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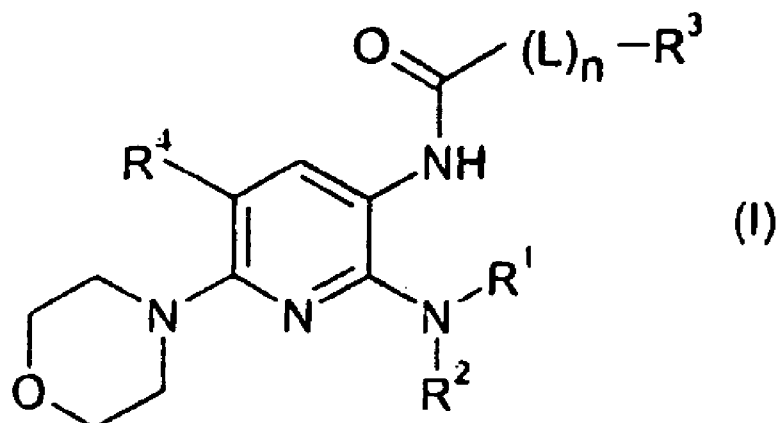
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(54) Title: SUBSTITUTED PYRIDINE DERIVATIVES AND THEIR MEDICAL USE



(57) Abstract: The present application discloses novel substituted morpholinyl-pyridine derivatives (I) and their use as modulators of the voltage gated K_v7 (KCNQ) potassium ion channels. In other aspects the application discloses the use of these compounds, in a method for therapy and to pharmaceutical compositions comprising these compounds, a stereoisomer or a mixture of its stereoisomers, or a pharmaceutically-acceptable addition salt thereof, or an N-oxide thereof.

SUBSTITUTED PYRIDINE DERIVATIVES AND THEIR MEDICAL USE

TECHNICAL FIELD

The present invention relates to novel substituted morpholinyl-pyridine derivatives, to their use in therapy, to pharmaceutical compositions comprising the derivatives, to the use of said derivatives in the manufacture of a medicament, and to therapeutic methods comprising the administration of the derivatives. The present derivatives are useful for treating a disorder, disease or a condition of a subject, which disorder, disease or condition is responsive to activation of K_v7 channels.

10 BACKGROUND ART

Potassium (K^+) channels are structurally and functionally diverse families of K^+ -selective channel proteins, which are ubiquitous in cells, indicating their central importance in regulating a number of key cell functions. While widely distributed as a class, K^+ channels are differentially distributed as individual members of this class or as families.

Recently a new family of potassium channels, the KCNQ channels, now also designated K_v7 , of which $K_v7.1$ - $K_v7.5$ have currently been characterised, has attracted attention as target for therapeutic development.

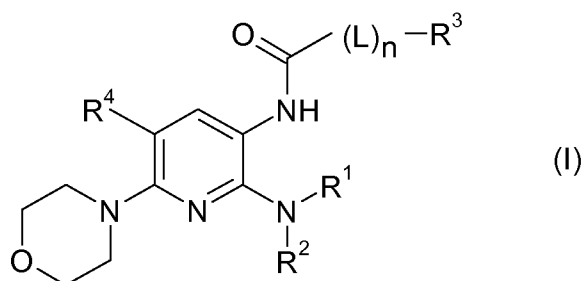
Due to the distribution of K_v7 channels within the organism, K_v7 channel modulators are considered potentially useful for the treatment or alleviation of conditions as diverse as CNS disorders, psychiatric disorders, CNS damage caused by trauma, stroke or neurodegenerative illness or diseases, a variety of neuronal hyperexcitability disorders and conditions, epilepsy, pain, neuropathic pain, migraine, tension type headache, learning and cognitive disorders, motion and motor disorders, multiple sclerosis, cardiac disorders, heart failure, cardiomyopathia, inflammatory diseases, ophthalmic conditions, deafness, progressive hearing loss, tinnitus, obstructive or inflammatory airway diseases, for inducing or maintaining bladder control including the treatment or prevention of urinary incontinence.

WO2006/092143 (Lundbeck A/S) discloses substituted pyridine derivatives useful as openers of the KCNQ family potassium ion channels. However, this document does not disclose or suggest pyridine derivatives substituted with two heterocyclic rings.

SUMMARY OF THE INVENTION

The present invention discloses novel substituted morpholinyl-pyridine compounds having medical utility for combating disorders, diseases or conditions responsive to activation of K_v7 channels.

In one embodiment the present invention provides compounds of Formula (I)



a stereoisomer or a mixture of its stereoisomers, or a pharmaceutically-acceptable addition salt thereof, or an N-oxide thereof, wherein R^1 , R^2 , R^3 , R^4 , L and n are as
5 defined below.

In another embodiment the invention provides pharmaceutical compositions comprising a therapeutically effective amount of a compound of the invention, a stereoisomer or a mixture of its stereoisomers, or a pharmaceutically-acceptable addition salt thereof, or an N-oxide thereof or a pharmaceutically-acceptable addition
10 salt thereof.

In another embodiment the invention relates to the use of a compound of the invention, a stereoisomer or a mixture of its stereoisomers, or a pharmaceutically-acceptable addition salt thereof, or an N-oxide thereof, for the manufacture of pharmaceutical compositions.

15 In another embodiment the invention relates to the use of a compound of the invention, a stereoisomer or a mixture of its stereoisomers, or a pharmaceutically-acceptable addition salt thereof, or an N-oxide thereof, for the manufacture of a pharmaceutical composition for the treatment, prevention or alleviation of a disease or a disorder or a condition of a living animal body, including a human, which disorder,
20 disease or condition is responsive to activation of K_v7 channels.

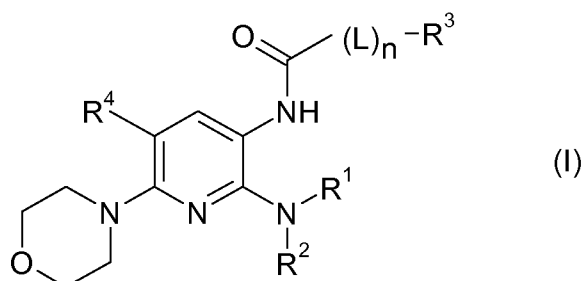
In another embodiment the invention provides a method of treatment, prevention or alleviation of a disease or a disorder or a condition of a living animal body, including a human, which disorder, disease or condition is responsive to activation of K_v7 channels, which method comprises the step of administering to such a living animal body in
25 need thereof, a therapeutically effective amount of a compound of the invention, a stereoisomer or a mixture of its stereoisomers, or a pharmaceutically-acceptable addition salt thereof, or an N-oxide thereof or a pharmaceutically-acceptable addition salt thereof.

Another embodiment of the invention is the provision of compounds with optimal
30 pharmacodynamic and/or pharmacokinetic properties such as kinetic behaviour, bio-availability, solubility, efficacy and/or adverse effects.

Other embodiments 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 one embodiment the present invention provides compounds of Formula (I)



- 5 a stereoisomer or a mixture of its stereoisomers, or a pharmaceutically-acceptable addition salt thereof, or an N-oxide thereof, wherein

R^1 and R^2 , independently of each other, represent C_{1-6} -alkyl; or

- 10 R^1 and R^2 , together with the nitrogen to which they are attached, form a heterocyclic ring selected from pyrrolidinyl, 2,5-dihydro-1*H*-pyrrol-1-yl, piperidinyl and morpholinyl, which pyrrolidinyl and piperidinyl is optionally substituted one or more times with a substituent selected from the group consisting of halogen, hydroxy, amino, C_{1-6} -alkyl, trifluoromethyl, C_{1-6} -alkoxy, hydroxy- C_{1-6} -alkyl and C_{1-6} -alkoxy- C_{1-6} -alkyl;

15

L represents a linker selected from $-CR'R''-$ and $-O-CR'R''-$, wherein R' and R'' , independently of each other, represent hydrogen, C_{1-6} -alkyl or halogen;

n is 0 or 1;

20

R^3 represents C_{1-6} -alkyl or phenyl, which phenyl is optionally substituted one or more times with substituents selected from C_{1-6} -alkyl, C_{1-6} -alkoxy, halogen and trifluoromethyl; and

- 25 R^4 represents C_{1-6} -alkyl.

In another embodiment of the invention, in Formula (I), R^1 and R^2 , independently of each other, represent C_{1-6} -alkyl, such as methyl.

- In another embodiment of the invention, in Formula (I), R^1 and R^2 , together with the nitrogen to which they are attached, represent 2,5-dihydro-1*H*-pyrrol-1-yl.
- 30

In another embodiment of the invention, in Formula (I), R^1 and R^2 , together with the nitrogen to which they are attached, represent morpholinyl.

