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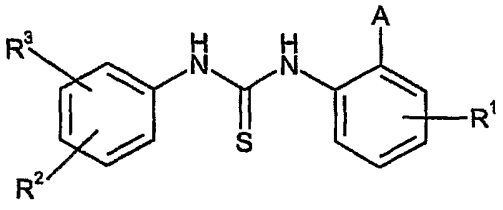
(54) **Title:** NOVEL BIPHENYL THIO-UREA DERIVATIVES USEFUL AS POTASSIUM CHANNEL MODULATORS



(I)

(57) **Abstract:** The invention relates to novel biphenyl thio-urea derivatives of Formula (I), wherein A represents hydroxy or tetrazolyl; R^1 represents halo, hydroxy or phenyl, which phenyl may optionally be substituted with halo; and R^2 and R^3, independent of each other, represent halo, trifluoromethyl, nitro and/or phenyl, that are found to be potent modulators of ion channels and, as such, they are valuable candidates for the treatment of disease or disorders as diverse as those which are responsive to modulation of ion channels.

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NOVEL BIPHENYL THIO-UREA DERIVATIVES USEFUL AS POTASSIUM CHANNEL MODULATORS

TECHNICAL FIELD

This invention relates to novel biphenyl thio-urea derivatives that are found to be potent modulators of ion channels and, as such, they are valuable candidates for the treatment of diseases or disorders as diverse as those which are responsive to modulation of ion channels.

BACKGROUND ART

Ion channels are cellular proteins that regulate the flow of ions through cellular membranes of all cells and are classified by their selective permeability to the different of ions (potassium, chloride, sodium etc.). Potassium channels, which represent the largest and most diverse sub-group of ion channels, selectively pass potassium ions and, doing so, they principally regulate the resting membrane potential of the cell and/or modulate their level of excitation.

Dysfunction of potassium channels, as well as other ion channels, generates loss of cellular control resulting in altered physiological functioning and disease conditions. Ion channel blockers and openers, by their ability to modulate ion channel function and/ or regain ion channel activity in acquired or inherited channelopathies, are being used in the pharmacological treatment of a wide range of pathological diseases and have the potential to address an even wider variety of therapeutic indications. For instance, the primary indications for potassium channel openers encompass conditions as diverse as diabetes, arterial hypertension, cardiovascular diseases, urinary incontinence, atrial fibrillation, epilepsy, pain, and cancer.

Among the large number of potassium channel types, the large-conductance calcium-activated potassium channel subtype is an obvious site for pharmacological intervention and for the development of new potassium channel modulators. Their physiological role has been especially studied in the nervous system, where they are key regulators of neuronal excitability and of neurotransmitter release, and in smooth muscle, where they are crucial in modulating the tone of vascular, broncho-tracheal, urethral, uterine or gastro-intestinal musculature.

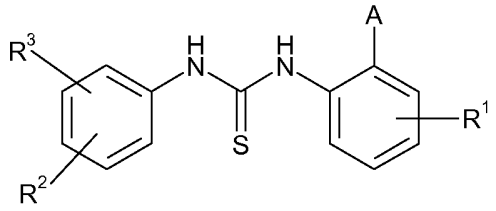
Given these implications, small agents with BK-opening properties could have a potentially powerful influence in the modulation and control of numerous consequences of muscular and neuronal hyperexcitability, such as asthma, urinary

incontinence and bladder spasm, gastroenteric hypermotility, psychoses, post-stroke neuroprotection, convulsions and anxiety. As far as the cardiovascular system is concerned, the physiological function of these ion channels represents a fundamental steady state mechanism, modulating vessel depolarisation, vasoconstriction and increases of intravascular pressure, and the development of selective activators of BK channels is seen as a potential pharmacotherapy of vascular diseases, including hypertension, erectile dysfunction, coronary diseases and vascular complications associated with diabetes or hypercholesterolemia.

WO 97/45400 describes diphenyl urea derivatives useful as chloride channel blockers, and WO 2004/046090 describes aryl ureido benzoic acid derivatives useful as selective and non-competitive antagonists of the ionotropic GluR5 receptor. However, the biphenyl thio-urea derivatives of the present invention have not been reported.

SUMMARY OF THE INVENTION

Is an object of the invention to provide novel biphenyl thio-urea derivatives useful as ion channel modulators. The biphenyl thio-urea derivatives of the invention may be characterised by Formula I



(I)

an enantiomer or a mixture of its enantiomers, or a pharmaceutically-acceptable addition salt thereof, wherein

A represents hydroxy or tetrazolyl;

R^1 represents halo, hydroxy or phenyl, which phenyl may optionally be substituted with halo; and

R^2 and R^3, independent of each other, represent halo, trifluoromethyl, nitro and/or phenyl.

