5-CARBOXAMIDO SUBSTITUED THIAZOLE DERIVATIVES THAT INTERACT WITH ION CHANNELS, IN PARTICULAR WITH ION CHANNELS FROM THE KV FAMILY

Field of the invention

The present invention relates to compounds that interact with ion channels.

In particular, the invention relates to compounds that interact with ion channels from the Kv family, and in particular from the Kv4 subfamily.

The invention also relates to methods for preparing said compounds, to pharmaceutical compositions that contain said compounds, and to the use of said compounds in methods for treatment of the human and animal body and/or to the use of said compounds in the preparation of such pharmaceutical compositions.

The compounds of the invention for example can be used in the prevention and/or treatment of conditions or diseases associated with ion channels, in particular in the prevention and/or treatment of conditions and diseases associated with ion channels of the Kv family, and more in particular in the prevention and/or treatment of conditions and diseases associated with ion channels of the Kv4 family.

Other aspects, embodiments, uses and advantages of the invention will become clear from the further description below.

Background to the invention

Kv4 channels, as well as their encoding sequences, their biological function/activity and their disease associations have been described in the art, see for example Bahring et al., *J.Biol.Chem.*, Vol. 276, no. 26, 233888-23894 (2001); Baldwin et al., *Neuron* 7: 471-483 (1991); Dixon et al., *Circ. Res.* 79: 659-688 (1996); Dilks et al., *J. Neurophysiol.* 81: 1974-1977 (1999); Kuo et al., *Cell*, Vol. 107, 801-813 (2001); Pak et al., *Proc. Natl. Acad. Sci USA* 88; 4386-4390 (1991); Ohya et al., *FEBS Lett. 420:47-53 (1997);* Roberts and Tamkun, *Proc. Natl. Acad. Sci USA* 88; 1798-1802; Rudy et al., *Mol. Cell. Neurosci.* 2; 89-102 (1991); Serodio et al., J. Neurophysiol 75: 2174-2179 (1996); Serodio and Rudy, *J. Neurophysiol.* 79: 1081-1091 (1998); and Takimoto et al., *Circ. Res.* 81: 553-539 (1997), and the further references cited therein.

Generally, being voltage-gated potassium channels, Kv4 channels are *inter alia* involved in membrane depolarisation and repolarisation events, e.g. as part of and/or following neuronal firing and/or as part of the cycle of muscle contraction/relaxation.

In particular, and as mentioned in the above references, Kv4 channels are believed to be involved in the native A-type currents that are generated by various types of primary cells (Dilks et al., supra), in particular in muscle and neuronal cells. Kv4.2 and Kv4.3 transcripts have been found in most neurons, and in particular in CNS neurons (see Serodio and Rudy, supra, who discuss the distribution of Kv4 channels in rat brain); as well as in heart muscle (see Dixon et al. and by Serodio et al., both supra, who discuss the abundance and distribution of Kv4 transcripts in the hearts of rat, dog and human). It has also been found that, compared to Kv-type channels from other families such as Kv1-type channels, Kv4 channels activate and inactivate at subthreshold potentials, inactivate with time constants that change very little as a function of voltage (even at very negative potentials), and recover very fast from inactivation (see Rudy and Serodio, supra).

In neuronal cells, and in particular in neurons in the brain, Kv4 channels are *inter alia* believed to play an important role in the modulation of the firing rate, action potential initiation, shaping burst pattern and postsynaptic signal integration (Dilks et al., and Bahring et al., supra), and are believed to be associated with the physiological states/disorders that result from such activity (Serodio and Rudy, supra).

In the heart, the Kv4 channels are *inter alia* believed to play a major role in the calcium-independent A-type currents in the cardiac muscle (the "transient outward current or" I_{to}), and in particular in the cardiac ventricular muscle, and are thus believed to be involved in early repolarization and hence the overall duration of the action potential and the length of the refractory period (Serodio and Rudy, supra). Because of this, Kv4 channels are believed to be associated with (the susceptibility to) cardiac disorders such as arrhythmia and other types of heart failure (Kuo et al., supra).

So far, three mammalian Kv4 genes - referred to as Kv4.1 (also known as mSha1), Kv4.2 (also known as RK5) and Kv4.3, respectively - have been cloned and characterized, i.e. from rat and dog (Dixon et al, Serodio et al., Ohya et al. and Takimoto et al., all supra) and from human (Dilks et al., and Bahring et al., supra; see also for example WO 98/42833 and US-A-6,395,477).

The sequences of genes encoding mammalian Kv4 channels are also available from publicly accessible databases such as GenBank/NCBI, e.g. Kv4.1 from mouse (accession number NP_032449 and A38372); Kv4.1 from human (accession number BAA96454, AAF65617 and AF65516); Kv4.2 from mouse (accession number NP_062671 and AAD16972), Kv4.2 from rat (accession number NP_113918); Kv4.2 from human (accession number AAD22053 and CAB56841); Kv4.3 from mouse (accession numbers

NM_019931 and AF384170), Kv4.3 from rat (accession number U42975) and Kv4.3 from human (accession number XM_052127).

The above references also indicate that further channels from the Kv4 family may be identified and cloned in future, for example from neurons in the brain that show Kv4-like subthreshold-operating A channels, but do not show abundant expression of Kv4.1, Kv4.2 and/or Kv4.3 transcripts (see Serodio and Rudy, supra) or other suitable tissues/cells.

As mentioned above, the Kv4 channels in mammals also have a high degree of sequence identity (>70%) with, and thus are considered closely related to, the *Shal*-like gene product, which encodes a potassium channel in *Drosophila melanogaster* (see Baldwin et al, supra, and also WO 01/58952).

An assay for determining the influence of a compound on Kv channels, in which a transgenic line of *Caenorhabditis elegans* expressing a heterologous Kv channel, such as a human Kv4.3 channel, is used, is described in the International application WO 03/097682 by Applicant. Other assays and techniques for determining the influence of a test compound on ion channels in general, and on a Kv channel in particular, such as FLIPR-techniques and use of oocytes, will be clear to the skilled person, and are also mentioned in WO 03/097682. Such assays can be used to determine whether a compound "interacts with such an ion channel. As mentioned below and for the purposes of the present description and attached claims, a compound is considered to "interact with an ionchannel, such as an ion channel of the Kv family and in particular of the Kv4 subfamily, if such a compound acts as an antagonist of said ion channel and/or of the biological function(s) and/or pathways associated with said ion channels, and in particular if such a compound can fully or partially "block" such an ion channel.

In view of the biological functions and disease associations mentioned above, compounds that interact with ion channels can find use as pharmaceutically active agents, in particular for the prevention and/or treatment of diseases and disorders associated with the ion channels with which the compound interact. By means of non-limiting example, compounds that interact with ion channels from the Kv 4 subfamily, and in particular with Kv4.3 ion channels (e.g. the compounds as further described herein below) could be used in (the preparation of pharmaceutical compositions for) the prevention and/or treatment of cardiac disorders such as arrhythmia, hypertension-induced heart disorders such as hypertension-induced cardiac hypertrophy (e.g. ventricular hypertrophy), and disorders of the nervous system and neurological disorders such as epilepsy, stroke, traumatic brain

injury, spinal cord injury, anxiety, insomnia, Alzheimer's disease, encephalomyelitis, multiple sclerosis, demyelinating disease, and Parkinson's syndrome.

A major drawback of some of the known compounds involves that the drugs do not work in a selective manner, i.e. they do not select between different ion channels. For instance many of these compounds also block a potassium channel called the human ether-à-go-go related gene (hERG) potassium channel. Compounds that block this channel with high potency may cause reactions which are fatal. This undesired blockade can cause acquired long QT syndrome, a disorder that puts patients at risk for life-threatening arrhythmias. Cardiac arrhythmias are the leading cause of sudden death in the United States, according to the American Heart Association. The FDA now requires that every drug be assayed for hERG block before it is approved. Even medicines that might be beneficial for the vast majority of patients do not make it to the market or have been pulled from the market - if they block hERG.

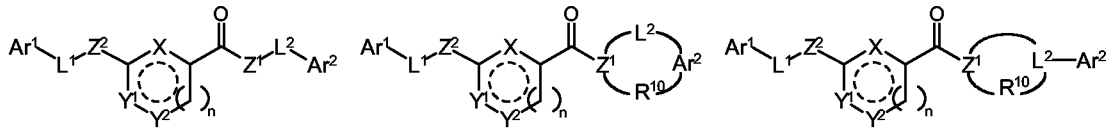
Thus, in addition to being able to modulate a particular Kv channel, it is desirable to find compounds that are selective to Kv channel when compared to the hERG channel. Thus, there is a need to find compounds that modulate the Kv channel, while not inhibiting the hERG channel.

There remains an urgent need in the art for finding new compounds, which overcome the above-mentioned drawbacks.

It is therefore an object of the invention to provide compounds that interact with ion channels, in particular with ion channels from the Kv family, more in particular with ion channels from the Kv4 subfamily, and especially with Kv4.3 channels, in particular in vertebrates, more in particular in warm-blooded animals, even more in particular in mammals, and especially in human beings. It is a further object of the present invention to provide compounds that interact with ion channels, in particular Kv ion channels and which are selective to Kv ion channels when compared to the hERG channel.

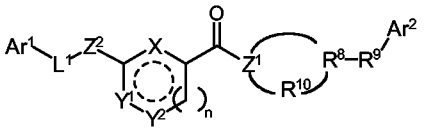
Summary of the invention

In a first aspect the present invention relates to compounds of Formula I, II, III or IV, stereoisomers, tautomers, racemics, prodrugs, metabolites thereof, or a pharmaceutically acceptable salt and/or solvate thereof,



5

I II III



IV

wherein when X is O, Y^1 is selected from N or CH=, and n is 0,

wherein when X is N, Y^1 is selected from S, O, N or CH=, and n is 0 or Y1 is selected from N or CH=and n is 1,

wherein when X is S, Y^1 is selected from N or CH=, and n is 0,

wherein when X is CH=, Y^1 is selected from O, N or S, and n is 0 or 1,

wherein Y^2 is selected from $C(R^2)$- or N,

wherein n is an integer selected from 0 or 1,

wherein Z^1 is selected from $-N(R^3)-$, -O-, $-N(R^3)-NH-$, or $-CH_2-$ in Formula I, and Z^1 is selected from N, or CH in Formula II, III or IV,

wherein Z^2 is selected from $-N(R^1)-$, -O-, or -S-,

wherein R^1 and R^3 are each independently selected from hydrogen, alkyl, alkylcarbonyl, cycloalkyl, alkenyl, alkynyl, aryl, heteroaryl, heterocyclyl, aralkyl, cycloalkylalkyl or acyl, optionally substituted by one or more substituents,

wherein R^2 is selected from hydrogen alkyl, cycloalkyl, alkenyl or alkynyl, optionally substituted by one or more substituents,

wherein Ar^1 is selected from aryl, heterocyclyl or heteroaryl, optionally substituted by one or more substituents selected from halogen, hydroxy, nitro, amino, azide, cyano, alkyl, cycloalkyl, alkylamino, alkoxy, $-SO_2-NH_2$, aryl, heteroaryl, haloalkyl, haloalkoxy, haloaryl, carboxy, alkyloxycarbonyl, alkylaminocarbonyl, heteroarylalkyl, alkylsulfonamide, heterocyclyl, alkylcarbonylaminoalkyl, aryloxy, alkylcarbonyl, acyl, arylcarbonyl, aminocarbonyl, alkylsulfoxide, $-SO_2R^{15}$, or alkylthio, wherein R^{15} is alkyl or cycloalkyl,

wherein Ar^2 is selected from aryl, heterocyclyl, or heteroaryl, optionally substituted by one or more substituents selected from halogen, hydroxy, nitro, amino, azide, cyano, alkyl, cycloalkyl, alkylamino, alkoxy, $-SO_2-NH_2$, $-SO_2R^{15}$, aryl, heteroaryl, heteroarylalkyl, haloalkyl, haloalkoxy, haloaryl, carboxy, alkyloxycarbonyl, alkylaminocarbonyl, alkylsulfonamide, heterocyclyl, alkylcarbonylaminoalkyl, aryloxy, alkylcarbonyl, acyl, arylcarbonyl, aminocarbonyl, alkylsulfoxide, or alkylthio, wherein R^{15} is alkyl or cycloalkyl,

wherein L^2 is a linking group selected from a single bond, a group of Formula $-R^8-R^9-$, alkylyn, N, cycloalkylene, $-NH-(C(R^4)(R^4))_q-$, $-(C(R^4)(R^4))_q-$, $-C(R^4)=$, $-(C(R^4)(R^4))_v-O-(C(R^4)(R^4))_w-$, $-(C(R^4)(R^4))_v-(C(R^4))_w=$, $-(C(R^4)(R^4))_q-(C=O)-$, or cycloalkylenoxyalkylene, wherein $-(C(R^4)(R^4))_q-$, $(C(R^4)(R^4))_w$ and $-(C(R^4)(R^4))_v-$ are each independently aliphatic or form a cycloalkyl, wherein each R^4 is independently selected from hydrogen, alkyl, hydroxyl, alkylaminoalkyl, carboxy, hydroxyalkyl, alkoxyalkyl, alkylamino, or alkyloxycarbonyl; q is an integer between 0 and 6; v is an integer between 0 and 6 and w is an integer between 0 and 6,

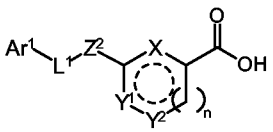
wherein L^1 is a linking group selected from a single bond, $-(C(R^4)(R^4))_q-$, or $-(C(R^4)(R^4))_q-(C=O)-$, wherein each R^4 is independently selected from hydrogen, alkyl, hydroxyl, alkylaminoalkyl, carboxy, hydroxyalkyl, alkoxyalkyl, alkylamino, or alkyloxycarbonyl; q is an integer between 0 and 6;

wherein R^8 is alkylyn, $-(C(R^4)(R^4))_p-C(R^{14})$ or $-(C(R^4)(R^4))_p-C(R^4)=C$, wherein R^9 is selected from a single bond, $-(C(R^4)(R^4))_q-$, or C(=O)-, wherein R^{14} is selected from hydrogen, hydroxyl or alkyl, wherein p is an integer between 0 and 3,

wherein R^{10} is selected from $-(C(R^4)(R^4))_m-$, $-(C(R^4)(R^4))_m-C(=O)O-(C(R^4)(R^4))_q-$, or $-(C(R^4)(R^4))_m-N(R^{12})-(C(R^4)(R^4))_q-$, wherein m is an integer between 1 and 6, wherein R^{12} is selected from hydrogen, alkyl, aryl, arylalkyl or alkylcarbonyl, and

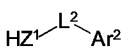
wherein the dotted ring represents one or several double bonds placed in any particular position of the bond forming the ring.

In a second aspect, the present invention relates to a method for synthesizing a compound having the structural Formula I, II, III or IV comprising the step of condensing a compound of Formula XXX:

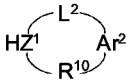


XXX

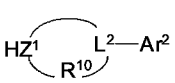
with a compound of Formula XXXI, XXXII, XXXIII or XXXIV :



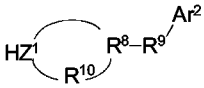
XXXI



XXXII

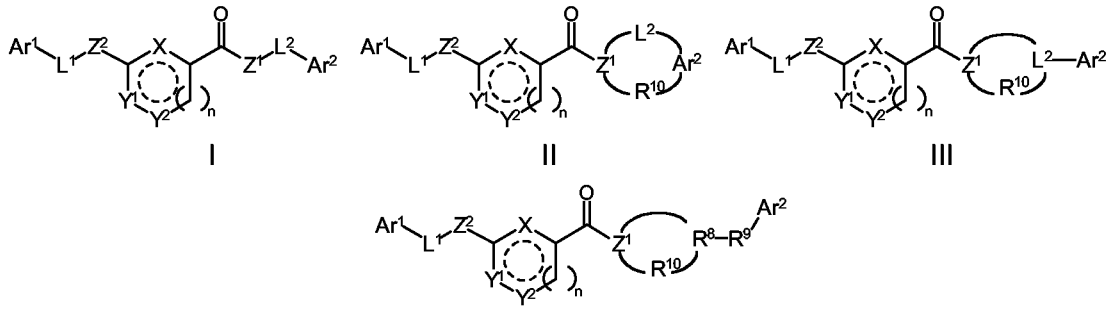


XXXIII



XXXIV

hereby obtaining a compound of Formula I, II, III or IV,



I II III

IV

wherein Ar^1, Ar^2, L^1, L^2, X, Y^1, Y^2, R^{10}, R^8 and R^9 have the same meaning as that defined hereinabove.

It was surprisingly found that the compounds of the invention interact with ion channels as shown in the examples below, in particular with ion channels from the Kv family, more in particular with ion channels from the Kv4 subfamily, and especially with Kv4.3 channels. Kv4.3 ions channels are associated to various conditions or diseases. In a further aspect the present invention provides a compound of Formula I, II, III or IV for use as a medicament.

The compounds of the present invention are particularly useful for the preparation of a medicament in the prevention and/or treatment of conditions or diseases associated with ion channels of the Kv4 family. Non-limiting examples of said conditions or diseases associated with ion channels of the Kv4 family can be selected from the group comprising cardiac disorders including arrhythmia, hypertension-induced heart disorders including hypertension-induced cardiac hypertrophy, disorders of the nervous system and neurological disorders including epilepsy, stroke, traumatic brain injury, spinal cord injury, anxiety, insomnia, encephalomyelitis, Alzheimer's disease multiple sclerosis, demyelinating disease, and Parkinson's syndrome. In an embodiment the present invention provides for the use of a compound of the invention for the preparation of a medicament for treating cardiac disorders. In another embodiment the present invention provides for the use of a compound of the invention for the preparation of a medicament for treating disorders of the nervous system.

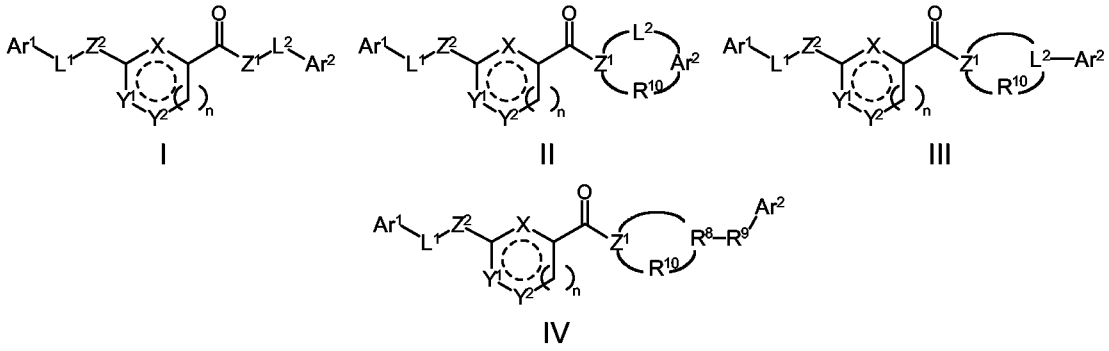
In yet another aspect, the present invention provides a pharmaceutical composition comprising a pharmaceutically acceptable excipient and a therapeutically effective amount of a compound according to the invention. Said composition is particularly useful in the prevention and/or treatment of conditions or diseases associated with ion channels of the Kv4 family such as the one cited herein. Said composition is particularly suited for example in the treatment of cardiac disorders and disorders of the nervous system.

It was also surprisingly found that the compounds of the present invention interact with ion channels of the Kv1 subfamily, and especially with Kv1.5 channels.

The present invention also provides a method of treating cardiac disorders comprising administrating to an individual in need of such treatment a pharmaceutical composition to the invention. In another embodiment, the present invention provides a method of treating disorders of the nervous system comprising administrating to an individual in need of such treatment a pharmaceutical composition to the invention.

Description of the invention

Thus, in a first aspect, the invention relates to a compound of Formula I, II, III or IV,



I II III

IV

stereoisomers, tautomers, racemics, prodrugs, metabolites thereof, or a pharmaceutically acceptable salt and/or solvate thereof,

wherein when X is O, Y^1 is selected from N or CH=, and n is 0,

wherein when X is N, Y^1 is selected from S, O, N or CH=, and n is 0 or Y1 is selected from N or CH=and n is 1,

wherein when X is S, Y^1 is selected from N or CH=, and n is 0,

wherein when X is CH=, Y^1 is selected from O, N or S, and n is 0 or 1,

wherein Y^2 is selected from $C(R^2)$- or N,

wherein n is an integer selected from 0 or 1,

wherein Z^1 is selected from $-N(R^3)-$, -O-, $-N(R^3)$-NH-, or CH_2- in Formula I, and Z^1 is selected from N, or CH in Formula II, III or IV, and

wherein Z^2 is selected from $N(R^1)$-, -O-, or S-.

The dotted ring represents one or several double bonds placed in any particular position of the bond forming the ring.

In an embodiment, X is nitrogen, Y^1 is sulfur, Y^2 is $C(R^2)$-, and n is 0, wherein R^2 has the same meaning as defined herein. In another embodiment of the present invention X is sulfur, Y^1 is nitrogen, Y^2 is $C(R^2)$-, and n is 0, wherein R^2 has the same meaning as defined herein. In another embodiment, X is oxygen, Y^1 is nitrogen, Y^2 is $C(R^2)$-, and n is 0, wherein R^2 has the same meaning as defined herein. In yet another embodiment, X is nitrogen, Y^1 is nitrogen, Y^2 is $C(R^2)$-, and n is 0, wherein R^2 has the same meaning as defined herein. According to a further embodiment, X is sulfur, Y^1 is CH-, Y^2 is $C(R^2)$-, and n is 0, wherein R^2 has the same meaning as defined herein. In yet a further embodiment, X is nitrogen, Y^1 is nitrogen, Y^2 is $C(R^2)$-, and n is 1, wherein R^2 has the same meaning as defined. In another embodiment, X is oxygen, Y^1 is nitrogen, Y^2 is nitrogen, and n is 0.

R^1 and R^3 can be each independently selected from hydrogen, alkyl, alkylcarbonyl, cycloalkyl, alkenyl, alkynyl, aryl, heteroaryl, heterocyclyl, aralkyl, cycloalkylalkyl or acyl, optionally substituted by one or more substituents. R^2 can be hydrogen or an optionally substituted alkyl, cycloalkyl, alkenyl or alkynyl. For example, encompassed R^2 radical can be chosen from hydrogen, an alkyl group, or a cycloalkyl group, preferably hydrogen or a C_1-C_4 alkyl group. In an embodiment of the present invention, R^2 is hydrogen or a methyl group.

Ar^1 and Ar^2 can be each independently selected from aryl, heterocyclyl or heteroaryl, optionally substituted by one or more substituents selected from halogen, hydroxy, nitro, amino, azide, cyano, alkyl, cycloalkyl, alkylamino, alkoxy, $-SO_2-NH_2$, aryl, heteroaryl, haloalkyl, haloalkoxy, haloaryl, carboxy, alkyloxycarbonyl, alkylaminocarbonyl, heteroarylalkyl, alkylsulfonamide, heterocyclyl, alkylcarbonylaminoalkyl, aryloxy, alkylcarbonyl, acyl, arylcarbonyl, aminocarbonyl, alkylsulfoxide, $-SO_2R^{15}$, or alkylthio, wherein R^{15} is alkyl or cycloalkyl. Ar^1 is either unsubstituted or substituted by 1 to 5, preferably 1 to 3 and most preferably 1 or 2 aromatic substituents. Ar^2 is either unsubstituted or substituted by 1 to 5, preferably 1 to 3 and most preferably 1 or 2 aromatic substituents.

L^2 represents a linking group selected from a single bond, a group of Formula $-R^8-R^9-$, alkylyn, cycloalkylene, $-NH-(C(R^4)(R^4))_q-$, $-(C(R^4)(R^4))_q-$, $-C(R^4)=$, $-(C(R^4)(R^4))_v-O-(C(R^4)(R^4))_w-$, $-(C(R^4)(R^4))_v-(C(R^4))_w=$, $-(C(R^4)(R^4))_q-(C=O)-$, or cycloalkylenoxyalkylene, wherein $-(C(R^4)(R^4))_q-$, $(C(R^4)(R^4))_w$ and $-(C(R^4)(R^4))_v-$ are each independently aliphatic or form a cycloalkyl, wherein each R^4 is independently selected from hydrogen, alkyl, hydroxyl, alkylaminoalkyl, carboxy, hydroxyalkyl, alkoxyalkyl,

alkylamino, or alkyloxycarbonyl; q is an integer between 0 and 6, preferably 0, 1, 2, 3 or 4, preferably, 0, 1 or 2; v is an integer between 0 and 6 preferably 0, 1, 2, 3 or 4, preferably, 0, 1 or 2; and w is an integer between 0 and 6 preferably 0, 1, 2, 3 or 4, preferably, 0, 1 or 2, wherein R^8 is alkylyn, $-(C(R^4)(R^4))_p-C(R^{14})$ or $-(C(R^4)(R^4))_p-C(R^4)=C$, wherein R^9 is selected from a single bond, $-(C(R^4)(R^4))_q-$, or C(=O)-, wherein R^{14} is selected from hydrogen, hydroxyl or alkyl, wherein p is an integer between 0 and 3, and

wherein R^{10} is selected from $-(C(R^4)(R^4))_m-$, $-(C(R^4)(R^4))_m-C(=O)O-(C(R^4)(R^4))_q-$, or $-(C(R^4)(R^4))_m-N(R^{12})-(C(R^4)(R^4))_q-$, wherein m is an integer between 1 and 6, preferably 1, 2 or 3, wherein R^{12} is selected from hydrogen, alkyl, aryl, arylalkyl or alkylcarbonyl.

L^1 represents a linking group selected from a single bond, $-(C(R^4)(R^4))_q-$, or $-(C(R^4)(R^4))_q-(C=O)-$, wherein each R^4 is independently selected from hydrogen, alkyl, hydroxyl, alkylaminoalkyl, carboxy, hydroxyalkyl, alkoxyalkyl, alkylamino, or alkyloxycarbonyl; q is an integer between 0 and 6, preferably, 0, 1, 2 or 3.

When describing the compounds of the invention, the terms used are to be construed in accordance with the following definitions, unless a context dictates otherwise:

The term "alkyl by itself or as part of another substituent, refers to a straight or branched saturated hydrocarbon group joined by single carbon-carbon bonds having 1 to 10 carbon atoms, for example 1 to 8 carbon atoms, for example 1 to 6 carbon atoms, preferably 1 to 4 carbon atoms. When a subscript is used herein following a carbon atom, the subscript refers to the number of carbon atoms that the named group may contain. Thus, for example, C_{1-4}alkyl means an alkyl of one to four carbon atoms. Examples of alkyl groups are methyl, ethyl, propyl, isopropyl, butyl, isobutyl, *sec*-butyl, *tert*-butyl, 2-methylbutyl, pentyl iso-amyl and its isomers, hexyl and its isomers, heptyl and its isomers and octyl and its isomer.

The term "optionally substituted alkyl" refers to an alkyl group optionally substituted with one or more substituents (for example 1 to 4 substituents, or 1 to 2 substituents) at any available point of attachment. Non-limiting examples of such substituents include halogen, hydroxy, carbonyl, nitro, amino, oximes, imines, azide, hydrazines, cyano, alkyl, aryl, heteroaryl, cycloalkyl, acyl, alkylamino, alkoxy, thiol, alkylthio, carboxylic acid, acylamino, alkyl esters, carbamates, thioamides, urea, sulphonamides and the like.

When the term "alkyl" is used as a suffix following another term, as in "hydroxyalkyl," this is intended to refer to an alkyl group, as defined above, being substituted with one or two (preferably one) substituent(s) selected from the other, specifically-named group, also as

defined herein. For example, "hydroxyalkyl" includes 2-hydroxyethyl, 1-(hydroxymethyl)-2-methylpropyl, 3,4-dihydroxybutyl, and so forth. "Alkoxyalkyl" refers to an alkyl group substituted with one to two of OR', wherein R' is alkoxy as defined below. For example, "aralkyl or "(aryl)alkyl refers to a substituted alkyl group as defined above wherein at least one of the alkyl substituents is an aryl as defined below, such as benzyl.

The term "hydroxyalkyl" refers to a -R^a-OH group wherein R^a is alkylene as defined herein.

The term "cycloalkyl by itself or aspart of another substituent, includes all saturated or partially saturated (containing 1 or 2 double bonds) hydrocarbon groups containing 1 to 3 rings, including monocyclic, bicyclic or polycyclic alkyl groups wherein each cyclic moiety has from 3 to 8 carbon atoms, for example 3 to 7 carbon atoms, for example 3 to 6 carbon atoms, for example 3 to 5 carbon atoms. The further rings of multi-ringcycloalkyls may be either fused, bridged and/or joined through one or more spiro unions. Examples of monocyclic cycloalkyl radicals include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl and the like. Examples of polycyclic cycloalkyl radicals include decahydronaphthyl, bicyclo [5.4.0] undecyl, adamantyl, and the like. An "optionally substituted cycloalkyl refers to a cycloalkyl having optionally one or more substituents (for example 1 to 3 substituents, or 1 to 2 substituents), selected from those defined above for substituted alkyl. When the suffix "ene" is used in conjunction with a cyclic group, this is intended to mean the cyclic group as defined herein having two single bonds as points of attachment to other groups.

The term "alkenyl by itself or as part of another substituent, refers to a straight or branched alkyl chain containing at least one unsaturation in the form of a single carbon to carbon double bond and having 2 to 10 carbon atoms, for example 2 to 8 carbon atoms, preferably 2 to 6 carbon atoms, more preferably 2 to 4 carbon atoms. Examples of alkenyl groups are ethenyl, 2-propenyl, 2-butenyl, 3-butenyl, 2-pentenyl and its isomers, 2-hexenyl and its isomers, 2-heptenyl and its isomers, 2-octenyl and its isomers, 2,4-pentadienyl and the like. An optionally substituted alkenyl refers to an alkenyl having optionally one or more substituents (for example 1 to 3 substituents, or 1 to 2 substituents), selected from those defined above for substituted alkyl.

The term "alkynyl by itself or as part of another substituent, refers to a straight or branched alkyl chain containing at least one unsaturation in the form of a single carbon to carbon triple bond and having 2 to 10 carbon atoms, for example 2 to 8 carbon atoms, preferably 2 to 6 carbon atoms, more preferably 2 to 4 carbon atoms. Examples alkynyl groups are ethynyl, 2-propynyl, 2-butynyl, 3-butynyl, 2-pentynyl and its isomers, 2-hexynyl

and its isomers, 2-heptynyl and its isomers, 2-octynyl and its isomers and the like. An optionally substituted alkynyl refers to an alkynyl having optionally one or more substituents (for example 1 to 4 substituents, or 1 to 2 substituents), selected from those defined above for substituted alkyl.

Where alkyl groups as defined are divalent, i.e., with two single bonds for attachment to two other groups, they are termed "alkylene" groups. Non-limiting examples of alkylene groups includes methylene, ethylene, methylmethylene, trimethylene, propylene, tetramethylene, ethylethylene, 1,2-dimethylethylene, pentamethylene and hexamethylene. Similarly, where alkenyl groups as defined above and alkynyl groups as defined above, respectively, are divalent radicals having single bonds for attachment to two other groups, they are termed "alkenylene" and "alkynylene" respectively.

Where alkyl groups as defined are trivalent, i.e., with three single bonds for attachment to three other groups, they are termed "alkylyne" or "alkyline" groups. Non-limiting example of such alkylyne include, methine, 1,1,2-ethyline, and the like.

The term "aryl as used herein by itself or aspart of another group refers but is not limited to 5 to 14 carbon-atom homocyclic (i.e., hydrocarbon) monocyclic, bicyclic or tricyclic aromatic rings or ring systems containing 1 to 4 rings which are fused together or linked covalently, typically containing 5 to 8 atoms; at least one of which is aromatic. The aromatic ring may optionally include one to three additional rings (either cycloalkyl, heterocyclyl or heteroaryl) fused thereto.

Non-limiting examples of aryl comprise phenyl, biphenylyl, biphenylenyl, 5- or 6-tetralinyl, 1-, 2-, 3-, 4-, 5-, 6-, 7- or 8-azulenyl, 1- or 2-naphthyl, 1-, 2- or 3-indenyl, 1-, 2- or 9-anthryl, 1- 2-, 3-, 4- or 5-acenaphtylenyl, 3-, 4- or 5-acenaphtenyl, 1-, 2-, 3-, 4- or 10-phenanthryl, 1- or 2-pentalenyl, 1, 2-, 3- or 4-fluorenyl, 4- or 5-indanyl, 5-, 6-, 7- or 8-tetrahydronaphthyl, 1,2,3,4-tetrahydronaphthyl, 1,4-dihydronaphthyl, dibenzo[a,d]cylcoheptenyl, 1-, 2-, 3-, 4- or 5-pyrenyl.