In another embodiment of the invention, in Formula (I), R^1 and R^2 , together with the nitrogen to which they are attached, represent pyrrolidinyl which is optionally substituted one or more times with a substituent selected from the group consisting of halogen, hydroxy, amino, C_{1-6} -alkyl, trifluoromethyl, C_{1-6} -alkoxy, hydroxy- C_{1-6} -alkyl and C_{1-6} -alkoxy- C_{1-6} -alkyl. In another embodiment R^1 and R^2 , together with the nitrogen to which they are attached, represent pyrrolidinyl. In another embodiment R^1 and R^2 , together with the nitrogen to which they are attached, represent pyrrolidinyl which is substituted one or two times with a substituent selected from the group consisting of halogen, hydroxy, amino, C_{1-6} -alkyl, trifluoromethyl and C_{1-6} -alkoxy. In another embodiment R^1 and R^2 , together with the nitrogen to which they are attached, represent pyrrolidinyl substituted one time with a substituent selected from the group consisting of halogen, hydroxy, amino, C_{1-6} -alkyl, trifluoromethyl and C_{1-6} -alkoxy. In another embodiment R^1 and R^2 , together with the nitrogen to which they are attached, represent pyrrolidinyl substituted one time with halogen. In another embodiment R^1 and R^2 , together with the nitrogen to which they are attached, represent pyrrolidinyl substituted one time with fluoro. In another embodiment R^1 and R^2 , together with the nitrogen to which they are attached, represent pyrrolidinyl substituted one time with C_{1-6} -alkyl, such as methyl. In another embodiment R^1 and R^2 , together with the nitrogen to which they are attached, represent pyrrolidinyl substituted one time with trifluoromethyl. In another embodiment R^1 and R^2 , together with the nitrogen to which they are attached, represent pyrrolidinyl substituted two times with a substituent selected from the group consisting of halogen, hydroxy, amino, C_{1-6} -alkyl, trifluoromethyl and C_{1-6} -alkoxy. In another embodiment R^1 and R^2 , together with the nitrogen to which they are attached, represent pyrrolidinyl substituted two times with halogen. In another embodiment R^1 and R^2 , together with the nitrogen to which they are attached, represent pyrrolidinyl substituted two times with C_{1-6} -alkyl, such as methyl.

In another embodiment of the invention, in Formula (I), R^1 and R^2 , together with the nitrogen to which they are attached, represent piperidinyl which is optionally substituted one or more times with a substituent selected from the group consisting of halogen, hydroxy, amino, C_{1-6} -alkyl, trifluoromethyl, C_{1-6} -alkoxy, hydroxy- C_{1-6} -alkyl and C_{1-6} -alkoxy- C_{1-6} -alkyl. In another embodiment R^1 and R^2 , together with the nitrogen to which they are attached, represent piperidinyl. In another embodiment R^1 and R^2 , together with the nitrogen to which they are attached, represent piperidinyl which is substituted one or two times with a substituent selected from the group consisting of halogen, hydroxy, amino, C_{1-6} -alkyl, trifluoromethyl and C_{1-6} -alkoxy. In another embodiment R^1 and R^2 , together with the nitrogen to which they are attached, represent piperidinyl substituted one time with a substituent selected from the group consisting of halogen, hydroxy, amino, C_{1-6} -alkyl, trifluoromethyl and C_{1-6} -alkoxy. In

another embodiment R^1 and R^2 , together with the nitrogen to which they are attached, represent piperidinyl substituted one time with halogen. In another embodiment R^1 and R^2 , together with the nitrogen to which they are attached, represent piperidinyl substituted one time with fluoro. In another embodiment R^1 and R^2 , together with the nitrogen to which they are attached, represent piperidinyl substituted one time with C_{1-6} -alkyl, such as methyl. In another embodiment R^1 and R^2 , together with the nitrogen to which they are attached, represent piperidinyl substituted one time with trifluoromethyl. In another embodiment R^1 and R^2 , together with the nitrogen to which they are attached, represent piperidinyl substituted two times with a substituent selected from the group consisting of halogen, hydroxy, amino, C_{1-6} -alkyl, trifluoromethyl and C_{1-6} -alkoxy. In another embodiment R^1 and R^2 , together with the nitrogen to which they are attached, represent piperidinyl substituted two times with halogen. In another embodiment R^1 and R^2 , together with the nitrogen to which they are attached, represent piperidinyl substituted two times with C_{1-6} -alkyl, such as methyl.

15 In another embodiment of the invention, in Formula (I), L represents $-CR'R''-$, wherein R' and R'' , independently of each other, represent hydrogen, C_{1-6} -alkyl or halogen. In another embodiment L represents $-CR'R''-$, wherein R' and R'' , independently of each other, represent hydrogen or C_{1-6} -alkyl. In another embodiment of the invention L represents $-CH_2-$. In another embodiment L represents $-CR'R''-$, wherein one of R' and R'' represent hydrogen, and the other one of R' and R'' represent C_{1-6} -alkyl, e.g. methyl.

In another embodiment of the invention, in Formula (I), L represents $-O-CR'R''-$, wherein R' and R'' , independently of each other, represent hydrogen, C_{1-6} -alkyl or halogen. In another embodiment L represents $-O-CR'R''-$, wherein R' and R'' , independently of each other, represent hydrogen or C_{1-6} -alkyl. In another embodiment of the invention L represents $-O-CH_2-$. In another embodiment L represents $-O-CR'R''-$, wherein one of R' and R'' represent hydrogen, and the other one of R' and R'' represent C_{1-6} -alkyl, e.g. methyl.

In another embodiment of the invention, in Formula (I), n is 0.

30 In another embodiment of the invention, in Formula (I), n is 1.

In another embodiment of the invention, in Formula (I), R^3 represents C_{1-6} -alkyl, such as methyl, ethyl, propyl or *tert*-butyl. In another embodiment, R^3 represents methyl. In another embodiment, R^3 represents ethyl. In another embodiment, R^3 represents *tert*-butyl.

35 In another embodiment of the invention, in Formula (I), R^3 represents phenyl, which is optionally substituted one or more times with substituents selected from C_{1-6} -alkyl, C_{1-6} -alkoxy, halogen and trifluoromethyl.

In another embodiment of the invention, in Formula (I), R^3 represents phenyl.

In another embodiment of the invention, in Formula (I), R^3 represents phenyl, which is substituted one time with a substituent selected from C_{1-6} -alkyl, C_{1-6} -alkoxy, halogen and trifluoromethyl. In another embodiment R^3 represents phenyl which is substituted one time with C_{1-6} -alkyl, such as methyl. In another embodiment R^3 represents phenyl which is substituted one time with halogen. In another embodiment R^3 represents phenyl which is substituted one time with C_{1-6} -alkoxy. In another embodiment R^3 represents phenyl which is substituted one time with trifluoromethyl.

In another embodiment of the invention, in Formula (I), R^3 represents phenyl, which is substituted two times with substituents selected from C_{1-6} -alkyl, C_{1-6} -alkoxy, halogen and trifluoromethyl. In another embodiment R^3 represents phenyl which is substituted two times with C_{1-6} -alkyl, e.g. methyl. In another embodiment R^3 represents phenyl which is substituted two times with C_{1-6} -alkoxy. In another embodiment R^3 represents phenyl which is substituted two times with halogen. In another embodiment R^3 represents phenyl which is substituted two times with fluoro. In another embodiment R^3 represents phenyl which is substituted two times with trifluoromethyl.

In another embodiment of the invention, in Formula (I), R^4 represents C_{1-6} -alkyl, e.g. methyl.

In another embodiment of the invention, in Formula (I), R^1 and R^2 , independently of each other, represent C_{1-6} -alkyl; L represents a linker selected from -CR'R''- and -O-CR'R''-, wherein R' and R'' , independently of each other, represent hydrogen, C_{1-6} -alkyl or halogen; n is 0 or 1; R^3 represents C_{1-6} -alkyl or phenyl, which phenyl is optionally substituted one or more times with substituents selected from C_{1-6} -alkyl, C_{1-6} -alkoxy, halogen and trifluoromethyl; and R^4 represents C_{1-6} -alkyl.

In another embodiment of the invention, in Formula (I), R^1 and R^2 , together with the nitrogen to which they are attached, form a heterocyclic ring selected from pyrrolidinyl, 2,5-dihydro-1H-pyrrol-1-yl, piperidinyl and morpholinyl, which pyrrolidinyl and piperidinyl is optionally substituted one or more times with a substituent selected from the group consisting of halogen, hydroxy, amino, C_{1-6} -alkyl, trifluoromethyl, C_{1-6} -alkoxy, hydroxy- C_{1-6} -alkyl and C_{1-6} -alkoxy- C_{1-6} -alkyl; L represents a linker selected from -CR'R''- and -O-CR'R''-, wherein R' and R'' , independently of each other, represent hydrogen, C_{1-6} -alkyl or halogen; n is 0 or 1; R^3 represents C_{1-6} -alkyl or phenyl, which phenyl is optionally substituted one or more times with substituents selected from C_{1-6} -alkyl, C_{1-6} -alkoxy, halogen and trifluoromethyl; and R^4 represents C_{1-6} -alkyl.

In another embodiment of the invention, in Formula (I), R^1 and R^2 , independently of each other, represent C_{1-6} -alkyl; L represents a linker -CR'R''-, wherein R' and R'' , independently of each other, represent hydrogen, C_{1-6} -alkyl or halogen; n is 1; R^3 represents C_{1-6} -alkyl or phenyl, which phenyl is optionally substituted one or more times with substituents selected from C_{1-6} -alkyl, C_{1-6} -alkoxy, halogen and trifluoromethyl; and R^4 represents C_{1-6} -alkyl.