In another aspect the invention provides pharmaceutical compositions comprising a therapeutically effective amount of the biphenyl thio-urea derivative of the invention.

In a third aspect the invention relates to the use of the biphenyl thio-urea derivative of the invention for the manufacture of pharmaceutical compositions.

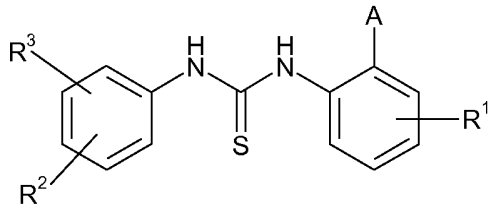
In a fourth aspect the invention provides a kit of parts comprising at least two separate unit dosage forms (A) and (B1) or (B2): (A) a biphenyl thio-urea derivative according to the invention; and (B1) a phosphodiesterase inhibitor, or (B2) an agent that potentiates endothelium-derived hyperpolarizing factor-mediated responses; and optionally (C) instructions for the simultaneous, sequential or separate administration of the biphenyl thio-urea derivative of A, and the phosphodiesterase inhibitor of B1, or an agent that potentiates endothelium-derived hyperpolarizing factor-mediated responses of B2, to a patient in need thereof.

In a further aspect the invention provides 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 disorder, disease or condition is responsive to modulation of ion channels, which method comprises the step of administering to such a living animal body in need thereof, a therapeutically effective amount of the biphenyl thio-urea derivative of the invention.

Other objects of the invention will be apparent to the person skilled in the art from the following detailed description and examples.

DETAILED DISCLOSURE OF THE INVENTION

In its first aspect the invention provides novel biphenyl thio-urea derivatives of Formula I



(I)

an enantiomer or a mixture of its enantiomers, or a pharmaceutically-acceptable addition salt thereof, wherein

A represents hydroxy or tetrazolyl;

R^1 represents halo, hydroxy or phenyl, which phenyl may optionally be substituted with halo; and

R^2 and R^3, independent of each other, represent halo, trifluoromethyl, nitro and/or phenyl.

In a preferred embodiment the biphenyl thio-urea derivative of the invention is a compound of Formula I, wherein A represents hydroxy or tetrazolyl.

In a more preferred embodiment A represents hydroxy.

In another more preferred embodiment A represents tetrazolyl.

In an even more preferred embodiment A represents 1H-tetrazol-5-yl.

In another preferred embodiment the biphenyl thio-urea derivative of the invention is a compound of Formula I, wherein R^1 represents halo, hydroxy or phenyl, which phenyl may optionally be substituted with halo.

In a more preferred embodiment R^1 represents halo.

In an even more preferred embodiment R^1 represents chloro or bromo.

In a still more preferred embodiment R^1 represents chloro.

In yet another more preferred embodiment R^1 represents bromo.

In a third preferred embodiment the biphenyl thio-urea derivative of the invention is a compound of Formula I, wherein R^2 and R^3, independent of each other, represent halo, trifluoromethyl, nitro and/or phenyl.

In a more preferred embodiment R^2 and R^3, independent of each other, represent halo and/or trifluoromethyl.

In an even more preferred embodiment R^2 and R^3, independent of each other, represent fluoro, chloro and/or trifluoromethyl.

In a still more preferred embodiment R^2 represents chloro or trifluoromethyl; and R^3 represents trifluoromethyl.

In a yet more preferred embodiment R^2 represents *o*-chloro or an *m*-trifluoromethyl group; and R^3 represents an *m*-trifluoromethyl group.

In a most preferred embodiment the biphenyl thio-urea derivative of the invention is

1-(3,5-Bis-trifluoromethyl-phenyl)-3-[4-bromo-2-(1H-tetrazol-5-yl)-phenyl]-thiourea; or

1-(5-Chloro-2-hydroxy-phenyl)-3-(2-chloro-5-trifluoromethyl-phenyl)-thiourea;

or a pharmaceutically-acceptable addition 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.

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, the hydrobromide, the nitrate, the perchlorate, the phosphate, the sulphate, the formate, the acetate, the aconate, the ascorbate, the benzenesulphonate, the benzoate, the cinnamate, the citrate, the embonate, the enantate, the fumarate, the glutamate, the glycolate, the lactate, the maleate, the malonate, the mandelate, the methanesulphonate, the naphthalene-2-sulphonate derived, the phthalate, the salicylate, the sorbate, the stearate, the succinate, the tartrate, the toluene-p-sulphonate, and the like. Such salts may be formed by procedures well known and described in the art.

