-pyrimidin-4-yl]-phenyl-amine (Compound B2)
Was prepared according to Method B from 2,4-dichloro-6-methylpyrimidine, aniline and 3,5-dimethylpyrazole. Mp.134.5-138.8°C.

(4-Chloro-phenyl)-[2-(3,5-dimethyl-pyrazol-1-yl)-6-methyl-pyrimidin-4-yl]-amine (Compound B3)
Was prepared according to Method B from 2,4-dichloro-6-methylpyrimidine, 4-chloroaniline and 3,5-dimethylpyrazole. Mp. 181-183.2°C.

(3,4-Dichloro-phenyl)-[2-(3,5-dimethyl-pyrazol-1-yl)-6-methyl-pyrimidin-4-yl]-amine (Compound B4)
Was prepared according to Method B from 2,4-dichloro-6-methylpyrimidine, 3,4-dichloroaniline and 3,5-dimethylpyrazole. Mp. 135.3-137.8°C.

[2-(3,5-Dimethyl-pyrazol-1-yl)-6-methyl-pyrimidin-4-yl]-(4-methoxy-phenyl)-amine (Compound B5)
Is prepared according to Method B from 2,4-dichloro-6-methylpyrimidine, *p*-anisidine and 3,5-dimethylpyrazole.

[2-(3,5-Dimethyl-pyrazol-1-yl)-6-methyl-pyrimidin-4-yl]-(3-trifluoromethyl-phenyl)-amine (Compound B6)
Is prepared according to Method B from 2,4-dichloro-6-methylpyrimidine, 3-trifluoromethylaniline and 3,5-dimethylpyrazole. Mp. 130.5-133.6°C.

[2-(3,5-Dimethyl-pyrazol-1-yl)-6-methyl-pyrimidin-4-yl]-naphthalen-2-yl-amine (Compound B7)

Was prepared according to Method B from 2,4-dichloro-6-methylpyrimidine, 2-naphlylamine and 3,5-dimethylpyrazole. LC-ESI-HRMS of [M+H]+ shows 330.1729 Da. Calc. 330.17187 Da, dev. 3.1 ppm.

[2-(3,5-Dimethyl-pyrazol-1-yl)-pyrimidin-4-yl]-(3-trifluoromethyl-phenyl)-amine (Compound B8)

Was prepared according to Method B from 2,4-dichloropyrimidine, 3-trifluoromethylaniline and 3,5-dimethylpyrazole. Mp.98.5-99.6°C.

(4-Chloro-phenyl)-[2-(3,5-dimethyl-pyrazol-1-yl)-pyrimidin-4-yl]-amine (Compound B9)

Was prepared according to Method B from 2,4-dichloropyrimidine, 4-chloroaniline and 3,5-dimethylpyrazole. Mp 135.5-140.0°C.

[5-Bromo-2-(3,5-dimethyl-pyrazol-1-yl)-pyrimidin-4-yl]-(4-chloro-phenyl)-amine (Compound B10)

Was prepared according to Method B from 5-bromo-2,4-dichloropyrimidine, 4-chloroaniline and 3,5-dimethylpyrazole. Mp.144.5-154.0°C.

[2-(3,5-Dimethyl-pyrazol-1-yl)-pyrimidin-4-yl]-p-tolyl-amine (Compound B11)

Was prepared according to Method B from 2,4-dichloropyrimidine, *p*-toluidine and 3,5-dimethylpyrazole.Mp. 52-55.6°C.

(4-Chloro-phenyl)-[2-(3,5-dimethyl-pyrazol-1-yl)-5-methyl-pyrimidin-4-yl]-amine (Compound B12)

Was prepared according to Method B from 2,4-dichloro-5-methylpyrimidine, 4-chloroaniline and 3,5-dimethylpyrazole. Mp. 179.2-182.3°C.

[5-Chloro-2-(3,5-dimethyl-pyrazol-1-yl)-pyrimidin-4-yl]-(4-chloro-phenyl)-amine (Compound B13)

Was prepared according to Method B from 2,4,5-trichloropyrimidine, 4-chloroaniline and 3,5-dimethylpyrazole. LC-ESI-HRMS of [M+H]+ shows 334.064 Da. Calc. 334.062626 Da, dev. 4.1 ppm.