In another embodiment of the invention, in Formula (I), R^1 and R^2 , together with the nitrogen to which they are attached, form a heterocyclic ring selected from pyrrolidinyl, 2,5-dihydro-1*H*-pyrrol-1-yl, piperidinyl and morpholinyl, which pyrrolidinyl and piperidinyl is optionally substituted one or more times with a substituent selected
5 from the group consisting of halogen, hydroxy, amino, C_{1-6} -alkyl, trifluoromethyl, C_{1-6} -alkoxy, hydroxy- C_{1-6} -alkyl and C_{1-6} -alkoxy- C_{1-6} -alkyl; L represents a linker -CR'R''-, wherein R' and R'', independently of each other, represent hydrogen, C_{1-6} -alkyl or halogen; n is 1; R^3 represents C_{1-6} -alkyl or phenyl, which phenyl is optionally substituted one or more times with substituents selected from C_{1-6} -alkyl, C_{1-6} -alkoxy,
10 halogen and trifluoromethyl; and R^4 represents C_{1-6} -alkyl.

In another embodiment of the invention, in Formula (I), R^1 and R^2 , independently of each other, represent C_{1-6} -alkyl; L represents a linker -O-CR'R''-, wherein R' and R'', independently of each other, represent hydrogen, C_{1-6} -alkyl or halogen; n is 1; R^3 represents C_{1-6} -alkyl or phenyl, which phenyl is optionally substituted one or more
15 times with substituents selected from C_{1-6} -alkyl, C_{1-6} -alkoxy, halogen and trifluoromethyl; and R^4 represents C_{1-6} -alkyl.

In another embodiment of the invention, in Formula (I), R^1 and R^2 , together with the nitrogen to which they are attached, form a heterocyclic ring selected from pyrrolidinyl, 2,5-dihydro-1*H*-pyrrol-1-yl, piperidinyl and morpholinyl, which pyrrolidinyl
20 and piperidinyl is optionally substituted one or more times with a substituent selected from the group consisting of halogen, hydroxy, amino, C_{1-6} -alkyl, trifluoromethyl, C_{1-6} -alkoxy, hydroxy- C_{1-6} -alkyl and C_{1-6} -alkoxy- C_{1-6} -alkyl; L represents a linker -O-CR'R''-, wherein R' and R'', independently of each other, represent hydrogen, C_{1-6} -alkyl or halogen; n is 1; R^3 represents C_{1-6} -alkyl or phenyl, which phenyl is optionally
25 substituted one or more times with substituents selected from C_{1-6} -alkyl, C_{1-6} -alkoxy, halogen and trifluoromethyl; and R^4 represents C_{1-6} -alkyl.

In another embodiment of the invention, in Formula (I), R^1 and R^2 , independently of each other, represent C_{1-6} -alkyl; n is 0; R^3 represents C_{1-6} -alkyl or phenyl, which phenyl is optionally substituted one or more times with substituents selected from C_{1-6} -
30 alkyl, C_{1-6} -alkoxy, halogen and trifluoromethyl; and R^4 represents C_{1-6} -alkyl.

In another embodiment of the invention, in Formula (I), R^1 and R^2 , together with the nitrogen to which they are attached, form a heterocyclic ring selected from pyrrolidinyl, 2,5-dihydro-1*H*-pyrrol-1-yl, piperidinyl and morpholinyl, which pyrrolidinyl
and piperidinyl is optionally substituted one or more times with a substituent selected
35 from the group consisting of halogen, hydroxy, amino, C_{1-6} -alkyl, trifluoromethyl, C_{1-6} -alkoxy, hydroxy- C_{1-6} -alkyl and C_{1-6} -alkoxy- C_{1-6} -alkyl; n is 0; R^3 represents C_{1-6} -alkyl or phenyl, which phenyl is optionally substituted one or more times with substituents selected from C_{1-6} -alkyl, C_{1-6} -alkoxy, halogen and trifluoromethyl; and R^4 represents C_{1-6} -alkyl.

In another embodiment of the invention, in Formula (I), R^1 and R^2 , together with the nitrogen to which they are attached, form a heterocyclic ring selected from pyrrolidinyl which is optionally substituted one time with halogen, L represents $-CH_2-$, n is 1, R^3 represents C_{1-6} -alkyl or phenyl, which phenyl is optionally substituted one or two
5 times with halogen and R^4 represents methyl.

In another embodiment of the invention, in Formula (I), R^1 and R^2 , together with the nitrogen to which they are attached, form a heterocyclic ring selected from pyrrolidinyl, L represents $-CH_2-$, n is 1, R^3 represents C_{1-6} -alkyl or phenyl, which phenyl is optionally substituted one or two times with halogen and R^4 represents methyl.

10 In another embodiment of the invention, in Formula (I), R^1 and R^2 , together with the nitrogen to which they are attached, form a heterocyclic ring selected from pyrrolidinyl, which is optionally substituted one time with halogen, L represents $-CH_2-$, n is 1, R^3 represents C_{1-6} -alkyl, e.g. *tert*-butyl, and R^4 represents methyl.

In another embodiment of the invention, in Formula (I), R^1 and R^2 , together with
15 the nitrogen to which they are attached, form a heterocyclic ring selected from pyrrolidinyl, which is substituted one time with halogen, L represents $-CH_2-$, n is 1, R^3 represents C_{1-6} -alkyl, e.g. *tert*-butyl, and R^4 represents methyl.

In another embodiment of the invention, in Formula (I), R^1 and R^2 , together with the nitrogen to which they are attached, form a heterocyclic ring selected from pyrrolidinyl, L represents $-CH_2-$, n is 1, R^3 represents C_{1-6} -alkyl, e.g. *tert*-butyl, and R^4
20 represents methyl.

In another embodiment of the invention, in Formula (I), R^1 and R^2 , together with the nitrogen to which they are attached, form a heterocyclic ring selected from pyrrolidinyl, L represents $-CH_2-$, n is 1, R^3 represents phenyl substituted two times with
25 halogen and R^4 represents methyl.

In another embodiment of the invention, in Formula (I), R^1 and R^2 , together with the nitrogen to which they are attached, form a heterocyclic ring selected from piperidinyl which is optionally substituted one time with halogen, L represents $-CH_2-$, n is 1, R^3 represents C_{1-6} -alkyl or phenyl, which phenyl is optionally substituted one or
30 two times with halogen and R^4 represents methyl.

In another embodiment of the invention, in Formula (I), R^1 and R^2 , together with the nitrogen to which they are attached, form a heterocyclic ring selected from piperidinyl, L represents $-CH_2-$, n is 1, R^3 represents C_{1-6} -alkyl or phenyl, which phenyl is optionally substituted one or two times with halogen and R^4 represents methyl.

35 In another embodiment of the invention, in Formula (I), R^1 and R^2 , together with the nitrogen to which they are attached, form a heterocyclic ring selected from piperidinyl, L represents $-CH_2-$, n is 1, R^3 represents C_{1-6} -alkyl, e.g. *tert*-butyl, and R^4 represents methyl.

In another embodiment of the invention, in Formula (I), R^1 and R^2 , together with the nitrogen to which they are attached, form a heterocyclic ring selected from piperidinyl, L represents $-CH_2-$, n is 1, R^3 represents phenyl substituted two times with halogen and R^4 represents methyl.

5 In another embodiment of the invention, in Formula (I), R^1 and R^2 , together with the nitrogen to which they are attached, form a heterocyclic ring selected from morpholinyl, L represents $-CH_2-$, n is 1, R^3 represents C_{1-6} -alkyl or phenyl, which phenyl is optionally substituted one or two times with halogen and R^4 represents methyl.

10 In another embodiment of the invention, in Formula (I), R^1 and R^2 , together with the nitrogen to which they are attached, form a heterocyclic ring selected from morpholinyl, L represents $-CH_2-$, n is 1, R^3 represents C_{1-6} -alkyl, e.g. *tert*-butyl, and R^4 represents methyl.

In another embodiment of the invention, in Formula (I), R^1 and R^2 , together with
15 the nitrogen to which they are attached, form a heterocyclic ring selected from morpholinyl, L represents $-CH_2-$, n is 1, R^3 represents phenyl substituted two times with halogen and R^4 represents methyl.

In another embodiment of the invention, in Formula (I), R^1 and R^2 , together with the nitrogen to which they are attached, form a heterocyclic ring which is pyrrolidinyl
20 which is substituted one time with halogen, L represents $-CH(CH_3)-$ or $-O-CH_2-$, n is 1, R^3 represents C_{1-6} -alkyl or phenyl, and R^4 represents C_{1-6} -alkyl.

In another embodiment of the invention, in Formula (I), R^1 and R^2 , together with the nitrogen to which they are attached, form a heterocyclic ring which is piperidinyl, which is substituted one time with halogen, L represents $-CH(CH_3)-$ or $-O-CH_2-$, n is 1,
25 R^3 represents C_{1-6} -alkyl or phenyl, and R^4 represents C_{1-6} -alkyl.

In another embodiment of the invention, in Formula (I), R^1 and R^2 , together with the nitrogen to which they are attached, form a heterocyclic ring which is morpholinyl, L represents $-CH(CH_3)-$ or $-O-CH_2-$, n is 1, R^3 represents C_{1-6} -alkyl or phenyl, and R^4 represents C_{1-6} -alkyl.

30 In another embodiment of the invention, in Formula (I), R^1 and R^2 , together with the nitrogen to which they are attached, form a heterocyclic ring which is pyrrolidinyl which is substituted one time with halogen, L represents $-CH(CH_3)-$, n is 1, R^3 represents C_{1-6} -alkyl or phenyl, and R^4 represents methyl.

