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(54) **Title**: NOVEL 2,3-DIAMINO-QUINAZOLINONE DERIVATIVES AND THEIR MEDICAL USE

(57) **Abstract**: The present invention relates to novel 2,3-diamino-quinazolinone derivatives having medical utility, to use of the derivatives for the manufacture of a medicament, to pharmaceutical compositions comprising the derivatives, and to methods of treating a disorder, disease or a condition responsive to activation of K_V7 channels.

NOVEL 2,3-DIAMINO-QUINAZOLINONE DERIVATIVES AND THEIR MEDICAL USE

TECHNICAL FIELD

This invention relates to novel 2,3-diamino-quinazolinone derivatives having medical utility, to use of the 2,3-diamino-quinazolinone derivatives of the invention for the manufacture of a medicament, to pharmaceutical compositions comprising the 2,3-diamino-quinazolinone derivatives of the invention, and to methods of treating a disorder, disease or a condition of a subject, which disorder, disease or condition is responsive to activation of K_v7 channels.

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.

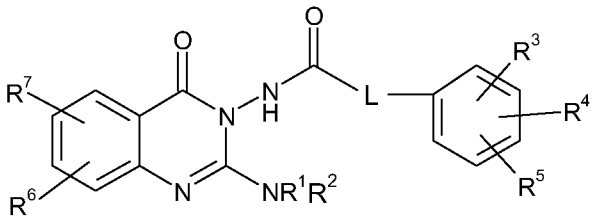
Recently a new family of potassium channels, the KCNQ channels, now also designated K_v7, of which $K_v7.1$-$K_v7.5$ have currently been characterised, has attracted attention as target for therapeutic development.

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.

SUMMARY OF THE INVENTION

The present invention discloses novel 2,3-diamino-quinazolinone compounds having medical utility for combating disorders, diseases or conditions responsive to activation of K_v7 channels.

In one embodiment the present invention provides 2,3-diamino-quinazolinone compounds of formula (I)



(I)

a stereoisomer or a mixture of its stereoisomers, or a pharmaceutically-acceptable addition salt thereof, or an N-oxide thereof, wherein L, R^1, R^2, R^3, R^4, R^5, R^6 and R^7 are as 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 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.

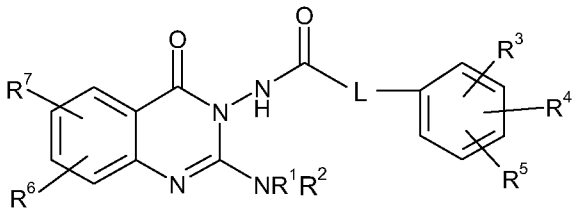
In another embodiment the invention relates to the use of a compound of the invention, a stereoisomer or a mixture of its stereoisomers, or a pharmaceutically-acceptable addition salt thereof, or an N-oxide thereof, for the manufacture of a pharmaceutical composition for the treatment, prevention or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

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 2,3-diamino-quinazolinone compounds of formula (I)



(I)

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

L represents a linker selected from -(CR'R'')$_2$–, –CR'R''–S–, –CR'R''-O – or  ; wherein R' and R'', independently of each other, represent hydrogen, C_{1-6}-alkyl or halogen;

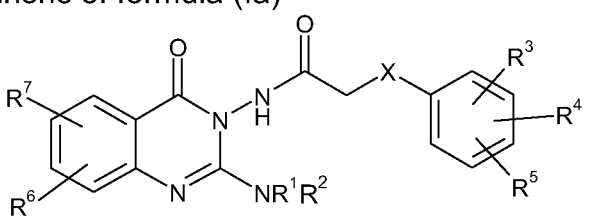
R^1 and R^2, independently of each other, represent C_{1-6}-alkyl, hydroxy-C_{1-6}-alkyl-, C_{1-6}-alkoxy-C_{1-6}-alkyl-, phenyl, phenyl-C_{1-6}-alkyl-, which phenyl is optionally substituted with one or two times with a substituent selected from the group consisting of C_{1-6}-alkoxy, halogen and cyano; 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, thiazolidinyl, piperidinyl, piperazinyl and morpholinyl, which pyrrolidinyl, piperidinyl, piperazinyl and morpholinyl 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-;

R^3, R^4 and R^5, independently of each other, represent hydrogen, C_{1-6}-alkyl, halogen, trihalomethyl, hydroxy, C_{1-6}-alkoxy, trifluoromethoxy, amino, cyano or nitro; and

R^6 and R^7, independently of each other, represent hydrogen, C_{1-6}-alkyl, halogen, trihalomethyl, hydroxy, C_{1-6}-alkoxy, trifluoromethoxy, amino, nitro, cyano or phenyl.

In another embodiment of the invention the compound of the invention is a 2,3-diamino-quinazolinone of formula (Ia)

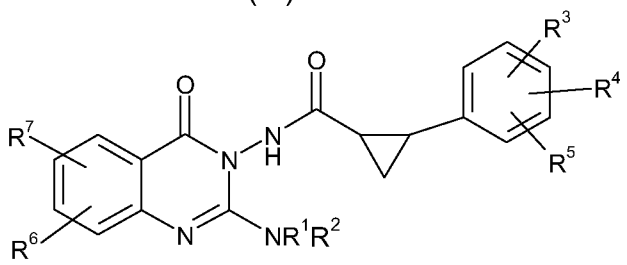


(Ia)

a stereoisomer or a mixture of its stereoisomers, or a pharmaceutically-acceptable addition salt thereof, or an N-oxide thereof, wherein X represents -CR'R''-, –S–, or

–O–, wherein R' and R'', independently of each other, represent hydrogen, C_{1-6}-alkyl or halogen, and R^1, R^2, R^3, R^4, R^5, R^6 and R^7 are as defined above.

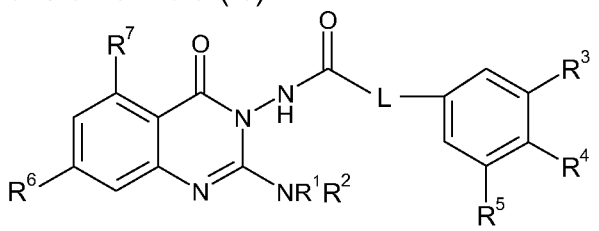
In another embodiment of the invention the compound of the invention is a 2,3-diamino-quinazolinone of formula (Ib)



(Ib)

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, R^5, R^6 and R^7 are as defined above.

In another embodiment of the invention the compound of the invention is a 2,3-diamino-quinazolinone of formula (Ic)



(Ic)

a stereoisomer or a mixture of its stereoisomers, or a pharmaceutically-acceptable addition salt thereof, or an N-oxide thereof, wherein L, R^1, R^2, R^3, R^4, R^5, R^6 and R^7 are as defined above.

In another embodiment of the invention, in formula (I) or (Ic), L represents -(CR'R'')$_2$-, wherein R' and R'', independently of each other, represent hydrogen, C_{1-6}-alkyl or halogen. In another embodiment L represents -(CR'R'')$_2$-, wherein R' and R'' represents hydrogen. In another embodiment L represents -(CR'R'')$_2$-, wherein R' and R'', independently of each other, represent hydrogen or C_{1-6}-alkyl. In another embodiment L represents -(CR'R'')$_2$-, wherein R' and R'' represents C_{1-6}-alkyl. In another embodiment L represents -(CR'R'')$_2$-, wherein R' and R'' independently of each other, represents hydrogen or halogen. In another embodiment L represents -(CR'R'')$_2$-, wherein R' and R'' independently of each independently of each other, represent C_{1-6}-alkyl or halogen. In another embodiment L represents -CH_2-(CR'R'')$_2$-, wherein R' and R'', independently of each other, represent hydrogen, C_{1-6}-alkyl or halogen. In another embodiment L represents -CH_2-CH_2-. In another embodiment L represents -CH_2-(CR'R'')$_2$-, wherein R' and R'', independently of each other, represent hydrogen or

C_{1-6}-alkyl. In another embodiment L represents -CH_2-(CR'R'')$_2$-, wherein R' and R'' represents C_{1-6}-alkyl. In another embodiment L represents -CH_2-(CR'R'')$_2$-, wherein R' and R'' independently of each other, represents hydrogen or halogen. In another embodiment L represents -CH_2-(CR'R'')$_2$-, wherein R' and R'' independently of each independently of each other, represent C_{1-6}-alkyl or halogen.