Example 2

Biological Activity

This example demonstrates the biological activity of a compound representative of the invention (Compound A2). The ionic current through small-conductance Ca^{2+}-activated K^+ channels (SK channels, subtype 3) is recorded using the whole-cell configuration of the patch-clamp technique.

The small-conductance Ca^{2+}-activated K^+ channel, subtype 3 (SK3) was cloned from human skeletal muscle and stably expressed in HEK293 cells.

Stable Expression of SK3 in HEK293 Cells

Human SK3 (hSK3) was sub-cloned into the expression vector pNS3n, a customized vector derived from pcDNA3 (InVitrogen) to give the plasmid construct pNS3_hSK3. HEK293 tissue culture cells were grown in DMEM (Dulbecco's Modified Eagle Medium) supplemented with 10% FCS (foetal calf serum) at 37°C in 5% CO_2. Cells cultured to 50% confluency in a T25 cell culture flask were transfected with 2.5 µg pNS3_hSK3 using lipofectamin (InVitrogen). Transfected cells were selected in media supplemented with 0.25mg/ml Zeocin. Single clones were picked and propagated in selection media until sufficient cells for freezing were available. Hereafter the cells were cultured in regular medium without selection agent. Expression of functional hSK3 channels was verified by patch-clamp measurements.

Whole-Cell Recordings

Experiments are carried out on one of several patch-clamp set-ups. Cells plated on coverslips are placed in a 15 µl perfusion chamber (flowrate ~1 ml/min) mounted on an IMT-2 microscope. The microscopes are placed on vibration-free tables in grounded Faraday cages. All experiments are performed at room temperature (20-22°C). EPC-9 patch-clamp amplifiers (HEKA-electronics, Lambrect, Germany) are connected to Macintosh computers via ITC16 interfaces. Data are stored directly on the hard-disk and analysed by IGOR software (Wavemetrics, Lake Oswega, OR, USA).

The whole-cell configuration of the patch-clamp technique is applied. In short: The tip of a borosilicate pipette (resistance 2-4 MΩ) is gently placed on the cell membrane using remote control systems. Light suction results in the formation of a giga seal (pipette resistance increases to more than 1 GΩ) and the cell membrane underneath the pipette is then ruptured by more powerful suction. Cell capacitance is electronically compensated and the resistance between the pipette and the cell interior (the series resistance, Rs) is measured and compensated for. Usually the cell capacitance ranges from 5 to 20 pF (depending on cell size) and the series resistance is in the range 3 to 6 MΩ. Rs- as well as capacitance compensation are updated during the experiments (before each stimulus). All experiments with drifting Rs-values are discharged. Leak-subtractions are not performed.

Solutions

The extracellular (bath) solution contains (in mM): 140 NaCl, 4 KCl, 0.1 $CaCl_2$, 3 $MgCl_2$, 10 HEPES (pH = 7.4 with HCl). The test compound was dissolved 1000 times in DMSO from a concentrated stock solution and then diluted in the extracellular solution.

The intracellular (pipette) solution has the following composition (in mM): 105 KCl, 45 KOH, 10 EGTA, 1.21 $MgCl_2$, 7.63 $CaCl_2$, and 10 HEPES (pH = 7.2 with HCl). The calculated free concentration of Ca^{2+} in this solution is 300 nM and that of Mg^{2+} is 1 mM.

Quantification

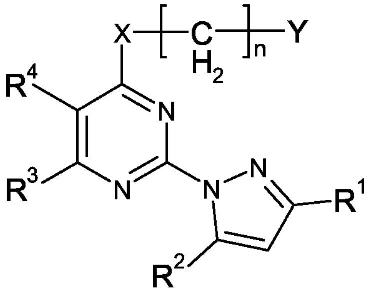
After establishment of the whole-cell configuration, voltage-ramps (normally -120 to +30 mV) are applied to the cell every 5 seconds from a holding potential of -80 mV. A stable baseline current is obtained within a period of 100-500 seconds, and the compound is then added by changing to an extracellular solution containing the test compound. Very little endogenous current (<200 pA at 30 mV compared to 2-10 nA SK3 current) is activated under these circumstances in native HEK293 cells.