Examples of pharmaceutically acceptable cationic salts of a chemical compound of the invention include, without limitation, the sodium, the potassium, the calcium, the magnesium, the lithium, and the ammonium salt, and the like, of a chemical compound of the invention containing an anionic group. Such cationic salts may be formed by procedures well known and described in the art.

Methods of Preparation

The compounds according to the invention may be prepared by conventional methods for chemical synthesis, e.g. those described in the working examples.

Biological Activity

The compounds of the invention have been found to possess ion channel modulating activity as measured by standard electrophysiological methods. Due to their activity at the potassium channels, the compounds of the invention are considered useful for the treatment of a wide range of diseases and conditions.

In a special embodiment, the compounds of the invention are considered useful for the treatment, prevention or alleviation of a respiratory disease, epilepsy, convulsions, seizures, absence seizures, vascular spasms, coronary artery spasms, motor neuron diseases, myokymia, renal disorders, polycystic kidney disease, bladder hyperexcitability, bladder spasms, urinogenital disorders, urinary incontinence, bladder outflow obstruction, erectile dysfunction, gastrointestinal dysfunction, gastrointestinal hypomotility disorders, gastrointestinal motility insufficiency, postoperative ileus, constipation, gastroesophageal reflux disorder, secretory diarrhoea, an obstructive or inflammatory airway disease, ischaemia, cerebral ischaemia, ischaemic heart disease, angina pectoris, coronary heart disease, ataxia, traumatic brain injury, stroke, Parkinson's disease, bipolar disorder, psychosis, schizophrenia, autism, anxiety, mood disorders, depression, manic depression, psychotic disorders, dementia, learning deficiencies, age related memory loss, memory and attention deficits, Alzheimer's disease, amyotrophic lateral sclerosis (ALS), dysmenorrhoea, narcolepsy, sleeping disorders, sleep apnoea, Reynaud's

disease, intermittent claudication, Sjögren's syndrome, xerostomia, arrhythmia, cardiovascular disorders, hypertension, myotonic dystrophy, myotonic muscle dystrophia, spasticity, xerostomia, diabetes Type II, hyperinsulinemia, premature labour, cancer, brain tumours, inflammatory bowel disease, irritable bowel syndrome, colitis, colitis Crohn, immune suppression, hearing loss, migraine, pain, neuropathic pain, inflammatory pain, trigeminal neuralgia, vision loss, rhinorrhoea, ocular hypertension (glaucoma), baldness, cardiac arrhythmia, atrial arrhythmia, ventricular arrhythmia, atrial fibrillation, ventricular fibrillation, tachyarrhythmia, atrial tachyarrhythmia, ventricular tachyarrhythmia, bradyarrhythmia, or any other abnormal rhythm, e.g. caused by myocardial ischaemia, myocardial infarction, cardiac hypertrophy or cardiomyopathy.

In a more preferred embodiment, the compounds of the invention are considered useful for the treatment, prevention or alleviation of a respiratory disease, urinary incontinence, erectile dysfunction, anxiety, epilepsy, psychosis, schizophrenia, bipolar disorder, depression, amyotrophic lateral sclerosis (ALS), Parkinson's disease or pain.

In another more preferred embodiment, the compounds of the invention are considered useful for the treatment, prevention or alleviation of psychosis, schizophrenia, bipolar disorder, depression, epilepsy, Parkinson's disease or pain.

In a third more preferred embodiment, the compounds of the invention are considered useful for the treatment, prevention or alleviation of pain, mild or moderate or severe pain, pain of acute, chronic or recurrent character, pain caused by migraine, postoperative pain, phantom limb pain, inflammatory pain, neuropathic pain, chronic headache, central pain, pain related to diabetic neuropathy, to post therapeutic neuralgia, or to peripheral nerve injury.

In a fourth more preferred embodiment, the compounds of the invention are considered useful for the treatment, prevention or alleviation of cardiac arrhythmia, atrial arrhythmia, ventricular arrhythmia, atrial fibrillation, ventricular fibrillation, tachyarrhythmia, atrial tachyarrhythmia, ventricular tachyarrhythmia, bradyarrhythmia, or any other abnormal rhythm, e.g. caused by myocardial ischaemia, myocardial infarction, cardiac hypertrophy, cardiomyopathy or a genetic disease.

In a fifth more preferred embodiment, the compounds of the invention are considered useful for the treatment, prevention or alleviation of cardiac ischemia, ischemic heart disease, hypertrophic heart, cardiomyopathy or failing heart.

In a sixth more preferred embodiment, the compounds of the invention are considered useful for the treatment, prevention or alleviation of a cardiovascular disease. In a more preferred embodiment the cardiovascular disease is atherosclerosis, ischemia/reperfusion, hypertension, restenosis, arterial inflammation, myocardial ischaemia or ischaemic heart disease.