The aryl ring can optionally be substituted by one or more aromatic substituents. An "optionally substituted aryl refers tœan aryl having optionally one or more substituents (for example 1 to 5 substituents, or 1 to 2 substituents) at any available point of attachment. Non-limiting examples of such substituents are selected from halogen, hydroxy, carbonyl, nitro, amino, azido, hydrazine, cyano, alkyl, aryl, heteroaryl, heteroarylalkyl, cycloalkyl, acyl, alkylamino, alkylaminocarbonyl, $-SO_2R^{15}$, alkylcarbonyloxy, fused heterocyclyl, haloalkyl, alkylcarbonyl, aryloxy, arylcarbonyl, haloalkoxy, alkoxy, thiol, alkylthio, haloaryl,

carboxy, acylamino, alkyl esters, carbamate, thioamide, urea, or sulphonamide, and the like, wherein R^{15} is alkyl or cycloalkyl.

The term "aryloxy" as used herein denotes a group -O-aryl, wherein aryl is as defined above.

The term "aroyl" as used herein denotes a group -C(O)-aryl, wherein aryl is as defined above.

The term "heteroaryl as used herein by itself or as part of another group refers but is not limited to 5 to 12 carbon-atom aromatic rings or ring systems containing 1 to 3 rings which are fused together or linked covalently, typically containing 5 to 8 atoms; at least one of which is aromatic in which one or more carbon atoms in one or more of these rings can be replaced by oxygen, nitrogen or sulfur atoms where the nitrogen and sulfur heteroatoms may optionally be oxidized and the nitrogen heteroatoms may optionally bequaternized. Such rings may be fused to an aryl, cycloalkyl, heteroaryl or heterocyclyl ring. An "optionally substituted heteroaryl refers to a heteroaryl having optionally one or more substituents (for example 1 to 4 substituents, or 1 to 2 substituents), selected from those defined above for substituted aryl.

Non-limiting examples of heteroaryl can be 2- or 3-furyl, 2- or 3-thienyl, 1-, 2- or 3-pyrrolyl, 1-, 2-, 4- or 5-imidazolyl, 1-, 3-, 4- or 5-pyrazolyl, 3-, 4- or 5-isoxazolyl, 2-, 4- or 5-oxazolyl, 3-, 4- or 5-isothiazolyl, 2-, 4- or 5-thiazolyl, 1,2,3-triazol-1-, -2-, -4- or -5-yl, 1,2,4-triazol-1-, -3-, -4- or -5-yl, 1,2,3-oxadiazol-4- or -5-yl, 1,2,4-oxadiazol-3- or -5-yl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,3-thiadiazol-4- or -5-yl, 1,2,4-thiadiazol-3- or -5-yl, 1,2,5-thiadiazol-3- or -4-yl, 1,3,4-thiadiazolyl, 1- or 5-tetrazolyl, 2-, 3- or 4-pyridyl, 3- or 4-pyridazinyl, 2-, 4-, 5- or 6-pyrimidinyl, 2-, 3-, 4-, 5- 6-2H-thiopyranyl, 2-, 3- or 4-4H-thiopyranyl, 2-, 3-, 4-, 5-, 6- or 7-benzofuryl, 1-, 3-, 4- or 5-isobenzofuryl, 2-, 3-, 4-, 5-, 6- or 7-benzothienyl, 1-, 3-, 4- or 5-isobenzothienyl, 1-, 2-, 3-, 4-, 5-, 6- or 7-indolyl, 2- or 3-pyrazinyl, 1,4-oxazin-2- or -3-yl, 1,4-dioxin-2- or -3-yl, 1,4-thiazin-2- or -3-yl, 1,2,3-triazinyl, 1,2,4-triazinyl, 1,3,5-triazin-2-, -4- or -6-yl, thieno[2,3-b]furan-2-, -3-, -4-, or -5-yl, 1-, 2-, 4- or 5-benzimidazolyl, 1-, 3-, 4-, 5-, 6- or 7-benzopyrazolyl, 3-, 4-, 5-, 6- or 7-benzisoxazolyl, 2-, 4-, 5-, 6- or 7-benzoxazolyl, 3-, 4-, 5-, 6- or 7-benzisothiazolyl, 2-, 4-, 5-, 6- or 7-benzothiazolyl, 1-, 2-thianthrenyl, 3-, 4- or 5-isobenzofuranyl, 1-, 2-, 3-, 4- or 9-xanthenyl, 1-, 2-, 3- or 4-phenoxathiinyl, 2-, 3-pyrazinyl, 1-, 2-, 3-, 4-, 5-, 6-, 7- or 8-indolizinyl, 2-, 3-, 4- or 5-isoindolyl, 1-, 2-, 3-, 4-, 5-, 6- or 7-indazolyl, 2-, 6-, 7- or 8-purinyl, 4-, 5- or 6-phthalazinyl, 2-, 3- or 4-naphthyridinyl, 2-, 5- or 6-quinoxalinyl, 2-, 4-, 5-, 6-, 7- or 8-quinazolinyl, 1-, 2-, 3- or 4-quinolizinyl, 2-, 3-, 4-, 5-, 6-, 7-, or 8-quinolinyl(quinolyl), 2-, 4-, 5-, 6-, 7- or 8-

quinazolyl, 1-, 3-, 4-, 5-, 6-, 7- or 8-isoquinolinyl(isoquinolyl), 3-, 4-, 5-, 6-, 7- or 8-cinnolinyl, 2-, 4-, 6- or 7-pteridinyl, 1-, 2-, 3-, 4- or 9-carbazolyl, 1-, 2-, 3-, 4-, 5-, 6-, 7-, 8- or 9-carbolinyl, 1-, 2-, 3-, 4-, 5-, 6-, 7-, 8-, 9- or 10-phenanthridinyl, 1-, 2-, 3- or 4-acridinyl, 1-, 2-, 3-, 4-, 5-, 6-, 7-, 8- or 9-perimidinyl, 2-, 3-, 4-, 5-, 6-, 7-, 8-, 9- or 10-(1,7)phenanthrolinyl, 1- or 2-phenazinyl, 1-, 2-, 3-, 4-, or 10-phenothiazinyl, 3- or 4-furazanyl, 1-, 2-, 3-, 4-, or 10-phenoxazinyl, azepinyl, diazepinyl, dibenzo[b,f]azepinyl, dioxanyl, thietanyl, oxazolyl dibenzo[a,d]cylcoheptenyl, or additionally substituted derivatives thereof.

The terms "heterocyclyl" or "heterocyclo" as used herein by itself or as part of another group refer to non-aromatic, fully saturated or partially unsaturated cyclic groups (for example, 3 to 13 member monocyclic, 7 to 17 member bicyclic, or 10 to 20 member tricyclic ring systems, or containing a total of 3 to 10 ring atoms) which have at least one heteroatom in at least one carbon atom-containing ring. Each ring of the heterocyclic group containing a heteroatom may have 1,2, 3 or 4 heteroatoms selected from nitrogen atoms, oxygen atoms and/or sulfur atoms, where the nitrogen and sulfur heteroatoms may optionally be oxidized and the nitrogen heteroatoms may optionally be quaternized. The heterocyclic group may be attached at any heteroatom or carbon atom of the ring or ring system, where valence allows. The rings of multi-ring heterocycles may be fused, bridged and/or joined through one or more spiro atoms. An "optionally substituted heterocyclyl refers to a heterocyclic having optionally one or more substituents (for example 1 to 4 substituents, or 1 to 2 substituents), selected from those defined above for substituted aryl.

Exemplary heterocyclic groups include piperidinyl, azetidinyl, imidazolinyl, imidazolidinyl, isoxazolinyl, oxazolidinyl, isoxazolidinyl, thiazolidinyl, isothiazolidinyl, piperidyl, succinimidyl, 3H-indolyl, indolinyl, isoindolinyl, chromenyl, isochromanyl, xanthenyl, 2H-pyrrolyl, 1-pyrrolinyl, 2-pyrrolinyl, 3-pyrrolinyl, pyrrolidinyl, 4H-quinolizinyl, 4aH-carbazolyl, 2-oxopiperazinyl, piperazinyl, homopiperazinyl, 2-pyrazolinyl, 3-pyrazolinyl, pyranyl, dihydro-2H-pyranyl, 4H-pyranyl, 3,4-dihydro-2H-pyranyl, triazinyl, cinnolinyl, phthalazinyl, azepinyl, oxetanyl, thietanyl, 3-dioxolanyl, 1,4-dioxanyl, 2,5-dioximidazolidinyl, 2,2,4-piperidonyl, 2-oxopiperidinyl, 2-oxopyrrolodinyl, 2-oxoazepinyl, indolinyl, tetrahydropyranyl, tetrahydrofuranyl, tetrehydrothienyl, tetrahydroquinolinyl, tetrahydroisoquinolinyl, thiomorpholinyl, thiomorpholinyl sulfoxide, thiomorpholinyl sulfone, 1,3-dioxolanyl, 1,4-oxathianyl, 1,4-dithianyl, 1,3,5-trioxanyl, 6H-1,2,5-thiadiazinyl, 2H-1,5,2-dithiazinyl, 2H-oxocinyl, 1H-pyrrolizinyl, tetrahydro-1,1-dioxothienyl, N-

formylpiperazinyl, 2,3-dihydrobenzo[1,4]dioxin-2-yl, 2,3-dihydrobenzo[1,4]dioxin-6-yl, and morpholinyl.

The term "aralkyl" by itself or as part of another substituent refers to a group having as alkyl moiety the aforementioned alkyl attached to one of the aforementioned aryl rings. Examples of aralkyl radicals include benzyl, phenethyl, dibenzylmethyl, methylphenylmethyl, 3- (2-naphthyl)-butyl, and the like.

The term "cycloalkylalkyl" by itself or as part of another substituent refers to a group having one of the aforementioned cycloalkyl groups attached to one of the aforementioned alkyl chains. Examples of such cycloalkylalkyl radicals include cyclopropylmethyl, cyclobutylmethyl, cyclopentylmethyl, cyclohexylmethyl, 1-cyclopentylethyl, 1-cyclohexylethyl, 2-cyclopentylethyl, 2-cyclohexylethyl, cyclobutylpropyl, cyclopentylpropyl, 3-cyclopentylbutyl, cyclohexylbutyl and the like.

The term "heterocyclyl-alkyl" by itself or as part of another substituents refers to a group having one of the aforementioned heterocyclyl group attached to one of the aforementioned alkyl group, i.e., to a group R^b-R^c wherein R^b is alkylene or alkylene substituted by alkyl group and R^c is a heterocyclyl group.

The term "acyl" by itself or as part of another substituent refers to an alkanoyl group having 2 to 6 carbon atoms or a phenylalkanoyl group whose alkanoyl moiety has 1 to 4 carbon atoms, i.e; a carbonyl group linked to a radical such as, but not limited to, alkyl, aryl, more particularly, the group COR^{11}, wherein R^{11} can be selected from alkyl, aryl, substituted alkyl, or substituted aryl, as defined herein. The term acyl therefore encompasses the group alkylcarbonyl (COR^{11}), wherein R^{11} is alkyl. Said acyl can be exemplified by acetyl, propionyl, butyryl, valeryl and pivaloyl, benzoyl, phenylacetyl, phenylpropionyl and phenylbutytyl.

The term "alkylamino" by itself or as part of another substituent refers to a group consisting of an amino groups attached to one or two independently selected and optionally substituted alkyl groups, cycloalkyl groups, arylalkyl or cycloalkylalkyl groups i.e., $N(R^6)(R^7)$ wherein R^6 and R^7 are each independently selected from hydrogen, cycloalkyl, arylalkyl, cycloalkylalky or alkyl. Non-limiting examples of alkylamino groups include methylamino ($NHCH_3$), ethylamino ($NHCH_2CH_3$), n-propylamino, isopropylamino, n-butylamino, isobutylamino, sec-butylamino, tert-butylamino, n-hexylamino, and the like.

The term "keto" as used herein refers to the group =O.

The term "amino" refers to the group NH_2.

The term "aminocarbonyl" refers to the group -(C=O)-NH_2.

The term "aminoalkyl" refers to the group -R^b-NR^dR^e wherein R^b is alkylene or substituted alkylene, R^d is hydrogen or alkyl or substituted alkyl as defined herein, and R^e is hydrogen or alkyl as defined herein.

The term "alkylaminocarbonyl" refers to a group -(C=O)-NR^dR^e wherein R^d is hydrogen or alkyl or substituted alkyl as defined herein, and R^e is alkyl or substituted alkyl as defined herein.

The term "alkylaminocarbonylamino" refers to a group -NH(C=O)-NR^dR^e or -NR'(C=O)-NR^dR^e wherein R^d is hydrogen or alkyl or substituted alkyl as defined herein, and R^e is alkyl or substituted alkyl as defined herein, wherein R is alkyl or substituted alkyl.

The term "carboxy" refers to the group -CO_2H. Thus, a carboxyalkyl is an alkyl group as defined above having at least one substituent that is -CO_2H.

The term "alkoxycarbonyl" refers to a carboxy group linked to an alkyl radical i. e. to form C(=O)OR^{11}, wherein R^{11} is as defined above for acyl.

The term "alkylcarbonyloxy" refers to a O-C(=O)R^{11} wherein R^{11} is as defined above for acyl.

The term "alkylamidyl" or "alkylamide" refers to an alkylcarbonylamino group of Formula -NH(C=O)R or -NR'(C=O)R, wherein R and R are each independently alkyl or substituted alkyl.

The term "alkylcarbonylaminoalkyl" refers to a group -R^b-NR^d-C(=O)-R^e wherein R^b is alkylene or alkylene substituted by alkyl, R^d is hydrogen or alkyl as defined herein, and R^e is alkyl as defined herein.

The term "alkylamino(alkylsubstituted)alkyl" refers to a group -R^f-NR^dR^e wherein R^f is alkylene substituted by alkyl, R^d is hydrogen or alkyl or substituted alkyl as defined herein, and R^e is alkyl or substituted alkyl as defined herein.

The term "alkoxy" by itself or as part of another substituent refers to a group consisting of an oxygen atom attached to one optionally substituted straight or branched alkyl group, cycloalkyl group, arylalkyl or cycloalkylalkyl group. Non-limiting examples of suitable alkoxy group include methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, iso-butoxy, sec-butoxy, tert-butoxy, hexanoxy and the like.

The term "alkylthio" by itself or as part of another substituent refers to a group consisting of a sulfur atom attached to one optionally substituted alkyl group, cycloalkyl group, arylalkyl or cycloalkylalkyl group. Non-limiting examples of alkylthio groups include methylthio (SCH_3), ethylthio (SCH_2CH_3), n-propylthio, isopropylthio, n-butylthio, isobutylthio, sec-butylthio, tert-butylthio, n-hexylthio, and the like.

The term "acylamino" by itself or as part of another substituent refers to a group consisting of an amino group attached to one or two independently selected acyl groups as described before. In case the two acyl groups of a dicarboxylic acid are attached to the amino group these represent imides such as phtalimides, maleimides and the like, and are encompassed in the meaning of the term acylamino.

The term "halo" or "halogen" as a group or part of a group is generic for fluoro, chloro, bromo or iodo.

The term "haloalkyl" alone or in combination, refers to an alkyl radical having the meaning as defined above wherein one or more hydrogens are replaced with a halogen as defined above. Non-limiting examples of such haloalkyl radicals include chloromethyl, 1-bromoethyl, fluoromethyl, difluoromethyl, trifluoromethyl, 1,1,1-trifluoroethyl and the like.

The term "haloaryl" alone or in combination, refers to an aryl radical having the meaning as defined above wherein one or more hydrogens are replaced with a halogen as defined above.

The term "haloalkoxy" alone or in combination refers to a group of Formula -O-alkyl wherein the alkyl group is substituted by 1, 2 or 3 halogen atoms. For example, "haloalkoxy" includes $-OCF_3$ and $OCHF_2$.

The term "sulphonamide" alone or in combination refers to a group of Formula SO_2-NR^dR^e wherein R^d is hydrogen or alkyl or substituted alkyl as defined herein, and R^e is hydrogen or alkyl as defined herein.

As used herein, the term "optionally substituted alkyl, cycloalkyl, alkenyl or alkynyl" means "optionally substituted alkyl, optionally substituted cycloalkyl, optionally substituted alkenyl or optionally substituted alkynyl", wherein the substituents are the same as that described above for substituted alkyl.

Whenever the term "substituted" is used in the present invention, it is meant to indicate that one or more hydrogens on the atom indicated in the expression using "substituted" is replaced with a selection from the indicated group, provided that the indicated atom's

normal valency is not exceeded, and that the substitution results in a chemically stable compound, i.e. a compound that is sufficiently robust to survive isolation to a useful degree of purity from a reaction mixture, and formulation into a therapeutic agent.

Whenever used in the present invention the term "compounds of the invention or a similar term is meant to include the compounds of general Formula I, II, III or IV and any subgroup thereof. This term also refers to the compounds as depicted in Table 1 and 13 and their derivatives, *N*-oxides, salts, solvates, hydrates, stereoisomeric forms, racemic mixtures, tautomeric forms, optical isomers, analogues, pro-drugs, esters and metabolites, as well as their quaternized nitrogen analogues. The *N*-oxide forms of said compounds are meant to comprise compounds wherein one or several nitrogen atoms are oxidized to the so-called *N*-oxide.

As used in the specification and the appended claims, the singular forms "a", "an," and "the" include plural referents unless the context clearly dictates otherwise. By way of example, "a compound" means one compound or more than one compound.

Asterisks (*) are used herein to indicate the point at which a mono-, bi- or trivalent radical depicted is connected to the structure to which it relates and of which the radical forms part.

The term "pro-drug as used hereinmeans the pharmacologically acceptable derivatives such as esters, amides and phosphates, such that the resulting *in vivo* biotransformation product of the derivative is the active drug. The reference by Goodman and Gilman (The Pharmacological Basis of Therapeutics, 8th Ed, McGraw-Hill, Int. Ed. 1992, "Biotransformation of Drugs , p 13-15) describing pro-drugs generally is hereby incorporated. Pro-drugs of the compounds of the invention can be prepared by modifying functional groups present in said component in such a way that the modifications are cleaved, either in routine manipulation or *in vivo*, to the parent component. Typical examples of pro-drugs are described for instance in WO 99/33795, WO 99/33815, WO 99/33793 and WO 99/33792 all incorporated herein by reference. Pro-drugs are characterized by increased bio-availability and are readily metabolized into the active inhibitors *in vivo*.

In an particular embodiment, the present invention provides compounds of Formula I, II, III or IV, wherein, Y^1, Y^2, Z^1, Z^2 have the same meaning as that defined above and wherein Ar^1 is selected from 2- or 3-furyl, 2- or 3-thienyl, 1-, 2- or 3-pyrrolyl, 1-, 2-, 4- or 5-imidazolyl, 1-, 3-, 4- or 5-pyrazolyl, 3-, 4- or 5-isoxazolyl, 2-, 4- or 5-oxazolyl, 3-, 4- or 5-isothiazolyl, 2-, 4- or 5-thiazolyl, 1,2,3-triazol-1-, -2-, -4- or -5-yl, 1,2,4-triazol-1-, -3-, -4- or

-5-yl, 1,2,3-oxadiazol-4- or -5-yl, 1,2,4-oxadiazol-3- or -5-yl, 1,2,3-thiadiazol-4- or -5-yl, 1,2,4-thiadiazol-3- or -5-yl, 1,2,5-thiadiazol-3- or -4-yl, 1- or 5-tetrazolyl, phenyl, 2-, 3- or 4-pyridyl, 3- or 4-pyridazinyl, 2-, 4-, 5- or 6-pyrimidinyl, 2-, 3-, 4-, 5- 6-2H-thiopyranyl, 2-, 3- or 4-4H-thiopyranyl, 2-, 3-, 4-, 5-, 6- or 7-benzofuryl, 2-, 3-, 4-, 5-, 6- or 7-benzothienyl, benzimidazolonyl, 1,3-benzodioxolyl, 1-, 2-, 3-, 4-, 5-, 6- or 7-indolyl, 1-, 2-, 4- or 5-benzimidazolyl, 1-, 3-, 4-, 5-, 6- or 7-benzopyrazolyl, 3-, 4-, 5-, 6- or 7-benzisoxazolyl, 2-, 4-, 5-, 6- or 7-benzoxazolyl, 3-, 4-, 5-, 6- or 7-benzisothiazolyl, 2-, 4-, 5-, 6- or 7-benzthiazolyl, 1- or 2- naphthyl, 2-, 3-, 4-, 5-, 6-, 7-, 8-quinolinyl, 2-, 4-, 5-, 6-, 7- or 8-quinazolyl, 1-, 3-, 4-, 5-, 6-, 7-, 8-isoquinolinyl, 2,3-dihydrobenzo[1,4]dioxin-2-yl, 2,3-dihydrobenzo[1,4]dioxin-6-yl, 2,3-dihydrobenzofurany-5-yl, indanyl, 1,3-dihydrobenzoimidazol2-one, 1, 2, 3, 4-tetrahydronapthtlanel-1-yl or 1-, 2-, 3-, 4- or 9-carbazolyl, optionally substituted by one or more substituents selected from halogen, hydroxy, nitro, amino, azido, cyano, alkyl, cycloalkyl, alkylamino, alkoxy, $-SO_2-NH_2$, aryl, heteroaryl, heteroarylalkyl, haloalkyl, haloalkoxy, haloaryl, carboxy, alkyloxycarbonyl, alkylaminocarbonyl, alkylsulfonamide, heterocyclyl, alkylcarbonylaminoalkyl, aryloxy, alkylcarbonyl, acyl, arylcarbonyl, aminocarbonyl, alkylsulfoxide, or alkylthio,

wherein Ar^2 is selected from 2- or 3-furyl, 2- or 3-thienyl, 1-, 2- or 3-pyrrolyl, 1-, 2-, 4- or 5-imidazolyl, 1-, 3-, 4- or 5-pyrazolyl, 3-, 4- or 5-isoxazolyl, 2-, 4- or 5-oxazolyl, 3-, 4- or 5-isothiazolyl, 2-, 4- or 5-thiazolyl, 1,2,3-triazol-1-, -2-, -4- or -5-yl, 1,2,4-triazol-1-, -3-, -4- or -5-yl, 1,2,3-oxadiazol-4- or -5-yl, 1,2,4-oxadiazol-3- or -5-yl, 1,2,3-thiadiazol-4- or -5-yl, 1,2,4-thiadiazol-3- or -5-yl, 1,2,5-thiadiazol-3- or -4-yl, 1- or 5-tetrazolyl, phenyl, 2-, 3- or 4-pyridyl, 3- or 4-pyridazinyl, 2-, 4-, 5- or 6-pyrimidinyl, 2,3-dihydrobenzo[1,4]dioxin-2-yl, 2,3-dihydrobenzo[1,4]dioxin-6-yl, 2,3-dihydrobenzofurany-5-yl, indanyl, 1,3-dihydrobenzoimidazol2-one, 1, 2, 3, 4-tetrahydronapthtlanel-1-yl, 2-, 3-, 4-, 5- 6-2H-thiopyranyl, 2-, 3- or 4-4H-thiopyranyl, 2-, 3-, 4-, 5-, 6- or 7-benzofuryl, 2-, 3-, 4-, 5-, 6- or 7-benzothienyl, benzimidazolonyl, 1,3-benzodioxolyl, 1-, 2-, 3-, 4-, 5-, 6- or 7-indolyl, 1-, 2-, 4- or 5-benzimidazolyl, 1-, 3-, 4-, 5-, 6- or 7-benzopyrazolyl, 3-, 4-, 5-, 6- or 7-benzisoxazolyl, 2-, 4-, 5-, 6- or 7-benzoxazolyl, 3-, 4-, 5-, 6- or 7-benzisothiazolyl, 2-, 4-, 5-, 6- or 7-benzthiazolyl, 1- or 2- naphthyl, 2-, 3-, 4-, 5-, 6-, 7-, 8-quinolinyl, 2-, 4-, 5-, 6-, 7- or 8-quinazolyl, 1-, 3-, 4-, 5-, 6-, 7-, 8-isoquinolinyl, or 1-, 2-, 3-, 4- or 9-carbazolyl, optionally substituted by one or more substituents selected from halogen, hydroxy, nitro, amino, azido, cyano, alkyl, cycloalkyl, alkylamino, alkoxy, $-SO_2-NH_2$, aryl, heteroaryl, heteroarylalkyl, haloalkyl, haloalkoxy, haloaryl, carboxy, alkyloxycarbonyl, alkylaminocarbonyl, alkylsulfonamide, heterocyclyl, alkylcarbonylaminoalkyl, aryloxy, alkylcarbonyl, acyl, arylcarbonyl, aminocarbonyl, alkylsulfoxide, or alkylthio,

wherein L^2 is a linking group selected from a single bond, a group of Formula $-R^8-R^9-$, alkylyn, N, cycloalkylene, $-NH-(C(R^4)(R^4))_q-$, $-(C(R^4)(R^4))_q-$, $-C(R^4)=$, $-(C(R^4)(R^4))_v-O-(C(R^4)(R^4))_w-$, $-(C(R^4)(R^4))_v-(C(R^4))_w=$, $-(C(R^4)(R^4))_q-(C=O)-$, or cycloalkylenoxyalkylene, wherein $-(C(R^4)(R^4))_q-$, $(C(R^4)(R^4))_w$ and $-(C(R^4)(R^4))_v-$ are each independently aliphatic or form a cycloalkyl, wherein each R^4 is independently selected from hydrogen, alkyl, hydroxyl, alkylaminoalkyl, carboxy, hydroxyalkyl, alkoxyalkyl, alkylamino, or alkyloxycarbonyl; q is an integer between 0 and 6; v is an integer between 0 and 6 and w is an integer between 0 and 6,

wherein L^1 is a linking group selected from a single bond, $-(C(R^4)(R^4))_q-$, or $-(C(R^4)(R^4))_q-(C=O)-$, wherein each R^4 is independently selected from hydrogen, alkyl, hydroxyl, alkylaminoalkyl, carboxy, hydroxyalkyl, alkoxyalkyl, alkylamino, or alkyloxycarbonyl; q is an integer between 0 and 6;

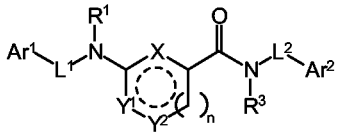
wherein R^8 is alkylyn, $-(C(R^4)(R^4))_p-C(R^{14})$ or $-(C(R^4)(R^4))_p-C(R^4)=C$, wherein R^9 is selected from a single bond, $-(C(R^4)(R^4))_q-$, or C(=O)-, wherein R^{14} is selected from hydrogen, hydroxyl or alkyl, wherein p is an integer between 0 and 3,

wherein R^{10} is selected from $-(C(R^4)(R^4))_m-$, $-(C(R^4)(R^4))_m-C(=O)O-(C(R^4)(R^4))_q-$, or $-(C(R^4)(R^4))_m-N(R^{12})-(C(R^4)(R^4))_q-$, wherein m is an integer between 1 and 6, wherein R^{12} is selected from hydrogen, alkyl, aryl, arylalkyl, or alkylcarbonyl,

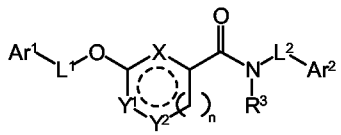
wherein R^1 and R^3 are each independently selected from hydrogen, C_1-C_8 alkyl, aryl, aralkyl, C_3-C_8 cycloalkyl, alkylcarbonyl, or acyl, and

wherein R^2 is selected from hydrogen, C_1-C_8 alkyl or C_3-C_8 cycloalkyl.

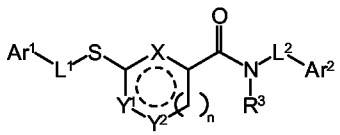
According to a preferred embodiment, the present invention provides compounds of Formula V to XIII,



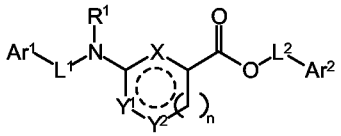
V



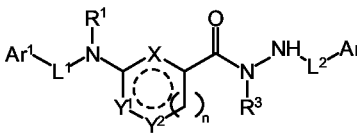
VI



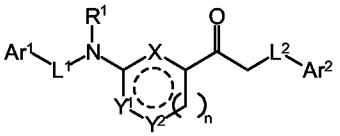
VII



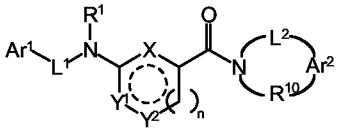
VIII

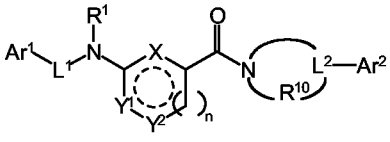


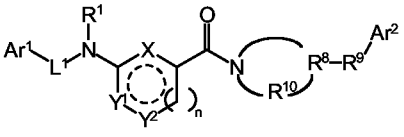
IX



X



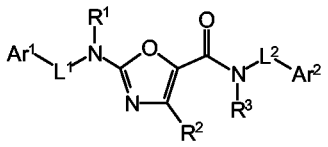




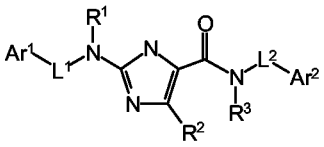
XI XII XIII

wherein X, Y^1, Y^2, R^1, n, R^3, R^8, R^9, R^{10}, L^1, L^2, Ar^1 and Ar^2 have the same meaning as that defined hereinabove.