Active compounds are quantified by calculating the change in baseline current at -20 mV. The current in the absence of compound is set to 100%. Activators will have values greater than 100, and a value of 200% indicates a doubling of the current. On the other hand, a value of 50% indicates that the compound has reduced the baseline current to half its value.

For activators a SC_{100} value may be estimated. The SC_{100} value is defined as the **S**timulating **C**oncentration required for increasing the baseline current by 100%. The SC_{100} value determined for Compound A2 of the invention was 0.1 μM, which is an indication of its strong SK3 activating properties.

CLAIMS:

1. A pyrazolyl-pyrimidine derivative of Formula I



(I)

an isomer or a mixture of its isomers, an N-oxide thereof, a prodrug thereof, or a pharmaceutically acceptable salt thereof, wherein

n is 0, 1, 2 or 3;

X represents O, S or NR'; wherein

R' represents hydrogen; alkyl, in particular methyl or ethyl, cycloalkyl, or cycloalkyl-alkyl;

or, when n is 0 and X is NR', R' together with Y and together with the nitrogen to which they are attached form a heterocyclic ring; which heterocyclic ring is optionally substituted one or two times with substituents selected from the group consisting of alkyl and phenyl;

Y represents alkyl, cycloalkyl, alkyl-cycloalkyl, amino-alkyl, alkyl-amino, alkyl-amino-alkyl, hydroxy-alkyl, alkoxy-alkyl, alkenyl, phenyl, benzyl, naphthyl, 1,2,3,4-tetrahydro-naphthyl, indenyl, 1,2-dihydro-indenyl, furanyl, thienyl, pyranyl, tetrahydro-pyran-4-yl, pyridinyl, indolinyl or quinolinyl, which phenyl, benzyl, naphthyl, 1,2,3,4-tetrahydro-naphthyl, indenyl, 1,2-dihydro-indenyl, furanyl, thienyl, pyranyl, 2,3,5,6-tetrahydro-4*H*-pyran-4-yl, pyridinyl, indolinyl and quinolinyl groups may optionally be substituted one or more times with substituents selected from the group consisting of alkyl, amino-alkyl, alkyl-amino, alkyl-amino-alkyl, hydroxy-alkyl, alkoxy-alkyl, cycloalkyl, cycloalkyl-alkyl, alkenyl, halo, haloalkyl, hydroxy, alkoxy, methylenedioxy, haloalkoxy, cyano, nitro, amino, phenyl and morpholinyl;

or, when n is 0 and X is NR', Y together with R' and together with the nitrogen to which they are attached form a heterocyclic ring; which heterocyclic ring is optionally substituted one or two times with substituents selected from the group consisting of alkyl and phenyl; and

R^1, R^2, R^3 and R^4, independently of each other, represent hydrogen, alkyl; cycloalkyl, cycloalkyl-alkyl, cycloalkyl, cycloalkyl-alkyl, halo, haloalkyl, hydroxy, alkoxy, alkoxy-carbonyl, haloalkoxy, cyano, nitro and/or amino.

2. The pyrazolyl-pyrimidine derivative of claim 1, wherein n is 0, 1, 2 or 3.

3. The pyrazolyl-pyrimidine derivative of either one of claims 1-2, wherein

X represents O, S or NR'; wherein

R' represents hydrogen, alkyl, cycloalkyl or cycloalkyl-alkyl;

or, when n is 0 and X is NR', R' together with Y and together with the nitrogen to which they are attached form a heterocyclic ring, which heterocyclic ring is optionally substituted one or two times with substituents selected from the group consisting of alkyl and phenyl.

4. The pyrazolyl-pyrimidine derivative of either one of claims 1-2, wherein

X represents O, S or NR'; wherein

R' represents hydrogen, alkyl, cycloalkyl or cycloalkyl-alkyl.