In a seventh more preferred embodiment, the compounds of the invention are considered useful for the treatment, prevention or alleviation of cardiac arrhythmia, atrial fibrillation and/or ventricular tachyarrhythmia.

In an eight more preferred embodiment, the compounds of the invention are considered useful for obtaining preconditioning of the heart. Preconditioning, which includes ischemic preconditioning and myocardial preconditioning, describes short periods of ischemic events before initiation of a long lasting ischemia. The compounds of the invention are believed having an effect similar to preconditioning obtained by such ischemic events. Preconditioning protects against later tissue damage resulting from the long lasting ischemic events.

In an ninth more preferred embodiment, the compounds of the invention are considered useful for the treatment, prevention or alleviation of schizophrenia, depression or Parkinson's disease.

In a tenth more preferred embodiment, the compounds of the invention are considered useful for the treatment, prevention or alleviation of an obstructive or inflammatory airway disease. In a more preferred embodiment the the obstructive or inflammatory airway disease is an airway hyperreactivity, a pneumoconiosis such as aluminosis, anthracosis, asbestosis, chalicosis, ptilosis, siderosis, silicosis, tabacosis and byssinosis, a chronic obstructive pulmonary disease (COPD), bronchitis, excerbation of airways hyperreactivity or cystic fibrosis.

In its most preferred embodiment the obstructive airway disease is chronic obstructive pulmonary disease (COPD).

In an eleventh more preferred embodiment, the compounds of the invention are considered useful for the treatment, prevention or alleviation of a sexual dysfunction, incl. male sexual dysfunction and female sexual dysfunction, and incl. male erectile dysfunction.

In an even more preferred embodiment the compound of the invention may be co-administered with a phosphodiesterase inhibitor, in particular a phosphodiesterase 5 (PDE5) inhibitor, e.g. sildenafil, tadalafil, vardenafil and dipyridamole, or with an agent that potentiates endothelium-derived hyperpolarizing factor-mediated responses, in particular calcium dobesilate or similar 2,5-dihydroxybenzenesulfonate analogs.

In a most preferred embodiment the compound of the invention is used in a combination therapy together with sildenafil, tadalafil, vardenafil or calcium dobesilate.

It is at present contemplated that a suitable dosage of the active pharmaceutical ingredient (API) is within the range of from about 0.1 to about 1000 mg API per day, more preferred of from about 10 to about 500 mg API per day, most preferred of from about 30 to about 100 mg API per day, dependent, however, upon the exact mode of administration, the form in which it is administered, the indication

considered, the subject and in particular the body weight of the subject involved, and further the preference and experience of the physician or veterinarian in charge.

Preferred compounds of the invention show a biological activity in the sub-micromolar and micromolar range, i.e. of from below 1 to about 100 μM.

Pharmaceutical Compositions

In another aspect the invention provides novel pharmaceutical compositions comprising a therapeutically effective amount of a compound of the invention.

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, in a pharmaceutical composition together with one or more adjuvants, excipients, carriers, buffers, diluents, and/or other customary pharmaceutical auxiliaries.

In a preferred embodiment, the invention provides pharmaceutical compositions comprising the compound of the invention together with one or more pharmaceutically acceptable carriers therefore, and, optionally, other therapeutic and/or prophylactic ingredients, know and used in the art. The carrier(s) must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and not harmful to the recipient thereof.

The pharmaceutical composition of the invention may be administered by any convenient route, which suits the desired therapy. Preferred routes of administration include oral administration, in particular in tablet, in capsule, in dragé, in powder, or in liquid form, and parenteral administration, in particular cutaneous, subcutaneous, intramuscular, or intravenous injection. The pharmaceutical composition of the invention can be manufactured by any person skilled in the art, by use of standard methods and conventional techniques, appropriate to the desired formulation. When desired, compositions adapted to give sustained release of the active ingredient may be employed.

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).

The actual dosage depends on the nature and severity of the disease being treated, 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.

Pharmaceutical Kits of Parts

According to the invention there is also provided a kit of parts comprising at least two separate unit dosage forms (A) and (B):

(A) a biphenyl thio-urea derivative of the invention; and

(B1) a phosphodiesterase inhibitor, or

(B2) an agent that potentiates endothelium-derived hyperpolarizing factor-mediated responses; and optionally

(C) instructions for the simultaneous, sequential or separate administration of the biphenyl thio-urea derivative of A, and the phosphodiesterase inhibitor of B1, or an agent that potentiates endothelium-derived hyperpolarizing factor-mediated responses of B2, to a patient in need thereof.

In a more preferred embodiment the phosphodiesterase inhibitor for use according to the invention (B1) is a phosphodiesterase 5 (PDE5) inhibitor, and in an even more preferred embodiment the phosphodiesterase inhibitor for use according to the invention is sildenafil, tadalafil or vardenafil.