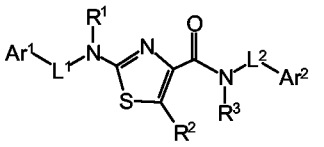
According to another embodiment, the present invention provides compounds of Formula XIV to XXIX,



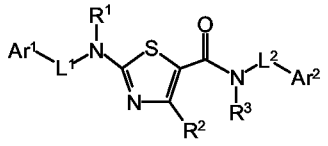
XIV



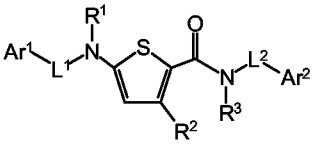
XV



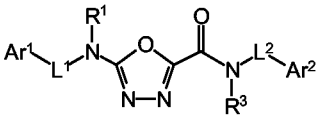
XVI



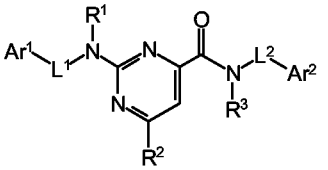
XVII



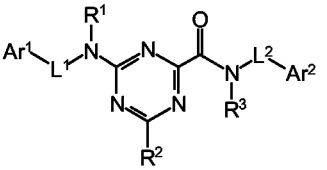
XVIII



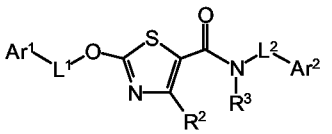
XIX



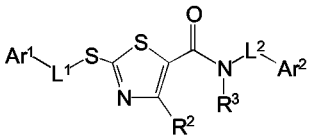
XX



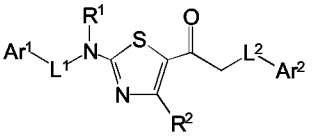
XXI



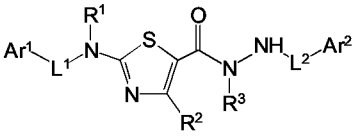
XXII



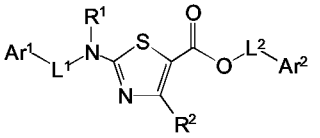
XXIII



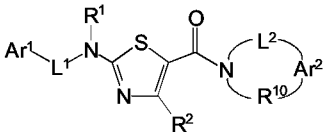
XXIV



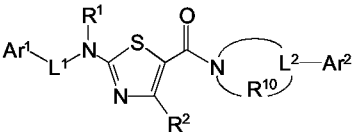
XXV



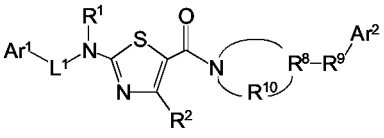
XXVI



XXVII



XXVIII



XXIX

wherein Ar^1 is selected from 2- or 3-furyl, 2- or 3-thienyl, 1-, 2- or 3-pyrrolyl, 1-, 2-, 4- or 5-imidazolyl, 1-, 3-, 4- or 5-pyrazolyl, 3-, 4- or 5-isoxazolyl, 2-, 4- or 5-oxazolyl, 3-, 4- or 5-isothiazolyl, 2-, 4- or 5-thiazolyl, 1,2,3-triazol-1-, -2-, -4- or -5-yl, 1,2,4-triazol-1-, -3-, -4- or -5-yl, 1,2,3-oxadiazol-4- or -5-yl, 1,2,4-oxadiazol-3- or -5-yl, 1,2,3-thiadiazol-4- or -5-yl, 1,2,4-thiadiazol-3- or -5-yl, 1,2,5-thiadiazol-3- or -4-yl, 1- or 5-tetrazolyl, phenyl, 2-, 3- or 4-pyridyl, 3- or 4-pyridazinyl, 2-, 4-, 5- or 6-pyrimidinyl, 2-, 3-, 4-, 5- 6-2H-thiopyranyl, 2-, 3-

or 4-4H-thiopyranyl, 2-, 3-, 4-, 5-, 6- or 7-benzofuryl, 2-, 3-, 4-, 5-, 6- or 7-benzothienyl, benzimidazolonyl, 1,3-benzodioxolyl, 1-, 2-, 3-, 4-, 5-, 6- or 7-indolyl, 1-, 2-, 4- or 5-benzimidazolyl, 1-, 3-, 4-, 5-, 6- or 7-benzopyrazolyl, 3-, 4-, 5-, 6- or 7-benzisoxazolyl, 2-, 4-, 5-, 6- or 7-benzoxazolyl, 3-, 4-, 5-, 6- or 7-benzisothiazolyl, 2-, 4-, 5-, 6- or 7-benzthiazolyl, 1- or 2- naphthyl, 2-, 3-, 4-, 5-, 6-, 7-, 8-quinolinyl, 2-, 4-, 5-, 6-, 7- or 8-quinazolyl, 1-, 3-, 4-, 5-, 6-, 7-, 8-isoquinolinyl, 2,3-dihydrobenzo[1,4]dioxin-2-yl, 2,3-dihydrobenzo[1,4]dioxin-6-yl, 2,3-dihydrobenzofurany-5-yl, indanyl, 1,3-dihydrobenzoimidazol2-one, 1, 2, 3, 4-tetrahydronapthtlanel-1-yl or 1-, 2-, 3-, 4- or 9-carbazolyl, optionally substituted by one or more substituents selected from halogen, hydroxy, nitro, amino, azido, cyano, alkyl, cycloalkyl, alkylamino, alkoxy, $-SO_2-NH_2$, aryl, heteroaryl, heteroarylalkyl, haloalkyl, haloalkoxy, haloaryl, carboxy, alkyloxycarbonyl, alkylaminocarbonyl, alkylsulfonamide, heterocyclyl, alkylcarbonylaminoalkyl, aryloxy, alkylcarbonyl, acyl, arylcarbonyl, aminocarbonyl, alkylsulfoxide, or alkylthio,

wherein Ar^2 is selected from 2- or 3-furyl, 2- or 3-thienyl, 1-, 2- or 3-pyrrolyl, 1-, 2-, 4- or 5-imidazolyl, 1-, 3-, 4- or 5-pyrazolyl, 3-, 4- or 5-isoxazolyl, 2-, 4- or 5-oxazolyl, 3-, 4- or 5-isothiazolyl, 2-, 4- or 5-thiazolyl, 1,2,3-triazol-1-, -2-, -4- or -5-yl, 1,2,4-triazol-1-, -3-, -4- or -5-yl, 1,2,3-oxadiazol-4- or -5-yl, 1,2,4-oxadiazol-3- or -5-yl, 1,2,3-thiadiazol-4- or -5-yl, 1,2,4-thiadiazol-3- or -5-yl, 1,2,5-thiadiazol-3- or -4-yl, 1- or 5-tetrazolyl, phenyl, 2-, 3- or 4-pyridyl, 3- or 4-pyridazinyl, 2-, 4-, 5- or 6-pyrimidinyl, 2,3-dihydrobenzo[1,4]dioxin-2-yl, 2,3-dihydrobenzo[1,4]dioxin-6-yl, 2,3-dihydrobenzofurany-5-yl, indanyl, 1,3-dihydrobenzoimidazol2-one, 1, 2, 3, 4-tetrahydronapthtlanel-1-yl, 2-, 3-, 4-, 5- 6-2H-thiopyranyl, 2-, 3- or 4-4H-thiopyranyl, 2-, 3-, 4-, 5-, 6- or 7-benzofuryl, 2-, 3-, 4-, 5-, 6- or 7-benzothienyl, benzimidazolonyl, 1,3-benzodioxolyl, 1-, 2-, 3-, 4-, 5-, 6- or 7-indolyl, 1-, 2-, 4- or 5-benzimidazolyl, 1-, 3-, 4-, 5-, 6- or 7-benzopyrazolyl, 3-, 4-, 5-, 6- or 7-benzisoxazolyl, 2-, 4-, 5-, 6- or 7-benzoxazolyl, 3-, 4-, 5-, 6- or 7-benzisothiazolyl, 2-, 4-, 5-, 6- or 7-benzthiazolyl, 1- or 2- naphthyl, 2-, 3-, 4-, 5-, 6-, 7-, 8-quinolinyl, 2-, 4-, 5-, 6-, 7- or 8-quinazolyl, 1-, 3-, 4-, 5-, 6-, 7-, 8-isoquinolinyl, or 1-, 2-, 3-, 4- or 9-carbazolyl, optionally substituted by one or more substituents selected from halogen, hydroxy, nitro, amino, azido, cyano, alkyl, cycloalkyl, alkylamino, alkoxy, $-SO_2-NH_2$, aryl, heteroaryl, heteroarylalkyl, haloalkyl, haloalkoxy, haloaryl, carboxy, alkyloxycarbonyl, alkylaminocarbonyl, alkylsulfonamide, heterocyclyl, alkylcarbonylaminoalkyl, aryloxy, alkylcarbonyl, acyl, arylcarbonyl, aminocarbonyl, alkylsulfoxide, or alkylthio,

wherein L^2 is a linking group selected from a single bond, a group of Formula $-R^8-R^9-$, alkylyn, N, cycloalkylene, $-NH-(C(R^4)(R^4))_q-$, $-(C(R^4)(R^4))_q-$, $-C(R^4)=$, $-(C(R^4)(R^4))_v-O-(C(R^4)(R^4))_w-$, $-(C(R^4)(R^4))_v-(C(R^4))_w=$, $-(C(R^4)(R^4))_q-(C=O)-$, or

cycloalkylenoxyalkylene, wherein -$(C(R^4)(R^4))_q$-, $(C(R^4)(R^4))_w$ and -$(C(R^4)(R^4))_v$- are each independently aliphatic or form a cycloalkyl, wherein each R^4 is independently selected from hydrogen, alkyl, hydroxyl, alkylaminoalkyl, carboxy, hydroxyalkyl, alkoxyalkyl, alkylamino, or alkyloxycarbonyl; q is an integer between 0 and 6; v is an integer between 0 and 6 and w is an integer between 0 and 6,

wherein L^1 is a linking group selected from a single bond, -$(C(R^4)(R^4))_q$-, or -$(C(R^4)(R^4))_q$-(C=O)-, wherein each R^4 is independently selected from hydrogen, alkyl, hydroxyl, alkylaminoalkyl, carboxy, hydroxyalkyl, alkoxyalkyl, alkylamino, or alkyloxycarbonyl; q is an integer between 0 and 6;

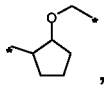
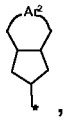
wherein R^8 is alkylyn, -$(C(R^4)(R^4))_p$-$C(R^{14})$ or -$(C(R^4)(R^4))_p$-$C(R^4)$=C, wherein R^9 is selected from a single bond, -$(C(R^4)(R^4))_q$-, or C(=O)-, wherein R^{14} is selected from hydrogen, hydroxyl or alkyl, wherein p is an integer between 0 and 3,

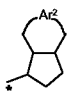
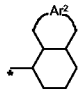
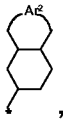
wherein R^{10} is selected from -$(C(R^4)(R^4))_m$-, -$(C(R^4)(R^4))_m$-C(=O)O-$(C(R^4)(R^4))_q$-, or -$(C(R^4)(R^4))_m$-$N(R^{12})$-$(C(R^4)(R^4))_q$-, wherein m is an integer between 1 and 6, wherein R^{12} is selected from hydrogen, alkyl, aryl, arylalkyl, or alkylcarbonyl, and

wherein R^1 and R^3 are each independently selected from hydrogen, C_1-C_8 alkyl, aryl, aralkyl, C_3-C_8 cycloalkyl, alkylcarbonyl, or acyl, R^2 is selected from hydrogen, C_1-C_8 alkyl or C_3-C_8 cycloalkyl.

According to another embodiment, the present invention provides compound having a structural Formula selected from Formula XIV to XXVI, wherein Ar^1 is selected from phenyl, 6-indolyl, 1-napthyl, 2-naphtly, 2,3-dihydrobenzo[1,4]dioxin-2-yl, 2,3-dihydrobenzo[1,4]dioxin-6-yl, indanyl, 1,3-dihydrobenzoimidazol2-one, 1, 2, 3, 4-tetrahydronapthtlanel-1-yl, 2-benzofuran-5-yl, pyridin-4-yl, 1,3-benzodioxolyl, benzimidazolonyl, 3-thiophenyl, or 5-(2,3-dihydro)benzofuranyl, optionally substituted with one to 4 substituent selected from F, Cl, Br, -CH_3, t-bu, -OCH_3, -NO_2, -CO_2H, -C(=O)-$N(CH_3)_2$, -O-C(=O)-CH_3, , , , -CH_2-CH_3, phenyl, N-morpholino, -SO_2-CH_3, -CF_3, -OCF_3, -CH_2-NH-C(=O)-CH_3, -S-CH_3, -C(=O)-CH_3, -C(=O)O-CH_3, -C(=O)O-CH_2-CH_3, -C(=O)NH_2, -$N(CH_3)_2$, -SO_2-$N(CH_3)_2$, phenoxyl, benzoyl, -$C(CH_3)_3$, -O-$(CH_2)_2$-CH_3, -OH or CN,

wherein L^2 is selected from single bond, -CH_2-, -$(CH_2)_2$-, -$(CH_2)_3$-, -$CH(CH_2OH)$-, -$CH(CH_2$-O-$CH_3)$-, -$CH(CH_3)$-, -$CH(CH_2$-$CH_3)$-, -$CH(CO_2H)$-, -$CH(CO_2CH_3)$-,

$-(CH_2)_2-O-CH_2-$, $-CH(,CH_2-N(CH_3)_2)-$, $-(CH_2)_2-CH=$, or , or wherein L^2-Ar^2 is ,

,  or ,

wherein Ar^2 is selected from phenyl, 1-naphthyl or 2-naphthyl, pyridin-4-yl, 1,3-benzodioxolyl, benzimidazolonyl, pyridin-3-yl, pyridin-2-yl, 5-indolyl, 8-quinolinyl, 2-thiophenyl, 2,3-dihydrobenzofuran-5-yl, 2-thienyl, 3-thienyl, 2,3-dihydrobenzo[1,4]dioxin-2-yl, 2,3-dihydrobenzo[1,4]dioxin-6-yl, indanyl, 1,3-dihydrobenzoimidazol-2-one, benzo(1,3)dioxo-5-yl, indan-1-yl, 1, 2, 3, 4-tetrahydronapthtlanel-1-yl, 2-benzofuran-5-yl, pyridin-4-yl, 2-benzoxazolyl, or 5-benzofuranyl, optionally substituted by one or more substituents selected from nitro, $-SO_2-NH_2$, F, Cl, Br, OH, $-CH_3$, $-OCH_3$, $-NO_2$, $-CO_2H$, $-C(=O)-N(CH_3)_2$, $-O-C(=O)-CH_3$, , , , , N-morpholino, $-CH_2-CH_3$, phenyl, $-SO_2-CH_3$, $-CF_3$, $-OCF_3$, $-CH_2-NH-C(=O)-CH_3$, $-S-CH_3$, $-C(=O)-CH_3$, $-C(=O)O-CH_3$, $-C(=O)O-CH_2-CH_3$, $-C(=O)NH_2$, $-N(CH_3)_2$, $-SO_2-N(CH_3)_2$, phenoxyl, benzoyl, $-C(CH_3)_3$, $-O-(CH_2)_2-CH_3$, or CN,

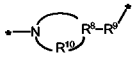
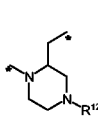
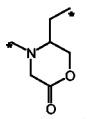
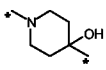
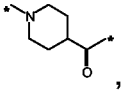
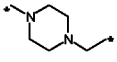
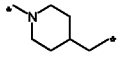
wherein L^1 is single bond or C(=O)-,

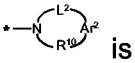
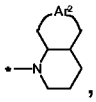
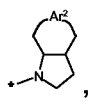
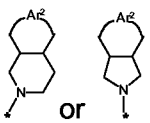
wherein R^1 is selected from hydrogen, $-CH_3$, or $-C(=O)-CH_3$,

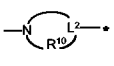
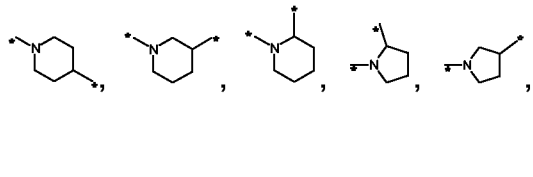
wherein R^3 is selected from hydrogen, $-CH_3$, phenyl, benzyl or $-C(=O)-CH_3$, and

wherein R^2 is selected from hydrogen, $-CH_3$, or $-C(=O)-CH_3$.

In yet a further embodiment, the present invention provides compounds having a structural Formula selected from Formula XXVII to XXIX,

wherein the group  is selected from , , , , , , , , ,  or 

wherein the group  is selected from , ,  or ,

wherein the group  is selected from 

wherein R^{12} is selected from hydrogen, CH_3-C(=O)-, CH_3- or benzyl,

wherein Ar^1 is selected from phenyl, 6-indolyl, 1-napthyl, 2-naphtly, 2,3-dihydrobenzo[1,4]dioxin-2-yl, 2,3-dihydrobenzo[1,4]dioxin-6-yl, indanyl, 1,3-dihydrobenzoimidazol2-one, 1, 2, 3, 4-tetrahydronapthtlanel-1-yl, 2-benzofuran-5-yl, pyridin-4-yl, 3-thienyl, 1,3-benzodioxolyl, benzimidazolonyl, or 5-(2,3-dihydro)benzofuranyl, optionally substituted with one to 4 substituent selected from F, Cl, Br, $-CH_3$, t-bu, $-OCH_3$, $-NO_2$, $-CO_2H$, $-C(=O)-N(CH_3)_2$, $-O-C(=O)-CH_3$, , , , N-morpholino, $-CH_2-CH_3$, phenyl, $-SO_2-CH_3$, $-CF_3$, $-OCF_3$, $-CH_2-NH-C(=O)-CH_3$, $-S-CH_3$, $-C(=O)-CH_3$, $-C(=O)O-CH_3$, $-C(=O)NH_2$, $-N(CH_3)_2$, $-SO_2-N(CH_3)_2$, phenoxyl, benzoyl, $-C(CH_3)_3$, $-O-(CH_2)_2-CH_3$, -OH or CN,

wherein Ar^2 is selected from phenyl, 1-naphthyl or 2-naphthyl, pyridin-4-yl, pyridin-3-yl, pyridin-2-yl, 5-indolyl, 8-quinolinyl, 2-thiophenyl, 2-benzoxazolyl, 1,3-benzodioxolyl, 2,3-dihydrobenzofuran-5-yl, 2-thienyl, 3-thienyl, 2,3-dihydrobenzo[1,4]dioxin-2-yl, 2,3-dihydrobenzo[1,4]dioxin-6-yl, indanyl, 1,3-dihydrobenzoimidazol-2-one, benzo(1,3)dioxo-5-yl, indan-1-yl, 1, 2, 3, 4-tetrahydronapthtlanel-1-yl, 2-benzofuran-5-yl, pyridin-4-yl, benzimidazolonyl, or 5-benzofuranyl, optionally substituted by one or more substituents selected from nitro, $-SO_2-NH_2$, F, Cl, Br, OH, $-CH_3$, $-OCH_3$, $-NO_2$, $-CO_2H$, $-C(=O)-N(CH_3)_2$, $-O-C(=O)-CH_3$, , , , , N-morpholino, $-CH_2-CH_3$, phenyl, $-SO_2-CH_3$, $-CF_3$, $-OCF_3$, $-CH_2-NH-C(=O)-CH_3$, $-S-CH_3$, $-C(=O)-CH_3$, $-C(=O)O-CH_3$, $-C(=O)O-CH_2-CH_3$, $-C(=O)NH_2$, $-N(CH_3)_2$, $-SO_2-N(CH_3)_2$, phenoxyl, benzoyl, $-C(CH_3)_3$, $-O-(CH_2)_2-CH_3$, or CN, wherein R^1 is selected from hydrogen, $-CH_3$, or -C(=O)-CH_3,

wherein L^1 is single bond or C(=O)-,

wherein R^3 is selected from hydrogen, $-CH_3$, phenyl, benzyl or -C(=O)-CH_3, and

wherein R^2 is selected from hydrogen, $-CH_3$, or -C(=O)-CH_3.

In one embodiment, the invention relates to compounds of Formula V, wherein X, Y^1, Y^2, R^1, n, R^3, R^8, R^9, R^{10}, L^1, L^2, Ar^1 and Ar^2 have the same meaning as that defined hereinabove, preferably of compounds of Formula XVII, wherein Ar^1 is selected from 2- or

3-furyl, 2- or 3-thienyl, 1-, 2- or 3-pyrrolyl, 1-, 2-, 4- or 5-imidazolyl, 1-, 3-, 4- or 5-pyrazolyl, 3-, 4- or 5-isoxazolyl, 2-, 4- or 5-oxazolyl, 3-, 4- or 5-isothiazolyl, 2-, 4- or 5-thiazolyl, 1,2,3-triazol-1-, -2-, -4- or -5-yl, 1,2,4-triazol-1-, -3-, -4- or -5-yl, 1,2,3-oxadiazol-4- or -5-yl, 1,2,4-oxadiazol-3- or -5-yl, 1,2,3-thiadiazol-4- or -5-yl, 1,2,4-thiadiazol-3- or -5-yl, 1,2,5-thiadiazol-3- or -4-yl, 1- or 5-tetrazolyl, phenyl, 2-, 3- or 4-pyridyl, 3- or 4-pyridazinyl, 2-, 4-, 5- or 6-pyrimidinyl, 2-, 3-, 4-, 5- 6-2H-thiopyranyl, 2-, 3- or 4-4H-thiopyranyl, 2-, 3-, 4-, 5-, 6- or 7-benzofuryl, 2-, 3-, 4-, 5-, 6- or 7-benzothienyl, benzimidazolonyl, 1,3-benzodioxolyl, 1-, 2-, 3-, 4-, 5-, 6- or 7-indolyl, 1-, 2-, 4- or 5-benzimidazolyl, 1-, 3-, 4-, 5-, 6- or 7-benzopyrazolyl, 3-, 4-, 5-, 6- or 7-benzisoxazolyl, 2-, 4-, 5-, 6- or 7-benzoxazolyl, 3-, 4-, 5-, 6- or 7-benzisothiazolyl, 2-, 4-, 5-, 6- or 7-benzthiazolyl, 1- or 2- naphthyl, 2-, 3-, 4-, 5-, 6-, 7-, 8-quinolinyl, 2-, 4-, 5-, 6-, 7- or 8-quinazolyl, 1-, 3-, 4-, 5-, 6-, 7-, 8-isoquinolinyl, 2,3-dihydrobenzo[1,4]dioxin-2-yl, 2,3-dihydrobenzo[1,4]dioxin-6-yl, 2,3-dihydrobenzofurany-5-yl, indanyl, 1,3-dihydrobenzoimidazol2-one, 1, 2, 3, 4-tetrahydronapthtlanel-1-yl or 1-, 2-, 3-, 4- or 9-carbazolyl, optionally substituted by one or more substituents selected from halogen, hydroxy, nitro, amino, azido, cyano, alkyl, cycloalkyl, alkylamino, alkoxy, $-SO_2-NH_2$, aryl, heteroaryl, heteroarylalkyl, haloalkyl, haloalkoxy, haloaryl, carboxy, alkyloxycarbonyl, alkylaminocarbonyl, alkylsulfonamide, heterocyclyl, alkylcarbonylaminoalkyl, aryloxy, alkylcarbonyl, acyl, arylcarbonyl, aminocarbonyl, alkylsulfoxide, or alkylthio, wherein Ar^2 is selected from 2- or 3-furyl, 2- or 3-thienyl, 1-, 2- or 3-pyrrolyl, 1-, 2-, 4- or 5-imidazolyl, 1-, 3-, 4- or 5-pyrazolyl, 3-, 4- or 5-isoxazolyl, 2-, 4- or 5-oxazolyl, 3-, 4- or 5-isothiazolyl, 2-, 4- or 5-thiazolyl, 1,2,3-triazol-1-, -2-, -4- or -5-yl, 1,2,4-triazol-1-, -3-, -4- or -5-yl, 1,2,3-oxadiazol-4- or -5-yl, 1,2,4-oxadiazol-3- or -5-yl, 1,2,3-thiadiazol-4- or -5-yl, 1,2,4-thiadiazol-3- or -5-yl, 1,2,5-thiadiazol-3- or -4-yl, 1- or 5-tetrazolyl, phenyl, 2-, 3- or 4-pyridyl, 3- or 4-pyridazinyl, 2-, 4-, 5- or 6-pyrimidinyl, 2,3-dihydrobenzo[1,4]dioxin-2-yl, 2,3-dihydrobenzo[1,4]dioxin-6-yl, 2,3-dihydrobenzofurany-5-yl, indanyl, 1,3-dihydrobenzoimidazol2-one, 1, 2, 3, 4-tetrahydronapthtlanel-1-yl, 2-, 3-, 4-, 5- 6-2H-thiopyranyl, 2-, 3- or 4-4H-thiopyranyl, 2-, 3-, 4-, 5-, 6- or 7-benzofuryl, 2-, 3-, 4-, 5-, 6- or 7-benzothienyl, benzimidazolonyl, 1,3-benzodioxolyl, 1-, 2-, 3-, 4-, 5-, 6- or 7-indolyl, 1-, 2-, 4- or 5-benzimidazolyl, 1-, 3-, 4-, 5-, 6- or 7-benzopyrazolyl, 3-, 4-, 5-, 6- or 7-benzisoxazolyl, 2-, 4-, 5-, 6- or 7-benzoxazolyl, 3-, 4-, 5-, 6- or 7-benzisothiazolyl, 2-, 4-, 5-, 6- or 7-benzthiazolyl, 1- or 2- naphthyl, 2-, 3-, 4-, 5-, 6-, 7-, 8-quinolinyl, 2-, 4-, 5-, 6-, 7- or 8-quinazolyl, 1-, 3-, 4-, 5-, 6-, 7-, 8-isoquinolinyl, or 1-, 2-, 3-, 4- or 9-carbazolyl, optionally substituted by one or more substituents selected from halogen, hydroxy, nitro, amino, azido, cyano, alkyl, cycloalkyl, alkylamino, alkoxy, $-SO_2-NH_2$, aryl, heteroaryl, heteroarylalkyl, haloalkyl, haloalkoxy, haloaryl, carboxy, alkyloxycarbonyl,

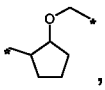
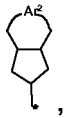
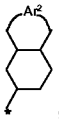
alkylaminocarbonyl, alkylsulfonamide, heterocyclyl, alkylcarbonylaminoalkyl, aryloxy, alkylcarbonyl, acyl, arylcarbonyl, aminocarbonyl, alkylsulfoxide, or alkylthio, wherein L^2 is a linking group selected from a single bond, a group of Formula $-R^8-R^9-$, alkylyn, N, cycloalkylene, $-NH-(C(R^4)(R^4))_q-$, $-(C(R^4)(R^4))_q-$, $-C(R^4)=$, $-(C(R^4)(R^4))_v-O-(C(R^4)(R^4))_w-$, $-(C(R^4)(R^4))_v-(C(R^4))_w=$, $-(C(R^4)(R^4))_q-(C=O)-$, or cycloalkylenoxyalkylene, wherein $-(C(R^4)(R^4))_q-$, $(C(R^4)(R^4))_w$ and $-(C(R^4)(R^4))_v-$ are each independently aliphatic or form a cycloalkyl, wherein each R^4 is independently selected from hydrogen, alkyl, hydroxyl, alkylaminoalkyl, carboxy, hydroxyalkyl, alkoxyalkyl, alkylamino, or alkyloxycarbonyl; q is an integer between 0 and 6; v is an integer between 0 and 6 and w is an integer between 0 and 6, wherein L^1 is a linking group selected from a single bond, $-(C(R^4)(R^4))_q-$, or $-(C(R^4)(R^4))_q-(C=O)-$, wherein each R^4 is independently selected from hydrogen, alkyl, hydroxyl, alkylaminoalkyl, carboxy, hydroxyalkyl, alkoxyalkyl, alkylamino, or alkyloxycarbonyl; q is an integer between 0 and 6;

wherein R^8 is alkylyn, $-(C(R^4)(R^4))_p-C(R^{14})$ or $-(C(R^4)(R^4))_p-C(R^4)=C$, wherein R^9 is selected from a single bond, $-(C(R^4)(R^4))_q-$, or C(=O)-, wherein R^{14} is selected from hydrogen, hydroxyl or alkyl, wherein p is an integer between 0 and 3,

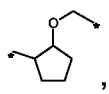
wherein R^{10} is selected from $-(C(R^4)(R^4))_m-$, $-(C(R^4)(R^4))_m-C(=O)O-(C(R^4)(R^4))_q-$, or $-(C(R^4)(R^4))_m-N(R^{12})-(C(R^4)(R^4))_q-$, wherein m is an integer between 1 and 6, wherein R^{12} is selected from hydrogen, alkyl, aryl, arylalkyl, or alkylcarbonyl, and

wherein R^1 and R^3 are each independently selected from hydrogen, C_1-C_8 alkyl, aryl, aralkyl, C_3-C_8 cycloalkyl, alkylcarbonyl, or acyl, R^2 is selected from hydrogen, C_1-C_8 alkyl or C_3-C_8 cycloalkyl.

Preferably, the invention relates to compounds of Formula XVII, wherein Ar^1 is selected from phenyl, 6-indolyl, 1-napthyl, 2-naphtly, 2,3-dihydrobenzo[1,4]dioxin-2-yl, 2,3-dihydrobenzo[1,4]dioxin-6-yl, indanyl, 1,3-dihydrobenzoimidazol2-one, 2-, 3-, 4-, 5-, 6-, 7-, 8-quinolinyl, 2-, 4-, 5-, 6-, 7- or 8-quinazolyl, 1-, 3-, 4-, 5-, 6-, 7-, 8-isoquinolinyl, 1, 2, 3, 4-tetrahydronapthtlanel-1-yl, 2-benzofuran-5-yl, pyridin-4-yl, 1,3-benzodioxolyl, benzimidazolonyl, 3-thiophenyl, or 5-(2,3-dihydro)benzofuranyl, optionally substituted with one to 4 substituent selected from F, Cl, Br, $-CH_3$, t-bu, $-OCH_3$, $-NO_2$, $-CO_2H$, $-C(=O)-N(CH_3)_2$, $-O-C(=O)-CH_3$, , , , $-CH_2-CH_3$, phenyl, N-morpholino, $-SO_2-CH_3$, $-CF_3$, $-OCF_3$, $-CH_2-NH-C(=O)-CH_3$, $-S-CH_3$, $-C(=O)-CH_3$, $-C(=O)O-CH_3$, $-C(=O)O-CH_2-CH_3$, $-C(=O)NH_2$, $-N(CH_3)_2$, $-SO_2-N(CH_3)_2$, phenoxyl, benzoyl, $-C(CH_3)_3$, $-O-(CH_2)_2-CH_3$, -OH or CN,

wherein L^2 is selected from single bond, $-CH_2-$, $-(CH_2)_2-$, $-(CH_2)_3-$, $-CH(CH_2OH)-$, $-CH(CH_2-O-CH_3)-$, ---$CH(CH_3)-$, $-CH(CH_2-CH_3)-$, $-CH(CO_2H)-$, $-CH(CO_2CH_3)-$, $-(CH_2)_2-O-CH_2-$, $-CH(,CH_2-N(CH_3)_2)-$, $-(CH_2)_2-CH=$, or , or wherein L^2-Ar^2 is , ,  or , wherein Ar^2 is selected from phenyl, 1-naphthyl or 2-naphthyl, pyridin-4-yl, 1,3-benzodioxolyl, benzimidazolonyl, pyridin-3-yl, pyridin-2-yl, 5-indolyl, 8-quinolinyl, 2-thiophenyl, 2,3-dihydrobenzofuran-5-yl, 2-thienyl, 3-thienyl, 2,3-dihydrobenzo[1,4]dioxin-2-yl, 2,3-dihydrobenzo[1,4]dioxin-6-yl, indanyl, 1,3-dihydrobenzoimidazol-2-one, benzo(1,3)dioxo-5-yl, indan-1-yl, 1, 2, 3, 4-tetrahydronapthtlanel-1-yl, 2-benzofuran-5-yl, pyridin-4-yl, 2-benzoxazolyl, or 5-benzofuranyl, optionally substituted by one or more substituents selected from nitro, $-SO_2-NH_2$, F, Cl, Br, OH, $-CH_3$, $-OCH_3$, $-NO_2$, $-CO_2H$, $-C(=O)-N(CH_3)_2$, $-O-C(=O)-CH_3$, , , , , N-morpholino, $-CH_2-CH_3$, phenyl, $-SO_2-CH_3$, $-CF_3$, $-OCF_3$, $-CH_2-NH-C(=O)-CH_3$, $-S-CH_3$, $-C(=O)-CH_3$, $-C(=O)O-CH_3$, $-C(=O)O-CH_2-CH_3$, $-C(=O)NH_2$, $-N(CH_3)_2$, $-SO_2-N(CH_3)_2$, phenoxyl, benzoyl, $-C(CH_3)_3$, $-O-(CH_2)_2-CH_3$, or CN, wherein L^1 is single bond or C(=O)-, wherein R^1 is selected from hydrogen, $-CH_3$, or $-C(=O)-CH_3$, wherein R^3 is selected from hydrogen, $-CH_3$, phenyl, benzyl or $-C(=O)-CH_3$, and wherein R^2 is selected from hydrogen, $-CH_3$, or $-C(=O)-CH_3$.

Preferably, the invention relates to compounds of Formula XVII, wherein Ar^1 is selected from 2-, 3-, 4-, 5-, 6-, 7-, 8-quinolinyl, 2-, 4-, 5-, 6-, 7- or 8-quinazolyl, 1-, 3-, 4-, 5-, 6-, 7-, 8-isoquinolinyl, optionally substituted with one to 4 substituent selected from F, Cl, Br, $-CH_3$, t-bu, $-OCH_3$, $-NO_2$, $-CO_2H$, $-C(=O)-N(CH_3)_2$, $-O-C(=O)-CH_3$, , , , $-CH_2-CH_3$, phenyl, N-morpholino, $-SO_2-CH_3$, $-CF_3$, $-OCF_3$, $-CH_2-NH-C(=O)-CH_3$, $-S-CH_3$, $-C(=O)-CH_3$, $-C(=O)O-CH_3$, $-C(=O)O-CH_2-CH_3$, $-C(=O)NH_2$, $-N(CH_3)_2$, $-SO_2-N(CH_3)_2$, phenoxyl, benzoyl, $-C(CH_3)_3$, $-O-(CH_2)_2-CH_3$, -OH or CN,

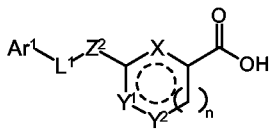
wherein L^2 is , wherein Ar^2 is selected from phenyl, 1-naphthyl or 2-naphthyl, pyridin-4-yl, pyridin-3-yl, pyridin-2-yl, 8-quinolinyl, optionally substituted by one or more substituents selected from nitro, $-SO_2-NH_2$, F, Cl, Br, OH, $-CH_3$, $-OCH_3$, $-NO_2$, $-CO_2H$, $-C(=O)-N(CH_3)_2$, $-O-C(=O)-CH_3$, , , , , N-morpholino, $-CH_2-CH_3$,

phenyl, -SO_2-CH_3, -CF_3, -OCF_3, -CH_2-NH-C(=O)-CH_3, -S-CH_3, -C(=O)-CH_3, -C(=O)O-CH_3, -C(=O)O- CH_2-CH_3, -C(=O)NH_2, -$N(CH_3)_2$, -SO_2-$N(CH_3)_2$, phenoxyl, benzoyl, -$C(CH_3)_3$, -O-$(CH_2)_2$-CH_3, or CN, wherein L^1 is C(=O)-, wherein R^1 is hydrogen, wherein R^3 is hydrogen, and wherein R^2 is selected from hydrogen, -CH_3, or -C(=O)-CH_3. Most preferably, the invention relates to compound **94**: 4-methyl-2-(quinolin-8-ylamino)-thiazole-5-carboxylic acid ((1S,2S)-2-benzyloxycyclopent-1-yl) amide.

The present invention encompasses all the compounds having a Formula selected from Formula I to XXIX, as well as the specific compounds listed in Table 13.