5. The pyrazolyl-pyrimidine derivative of either one of claims 1-2, wherein

n is 0;

X is NR'; and

R' together with Y and together with the nitrogen to which they are attached form a heterocyclic ring, which heterocyclic ring is optionally substituted one or two times with substituents selected from the group consisting of alkyl and phenyl.

6. The pyrazolyl-pyrimidine derivative of any one of claims 1-5, wherein

Y represents alkyl, cycloalkyl, alkyl-cycloalkyl, amino-alkyl, alkyl-amino, alkyl-amino-alkyl, hydroxy-alkyl, alkoxy-alkyl, alkenyl, phenyl, benzyl, naphthyl, 1,2,3,4-tetrahydro-naphthyl, indenyl, 1,2-dihydro-indenyl, furanyl, thienyl, pyranyl, tetrahydro-pyran-4-yl, pyridinyl, indolinyl or quinolinyl, which phenyl, benzyl, naphthyl, 1,2,3,4-tetrahydro-naphthyl, indenyl, 1,2-dihydro-indenyl, furanyl, thienyl, pyranyl, 2,3,5,6-tetrahydro-4*H*-pyran-4-yl, pyridinyl, indolinyl and quinolinyl groups may optionally be substituted one or more times with substituents selected from the group consisting of alkyl, amino-alkyl, alkyl-amino, alkyl-amino-alkyl, hydroxy-alkyl, alkoxy-alkyl, cycloalkyl, cycloalkyl-alkyl, alkenyl, halo, haloalkyl, hydroxy, alkoxy, methylenedioxy, haloalkoxy, cyano, nitro, amino, phenyl and morpholinyl.

7. The pyrazolyl-pyrimidine derivative of claim 6, wherein

Y represents alkyl, cycloalkyl, alkyl-cycloalkyl, hydroxy-alkyl, alkenyl, phenyl, benzyl, or naphthyl, which phenyl, benzyl and naphthyl groups may optionally be substituted one or two times with substituents selected from the group consisting of alkyl, halo, haloalkyl and alkoxy.

8. The pyrazolyl-pyrimidine derivative of claim 6, wherein

Y represents phenyl, benzyl, or naphthyl, which phenyl, benzyl and naphthyl groups may optionally be substituted one or two times with substituents selected from the group consisting of methyl, fluoro, chloro, trifluoromethyl and methoxy.

9. The pyrazolyl-pyrimidine derivative of any one of claims 1-8, wherein

R^1, R^2, R^3 and R^4, independently of each other, represent hydrogen, alkyl, cycloalkyl, cycloalkyl-alkyl, cycloalkyl, cycloalkyl-alkyl, halo, haloalkyl, hydroxy, alkoxy, alkoxy-carbonyl, haloalkoxy, cyano, nitro and/or amino.

10. The pyrazolyl-pyrimidine derivative of claim 1, wherein

n is 0;

X is NH;

Y represents alkyl, cycloalkyl, alkyl-cycloalkyl, hydroxy-alkyl, phenyl, benzyl or naphthyl;

R^1 and R^2 represent methyl;

R^3 represents hydrogen, methyl, ethyl or propyl; and

R^4 represents hydrogen, methyl, ethyl, propyl, chloro, bromo, ethoxy-carbonyl and/or cyano.

11. The pyrazolyl-pyrimidine derivative of claim 1, wherein

n is 0;

X is NH;

Y represents phenyl or benzyl, which phenyl and benzyl groups may optionally be substituted one or two times with substituents selected from the group consisting of alkyl, halo, haloalkyl and alkoxy;

R^1 and R^2 represent methyl;

R^3 represents hydrogen, methyl, ethyl or propyl; and

R^4 represents hydrogen, methyl, ethyl, propyl, chloro, bromo, ethoxy-carbonyl or cyano.