In another embodiment of the invention, in formula (I) or (Ic), L represents -CR'R''-S-, wherein R' and R'', independently of each other, represent hydrogen, C_{1-6}-alkyl or halogen. In another embodiment L represents -CR'R''-S-, wherein R' and R'', independently of each other, represent hydrogen or C_{1-6}-alkyl. In another embodiment L represents –CH_2-S-. In another embodiment L represents -CR'R''-S-, wherein R' and R'' represents C_{1-6}-alkyl. In another embodiment L represents -CR'R''-S-, wherein R' and R'' independently of each other, represents hydrogen or halogen. In another embodiment L represents -CR'R''-S-, wherein R' and R'' independently of each independently of each other, represent C_{1-6}-alkyl or halogen.

In another embodiment of the invention, in formula (I) or (Ic), L represents -CR'R''-O-, wherein R' and R'', independently of each other, represent hydrogen, C_{1-6}-alkyl or halogen. In another embodiment L represents –CR'R''-O-, wherein R' and R'', independently of each other, represent hydrogen or C_{1-6}-alkyl. In another embodiment L represents –CH_2-O-. In another embodiment L represents –CR'R''-O-, wherein R' and R'' represents C_{1-6}-alkyl. In another embodiment L represents –CR'R''-O-, wherein R' and R'' independently of each other, represents hydrogen or halogen. In another embodiment L represents –CR'R''-O-, wherein R' and R'' independently of each independently of each other, represent C_{1-6}-alkyl or halogen.

In another embodiment of the invention, in formula (I) or (Ic), L represents

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In another embodiment of the invention, in formula (Ia), X represents -CR'R''-, wherein R' and R'', independently of each other, represent hydrogen, C_{1-6}-alkyl or halogen. In another embodiment X represents –CH_2-. In another embodiment X represents -CR'R''-, wherein R' and R'', independently of each other, represent hydrogen or C_{1-6}-alkyl. In another embodiment X represents -CR'R''-, wherein R' and R'' represents C_{1-6}-alkyl. In another embodiment X represents -CR'R''-, wherein R' and R'' independently of each other, represents hydrogen or halogen. In another embodiment X represents -CR'R''-, wherein R' and R'' independently of each independently of each other, represent C_{1-6}-alkyl or halogen.

In another embodiment of the invention, in formula (Ia), X represents -S-.

In another embodiment of the invention, in formula (Ia), X represents -O-.

In another embodiment of the invention, in formula (I), (Ia), (Ib) or (Ic), R^1 and R^2, independently of each other, represent C_{1-6}-alkyl, hydroxy-C_{1-6}-alkyl-, C_{1-6}-alkoxy-

C_{1-6}-alkyl-, phenyl or phenyl-C_{1-6}-alkyl-, which phenyl is optionally substituted with one or two times with a substituent selected from the group consisting of C_{1-6}-alkoxy, halogen and cyano. In another embodiment, R^1 and R^2, independently of each other, represent C_{1-6}-alkyl, hydroxy-C_{1-6}-alkyl-, C_{1-6}-alkoxy-C_{1-6}-alkyl- or phenyl-C_{1-6}-alkyl-, which phenyl is optionally substituted with one or two times with a substituent selected from the group consisting of C_{1-6}-alkoxy, halogen and cyano. In another embodiment R^1 and R^2, independently of each other, represent C_{1-6}-alkyl, C_{1-6}-alkoxy-C_{1-6}-alkyl- or phenyl-C_{1-6}-alkyl-, which phenyl is optionally substituted with one or two times with a substituent selected from the group consisting of C_{1-6}-alkoxy, halogen and cyano. In another embodiment R^1 and R^2, independently of each other, represent C_{1-6}-alkyl, C_{1-6}-alkoxy-C_{1-6}-alkyl-, phenyl-C_{1-6}-alkyl-. In another embodiment R^1 and R^2 both represent C_{1-6}-alkyl. In another embodiment R^1 and R^2 both represent methyl. In another embodiment R^1 and R^2, independently of each other represent methyl and ethyl. In another embodiment R^1 and R^2, independently of each other represent methyl and propyl. In another embodiment R^1 and R^2, independently of each other represent methyl and isopropyl. In another embodiment R^1 and R^2, independently of each other, represent C_{1-6}-alkyl and C_{1-6}-alkoxy-C_{1-6}-alkyl. In another embodiment R^1 and R^2, independently of each other, represent methyl and methoxyethyl. In another embodiment R^1 and R^2, independently of each other, represent C_{1-6}-alkyl, and phenyl-C_{1-6}-alkyl-. In another embodiment R^1 and R^2, independently of each other, represent C_{1-6}-alkyl, and benzyl. In another embodiment R^1 and R^2, independently of each other, represent methyl and benzyl.

In another embodiment of the invention, in formula (I), (Ia), (Ib) or (Ic), 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, thiazolidinyl, piperidinyl, piperazinyl and morpholinyl, which pyrrolidinyl, piperidinyl, piperazinyl and morpholinyl 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 of the invention, in formula (I), (Ia), (Ib) or (Ic), 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 and trifluoromethyl. 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 and trifluoromethyl. 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 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 and trifluoromethyl. 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), (Ia), (Ib) or (Ic), R^1 and R^2, together with the nitrogen to which they are attached, represent 2,5-dihydro-1*H*-pyrrol-1-yl.

In another embodiment of the invention, in formula (I), (Ia), (Ib) or (Ic), R^1 and R^2, together with the nitrogen to which they are attached, represent thiazolidinyl.

In another embodiment of the invention, in formula (I), (Ia), (Ib) or (Ic), 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 of the invention, in formula (I), (Ia), (Ib) or (Ic), R^1 and R^2, together with the nitrogen to which they are attached, represent piperazinyl 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 of the invention, in formula (I), (Ia), (Ib) or (Ic), R^1 and R^2, together with the nitrogen to which they are attached, represent morpholinyl, 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 morpholinyl. In another embodiment R^1 and R^2, together with the nitrogen to which they are attached, represent morpholinyl 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 of the invention, in formula (I), (Ia), (Ib) or (Ic), R^3, R^4 and R^5, independently of each other, represent hydrogen, C_{1-6}-alkyl, halogen, trihalomethyl, hydroxy, C_{1-6}-alkoxy, trifluoromethoxy, amino, cyano or nitro. In another embodiment R^3, R^4 and R^5, independently of each other, represent hydrogen, C_{1-6}-alkyl, halogen, trihalomethyl or C_{1-6}-alkoxy. In another embodiment R^3, R^4 and R^5, independently of each other, represent hydrogen, C_{1-6}-alkyl, halogen, trifluoromethyl or C_{1-6}-alkoxy. In another embodiment R^3, R^4 and R^5, independently of each other, represent hydrogen, C_{1-6}-alkyl or halogen. In another embodiment R^3, R^4 and R^5, independently of each other, represent hydrogen or C_{1-6}-alkyl. In another embodiment R^3, R^4 and R^5, independently of each other, represent hydrogen or halogen. In another embodiment all of R^3, R^4 and R^5 represent hydrogen. In another embodiment, two of R^3, R^4 and R^5 represent hydrogen and the remaining one of R^3, R^4 and R^5 represent halogen. In another embodiment, two of R^3, R^4 and R^5 represent hydrogen and the remaining one of R^3, R^4 and R^5 represent fluoro. In another embodiment, two of R^3, R^4 and R^5 represent hydrogen and the remaining of R^3, R^4 and R^5 represent chloro. In another embodiment, two of R^3, R^4 and R^5 represent hydrogen and the remaining one of R^3, R^4 and R^5 represent C_{1-6}-alkyl. In another embodiment, two of R^3, R^4 and R^5 represent halogen and the remaining one of R^3, R^4 and R^5 represent hydrogen.

In another embodiment of the invention, in formula (Ic), R^3 represents halogen and R^4 and R^5 represent hydrogen. In another embodiment R^3 represents fluoro and R^4 and R^5 represent hydrogen. In another embodiment R^3 represents chloro and R^4 and R^5 represent hydrogen. In another embodiment R^4 represents halogen or C_{1-6}-alkyl and R^3 and R^5 represent hydrogen. In another embodiment R^5 represents halogen and R^3 and R^4 represent hydrogen. In another embodiment R^3 and R^5 represent halogen and R^4 represent hydrogen. In another embodiment R^4 represents C_{1-6}-alkyl R^3 and R^5 represent hydrogen.