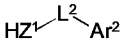
The present invention also relates to methods for the preparation of the compounds according to the present invention, using for example structurally related compounds. In an embodiment of the present invention, the compounds of the present invention can be prepared using the non-limiting methods described hereunder and in the examples.

In a preferred embodiment, the method for preparing the compounds of the invention comprises the step of condensation of a compound of Formula XXX:



XXX

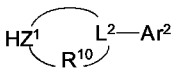
with a compound of Formula XXXI, XXXII, XXXIII or XXXIV:



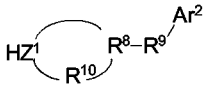
XXXI



XXXII

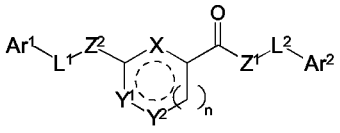


XXXIII

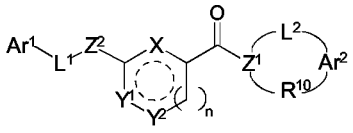


XXXIV

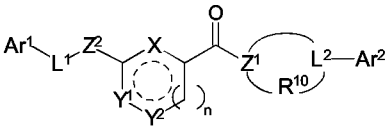
hereby obtaining a compound of Formula I, II, III or IV,



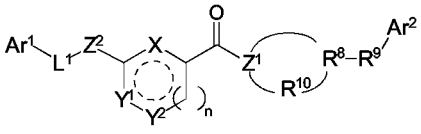
I



II



III



IV

wherein Ar^1, Ar^2, L^1, L^2, X, Y^1, Y^2, R^{10}, R^8 and R^9 have the same meaning as that defined herein above.

The reaction can generally be performed by condensing the compound of Formula XXX with a compound of Formula XXXI, XXXII, XXXIII or XXXIV.

The condensation can be performed via the formation of the acyl chloride of the acid of Formula XXX and then by the coupling of said acyl chloride with the amine of Formula XXXI, XXXII, XXXIII or XXXIV. In another embodiment, the condensation can be performed by using a suitable coupling agent, in a suitable solvent, in the presence of suitable base. The suitable coupling agent can be selected from the group comprising dicyclo-hexylcarbodiimide, hydroxybenzotriazole, o-benzotriazol-1-yl-N,N,N ,N-4-tetramethyluronium hexafluorophosphate and the like and mixture thereof. The suitable solvent can be selected from the group comprising dichloromethane, dimethylformamide and the like or mixture thereof. Non limiting examples of suitable base comprise potassium carbonate, diisopropylethylamine, triethylamine, triisopropylamine and the like.

As described above, the condensation can be realized via formation of the corresponding acyl chloride and then coupling with the desired amine. In another embodiment the condensation can be performed using a suitable coupling agent, such as hydroxybenzotriazole (HOBT), o-benzotriazol-1-yl-N,N,N ,N-4tetramethyluronium hexafluorophosphate (TBTU) and the like at a suitable molar ratio, for example between 1:1 to 1:3 relative to the acid derivative; in a suitable solvent or solvent mixture, such as dichloromethane (DCM) or dimethylformamide (DMF) and the like; at a suitable temperature, usually between 0°C and the boiling point of the solvent used; for a suitable period of time, usually between 0.25 hr and 48 hrs; in the presence of a suitable base, for example an organic base such as potassium carbonate (K_2CO_3), diisopropylethylamine (DIEA), triethylamine (TEA), triisopropylamine and the like, in an amount between 0.1 and 5.0 equivalents.

The starting material for this reaction is either commercially available or can be prepared in a manner known per se.

The compounds of the present invention may then be isolated from the reaction mixture and may optionally be further purified, using techniques known per se, such as evaporation of the solvent, washing, trituration, recrystallisation from a suitable solvent or solvent mixture, and chromatographic techniques, such as column chromatography -for example using silica gel or C18 as solid phase- or preparative thin layer chromatography.

The term "stereoisomer as usedherein, defines all possible compounds made up of the same atoms bonded by the same sequence of bonds but having different three-dimensional structures which are not interchangeable, which the compounds of the

present invention may possess. It will be clear to the skilled person that some of the compounds of the invention may contain one or more asymmetric carbon atoms that serve as a chiral center, which may lead to different optical forms (e.g. enantiomers or diastereoisomers). Unless otherwise mentioned or indicated, the chemical designation of a compound herein encompasses all such optical forms in all possible configurations as well as the mixture of all possible stereochemically isomeric forms, which said compound may possess. Said mixture may contain all diastereomers and/or enantiomers of the basic molecular structure of said compound. All stereochemically isomeric forms of the compounds of the invention either in pure form or in admixture with each other are intended to fall within the scope of the present invention.

More generally, from the above, it will be clear to the skilled person that some of the compounds of the invention may exist in the form of different isomers and/or tautomers, including but not limited to geometrical isomers, conformational isomers, and stereochemical isomers (i.e. enantiomers and diastereoisomers) and isomers that correspond to the presence of the same substituents on different positions of the rings present in the compounds of the invention. All such possible isomers, tautomers and mixtures thereof are included within the scope of the invention.

It will also be clear that when the desired compounds of the invention, and/or the starting materials, precursors and/or intermediates used in the preparation thereof, contain functional groups that are sensitive to the reaction conditions used in the preparation of the compounds of the invention (i.e. that would undergo undesired reactions under those conditions if they were not suitably protected) can be protected during said reaction with one or more suitable protective group, which protective group can then be suitably removed after either completion of said reaction and/or as a later or final step in the preparation of the compounds of the invention. Protected forms of the inventive compounds are included within the scope of the present invention. Suitable protective groups, as well as methods and conditions for inserting them and removing them, will be clear to the skilled person and are generally described in the standard handbooks of organic chemistry, such as Greene and Wuts, "*Protective groups in organic synthesis*", 3rd Edition, Wiley and Sons, 1999, which is incorporated herein by reference in its entirety. It will also be clear to the skilled person that compounds of the invention in which one or more functional groups have been protected with suitable functional groups can find use as intermediates in the production and/or synthesis of the compounds of the invention, and as such form a further aspect of the invention.

The present invention further encompasses compounds obtainable by the methods according to the invention.

It was surprisingly found that the compounds of the invention interact with ion channels as shown in the examples below, in particular with ion channels from the Kv family, more in particular with ion channels from the Kv4 subfamily, and especially with Kv4.3 channels.

By "interact with" is meant that the compounds of the invention act as antagonists of said ion channel(s) and/or of the biological function(s) and/or pathways associated with these channels, and in particular that the compounds of the invention can fully or partially "block" said channels. Preferably, the compounds of the invention interact with ion channels from an animal, preferably a vertebrate animal, more preferably a warm-blooded animal, even more preferably a mammal, and most preferably a human being.

In an embodiment of the present invention, the compounds of the invention act as antagonists of said ion channels and/or of the biological functions or pathways associated therewith. Preferably, the compounds of the invention block said ion channels.

In a further embodiment, the compounds of the invention act as antagonists of ion channels from the Kv family and/or of the biological functions or pathways associated therewith. Also, preferably, the compounds of the invention block ion channels from the Kv family.

In a yet further embodiment, the compounds of the invention act as antagonists of ion channels from the Kv4 subfamily and/or of the biological functions or pathways associated therewith. Also, preferably, the compounds of the invention block ion channels from the Kv4 sub family.

According to a yet further embodiment, the compounds of the invention act as antagonists of the Kv4.3 ion channel and/or of the biological functions or pathways associated therewith. Also, most preferably, the compounds of the invention block the Kv4.3 ion channel.

According to a further aspect, the compounds of the invention which block the Kv4.3 ion channels, also block ion channels of the Kv1 subfamily, especially the Kv1.5 ion channel.

Whether a compound of the invention interacts with an ion channel can be determined using a suitable technique or assay, such as the assays described in the examples.

The compounds of the invention can therefore generally be used (1) as antagonists of ion channels and/or of the biological functions or pathways associated therewith, i.e. in an *in*

vitro, *in vivo* or therapeutic setting; (2) as blockers of ion channels, i.e. in an *in vitro*, *in vivo* or therapeutic setting; and/or (3) as pharmaceutically active agents, in particular in (the preparation of pharmaceutical compositions for) the prevention and/or treatment of conditions or diseases associated with said ion channels.

In particular, the compounds of the invention that interact with ion channels from the Kv family can be used (1) as antagonists of ion channels from the Kv family and/or of the biological functions or pathways associated therewith, i.e. in an *in vitro*, *in vivo* or therapeutic setting; (2) as blockers of ion channels from the Kv family, i.e. in an *in vitro*, *in vivo* or therapeutic setting; and/or (3) as pharmaceutically active agents, in particular in (the preparation of pharmaceutical compositions for) the prevention and/or treatment of conditions or diseases associated with ion channels from the Kv family.

More in particular, the compounds of the invention that interact with ion channels from the Kv4 subfamily can be used (1) as antagonists of ion channels from the Kv4 subfamily and/or of the biological functions or pathways associated therewith, i.e. in an *in vitro*, *in vivo* or therapeutic setting; (2) as blockers of ion channels from the Kv4 subfamily, i.e. in an *in vitro*, *in vivo* or therapeutic setting; and/or (3) as pharmaceutically active agents, in particular in (the preparation of pharmaceutical compositions for) the prevention and/or treatment of conditions or diseases associated with ion channels from the Kv4 sub family.

Even more in particular, the compounds of the invention that interact with the Kv4.3 ion channels from the Kv4 subfamily can in particular be used (1) as antagonists of the Kv4.3 ion channel and/or of the biological functions or pathways associated therewith, i.e. in an *in vitro*, *in vivo* or therapeutic setting; (2) as blockers of the Kv4.3 ion channel, i.e. in an *in vitro*, *in vivo* or therapeutic setting; and/or (3) as pharmaceutically active agents, in particular in (the preparation of pharmaceutical compositions for) the prevention and/or treatment of conditions or diseases associated with the Kv4.3 ion channel.

According to a further embodiment, the compounds of the invention that interact with ion channels from the Kv1 subfamily can be used (1) as antagonists of ion channels from the Kv1 subfamily and/or of the biological functions or pathways associated therewith, i.e. in an *in vitro*, *in vivo* or therapeutic setting; (2) as blockers of ion channels from the Kv1 subfamily, i.e. in an *in vitro*, *in vivo* or therapeutic setting; and/or (3) as pharmaceutically active agents, in particular in (the preparation of pharmaceutical compositions for) the prevention and/or treatment of conditions or diseases associated with ion channels from the Kv1 sub family.

More in particular, the compounds of the invention that interact with the Kv 1.5 ion channels from the Kv1 subfamily can in particular be used (1) as antagonists of the Kv1.5 ion channel and/or of the biological functions or pathways associated therewith, i.e. in an *in vitro*, *in vivo* or therapeutic setting; (2) as blockers of the Kv1.5 ion channel, i.e. in an *in vitro*, *in vivo* or therapeutic setting; and/or (3) as pharmaceutically active agents, in particular in (the preparation of pharmaceutical compositions for) the prevention and/or treatment of conditions or diseases associated with the Kv1.5 ion channel.

In a further aspect, the present invention provides a compound of Formula I, II, III or IV for use as a medicament. Furthermore, the present invention provides a compound of Formula I, II, III or IV for use as an ion channel blocker. In addition, the present invention provides a compound of Formula I, II, III or IV for use as a blocker of an ion-channel of the Kv4 family of ion channels. In particular, the present invention provides a compound of Formula I, II, III or IV for use as a blocker of an ion-channel of the Kv4.3 family of ion-channels. Further, the present invention provides a compound of Formula I, II, III or IV for use as a blocker of an ion channel of the Kv1 family of ion channels. In particular, the present invention provides a compound of Formula I, II, III or IV for use as a blocker of an ion channel of the Kv1.5 family of ion channels.

The present invention further provides for the use of a compound according to the invention for the preparation of a medicament in the prevention and/or treatment of conditions or diseases associated with ion channels of the Kv4 and/or Kv1 family.

Such diseases and disorders will be clear to the skilled person. For example, conditions and diseases associated with the Kv4.3 ion channel, in particular in humans, include cardiac disorders such as arrhythmia, hypertension-induced heart disorders such as hypertension-induced cardiac hypertrophy (e.g. ventricular hypertrophy), and disorders of the nervous system such as epilepsy, stroke, traumatic brain injury, spinal cord injury, anxiety, insomnia, encephalomyelitis, Alzheimer's disease, multiple sclerosis, demyelinating disease and Parkinson's syndrome; and the compounds of the invention that interact with Kv4.3 ion channels can be used in the prevention and/or treatment of such conditions and diseases.

Similar conditions and diseases are associated with the Kv1.5 ion channel and can be used in prevention and/or treatment of such conditions and diseases. For instance, class III anti-arrhythmic drugs exert their effects by a blockade of cardiac potassium channels, resulting in a prolongation of repolarization and refractoriness. I(Kur), the ultra-rapid delayed rectifier current was identified in human atrial but not ventricular tissue.

Consequently, it contributes to the repolarisation of the action potential in the atrium only. The Kv1.5 protein is supposed to be a critical cardiac voltage-gated potassium channel to form the I(Kur). Compounds inhibiting Kv1.5 would delay repolarisation of the action potential in the atrium and consequently prolong the atrial refractory period. Assuming high selectivity of a Kv1.5 inhibitor over hERG, such inhibitor would not interfere with ventricular repolarization, which has been associated with pro-arrhythmia, e.g. *torsades de pointes*. Therefore, Kv1.5 inhibitors are of special interest in the treatment of atrial tachyarrhythmias such as atrial fibrillation. Therefore, according to a further embodiment, the present invention also relates to the use of the compounds that interact with Kv1.5 ion channels for prevention and/or treatment of the conditions and diseases given above and related with Kv4.3 ion channel associated diseases. Preferred compounds for use in treating these conditions or diseases are compounds that show activity for both the Kv4.3 and the Kv1.5 ion channel. For example, the compounds are suitable for the treatment and/or prevention of various disorders: cardiac arrhythmias, including supraventricular arrhythmias, atrial arrhythmias, atrial fibrillation, atrial flutters, complications of cardiac ischemia. The compounds may also, for example, be employed for the termination of existing atrial fibrillation or flutters for the recovery of the sinus rhythm (cardio version). Moreover, the substances may reduce the susceptibility to the formation of new fibrillation events (maintenance of the sinus rhythm, prophylaxis).

The compounds according to the invention can also be used as heart rate control agents, angina pectoris including relief of Prinzmetal's symptoms, vasospastic symptoms and variant symptoms; gastrointestinal disorders including reflux esophagitis, functional dispepsia, motility disorders (including constipation and diarrhea), and irritable bowel syndrome, disorders of vascular and visceral smooth muscle including asthma, chronic obstructive pulmonary disease, adult respiratory distress syndrome, peripheral vascular disease (including intermittent claudication), venous insufficiency, impotence, cerebral and coronary spasm and Raynaud's disease, inflammatory and immunological disease including inflammatory bowel disease, rheumatoid arthritis, graft rejection, asthma. chronic obstructive pulmonary disease, cystic fibrosis and atherosclerosis, cell poliferative disorders including restenosis and cancer (including leukemia), disorders of the auditory system, disorders of the visual system including macular degeneration and cataracts, diabetes including diabetic retinopathy, diabetic nephropathy and diabetic neuropathy, muscle disease including myotonia and wasting, peripheral neuropathy, cognitive disorders, migraine, memory loss including Alzheimer's and dementia, CNS mediated

motor dysfunction including Parkinson's disease, and ataxia, epilepsy, and other ion channel mediated disorders.

As inhibitors of the K1 subfamily of voltage-gated K+ channels compounds according to the present invention are useful to treat a variety of disorders including resistance by transplantation of organs or tissue, graft-versus-host diseases brought about by medulla ossium transplantation, rheumatoid arthritis, systemic lupus erythematosus, hashimoto's thyroiditis, multiple sclerosis, myasthenia gravis, type I diabetes uveitis, juvenile-onset or recent-onset diabetes mellitus, posterior uveitis, allergic encephalomyelitis, glomerulonephritis, infectious diseases caused by pathogenic microorganisms, inflammatory and hyperproliferative skin diseases, psoriasis, atopical dermatitis, contact dermatitis, eczematous dermatitises, seborrhoeis dermatitis, Lichen planus, Pemphigus, bullous pemphigoid, Epidermolysis bullosa, urticaria, angioedemas, vasculitides, erythemas, cutaneous eosinophilias, Lupuserythematosus, acne, Alopecia areata, keratoconjunctivitis, vernal conjunctivitis, uveitis associated with Behcet's disease, keratitis, herpetic keratitis, conical cornea, dystrophia epithelialis corneae, corneal leukoma, ocular pemphigus, Mooren's ulcer, Scleritis, Graves' opthalmopathy, Vogt-Koyanagi-Harada syndrome, sarcoidosis, pollen allergies, reversible obstructive airway disease, bronchial asthma, allergic asthma, intrinsic asthma, extrinsic asthma, dust asthma, chronic or inveterate asthma, late asthma and airway hyper-responsiveness, bronchitis, gastric ulcers, vascular damage caused by ischemic diseases and thrombosis, ischemic bowel diseases, inflammatory bowel diseases, necrotizing enterocolitis, intestinal lesions associated with thermal burns and leukotriene B4-mediated diseases, Coeliaz diseases, proctitis, eosinophilic gastroenteritis, mastocytosis, Crohn's disease, ulcerative colitis, migraine, rhinitis, eczema, interstitial nephritis, Good-pasture's syndrome, hemolyticuremic syndrome, diabetic nephropathy, multiple myositis, Guillain-Barre syndrome, Meniere's disease, polyneuritis, multiple neuritis, mononeuritis, radiculopathy, hyperthroidism, Basedow's disease, pure red cell aplasia, aplastic anemia, hypoplastic anemia, idiopathic thrombocytopenic purpura, autoimmune hemolytic anemia, agranulocytosis, pernicious anemia, megaloblastic anemia, anerythroplasia, osteoporosis, sarcoidosis, fibroid lung, idopathic interstitial pneumonia, dermatomyositis, leukoderma vulgaris, ichthyosis vulgaris, photoallergic sensitivity, cutaneous T cell lymphoma, arteriosclerosis, atherosclerosis, aortitis syndrome, polyarteritis nodosa, myocardosis, scleroderma, Wegener's granuloma, Sjogren's syndrome, adiposis, eosinophilic fascitis, lesions of gingiva, periodontium, alveolar bone, substantia osses dentis, glomerulonephritis, male pattern alopecia or alopecia senilis by preventing epilation or

providing hair germination and/or promoting hair generation and hair growth, muscular dystrophy, Pyoderma and Sezary's syndrome, Addison's disease, ischemia-reperfusion injury of organs which occurs upon preservation, transplantation or ischemic disease, endotoxin-shock, pseudomembranous colitis, colitis caused by drug or radiation, ischemic acute renal insufficiency, chronic renal insufficiency, toxinosis caused by lung-oxygen or drugs, lung cancer, pulmonary emphysema, cataracta, siderosis, retinitis, pigentosa, senile macular degeneration, vitreal scarring, corneal alkali burn, dermatitis erythema multiforme, linear IgA ballous dermatitis and cement dermatitis, gingivitis, periodontitis, sepsis, pancreatitis, diseases caused by environmental pollution, aging, carcinogenis, metastatis of carcinoma and hypobaropathy, disease caused by histamine or leukotriene-C4 release, Behcet's disease, autoimmune hepatitis, primary biliary cirrhosis sclerosing cholangitis, partial liver resection, acute liver necrosis, necrosis caused by toxin, viral hepatitis, shock, or anoxia, B-virus hepatitis, nonA/non-B hepatitis, cirrhosis, alcoholic cirrhosis, hepatic failure, fulminant hepatic failure, late-onset hepatic failure, "acute-on-chronic" liver failure, augmentation of chemotherapeutic effect, cytomegalovirus infection, HCMV infection, AIDS, cancer, senile dementia, trauma, and chronic bacterial infection.

The compounds of the present invention are antiarrhythmic agents which are useful in the prevention and treatment (including partial alleviation or cure) of arrhythmias. As inhibitors of Kv1.5, compounds within the scope of the present invention are particularly useful in the selective prevention and treatment of supraventricular arrhythmias such as atrial fibrillation, and atrial flutter.

Whether a compound of the invention interacts with an ion channel, such as with an ion channel of the Kv family, for example an ion channel of the Kv4 or Kv1 subfamily, such as the Kv4.3 or the Kv1.5 ion channel, respectively, can be determined using a suitable technique or assay, such as the assays and techniques referred to herein or other suitable assays or techniques known in the art.

For pharmaceutical use, the compounds of the invention may be used as a free acid or base, and/or in the form of a pharmaceutically acceptable acid-addition and/or base-addition salt (e.g. obtained with non-toxic organic or inorganic acid or base), in the form of a hydrate, solvate and/or complex, and/or in the form or a pro-drug or pre-drug, such as an ester. As used herein and unless otherwise stated, the term "solvate includes any combination which may be formed by a compound of this invention with a suitable inorganic solvent (e.g. hydrates) or organic solvent, such as but not limited to alcohols, ketones, esters and the like. Such salts, hydrates, solvates, etc. and the preparation

thereof will be clear to the skilled person; reference is for instance made to the salts, hydrates, solvates, etc. described in US-A-6,372,778, US-A-6,369,086, US-A-6,369,087 and US-A-6,372,733.

The pharmaceutically acceptable salts of the compounds according to the invention, i.e. in the form of water-, oil-soluble, or dispersible products, include the conventional non-toxic salts or the quaternary ammonium salts which are formed, e.g., from inorganic or organic acids or bases. Examples of such acid addition salts include acetate, adipate, alginate, aspartate, benzoate, benzenesulfonate, bisulfate, butyrate, citrate, camphorate, camphorsulfonate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, fumarate, glucoheptanoate, glycerophosphate, hemisulfate, heptanoate, hexanoate, hydrochloride, hydrobromide, hydroiodide, 2-hydroxyethanesulfonate, lactate, maleate, methanesulfonate, 2-naphthalene-sulfonate, nicotinate, oxalate, pamoate, pectinate, persulfate, 3-phenylpropionate, picrate, pivalate, propionate, succinate, tartrate, thiocyanate, tosylate, and undecanoate. Base salts include ammonium salts, alkali metal salts such as sodium and potassium salts, alkaline earth metal salts such as calcium and magnesium salts, salts with organic bases such as dicyclohexylamine salts, N-methyl-D-glucamine, and salts with amino acids such a sarginine, lysine, and so forth. Also, the basic nitrogen-containing groups may be quaternized with such agents as lower alkyl halides, such as methyl, ethyl, propyl, and butyl chloride, bromides and iodides; dialkyl sulfates like dimethyl, diethyl, dibutyl; and diamyl sulfates, long chain halides such as decyl, lauryl, myristyl and stearyl chlorides, bromides and iodides, aralkyl halides like benzyl and phenethyl bromides and others. Other pharmaceutically acceptable salts include the sulfate salt ethanolate and sulfate salts.

In another embodiment, the present invention relates to a pharmaceutical composition comprising a pharmaceutically acceptable excipient and a therapeutic amount of a compound according to the invention.

The term "therapeutically effective amount" as used herein means that amount of active compound or component or pharmaceutical agent that elicits the biological or medicinal response in a tissue, system, animal or human that is being sought by a researcher, veterinarian, medical doctor or other clinician, which includes alleviation of the symptoms of the disease being treated.

The pharmaceutical composition can be prepared in a manner known per se to one of skill in the art. For this purpose, at least one compound having Formula I, II, III or IV, one or more solid or liquid pharmaceutical excipients and, if desired, in combination with other

pharmaceutical active compounds, are brought into a suitable administration form or dosage form which can then be used as a pharmaceutical in human medicine or veterinary medicine.

Generally, for pharmaceutical use, the compounds of the inventions may be formulated as a pharmaceutical preparation comprising at least one compound of the invention and at least one pharmaceutically acceptable carrier, diluent or excipient and/or adjuvant, and optionally one or more further pharmaceutically active compounds. By means of non-limiting examples, such a formulation may be in a form suitable for oral administration, for parenteral administration (such as by intravenous, intramuscular or subcutaneous injection or intravenous infusion), for topical administration, for administration by inhalation, by a skin patch, by an implant, by a suppository, etc. Such suitable administration forms - which may be solid, semi-solid or liquid, depending on the manner of administration - as well as methods and carriers, diluents and excipients for use in the preparation thereof, will be clear to the skilled person; reference is again made to for instance US-A-6,372,778, US-A-6,369,086, US-A-6,369,087 and US-A-6,372,733, as well as to the standard handbooks, such as the latest edition of Remington s Pharmaceutica Sciences.

Some preferred, but non-limiting examples of such preparations include tablets, pills, powders, lozenges, sachets, cachets, elixirs, suspensions, emulsions, solutions, syrups, aerosols, ointments, creams, lotions, soft and hard gelatin capsules, suppositories, sterile injectable solutions and sterile packaged powders (which are usually reconstituted prior to use) for administration as a bolus and/or for continuous administration, which may be formulated with carriers, excipients, and diluents that are suitable per se for such formulations, such as lactose, dextrose, sucrose, sorbitol, mannitol, starches, gum acacia, calcium phosphate, alginates, tragacanth, gelatin, calcium silicate, microcrystalline cellulose, polyvinylpyrrolidone, polyethylene glycol, cellulose, (sterile) water, methylcellulose, methyl- and propylhydroxybenzoates, talc, magnesium stearate, edible oils, vegetable oils and mineral oils or suitable mixtures thereof. The formulations can optionally contain other pharmaceutically active substances (which may or may not lead to a synergistic effect with the compounds of the invention) and other substances that are commonly used in pharmaceutical formulations, such as lubricating agents, wetting agents, emulsifying and suspending agents, dispersing agents, desintegrants, bulking agents, fillers, preserving agents, sweetening agents, flavoring agents, flow regulators, release agents, and the like. The compositions may also be formulated so as to provide rapid, sustained or delayed release of the active compound(s) contained therein, for

example using liposomes or hydrophilic polymeric matrices based on natural gels or synthetic polymers. In order to enhance the solubility and/or the stability of the compounds of a pharmaceutical composition according to the invention, it can be advantageous to employ α-, β- or γ-cyclodextrins or their derivatives. In addition, co-solvents such as alcohols may improve the solubility and/or the stability of the compounds. In the preparation of aqueous compositions, addition of salts of the compounds of the invention can be more suitable due to their increased water solubility.

Appropriate cyclodextrins are α-, β- or γ-cyclodextrins (CDs) or ethers and mixed ethers thereof wherein one or more of the hydroxy groups of the anhydroglucose units of the cyclodextrin are substituted with alkyl, particularly methyl, ethyl or isopropyl, e.g. randomly methylated β-CD; hydroxyalkyl, particularly hydroxyethyl, hydroxypropyl or hydroxybutyl; carboxyalkyl, particularly carboxymethyl or carboxyethyl; alkylcarbonyl, particularly acetyl; alkoxycarbonylalkyl or carboxyalkoxyalkyl, particularly carboxymethoxypropyl or carboxyethoxypropyl; alkylcarbonyloxyalkyl, particularly 2-acetyloxypropyl. Especially noteworthy as complexants and/or solubilizers are β-CD, randomly methylated β-CD, 2,6-dimethyl- β-CD, 2-hydroxyethyl-β-CD, 2-hydroxyethyl-γ-CD, 2-hydroxypropyl-γ-CD and (2-carboxymethoxy)propyl- β-CD, and in particular 2-hydroxypropyl- β-CD (2-HP- β-CD). The term mixed ether denotes cyclodextrin derivatives wherein at least two cyclodextrin hydroxy groups are etherified with different groups such as, for example, hydroxypropyl and hydroxyethyl. An interesting way of formulating the compounds in combination with a cyclodextrin or a derivative thereof has been described in EP-A-721,331. Although the formulations described therein are with antifungal active ingredients, they are equally interesting for formulating the compounds. Said formulations may also be rendered more palatable by adding pharmaceutically acceptable sweeteners and/or flavors. In particular, the present invention encompasses a pharmaceutical composition comprising an effective amount of a compound according to the invention with a pharmaceutically acceptable cyclodextrin. The present invention also encompasses cyclodextrin complexes consisting of a compound according to the invention and a cyclodextrin.

More in particular, the compositions may be formulated in a pharmaceutical formulation comprising a therapeutically effective amount of particles consisting of a solid dispersion of the compounds of the invention and one or more pharmaceutically acceptable water-soluble polymers.

The term "a solid dispersion" defines a system in a solid state (as opposed to a liquid or gaseous state) comprising at least two components, wherein one component is dispersed

more or less evenly throughout the other component or components. When said dispersion of the components is such that the system is chemically and physically uniform or homogenous throughout or consists of one phase as defined in thermodynamics, such a solid dispersion is referred to as "a solid solution". Solid solutions are preferred physical systems because the components therein are usually readily bioavailable to the organisms to which they are administered. The term "a solid dispersion" also comprises dispersions that are less homogenous throughout than solid solutions. Such dispersions are not chemically and physically uniform throughout or comprise more than one phase.

The water-soluble polymer is conveniently a polymer that has an apparent viscosity of 1 to 100 mPa.s when dissolved in a 2 % aqueous solution at 20°C solution. Preferred water-soluble polymers are hydroxypropyl methylcelluloses or HPMC. HPMC having a methoxy degree of substitution from about 0.8 to about 2.5 and a hydroxypropyl molar substitution from about 0.05 to about 3.0 are generally water soluble. Methoxy degree of substitution refers to the average number of methyl ether groups present per anhydroglucose unit of the cellulose molecule. Hydroxy-propyl molar substitution refers to the average number of moles of propylene oxide which have reacted with each anhydroglucose unit of the cellulose molecule.

It may further be convenient to formulate the compounds in the form of nanoparticles which have a surface modifier adsorbed on the surface thereof in an amount sufficient to maintain an effective average particle size of less than 1000 nm. Suitable surface modifiers can preferably be selected from known organic and inorganic pharmaceutical excipients. Such excipients include various polymers, low molecular weight oligomers, natural products and surfactants. Preferred surface modifiers include nonionic and anionic surfactants.

Yet another interesting way of formulating the compounds according to the invention involves a pharmaceutical composition whereby the compounds are incorporated in hydrophilic polymers and applying this mixture as a coat film over many small beads, thus yielding a composition with good bio-availability which can conveniently be manufactured and which is suitable for preparing pharmaceutical dosage forms for oral administration. Said beads comprise (a) a central, rounded or spherical core, (b) a coating film of a hydrophilic polymer and an antiretroviral agent and (c) a seal-coating polymer layer. Materials suitable for use as cores in the beads are manifold, provided that said materials are pharmaceutically acceptable and have appropriate dimensions and firmness.

Examples of such materials are polymers, inorganic substances, organic substances, and saccharides and derivatives thereof.

The above preparations may be prepared in a manner known per se, which usually involves mixing the active substance(s) to be used with the one or more pharmaceutically acceptable carriers, which necessary under aseptic conditions. Reference is again made to US-A-6,372,778, US-A-6,369,086, US-A-6,369,087 and US-A-6,372,733 and the further prior art mentioned above, as well as to the standard handbooks, such as the latest edition of Remington s Pharmaceutical Sciences.

The pharmaceutical preparations of the invention are preferably in a unit dosage form, and may be suitably packaged, for example in a box, blister, vial, bottle, sachet, ampoule or in any other suitable single-dose or multi-dose holder or container (which may be properly labeled); optionally with one or more leaflets containing product information and/or instructions for use. Generally, such unit dosages will contain between 1 and 1000 mg, and usually between 5 and 500 mg, of the at least one compound of the invention, e.g. about 10, 25, 50, 100, 200, 300 or 400 mg per unit dosage.

The compounds can be administered by a variety of routes including the oral, rectal, transdermal, subcutaneous, intravenous, intramuscular or intranasal routes, depending mainly on the specific preparation used and the condition to be treated or prevented, and with oral and intravenous administration usually being preferred.

The compound of the invention will generally be administered in an effective amount, which, upon suitable administration, is sufficient to achieve the desired therapeutic or prophylactic effect in the individual to which it is administered. Usually, depending on the condition to be prevented or treated and the route of administration, such an effective amount will usually be between 0.01 to 1000 mg, more often between 0.1 and 500 mg, such as between 0.1 and 250 mg, for example about 0.1, 1, 5, 10, 20, 50, 100, 150, 200 or 250 mg, per kilogram body weight day of the patient per day, which may be administered as a single daily dose, divided over one or more daily doses, or essentially continuously, e.g. using a drip infusion. The amount(s) to be administered, the route of administration and the further treatment regimen may be determined by the treating clinician, depending on factors such as the age, gender and general condition of the patient and the nature and severity of the disease/symptoms to be treated. Reference is again made to US-A-6,372,778, US-A-6,369,086, US-A-6,369,087 and US-A-6,372,733 and the further prior art mentioned above, as well as to the standard handbooks, such as the latest edition of Remington s Pharmaceutical Sciences. It will be understood, however,

that specific dose level and frequency of dosage for any particular patient may be varied and will depend upon a variety of factors including the activity of the specific compound employed, the metabolic stability and length of action of that compound, the age, body weight, general health, sex, diet, mode and time of administration, rate of excretion, drug combination, the severity of the particular condition.