12. The pyrazolyl-pyrimidine derivative of claim 1, which is

Benzyl-[2-(3,5-dimethyl-pyrazol-1-yl)-6-methyl-pyrimidin-4-yl]-amine;

Cyclopentyl-[2-(3,5-dimethyl-pyrazol-1-yl)-6-methyl-pyrimidin-4-yl]-amine;

[2-(3,5-Dimethyl-pyrazol-1-yl)-6-methyl-pyrimidin-4-yl]-diethyl-amine;

[2-(3,5-Dimethyl-pyrazol-1-yl)-6-methyl-pyrimidin-4-yl]-phenyl-amine;

[2-(3,5-Dimethyl-pyrazol-1-yl)-6-methyl-pyrimidin-4-yl]-*p*-tolyl-amine;

(3,4-Dichloro-phenyl)-[2-(3,5-dimethyl-pyrazol-1-yl)-6-methyl-pyrimidin-4-yl]-amine;

[2-(3,5-Dimethyl-pyrazol-1-yl)-6-methyl-pyrimidin-4-yl]-naphthalen-2-yl-amine;

[2-(3,5-Dimethyl-pyrazol-1-yl)-pyrimidin-4-yl]-(3-trifluoromethyl-phenyl)-amine;

Cyclohexyl-[2-(3,5-dimethyl-pyrazol-1-yl)-pyrimidin-4-yl]-amine;

[5-Chloro-2-(3,5-dimethyl-pyrazol-1-yl)-pyrimidin-4-yl]-cyclohexyl-amine;

(4-Chloro-phenyl)-[2-(3,5-dimethyl-pyrazol-1-yl)-pyrimidin-4-yl]-amine;

[5-Bromo-2-(3,5-dimethyl-pyrazol-1-yl)-pyrimidin-4-yl]-(4-chloro-phenyl)-amine;

[2-(3,5-Dimethyl-pyrazol-1-yl)-pyrimidin-4-yl]-p-tolyl-amine;

(4-Chloro-phenyl)-[2-(3,5-dimethyl-pyrazol-1-yl)-5-methyl-pyrimidin-4-yl]-amine;

[5-Bromo-2-(3,5-dimethyl-pyrazol-1-yl)-pyrimidin-4-yl]-cyclohexyl-amine; or

[5-Chloro-2-(3,5-dimethyl-pyrazol-1-yl)-pyrimidin-4-yl]-(4-chloro-phenyl)-amine;

or a pharmaceutically acceptable salt thereof.

13. A pharmaceutical composition comprising a therapeutically-effective amount of a pyrazolyl-pyrimidine derivative according to any of claims 1-12, or a pharmaceutically-acceptable addition salt thereof, or a prodrug thereof, together with at least one pharmaceutically-acceptable carrier or diluent.

14. The use of a chemical compound according to any of claims 1-12 for the manufacture of a medicament for the treatment, prevention or alleviation of a disease or a disorder or a condition of a mammal, including a human, which disease, disorder or condition is associated with the activity of potassium channels.

15. The use according to claim 14, wherein the disease or a disorder associated with the activity of potassium channels is a respiratory disease, epilepsy, seizures, absence seizures, convulsions, vascular spasms, coronary artery spasms, renal disorders, polycystic kidney disease, bladder spasms, urinary incontinence, bladder outflow obstruction, irritable bowel syndrome, gastrointestinal dysfunction, secretory diarrhoea, ischaemia, cerebral ischaemia, ischaemic heart disease, angina pectoris, coronary heart disease, traumatic brain injury, psychosis, schizophrenia, anxiety, depression, dementia, memory and attention deficits, Alzheimer’s disease, amyotrophic lateral sclerosis (ALS), dysmenorrhea, narcolepsy, Reynaud’s disease, intermittent claudication, Sjorgren’s syndrome, migraine, arrhythmia, hypertension,

absence seizures, myotonic muscle dystrophia, xerostomi, diabetes type II, hyperinsulinemia, premature labour, baldness, cancer, immune suppression or pain.

16. The use according to claim 14, wherein the disease or a disorder associated with the activity of potassium channels is a respiratory disease, urinary incontinence, anxiety, epilepsy, psychosis, schizophrenia, amyotrophic lateral sclerosis (ALS) or pain.