In another embodiment of the invention, in Formula (I), R^1 and R^2 , together with
35 the nitrogen to which they are attached, form a heterocyclic ring which is pyrrolidinyl which is substituted one time with halogen, L represents $-CH(CH_3)-$, n is 1, R^3 represents C_{1-6} -alkyl, and R^4 represents methyl.

In another embodiment of the invention, in Formula (I), R^1 and R^2 , together with the nitrogen to which they are attached, form a heterocyclic ring which is pyrrolidinyl

which is substituted one time with halogen, L represents -CH(CH₃)-, n is 1, R³ represents phenyl, and R⁴ represents methyl.

In another embodiment of the invention, in Formula (I), R¹ and R², together with the nitrogen to which they are attached, form a heterocyclic ring which is pyrrolidinyl
 5 which is substituted one time with halogen, L represents -O-CH₂-, n is 1, R³ represents C₁₋₆-alkyl, and R⁴ represents methyl.

In another embodiment of the invention the compound of the invention is:
 3,3-Dimethyl-N-(5-methyl-6-morpholin-4-yl-2-pyrrolidin-1-yl-pyridin-3-yl)-butyramide;
 2-(3,5-Difluoro-phenyl)-N-(5-methyl-6-morpholin-4-yl-2-pyrrolidin-1-yl-pyridin-3-yl)-
 acetamide;
 N-[2-((R)-3-Fluoro-pyrrolidin-1-yl)-5-methyl-6-morpholin-4-yl-pyridin-3-yl]-3,3-dimethyl-
 butyramide;
 (S)-N-[2-((R)-3-Fluoro-pyrrolidin-1-yl)-5-methyl-6-morpholin-4-yl-pyridin-3-yl]-2-
 phenyl-propionamide;
 [2-((R)-3-Fluoro-pyrrolidin-1-yl)-5-methyl-6-morpholin-4-yl-pyridin-3-yl]-carbamic acid
 ethyl ester;
 or a stereoisomer or a mixture of its stereoisomers, or a pharmaceutically-acceptable
 addition salt thereof, or an N-oxide thereof.

In another embodiment of the invention the compound of the invention is:
 (S)-N-[2-((R)-3-Fluoro-pyrrolidin-1-yl)-5-methyl-6-morpholin-4-yl-pyridin-3-yl]-2-methyl-
 butyramide;
 or a stereoisomer or a mixture of its stereoisomers, or a pharmaceutically-acceptable
 addition salt thereof, or an N-oxide thereof.

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

Definition of Terms

As used throughout the present specification and appended claims, the
 following terms have the indicated meaning:

15 The term "C₁₋₆-alkyl" as used herein means a saturated, branched or straight
 hydrocarbon group having from 1-6 carbon atoms, e.g. C₁₋₃-alkyl, C₁₋₄-alkyl, C₁₋₆-alkyl,
 C₂₋₆-alkyl, C₃₋₆-alkyl, and the like. Representative examples are methyl, ethyl, propyl
 (e.g. prop-1-yl, prop-2-yl (or *iso*-propyl)), butyl (e.g. 2-methylprop-2-yl (or *tert*-butyl),
 but-1-yl, but-2-yl), pentyl (e.g. pent-1-yl, pent-2-yl, pent-3-yl), 2-methylbut-1-yl, 3-
 20 methylbut-1-yl, hexyl (e.g. hex-1-yl), and the like.

The term "halo" or "halogen" means fluorine, chlorine, bromine or iodine.

The term "hydroxy" shall mean the radical -OH.

The term "amino" shall mean the radical -NH₂.

The term "trihalomethyl" means trifluoromethyl, trichloromethyl, and similar trihalo-substituted methyl groups.

The term "C₁₋₆-alkoxy" as used herein refers to the radical -O-C₁₋₆-alkyl.

Representative examples are methoxy, ethoxy, propoxy (e.g. 1-propoxy, 2-propoxy),
5 butoxy (e.g. 1-butoxy, 2-butoxy, 2-methyl-2-propoxy), pentoxy (1-pentoxy, 2-pentoxy),
hexoxy (1-hexoxy, 3-hexoxy), and the like.

The term "hydroxy-C₁₋₆-alkyl" as used herein refers to alkyl substituted one or more times at any carbon atom(s) with hydroxyl. Representative examples are hydroxymethyl, hydroxyethyl (e.g. 1-hydroxyethyl, 2-hydroxyethyl) and the like.

10 The term "C₁₋₆-alkoxy-C₁₋₆-alkyl" as used herein refers to an C₁₋₆-alkyl-O-C₁₋₆-alkyl group, wherein the C₁₋₆-alkyl and C₁₋₆-alkyl-O- are as defined above. Representative examples are methoxy-methyl, methoxy-ethyl, ethoxy-methyl, and ethoxy-ethyl.

The term "optionally substituted" as used herein means that the groups in
15 question are either unsubstituted or substituted with one or more of the substituents specified. When the group(s) in question is/are substituted with more than one substituent the substituents may be the same or different.

Certain of the defined terms may occur more than once in the structural formulae, and upon such occurrence each term shall be defined independently of the
20 other.

The term "treatment" as used herein means the management and care of a patient for the purpose of combating a disease, disorder or condition. The term is intended to include the delaying of the progression of the disease, disorder or condition, the alleviation or relief of symptoms and complications, and/or the cure or
25 elimination of the disease, disorder or condition. The patient to be treated is preferably a mammal, in particular a human being.

The terms "disease", "condition" and "disorder" as used herein are used interchangeably to specify a state of a patient which is not the normal physiological state of man.

30 The term "medicament" as used herein means a pharmaceutical composition suitable for administration of the pharmaceutically active compound to a patient.

The term "pharmaceutically acceptable" as used herein means suited for normal pharmaceutical applications, i.e. giving rise to no adverse events in patients etc.

The term "effective amount" as used herein means a dosage which is sufficient
35 in order for the treatment of the patient to be effective compared with no treatment.

The term "therapeutically effective amount" of a compound as used herein means an amount sufficient to cure, alleviate or partially arrest the clinical manifestations of a given disease and its complications. An amount adequate to accomplish this is defined as "therapeutically effective amount". Effective amounts for

each purpose will depend on the severity of the disease or injury as well as the weight and general state of the subject. It will be understood that determining an appropriate dosage may be achieved using routine experimentation, by constructing a matrix of values and testing different points in the matrix, which is all within the ordinary skills of
5 a trained physician or veterinary.

Pharmaceutically Acceptable Salts

The compounds 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 compounds of the invention.

10 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,
15 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 benzene-sulphonate derived from benzenesulphonic 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
20 fumarate derived from fumaric acid, the glutamate derived from glutamic acid, the glycollate 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 methanesulphonate derived from methane sulphonic acid, the naphthalene-2-sulphonate derived from naphthalene-2-sulphonic acid, the
25 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.

30 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.

Examples of pharmaceutically acceptable cationic salts of a chemical compound
35 of the invention include, without limitation, the sodium, the potassium, the calcium, the magnesium, the zinc, the aluminium, the lithium, the choline, the lysine, 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.

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 benzene-sulphonate, 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 zinc, the aluminium, the lithium, the choline, the lysine, 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.

Steric Isomers

The compounds of the present invention may exist in (+) and (-) forms as well as in racemic forms ($\pm$). The racemates of these isomers and the individual isomers themselves are within the scope of the present invention.

Racemic forms can be resolved into the optical antipodes by known methods and techniques. One way of separating the diastereomeric salts is by use of an optically active acid, and liberating the optically active amine compound by treatment with a base. Another method for resolving racemates into the optical antipodes is based upon chromatography on an optical active matrix. Racemic compounds of the present invention can thus be resolved into their optical antipodes, e.g., by fractional crystallisation of d- or l- (tartrates, mandelates, or camphorsulphonate) salts for example.

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.

Methods of Preparation

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

Also one compound of the invention can be converted to another compound of the invention using conventional methods.

The end products of the reactions described herein may be isolated by conventional techniques, e.g. by extraction, crystallisation, distillation, chromatography, etc.
10

Biological Activity

The compounds of the invention have been found useful as modulators of the K_v7 (KCNQ) potassium channels. At present five such channels are known, i.e. the $K_v7.1$ (KCNQ1) channel, the $K_v7.2$ (KCNQ2) channel, the $K_v7.3$ (KCNQ3) channel, the
15 $K_v7.4$ (KCNQ4) channel, and the $K_v7.5$ (KCNQ5) channel, and heteromeric combinations hereof. Moreover, the modulatory activity may be inhibitory (i.e. inhibitory activity) or stimulatory (i.e. activating activity).

The modulatory activity may be determined using conventional methods, e.g. binding or activity studies, known in the art, e.g. as described in WO 2004/080377
20 (NeuroSearch A/S) .

In one aspect of the invention, the compounds of the invention show stimulating activity at $K_v7.2$, $K_v7.3$, $K_v7.4$ and/or $K_v7.5$ potassium channels, and heteromeric combinations hereof. Compounds of the invention are selective, e.g. showing $K_v7.2$, $K_v7.2+$ $K_v7.3$, and/or $K_v7.4$ potassium channel activation.

25 Accordingly, the compounds of the invention are considered useful for the 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 a K_v7 potassium channel.