In another embodiment of the invention, in formula (I), (Ia), (Ib) or (Ic), R^6 and R^7, independently of each other, represent hydrogen, C_{1-6}-alkyl, halogen, trihalomethyl, hydroxy, C_{1-6}-alkoxy, trifluoromethoxy, amino, nitro, cyano or phenyl. In another embodiment R^6 and R^7, independently of each other, represent hydrogen, C_{1-6}-alkyl, halogen, trihalomethyl, C_{1-6}-alkoxy, trifluoromethoxy or cyano. In another embodiment R^6 and R^7, independently of each other, represent hydrogen, C_{1-6}-alkyl, halogen, trifluoromethyl, C_{1-6}-alkoxy, trifluoromethoxy or cyano. In another embodiment R^6 and R^7, independently of each other, represent hydrogen or halogen. In another embodiment R^6 and R^7 both represent hydrogen. In another embodiment R^6 and R^7 both represent halogen. In another embodiment R^6 and R^7 both represent fluoro.

In another embodiment of the invention, in formula (Ic), R^6 represents halogen and R^7 represents hydrogen. In another embodiment, R^6 represents fluoro and R^7 represents hydrogen. In another embodiment, R^6 represents hydrogen and R^7

represents halogen. In another embodiment, R^6 represents hydrogen and R^7 represents fluoro. In another embodiment, R^6 and R^7 represent halogen. In another embodiment, R^6 and R^7 represent fluoro. In another embodiment, R^6 and R^7 represent hydrogen.

In another embodiment of the invention, in formula (I), L represent $-(CH_2)_2-$, R^1 and R^2, together with the nitrogen to which they are attached, form a pyrrolidinyl ring, R^3, R^4 and R^5, independently of each other, represent hydrogen or halogen, and R^6 and R^7, independently of each other, represent hydrogen or halogen.

In another embodiment of the invention, in formula (Ia), X represent $-CH_2-$, R^1 and R^2, together with the nitrogen to which they are attached, form a pyrrolidinyl ring, R^3, R^4 and R^5, independently of each other, represent hydrogen or halogen, and R^6 and R^7, independently of each other, represent hydrogen or halogen.

In another embodiment of the invention, in formula (Ic), L represent $-(CH_2)_2-$, R^1 and R^2, together with the nitrogen to which they are attached, form a pyrrolidinyl ring, one of R^3 and R^5 represent halogen and the remaining of R^3, R^4 and R^5 represent hydrogen; R^6 and R^7, independently of each other, represent hydrogen or halogen.

In another embodiment of the invention, in formula (Ic), L represent $-(CH_2)_2-$, R^1 and R^2, together with the nitrogen to which they are attached, form a pyrrolidinyl ring, one of R^3 and R^5 represent halogen and the remaining of R^3, R^4 and R^5 represent hydrogen; and one of R^6 and R^7, represent halogen and the remaining of R^6 and R^7 represent hydrogen.

In another embodiment of the invention, in formula (Ic), L represent $-(CH_2)_2-$, R^1 and R^2, together with the nitrogen to which they are attached, form a pyrrolidinyl ring, R^3 and R^5 represent halogen and the remaining of R^3, R^4 and R^5 represent hydrogen; and represent and R^6 and R^7, independently of each other, represent hydrogen or halogen.

In another embodiment of the invention, in formula (Ic), L represent $-(CH_2)_2-$, R^1 and R^2, together with the nitrogen to which they are attached, form a pyrrolidinyl ring, R^3 and R^5 represent halogen and the remaining or R^3, R^4 and R^5 represent hydrogen; and R^6 and R^7 halogen.

In another embodiment of the invention, in formula (Ic), L represent $-(CH_2)_2-$, R^1 and R^2, together with the nitrogen to which they are attached, form a pyrrolidinyl ring, all of R^3, R^4 and R^5 represent hydrogen; and R^6 and R^7, independently of each other, represent hydrogen or halogen.

In another embodiment of the invention, in formula (Ic), L represent $-(CH_2)_2-$, R^1 and R^2, together with the nitrogen to which they are attached, form a pyrrolidinyl ring, all of R^3, R^4, R^5, R^6 and R^7 represent hydrogen.

In another embodiment of the invention, in formula (I), L represent $-CH_2-S-$, R^1 and R^2, together with the nitrogen to which they are attached, form a pyrrolidinyl ring,

R^3, R^4 and R^5, independently of each other, represent hydrogen, C_{1-6}-alkyl or halogen, and R^6 and R^7, independently of each other, represent hydrogen or halogen.

In another embodiment of the invention, in formula (Ia), X represent –S–, R^1 and R^2, together with the nitrogen to which they are attached, form a pyrrolidinyl ring, R^3, R^4 and R^5, independently of each other, represent hydrogen, C_{1-6}-alkyl or halogen, and R^6 and R^7 represent hydrogen.

In another embodiment of the invention, in formula (Ic), L represent -CH_2–S-, R^1 and R^2, together with the nitrogen to which they are attached, form a pyrrolidinyl ring, R^4 represent hydrogen, C_{1-6}-alkyl or halogen, and R^6 and R^7 represent hydrogen.

In another embodiment of the invention, in formula (I), L represent -CH_2–O-, R^1 and R^2, together with the nitrogen to which they are attached, form a pyrrolidinyl ring, R^3, R^4 and R^5, independently of each other, represent hydrogen or halogen, and R^6 and R^7, independently of each other, represent hydrogen or halogen.

In another embodiment of the invention, in formula (Ia), X represent –O–, R^1 and R^2, together with the nitrogen to which they are attached, form a pyrrolidinyl ring, R^3, R^4 and R^5, independently of each other, represent hydrogen or halogen, and R^6 and R^7, independently of each other, represent hydrogen or halogen.

In another embodiment of the invention, in formula (Ic), L represent -CH_2–O–, R^1 and R^2, together with the nitrogen to which they are attached, form a pyrrolidinyl ring, R^3, R^4 and R^5, independently of each other, represent hydrogen or halogen, and R^6 and R^7, independently of each other, represent hydrogen or halogen.

In another embodiment of the invention, in formula (I) or (Ic), L represent -CH_2–O–, R^1 and R^2, together with the nitrogen to which they are attached, form a pyrrolidinyl ring, and R^3, R^4, R^5, R^6 and R^7 represent hydrogen.

In another embodiment of the invention, in formula (I), L represent -CH_2–$CH(CH_3)$–, R^1 and R^2, together with the nitrogen to which they are attached, form a pyrrolidinyl ring, R^3, R^4 and R^5, independently of each other, represent hydrogen or halogen, and R^6 and R^7, independently of each other, represent hydrogen or halogen.

In another embodiment of the invention, in formula (Ia), X represent –$CH(CH_3)$–, R^1 and R^2, together with the nitrogen to which they are attached, form a pyrrolidinyl ring, R^3 and R^4, independently of each other, represent halogen, and the remaining of R^3, R^4 and R^5 represent hydrogen, and R^6 and R^7, independently of each other, represent hydrogen or halogen.

In another embodiment of the invention, in formula (Ic), L represent -CH_2–$CH(CH_3)$–, R^1 and R^2, together with the nitrogen to which they are attached, form a pyrrolidinyl ring, R^3 and R^4, independently of each other, represent halogen, and the remaining of R^3, R^4 and R^5 represent hydrogen, and R^6 and R^7, both represent hydrogen or halogen.

In another embodiment of the invention, in formula (I), L represent -$(CH_2)_2$–, R^1 and R^2, independently of each other, represent C_{1-6}-alkyl or C_{1-6}-alkoxy-C_{1-6}-alkyl-, R^3, R^4 and R^5, independently of each other, represent hydrogen or halogen, and R^6 and R^7, independently of each other, represent hydrogen or halogen.

In another embodiment of the invention, in formula (Ic), L represent -$(CH_2)_2$–, R^1 and R^2, independently of each other, represent C_{1-6}-alkyl or C_{1-6}-alkoxy-C_{1-6}-alkyl-, R^3 represents halogen, and R^6 and R^7 represent hydrogen.

In another embodiment of the invention, in formula (I), L represent -$(CH_2)_2$–, R^1 and R^2, independently of each other, represent C_{1-6}-alkyl, or phenyl-C_{1-6}-alkyl-, R^3, R^4 and R^5, independently of each other, represent hydrogen or halogen, and R^6 and R^7, independently of each other, represent hydrogen or halogen.

In another embodiment of the invention, in formula (Ia), X represent -CH_2–, R^1 and R^2, independently of each other, represent C_{1-6}-alkyl, or benzyl; R^3, R^4 and R^5, independently of each other, represent hydrogen or halogen, and R^6 and R^7, independently of each other, represent hydrogen or halogen.

In another embodiment of the invention, in formula (Ic), L represent -$(CH_2)_2$–, R^1 and R^2, independently of each other, represent C_{1-6}-alkyl, or benzyl; R^3 and R^5, independently of each other, represent halogen, and the remaining of R^3, R^4 and R^5 represent hydrogen, and R^6 and R^7 represent hydrogen.