In another more preferred embodiment the agent that potentiates endothelium-derived hyperpolarizing factor-mediated responses for use according to the invention (B2) is calcium dobesilate.

The biphenyl thio-urea derivative of the invention and the phosphodiesterase inhibitor or the agent that potentiates endothelium-derived hyperpolarizing factor-mediated responses for use according to the invention may preferably be provided in a form that is suitable for administration in conjunction with the other. This is intended to include instances where one or the other of two formulations may be administered (optionally repeatedly) prior to, after, and/or at the same time as administration with the other component.

Also, the biphenyl thio-urea derivative of the invention and the phosphodiesterase inhibitor or the agent that potentiates endothelium-derived hyperpolarizing factor-mediated responses for use according to the invention may be administered in a combined form, or separately or separately and sequentially, wherein the sequential administration is close in time or remote in time. This may in particular include that two formulations are administered (optionally repeatedly) sufficiently closely in time for there to be a beneficial effect for the patient, that is greater over the course of the treatment of the relevant condition than if either of the

two formulations are administered (optionally repeatedly) alone, in the absence of the other formulation, over the same course of treatment. Determination of whether a combination provides a greater beneficial effect in respect of, and over the course of treatment of, a particular condition, will depend upon the condition to be treated or prevented, but may be achieved routinely by the person skilled in the art.

When used in this context, the terms "administered simultaneously" and "administered at the same time as" include that individual doses of the positive allosteric nicotine receptor modulator and the cognitive enhancer are administered within 48 hours, e.g. 24 hours, of each other.

Bringing the two components into association with each other, includes that components (A) and (B) may be provided as separate formulations (i.e. independently of one another), which are subsequently brought together for use in conjunction with each other in combination therapy; or packaged and presented together as separate components of a "combination pack" for use in conjunction with each other in combination therapy.

Methods of Therapy

In another aspect the invention provides a method of treatment, prevention or alleviation of a disease, disorder or condition of a living animal body, including a human, which disorder, disease or condition is responsive to activation of an ion channel, and in particular a potassium channel or a chloride channel, which method comprises the step of administering to such a living animal body in need thereof, a therapeutically effective amount a compound capable of activating the ion channel, or a pharmaceutically-acceptable addition salt thereof.

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

It is at present contemplated that a suitable dosage of the active pharmaceutical ingredient (API) is within the range of from about 0.1 to about 1000 mg API per day, more preferred of from about 1 to about 500 mg API per day, most preferred of from about 1 to about 100 mg API per day, dependent, however, upon the exact mode of administration, the form in which it is administered, the indication considered, the subject and in particular the body weight of the subject involved, and further the preference and experience of the physician or veterinarian in charge.

BRIEF DESCRIPTION OF THE DRAWING

The present invention is further illustrated by reference to the accompanying drawing, in which Fig. 1 shows the BK channel opening activity [current (μA) vs. time (s)] of the thiourea derivative representative of the invention, i.e. compound 1,

determined by a standard electrophysiological method using BK channels heterologously expressed in *Xenopus laevis* oocytes.

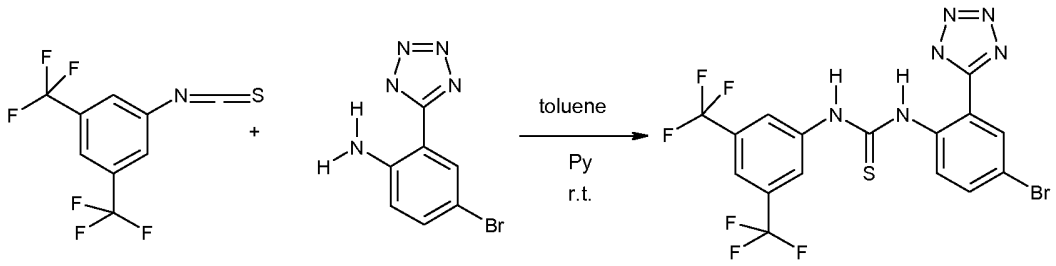
EXAMPLES

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

Scheme 1



1-(3,5-Bis-trifluoromethyl-phenyl)-3-[4-bromo-2-(1H-tetrazol-5-yl)-phenyl]-thiourea (Compound 1)

To an ice-cooled and stirred solution of 4-bromo-2-(1H-tetrazol-5-yl)-phenylamine (0.883 g, 1 eq) prepared as described in US 20020037905 (0.883 g, 1 eq) in dry pyridine (2 ml) and dry toluene (5 ml), a solution of commercially available 3,5-bis(trifluoromethyl)phenylisothiocyanate (1 g, 1 eq) in dry toluene (10 ml) is added drop-wise and under nitrogen. Stirring is then continued at room temperature for 3 hours under a nitrogen flow, and the resulting suspension is finally evaporated to dryness. The solid residue (~1.80 g) is dissolved by addition of water (15 ml) and drops of NaOH 4M (until pH ~11/12), and the resulting solution is stirred at room temperature for a few minutes. The water phase is first extracted several times with dichloromethane and later acidified by HCl (4M) (ph ~5). The white solid precipitated is filtered, washed with water and dried (1.32 g, 70%) and purified by crystallisation from a mixture of toluene and petroleum ether (40-60).