Due to the distribution of KCNQ channels within the organism, KCNQ channel
30 modulators are considered useful for the treatment or alleviation of conditions as diverse as an affective disorder, a neuro-physiological disorder, an anxiety disorder, depression, a bipolar disorder, a sleep disorder, addiction, an eating disorder, a phobia, a neurodegenerative disorder, Parkinson's disease, a mood disorder, a psychotic disorder, a compulsive behaviour, mania, psychosis, schizophrenia,
35 dementia, Alzheimer's disease, epilepsy, convulsions, seizure disorders, absence seizures, vascular spasms, coronary artery spasms, tremor, muscle spasms, myasthenia gravis, a motor neuron disease, motion and motor disorders, a tic disorder, a Parkinson-like motor disorder, essential tremors, multiple sclerosis, amyelotrophic

lateral sclerosis (ALS), multiple system atrophy, corticobasal degeneration, HIV associated dementia, Huntington's disease, Pick's disease, torsades de pointes, functional bowel disorders, CNS damage caused by trauma, stroke or neurodegenerative illness or diseases, ataxia, myokymia, spasticity, myopathy, learning and cognitive disorders, memory dysfunction, memory impairment, age-associated memory loss, Down's syndrome, pain, acute or chronic pain, mild pain, moderate or severe pain, neuropathic pain, central pain, pain related to diabetic neuropathy, to postherpetic neuralgia, to peripheral nerve injury, somatic pain, visceral pain or cutaneous pain, pain caused by inflammation or by infection, postoperative pain, phantom limb pain, neuronal hyperexcitability disorders, peripheral nerve hyperexcitability, chronic headache, migraine, migraine-related disorders, tension-type headache, heart failure, cardiac disorders, cardiomyopathy, cardiac arrhythmia, cardiac ischaemia, long QT syndrome, inflammatory diseases or conditions, inflammatory bowel disease, Crohn's disease, ulcerative colitis, Creutzfeld-Jacobs disease, an obstructive or inflammatory airway disease, asthma, an airway hyper reactivity, pneumoconiosis, aluminosis, anthracosis, asbestosis, chalicosis, ptilosis, siderosis, silicosis, tabacosis, byssinosis, chronic obstructive pulmonary disease (COPD), exacerbation of airways hyper reactivity, cystic fibrosis, hearing impairment or hearing loss, progressive hearing loss, tinnitus, a drug-dependence or drug-addiction disorder, hyperactive gastric motility, ophthalmic conditions, erectile dysfunction, fibromylgia, for inducing or maintaining bladder control, nocturia, bladder spasms, overactive bladder (OAB), bladder outflow obstruction, interstitial cystitis (IC) (also called painful bladder syndrome) and urinary incontinence.

In another embodiment the disease, disorder or condition contemplated according to the invention is an anxiety disorder such as panic disorder, agoraphobia, phobias, social anxiety disorder, obsessive-compulsive disorder and post-traumatic stress disorder. In another embodiment the disease, disorder or condition contemplated according to the invention is anxiety. In another embodiment the disease, disorder or condition contemplated according to the invention is schizophrenia.

In one embodiment the compounds of the invention are considered useful for treatment, prevention or alleviation of a disease, disorder or adverse condition of the CNS. In another embodiment, the disease, disorder or condition is an affective disorder, a neuro-physiological disorder, an anxiety disorder, depression, a bipolar disorder, a sleep disorder, addiction, an eating disorder, a phobia, a neurodegenerative disorder, Parkinson's disease, a mood disorder, a psychotic disorder, a compulsive behaviour, mania, psychosis or schizophrenia. In another embodiment the compounds of the invention are useful for the treatment or alleviation of schizophrenia. In another embodiment the compounds of the invention are useful for the treatment or alleviation of depression. In another embodiment the compounds of

the invention are useful for the treatment or alleviation of bipolar disorder. In another embodiment the compounds of the invention are considered useful for treatment, prevention or alleviation of a CNS damage caused by trauma or by a spinal cord damage, stroke, traumatic brain injury, a neurodegenerative illness or disease, dementia, Alzheimer's disease, a motor neuron disease, a Parkinson-like motor disorder, multiple sclerosis, amyotrophic lateral sclerosis (ALS), multiple system atrophy, HIV associated dementia, Huntington's disease, Pick's disease, torsades de pointes, tremor, muscle spasms, myasthenia gravis, convulsions, ataxia, myokymia, seizures, epilepsy or spasticity. In another embodiment the compounds of the invention are useful for the treatment or alleviation of epilepsy.

In another embodiment the compounds of the invention are considered useful for treatment, prevention or alleviation of pain, including acute and chronic pain, mild pain, moderate or even severe pain of acute, chronic or recurrent character, as well as postoperative pain, phantom limb pain, chronic headache, post therapeutic neuralgia, neuropathic pain, central pain, or pain related to diabetic neuropathy, to postherpetic neuralgia, to peripheral nerve injury or drug addiction, migraine and migraine-related disorders and to tension-type headache. In another embodiment the pain is somatic pain, incl. visceral pain or cutaneous pain, or pain caused by inflammation or by infection. In another embodiment the pain is neuropathic, e.g. caused by injury to the central or peripheral nervous system, e.g. due to tissue trauma, infection, diabetes, an autoimmune disease, arthritis or neuralgia. In another embodiment the compounds of the invention are useful for the treatment, prevention or alleviation of pain. In another embodiment the compounds of the invention are useful for the treatment or alleviation of neuropathic pain.

In another embodiment the compounds of the invention are considered useful for treatment, prevention or alleviation of addiction, e.g. drug addiction, drug abuse, cocaine abuse, nicotine abuse, tobacco abuse, alcohol addiction or alcoholism, or withdrawal symptoms caused by the termination of abuse of chemical substances, in particular opioids, heroin, cocaine and morphine, benzodiazepines and benzodiazepine-like drugs, and alcohol.

In another embodiment the compounds of the invention are considered useful for treatment, prevention or alleviation of a learning and cognitive disorder, memory dysfunction, memory impairment, age-associated memory loss or Down's syndrome. In another embodiment the compounds of the invention are useful for the treatment or alleviation of cognition.

In another embodiment the compounds of the invention are considered useful for treatment, prevention or alleviation of chronic headache, migraine, migraine-related disorders or tension-type headache. In another embodiment the compounds of the invention are considered useful for treatment or alleviation of migraine.

In another embodiment the compounds of the invention are considered useful for treatment, prevention or alleviation of a disease, disorder or condition associated with the heart or skeletal muscle, heart failure, cardiomyopathia, cardiac arrhythmia, cardiac ischaemia or long QT syndrome.

5 In another embodiment the compounds of the invention are considered useful for treatment, prevention or alleviation of an inflammatory disease or condition, inflammatory bowel disease, Crohn's disease, ulcerative colitis or Creutzfeld-Jacobs disease.

In another embodiment the compounds of the invention are considered useful
10 for treatment, prevention or alleviation of asthma, an obstructive or inflammatory airway disease, an airway hyper reactivity, a pneumoconiosis such as aluminosis, anthracosis, asbestosis, chalicosis, ptilosis, siderosis, silicosis, tabacosis and byssinosis, a chronic obstructive pulmonary disease (COPD), exacerbation of airways hyper reactivity or cystic fibrosis. In another embodiment the compounds of the
15 invention are considered useful for treatment or alleviation of asthma.

In another embodiment the compounds of the invention are considered useful for treatment, prevention or alleviation of progressive hearing loss or tinnitus.

In another embodiment the compounds of the invention are considered useful for treatment, prevention or alleviation of an ophthalmic disorder, a drug-dependence
20 or drug-addiction disorder or hyperactive gastric motility.

In another embodiment the compounds of the invention are considered useful for treatment, prevention or alleviation of nocturia, bladder spasms, overactive bladder (OAB), interstitial cystitis (IC) and urinary incontinence. In another embodiment the compounds of the invention are considered useful for treatment or alleviation of urinary
25 incontinence.

Pharmaceutical Compositions

Viewed from one aspect the invention relates to the use of a compound of the invention, or a pharmaceutically-acceptable addition salt thereof, for the manufacture of a pharmaceutical composition for the treatment, prevention or alleviation of a
30 disease or a disorder or a condition of a mammal, including a human, which disease, disorder or condition is responsive to modulation of K_v7 channels.

Viewed from another aspect, the invention provides pharmaceutical compositions comprising a therapeutically-effective amount of a compound of the invention, or a pharmaceutically-acceptable addition salt thereof, together with at least one pharma-
35 ceutically-acceptable carrier or diluent, for the treatment, prevention or alleviation of a disease or a disorder or a condition that is responsive to modulation of K_v7 channels.

While a compound for use according to the invention 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 another embodiment, the invention provides pharmaceutical compositions comprising a compound of the invention, together with one or more pharmaceutically acceptable carriers therefore, and, optionally, other therapeutic and/or prophylactic ingredients, known 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 may be prepared by the skilled person using standard and conventional techniques appropriate for the desired formulation. When desired, compositions adapted to give sustained release of the active ingredient may be employed.

Pharmaceutical compositions of the invention may be those suitable for oral, rectal, bronchial, nasal, pulmonary, 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 which may also act as diluents, flavouring agents, solubilizers, lubricants, suspending agents, binders, preservatives, tablet disintegrating agents, or an encapsulating material.

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

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

The powders and tablets preferably contain from five or ten to about seventy percent of the active compound. Suitable carriers are magnesium carbonate, magnesium stearate, talc, sugar, lactose, pectin, dextrin, starch, gelatin, tragacanth, methylcellulose, sodium carboxymethylcellulose, a low melting 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 homogeneous 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.