In another embodiment of the invention, in formula (I), L represent -$(CH_2)_2$–, R^1 and R^2 both represent C_{1-6}-alkyl, R^3, R^4 and R^5, independently of each other, represent hydrogen or halogen, and R^6 and R^7, independently of each other, represent hydrogen or halogen.

In another embodiment of the invention, in formula (Ia), X represent -CH_2–, R^1 and R^2 both represent C_{1-6}-alkyl, one of R^3, R^4 and R^5 represent halogen and the remaining of R^3, R^4 and R^5 represent hydrogen, and R^6 and R^7, independently of each other, represent hydrogen or halogen.

In another embodiment of the invention, in formula (Ic), L represent -$(CH_2)_2$–, R^1 and R^2 both represent C_{1-6}-alkyl, R^3 represent halogen, and R^6 and R^7, independently of each other, represent hydrogen or halogen.

In another embodiment of the invention, in formula (Ib), R^1 and R^2, together with the nitrogen to which they are attached, form a pyrrolidinyl ring, R^3, R^4 and R^5, independently of each other, represent hydrogen or halogen, and R^6 and R^7, independently of each other, represent hydrogen or halogen.

In another embodiment of the invention, in formula (Ib), R^1 and R^2, together with the nitrogen to which they are attached, form a pyrrolidinyl ring, R^3 represents halogen, and R^6 and R^7, independently of each other, represent hydrogen or halogen.

In another embodiment of the invention, in formula (Ib), R^1 and R^2 both represent C_{1-6}-alkyl, R^3, R^4 and R^5, independently of each other, represent hydrogen or halogen, and R^6 and R^7, independently of each other, represent hydrogen or halogen.

In another embodiment of the invention, in formula (Ib), R^1 and R^2 both represent C_{1-6}-alkyl, R^3 represents halogen, and one of R^6 and R^7 represent halogen and the other one of R^6 and R^7 represent hydrogen.

In another embodiment of the invention, in formula (Ib), R^1 and R^2 both represent C_{1-6}-alkyl, R^3 represents halogen, and R^6 and R^7 both represent halogen.

In another embodiment of the invention the compound of the invention is:

N-(7-Fluoro-4-oxo-2-pyrrolidin-1-yl-4*H*-quinazolin-3-yl)-3-(3-fluoro-phenyl)-propionamide;

3-(3-Fluoro-phenyl)-*N*-{2-[(2-methoxy-ethyl)-methyl-amino]-4-oxo-4*H*-quinazolin-3-yl}-propionamide;

N-[2-(Benzyl-methyl-amino)-4-oxo-4*H*-quinazolin-3-yl]-3-(3-fluoro-phenyl)-propionamide;

N-[2-(Benzyl-methyl-amino)-4-oxo-4*H*-quinazolin-3-yl]-3-(3,5-difluoro-phenyl)-propionamide;

3-(3-Fluoro-phenyl)-*N*-(4-oxo-2-pyrrolidin-1-yl-4*H*-quinazolin-3-yl)-propionamide;

N-(4-Oxo-2-pyrrolidin-1-yl-4*H*-quinazolin-3-yl)-3-phenyl-propionamide;

N-(2-Dimethylamino-7-fluoro-4-oxo-4*H*-quinazolin-3-yl)-3-(3-fluoro-phenyl)-propionamide;

N-(4-Oxo-2-pyrrolidin-1-yl-4*H*-quinazolin-3-yl)-2-phenylsulfanyl-acetamide;

N-(4-Oxo-2-pyrrolidin-1-yl-4*H*-quinazolin-3-yl)-2-phenoxy-acetamide;

N-(5-Fluoro-4-oxo-2-pyrrolidin-1-yl-4*H*-quinazolin-3-yl)-3-(3-fluoro-phenyl)-propionamide;

2-(4-Fluoro-phenylsulfanyl)-*N*-(4-oxo-2-pyrrolidin-1-yl-4*H*-quinazolin-3-yl)-acetamide;

N-(5,7-Difluoro-4-oxo-2-pyrrolidin-1-yl-4*H*-quinazolin-3-yl)-3-(3-fluoro-phenyl)-propionamide;

2-(4-tert-Butyl-phenylsulfanyl)-*N*-(4-oxo-2-pyrrolidin-1-yl-4*H*-quinazolin-3-yl)-acetamide;

N-[5,7-Difluoro-2-(isopropyl-methyl-amino)-4-oxo-4*H*-quinazolin-3-yl]-3-(3-fluoro-phenyl)-propionamide;

N-(5,7-Difluoro-4-oxo-2-pyrrolidin-1-yl-4*H*-quinazolin-3-yl)-3-(3,5-difluoro-phenyl)-propionamide;

(S)-*N*-(5,7-Difluoro-4-oxo-2-pyrrolidin-1-yl-4*H*-quinazolin-3-yl)-3-phenyl-butyramide;

3-(4-Chloro-phenyl)-*N*-(4-oxo-2-pyrrolidin-1-yl-4*H*-quinazolin-3-yl)-butyramide;

3-(3-Fluoro-phenyl)-*N*-(4-oxo-2-pyrrolidin-1-yl-4*H*-quinazolin-3-yl)-butyramide;

cis-2-(4-Chloro-phenyl)-cyclopropanecarboxylic acid (2-dimethylamino-7-fluoro-4-oxo-4*H*-quinazolin-3-yl)-amide;

cis-2-(4-Chloro-phenyl)-cyclopropanecarboxylic acid [5,7-difluoro-2-(isopropyl-methyl-

amino)-4-oxo-4*H*-quinazolin-3-yl]-amide;
cis-2-(4-Chloro-phenyl)-cyclopropanecarboxylic acid (5,7-difluoro-4-oxo-2-pyrrolidin-1-yl-4*H*-quinazolin-3-yl)-amide;
cis-2-(4-Chloro-phenyl)-cyclopropanecarboxylic acid [2-(ethyl-methyl-amino)-7-fluoro-4-oxo-4*H*-quinazolin-3-yl]-amide;
cis-2-(4-Chloro-phenyl)-cyclopropanecarboxylic acid [7-fluoro-2-(isopropyl-methyl-amino)-4-oxo-4*H*-quinazolin-3-yl]-amide;
cis-2-(4-Chloro-phenyl)-cyclopropanecarboxylic acid [2-(ethyl-methyl-amino)-5,7-difluoro-4-oxo-4*H*-quinazolin-3-yl]-amide;
cis-2-(4-Chloro-phenyl)-cyclopropanecarboxylic acid (8-fluoro-4-oxo-2-pyrrolidin-1-yl-4*H*-quinazolin-3-yl)-amide; 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 Terms

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

The term "C_{1-6}-alkyl" as used herein means a saturated, branched or straight hydrocarbon group having from 1-6 carbon atoms, e.g. C_{1-3}-alkyl, C_{1-4}-alkyl, C_{1-6}-alkyl, C_{2-6}-alkyl, C_{3-6}-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-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 "cyano" shall mean the radical -CN.

The term "amino" shall mean the radical $-NH_2$.

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

The term "C_{1-6}-alkoxy" as used herein refers to the radical -O-C_{1-6}-alkyl. Representative examples are methoxy, ethoxy, propoxy (e.g. 1-propoxy, 2-propoxy), 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-C_{1-6}-alkyl" as used herein refers to alkyl substituted one or more times at any carbon atom(s) with hydroxyl. Representative examples are hydroxymethyl, hydoxyethyl (e.g. 1-hydroxyethyl, 2-hydroxyethyl) and the like.

The term "C_{1-6}-alkoxy-C_{1-6}-alkyl-" as used herein refers to an C_{1-6}-alkyl-O-C_{1-6}-alkyl group, wherein the C_{1-6}-alkyl and C_{1-6}-alkyl-O- are as defined above. Represen-

tative examples are methoxy-methyl, methoxy-ethyl, ethoxy-methyl, ethoxy-ethyl and the like.

The term "phenyl-C_{1-6}-alkyl-" as used herein refers to phenyl attached through an alkyl group having the indicated number of carbon atoms Representative examples are benzyl, phenylethyl, 3-phenylpropyl and the like.

The term "optionally substituted" as used herein means that the groups in 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 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 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.

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 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 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.

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

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

Examples of pharmaceutically acceptable cationic salts of a 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 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 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 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 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 (±). 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 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.

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 $K_v7.4$ (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, or as described under the section, Pharmacological methods.

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.

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 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, 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, 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, cardiomyopathia, 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), excerbation 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, for inducing or maintaining bladder control, nocturia, bladder spasms, overactive bladder (OAB), bladder outflow obstruction, interstitial cystitis (IC) (also called painfull 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 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, amyelotrophic 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, prevention 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 and 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 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.