Thus, in a further aspect, the invention relates to a composition and in particular a composition for pharmaceutical use, which contains at least one compound of the invention and at least one suitable carrier (i.e. a carrier suitable for pharmaceutical use). The invention also relates to the use of a compound of the invention in the preparation of such a composition.

In accordance with the method of the present invention, said pharmaceutical composition can be administered separately at different times during the course of therapy or concurrently in divided or single combination forms. The present invention is therefore to be understood as embracing all such regimes of simultaneous or alternating treatment and the term "administering" is to be interpreted accordingly.

For an oral administration form, the compositions of the present invention can be mixed with suitable additives, such as excipients, stabilizers or inert diluents, and brought by means of the customary methods into the suitable administration forms, such as tablets, coated tablets, hard capsules, aqueous, alcoholic, or oily solutions. Examples of suitable inert carriers are gum arabic, magnesia, magnesium carbonate, potassium phosphate, lactose, glucose, or starch, in particular, corn starch. In this case, the preparation can be carried out both as dry and as moist granules. Suitable oily excipients or solvents are vegetable or animal oils, such as sunflower oil or cod liver oil. Suitable solvents for aqueous or alcoholic solutions are water, ethanol, sugar solutions, or mixtures thereof. Polyethylene glycols and polypropylene glycols are also useful as further auxiliaries for other administration forms. As immediate release tablets, these compositions may contain microcrystalline cellulose, dicalcium phosphate, starch, magnesium stearate and lactose and/or other excipients, binders, extenders, disintegrants, diluents and lubricants known in the art.

When administered by nasal aerosol or inhalation, these compositions may be prepared according to techniques well-known in the art of pharmaceutical formulation and may be prepared as solutions in saline, employing benzyl alcohol or other suitable preservatives, absorption promoters to enhance bioavailability, fluorocarbons, and/or other solubilizing or dispersing agents known in the art. Suitable pharmaceutical formulations for

administration in the form of aerosols or sprays are, for example, solutions, suspensions or emulsions of the compounds of the invention or their physiologically tolerable salts in a pharmaceutically acceptable solvent, such as ethanol or water, or a mixture of such solvents. If required, the formulation can also additionally contain other pharmaceutical auxiliaries such as surfactants, emulsifiers and stabilizers as well as a propellant.

For subcutaneous or intravenous administration, the compound according to the invention, if desired with the substances customary therefore such as solubilizers, emulsifiers or further auxiliaries are brought into solution, suspension, or emulsion. The compounds of the invention can also be lyophilized and the lyophilizates obtained used, for example, for the production of injection or infusion preparations. Suitable solvents are, for example, water, physiological saline solution or alcohols, e.g. ethanol, propanol, glycerol, in addition also sugar solutions such as glucose or mannitol solutions, or alternatively mixtures of the various solvents mentioned. The injectable solutions or suspensions may be formulated according to known art, using suitable non-toxic, parenterally-acceptable diluents or solvents, such as mannitol, 1,3-butanediol, water, Ringer's solution or isotonic sodium chloride solution, or suitable dispersing or wetting and suspending agents, such as sterile, bland, fixed oils, including synthetic mono- or diglycerides, and fatty acids, including oleic acid.

When rectally administered in the form of suppositories, these formulations may be prepared by mixing the compounds according to the invention with a suitable non-irritating excipient, such as cocoa butter, synthetic glyceride esters or polyethylene glycols, which are solid at ordinary temperatures, but liquefy and/or dissolve in the rectal cavity to release the drug.

The compounds according to the invention were found to act as antagonist of ion channels from the Kv family more in particular from the Kv4 subfamily and/or of the biological functions or pathways associated therewith. The compounds according to the invention were also found to act as antagonist of ion channels from the Kv1 subfamily and/or of the biological functions or pathways associated therewith.

The compounds of the invention can therefore be used (1) as antagonists of ion channels and/or of the biological functions or pathways associated therewith, i.e. in an vitro, in vivo or therapeutic setting; (2) as blockers of ion channels, i.e. in an vitro, in vivo or therapeutic setting; and/or (3) as pharmaceutically active agents, in particular in (the preparation of pharmaceutical compositions for) the prevention and/or treatment of conditions or diseases associated with said ion channels. In addition the compounds according to the

invention showed very low activity or no activity with respect to the hERG channel, and are thereby selective.

As indicated above, due to the blocking activity on the above mentioned ion channels the compounds according to the present invention are particularly useful in the prevention and/or treatment of conditions or diseases associated with ion channels from the Kv family. Such diseases and disorders will be clear to the skilled person. For example, conditions and diseases associated with the Kv4.3 ion channel, in particular in humans, include cardiac disorders such as arrhythmia, hypertension-induced heart disorders such as hypertension-induced cardiac hypertrophy (e.g. ventricular hypertrophy), and disorders of the nervous system such as epilepsy, stroke, traumatic brain injury, spinal cord injury, anxiety, insomnia, encephalomyelitis, Alzheimer's disease, multiple sclerosis, demyelinating disease and Parkinson's syndrome. The compounds according to the present invention interact with Kv 4.3 ion channels and can be used in the prevention and/or treatment of such conditions and diseases. In addition, conditions and diseases associated with the Kv1.5 ion channel, in particular in humans, include the same diseases and disorders as mentioned above as for the Kv4.3 ion channel. The compounds according to the invention that interact with Kv1.5 ion channel are particularly useful in the prevention and/or treatment of atrial tachyarrhythmias such as atrial fibrillation.

Therefore, in another embodiment, the present invention also relates to the use of the compounds according to the invention or to a pharmaceutical composition comprising said compounds in the treatment of cardiac disorders such as arrhythmia, hypertension-induced heart disorders such as hypertension-induced cardiac hypertrophy (e.g. ventricular hypertrophy), and disorders of the nervous system such as epilepsy, stroke, spinal cord injury, traumatic brain injury, anxiety, insomnia, encephalomyelitis, Alzheimer's disease, multiple sclerosis, demyelinating disease and Parkinson's syndrome. In a further embodiment, the present invention also relates to the use of the compounds according to the invention or to a pharmaceutical composition comprising said compounds in the treatment of cardiac disorders such as arrhythmia. In another further embodiment, the present invention also relates to the use of the compounds according to the invention or to a pharmaceutical composition comprising said compounds in the treatment of disorders of the nervous system.

A method of treating cardiac disorders comprises administering to an individual in need of such treatment a pharmaceutical composition comprising the compounds according to the invention. A method of treating disorders of the nervous system comprises administering

to an individual in need of such treatment a pharmaceutical composition comprising the compounds according to the invention.

It is also envisaged that the above compounds and compositions may be of value in the veterinary field, which for the purposes herein not only includes the prevention and/or treatment of diseases in animals, but also -for economically important animals such as cattle, pigs, sheep, chicken, fish, etc.- enhancing the growth and/or weight of the animal and/or the amount and/or the quality of the meat or other products obtained from the animal. Thus, in a further aspect, the invention relates to a composition for veterinary use that contains at least one compound of the invention (i.e. a compound that has been identified, discovered and/or developed using a nematode or method as described herein) and at least one suitable carrier (i.e. a carrier suitable for veterinary use). The invention also relates to the use of a compound of the invention in the preparation of such a composition. It is also envisaged that the above compounds and compositions may be of value as insecticides.

The invention will now be illustrated by means of the following synthetic and biological examples, which do not limit the scope of the invention in any way.

Examples

Example 1: Preparation of the compounds according to the present invention

The practice of the present invention will employ, unless otherwise indicated, conventional techniques of synthetic organic chemistry, biological testing, and the like, which are within the skill of the art. Such techniques are explained fully in the literature. Unless indicated otherwise, the purity of the compounds was confirmed by liquid chromatography/mass spectrometry (LC/MS), according to method A or method B as follows:

***Method A* (gradient 5 min):**

HPLC: Waters Alliance 2690 with photodiode array detector Waters 996. Mass spectrometer: Micromass Platform ZMD LC. Ionization: electrospray (polarity: negative and positive).

Method:

Phase: Tosohaas TSK-gel super ODS (100 Å, 2µm), column: 4.6x50 mm; Solvent A: Water and formic acid (26.5 mM); Solvent B: Acetonitrile and formic acid (17 mM); Flow: 2.75 ml/min; Gradient 5 mn: From 100 % A & 0 % B to 20% A & 80 % B in 3 min. Isocratic 80 % B for 1 min. From 80 % B & 20% A to 0 %B and 100% A in 0.5 min. Isocratic 100 % A for 0.5 min

***Method B* (gradient 12 min):**

HPLC: Waters 2525 with photodiode array detector Waters 2996 Mass spectrometer: Micromass Platform ZQ. Ionization: electrospray (polarity: negative and positive).

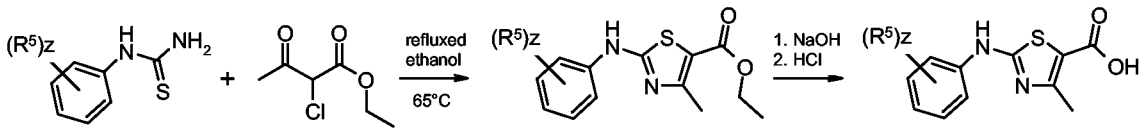
Method:

Phase X-Terra C18 MS (100 Å, 5µm), 4.6x100 mm; Solvent A: Water and formic acid (26.5 mM); Solvent B: Acetonitrile and formic acid (17 mM); Flow: 1.75 ml/min; Gradient 12 mn: Isocratic 95% A & 5% B for 1 min. From 95% A & 5% B to 5% A & 95% B in 5 min. Isocratic 95% B for 2 min. From 95% B & 5% A to 5%B and 95% A in 0.1 min. Isocratic 95% A & 5% B for 3.9 min

NMR spectra were determined on a Varian Mercury 300 MHz NMR using the indicated solvent as an internal reference. Melting points were determined on a Büchi B-540 and are non-corrected. All reagents used were either obtained commercially or were prepared in a manner known per se.

Methods of preparation

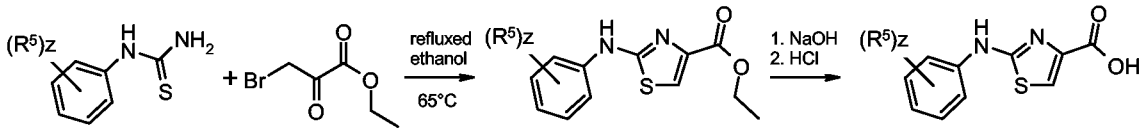
Compounds of Formula I, II, III or IV may be prepared according to the following schemes and the knowledge of one skilled in the art.



Scheme 1

Protocol A:

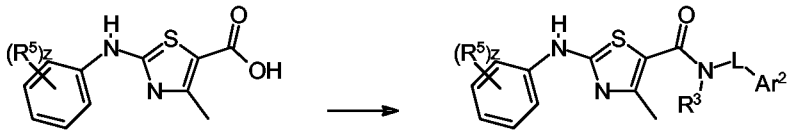
Ethyl-2-chloroaceto-acetate (1.2 eq, 12 mmol) was added to a solution of the thiourea (10 mmol) in ethanol (20 ml). The mixture was stirred overnight at 65°C. The reaction mixture was cooled to room temperature and the solvent was removed under reduced pressure. The ester (10 mmol) was dissolved in ethanol (4 ml) and 2N NaOH (20 ml) was added. The reaction mixture was stirred overnight at 65°C. The reaction mixture was cooled to room temperature and ethanol was removed under reduced pressure. The residue was diluted with water (20 ml) and was extracted with EtOAc (2x20 ml). The water layer was cooled to 0°C and acidified with concentrated HCl. The precipitate was filtered, washed with water (3x10 ml) and dried under reduced pressure.



Scheme 2

Protocol B:

Ethyl bromopyruvate (6 mmol) was added to a solution of the thiourea (5 mmol) in ethanol (12 ml). The mixture was stirred overnight at 65°C. The reaction mixture was cooled to room temperature and the solvent was removed under reduced pressure.
The ester (10 mmol) was dissolved in ethanol (1.5 ml) and 2N NaOH (10 ml) was added. The reaction mixture was stirred overnight at 65°C. The reaction mixture was cooled to room temperature and ethanol was removed under reduced pressure. The residue was diluted with water (20 ml) and was extracted with EtOAc (2x20 ml). The water layer was cooled to 0°C and acidified with concentrated HCl. The precipitate was filtered, washed with water (3x10 ml) and dried under reduced pressure.



Scheme 3

The groups R^3, and Ar^2 have the same meaning as that defined herein and L is L^2 and R^5 is selected from the group comprising hydrogen, halogen, hydroxy, nitro, amino, azide, cyano, alkyl, cycloalkyl, alkylamino, alkoxy, $-SO_2-NH_2$, aryl, heteroaryl, haloalkyl, haloalkoxy, carboxy, alkyloxycarbonyl, alkylaminocarbonyl, heteroarylalkyl, alkylsulfonamide, heterocyclyl, alkylcarbonylaminoalkyl, aryloxy, alkylcarbonyl, acyl, arylcarbonyl, aminocarbonyl, alkylsulfoxide, $-SO_2R^{15}$, or alkylthio, wherein R^{15} is alkyl or cycloalkyl, and z is an integer between 1 and 3.

Protocol C:

The acid derivative (0.5 mmol) was dissolved in a mixture of DMF (0.5 ml) and DIEA (1.5 mmol). A solution of TBTU (0.5 mmol) and HOBt (0.1 mmol) in DMF (0.5 ml) was added and the mixture was stirred at room temperature for 30 minutes. The amine (0.5 mmol) was added and the reaction mixture was stirred at room temperature for a period of 3 to 24 hours. DMF was removed under reduced pressure. The residue (0.48 mmol) was diluted with EtOAc (5 ml) or DCM (5 ml) and washed with 0.5N HCl (2x5 ml), 0.5N NaOH (2x5 ml) and water (2x5 ml) or with 1N $NaHCO_3$ (2x5 ml) and water (2x5 ml). The organic layer was dried over $MgSO_4$ and the solvent was evaporated under vacuum. The residue was purified by semi-prep HPLC or by recrystallization.

Protocol D: (Scheme 4)

The acid derivative (4.8 mmol) was dissolved in a mixture of DMF (10 drops) and DCM (20 ml). Oxalylchloride (11.6 mmol) was added and the solution was stirred at room temperature for 1.5 hours. The solvent was evaporated under reduced pressure. The residue (0.48 mmol) was dissolved in DCM (1 ml) and added to a solution of the amine (0.55 mmol) containing DIEA (0.59 mmol) in DMF (1 ml). The mixture was stirred at room temperature for 16 hours. The mixture was diluted with DCM (15 ml), washed with water (2x15 ml), 1N HCl (15 ml), 1N NaOH (15 ml) and brine (2x15 ml). The organic layer was dried over $MgSO_4$ and the solvent was removed under reduced pressure.

Protocol E: (Scheme 4)

The bromo derivative (0.23 mmol), Pd(OAc)2 (0.023 mmol), BINAP (0.026 mmol) and Cs_2CO_3 were dissolved in dry 1,4-dioxane (2.5 ml). o-Anisidine (0.33 mmol) was added and the mixture was stirred at 110°C under argon atmosphere for 4 hours. The mixture was diluted with water (15 ml) and extracted with EtOAc (3x15 ml). The combined organic phases were washed with water (2x15 ml), brine (2x15 ml) and 1N HCl (2x15 ml). The organic layer was dried over $MgSO_4$ and the solvent was removed under reduced pressure. The residue was purified by semi-preparative HPLC.

Protocol F: (Scheme 6)

A mixture of pyruvaldehyde dimethylacetal (125 mmol) and dimethylformamide dimethylacetal (437.5 mmol) was stirred under nitrogen atmosphere at 100°C for 18 hours. The reaction mixture was cooled to room temperature and evaporated to dryness under reduced pressure.

Protocol G: (Scheme 7)

To an ice-cooled mixture of o-anisidine (250 mmol) in EtOH (60 ml) was added dropwise and under stirring nitric acid (18 ml of 70% solution in H_2O). After complete addition, cyanamide (50 ml of 50% solution in H_2O) was added and the mixture was heated under nitrogen atmosphere at 100°C for 18 hours. After cooling to room temperature, the mixture was poured into an excess of t-butyl methyl ether (100 ml). The precipitate was filtered, washed with t-butyl methyl ether (2x100 ml) and dried under vacuum.

Protocol H: (Scheme 5)

Sodium ethoxide (55 mmol) was added to a mixture of o-methoxyphenylguanidine nitrate (55 mmol) and (E)-4-dimethylamino-1,1-dimethoxy-but-3-en-2-one (55 mmol) in EtOH (165 ml). The mixture was stirred under nitrogen atmosphere for 30 hours. The solvent was removed under reduced pressure and water (200 ml) was added. The pH was adjusted to neutral with concentrated HCl and the mixture was extracted with EtOAc (3x200 ml). The combined organic phases were washed with brine (3x200 ml), dried over $MgSO_4$ and the solvent was removed under reduced pressure.

Protocol I: (Scheme 5)

A mixture of 2-(2-methoxy-phenylamino)-4- pyrimidine-dimethylacetal (40 mmol) and 1N HCl (400 ml) was heated under nitrogen atmosphere at 60ºC for 3 hours. After cooling to room temperature, the mixture was added dropwise over a period of 30 minutes to a stirred solution of H_2O (200 ml), NaOH (0.6 mol) and $KMnO_4$ (0.2 mol) at 95ºC. The mixture was stirred at 95ºC during an additional 30 minutes and then cooled to room temperature. After filtration of MnO_2, the pH was adjusted to 4 with concentrated HCl and water was removed under reduced pressure. The residue was extracted with warm MeOH (2x100 ml) and the solvent was removed under reduced pressure. The residue was purified by flash chromatography.

Protocol J:

$SOCl_2$ (7 ml) and DMF (1 drop) were added to the carboxylic acid (0.5 mmol) and the mixture was stirred at 45°C for 30 minutes. The excess of $SOCl_2$ was removed under reduced pressure. Traces of $SOCl_2$ were removed by distillation from DCM (2x3 ml). The acyl chloride was dissolved in DCM (3 ml) and added to a stirred mixture of the amine (0.5 mmol), Et_3N (2.5 mmol) or DIEA (2.5 mmol) in DCM (3 ml) at 0ºC under nitrogen atmosphere. The mixture was stirred at 0ºC for 30 min and then allowed to warm up to room temperature. The mixture was poured into water (20 ml) and extracted with DCM (3x20 ml). The combined organic phases were dried over $MgSO_4$ and the solvent was removed under reduced pressure. The residue was purified by flash chromatography or semi-preparative HPLC.

Protocol K: (Scheme 8)

$SOCl_2$ (20 ml) and DMF (4 drops) were added to 2-(2-methoxy-phenylamino)-4-methyl-thiazole-5-carboxylic acid (3.8 mmol) and the mixture was stirred at 50°C for 2 hours. The excess of $SOCl_2$ was removed under reduced pressure. Traces of $SOCl_2$ were removed by distillation from DCM (2x10 ml). The acyl chloride was dissolved in dry THF (5 ml) and

added dropwise to a cooled (0ºC) mixture of 1M NaHDMS (19 mmol) and ethylphenylacetate (19 mmol) in dry THF (19 ml). The reaction mixture was stirred at 0ºC for 1 hour and at room temperature for 16 hours. The mixture was poured into water (50 ml) and extracted with t-butyl methyl ether (3x50 ml). The combined organic phases were washed with brine (3x100 ml), dried over $MgSO_4$ and the solvent was removed under reduced pressure. The residue was purified by flash chromatography.

Protocol L: (Scheme 8)

KI (1.66 mmol) and LiCl (1.66 mmol) were added under nitrogen atmosphere to a suspension of 3-[2-(2-methoxy-phenylamino)-4-methyl-thiazol-5-yl]-3-oxo-2-phenyl-propionic acid ethyl ester (0.83 mmol) in lutidine (3 ml). The mixture was heated at 150ºC for 8 hours. After cooling to room temperature, the reaction mixture was concentrated under reduced pressure and the residue was purified by flash chromatography.

Protocol M:

2-Bromo-4-methyl-thiazole-5-carboxylic acid ethyl ester (0.8 mmol) and the nucleophile (0.8 mmol) were dissolved in DMF (1 ml). K_2CO_3 (0.96 mmol) was added and the mixture was stirred at 80°C for 3 hours. After cooling to room temperature, the solvent was removed under reduced pressure. The residue was dissolved in ethanol (5 ml) and 2N NaOH (10 ml) was added. The mixture was stirred at 65°C for 4 hours. The reaction mixture was cooled to room temperature and poured into a 20% $KHSO_4$ solution (100 ml). The precipitate was filtered, washed with water (3 x 100 ml) and dried under reduced pressure.

Protocol N:

The nucleophile (0.36 mmol) and the electrophile (0.36 mmol) were dissolved in DMF (3 ml). K_2CO_3 (0.43 mmol) was added and the mixture was stirred at 80°C for 24 hours. After cooling to room temperature, the solvent was removed under reduced pressure. The residue was washed with MeOH (2x20 ml) and the solvent of the filtrate was removed under reduced pressure. The residue was purified by flash chromatography.

Protocol O:

Ethyl-2-chloroaceto-acetate (1.6 mmol) was added to a solution of the thiourea (1.3 mmol) in EtOH (5 ml). The mixture was stirred at 65°C for 4 hours. After cooling down to room temperature, the solvent was removed under reduced pressure. The residue was dissolved in a mixture of THF (8 ml) and DMF (2 ml) and 1N LiOH (10 ml) was added. The mixture was stirred at room temperature for 48 hours. Water (50 ml) was added and the

pH was adjusted to neutral using 1N HCl. The water layer was extracted with EtOAc (3x50 ml). The combined organic phases were dried over $MgSO_4$ and the solvent was removed under reduced pressure.

Protocol P: (Scheme 9)

Na_2CO_3 (0.62 mmol) was added to a solution of [4-({[2-(2-methoxy-phenylamino)-4-methyl-thiazole-5-carbonyl]-amino}-methyl)-benzyl]-carbamic acid tert-butyl ester (0.57 mmol) in THF (5 ml). Benzylchloroformate (1.37 mmol) was added dropwise and the mixture was stirred at room temperature over a period of 3 days. The solvent was removed under reduced pressure and the residue was dissolved in DCM (50 ml). The organic layer was washed with water (3x50 ml), dried over $MgSO_4$ and the solvent was removed under reduced pressure. The residue was purified by flash chromatography.

Protocol Q: (Scheme 9)

{5-[4-(tert-butoxycarbonylamino-methyl)-benzylcarbamoyl]-4-methyl-thiazol-2-yl}-(2-methoxy-phenyl)-carbamic acid benzyl ester (0.46 mmol) was dissolved in a mixture of acetonitrile (2.5 ml) and 2N HCl (2.5 ml). The solution was stirred at 50°C for 3 hours. The solvent was removed under reduced pressure and the residue was purified by flash chromatography.

Protocol R: (Scheme 9)

Pyridine (0.29 mmol) and acetic anhydride (029 mmol) were added to a solution of the amine (0.29 mmol) in DCM (2 ml). The mixture was stirred overnight at room temperature. The mixture was diluted with DCM (20 ml) and washed with 0.5M HCl. The organic phase was dried over $MgSO_4$ and the solvent was removed under reduced pressure.

Protocol S: (Scheme 9)

{5-[4-(acetylamino-methyl)-benzylcarbamoyl]-4-methyl-thiazol-2-yl}-(2-methoxy-phenyl)-carbamic acid benzyl ester (0.16 mmol) was dissolved in a mixture of methanol (2 ml) and 1M HCl (2 ml). A spatula of Pd/C was added and the mixture was stirred at room temperature under hydrogen atmosphere for 6 hours. The Pd/C was filtered and the solvent was removed under reduced pressure. The residue was purified by flash chromatography.

Protocol T:

The corresponding ester (0.87 mmol) was dissolved in ethanol (4 ml) and 1N LiOH (0.87 mmol) was added. The mixture was stirred at 50°C for 5 hours. The pH was adjusted to 2

with 2N HCl. The precipitate was filtered, washed with water (2x20 ml) and dried under reduced pressure.

Protocol U:

The acyl chloride (1.2 mmol) was dissolved in DCM (2 ml) and added to a stirred mixture of the amine (1.2 mmol) and DIEA (3.6 mmol) in DCM (3 ml) at 0°C under nitrogen atmosphere. The mixture was stirred at 0°C for 30 min and then allowed to warm up to room temperature. The mixture was poured into water (20 ml) and extracted with DCM (3x20 ml). The combined organic phases were dried over $MgSO_4$ and the solvent was removed under reduced pressure. The residue was purified by recrystallization from ethanol. Ethanol (2 ml) and 1N LiOH (10 mmol) were added to the ester (0.7 mmol). The mixture was stirred overnight at room temperature. The reaction mixture was poured into a 20% $KHSO_4$ solution (100 ml). The precipitate was filtered, washed with water (3 x 100 ml) and dried under reduced pressure.

Protocol V:

Ethyl-2-chloroaceto-acetate (0.6 mmol) was added to a solution of the thiourea (0.5 mmol) in ethanol (20 ml). The mixture was stirred at 65°C for 16 hours. The reaction mixture was cooled to room temperature and the solvent was removed under reduced pressure.

The obtained ester (0.44 mmol) was dissolved in methanol (1 ml) and sodium methanolate (1.32 mmol) and methyl iodide (2.64 mmol) were added. The mixture was stirred at 50°C for 5 days. The reaction mixture was cooled to room temperature and the solvent was removed under reduced pressure. The residue was purified by semi-preparative HPLC.

The product (0.27 mmol) was dissolved in ethanol (0.7 ml) and 2N NaOH (0.7 ml) was added. The reaction mixture was stirred at 50°C for 16 hours. The reaction mixture was cooled to room temperature and ethanol was removed under reduced pressure. The residue was diluted with water (20 ml) and was extracted with EtOAc (2x20 ml). The water layer was cooled to 0°C and acidified with concentrated HCl. The precipitate was filtered, washed with water (3x10 ml) and dried under reduced pressure.

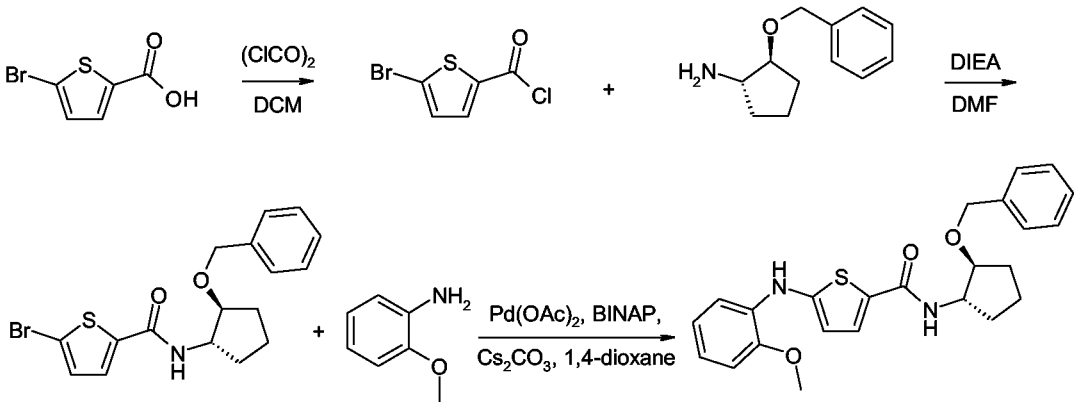
The present invention further encompasses compounds number **15** to **181** and **210** to **226** as illustrated in Tables 13 as well as stereoisomers, tautomers, racemics, prodrugs, metabolites thereof, or a pharmaceutically acceptable salt and/or solvate thereof.

The present invention also encompasses the synthesis intermediates **1** to **14**, and **182** to **209**.

Compounds **15, 16, 17, 67, 70** and **71** were made from acid **1**. Compounds **18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65** and **66** were made from acid **2**. Compound **29** was made from acid **8**. Compounds **30, 52** and **54** were made from acid **3**.

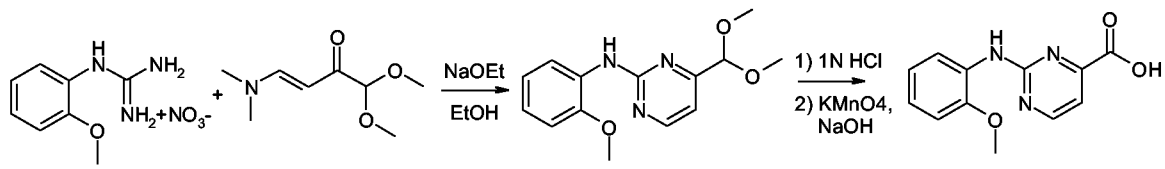
Compounds **31, 53, 55, 68, 82, 83, 84, 85, 86, 97, 98, 102, 103, 104, 105, 106, 108, 118, 123, 124, 125, 130, 131, 132, 136, 137, 138, 140, 141, 142, 143, 144, 145, 146, 147, 149, 150, 151, 152, 154, 156, 157, 158, 159, 160, 161, 162, 163, 164, 165, 166, 168, 170, 173, 174, 175, 176, 177, 214, 215, 216, 217, 218, 219** and **220** were made from acid **5**. Compound **32** was made from acid **4**. Compounds **33** and **69** were made from acid **6**. Compounds **34** and **35** were made from acid **7**. Compounds **36, 37** and **38** were made from acid **9**. Compound **39** was made from acid **10**. Compounds **40, 41, 42** and **72** were made from acid **11**. Compounds **43, 44, 45** and **46** were made from acid **12**. Compounds **47, 48** and **49** were made from acid **13**. Compounds **50** and **51** were made from acid **14**. Compound **210** was made from acid **182**.

Compound **75** was made from intermediate **200** according to scheme 4.



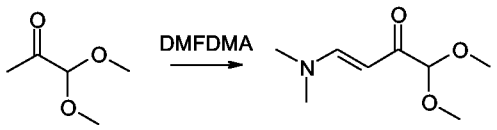
Scheme 4

Compound **76** was made from acid **183**, which was prepared from intermediate **203** (Scheme 5).

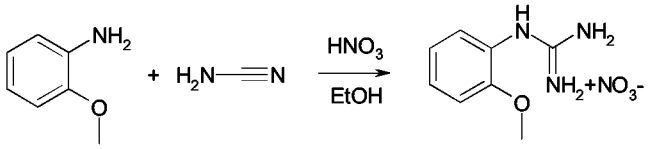


Scheme 5

Compound **203** was made from intermediates **201** and **202** according to Schemes 6 and 7.

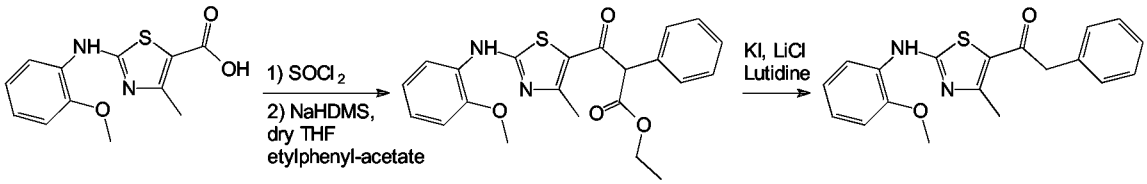


Scheme 6



Scheme 7

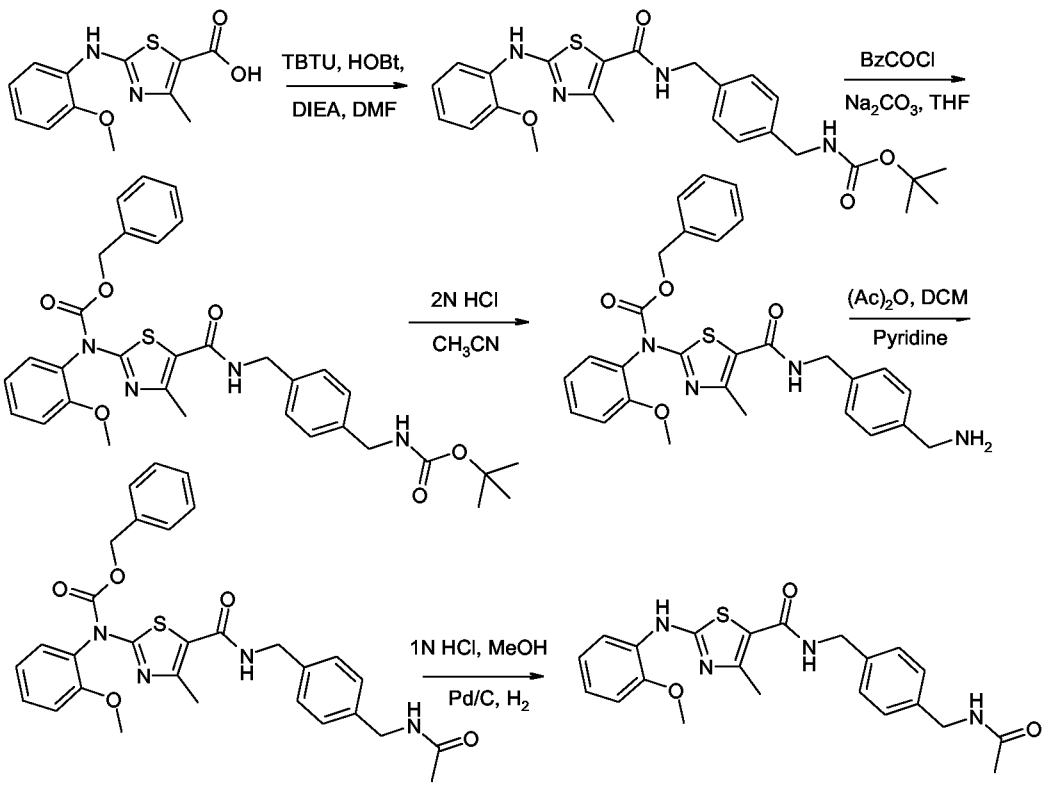
Compound **79** was made from intermediate **204** according to scheme **8**.