LC-ESI-HRMS of [M-H]- shows 508.9639 Da. Calc. 508.961871 Da, dev. 4 ppm. ^{1}HNMR (DMSO-d6): δ 7.70 – 8.13 (m, 6H, H aromatics); 10.20 (s, NH, 1 H); 10,35 (s, NH, 1H). M.p. 207-208.

Synthesis of 1-(5-Chloro-2-hydroxy-phenyl)-3-(2-chloro-5-trifluoromethyl-phenyl)-thiourea (Compound 2)

To a solution of commercial 5-chloro-2-hydroxyaniline (0.30 g, 1 eq) in dry tetrahydrofuran (5 ml), a solution of commercial 2-chloro-5-(trifluoromethyl)-phenylisothiocyanate in dry tetrahydrofuran (3 ml) is added drop wise with stirring. Stirring is continued at room temperature for one hour and the reaction mixture is then evaporated to dryness. The solid residue is purified by crystallisation from a mixture of chloroform and petroleum ether (40-60) (0.80 g, 70% yield).

LC-ESI-HRMS of [M-H]- shows 378.9687 Da. Calc. 378.968649 Da, dev. 0.1 ppm.

Example 2

Biological activity

Expression and Functional Characterization of the BK Channel

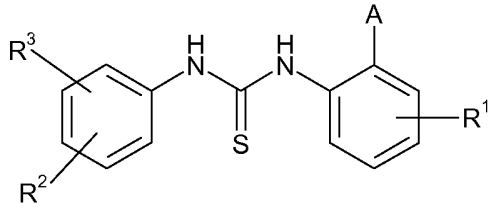
The present invention is further illustrated by reference to the accompanying drawing, in which Fig. 1 shows the BK channel opening activity [current (μA) vs. time (s)] of a thiourea derivative representative of the invention, i.e. Compound 1, determined by a standard electrophysiological method using BK channels heterologously expressed in *Xenopus laevis* oocytes.

The electrical current through the BK channel is measured conventional two-electrode voltage clamp. BK current is activated by repeated step protocols. In brief, this protocol goes from a resting membrane potential of -40 mV lasting for 5 s to a depolarised step to +30 mV lasting for 1 s. The protocol was repeated continuously.

Having reached a stable current level, Compound 1 was added in increasing concentrations. Between each application compound was washed out until baseline current activity was obtained. A marked increase in the current activated by depolarisation could be observed. After addition of 1, 3 and 10 μM, respectively, of Compound 1, the results are presented in Fig. 1.

CLAIMS

1. A biphenyl thio-urea derivative of Formula I



(I)

an enantiomer or a mixture of its enantiomers, or a pharmaceutically-acceptable addition salt thereof, wherein

A represents hydroxy or tetrazolyl;

R^1 represents halo, hydroxy or phenyl, which phenyl may optionally be substituted with halo; and

R^2 and R^3, independent of each other, represent halo, trifluoromethyl, nitro and/or phenyl.

2. The biphenyl thio-urea derivative of claim 1, wherein A represents hydroxy or tetrazolyl.

3. The biphenyl thio-urea derivative of either one of claims 1-2, wherein R^1 represents halo, hydroxy or phenyl, which phenyl may optionally be substituted with halo.

4. The biphenyl thio-urea derivative of any one of claims 1-3, wherein R^2 and R^3, independent of each other, represent halo, trifluoromethyl, nitro and/or phenyl.

5. The biphenyl thio-urea derivative of claim 1 which is

1-(3,5-Bis-trifluoromethyl-phenyl)-3-[4-bromo-2-(1H-tetrazol-5-yl)-phenyl]-thiourea; or

1-(5-Chloro-2-hydroxy-phenyl)-3-(2-chloro-5-trifluoromethyl-phenyl)-thiourea;

or a pharmaceutically-acceptable addition salt thereof.

6. A pharmaceutical composition comprising a therapeutically effective amount of the biphenyl thio-urea derivative of any one of claims 1-5, or a

pharmaceutically-acceptable addition salt thereof, or a prodrug thereof, together with one or more adjuvants, excipients, carriers and/or diluents.