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 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), excerbation of airways hyper reactivity or cystic fibrosis. In another embodiment the compounds of the invention are considered useful for treatment, prevention 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 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, prevention or alleviation of urinary incontinence.

Pharmaceutical Compositions

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

While a 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 one embodiment, the invention provides pharmaceutical compositions comprising the compound of the invention, or a pharmaceutically acceptable salt or derivative thereof, together with one or more pharmaceutically acceptable carriers, 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.

Pharmaceutical compositions of the invention may be those suitable for oral, rectal, bronchial, nasal, pulmonal, 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 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 compound of the 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 compound of the invention or a pharmaceutically acceptable salt of a compound of the invention.

For preparing pharmaceutical compositions from a compound of the present invention, pharmaceutically acceptable carriers can be either solid or liquid. Solid form preparations include powders, tablets, pills, capsules, cachets, supposetories, 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 may 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, cellulose, starch, gelatin, tragacanth, methylcellulose, sodium carboxymethylcellulose, a low melting wax, cocoa butter, and the like. The term “preparation” is intended to include the formulation of the active compound with encapsulating material as carrier providing a capsule in which the active component, with or without carriers, is surrounded by a carrier, which is thus in association with it. Similarly, cachets and lozenges are included. Tablets, powders, capsules, pills, cachets, and lozenges can be used as solid forms suitable for oral administration.

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

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

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

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

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

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

Also included are solid form preparations, intended for conversion shortly before use to liquid form preparations for oral administration. Such liquid forms include solutions, suspensions, and emulsions. In addition to the active component such 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 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 base with the addition of suitable thickening and/or gelling agents. Lotions may be formulated with an aqueous or oily base and will in general also contain one or more emulsifying agents, stabilising agents, dispersing agents, suspending agents, thickening agents, or colouring agents.

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

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

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

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

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

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

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

In one embodiment, the invention provides tablets or capsules for oral administration.

In another embodiment, the invention provides liquids for intravenous administration and continuous infusion.

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

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

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

The actual dosage 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. Ranges are from about 0.1 μg/kg to about 10 mg/kg/day i.v., and from about 1 μg/kg to about 100 mg/kg/day p.o.

Methods of Therapy

In another aspect the invention provides a method for the 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 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 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 mg/kg i.v. and from about 0.1 to about 30 mg/kg p.o.

EXAMPLES

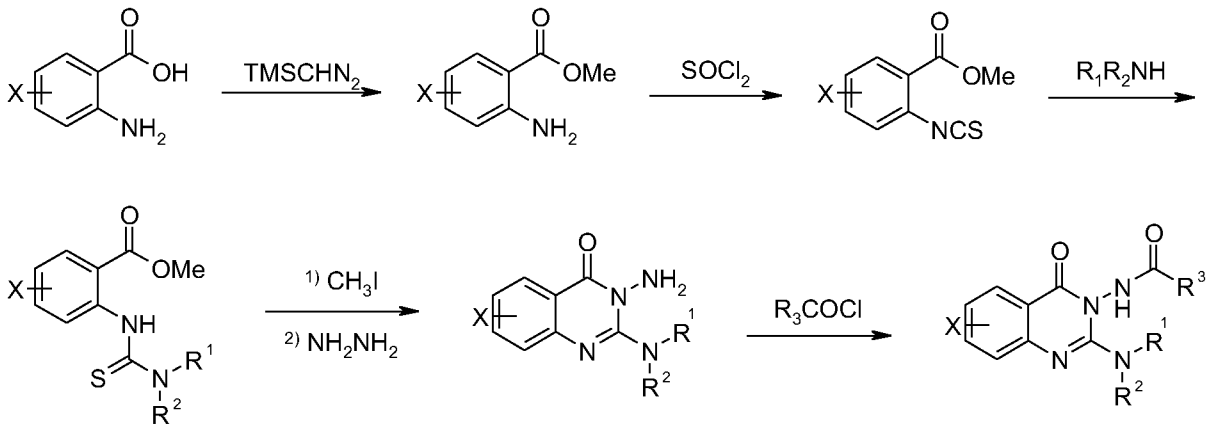
The following examples and general procedures refer to intermediate compounds and final products for general Formula (I) identified in the specification and

in the synthesis schemes. The preparation of the compounds of general Formula (I) of 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 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 starting materials.

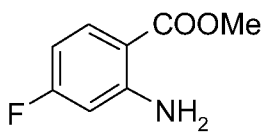
The abbreviations as used in the examples have the following meaning:
DCM: Dichloromethane
EtOAc: Ethyl acetate
THF: Tetrahydrofuran
DMF: N,N-dimethylformamide
MeCN: Acetonitrile
NMP: N-Methylpyrrolidinone
RT: room temperature

Preparative Example

Scheme 1:



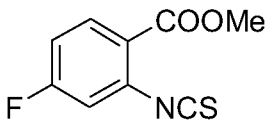
Methyl 2-amino-4-fluorobenzoate (Intermediate compound)



2-Amino-4-fluorobenzoic acid (10.0 g, 64.5 mmol) was dissolved in methanol (50 mL) and toluene (150 mL). (Trimethylsilyl)diazomethane (2M in diethyl ether, 48.3 mL,

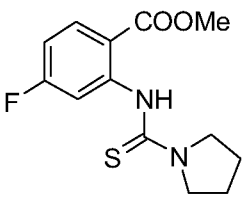
96.7 mmol) was added over 10 minutes at RT. Stirring was continued for 2 hours at RT. Water (300 mL) was added to the mixture and the volatiles were removed *in vacuo*. The remaining aqueous phase was cooled to 0°C for 30 minutes and the formed precipitate was collected by filtration, washed with water and dried to give pure title compound (10.4 g, 95%).

Methyl 4-fluoro-2-isothiocyanatobenzoate (Intermediate compound)



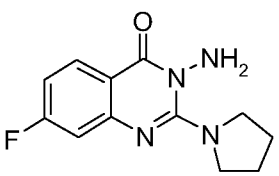
Methyl 2-amino-4-fluorobenzoate (7.3 g, 43.2 mmol) was dissolved in chloroform, followed by addition of water (150 mL) and sodium hydrogencarbonate (36.3 g, 432 mmol). Thiophosgene (3.73 mL, 47.5 mmol) was added and the mixture was stirred at RT for 2 hours. Water (250 mL) was added and the mixture was extracted with DCM. The combined organics were dried ($MgSO_4$) and evaporated to give the title compound (8.90 g, 98%).

Methyl 4-fluoro-2-[(pyrrolidine-1-carbothioyl)-amino]-benzoate (Intermediate compound)



Methyl 4-fluoro-2-isothiocyanatobenzoate (8.90 g, 42.1 mmol) was dissolved in THF (100 mL), followed by addition of pyrrolidine (7.04 mL, 84.3 mmol). The reaction mixture was stirred at RT. After 1 hour the mixture was poured into water (1 L). The formed precipitate was collected by filtration, washed with water and dried *in vacuo* to give pure title compound (10.0 g, 84%).

3-Amino-7-fluoro-2-pyrrolidin-1-yl-3*H*-quinazolin-4-one (Intermediate compound)

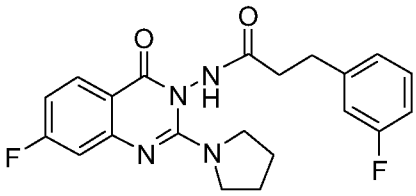


Methyl 4-fluoro-2-[(pyrrolidine-1-carbothioyl)-amino]-benzoate (10.0 g, 35.4 mmol) was dissolved in methanol (75 mL), followed by addition of iodomethane (4.41 mL, 70.8 mmol). The reaction mixture was heated at 45°C for 2 hours. The reaction mixture was evaporated to dryness and then redissolved in methanol (100 mL). Hydrazine monohydrate (5.15 mL, 106 mmol) was added followed by stirring at RT

overnight. The reaction mixture was poured into water (300 mL). The formed precipitate was collected by filtration, washed with water and dried *in vacuo* to give pure title compound (8.00 g, 91%).