5 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
10 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. In addition to the active component such
15 preparations may comprise colorants, flavours, stabilisers, buffers, artificial and natural sweeteners, dispersants, thickeners, solubilizing agents, and the like.

 For topical administration to the epidermis the chemical compound of 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
20 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
25 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
30 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
35 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 compounds 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
5 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.

10 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
15 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.
20

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
25 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, e.g. from about 1 to about 100 mg, or from about 1 to about 10 mg, are
30 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 $\mu\text{g/kg}$ i.v. and 1 $\mu\text{g/kg}$ 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
35 $\mu\text{g/kg}$ to about 10 mg/kg/day i.v., and from about 1 $\mu\text{g/kg}$ to about 100 mg/kg/day p.o.

Methods of Therapy

In another aspect the invention provides a method for the 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 activation of K_v7 channels, and which method comprises administering to such a living animal body, including a human, in need thereof an effective amount of a compound of the invention.

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

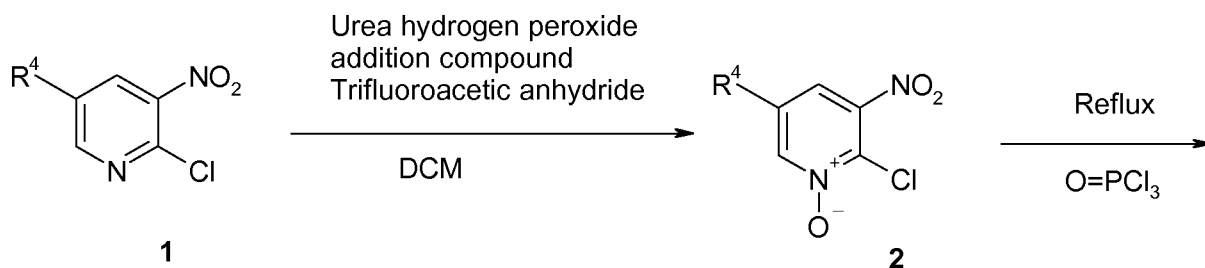
It is at present contemplated that suitable dosage ranges are 0.1 to 2000 milligrams daily, 10-1000 milligrams daily, and especially 30-100 milligrams daily, dependent as usual upon the exact mode of administration, form in which administered, the indication toward which the administration is directed, the subject
10 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 30 mg/kg i.v. and 500 mg/kg p.o. Preferred ranges are from about 0.001 to about 100
15 mg/kg i.v. and from about 0.1 to about 30 mg/kg p.o.

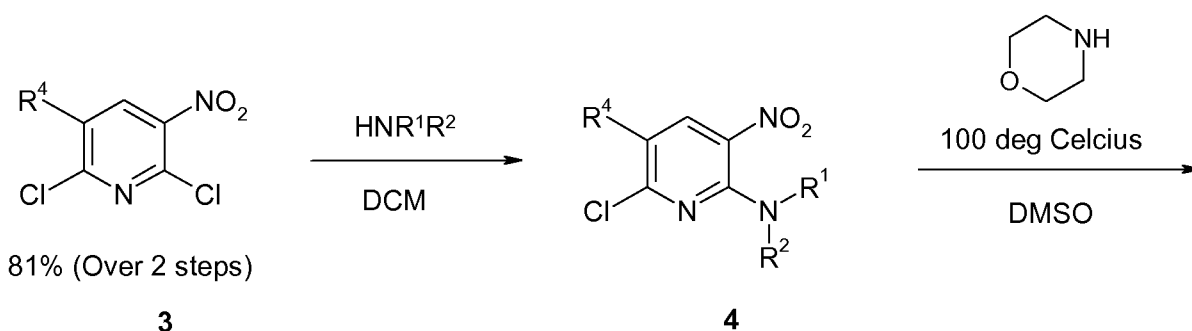
EXAMPLES

The following examples and general procedures refer to intermediate compounds and final products for general Formula (I) identified in the specification and in the synthesis schemes. The preparation of the compounds of general Formula (I) of
20 the present invention is described in detail using the following examples. Occasionally, the reaction may not be applicable as described to each compound included within the disclosed scope of the invention. The compounds for which this occurs will be readily recognised by those skilled in the art. In these cases the reactions can be successfully performed by conventional modifications known to those skilled in the art, which is, by
25 appropriate protection of interfering groups, by changing to other conventional reagents, or by routine modification of reaction conditions. Alternatively, other reactions disclosed herein or otherwise conventional will be applicable to the preparation of the corresponding compounds of the invention. In all preparative methods, all starting materials are known or may easily be prepared from known
30 starting materials.

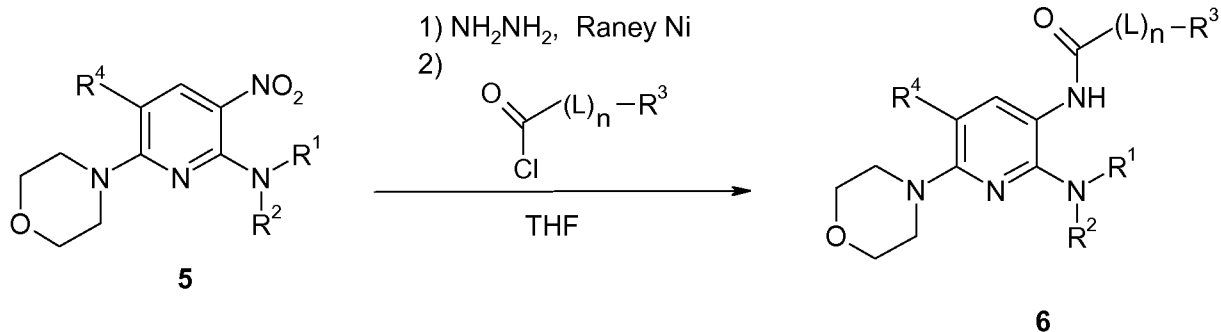
Synthetic scheme:



5



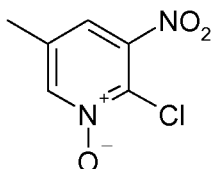
10



By reacting a solution of **1**, wherein R⁴ is as defined above, and urea hydrogen peroxide with trifluoroacetic anhydride, intermediate **2**, wherein R⁴ is as defined above, is obtained. By suspending intermediate **2** in POCl₃ and heating to reflux intermediate **3**, wherein R⁴ is as defined above, is obtained. By allowing intermediate **3** to be reacted with an amine, wherein R¹ and R² are as defined above, intermediate **4** wherein R¹ and R² are as defined above, is obtained. By reacting intermediate **4**, wherein R¹, R² and R⁴ are as defined above, with morpholine intermediate **5** wherein R¹, R² and R⁴ are as defined above, is obtained. In a one pot procedure intermediate **5** wherein R¹, R² and R⁴ are as defined above, is reduced with hydrazine/Raney nickel and subsequently reacted with an acid chloride, wherein L and R³ is as defined above, to provide compound **6**, wherein R¹, R², R⁴, L, n and R³ are as defined above.

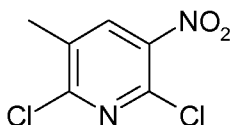
Preparative Examples

2-Chloro-5-methyl-3-nitropyridine-1-oxide (Intermediate)



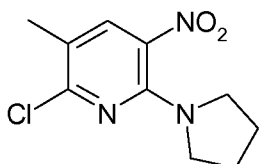
A solution of 2-chloro-5-methyl-5-nitropyridine (10 g; 56.8mmol) and UHP (urea
5 hydrogen peroxide addition compound; 11.2g; 119 mmol) in dichloromethane (250 mL)
was cooled to ca. 0 °C whereafter trifluoroacetic anhydride (16.5 mL; 119 mmol) was
slowly added. The reaction mixture was stirred at 0 °C for 30 min and then left with
stirring at rt. for 36 h. after which the reaction mixture was filtered, poured into water,
extracted with dichloromethane (2x), washed with brine, dried over Na₂SO₄ and
10 concentrated in vacuo to yield 10.7g (quant.) of a yellow solid.
e/z = 189/377 (>95%; LC-MS; ESI⁺); e/z = 189 (>95%; GC-MS; EI⁺)

2,6-Dichloro-3-methyl-5-nitropyridine



15 A suspension of 2-chloro-5-methyl-3-nitropyridine-1-oxide (4.0g; 21.2mmol) was
suspended in POCl₃ (ca. 20 mL) and heated to reflux temperature for three hours. The
reaction mixture was carefully added to prewarmed water, cooled, extracted with ethyl
acetate (3x), dried (Na₂SO₄), filtered and evaporated to 4.5g of a brownish solid.
The crude product was purified by flash column chromatography (add-on-column in
20 DCM; 5% ethyl acetate in heptane) to give 3.56g (81%) of an off-white solid.
e/z = 189 (>95%; GC-MS; EI⁺)

2-Chloro-3-methyl-5-nitro-6-pyrrolidin-1-yl-pyridine



25 To a solution of 2,6-dichloro-3-methyl-5-nitropyridine (2g, 9.7 mmol) in aceto-
nitrile (50 mL) is added triethylamine (4.1 mL; 29 mmol) followed by a slow addition of
pyrrolidine (870 µL, 10.6 mmol) and the reaction mixture is stirred at room temperature
for 3 h. The reaction mixture was then poured into water and acetonitrile was removed
in vacuo. The remaining aqueous phase was extracted with ethyl acetate (3x) and

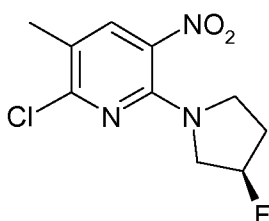
concentrated to yield 2.28g of a redish oil. The crude compound was purified by flash column chromatography (5% ethyl acetate in heptane, loaded with dichloromethane) to yield 1.8 g (77%) of a yellowish oil.