7. Use of a biphenyl thio-urea derivative of any one of claims 1-5, or a pharmaceutically-acceptable addition salt thereof, for the manufacture of a pharmaceutical composition/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 responsive to modulation of ion channels.

8. The use according to claim 7, wherein the disease, disorder or condition is a respiratory disease, epilepsy, convulsions, seizures, absence seizures, vascular spasms, coronary artery spasms, motor neuron diseases, myokymia, renal disorders, polycystic kidney disease, bladder hyperexcitability, bladder spasms, urinogenital disorders, urinary incontinence, bladder outflow obstruction, erectile dysfunction, gastrointestinal dysfunction, gastrointestinal hypomotility disorders, gastrointestinal motility insufficiency, postoperative ileus, constipation, gastroesophageal reflux disorder, secretory diarrhoea, an obstructive or inflammatory airway disease, ischaemia, cerebral ischaemia, ischaemic heart disease, angina pectoris, coronary heart disease, ataxia, traumatic brain injury, stroke, Parkinson's disease, bipolar disorder, psychosis, schizophrenia, autism, anxiety, mood disorders, depression, manic depression, psychotic disorders, dementia, learning deficiencies, age related memory loss, memory and attention deficits, Alzheimer's disease, amyotrophic lateral sclerosis (ALS), dysmenorrhea, narcolepsy, sleeping disorders, sleep apnea, Reynaud's disease, intermittent claudication, Sjögren's syndrome, xerostomia, arrhythmia, cardiovascular disorders, hypertension, myotonic dystrophy, myotonic muscle dystrophia, spasticity, xerostomi, diabetes Type II, hyperinsulinemia, premature labour, cancer, brain tumors, inflammatory bowel disease, irritable bowel syndrome, colitis, colitis Crohn, immune suppression, hearing loss, migraine, pain, neuropathic pain, inflammatory pain, trigeminal neuralgia, vision loss, rhinorrhoea, ocular hypertension (glaucoma), baldness, cardiac arrhythmia, atrial arrhythmia, ventricular arrhythmia, atrial fibrillation, ventricular fibrillation, tachyarrhythmia, atrial tachyarrhythmia, ventricular tachyarrhythmia, bradyarrhythmia, or any other abnormal rhythm, e.g. caused by myocardial ischaemia, myocardial infarction, cardiac hypertrophy or cardiomyopathy.

9. Use of a combination of

(A) a biphenyl thio-urea derivative according to any one of claims 1-5; and

(B1) a phosphodiesterase inhibitor, or

(B2) an agent that potentiates endothelium-derived hyperpolarizing factor-mediated responses;

or pharmaceutically-acceptable addition salts thereof,

for the manufacture of a medicament for the treatment or alleviation of sexual dysfunction.

10. The use of claim 9, wherein the sexual dysfunction is a male sexual dysfunction, a female sexual dysfunction or a male erectile dysfunction.

11. The use according to either one of claims 9-10, wherein the phosphor-diesterase inhibitor of is sildenafil, tadalafil or vardenafil; and the agent that potentiates endothelium-derived hyperpolarizing factor-mediated responses is calcium dobesilate.

12. A kit of parts comprising at least two separate unit dosage forms (A) and (B1) or (B2):

(A) a biphenyl thio-urea derivative according to any one of claims 1-5; and

(B1) a phosphodiesterase inhibitor, or

(B2) an agent that potentiates endothelium-derived hyperpolarizing factor-mediated responses; and optionally

(C) instructions for the simultaneous, sequential or separate administration of the biphenyl thio-urea derivative of A, and the phosphodiesterase inhibitor of B1, or an agent that potentiates endothelium-derived hyperpolarizing factor-mediated responses of B2, to a patient in need thereof.

13. 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 disorder, disease or condition is responsive to modulation of potassium channels, which method comprises the step of administering to such a living animal body in need thereof, a therapeutically effective amount of the biphenyl thio-urea derivative according to any one of claims 1-5.

14. A method of treatment or alleviation of a sexual dysfunction, which method comprises the step of administering to such a living animal body in need thereof, a therapeutically effective amount of a combination of

(A) a biphenyl thio-urea derivative according to claims 1-5; and

(B1) a phosphodiesterase inhibitor, or

(B2) an agent that potentiates endothelium-derived hyperpolarizing factor-mediated responses;

or pharmaceutically-acceptable addition salts thereof.