Scheme 8

Compound **80** was made from acid **184**. Acid **184** was made from phenol and 2-bromo-4-methyl-thiazole-5-carboxylic acid ethyl ester. Compound **81** was made from acid **185**. Acid **185** was made from thiophenol and 2-bromo-4-methyl-thiazole-5-carboxylic acid ethyl ester.

Compound **88** was made from intermediate **205**. Intermediate **205** was made from acid **5**. Compound **89** was made from acid **186.** Compound **92** was made from acid **187.** Compound **93** was made from acid **188.** Compound **94** was made from acid **189.** Compound **95** was made from acid **190.** Compound **96** was made from the intermediates **206, 207** and **208** according to scheme **9.**



Scheme 9

Compound **114** was made from intermediate **204**. Compound **126** was made from acid **191**. Compound **211** was made from acid **192**. Compound **129** was made from compound **68**. Compound **133** was made from acid **193**. Compound **153** was made from acid **194**. Compound **212** was made from compound **151**. Compound **172** was made from 2-o-tolylamino-thiazole-4-carboxylic acid. Compound **179** was made from acid **195**. Compound **180** was made from acid **196**. Compound **181** was made from acid **197**. Compound **213** was made from acid **198**. Compounds **221, 222** and **223** were made from acid **182**. Compounds **224, 225** and **226** were made from acid **199**.

Compound 1: 2-(4-fluoro-phenylamino)-4-methyl-thiazole-5-carboxylic acid

This compound was obtained from (4-fluoro-phenyl)-thiourea and ethyl 2-chloroacetoacetate, according to the protocol A.

Compound 2: 2-(4-bromo-phenylamino)-4-methyl-thiazole-5-carboxylic acid

This compound was obtained from (4-bromo-phenyl)-thiourea and ethyl 2-chloroacetoacetate, according to the protocol A.

Compound 3: 2-(4-chloro-phenylamino)-4-methyl-thiazole-5-carboxylic acid

This compound was obtained from (4-chloro-phenyl)-thiourea and ethyl 2-chloroacetoacetate, according to the protocol A.

Compound 4: 2-(2-methyl-phenylamino)-4-methyl-thiazole-5-carboxylic acid

This compound was obtained from (2-methyl-phenyl)-thiourea and ethyl 2-chloroacetoacetate, according to the protocol A .

Compound 5: 2-(2-methoxy-phenylamino)-4-methyl-thiazole-5-carboxylic acid

This compound was obtained from (2-methoxy-phenyl)-thiourea and ethyl 2-chloroacetoacetate, according to the protocol A.

Compound 6: 2-(2,4-dimethoxy-phenylamino)-4-methyl-thiazole-5-carboxylic acid

This compound was obtained from (2,4-dimethoxy-phenyl)-thiourea and ethyl 2-chloroacetoacetate, according to the protocol A.

Compound 7: 2-(5-chloro-2-methoxy-phenylamino)-4-methyl-thiazole-5-carboxylic acid

This compound was obtained from (5-chloro-2-methoxy-phenyl)-thiourea and ethyl 2-chloroacetoacetate, according to the protocol A.

Compound 8: 2-(4-bromo-phenyl-methylamino)-4-methyl-thiazole-5-carboxylic acid

In a round bottom flask containing the thiourea (0.5 mmole) was added 20 ml of ethyl-2-chloroaceto-acetate (1.2 eq; 0.6 mmole) in ethanol. The reaction was heated overnight at 65 °C. The medium was cooled to room temperature and the solvent evaporated under vacuum.

The obtained ester (150 mg; 0.44 mmole) was solubilised in dry methanol (0.5 M solution). Sodium methanolate (3 eq; 1.32 mmole) then methyl iodide (6 eq; 2.64 mmole) were added and the mixture stirred at 50°C for 5 days. The reaction was evaporated under reduced pressure and the residue was purified by HPLC.

The product (0.27 mmole) was diluted in 2N NaOH (5 eq; 1.35 mmole; 0.68 ml) and ethanol (0.67 ml). The reaction mixture was heated overnight at 50 °C. The medium was cooled to room temperature and the ethanol evaporated under reduced pressure. The aqueous layer was washed 2 times with ethyl acetate, cooled at 0 °C, and then acidified with concentrated HCl. The acid which precipitates was collected by filtration and finally washed 3 times with water (10 ml).

Compound 9: 2-(4-fluoro-phenylamino)-thiazole-4-carboxylic acid

This compound was obtained from (4-fluoro-phenyl)-thiourea and ethyl bromopyruvate, according to the protocol B.

Compound 10: 2-(4-bromo-phenylamino)-thiazole-4-carboxylic acid

This compound was obtained from (4-bromo-phenyl)-thiourea and ethyl bromopyruvate, according to the protocol B.

Compound 11: 2-(4-chloro-phenylamino)-thiazole-4-carboxylic acid

This compound was obtained from (4-chloro-phenyl)-thiourea and ethyl bromopyruvate, according to the protocol B.

Compound 12: 2-(3,5-dimethyl-phenylamino)-thiazole-4-carboxylic acid

This compound was obtained from (3,5-dimethyl-phenyl)-thiourea and ethyl bromopyruvate, according to the protocol B.

Compound 13: 2-phenylamino-thiazole-4-carboxylic acid

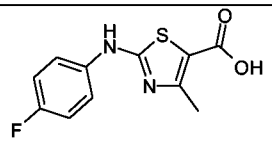
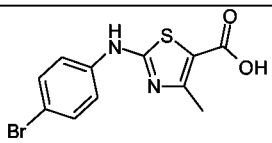
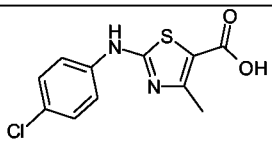
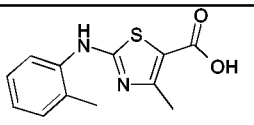
This compound was obtained from phenyl-thiourea and ethyl bromopyruvate, according to the protocol B.

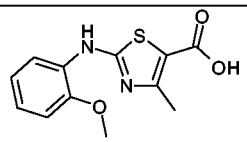
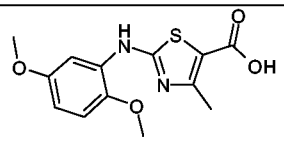
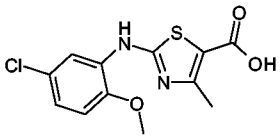
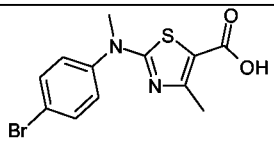
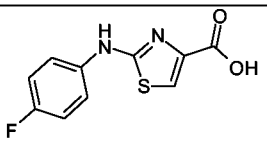
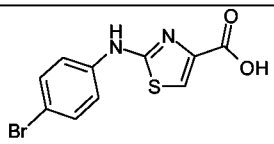
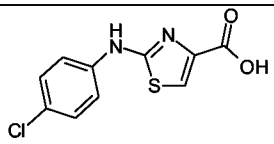
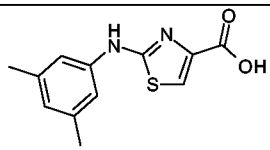
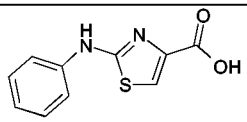
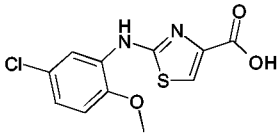
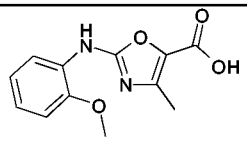
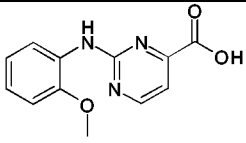
Compound 14: 2-(5-chloro-2-methoxy-phenylamino)-thiazole-4-carboxylic acid

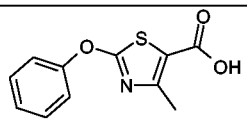
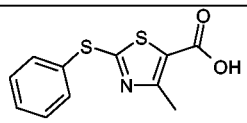
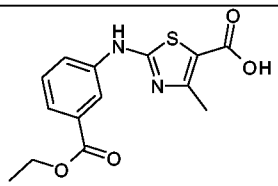
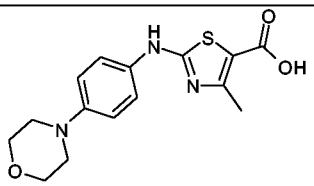
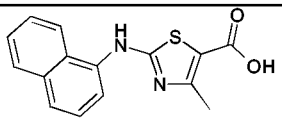
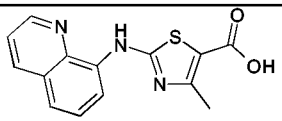
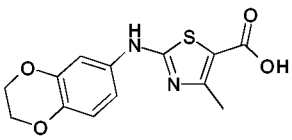
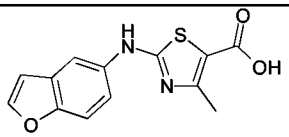
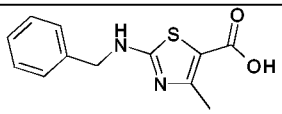
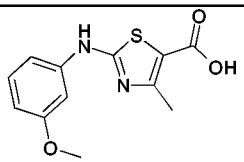
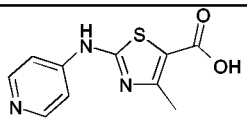
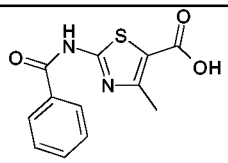
This compound was obtained from (5-chloro-2-methoxy-phenyl)-thiourea and ethyl bromopyruvate, according to the protocol B.

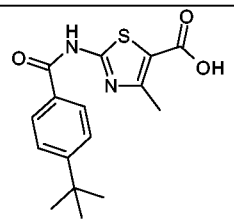
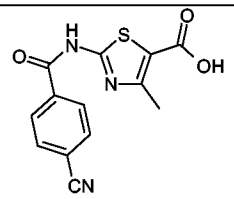
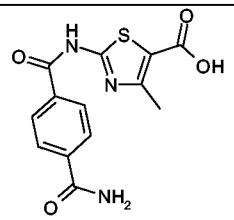
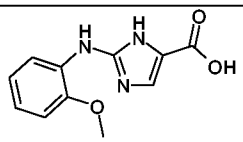
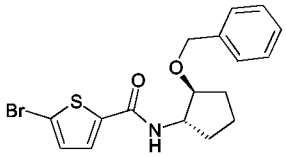
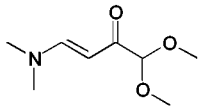
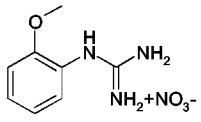
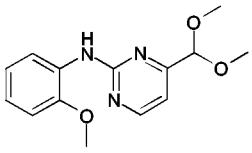
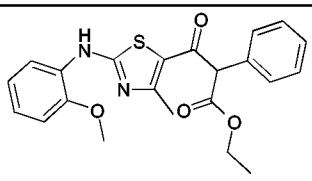
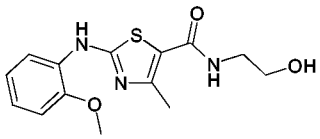
The structural formulas of the intermediates are listed in Table 1. The following abbreviations are used hereunder. P: protocol, Rt: retention time, Pu: purity. ES+: molecular ion obtained by electrospray in positive ion mode.

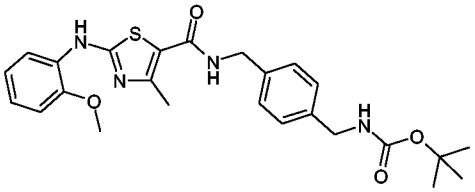
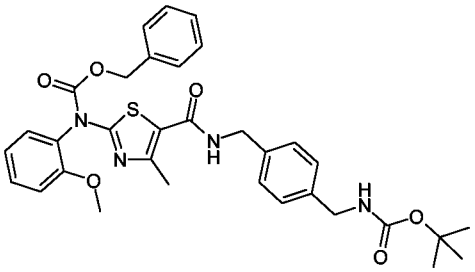
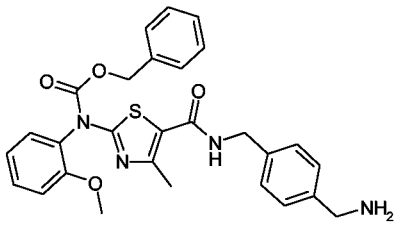
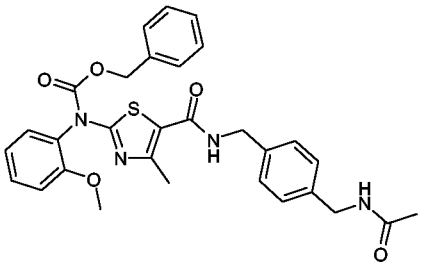
Table 1

Name	Compound	Structure	P	Rt	Pu	ES+
2-(4-fluoro-phenylamino)-4-methyl-thiazole-5-carboxylic acid	1		A	1.89	97	253
2-(4-bromo-phenylamino)-4-methyl-thiazole-5-carboxylic acid	2		A	2.26	100	313 - 315
2-(4-chloro-phenylamino)-4-methyl-thiazole-5-carboxylic acid	3		A	2.23	98	269 - 271
2-(2-methyl-phenylamino)-4-methyl-thiazole-5-carboxylic acid	4		A	1.81	96	249

Name	Compound	Structure	P	Rt	Pu	ES+
2-(2-methoxy-phenylamino)-4-methyl-thiazole-5-carboxylic acid	**5**		A	1.89	97	265
2-(2,4-dimethoxy-phenylamino)-4-methyl-thiazole-5-carboxylic acid	**6**		A	1.95	100	295
2-(5-chloro-2-methoxy-phenylamino)-4-methyl-thiazole-5-carboxylic acid	**7**		A	2.29	98	299 - 301
2-(4-bromo-phenyl-methylamino)-4-methyl-thiazole-5-carboxylic acid	**8**		V	2.27	98	327 - 329
2-(4-fluoro-phenylamino)-thiazole-4-carboxylic acid	**9**		B	1.77	100	239
2-(4-bromo-phenylamino)-thiazole-4-carboxylic acid	**10**		B	2.06	100	299 - 301
2-(4-chloro-phenylamino)-thiazole-4-carboxylic acid	**11**		B	1.99	100	255 - 257
2-(3,5-dimethyl-phenylamino)-thiazole-4-carboxylic acid	**12**		B	2.12	100	249
2-phenylamino-thiazole-4-carboxylic acid	**13**		B	1.70	92	221
2-(5-chloro-2-methoxy-phenylamino)-thiazole-4-carboxylic acid	**14**		B	2.07	100	285 - 287
2-(2-methoxy-phenylamino)-4-methyl-oxazole-5-carboxylic acid	**182**		A	ND	ND	249
2-(2-methoxy-phenylamino)-pyrimidine-4-carboxylic acid	**183**		I	ND	ND	246

Name	Compound	Structure	P	Rt	Pu	ES+
4-methyl-2-phenoxy-thiazole-5-carboxylic acid	**184**		M	1.93	95	236
4-methyl-2-phenylsulfanyl-thiazole-5-carboxylic acid	**185**		M	ND	ND	252
2-(3-ethoxycarbonyl-phenylamino)-4-methyl-thiazole-5-carboxylic acid	**186**		O	2.07	90	307
4-methyl-2-(4-morpholin-4-yl-phenylamino)-thiazole-5-carboxylic acid	**187**		M	1.49	90	320
4-methyl-2-(naphtalen-1-ylamino)-thiazole-5-carboxylic acid	**188**		A	1.96	97	285
4-methyl-2-(quinolin-8-ylamino)-thiazole-5-carboxylic acid	**189**		A	2.05	100	286
2-(2,3-dihydro-benzo[1,4]dioxin-6-ylamino-4-methyl-thiazole-5-carboxylic acid	**190**		A	1.61	100	293
2-(benzofuran-5-ylamino)-4-methyl-thiazole-5-carboxylic acid	**191**		A	2.00	100	275
2-(benzylamino)-4-methyl-thiazole-5-carboxylic acid	**192**		A	1.51	100	249
2-(3-methoxy-phenylamino)-4-methyl-thiazole-5-carboxylic acid	**193**		A	1.89	100	265
4-methyl-2-(pyridin-4-ylamino)- thiazole-5-carboxylic acid	**194**		A	0.93	100	236
2-benzoylamino-4-methyl-thiazole-5-carboxylic acid	**195**		U	1.69	100	263

Name	Compound	Structure	P	Rt	Pu	ES+
2-(4-tert-butyl-benzoylamino)-4-methyl-thiazole-5-carboxylic acid	**196**		U	2.34	100	319
2-(4-cyano-benzoylamino)-4-methyl-thiazole-5-carboxylic acid	**197**		U	1.63	100	288
2-(4-carbamoyl-benzoylamino)-4-methyl-thiazole-5-carboxylic acid	**198**		U	1.25	100	306
2-(2-methoxy-phenylamino)-3H-imidazole-4-carboxylic acid	**199**		B	ND	100	234
2-bromo-thiophene-5-carboxylic acid (1S,2S)-2-(benzyloxycyclopent-1-yl) amide	**200**		D	2.37	100	251
(E)-4-dimethylamino-1,1-dimethoxy-but-3-en-2-one	**201**		F	ND	ND	174
o-methoxyphenylguanidine nitrate	**202**		G	ND	ND	165
(4-dimethoxymethyl-pyrimidin-2-yl)-(2-methoxy-phenyl)amine	**203**		H	ND	ND	276
3-[2-(2-methoxy-phenylamino)-4-methyl-thiazol-5-yl]-3-oxo-2-phenyl-propionic acid ethyl ester	**204**		K	ND	ND	411
2-(2-methoxy-phenylamino)-4-methyl-thiazole-5-carboxylic acid (2-hydroxy-ethyl)-amide	**205**		C	1.55	90	308

Name	Compound	Structure	P	Rt	Pu	ES+
[4-({[2-(2-methoxy-phenylamino)-4-methyl-thiazole-5-carbonyl]-amino}-methyl)-benzyl]-carbamic acid tert-butyl ester	**206**		C	2.53	100	483
{5-[4-(tert-butoxycarbonylamino-methyl)-benzylcarbamoyl]-4-methyl-thiazol-2-yl}-(2-methoxy-phenyl)-carbamic acid benzyl ester	**207**		P	2.82	100	617
[5-(4-aminomethyl)-benzylcarbamoyl)-4-methyl-thiazol-2-yl]-(2-methoxy-phenyl)-carbamic acid benzyl ester	**208**		Q	2.38	100	517
{5-[4-(acetylamino-methyl)-benzylcarbamoyl]-4-methyl-thiazol-2-yl}-(2-methoxy-phenyl)-carbamic acid benzyl ester	**209**		R	2.42	100	559

Compound 15: 2-(4-fluoro-phenylamino)-4-methyl-thiazole-5-carboxylic acid (S)-1-(naphthalen-2-yl)ethyl amide

This compound was obtained from 2-(4-bromo-phenylamino)-4-methyl-thiazole-5-carboxylic acid and (S)-1-naphthalen-2-yl-ethylamine, according to the protocol C.

Compound 16: 2-(4-fluoro-phenylamino)-4-methyl-thiazole-5-carboxylic acid (R)-1-(naphthalen-2-yl)ethyl amide

This compound was obtained from 2-(4-fluoro-phenylamino)-4-methyl-thiazole-5-carboxylic acid and (R)-1-naphthalen-2-yl-ethylamine, according to the protocol C.

Compound 17: 2-(4-fluoro-phenylamino)-4-methyl-thiazole-5-carboxylic acid (4-nitro-benzyl)-propyl-amide

This compound was obtained from 2-(4-fluoro-phenylamino)-4-methyl-thiazole-5-carboxylic acid and (4-nitro-benzyl)-propyl-amine, according to the protocol C.

Compound 18: 2-(4-bromo-phenylamino)-4-methyl-thiazole-5-carboxylic acid (S)-1-(naphthalen-2-yl)ethyl amide

This compound was obtained from 2-(4-bromo-phenylamino)-4-methyl-thiazole-5-carboxylic acid and (S)-1-naphthalen-2-yl-ethylamine, according to the protocol C.

Compound 19: 2-(4-bromo-phenylamino)-4-methyl-thiazole-5-carboxylic acid (R)-1-(naphthalen-2-yl)ethyl amide

This compound was obtained from 2-(4-bromo-phenylamino)-4-methyl-thiazole-5-carboxylic acid and (R)-1-naphthalen-2-yl-ethylamine, according to the protocol C.

Compound 20: 2-(4-bromo-phenylamino)-4-methyl-thiazole-5-carboxylic acid benzylamide

This compound was obtained from 2-(4-bromophenylamino)-4-methylthiazole-5-carboxylic acid and benzylamine, according to the protocol C.

Compound 21: 2-(4-bromo-phenylamino)-4-methyl-thiazole-5-carboxylic acid (R)-1-(3-methoxyphenyl)ethyl amide

This compound was obtained from 2-(4-bromo-phenylamino)-4-methyl-thiazole-5-carboxylic acid and (R)-1-(3-methoxy-phenyl)-ethylamine, according to the protocol C.

Compound 22: 2-(4-bromo-phenylamino)-4-methyl-thiazole-5-carboxylic acid (R)-1-(4-nitrophenyl)ethyl amide

This compound was obtained from 2-(4-bromo-phenylamino)-4-methyl-thiazole-5-carboxylic acid and (R)-1-(4-nitro-phenyl)-ethylamine, according to the protocol C.

Compound 23: 2-(4-bromo-phenylamino)-4-methyl-thiazole-5-carboxylic acid 4-nitro-benzylamide

This compound was obtained from 2-(4-bromo-phenylamino)-4-methyl-thiazole-5-carboxylic acid and 4-nitro-benzylamine, according to the protocol C.

Compound 24: 2-(4-bromo-phenylamino)-4-methyl-thiazole-5-carboxylic acid 3,5-bis-trifluoromethyl-benzylamide

This compound was obtained from 2-(4-bromo-phenylamino)-4-methyl-thiazole-5-carboxylic acid and 3,5-bis-trifluoromethyl-benzylamine, according to the protocol C.

Compound 25: 2-(4-bromo-phenylamino)-4-methyl-thiazole-5-carboxylic acid (1R,2R)-2-(benzyloxycyclopent-1-yl) amide

This compound was obtained from 2-(4-bromo-phenylamino)-4-methylthiazole-5-carboxylic acid and (1R,2R)-2-benzyloxycyclopent-1-ylamine, according to the protocol C.

Compound 26: 2-(4-bromo-phenylamino)-4-methyl-thiazole-5-carboxylic acid (1S,2S)-2-(benzyloxycyclopent-1-yl) amide

This compound was obtained from 2-(4-bromo-phenylamino)-4-methyl-thiazole-5-carboxylic acid and (1S,2S)-2-benzyloxycyclopent-1-ylamine, according to the protocol C.

Compound 27: 2-(4-bromo-phenylamino)-4-methyl-thiazole-5-carboxylic acid naphth-1-yl methylamide

This compound was obtained from 2-(4-bromophenylamino)-4-methylthiazole-5-carboxylic acid and methyl-naphtalen-1-ylmethyl-amine, according to the protocol C.

Compound 28: 2-(4-bromo-phenylamino)-4-methyl-thiazole-5-carboxylic acid (4-nitro-benzyl)-propyl-amide

This compound was obtained from 2-(4-bromophenylamino)-4-methylthiazole-5-carboxylic acid and (4-nitro-benzyl)-propyl-amine, according to the protocol C.

Compound 29: 2-(4-bromo-phenyl-methylamino)-4-methyl-thiazole-5-carboxylic acid (1R,2R)-2-(benzyloxycyclopent-1-yl) amide

This compound was obtained from 2-(4-bromo-phenyl-methylamino)-4-methyl-thiazole-5-carboxylic acid and (1R,2R)-2-benzyloxycyclopent-1-ylamine, according to the protocol C.

Compound 30: 2-(4-chloro-phenylamino)-4-methyl-thiazole-5-carboxylic acid (1R,2R)-2-(benzyloxycyclopent-1-yl) amide

This compound was obtained from 2-(4-chloro-phenylamino)-4-methyl-thiazole-5-carboxylic acid and (1R,2R)-2-benzyloxycyclopent-1-ylamine, according to the protocol C.

Compound 31: 2-(2-methoxy-phenylamino)-4-methyl-thiazole-5-carboxylic acid (1R,2R)-2-(benzyloxycyclopent-1-yl) amide

This compound was obtained from 2-(2-methoxy-phenylamino)-4-methyl-thiazole-5-carboxylic acid and (1R,2R)-2-benzyloxycyclopent-1-ylamine, according to the protocol C.

Compound 32: 2-(4-bromo-phenylamino)-4-methyl-thiazole-5-carboxylic acid (S)-1-(naphthalen-2-yl)ethyl amide

This compound was obtained from 2-(2-methyl-phenylamino)-4-methyl-thiazole-5-carboxylic acid and (S)-1-naphthalen-2-yl-ethylamine, according to the protocol C.

Compound 33: 2-(2,5-dimethoxyphenylamino)-4-methylthiazole-5-carboxylic acid (1R, 2R)-2-(benzyloxycyclopent-1-yl) amide

This compound was obtained from 2-(2,5-dimethoxyphenylamino)-4-methylthiazole-5-carboxylic acid and (1R,2R)-2-benzyloxycyclopent-1-ylamine, according to the protocol C.

Compound 34: 2-(5-chloro-2-methoxy-phenylamino)-4-methyl-thiazole-5-carboxylic acid (R)-2-(3-methoxy-phenyl)ethyl amide

This compound was obtained from 2-(5-chloro-2-methoxy-phenylamino)-4-methyl-thiazole-5-carboxylic acid and (R)-1-(3-methoxy-phenyl)ethylamine, according to the protocol C.

Compound 35: 2-(5-chloro-2-methoxy-phenylamino)-4-methyl-thiazole-5-carboxylic acid (1R, 2R)-2-(benzyloxy cyclopent-1-yl) amide

This compound was obtained from 2-(5-chloro-2-methoxy-phenylamino)-4-methyl-thiazole-5-carboxylic acid and (1R,2R)-2-benzyloxycyclopent-1-ylamine, according to the protocol C.

Compound 36: 2-(4-fluoro-phenylamino)-thiazole-4-carboxylic acid (R)-1-(4-nitro-phenyl)ethyl amide

This compound was obtained from 2-(4-fluoro-phenylamino)-thiazole-4-carboxylic acid and (R)-1-(4-nitro-phenyl)ethylamine, according to the protocol C.

Compound 37: 2-(4-fluoro-phenylamino)-thiazole-4-carboxylic acid (1R,2R)-2-(benzyloxycyclopent-1-yl) amide

This compound was obtained from 2-(4-fluoro-phenylamino)-thiazole-4-carboxylic acid and (1R,2R)-2-benzyloxycyclopent-1-ylamine, according to the protocol C.

Compound 38: 2-(4-fluoro-phenylamino)-thiazole-4-carboxylic acid (1R,2R)-2-(benzyloxycyclohex-1-yl) amide

This compound was obtained from 2-(4-fluoro-phenylamino)-thiazole-4-carboxylic acid and (1R,2R)-2-benzyloxycyclohex-1-ylamine, according to the protocol C.

Compound 39: 2-(4-bromo-phenylamino)-thiazole-4-carboxylic acid (1R,2R)-2-(benzyloxycyclopent-1-yl) amide

This compound was obtained from 2-(4-bromo-phenylamino)-thiazole-4-carboxylic acid and (1R,2R)-2-benzyloxycyclopent -1-ylamine, according to the protocol C.

Compound 40: 2-(4-chloro-phenylamino)-thiazole-4-carboxylic acid (1R,2R)-2-(benzyloxycyclopent-1-yl) amide

This compound was obtained from 2-(4-chloro-phenylamino)-thiazole-4-carboxylic acid and (1R,2R)-2-benzyloxycyclopent-1-ylamine, according to the protocol C.

Compound 41: 2-(4-chloro-phenylamino)-thiazole-4-carboxylic acid (1S,2S)-2-(benzyloxycyclohex-1-yl) amide

This compound was obtained from 2-(4-chloro-phenylamino)-thiazole-4-carboxylic acid and (1S,2S)-2-benzyloxycyclohex-1-ylamine, according to the protocol C.

Compound 42: 2-(4-chloro-phenylamino)-thiazole-4-carboxylic acid (4-nitro-benzyl)-propyl-amide

This compound was obtained from 2-(4-chloro-phenylamino)-thiazole-4-carboxylic acid and (4-nitro-benzyl)-propyl-amine, according to the protocol C.

Compound 43: 2-(2,6-dimethyl-phenylamino)-thiazole-4-carboxylic acid (R)-1-(4-nitro-phenyl)ethyl amide

This compound was obtained from 2-(2,6-dimethyl-phenylamino)-thiazole-4-carboxylic acid and (R)-1-(4-nitro-phenyl)ethylamine, according to the protocol C.

Compound 44: 2-(3,5-dimethyl-phenylamino)-thiazole-4-carboxylic acid (S)-(1-methoxymethyl-2-phenyl-ethyl)-amide

This compound was obtained from 2-(3,5-dimethyl-phenylamino)-thiazole-4-carboxylic acid and (S)-1-methoxymethyl-2-phenyl-ethylamine, according to the protocol C.

Compound 45: 2-(3,5-dimethyl-phenylamino)-thiazole-4-carboxylic acid (1R,2R)-2-(benzyloxycyclopent-1-yl)-amide

This compound was obtained from 2-(3,5-dimethyl-phenylamino)-thiazole-4-carboxylic acid and (1R,2R)-2-benzyloxycyclopent -1-ylamine, according to the protocol C.

Compound 46: 2-(3,5-dimethyl-phenylamino)-thiazole-4-carboxylic acid (1S,2S)-2-(benzyloxycyclohex-1-yl) amide

This compound was obtained from 2-(3,5-dimethyl-phenylamino)-thiazole-4-carboxylic acid and (1S,2S)-2-benzyloxycyclohex-1-ylamine, according to the protocol C.

Compound 47: 2-phenylamino-thiazole-4-carboxylic acid 1-((R)-4-nitrophenyl-ethyl)-amide

This compound was obtained from 2-phenylamino-thiazole-4-carboxylic acid and (R)-1-(4-nitro-phenyl)ethylamine, according to the protocol C.

Compound 48: 2-phenylaminothiazole-4-carboxylic acid (1R,2R)-2-(benzyloxycyclopent-1-yl) amide

This compound was obtained from 2-phenylamino-thiazole-4-carboxylic acid and (1R,2R)-2-benzyloxycyclopent -1-ylamine, according to the protocol C.

Compound 49: 2-phenylamino-thiazole-4-carboxylic acid (1S,2S)-2-(benzyloxycyclohex-1-yl) amide

This compound was obtained from 2-phenylamino-thiazole-4-carboxylic acid and (1S,2S)-2-benzyloxycyclohex-1-ylamine, according to the protocol C.

Compound 50: 2-(5-chloro-2-methoxy-phenylamino)-thiazole-4-carboxylic acid (1S,2S)-2-(benzyloxycyclohex-1-yl) amide

This compound was obtained from 2-(5-chloro-2-methoxy-phenylamino)thiazole-4-carboxylic acid and (1S,2S)-2-benzyloxycyclohex-1-ylamine, according to the protocol C.

Compound 51: 2-(5-chloro-2-methoxy-phenylamino)-thiazole-4-carboxylic acid (1R,2R)-2-(benzyloxycyclohex-1-yl) amide

This compound was obtained from 2-(2-methoxy-5-chlorophenylamino)thiazole-4-carboxylic acid and (1R,2R)-2- benzyloxycyclohex -1-ylamine, according to the protocol C.