$m/z = 241/243$ (>95%; GC-MS; ESI^+), $m/z = 242/244$ (>95%; LC-MS; ESI^+)

5

In a similar manner was synthesized:

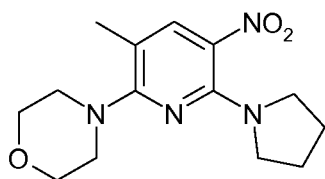
2-chloro-6-((*R*)-3-fluoro-pyrrolidin-1-yl)-3-methyl-5-nitro-pyridine



10 Yield 80% (85% purity), a yellow oil.

$m/z = 260/262$ (85%; LC-MS; ESI^+).

4-(3-Methyl-5-nitro-6-pyrrolidin-1-yl-pyridin-2-yl)-morpholine

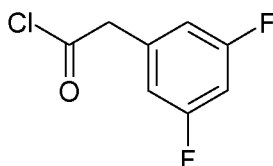


15 To a solution of 2-chloro-3-methyl-5-nitro-6-pyrrolidin-1-yl-pyridine (660 mg; 2.7 mmol) in DMSO (4 mL) was added triethylamine (1 mL) and morpholine (434 μ L; 5 mmol). The reaction mixture was heated to 100°C for ca. 2.5 h.

The reaction mixture was poured into water and extracted with ethylacetate (3x), dried over Na_2SO_4 and evaporated to dryness to yield 880 mg of a brownish oil.

20 $m/z = 293$ ($M+1$; >95%; LC-MS; ESI^+)

(3,5-Difluorophenyl)-acetyl chloride



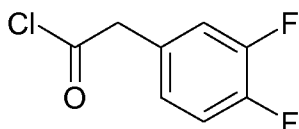
3,5-Difluorophenylacetic acid (47.5 g, 273 mmol) was dissolved in dry DCM
25 (300mL) followed by addition of oxalyl chloride (26.2 mL, 301 mmol). A nitrogen atmosphere was established and dry dimethylformamide (few drops) was added. The

mixture was stirred overnight at rt followed by evaporation *in vacuo* to yield the crude title compound (52.0 g, 100%). The product was used without further purification.

In a similar manner was synthesized :

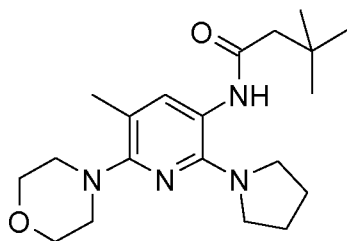
5

(3,4-Difluorophenyl)-acetyl chloride



Example 1

10 3,3-Dimethyl-N-(5-methyl-6-morpholin-4-yl-2-pyrrolidin-1-yl-pyridin-3-yl)-butyramide
(Compound 1.1)



To a solution of 4-(3-methyl-5-nitro-6-pyrrolidin-1-yl-pyridin-2-yl)-morpholine
15 (0.4 g, 1.4 mmol) in tetrahydrofuran (15 mL) was added Raney nickel catalyst (50%
slurry in water; 0.2 mL) and hydrazine monohydrate (202 μ L; 4.1 mmol). The reaction
mixture was kept in a nitrogen atmosphere and stirred at room temperature. The
reaction mixture is filtered over hyflo, the hyflo was rinsed with a little tetrahydrofuran
and the filtered solution was used as such in the next step.

20 To the solution in tetrahydrofuran (max. 0.36 g, 1.4 mmol) was added *t*-butyl-
acetyl chloride (194 μ L, 1.4 mmol). The reaction mixture was then stirred at room
temperature over the weekend whereafter the solution was evaporated to dryness and
purified using reversed phase column chromatography (95:5 $\rightarrow$ 5:95% H₂O:MeCN) to
give 270 mg (54%) pure compound as a white solid.

25 e/z = 361 (M+1; >95%; LC-MS; ESI⁺); mp: 179-180°C

LC-ESI-HRMS of [M+H]⁺ shows 361.2599 Da. Calc. 361.259806 Da.

In a similar manner was synthesized:

No	Structure	Name	LC-ESI-HRMS Meas.	LC-ESI-HRMS Calc.
1.2		2-(3,5-Difluoro-phenyl)-N-(5-methyl-6-morpholin-4-yl-2-pyrrolidin-1-yl-pyridin-3-yl)-acetamide	417.2101	417.2096
1.3		<i>N</i> -[2-((<i>R</i>)-3-Fluoro-pyrrolidin-1-yl)-5-methyl-6-morpholin-4-yl-pyridin-3-yl]-3,3-dimethyl-butamide	379.2504	379.2497
1.4		(<i>S</i>)- <i>N</i> -[2-((<i>R</i>)-3-Fluoro-pyrrolidin-1-yl)-5-methyl-6-morpholin-4-yl-pyridin-3-yl]-2-phenyl-propionamide		
1.5		[2-((<i>R</i>)-3-Fluoro-pyrrolidin-1-yl)-5-methyl-6-morpholin-4-yl-pyridin-3-yl]-carbamic acid ethyl ester	353.1978	353.1983

In a similar manner is synthesized:

5

No	Structure	Name	LC-ESI-HRMS Meas.	LC-ESI-HRMS Calc.
1.6		(<i>S</i>)- <i>N</i> -[2-((<i>R</i>)-3-Fluoro-pyrrolidin-1-yl)-5-methyl-6-morpholin-4-yl-pyridin-3-yl]-2-methyl-butamide		

PHARMACOLOGICAL METHODS

FLIPR-based characterization of K_v7.2+3 modulators

- 10 This experiment determines the ability of a test compound to modulate the activity of K_v7.2+3 channels heterologously expressed in human HEK293 cells. The ability is determined relative to retigabine. The activity is determined using a standard

thallium (I) sensitive assay, e.g. using a fluorometric method in a Fluorescent Image Plate Reader (FLIPR) as described below in more detail.

Full concentration/response curves are generated and EC₅₀ values are calculated based on max values. EC₅₀ values (Effective Concentration) represent the concentration of the test substance, at which 50% of the channel activity is obtained when compared to retigabine control responses. Maximal response determined relative to the reference (retigabine) response is calculated.

METHODS

10 **Cell culture**

Human HEK293 cells over-expressing human K_v7.2+3 are grown in culture medium (DMEM supplemented with 10% foetal bovine serum), in polystyrene culture flasks (175 mm²) in a humidified atmosphere of 5% CO₂ in air, at 37°C. Cell confluence should be 80-90% on day of plating. Cells are rinsed with 4 ml of PBS (phosphate buffered saline) and incubated 2 min with 1 ml of Trypsin-EDTA. After addition of 25 ml of culture medium cells are re-suspended by trituration with a 25 ml pipette.

The cells are seeded at a density of ~3x10⁶ cells/ml (25 µl/well) in black-walled, clear bottom, 384-well plates pre-treated with 0.01 g/l poly-D-lysine (20 µl/well for ≥30 min). Plated cells were allowed to proliferate for 24 h before loading with dye.

20

Loading with BTC-AM

BTC-AM (50 mg, Invitrogen) is added 25.5 µl DMSO. The BTC-AM stock solution (2 mM) is diluted to a final concentration of 2 µM in Cl⁻ free assay buffer (in mM: 140 Na⁺-gluconate, 2.5 K⁺-gluconate, 6 Ca²⁺-gluconate, 1 Mg²⁺ gluconate, 5 glucose, 10 HEPES, pH 7.3) containing 2 µM ouabain, 2 mM amaranth and 1 mM tartrazine.

The culture medium is aspirated from the wells, the cells are washed thrice in Cl⁻ free assay buffer, and 25 µl of the BTC-AM loading solution is added to each well. The cells are incubated at 37°C for 60 min.

30

TI⁺ influx measurements

After the loading period, the TI⁺-sensitive BTC fluorescence signal is measured over time using a FLIPR.

35 **FLIPR settings/Parameters**

Temperature:	Room temp.
First addition:	12 µl test or control compound after 15 sec at a rate of 30 µl/sec and starting height of 20 µl
Second addition:	12 µl stimulus buffer (Cl ⁻ free assay buffer supplemented

with 1 mM Ti_2SO_4 , 5 mM K_2SO_4 as well as the quenchers amaranth (2 mM) and tartrazine (1 mM)) is added after an additional 3 minutes at a rate of 30 $\mu\text{l}/\text{sec}$ and starting height of 30 μl

Reading intervals: First sequence - 3 sec x 5, 2 sec x 24 and 5 sec x 25
Second sequence - 1 sec x 5, 2 sec x 24 and 5 sec x 36

Addition plates (compound plate and stimulus plate) are placed in positions 2 and 3, respectively. Cell plates are placed in position 1 and run using the "KCNQ (two additions)" program. FLIPR will then take the appropriate measurements in accordance with the interval settings above. Fluorescence obtained after stimulation is
5 corrected for the mean basal fluorescence (in Cl^- free assay buffer).