17. The use according to claim 14, wherein the activity of potassium channels is a respiratory disease, in particular asthma, cystic fibrosis, chronic obstructive pulmonary disease (COPD) or rhinorrhea.

18. A method of treatment, prevention or alleviation of a disease or a disorder or a condition of a living animal body, including a human, which disease, disorder or condition is responsive to modulation of the potassium channels, and which method comprises comprising administering to such a living animal body, including a human, in need thereof a therapeutically-effective amount of a pyrazolyl-pyrimidine derivative of any of claims 1-12.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2006/060857

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D403/04 A61K31/505

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D

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

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

EPO-Internal, CHEM ABS Data, WPI Data, BEILSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 03/075828 A (ZETIQ TECHNOLOGIES LTD; GELVAN, DAN, JACOB; GOLTSMAN, LEV; CHAUSOVSKY,) 18 September 2003 (2003-09-18) Claims page 18 - page 20; compounds VI,VII,X,XI ----- -/--	1-4, 6-11,13

☒ Further documents are listed in the continuation of Box C.

☒ See patent family 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 26 May 2006	Date of mailing of the international search report 09/06/2006
Name and mailing address of the ISA/ 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	Authorized officer Von Daacke, A

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2006/060857

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DATABASE CAPLUS [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; SHIRAKAWA, KENZO ET AL SHIRAKAWA, KENZO ET AL: "Pyrimidine derivatives. XII. 2-(1-Pyrazolyl)pyrimidines. 2 Pyrimidine derivatives. XII. 2-(1-Pyrazolyl)pyrimidines. 2" XP002382701 retrieved from STN Database accession no. 1964:68217 RN 94905-91-6 abstract & TAKEDA KENKYUSHO NENPO , 22, 27-46 CODEN: TDKNAF; ISSN: 0371-5973 TAKEDA KENKYUSHO NENPO , 22, 27-46 CODEN: TDKNAF; ISSN: 0371-5973, 1963, -----	1-4,6-11
X	DATABASE CAPLUS [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; IVASHCHENKO, A. V. ET AL: "Prototropic tautomerism and conformational isomerism of 4-(N-arylamino)-2-(1H-pyrazol-1-yl)pyrimidines" XP002382702 retrieved from STN Database accession no. 1981:15048 RN 70074-11-2, 75971-87-8, 75971-88-9. abstract & KHIMIYA GETEROTSIKLICHESKIKH SOEDINENII , (8), 1114-19 CODEN: KGSSAQ; ISSN: 0453-8234, 1980, -----	1-4,6-11
X	JP 54 147921 A (HOKKO CHEMICAL INDUSTRY CO., LTD., JAPAN; MEIJI SEIKA KAISHA, LTD.) 19 November 1979 (1979-11-19) examples 1-14,21,23 -----	1-11
X	JP 54 117029 A (HOKKO CHEMICAL INDUSTRY CO., LTD., JAPAN; MEIJI MILK PRODUCTS CO., LTD) 11 September 1979 (1979-09-11) examples 3-5,11 -----	1-4,6-11
X	WO 2005/003099 A (VERTEX PHARMACEUTICALS INCORPORATED; WILSON, DEAN, MITCHELL; MARTINBOR) 13 January 2005 (2005-01-13) Claims,example 171 -----	1-18
A	WO 2004/064721 A (TANABE SEIYAKU CO., LTD; TAKAMURO IWAO; SEKINE YASUO; TSUBOI YASUNORI;) 5 August 2004 (2004-08-05) the whole document ----- -/--	1-18

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2006/060857

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 02/066036 A (BRISTOL-MYERS SQUIBB COMPANY) 29 August 2002 (2002-08-29) the whole document -----	1-18
A	US 2002/032198 A1 (GILBERT ADAM MATTHEW ET AL) 14 March 2002 (2002-03-14) the whole document -----	1-18

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP2006/060857

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

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

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

Although claim 18 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

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

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

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

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

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

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

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

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

Remark on Protest

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

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2006/060857

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