Compound 52: 2-(4-chloro-phenylamino)-4-methyl-thiazole-5-carboxylic acid (R)-1-(2-naphtalen-2-yl-ethyl)-amide

This compound was obtained from 2-(4-chloro-phenylamino)-4-methyl-thiazole-5-carboxylic acid and (R)-1-(2-naphtyl)ethylamine, according to the protocol C.

Compound 53: 2-(2-methoxy-phenylamino)-4-methyl-thiazole-5-carboxylic acid (R)-1-(2-naphtalen-2-yl-ethyl)-amide

This compound was obtained from 2-(2-methoxy-phenylamino)-4-methyl-thiazole-5-carboxylic acid and (R)-1-(2-naphtyl)ethylamine, according to the protocol C.

Compound 54: 2-(4-chloro-phenylamino)-4-methyl-thiazole-5-carboxylic acid (S)-1-(2-naphtalen-2-yl-ethyl)-amide

This compound was obtained from 2-(4-chloro-phenylamino)-4-methyl-thiazole-5-carboxylic acid and (S)-1-(2-naphtyl)ethylamine, according to the protocol C.

Compound 55: 2-(2-methoxy-phenylamino)-4-methyl-thiazole-5-carboxylic acid (S)-1-(2-naphtalen-2-yl-ethyl)-amide

This compound was obtained from 2-(2-methoxy-phenylamino)-4-methyl-thiazole-5-carboxylic acid and (S)-1-(2-naphtyl)ethylamine, according to the protocol C.

Compound 56: 2-(4-bromo-phenylamino)-4-methyl-thiazole-5-carboxylic acid (naphtalen-1-yl-methyl)-amide

This compound was obtained from 2-(4-bromo-phenylamino)-4-methyl-thiazole-5-carboxylic acid and 2-(aminomethyl)naphtalene, according to the protocol C.

Compound 57: 2-(4-bromo-phenylamino)-4-methyl-thiazole-5-carboxylic acid (pyridin-4-ylmethyl)-amide

This compound was obtained from 2-(4-bromo-phenylamino)-4-methyl-thiazole-5-carboxylic acid and 4-(aminomethyl)pyridine, according to the protocol C.

Compound 58: 2-(4-bromo-phenylamino)-4-methyl-thiazole-5-carboxylic acid (pyridin-3-ylmethyl)-amide

This compound was obtained from 2-(4-bromo-phenylamino)-4-methyl-thiazole-5-carboxylic acid and 3-(aminomethyl)pyridine, according to the protocol C.

Compound 59: 2-(4-bromo-phenylamino)-4-methyl-thiazole-5-carboxylic acid (pyridin-2-ylmethyl)-amide

This compound was obtained from 2-(4-bromo-phenylamino)-4-methyl-thiazole-5-carboxylic acid and 2-(aminomethyl)pyridine, according to the protocol C.

Compound 60: 2-(4-bromo-phenylamino)-4-methyl-thiazole-5-carboxylic acid 4-methoxy-benzylamide

This compound was obtained from 2-(4-bromo-phenylamino)-4-methyl-thiazole-5-carboxylic acid and 4-methoxybenzylamine, according to the protocol C.

Compound 61: 2-(4-bromo-phenylamino)-4-methyl-thiazole-5-carboxylic acid 3,4-dimethoxy-benzylamide

This compound was obtained from 2-(4-bromo-phenylamino)-4-methyl-thiazole-5-carboxylic acid and 3,4-dimethoxybenzylamine, according to the protocol C.

Compound 62: 2-(4-bromo-phenylamino)-4-methyl-thiazole-5-carboxylic acid 3-trifluoromethoxy-benzylamide

This compound was obtained from 2-(4-bromo-phenylamino)-4-methyl-thiazole-5-carboxylic acid and 4-trifluoromethoxybenzylamine, according to the protocol C.

Compound 63: 2-(4-bromo-phenylamino)-4-methyl-thiazole-5-carboxylic acid 4-fluoro-3-trifluoromethyl-benzylamide

This compound was obtained from 2-(4-bromo-phenylamino)-4-methyl-thiazole-5-carboxylic acid and 4-fluoro-3-trifluoromethyl-benzylamine, according to the protocol C.

Compound 64: 2-(4-bromo-phenylamino)-4-methyl-thiazole-5-carboxylic acid 4-dimethylamino-benzylamide

This compound was obtained from 2-(4-bromo-phenylamino)-4-methyl-thiazole-5-carboxylic acid and 4-dimethylaminobenzylamine, according to the protocol C.

Compound 65: 2-(4-bromo-phenylamino)-4-methyl-thiazole-5-carboxylic acid 3,5-dimethoxy-benzylamide

This compound was obtained from 2-(4-bromo-phenylamino)-4-methyl-thiazole-5-carboxylic acid and 3,5-dimethoxybenzylamine, according to the protocol C.

Compound 66: 2-(4-bromo-phenylamino)-4-methyl-thiazole-5-carboxylic acid 1,2,3,4-tetrahydroisoquinolinamide

This compound was obtained from 2-(4-bromo-phenylamino)-4-methyl-thiazole-5-carboxylic acid and 1,2,3,4-tetrahydroisoquinoline, according to the protocol C.

Compound 67: 2-(4-fluoro-phenylamino)-4-methyl-thiazole-5-carboxylic acid (1S,2S)-2-(benzyloxycyclopent-1-yl) amide

This compound was obtained from 2-(4-fluoro-phenylamino)-4-methyl-thiazole-5-carboxylic acid and (1S,2S)-2-benzyloxycyclopent-1-ylamine, according to the protocol C.

Compound 68: 2-(2-methoxy-phenylamino)-4-methyl-thiazole-5-carboxylic acid (1S,2S)-2-(benzyloxycyclopent-1-yl) amide

This compound was obtained from 2-(2-methoxy-phenylamino)-4-methyl-thiazole-5-carboxylic acid and (1S,2S)-2-benzyloxycyclopent-1-ylamine, according to the protocol C.

Compound 69: 2-(2,5-dimethoxy-phenylamino)-4-methyl-thiazole-5-carboxylic acid (R)-1-(2-naphtalen-2-yl-ethyl)-amide

This compound was obtained from 2-(2,5-dimethoxy-phenylamino)-4-methyl-thiazole-5-carboxylic acid and (R)-1-(2-naphtyl)ethylamine, according to the protocol C.

Compound 70: 2-(4-fluoro-phenylamino)-4-methyl-thiazole-5-carboxylic acid 4-dimethylamino-benzylamide

This compound was obtained from 2-(4-fluoro-phenylamino)-4-methyl-thiazole-5-carboxylic acid and 4-dimethylaminobenzylamine, according to the protocol C.

Compound 71: 2-(4-fluoro-phenylamino)-4-methyl-thiazole-5-carboxylic acid 4-sulfamoyl-benzylamide

This compound was obtained from 2-(4-fluoro-phenylamino)-4-methyl-thiazole-5-carboxylic acid and 4-(aminomethyl)benzenesulfonamide hydrochloride, according to the protocol C.

Compound 72: 2-(4-fluoro-phenylamino)-thiazole-4-carboxylic acid 4-dimethylamino-benzylamide

This compound was obtained from 2-(4-fluoro-phenylamino)-thiazole-4-carboxylic acid and 4-dimethylaminobenzylamine, according to the protocol C.

Example 2: Biological Assays using *C. elegans* screening

A *C. elegans* based high-throughput screen for Kv4.3 modulators has been used to establish an *in vivo* SAR (structure-activity relationships: the effect of chemical structure on biological activity) on Kv4.3 for the compounds according to the present invention.

This assay has employed a stable transgenic *C. elegans* strain that functionally expressed human Kv4.3 in the pharynx and a visible selection GFP maker in body-wall muscle.

The method to describe the construction of a transgenic *C. elegans* strain expressing human Kv4.3 has been described in WO 03/097682. Briefly, the actual used strain UG1755 has been generated by microinjection into the gonad of a wild-type strain N2 with a mix of 5 ng/µl plasmid pGV8 (human Kv4.3), 20 ng/µl pDW2821 (GFP-marker) and 40 ng/ul genomic *C. elegans* DNA. Transgenic animals have been isolated and submitted to integration of the extra-chromosomal array into the genome of *C. elegans*. A line with 50% transmission of the functional expressed human Kv4.3 has been mutagenized with gamma irradiation using a Cobalt source. About 12000 F2 animals have been singled out and their progeny has been screened for the 100% transmission of the GFP marker. Lines with 100% transmission of GFP have been considered as potentially integrated. These lines have been further tested and out-crossed with N2 strain two-times. All lines obtained have been tested for viability, GFP and human Kv4.3 expression. At the end of a selection process, UG1755 was identified as most suitable *C. elegans* strain amenable to high throughput screening (HTS). This stable strain has expressed human Kv4.3 as confirmed by electropharyngeograms (EPG) analysis. The method has been described in WO 03/097682. Briefly, dissected pharynxes of UG1755 *C. elegans* animals have been prepared and Electropharyngeograms (EPGs) have been recorded using an Axopatch-1D amplifier (Axon instruments). Pharynxes have been equilibrated for about 2 minutes in the bath solution (Dent s saline with 0.5% DMSO) until stableEPG recordings have been seen. Compound solution (DMSO or 100µM Flecainide) has been added to the bath solution. The number of ultra short EPGs (10-20ms) and normal EPGs (100-200ms) has been analyzed and given as ratio in percentage. Reduction of the number of ultra short EPGs indicates partial reversion to wild-type EPGs and consequently inhibition of human Kv4.3. 50-80% of the EPGs are the ultra short EPGs (Table 2). Human Kv4.3 has induced ultra short EPGs in UG1755 that can be modulated with Flecainide. In addition, standard qRT-PCR confirmed the presence of the human Kv4.3 transgene in UG1755 as well as human Kv4.3 protein has been detected with the human Kv4.3 antibody P 0358 in the pharynx of UG1755 animals.

Table 2: Flecainide modulates human Kv4.3 activity in transgenic *C. elegans* strain UG1755.

Strain	Before Application of Compound Ratio Ultra short to Normal EPGs in %	After Application of Compound Ratio Ultra short to Normal EPGs in %
UG1755 : DMSO (n=10)	76 ± 19	90 ± 5
UG1755: Flecainide (n=15)	83 ± 13	53 ± 24

Background of the assay:

The pharynx is the feeding organ of *C. elegans* and contracts rhythmically 3-4 times per second. The pharynx contraction is controlled by the nervous system via action potentials similar to the human myocyte and can thus be used to study human ion channel physiology *in vivo* in *C. elegans*.

Introducing the human Kv4.3 channel into the *C. elegans* pharynx influences the *C. elegans* action potential in a characteristic fashion. The additional number of potassium channels increases potassium ion efflux, enhances re-polarization and thereby shortens the action potential duration. The ultra short action potentials of the human Kv4.3 transgenic *C. elegans* pharynx can be restored to normal action potentials with 4-aminopyridine, a non-specific potassium channel blocker, or flecainide, a SCN5a and Kv4.3 blocker. The shortened action potentials of the *C. elegans* pharynx resulting from expression of human Kv4.3, changes the pharynx contraction-relaxation cycle and consequently reduces the pumping/feeding in these transgenic animals. This change of pumping is an end-point amenable to high-throughput screening technology. The pumping end-point can be technically translated into a high-throughput read-out by the use of a pro-fluorescent dye. The pro-fluorescent dye is taken up by *C. elegans* depending on its pumping activity and converted into a fluorescent dye by enzymes located in its intestines. After a defined incubation period, the change of fluorescence intensity in the intestine can be measured with a plate reader.

The screening of the compounds according to the present invention has been performed in the *C. elegans* based high-throughput screen for Kv4.3 modulators described above. The method for testing the activity on human Kv4.3 of the compounds according to the invention with *C. elegans* strains expressing human Kv4.3 for their activity is the same as the method described in WO 03/097682. The method for testing the compounds on wild-

type *C. elegans* strains not expressing human Kv4.3 is the same as the method described in WO 00/63427. Briefly, UG1755 animals have been grown in large numbers and staged young adults (no or only few eggs inside the uterus) have been harvested on the day of screening. Approximately 125 animals in 80 µl buffer have been dispensed per well of a "U shaped 96-well compound plate The compound plate contained already compound material at a final concentration of 30 µM in 0.3% DMSO. After one hour incubation 10 µl of tne fluorescent label Calcein AM (CAM) have been added to achieve a final concentration of 5 µM CAM and 0.8% DMSO. After another four hours of incubation at 20°C, the drinking of *C. elegans* animals (or the "reaction measured by the uptake of CAM) has been stopped by adding 10 µl of a 60 µM ivermectin solution. The fluorescence intensity (counts per second) has been measured 40 minutes after adding ivermectin with the Wallac plate reader at a wavelength of 535nm (after excitation at 485nm).

The active compounds have been identified and confirmed by dose-response analysis. An EC_{50} has been calculated and the results are listed under Table 3. Dose-response curves have been obtained at concentrations of 30 µM. EC_{50} has been calculated using XLfit 2.09 software package.

These compounds have been also tested in the same assay format using a *C. elegans* wild-type strain N2 and the corresponding EC_{50} has been calculated. The ratio of the EC_{50}s obtained for a compound on the two strains (transgenic expressing human Kv4.3 and wild-type) gives an indication on whether said compound is acting on human Kv4.3. The cut-off value to determine that a compound is potentially active on Kv4.3 was a ratio of 1.8 (EC_{50} on N2 divided by EC_{50} on the Kv4.3 expressing strain). The results of the ratio for the compounds according to the invention are listed under Table 3.

Table 3

Compound	EC_{50} (µM) Kv4.3 worm	EC_{50} (µM) Wild type worm N2	Ratio N2 / Kv4.3
15	10.1	24	2.4
16	32.1	> 60	> 1.8
18	13.5	33	2.4
19	7.0	33	4.7
20	25.0	> 60	>2.3
22	11 .7	> 30	> 2.6
23	14.6	41.0	2.8

Compound	EC_{50} (µM) Kv4.3 worm	EC_{50} (µM) Wild type worm N2	Ratio N2 / Kv4.3
24	17.1	> 30	> 1.7
25	10.3	> 30	>25
30	9.0	> 60	> 6.4
36	22.7	45	2.0
37	6.0	23	3.8
38	17.3	44	2.5
40	12.1	> 30	> 2.5
41	22	48	2.2
42	21.4	43	2.0
43	18.9	35	1.8
44	11.5	39.5	3.5
45	1.3	37	28.0
46	14	39	2.8
48	2	29.8	14.9
51	17	> 30	> 1.8

All the compounds tested were active on Kv4.3 at very low concentration. The compounds of the invention were also active on Kv1.5 ion channels as illustrated further in Example 4.

Example 3: Patch Clamp Assays

Cell Culture:

For this experiment, a recombinant CHO-K1 cell line stably expressing the human Kv4.3/KChIP2.2 potassium channel was used. The cells used for this experiment were kept in continuous culture under standard conditions (37°C, air supplemented with 7% CO_2). The CHO-K1 Kv4.3/KChIP2.2 cells were kept in Iscove s modified DMEM (Dulbecco's Modified Eagle's Medium) medium (IMEM) supplemented with 100 U/ml Penicillin, 100 µg/ml Streptomycin, 7% fetal calf serum (FCS), 2.5 µg/ml amphotericin, 400 µg/ml G418, and 400 µg/ml Zeocin™. Cells were passed every 3-4 days after detachment using a Trypsin solution. The quality of the cultured cells was guaranteed by vitality and contamination tests. The culture of the cells was performed as described in protocol D hereunder.

Protocol D: The cells were cultured in 94 mm culture dishes under the culturing conditions of 5 % CO_2 and 37 °C. Subculturing was performed every 3 - 4 days, by removing the

media and then rising the dish with 8 ml PBS (phosphate buffered saline). The PBS was removed and 1 ml Trypsin / EDTA was added to the cells. The cells were incubated about 2 min at 37°C or 5 min at room temperature and then the dish was rapped to detach and singularize the cells. To inactivate the enzyme 9 ml of media was added and the solution was pipetted up and down to break up clumps of cells. Part of the suspension was then transferred to a new 94 mm dish and media was added to a final volume of 8 ml. If necessary the cells could be seeded onto 35 mm or 94 mm dishes (2 ml media per 35 mm dish and 8 ml media per 94 mm dish). The media was changed every 2 - 3 days. The media used was the solution for culturing the cells described above. For stable cells antibiotic G418, Hygromycin, Blasticidin, or Zeocin were not added.

The PBS used was Dulbecco s PBS (1x),without Ca and Mg. The 10 x Trypsin/EDTA solution contained 5 g/l Trypsin, 2 g/l EDTA and 8.5 g/l NaCl. The 1 x Trypsin/EDTA was prepared by adding 450 ml PBS to 50 ml 10x Trypsin/EDTA.

At least 18 hours prior to electrophysiological experiments the cells were detached by application of iced PBS or Trypsin and replated on cover slips.

The preparation of cells for electrophysiological experiments was performed as described in protocol E hereunder.

Protocol E: The transfected cells and stable cells were transferred from 35 mm cell culture dishes onto coverslips using cold PBS: The media was removed and 0.3 ml of PBS (4-10°C) was added. The cells were incubated 5 min at room temperature. The dish was rapped to detach and singularize the cells and 1.7 ml media was added and the solution pipetted up and down to break up clumps of cells. Part of the cell suspension was then transferred to a 35 mm dish with coverslips and media. The transfected cells and stable cells could also be transferred from 35 mm cell culture dishes onto coverslips using trypsin: The media was removed and the dish rinsed with 3 ml PBS. The PBS was removed and 0.3 ml 1 x Trypsin / EDTA was added and the cells incubated 5 min at room temperature. The dish was rapped to detach and singularize the cells and 1.7 ml media was added and the solution pipetted up and down to break up clumps of cells. Part of the cell suspension was then transferred to a 35 mm dish with coverslips and media.

Preparation of solutions:

10 mM stock solutions of the compounds were prepared in DMSO. Solutions of the compounds were prepared by dilution of stock solution in bath solution. If the required stock solution volume was theoretically below 1 µl, bath solutions with higher compound

concentration were used for dilution. The maximal DMSO concentration during experiments was 0.1 % (v/v).

For patch clamp experiments the following solutions in demineralized water as vehicle were used (concentration in mM).

Bath (external) solution: 4 KCl, 135 NaCl, 2 $CaCl_2$, 1 $MgCl_2$, 10 D(+)-Glucose, 5 HEPES, pH 7.4 (NaOH).

Pipette (internal) solution: 130 KCl, 1 $MgCl_2$, 10 EGTA, 5 Na_2ATP, 5 HEPES, pH 7.4 (KOH).

Electrophysiological measurements:

Activity of the human Kv4.3/KChIP2.2 channel was investigated using the patch clamp technique in its whole cell mode. This means that the current needed for clamping the whole cell expressing the K^+-channel protein to a specific potential was measured. Experiments were performed using a patch clamp set-up. Technical equipment needed for manipulation of the cells was placed on a vibration-isolated table and shielded with a Faraday cage to minimize electrical noise. The amplifier and control system were placed in a rack outside the Faraday cage. The system consisted of an EPC9 or EPC10 patch clamp amplifier (HEKA, Lambrecht, Germany), and the perfusion system DADVC8 (ALA Scientific, New York, USA) controlled by the Pulse software package (HEKA, Lambrecht, Germany) installed on a personal computer. The pipettes used for patch clamping were made of borosilicate glass.

Measurements were performed at room temperature (20-25°C). In each experiment (i.e. each cell) only one concentration of the compounds was investigated no cumulative dosages were performed. Each cell acted as its own control. The effect of compounds on Kv4.3/KChIP2.2 mediated currents was investigated at one concentration (2 μM) with two replicates each (c=1, n=2).

Between voltage pulses the cell was clamped to a holding potential of -80 mV (inside). The test protocols are illustrated in Figure 1 and Table 4. The test protocol illustrated in Figure 1a was used to characterize the properties of the Kv4.3/KChIP2.2 channel and to check the quality of the individual patch clamp experiment (voltage control). The test protocol illustrated in Figure 1b shows the standard test pulse for determination of channel activity. Each test protocol consisted of 4 segments. Duration and voltage of the segments are listed in Table 4.

Table 4: Test protocols for electrophysiological investigation of human Kv4.3/KChIP2.2 channels

Protocol/segment	Duration (ms)	Voltage (mV)
a) IV activation (7 pulse protocols)- Figure 1a		
Holding potential 1 Holding potential 2	500 400	-80 -80
Activation (varies with each pulse)	300	-60/-40/-20/0/ 20/40/60
Holding potential 2	800	-80
b) Test pulse- Figure 1b		
Holding potential 1 Full activation	500 400	-80 -100
Activation (varies with each pulse) Holding potential 2	300 800	40 -80

After the whole cell configuration was established a current-voltage curve (IV activation 1; Figure 1a and Table 4a) was recorded under constant superfusion with bath solution to check for Kv4.3/KChIP2.2 expression and the quality of the individual patch clamp experiment (voltage control). Subsequently, 14 test pulses (series 1; Figure 1b and Table 4b) were applied at 0.1 Hz under constant superfusion with bath solution. The protocol was initiated by a voltage jump to 100 mV (400 ms) to achieve full inactivation. Then the Kv4.3/KChIP2.2 channels were transferred to the open state by depolarization to +40 mV for 300 milliseconds (activation). Only cells generating current amplitudes between 1 nA and 50 nA were used for the experimental procedure. No or negligible rundown was observed.

Then, 36 test pulses (series 2) were applied at 0.1 Hz under constant superfusion with the compound dissolved in bath solution. Finally, another current-voltage curve was recorded in the presence of the compounds (IV activation 2).

If the experimental parameters were still satisfying the experiment was extended to study the washout of the compound. To do this, the cell was again superfused with bath solution while up to 30 test pulses were applied at 0.1 Hz (series 3). The washout procedure was not necessary for correct data analysis.

All data were leak corrected using a P/n protocol with n=5 (see data analysis).

Typical Kv4.3/KChIP2.2 currents obtained in this experiment are shown in Figure 2. Figure 2 shows Kv4.3/KChIP2.2 channel mediated currents evoked by test protocols described in Figure 1 and Table 4. Figure 2a shows a typical current response to a test pulse in the absence and presence of the compound tested (2 µM compound 23, cell 2). In Figure 2b a typical IV curve determined 75ms after each voltage jump with and without

the compound tested (2 µM compound 23) is displayed. Duration and voltage of the segments are listed in Table 4, voltage protocols are depicted in Figure 1.

All test protocols / series and their use in data analysis are summarized in Table 5.

Table 5: Test protocols/ series and their use in the data analysis of electrophysiological measurements

Test protocols /series	Use for data analysis
IV activation 1	Kv4.3/KChIP2.2 channel characterization
Series 1 (14 x test pulse) Series 2 (36 x test pulse) IV activation 2 Series 3 (optional up to 30 x test pulse)	Determination of rundown, 100% control Determination of compound effects on current Determination of compound effects on IV curve Determination of washout properties of compound

Vehicle controls were performed in separate experiments during the experiment, using the compound vehicle (DMSO) at the highest concentration (0.1 %) applied in the experiment (n=2).

Data analysis

A leak correction was performed using a classical P/n protocol. The leak pulses should not reach the activation level of the channels, and thus were scaled down to 1/n of the original pulse amplitude. Here, n=5 was used. The current responses of the cell to the leak pulses were then multiplied by n to calculate a theoretical passive response of the cell to the test sequence. This calculated curve was then subtracted from the real response, leaving only the active part of the response.

Three different types of analysis were used: Inhibition at the peak current, inhibition of translocated charge and inhibition 75ms after activation at +40 mV (sustained current). The peak current / charge / current at 75ms was determined using the online analysis tool of the HEKA pulse software package. The cursors were placed in a way that the peak current was enclosed, the whole segment "activation (see Table 5) was selected or a cursor was placed at time 75ms. The resulting current peak amplitudes / translocated charges / current amplitudes at 75ms were exported as ASCII data file.

The resulting ASCII files were imported into the software package Prism (Graphpad Software, San Diego, USA) and further analyzed as described below. No rundown correction was necessary. The last 5 current peak amplitudes / translocated charges / current amplitudes at 75ms before application of compound solution were averaged and were used as 100% activity value. The last 5 current peak amplitudes / translocated

charges / current amplitudes at 75ms in presence of compound solution were averaged to give the inhibition value.

All data points were fitted with a Hill function with three independent parameters, wherein y_{max} is the maximum inhibition in %, IC_{50} is the concentration at half maximum inhibition and *hill* is the Hill coefficient.

$$y = \frac{y_{max}}{1 + \left\{ \frac{IC_{50}}{x} \right\}^{hill}}$$

The fit parameters y_{max}, IC_{50} and *hill* characterize the interaction of Kv4.3/KChIP2.2-channels expressed in CHO-K1 cells with the compound tested. The resulting curve fitting is displayed in a graph (% inhibition vs. log concentration) with the averaged results with error bars: Standard Error of the Means (SEM) wherein

$$SEM = \sqrt{\frac{\sum x^2 - (\sum x)^2 / n}{n(n-1)}}$$

In order to compare the results, IC_{50} values were estimated. Therefore, data were fitted using the Hill equation with fixed values for the Hill coefficient (hill=1) and the maximum inhibition at high concentrations (y_{max} = 100). Figure 3 exemplifies the dose-response curves for compound 23 and compound 18.

The results of the Patch Clamp experiments are shown in Table 13.

The compounds according to the invention were found to be particularly active against Kv4.3 ion channels.

In order to be maximally useful in treatment, it was also important to assess the side reactions which might occur. Thus, in addition to being able to modulate a particular calcium channel, it was shown that the compounds according to the invention had high selectivity for Kv4.3 versus the hERG channel.

Test system and test method for the hERG experiment

Test system:

For this experiment HEK 293 T-REx HERG cells (#23) were used. This cell line made by IonGate is characterized by the inducible expression of the hERG gene. The T-REx™ System (Invitrogen, Karlsruhe, Germany) is a tetracycline-regulated mammalian expression system that uses regulatory elements from the *E. coli* Tn*10*-encoded tetracycline (Tet) resistance operon. In the absence of Tet the expression is repressed.

Tetracycline regulation in the T-REx™ System is based on the binding of tetracycline to the Tet repressor and derepression of the promoter controlling expression of the hERG gene. Addition of Tet to the cell culture media results in expression of the hERG potassium channel.

To construct the HEK 293 T-REx HERG cell line, the hERG gene was ligated into the inducible expression vector pcDNA4/TO (→ pc4TO-HERG) and transfected into HEK 293 T-REx cells (this cell line stably expresses the Tet repressor and was purchased at Invitrogen). Stable cell clones were isolated after selection with Blasticidin (5 µg/ml) and Zeocin™ (300 µg/ml). The clones were electrophysiological characterized after induction with 1 µg/ml Tet. Clone #23 showed the best expression of the hERG potassium channel.

Test method

Experiments were performed using the patch clamp set-up. Technical equipment needed for manipulation of the cells was placed on a vibration-isolated table and shielded with a Faraday cage to minimize electrical noise. The amplifier and control system were placed in a rack outside the Faraday cage. The system consisted of an EPC9 or EPC10 patch clamp amplifier (HEKA, Lambrecht, Germany), and the perfusion system DADVC8 (ALA Scientific, New York, USA) controlled by the Pulse software package (HEKA, Lambrecht, Germany) installed on a personal computer.

Cell culture

The cells used for this experiment were kept in continuous culture under standard conditions (37°C, air supplemented with 5% CO_2). The HEK 293 T-REx HERG cells were kept in minimal essential medium (MEM) supplemented with 100 U/ml Penicillin, 100 µg/ml Streptomycin, 10% fetal calf serum (FCS), 1% non-essential amino acids (NEAA), 2.5 µg/ml amphotericin, 300 µg/ml Zeocin™ and 5 µg/ml Blasticidin. Cells were passed every 3-4 days after detachment using a Trypsin solution. The quality of the cultured cells was guaranteed by vitality and contamination tests. The culture of the cells was performed as described in protocol D described above.

At least 18 hours prior to electrophysiological experiments the cells were detached by application of iced PBS (phosphate buffered saline) or Trypsin and replated on cover slips. 1 µg/ml Tet was added to the cells to induce hERG expression.

The preparation of cells for electrophysiological experiments was performed according to protocol E described above. The solutions were prepared as described above under in the paragraph preparation of solutions.

Electrophysiological measurements:

Activity of the cardiac hERG channel was investigated using the patch clamp technique in its whole cell mode. This means that the current needed for clamping the whole cell expressing the K^+-channel protein to a specific potential was measured. The pipettes used for patch clamping were made of borosilicate glass. Measurements were performed at room temperature (20-25°C). In each experiment (i.e. each cell) only one concentration of the compound was investigated no cumulative dosages were performed. Each cell acted as its own control. The effect of the compounds on hERG mediated currents was investigated at one concentration (10 µM) with two replicates each (c=1, n=2).

Between voltage pulses the cell was clamped to a holding potential of -80 mV (inside).

The test protocols for electrophysiological investigation of hERG K^+-channels are illustrated in Figure 4 and Table 6. In Table 6 and Figure 4, (a) is the standard test pulse for determination of channel activity. (b) and (c) were used to characterize the properties of the hERG channel and to check the quality of the individual patch clamp experiment (voltage control). Each test protocol consisted of 6 segments. The duration and voltage of the segments are listed in Table 6.

Table 6

Protocol / segment	Duration (sec)	Voltage (mV)
a) Test pulse – Figure 8a		
Holding potential 1	0.25	-80
Leak-test	0.05	-40
Holding potential 2	0.25	-80
Activation	2.5	40
Tail-current test	1.5	-40
Holding potential 3	0.25	-80
b) IV activation (7 pulse protocols) – Figure 8b		
Holding potential 1	0.25	-80
Leak-test	0.05	-40
Holding potential 2	0.25	-80
Activation (varies with each pulse)	2.5	-60 / -40 / -20 / 0 / 20 / 40 / 60
Tail-current test	1.5	-40
Holding potential 3	0.25	-80
c) IV tail current (7 pulse protocols) – Figure 8c		
Holding potential 1	0.25	-80
Leak-test	0.05	-40
Holding potential 2	0.25	-80
Activation	2.5	40
Tail-current test (varies with each pulse)	1.5	-100 / -80 / -60 / -40 / -20 / 0 / 20
Holding potential 3	0.25	-80

After the whole cell configuration was established a series of pulses was applied to check for hERG expression and to optimize amplifier settings. However, only the following measurements were used for data analysis: 15 test pulses (Figure 4a and Table 6a) were applied at 0.1 Hz (series 1) under constant superfusion with bath solution. The protocol was initiated by a leak test at -40 mV (50 ms). After returning to the holding potential (-80 mV, 0.25 sec.) hERG channels were transferred to the inactive state by depolarisation to +40 mV for 2.5 seconds (activation). The maximum hERG tail current amplitude was measured at -40 mV (tail current test, 1.5 sec.). Only cells generating tail current amplitudes between 300 pA and 10 nA were used for the experimental procedure.

The hERG channel mediated currents evoked by test protocols for hERG channel testing in Figure 5. Figure 5a shows the test of channel activity with and without 10 µM compound 21 (upper trace). Figure 5b and 5c are the current response to protocol Table 6b (IV activation) and Table 6c (IV tail current).

Subsequently the current-voltage curve (IV-curve) was investigated using two pulse series under superfusion with bath solution. The pulse series "IV activation" varies the potential of the activating pulse between each consecutive pulse of the series (-60 to +60 mV in 20

mV intervals, Figure 4b and Table 6b). The tail current amplitude after activation at +60 mV had to be within ± 20% of the value found with +40 mV activation potential. The pulse series "IV tail current" varies the potential of the tail current test pulse between each consecutive pulse of the series (-100 to +20 mV in 20 mV intervals, Figure 4c and Table 6c). The maximum tail current amplitude (I_{max}) had to be measured at 40 mV (± 10% I_{max}). Test pulses for series "IV activation and "IV tail current were applied at 0.1 Hz.

After successful characterization of the current another 10 test pulses were applied at 0.1 Hz while the cell was superfused with bath solution (series 2). Series 1 and 2 were used to fit a mathematical function to the tail current peak values to determine the rundown of the signal amplitude. Another 30 test pulses (series 3) were applied while the cell was superfused with a solution containing the compounds in the desired concentration. More test pulses were applied if necessary (series 4).

If the experimental parameters were still satisfying the experiment was extended to study the washout of the compound. To do this, the cell was again superfused with bath solution while up to 20 test pulses were applied at 0.1 Hz (series 5). However, since the baseline was constructed by a fitting procedure to series 1 and 2 (rundown-correction) the washout procedure was not necessary for correct data analysis.

All test protocols / series and their use in data analysis of electrophysiological measurements are summarized in Table 7.