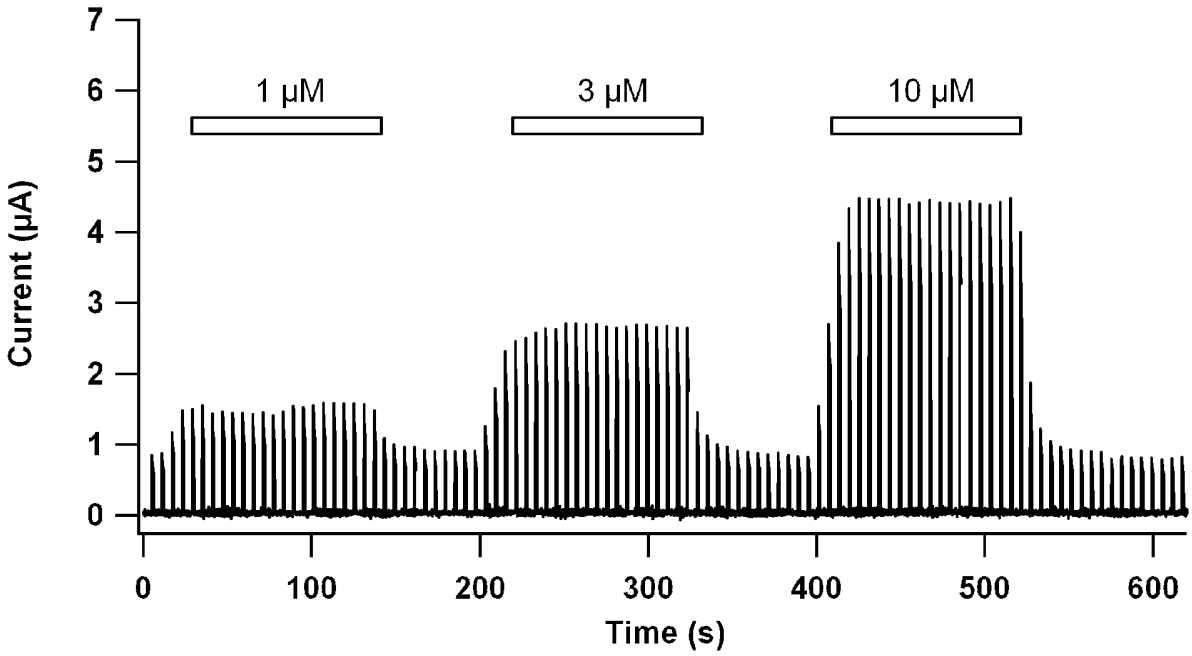

1 µM
3 µM
10 µM
Current (µA)
0
1
2
3
4
5
6
7
0
100
200
300
400
500
600
Time (s)

Fig. 1

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2007/064016

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07C335/18 C07D257/04 A61K31/17 A61P15/12

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)
C07C C07D A61K A61P

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, BEILSTEIN Data, WPI Data, CHEM ABS 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 94/22807 A (NEUROSEARCH) 13 October 1994 (1994-10-13) page 35, line 3; claims 1,2,4,7	1-14
X	ZHENPING TIAN, ET AL.: "A general synthesis of N-aryl- and N-alkyl-2-aminobenzoxazoles" TETRAHEDRON LETTERS, vol. 46, no. 48, 28 November 2005 (2005-11-28), pages 8341-8343, XP005134312 ELSEVIER SCIENCE PUBLISHERS, AMSTERDAM, NL ISSN: 0040-4039 table 1, 2nd and 3rd entries, intermediate thiourea derivatives; figure 1	1-4

-/--

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

[X] 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	Date of mailing of the international search report
28 April 2008	21/05/2008

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	English, Russell

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2007/064016

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	JU HEE YOON, ET AL.: "A facile synthesis of 2-aminothiazolo[5,4-b]pyridines and 2-Aminobenzoxazoles via Cyclization of Thioureas" HETEROCYCLES, vol. 65, no. 11, October 2005 (2005-10), pages 2729-2740, XP001536937 ELSEVIER SCIENCE PUBLISHERS, AMSTERDAM, NL compound 3g	1-4
X	DATABASE CHEMCATS [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; XP002477399 Database accession no. 2023678158 Order number M-620774	1-4
P,X	& "Scentific Exchange Product List" 30 January 2008 (2008-01-30), SCEINTIFIC EXCHANGE, INC. , CENTER OSSIPEE, NH, US	1-4
L	DATABASE REGISTRY [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; 12 August 2004 (2004-08-12), XP002477400 retrieved from STN Database accession no. 725706-17-2	

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP2007/064016

Box No. 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. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 13,14 are 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 No. 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 allsearchable claims.

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

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search reportcovers 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 and, where applicable, the payment of a protest fee.

[ ] The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

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

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2007/064016

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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		AU 683654 B2	20-11-1997
		AU 6537894 A	24-10-1994
		CA 2160128 A1	13-10-1994
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		US 5696138 A	09-12-1997