Example 1

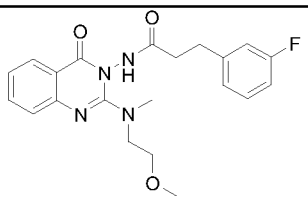
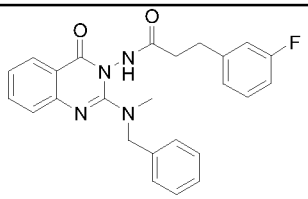
N-(7-Fluoro-4-oxo-2-pyrrolidin-1-yl-4*H*-quinazolin-3-yl)-3-(3-fluoro-phenyl)-propionamide (Compound 1.1)

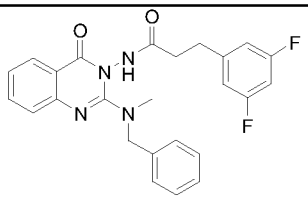
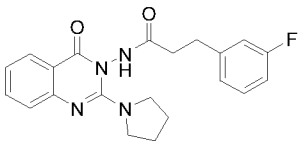
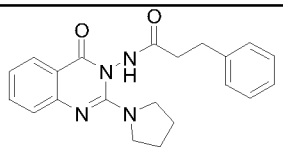
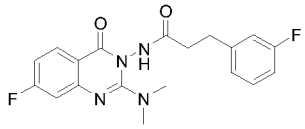
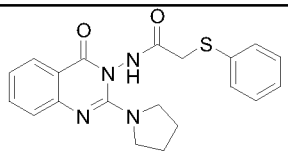
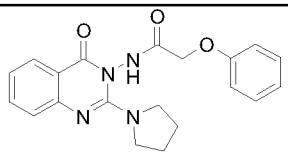
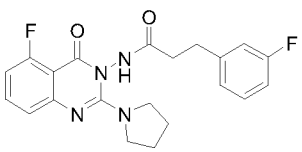
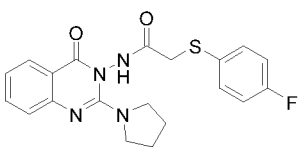
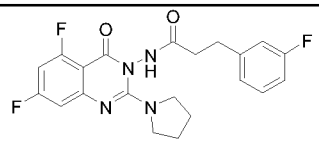


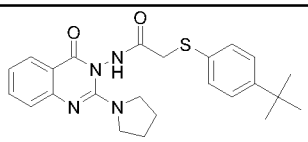
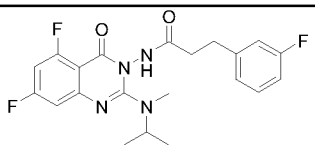
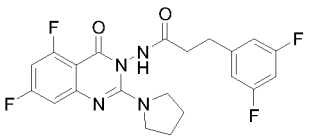
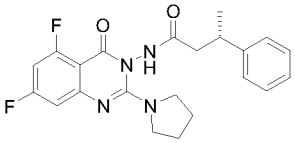
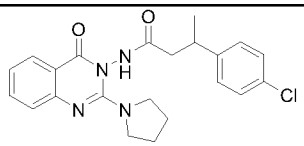
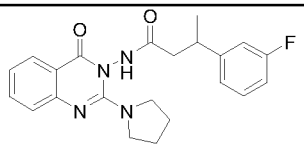
3-(3-Fluorophenyl)propionic acid (0.561 g, 3.34 mmol) was dissolved in dry DCM (20 mL), followed by addition of oxalyl chloride (315 µL, 3.61 mmol) and 2 drops of dry DMF. After 1 hour gas evolution had stopped and pyridine (223 µL, 2.78 mmol) was added, followed by addition of 3-amino-7-fluoro-2-pyrrolidin-1-yl-3*H*-quinazolin-4-one (0.690 g, 2.78 mmol). After stirring at RT for 1 minute additional pyridine (445 µL, 5.56 mmol) was added. The reaction mixture was stirred overnight at RT. The mixture was washed with 1M HCl (20 mL) and saturated $NaHCO_3$ (20 mL). The organic layer was cooled on an ice bath and the formed precipitate was collected by filtration to yield the title compound (0.350 g, 32%).

LC-ESI-HRMS of $[M+H]^+$ shows 399.1620 Da. Calc. 399.1633 Da.

The following compounds were synthesized employing a similar method to the one described above:

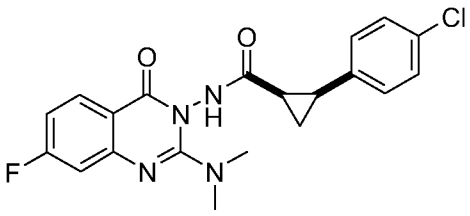
No	Structure	Name	LC-ESI-HRMS Meas. (Da)	LC-ESI-HRMS Calc. (Da)
1.2		3-(3-Fluoro-phenyl)-*N*-{2-[(2-methoxy-ethyl)-methyl-amino]-4-oxo-4*H*-quinazolin-3-yl}-propionamide	399.1834	399.1832
1.3		*N*-[2-(Benzyl-methyl-amino)-4-oxo-4*H*-quinazolin-3-yl]-3-(3-fluoro-phenyl)-propionamide	431.1875	431.1883

No	Structure	Name	LC-ESI-HRMS Meas. (Da)	LC-ESI-HRMS Calc. (Da)
1.4		*N*-[2-(Benzyl-methyl-amino)-4-oxo-4*H*-quinazolin-3-yl]-3-(3,5-difluoro-phenyl)-propionamide	449.1774	449.1789
1.5		3-(3-Fluoro-phenyl)-*N*-(4-oxo-2-pyrrolidin-1-yl-4*H*-quinazolin-3-yl)-propion-amide	381.1743	381.1727
1.6		*N*-(4-Oxo-2-pyrrolidin-1-yl-4*H*-quinazolin-3-yl)-3-phenyl-propionamide	363.1818	363.1821
1.7		*N*-(2-Dimethylamino-7-fluoro-4-oxo-4*H*-quinazolin-3-yl)-3-(3-fluoro-phenyl)-propionamide	373.1481	373.1476
1.8		*N*-(4-Oxo-2-pyrrolidin-1-yl-4*H*-quinazolin-3-yl)-2-phenylsulfanyl-acetamide	381.1386	381.1385
1.9		*N*-(4-Oxo-2-pyrrolidin-1-yl-4*H*-quinazolin-3-yl)-2-phenoxy-acetamide	365.1609	365.1614
1.10		*N*-(5-Fluoro-4-oxo-2-pyrro-lidin-1-yl-4*H*-quinazolin-3-yl)-3-(3-fluoro-phenyl)-propionamide	399.1648	399.1633
1.11		2-(4-Fluoro-phenylsulfanyl)-*N*-(4-oxo-2-pyrrolidin-1-yl-4*H*-quinazolin-3-yl)-acetamide	399.1288	399.1291
1.12		*N*-(5,7-Difluoro-4-oxo-2-pyrrolidin-1-yl-4*H*-quina-zolin-3-yl)-3-(3-fluoro-phenyl)-propionamide	417.1550	417.1538

No	Structure	Name	LC-ESI-HRMS Meas. (Da)	LC-ESI-HRMS Calc. (Da)
1.13		2-(4-tert-Butyl-phenyl-sulfanyl)-*N*-(4-oxo-2-pyrrolidin-1-yl-4*H*-quinazolin-3-yl)-acetamide	437.2013	437.2011
1.14		*N*-[5,7-Difluoro-2-(isopropyl-methyl-amino)-4-oxo-4*H*-quinazolin-3-yl]-3-(3-fluoro-phenyl)-propionamide	419.1695	419.1695
1.15		*N*-(5,7-Difluoro-4-oxo-2-pyrrolidin-1-yl-4*H*-quinazolin-3-yl)-3-(3,5-difluoro-phenyl)-propionamide	435.1439	435.1444
1.16		(S)-*N*-(5,7-Difluoro-4-oxo-2-pyrrolidin-1-yl-4*H*-quinazolin-3-yl)-3-phenyl-butyramide	413.1785	413.1789
1.17		3-(4-Chloro-phenyl)-*N*-(4-oxo-2-pyrrolidin-1-yl-4*H*-quinazolin-3-yl)-butyramide	411.1606	411.1588
1.18		3-(3-Fluoro-phenyl)-*N*-(4-oxo-2-pyrrolidin-1-yl-4*H*-quinazolin-3-yl)-butyramide	395.1895	395.1883

Example 2

cis-2-(4-Chloro-phenyl)-cyclopropanecarboxylic acid (2-dimethylamino-7-fluoro-4-oxo-4*H*-quinazolin-3-yl)-amide (Compound 2.1)