ANALYSIS

Characterization of active substances

Full concentration/response curves are generated and EC_{50} values ("Effective
10 Concentration"; the concentration at which 50% of the channel activity is obtained when compared to retigabine control responses) are calculated based on peak values. Maximal response determined relative to the reference (retigabine) response is calculated.

15 **Tabel 1**

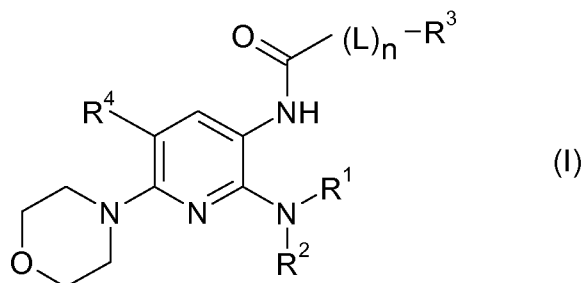
Test Compound	EC_{50} (μM)	Efficacy (%)
11	0.052 ± 0.063	98 ± 14
1.2	$0.00032 \pm 6.9\text{E-}05$	93 ± 1.4
1.3	3.3 ± 2.3	109 ± 1.4
1.4	6.3 ± 1.7	92 ± 11
1.5	13 ± 0.071	68 ± 24

From the foregoing it will be appreciated that, although specific embodiments of the invention have been described herein for purposes of illustration, various modifications may be made without deviating from the spirit and scope of the invention. Accord-
20 ding, the invention is not to be limited as by the appended claims.

The features disclosed in the foregoing description, in the claims and/or in the accompanying drawings, may both separately and in any combination thereof, be material for realising the invention in diverse forms thereof.

CLAIMS

1. A compound of Formula (I)



a stereoisomer or a mixture of its stereoisomers, or a pharmaceutically-acceptable addition salt thereof, or an N-oxide thereof, wherein

R^1 and R^2 , independently of each other, represent C_{1-6} -alkyl; or

R^1 and R^2 , together with the nitrogen to which they are attached, form a heterocyclic ring selected from pyrrolidinyl, 2,5-dihydro-1*H*-pyrrol-1-yl, piperidinyl and morpholinyl, which pyrrolidinyl and piperidinyl is optionally substituted one or more times with a substituent selected from the group consisting of halogen, hydroxy, amino, C_{1-6} -alkyl, trifluoromethyl, C_{1-6} -alkoxy, hydroxy- C_{1-6} -alkyl and C_{1-6} -alkoxy- C_{1-6} -alkyl;

L represents a linker selected from $-CR'R''-$ and $-O-CR'R''-$, wherein R' and R'' , independently of each other, represent hydrogen, C_{1-6} -alkyl or halogen;

n is 0 or 1;

R^3 represents C_{1-6} -alkyl or phenyl, which phenyl is optionally substituted one or more times with substituents selected from C_{1-6} -alkyl, C_{1-6} -alkoxy, halogen and trifluoromethyl; and

R^4 represents C_{1-6} -alkyl.

2. The compound according to claim 1, a stereoisomer or a mixture of its stereoisomers, or a pharmaceutically-acceptable addition salt thereof, or an N-oxide thereof, wherein R^1 and R^2 together with the nitrogen to which they are attached is pyrrolidinyl, which pyrrolidinyl is optionally substituted one or more times with halogen.

3. The compound according to claim 1 or 2, a stereoisomer or a mixture of its stereoisomers, or a pharmaceutically-acceptable addition salt thereof, or an *N*-oxide thereof, wherein *n* is 1 and *L* is $-CR'R''-$, wherein *R'* and *R''*, independently of each other, represents hydrogen or methyl.

5

4. The compound according to any one of the claims 1-3, a stereoisomer or a mixture of its stereoisomers, or a pharmaceutically-acceptable addition salt thereof, or an *N*-oxide thereof, wherein *R*³ represents phenyl, which phenyl is optionally substituted one or more times with halogen.

10

5. The compound according to any one of the claims 1-3, a stereoisomer or a mixture of its stereoisomers, or a pharmaceutically-acceptable addition salt thereof, or an *N*-oxide thereof, wherein *R*³ represents C₁₋₆-alkyl.

15 6. The compound according to any one of the claims 1-5, a stereoisomer or a mixture of its stereoisomers, or a pharmaceutically-acceptable addition salt thereof, or an *N*-oxide thereof, wherein *R*⁴ represents methyl.

7. The compound according to claim 1, which is:

20 3,3-Dimethyl-*N*-(5-methyl-6-morpholin-4-yl-2-pyrrolidin-1-yl-pyridin-3-yl)-butyramide;
2-(3,5-Difluoro-phenyl)-*N*-(5-methyl-6-morpholin-4-yl-2-pyrrolidin-1-yl-pyridin-3-yl)-
acetamide;

N-[2-((*R*)-3-Fluoro-pyrrolidin-1-yl)-5-methyl-6-morpholin-4-yl-pyridin-3-yl]-3,3-dimethyl-
butyramide;

25 (*S*)-*N*-[2-((*R*)-3-Fluoro-pyrrolidin-1-yl)-5-methyl-6-morpholin-4-yl-pyridin-3-yl]-2-phenyl-
propionamide;

[2-((*R*)-3-Fluoro-pyrrolidin-1-yl)-5-methyl-6-morpholin-4-yl-pyridin-3-yl]-carbamic acid
ethyl ester;

(*S*)-*N*-[2-((*R*)-3-Fluoro-pyrrolidin-1-yl)-5-methyl-6-morpholin-4-yl-pyridin-3-yl]-2-methyl-
30 butyramide;

or a stereoisomer or a mixture of its stereoisomers, or a pharmaceutically-acceptable
addition salt thereof, or an *N*-oxide thereof.

8. A pharmaceutical composition comprising a therapeutically effective amount of
35 the compound according to any one of the claims 1-7, a stereoisomer or a mixture of its
stereoisomers, or a pharmaceutically-acceptable addition salt thereof, or an *N*-oxide
thereof.

9. Use of the compound according to any one of the claims 1-7, a stereoisomer or a mixture of its stereoisomers, or a pharmaceutically-acceptable addition salt thereof, or an *N*-oxide thereof, for the manufacture of a pharmaceutical composition.

5 10. Use of the compound according to any one of the claims 1-7, a stereoisomer or a mixture of its stereoisomers, or a pharmaceutically-acceptable addition salt thereof, or an *N*-oxide thereof, for the manufacture of a pharmaceutical composition for the treatment, prevention or alleviation of a disease or a disorder responsive to activation of K_v7 channels.

10

11. The use according to claim 10, wherein the disease, disorder or condition is pain, neurodegenerative disorders, migraine, bipolar disorders, mania, epilepsy, convulsions, seizures and seizure disorders, anxiety, depression, schizophrenia and urinary incontinence.

15

12. The use according to claim 10, wherein the disease, disorder or condition is pain, mild, moderate or severe pain, acute, chronic or recurrent pain, neuropathic pain, pain caused by migraine, postoperative pain, phantom limb pain, neuropathic pain, chronic headache, tension type headache, central pain, pain related to diabetic neuropathy, to
20 post therapeutic neuralgia, or to peripheral nerve injury.

13. A compound according to any one of the claims 1-7, a stereoisomer or a mixture of its stereoisomers, or a pharmaceutically-acceptable addition salt thereof, or an *N*-oxide thereof, for use as a medicament.

25

14. A compound according to any one of the claims 1-7, a stereoisomer or a mixture of its stereoisomers, or a pharmaceutically-acceptable addition salt thereof, or an *N*-oxide thereof, for use in the treatment, prevention or alleviation of a disease or a disorder or a condition responsive to activation of K_v7 channels.

30

15. A method of treatment or alleviation of a disease or a disorder or a condition responsive to activation of K_v7 channels, which method comprises the step of administering to such a living animal body in need thereof, a therapeutically effective amount of the compound according to any one of the claims 1-7, a stereoisomer or a
35 mixture of its stereoisomers, or a pharmaceutically-acceptable addition salt thereof, or an *N*-oxide thereof.

INTERNATIONAL SEARCH REPORT

International application No

PCT/EP2010/051839

A. CLASSIFICATION OF SUBJECT MATTER

INV. A61P13/02 A61P25/00 A61K31/4439 C07D213/75
ADD.

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

C07D A61K 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, 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.
A	WO 2006/092143 A1 (LUNDBECK & CO AS H [DK]; TORNOEE CHRISTIAN WENZEL [DK]; KHANZHIN NIKOL) 8 September 2006 (2006-09-08) cited in the application claim 1	1-15
A	WO 2005/087754 A1 (LUNDBECK & CO AS H [DK]; WENZEL TORNOEE CHRISTIAN [DK]; ROTTLAENDER MA) 22 September 2005 (2005-09-22) cited in the application claim 1 ----- -/--	1-15

☒ 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

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"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

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"G" document member of the same patent family

Date of the actual completion of the international search

4 May 2010

Date of mailing of the international search report

17/05/2010

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Lewis, Sara

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2010/051839

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WU Y-J ET AL: "RECENT DEVELOPMENTS ON KCNQ POTASSIUM CHANNEL OPENERS" CURRENT MEDICINAL CHEMISTRY, BENTHAM SCIENCE PUBLISHERS BV, BE, vol. 12, no. 4, 1 January 2005 (2005-01-01), pages 453-460, XP009049808 ISSN: 0929-8673 page 456 - page 457; tables 1-2 -----	1-15

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.

PCT/EP2010/051839

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