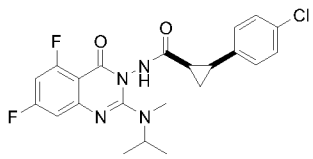
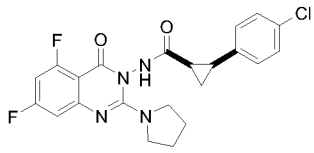
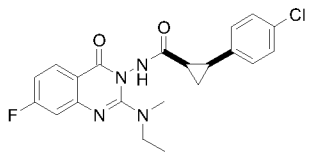
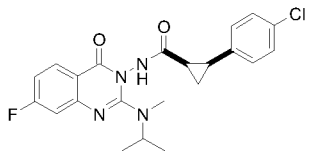
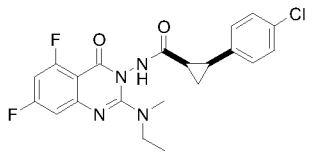
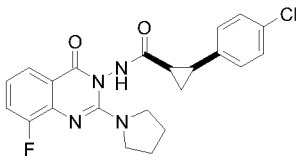


Copper(I) iodide (0.0130 g, 0.0683 mmol) and hydrotris-(3-phenylpyrazol-1-yl)borate,potassium-salt (0.0328 g, 0.0683 mmol) were suspended in dry DCM (30 mL) and the flask was evacuated and back filled with nitrogen (3 times). The suspension was stirred at RT for 2 hours. 4-Chlorostyrene (1.89 g, 13.7 mmol) was added via syringe followed by addition of ethyl diazoacetate (0.312 g, 2.73 mmol) in one portion. The reaction was stirred overnight at RT. The reaction was quenched with 1M HCl (30 mL), stirred for 10 minutes and the phases separated. The aqueous phase was extracted with additional DCM (20 mL) and the combined organic phases were dried ($MgSO_4$) and evaporated. The crude ester was dissolved in methanol (15 mL) and 4M NaOH (15 mL) was added. The mixture was refluxed for 2 hours. After cooling the reaction mixture was diluted with water (30 mL) and extracted with ether (20 mL). The aqueous phase was made acidic with 4M (HCl) (20 mL) and extracted with DCM (2 x 20 mL). The combined DCM phases were dried ($MgSO_4$) and evaporated yielding the crude 2-(4-chloro-phenyl)-cyclopropanecarboxylic acid (0.342 g, 64%) as a 4:1 mixture of *cis* and *trans*.

The crude 2-(4-Chloro-phenyl)-cyclopropanecarboxylic acid (0.319 g, 1.62 mmol) was dissolved in dry DCM (10 mL), followed by addition of oxalyl chloride (153 µL, 1.76 mmol) and 2 drops of dry DMF. After 1 hour gas evolution had stopped and pyridine (108 µL, 1.35 mmol) was added, followed by addition of 3-amino-2-dimethyl-amino-7-fluoro-3*H*-quinazolin-4-one (prepared according to the procedure described for the intermediate compound 3-amino-7-fluoro-2-pyrrolidin-1-yl-3*H*-quinazolin-4-one) (0.300 g, 1.35 mmol). After stirring at RT for 1 minute additional pyridine (216 µL, 2.70 mmol) was added. The reaction mixture was stirred overnight at RT. The mixture was washed with 1M HCl (10 mL) and saturated $NaHCO_3$ (10 mL). The organic phase was dried ($MgSO_4$) and evaporated. The crude product was purified using column chromatography (heptane/ethyl acetate) to yield the title compound as the major isomer (0.205 g, 38%).

LC-ESI-HRMS of $[M+H]^+$ shows 401.1165 Da. Calc. 401.1181 Da.

The following compounds were synthesized employing a similar method to the one described above:

No	Structure	Name	LC-ESI-HRMS Meas. (Da)	LC-ESI-HRMS Calc. (Da)
2.2		*cis*-2-(4-Chloro-phenyl)-cyclopropanecarboxylic acid [5,7-difluoro-2-(isopropyl-methyl-amino)-4-oxo-4*H*-quinazolin-3-yl]-amide	447.1422	447.1399
2.3		*cis*-2-(4-Chloro-phenyl)-cyclopropanecarboxylic acid (5,7-difluoro-4-oxo-2-pyrro-lidin-1-yl-4*H*-quinazolin-3-yl)-amide	445.1226	445.1243
2.4		*cis*-2-(4-Chloro-phenyl)-cyclopropanecarboxylic acid [2-(ethyl-methyl-amino)-7-fluoro-4-oxo-4*H*-quinazolin-3-yl]-amide	415.1342	415.1337
2.5		*cis*-2-(4-Chloro-phenyl)-cyclopropanecarboxylic acid [7-fluoro-2-(isopropyl-methyl-amino)-4-oxo-4*H*-quinazolin-3-yl]-amide	429.1493	429.1494
2.6		*cis*-2-(4-Chloro-phenyl)-cyclopropanecarboxylic acid [2-(ethyl-methyl-amino)-5,7-difluoro-4-oxo-4*H*-quina-zolin-3-yl]-amide	433.1248	433.1243
2.7		*cis*-2-(4-Chloro-phenyl)-cyclopropanecarboxylic acid (8-fluoro-4-oxo-2-pyrrolidin-1-yl-4*H*-quinazolin-3-yl)-amide	427.1328	427.1337

PHARMACOLOGICAL METHODS

FLIPR-based characterization of $K_V7.2+3$ modulators

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 EC_{50} values are calculated based on max values. EC_{50} 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

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 mm^2) in a humidified atmosphere of 5% CO_2 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 ~$3x10^6$ cells/ml (25 µl/well) in black-walled, clear bottom, 384-well plates pre-treated with 0.01 g/l poly-D-lysin (20 µl/well for ≥30 min). Plated cells were allowed to proliferate for 24 h before loading with dye.

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 Mg^{2+} 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.

Tl^+ influx measurements

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

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 Tl_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 µl/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 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 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.

Test Compound	EC_{50} (µM)	Efficacy (%)
1.1	0.26	154
1.2	9.5	130
1.3	1.6	118
1.4	3.9	40
1.5	0.41	148
1.6	0.66	96
1.7	2.5	112
1.8	3.3	103
1.9	12	75
1.10	0.34	100
1.11	2.2	106
1.12	0.032	122
1.13	2.1	41
1.14	0.45	109

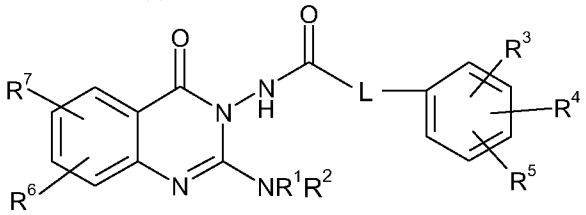
1.15	0.018	112
1.16	0.0028	68
1.17	0.10	85
1.18	0.015	98
2.1	1.4	118
2.2	0.45	116
2.3	0.83	109
2.4	0.94	114
2.5	0.93	114
2.6	0.50	110
2.7	0.27	101

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. Accordingly, 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)



(I)

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

L represents a linker selected from -(CR'R'')$_2$–, –CR'R''–S–, –CR'R''–O– or  ; wherein R' and R'', independently of each other, represent hydrogen, C_{1-6}-alkyl or halogen;

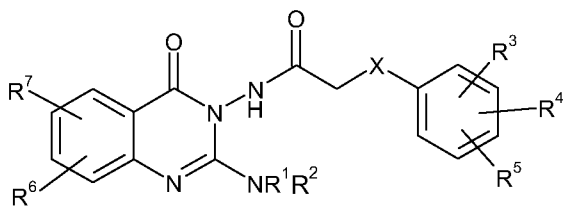
R^1 and R^2, independently of each other, represent C_{1-6}-alkyl, hydroxy-C_{1-6}-alkyl-, C_{1-6}-alkoxy-C_{1-6}-alkyl-, phenyl, phenyl-C_{1-6}-alkyl-, which phenyl is optionally substituted with one or two times with a substituent selected from the group consisting of C_{1-6}-alkoxy, halogen and cyano; 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, thiazolidinyl, piperidinyl, piperazinyl and morpholinyl, which pyrrolidinyl, piperidinyl, piperazinyl and morpholinyl 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-;

R^3, R^4 and R^5, independently of each other, represent hydrogen, C_{1-6}-alkyl, halogen, trihalomethyl, hydroxy, C_{1-6}-alkoxy, trifluoromethoxy, amino, cyano or nitro; and

R^6 and R^7, independently of each other, represent hydrogen, C_{1-6}-alkyl, halogen, trihalomethyl, hydroxy, C_{1-6}-alkoxy, trifluoromethoxy, amino, nitro, cyano or phenyl.

2. The compound according to claim 1 of formula (Ia)

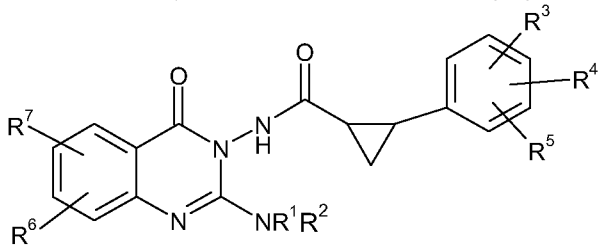


(Ia)

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

X represents -CR'R''-, –S–, or –O–, wherein R' and R'', independently of each other, represent hydrogen, C_{1-6}-alkyl or halogen, and R^1, R^2, R^3, R^4, R^5, R^6 and R^7 are as defined in claim 1.

3. The compound according to claim 1 of formula (Ib)



(Ib)

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, R^5, R^6 and R^7 are as defined in claim 1.

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

5. The compound according to any one of the claims 1-3, 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, form a pyrrolidinyl ring.

6. The compound according to any one of the claims 1-5, or a pharmaceutically-acceptable addition salt thereof, or an N-oxide thereof, wherein R^3, R^4 and R^5, independently of each other, represent hydrogen, C_{1-6}-alkyl or halogen.

7. The compound according to any one of the claims 1-6, or a pharmaceutically-acceptable addition salt thereof, or an N-oxide thereof, wherein R^6 and R^7, independently of each other, represent hydrogen or halogen.

8. The compound according to claim 1, which is:
N-(7-Fluoro-4-oxo-2-pyrrolidin-1-yl-4*H*-quinazolin-3-yl)-3-(3-fluoro-phenyl)-propionamide;
3-(3-Fluoro-phenyl)-*N*-{2-[(2-methoxy-ethyl)-methyl-amino]-4-oxo-4*H*-quinazolin-3-yl}-propionamide;

N-[2-(Benzyl-methyl-amino)-4-oxo-4*H*-quinazolin-3-yl]-3-(3-fluoro-phenyl)-propionamide;
N-[2-(Benzyl-methyl-amino)-4-oxo-4*H*-quinazolin-3-yl]-3-(3,5-difluoro-phenyl)-propionamide;
3-(3-Fluoro-phenyl)-*N*-(4-oxo-2-pyrrolidin-1-yl-4*H*-quinazolin-3-yl)-propionamide;
N-(4-Oxo-2-pyrrolidin-1-yl-4*H*-quinazolin-3-yl)-3-phenyl-propionamide;
N-(2-Dimethylamino-7-fluoro-4-oxo-4*H*-quinazolin-3-yl)-3-(3-fluoro-phenyl)-propionamide;
N-(4-Oxo-2-pyrrolidin-1-yl-4*H*-quinazolin-3-yl)-2-phenylsulfanyl-acetamide;
N-(4-Oxo-2-pyrrolidin-1-yl-4*H*-quinazolin-3-yl)-2-phenoxy-acetamide;
N-(5-Fluoro-4-oxo-2-pyrrolidin-1-yl-4*H*-quinazolin-3-yl)-3-(3-fluoro-phenyl)-propionamide;
2-(4-Fluoro-phenylsulfanyl)-*N*-(4-oxo-2-pyrrolidin-1-yl-4*H*-quinazolin-3-yl)-acetamide;
N-(5,7-Difluoro-4-oxo-2-pyrrolidin-1-yl-4*H*-quinazolin-3-yl)-3-(3-fluoro-phenyl)-propionamide;
2-(4-tert-Butyl-phenylsulfanyl)-*N*-(4-oxo-2-pyrrolidin-1-yl-4*H*-quinazolin-3-yl)-acetamide;
N-[5,7-Difluoro-2-(isopropyl-methyl-amino)-4-oxo-4*H*-quinazolin-3-yl]-3-(3-fluoro-phenyl)-propionamide;
N-(5,7-Difluoro-4-oxo-2-pyrrolidin-1-yl-4*H*-quinazolin-3-yl)-3-(3,5-difluoro-phenyl)-propionamide;
(S)-*N*-(5,7-Difluoro-4-oxo-2-pyrrolidin-1-yl-4*H*-quinazolin-3-yl)-3-phenyl-butyramide;
3-(4-Chloro-phenyl)-*N*-(4-oxo-2-pyrrolidin-1-yl-4*H*-quinazolin-3-yl)-butyramide;
3-(3-Fluoro-phenyl)-*N*-(4-oxo-2-pyrrolidin-1-yl-4*H*-quinazolin-3-yl)-butyramide;
cis-2-(4-Chloro-phenyl)-cyclopropanecarboxylic acid (2-dimethylamino-7-fluoro-4-oxo-4*H*-quinazolin-3-yl)-amide;
cis-2-(4-Chloro-phenyl)-cyclopropanecarboxylic acid [5,7-difluoro-2-(isopropyl-methyl-amino)-4-oxo-4*H*-quinazolin-3-yl]-amide;
cis-2-(4-Chloro-phenyl)-cyclopropanecarboxylic acid (5,7-difluoro-4-oxo-2-pyrrolidin-1-yl-4*H*-quinazolin-3-yl)-amide;
cis-2-(4-Chloro-phenyl)-cyclopropanecarboxylic acid [2-(ethyl-methyl-amino)-7-fluoro-4-oxo-4*H*-quinazolin-3-yl]-amide;
cis-2-(4-Chloro-phenyl)-cyclopropanecarboxylic acid [7-fluoro-2-(isopropyl-methyl-amino)-4-oxo-4*H*-quinazolin-3-yl]-amide;
cis-2-(4-Chloro-phenyl)-cyclopropanecarboxylic acid [2-(ethyl-methyl-amino)-5,7-difluoro-4-oxo-4*H*-quinazolin-3-yl]-amide;
cis-2-(4-Chloro-phenyl)-cyclopropanecarboxylic acid (8-fluoro-4-oxo-2-pyrrolidin-1-yl-4*H*-quinazolin-3-yl)-amide; or
a pharmaceutically-acceptable addition salt thereof.

9. A pharmaceutical composition comprising a therapeutically effective amount of the compound according to any one of the claims 1-8, or a pharmaceutically-acceptable addition salt thereof.

10. Use of the compound according to any one of the claims 1-8, or a pharmaceutically-acceptable addition salt thereof, for the manufacture of a pharmaceutical composition.

11. Use of the compound according to any one of the claims 1-8, or a pharmaceutically-acceptable addition salt 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 mammal, including a human, which disease, disorder or condition is responsive to activation of K_v7 channels.

12. The use according to claim 11, 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.

13. The use according to claim 12, wherein the disease, disorder or condition is pain, neuropathic pain, epilepsy or anxiety.

14. The use according to claim 12, 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 post therapeutic neuralgia, or to peripheral nerve injury.

15. A compound according to any of claims 1-8, any of its stereoisomers or a mixture of its stereoisomers, or an N-oxide thereof, or a pharmaceutically acceptable salt thereof, for use as a medicament.

16. A compound according to any of claims 1-8, any of its stereoisomers or a mixture of its stereoisomers, or an N-oxide thereof, or a pharmaceutically acceptable salt thereof, for use in the treatment, prevention or alleviation of a disease or a disorder or a condition of a mammal, including a human, which disorder, disease or condition is responsive to activation of K_v7 channels.

17. 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 need thereof, a therapeutically effective amount of the compound according to any one of the claims 1-7, or a pharmaceutically-acceptable addition salt thereof.

INTERNATIONAL SEARCH REPORT

International application No
PCT/DK2009/050293

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D239/95 A61K31/517 A61P25/00

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

B. FIELDS SEARCHED

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

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

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, 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.
Y	WO 2007/104717 A1 (NEUROSEARCH AS [DK]; BROWN WILLIAM DALBY [DK]; JESSEN CARSTEN [DK]; DE) 20 September 2007 (2007-09-20) page 9, line 23 - page 12, line 25; claims 1-9; examples 1,2	1,3-17
Y	WO 2005/025293 A2 (ICAGEN INC [US]; MCNAUGHTON-SMITH GRANT ANDREW [US]; AMATO GEORGE SALV) 24 March 2005 (2005-03-24) compounds 16,17,60,61,94,178,179, 194-200,270,281,287,288,318,324,325, 337-340,354; paragraphs [0036], [0047] - [0052]; claims 1,5,7,10,35; table 1	1-2,4-17

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[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
4 February 2010	18/02/2010

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, Fax: (+31–70) 340–3016	Guspanová, Jana

INTERNATIONAL SEARCH REPORT

International application No
PCT/DK2009/050293

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 2007/065913 A1 (NEUROSEARCH AS [DK]; SOERENSEN ULRIK SVANE [DK]; ERIKSEN BIRGITTE L [D) 14 June 2007 (2007-06-14) page 11, line 26 - page 12, line 36; claims 1,7,9-14; examples 1-13	1-17
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