Table 7

Test-protocols / series	Use for data analysis
Series 1 (15 x test pulse)	Determination of rundown
IV activation	hERG channel characterization
IV tail-current	hERG channel characterization
Series 2 (10 x test pulse)	Determination of rundown, 100 % control
Series 3 (up to 30 x test pulse)	Determination of compound effects on tail current
Series 4 (optional - up to 20 x test pulse)	Determination of compound effects on tail current
Series 5 (optional - up to 20 x test pulse)	Determination of washout properties of the compound

Vehicle controls were performed in separate experiments during the analysis, using the compound vehicle (DMSO) at the highest concentration (0.1 %) applied in the experiment (n=2).

Data analysis

The data analysis was based on the tail current peak amplitude mediated by hERG K^+ channels at -40 mV after activation at +40 mV. The peak current was determined using the online analysis tool of the HEKA pulse software package. The cursors were placed in a way that the peak current was enclosed. The current found at the leak test pulse (segment 2 in each test pulse) was set to zero. The resulting tail current peak amplitudes were exported as ASCII data file.

The resulting ASCII files were imported into the software package Prism (Graphpad Software, San Diego, USA) and further analyzed as described below. Series 1 and 2 were fitted using a suitable function (i.e. mono- or biexponential decay). The resulting function was used for rundown correction of the data set (series 1 to 5) by division. The last 5 tail current peak amplitudes before application of compound solution were averaged and were used as 100% activity value. The last 5 tail current peak amplitudes in presence of compound solution were averaged to give the inhibition value. All data points were fitted with a Hill function with three independent parameters, wherein y_{max} is the maximum inhibition in %, IC_{50} is the concentration at half maximum inhibition and *hill* is the Hill coefficient.

$$y = \frac{y_{max}}{1 + \left\{\frac{IC_{50}}{x}\right\}^{hill}}$$

The fit parameters y_{max}, IC_{50} and *hill* characterize the interaction of hERG K^+-channels expressed in HEK 293 cells with the compound tested. The resulting curve fitting is displayed in a graph (% inhibition vs. log concentration) with the averaged results with error bars: Standard Error of the Means (SEM) wherein

$$SEM = \sqrt{\frac{\sum x^2 - (\sum x)^2 / n}{n(n-1)}}$$

In order to compare the results, IC_{50} values were estimated. Therefore, data were fitted using the Hill equation with fixed values for the Hill coefficient (hill=1) and the maximum inhibition at high concentrations (y_{max} = 100). Figure 6 exemplifies the dose-response curves for compound 25 and compound 33.

The results showing the channel activity are illustrated in Table 8.

Table 8

Compound	IC_{50} (µM) Kv4.3	IC_{50} (µM) hERG	Ratio hERG / Kv4.3
16	1.84	28.00	47.8
18	3.85	26.50	6.9
19	2.72	89.99	33.1
30	1.25	10.96	8.7
31	2.91	25.34	8.7
33	3.35	33.48	10.0
34	1.62	8.73	5.4
52	0.34	24.20	65.4
54	2.41	15.80	6.6
55	2.02	10.20	5.0
56	1.07	7.04	6.6
60	0.39	3.00	7.7
63	0.16	5.29	33.1
64	0.83	> 100	> 120
65	0.18	1.63	9.1
66	0.34	9.88	29.1
68	0.54	7.95	14.7

The compounds showing a selectivity >5 (ratio value) for Kv4.3 vs hERG (Patch Clamp test) were considered as being very selective toward Kv4.3 channels.

So in addition to being actives on Kv4.3 ions channels at very low concentration, the compounds according to the invention proved to be very selective toward Kv4.3 ions channels when compared to the hERG channel.

In addition, Table 13 shows the effects on Kv4.3 and hERG of a non-limiting number of additional compounds of the invention. Unless provided otherwise, the compounds were investigated at one concentration (1 µM) on the Kv4.3-mediated potassium channel, in a patch clamp assay following a protocol as described in Example 3. The results are shown in Table 13. In Table 13, Kv4.3 charge in %: means the remaining current measured after application of the compound and relative to the blank, and Kv4.3 peak in %: means the remaining peak height measured after application of the compound and relative to the blank. As used herein the term "ND means not determined yet. Unless otherwise specified, the tests were performed at 1 µM for Kv4.3 charge and peak. The effects of a non-limiting number of additional compounds of the invention were investigated at 10 µm concentration unless provided otherwise on the hERG channel in patch clamp assay.

Example 4: Patch Clamp Assays using the Kv1.5 ion channel

The cDNA coding for Kv1.5 (GenBank Acc. No. M55513) was cloned into the pcDNA6- vector (Invitrogen, Leek, Netherlands). A C-terminal epitope-tag was introduced via PCR.

The plasmid was sequenced and subsequently introduced into cells. Clonal cell lines stably expressing the Kv1.5 channel were established. Expression of protein was analyzed by means of immunofluorescence using antibodies directed against the epitope-tag. The functional expression of the ion channels was validated electrophysiologically.

Cell culture

The experiments were performed using CHO cells stably expressing the Kv1.5 potassium channel.

Cells were grown at 37°C and 5% CO2 in 25 ml flasks (Greiner Bioone, Cellstar, Cat. No. 690160) in 6 ml MEM ALPHA Medium (Sigma, Taufkirchen, Germany, Cat No M8042) supplemented with 10% (v/v) heat inactivated fetal calf serum (Sigma, Cat. No. F9665), 1% (v/v) P/S/G-solution (Sigma, Cat. No. G6784) and G-418 (750 µg per millilitre medium; Sigma, Germany, Cat. No. A1720; 50mg/ml in water, Sigma, Germany, Cat. No. W3500).

Electrophysiology

Stimulation protocol for the Kv1.5-mediated current.

From a HP of -60 mV cells were hyperpolarised for 100 ms to 70 mV, followed by a 500 ms depolarisation to +50 mV. The current amplitude at the end of the test pulse to +50 mV was used for the analysis. Pulse cycling rate was 10 s (0.1 Hz).

Test item application protocol for the Kv1.5 mediated current

The application protocol of test compounds is depicted in Figure 7. The first 14 stimuli were required to achieve steady state of the current amplitude. Unspecific current reduction was calculated and served for correcting procedures during data analysis. After the 14_{th} stimulus the test compound application was started (indicated by an arrow) via teflon and silicone tubings and was assumed to reach the cell after 6 additional stimuli. The perfusion is adjusted by using a defined drop rate of 10 drops per 10-12 s. Up to three concentrations were applied successively to one cell followed by a wash period of 5 minutes. Total number of stimuli was 140. Effect of the test compound was analysed between stimulus nos. 21 and 50 (5 min., long dashed line) for the first concentration, between stimulus nos. 51 and 80 (5 min., short dashed line) for an additional 5 minutes. If the cell was still stable, a wash was added afterwards. Start of test compound application at the given concentration is indicated by arrows. Number of stimuli of each single episode are shown in the protocol of Figure 7.

Negative control

Vehicle (DMSO) control experiments were performed during study period and under identical conditions to verify the stability of current over time and to value cell condition.

Effects of test compounds on the Kv1.5 mediated current

The effects of the compounds were investigated at one concentration (2 µM or 1 µM) on the Kv1.5-mediated potassium channel. For comparison, the vehicle control experiments on the Kv1.5 mediated potassium channel. Results are presented in 9Table 9

Compound	Concentration	Relative remaining current (mean after 5 min)	Relative remaining current (mean after 8-10 min)
68	2 µM	0.66 (66%)	0.51 (51%)
75	1 µM	ND	77%
81	1 µM	ND	44%
94	1 µM	ND	79%
126	1 µM	ND	86%
DMSO	0.1%	1.00	0.96

Example 5: Ex-vivo organ studies in rats and guinea pigs

The compounds were checked for their effect on the force of contraction, stimulation threshold and for the Functional Refractory Period (FRP) in isolated rat left atria (Rat LA). Rat left atria functionally express the Kv4.3 ion channel, producing the I_{to} current of the action potential. In addition, the compounds were checked for these respective effects in isolated guinea pig right ventricular papillary muscle (GP pap. muscle), which do not express Kv4.3. The guinea pig action potential is dominated by hERG like ion channels for the refractory currents. Consequently, activity of hERG channels *in vivo* should be seen in GP pap muscle preparations.

***Method:* Rat LA (same method applies to GP pap. muscle)**

Assay principle

Left atria were mounted vertically in a two-chambered organ bath containing 100 ml of buffer solution (in mM: NaH_2PO_4 0.6, $MgSO_4$ 0.6, KCl 4.7, $NaHCO_3$ 25, glucose 4.5, NaCl 120, $CaCl_2$ 2.4). The solution was saturated with and circulated by a gas mixture containing 95% O_2 and 5 % CO_2. The temperature was kept constant at 30° C. Preload of the atria was set at about 8 mN. Electrical stimulation at 1 Hz was accomplished by rectangular pulses with a duration of 1.5 ms and a strength of 3.5 x threshold. The isometric force of the preparations was measured by force transducers, connected to

amplifiers, documented by a pen recorder and fed into a computer for evaluation. Force of contraction (FC), threshold stimulus (TS) and the functional refractory period (FRP) were measured at baseline (pre), 20 min after addition of compound, and after washout at the end of the experiment. Threshold stimulus, representing excitability of the tissue, was assessed by varying the voltage applied for electrical stimulation. TS was defined as the lowest voltage that induces a contraction of the tissue. The functional refractory period, representing the time needed for repolarization, was assessed by applying extra stimuli at varying time intervals from the preceding regular pacing stimulus. FRP was defined as the shortest interval between regular and extra stimulus that resulted in a contraction of the tissue in response to the extra stimulus.

Compound application

Compounds were tested by five cumulative administrations at 20 minute intervals beginning after an equilibration period of at least 60 minutes. Two washout intervals followed the measurement at the highest concentration of the compound. The results are depicted in Figures 8 and 9 and in Table 10.

Figure 8 shows the functional refractory period in isolated rat left atria for compound 68. Figure 9 shows the functional refractory period in isolated guinea pig papillary muscle for the same compound.

Table 10

Compound	**dFRP Rat (conc 10^{-5} mol/l)**	**dFRP Guinea Pig (conc 10^{-5} mol/l)**
68	13 ms	0 ms

Example 6: *In vivo* studies in mice

Transmitter implantation and ECG recording:

Male mice (NRMI) were anesthetized with a gas mixture of isoflurane, nitrous oxide and oxigen. Leads connected to a telemetry transmitter (TA10EA-F20, DSI, St.Paul, USA) were fixed by suture in the xiphoid and ventral neck region. The telemetry transmitter was placed under the skin on the back. Wounds were closed in layers and the animals were allowed to recover for at least 1 week.

Female guinea pigs (Charles River, Crl:HA(BR) were anesthetized by inhalative halothane anesthesia. The negative biopotential lead of the telemetry transmitter (TA11CTA-F40, DSI, St.Paul, USA) was fixed at muscle tissue in the right shoulder region, and the

positive lead was fixed in the region of 6th left rib of the thorax, mimicking a standard lead II configuration. The telemetry transmitter was placed in the abdominal cavity, fixed to the peritoneal muscle, and the incision was sutured in layers. After transmitter implantation, the animals were allowed to recover for at least 1 week.

Experimental study design, intraperitoneal (i.p.) application

On the day of the experiment the animals receive consecutive doses of vehicle i.p. at 60 min dosing intervals. ECG tracings (12 s duration) was recorded using the Data Sciences A.R.T. system. After completion of the experiment ECGs were analyzed automatically by Data Sciences ECG software (DSI, St.Paul, USA). QT and QRS intervals were measured manually in the stored ECGs. QTc was calculated from the QT interval and the corresponding heart rate using Bazett's formula. Heart rate was taken from the online analysis, given by the DSI Labpro and DSI A.R.T. systems (DSI, St.Paul, USA). Finally, ECG intervals were transferred to an Excel spreadsheet, checked for plausibility, and converted into 15 min averages.

Results in Mice

Consecutive dosing of the compounds of the invention led to a significant, dose-dependent but late onset prolongation of QT and QTc intervals in the mouse ECG. Results of vehicle and compound 68 are shown in Figures 10 and 11 respectively (vehicle and control injected i.p. (3-15 µM/kg)). PQ and QRS did not show dose-dependent changes. Heart rate showed a minor and not significant decrease. Locomotor activity showed a reproducible rise after each of the subsequent injections. Means ± SD, n=5.

Conclusions

The dose-dependent prolongation of QT and QTc, which in mouse depends on Kv4.2 and Kv4.3, and the lack of effects on PQ and QRS seen after consecutive application of the compounds indicate block of repolarizing K+ currents, which would be compatible with the compound's characterization as Kv4.3 blocker. It should be noted that in this experiment the highest dose tested was 15 µmol/kg, higher doses of up to 30 µmol/kg may evenly be tested in this model.

Example 7: Ex-vivo organ studies in rabbits

The compounds were checked for their effect on the QT interval, the $T_{p\text{-}e}$ interval (Yan and Antzelevitch, Circulation 1998; 98:1928-1936; Yan et al, Circulation 2001; 103:2851-2856) that approximates closely to transmural dispersion of repolarization (TDR), the $T_{p\text{-}e}$/QT ratio that reflects the potential of phase 2 early afterdepolarization (EAD) development in

sub- and/or endocardium (Joshi et al, Journal of Electrocardiology, 2004, 34 (suppl): 7-14) and the phenomena dependent on phase 2 EAD (i.e. R on T extrasystole and TdP) in the isolated arterially-perfused rabbit ventricular wedge preparation.

Method:

Arterially Perfused Rabbit Left Ventricular Wedge Preparations

Female rabbits weighting 2.5-3 kg were anticoagulated with heparin and anesthetized with pentobarbital (30-35 mg/kg, i.v.). The chest was opened via left thoracotomy, and the heart was excised and placed in a cardioplegic solution consisting of cold (4 °C) normal Tyrode s solution(in mmol/l: NaCl 129, KCl 4.0, $CaCl_2$ 1.8, NaH_2PO_4 0.9, $MgSO_4$ 0.5, $NaHCO_3$ 20, glucose 5.5). A transmural wedge, approximately 1.5 cm wide and 2-3 cm long, was dissected from the left ventricle and rapidly cannulated via the left anterior descending artery or the circumflex artery and perfused with cardioplegic solution for <4 min. The preparation was then transferred to a tissue bath (100 ml) and perfused with warm (35.7 ± 0.1 °C) Tyrode's solution containing 4 mM K^+ buffered ? with 95% O_2 and 5% CO_2. Perfusion pressure was set at 40-50 mmHg by using a peristaltic pump. The preparation was paced at a basic cycle length of 1000 ms and allowed to equilibrate for approximately 1 h, the time necessary to achieve electrical stability. Electrical pacing was delivered via bipolar silver electrodes insulated except at the tips and applied to the endocardial surface.

Experimental Protocol

After the preparation equilibrated for one hour, the experiment was initiated. During the infusion of the compounds, the preparation was stimulated from the endocardium at basic cycle lengths of 1000 ms from the beginning of the infusion to the 20th minute and then at 2000 ms from the 20th minute to the 30th minute. At the end of each pacing cycle length, the ECG signal was sampled for 1 to 2 min at a sampling rate of 1562 Hz (Spike 2 sofware, CED, England)

Electrophysiological Recordings from Rabbit Ventricular Wedge Preparations

A transmural ECG signal was recorded in all experiments. The QT interval was defined as the time from the onset of the QRS to the point at which the final downslope of the T wave across isoelectric line. The QT interval values were derived from the mean values of four consecutive beats. (*Yan and Antzelevitch, Circulation 1998; Yan et al, Circulation 2001; 103:2851-2856; and Antzelevitch, Journal of Electrocardiology 2004; 37(Suppl): 15-24).*

The compounds exhibited no significant effect on either QT or T_{p-e} intervals when perfused at the concentrations of 1 and 3 µmol/l for 30 min. The compounds did not induce any EAD, R-on-T ectopic beats or TdP at the tested concentrations.

The results for, for instance compound 68, are depicted in Table 11.

Conclusion: In the concentration range tested, the compounds of the invention did not produce any QT and T_{p-e} prolongation in the arterially perfused rabbit left ventricular wedge preparation, indicating that this compound is unlikely to pose any risk for the development of TdP in humans (*Joshi et al, Journal of Electrocardiology, 2004, 34 (suppl): 7-14*).

Table 11: Effects of Compound 68 on the QT and T_{p-e} intervals, as well as for EAD-dependent events measured at a pacing rate using 2000 ms BCL.

Compound	Parameter	Concentration (µmol/l)		
		0 (control)	1	3
Compound 68	QT (ms)	288.2±11.1	287.6±11.4	286.6±12.0
	T_{p-e} (ms)	52.2±3.7	52.0±3.9	51.4±4.0
	EAD	0/5	0/5	0/5
	TdP Score	**0.0±0.0**	**0.0±0.0**	**0.0±0.0**

Example 9: in Vitro studies in human atrial myocytes

The blocking profile of the compounds of the invention is determined on the following channels of the human atrial myocytes: I_{Na}, I_{to}, I_{sus} and I_{K1} channel currents.

Method:

Preparation of cells

Human atrial myocytes : Myocytes were prepared from specimens with grossly normal anatomical aspect, excised from hearts of patients with normal P-wave electrocardiogram, undergoing bypass surgery. Human atrial sample were obtained following approval by the ethical committee. Atrial tissue samples were quickly immersed in a cardioplegic solution (in mM: 50 KH_2PO_4, 8 $MgSO_4$, 10 $NaHCO_3$, 5 adenosine, 25 taurine, 140 glucose, and 100 mannitol, titrated to a pH of 7.4 and bubbled with 100% O_2 at 0-4°C) and rapidly delivered to the laboratory. The tissue was then minced onto 0.5-1 mm^2 chunks within 30 min after the excision procedure and transferred to a 50 ml conical tube containing wash solution deprived of Ca^{2+} (in mM: 137 NaCl, KH_2PO_4, 1 $MgSO_4$, 10 taurine, 10 glucose, 5 HEPES, and 100 µmol/L (□M) EGTA; pH = 7.4, room temperature 22-24°C). The tissue was subsequently incubated in 5 ml of solution (in mM: 137 NaCl, 5 KH_2PO_4, 1 $MgSO_4$, 10

taurine, 10 glucose, 5 HEPES) supplemented with 0.1% bovine albumin, 2.2 mg/ml collagenase type V and 1.0 mg/ml protease type XXIV (Sigma Chemical), pH = 7.4 , 37°C) and bubbled continuously with 100% O_2. The so obtained suspension was centrifuged after 20 min incubation, the supernatant discarded and the tissue chunks incubated in ~1 mg/ml collagenase in a digestion solution containing 100 µM $CaCl_2$ at 37°C. Microscopic examination of the incubation medium was performed every 5-10 min to determine the number and quality of the isolated cells. When the yield appeared to be maximal, the cell suspension was centrifuged at 10,000-20,000 g for 2 min and the resulting pellet resuspended in a modified Kraftbruhe solution (in mM: 25 KCl, 10 KH_2PO_4, 25 taurine, 0.5 EGTA, 22 glucose, 55 glutamic acid, and 0.1% bovine albumin, pH=7.3 (22-24°C) (Crimb and Cavero, 2003). In general, the isolation procedure produced an initial yield of ~40 - 60% rod-shaped, calcium tolerant cells which were used for patch experiments within 14 hr following their preparation.

Patched myocytes were only those disaggregated and rod shaped deprived of visible blebs (outbulging of the sarcolemma).

Solutions

For K currents: The ionic composition of the water solution used to superfuse HEK 293 or human atrial cells (external solution) for recording potassium currents (I_{to}, I_{sus}, I_{K1}, I_{HERG}) was (in mM): 137 NaCl, 4 KCl, 1.8 $CaCl_2$, 1.2 $MgCl_2$, 11 dextrose, 10 HEPES, adjusted to a pH of 7.4 with NaOH. I_{Ca} was blocked $CdCl_2$ (200 mM) added to this solution. The ionic composition of the internal solution of the patching pipette was (in mM): 130 KCl; 1 $MgCl_2$, 5 NaATP, 7 NaCl, 5 EGTA, 5 HEPES, pH=7.2 using KOH.

For sodium current : For study of the sodium current (I_{Na}) in human atrial myocytes, cells were superperfused with an external solution that consisted of (in mM): 115 TMA (Tetramethylammonium) chloride, 10 NaCl, 5 CsCl, 1.8 $CaCl_2$, 1.2 $MgCl_2$, 10 HEPES, 11 dextrose, pH adjusted to 7.4 with TMA-OH, whereas the composition of the internal solution was (in mM): 115 CsF, 20 CsCl, 10 NaF, 10 HEPES, 5 EGTA; pH adjusted to 7.2 with CsOH.

Reagents

The chemical products used to prepare external and internal solutions were purchased from Sigma-Aldrich Chemical Company, (Natick, MA 01760-2447, USA). The compounds of the invention were prepared as stock solutions of 10 mM of these compounds by using

DMSO (dimethylsulfoxide). The final concentration of DMSO in each concentration studied never exceeded 0.1%.

Measurement of ion currents

Experiments were performed at room temperature (20-25°C) for I_{Na} and at 32-34°C for I_{to}, I_{sus}, I_{K1}. Currents were measured using the whole-cell variant of the patch clamp method. Glass pipettes pulled from borosilicate glass by a horizontal puller (Sutter Instruments, USA), then fire polished to obtain tip openings of 1 to 2 µm. The tip resistance of these pipettes filled with internal solutions amounted to approximately 1 to 2 MΩ.

Bath temperature was controlled with a thermoelectric device (model no. 806-7243-01, Cambion/Midland Ross, Cambridge, MA) coupled to a thermistor inserted in the bath near to the cell under study.

An Axopatch 1-B amplifier (Axon Instruments, Foster City, CA) was used for whole-cell voltage clamping. Voltage clamp pulse delivery and data acquisition were controlled by an IBM PC running pClamp software (Axon Instruments).

After rupture of the cell membrane to enter the whole-cell mode, current amplitude and kinetics were allowed to stabilize for 3-7 min before initiating the experimental procedure. K^+ currents recorded from human atrial myocytes were elicited by a 500 ms pulse to + 60 mV from a holding potential of -50 mV for I_{to} and I_{sus}. I_{to} was measured as a peak current amplitude whereas I_{sus} as a current present at the end of the 500 ms voltage pulse. In addition, the area under the curve, before and after compound, were measured over the course of the pulse period. Peak I_{K1} current was generated by delivering 500 ms pulses to -100 mV from a holding potential of -75 mV.

Peak inward I_{Na} from human atrial myocytes was generated by pulses of 40 ms duration to -20mV from a holding potential of -140 mV delivered at 0.1 Hz frequency.

The compounds were tested at the following concentrations: 0.01 µM, 0.1 µM, 0.3 µM, 1 µM, 3 µM, 10 µM.

Vehicle

The vehicle was the same as that used to prepare the solution containing the test compound. In this experiment, the vehicle was DMSO and was obtained from Sigma Chemicals. Over the course of a typical experiment (approximately 10 minutes) the addition of the highest concentration of a 100:1 dilution vehicle is expected to produce minor reductions in hERG current amplitude (1.4% ± 1.5%, n = 11).

Expression of Results and Statistical Analysis

Raw data and mean ± SEM are given. Data are presented as % reduction of current amplitude. This is measured as current reduction after a steady-state effect has been reached in the presence of drug relative to current amplitude before drug was introduced (control). Each cell serves as its own control. Drug effects were compared by a paired Student s t-test for significance ($p<.05$) using MicroCal Origin, version 6.0 software.

Log-linear plots were created of the mean percent blockade ± SEM at the concentrations tested. If possible, a nonlinear curve fitting routine was utilized to fit a three-parameter Hill equation to the results using MicroCal Origin, version 6.0 software. The equation is:

$$y = V_{\max} \frac{x^n}{k^n + x^n}$$

where V_{max}, k, and n are unconstrained variables (except V_{max} >0). Since the V_{max} parameter will not be constrained to 100%, the parameter k does not represent an IC_{50} for ion channel blockade. Thus, the IC_{50} werr calculated from the inverse of the previous equation:

$$x = k\left(\frac{y}{V_{\max} - y}\right)^{1/n}$$

Positive control

Flecainide was used as a positive control to determine the sensitivity of cells for I_{to} blockade.

Results

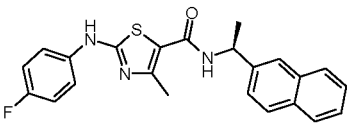
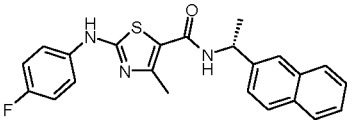
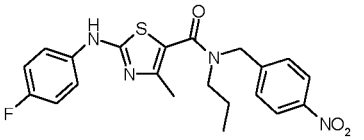
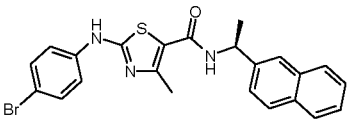
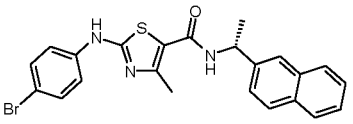
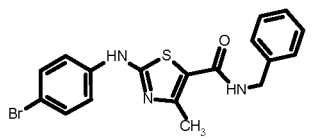
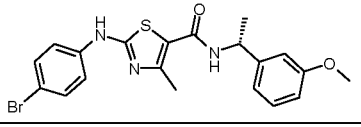
Table 12 and Figure 12 shows the inhibition of compound 68 on ion channel currents. Figure 12 shows the inhibition on the I_{TO} and Kv1.5 current. Dose-response analysis of compound 68 on the I_{TO} current revealed an IC_{50} = 0.8μM (diamonds). Dose-response analysis of compound 68 on Kv1.5 revealed an IC_{50} = 1.4μM (square). Activity on Kv1.5 is derived from subtracting the remaining current from the end of pulse current amplitude.

Table 12: Effects of Compound 68 on ion channel currents.

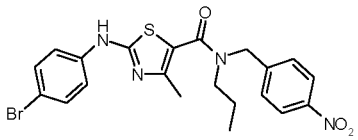
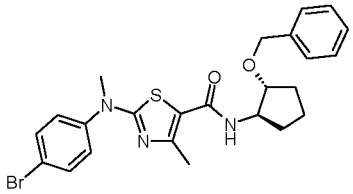
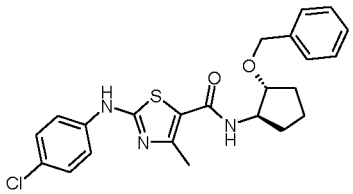
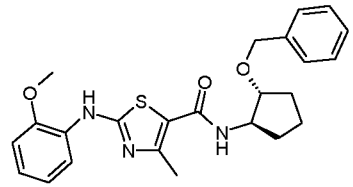
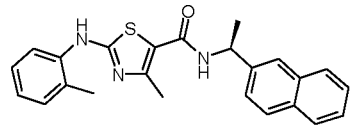
Current (example of underlying ion channel)	Block at 10µM in % (n= 3 cells)
I_{Na} (SCN5a)	0 ± 0.5
I_{K1} (Kir2.1)	-2.7 ± 2.0
I_{to} (Kv4.3)	82.0 ± 3.6
I_{sus} (Kv1.5 + additional channels)	55.2 ± 6.4
Kv1.5 ([§]calculated)	81.1 ± 3.7

[§] I_{sus} is the current measured at the end of the voltage pulse to +60mV. It consists of KV1.5 as well as a non-selective cation current. The ratio of these 2 currents can vary from cell to cell. Kv1.5 is derived from subtracting the remaining current from the end of pulse current amplitude. The remaining current was not sensitive to 4-AP (1mM).

Table 13 Effects of test compounds on the Kv4.3 mediated current

Name	Compound	Structure	P	Rt	Pu	ES+	m.p.	Kv4.3 charge	Kv4.3 peak	hERG
2-(4-fluoro-phenylamino)-4-methyl-thiazole-5-carboxylic acid ((S)-1-naphthalen-2-yl-ethyl)-amide	**15**		C	2.80	100	406	ND	ND	ND	ND
2-(4-fluoro-phenylamino)-4-methyl-thiazole-5-carboxylic acid ((R)-1-naphthalen-2-yl-ethyl)-amide	**16**		C	2.77	100	406	ND	IC50 1.84 µM	ND	IC50 28.00 µM
2-(4-fluoro-phenylamino)-4-methyl-thiazole-5-carboxylic acid (4-nitro-benzyl)-propyl-amide	**17**		C	2.73	100	429	ND	ND	ND	ND
2-(4-bromo-phenylamino)-4-methyl-thiazole-5-carboxylic acid ((S)-1-naphthalen-2-yl-ethyl)-amide	**18**		C	3.00	98	466-468	ND	IC50 3.85 µM	ND	IC50 26.50 µM
2-(4-bromo-phenylamino)-4-methyl-thiazole-5-carboxylic acid ((R)-1-naphthalen-2-yl-ethyl)-amide	**19**		C	3.01	100	466-468	ND	IC50 2.72 µM	ND	IC50 89.99 µM
2-(4-bromo-phenylamino)-4-methyl-thiazole-5-carboxylic acid benzylamide	**20**		C	2.65	100	402-404	ND	IC50 1.72 µM	ND	ND
2-(4-bromo-phenylamino)-4-methyl-thiazole-5-carboxylic acid [(R)-1-(3-methoxy-phenyl)-ethyl]amide	**21**		C	2.75	100	446-448	ND	IC50 1.26 µM	ND	ND

Name	Compound	Structure	P	Rt	Pu	ES+	m.p.	Kv4.3 charge	Kv4.3 peak	hERG
2-(4-bromo-phenylamino)-4-methyl-thiazole-5-carboxylic acid [(R)-1-(4-nitro-phenyl)-ethyl]amide	**22**		C	2.75	91	461-463	ND	ND	ND	ND
2-(4-bromo-phenylamino)-4-methyl-thiazole-5-carboxylic acid 4-nitro-benzylamide	**23**		C	2.64	100	447-449	ND	IC50 0.55 µM	ND	ND
2-(4-bromo-phenylamino)-4-methyl-thiazole-5-carboxylic acid 3,5-bis-trifluoromethyl-benzylamide	**24**		C	3.13	95	538-540	ND	ND	ND	ND
2-(4-bromo-phenylamino)-4-methyl-thiazole-5-carboxylic acid ((1R,2R)-2-benzyloxycyclopent-1-yl) amide	**25**		C	2.99	100	486-488	ND	IC50 1.32 µM	ND	ND
2-(4-bromo-phenylamino)-4-methyl-thiazole-5-carboxylic acid ((1S,2S)-2-benzyloxycyclopent-1-yl) amide	**26**		C	2.99	100	486-488	ND	IC50 2.18 µM	ND	ND
2-(4-bromo-phenylamino)-4-methyl-thiazole-5-carboxylic acid methyl-naphthalen-1-ylmethyl-amide	**27**		C	3.00	100	466-468	ND	IC50 2.77 µM	ND	ND

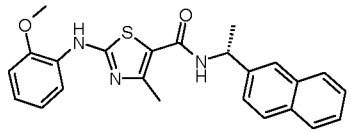
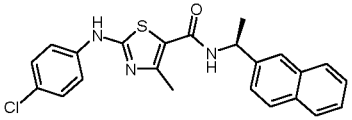
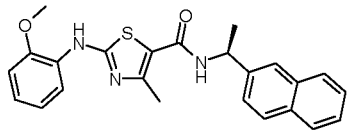
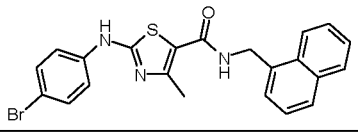
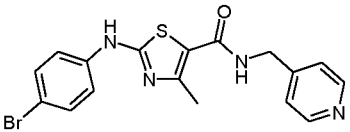
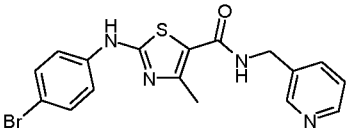
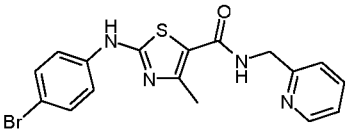
Name	Compound	Structure	P	Rt	Pu	ES+	m.p.	Kv4.3 charge	Kv4.3 peak	hERG
2-(4-bromo-phenylamino)-4-methyl-thiazole-5-carboxylic acid (4-nitro-benzyl)-propyl-amide	**28**		C	2.98	93	489-491	ND	IC50 1.06 µM	ND	ND
2-[(4-bromo-phenyl)-methyl-amino)-4-methyl-thiazole-5-carboxylic acid ((1R,2R)-2-benzyloxycyclopent-1-yl) amide	**29**		C	3.00	100	500-502	ND	IC50 2.13 µM	ND	ND
2-(4-chloro-phenylamino)-4-methyl-thiazole-5-carboxylic acid ((1R,2R)-2-benzyloxycyclopent-1-yl) amide	**30**		C	2.89	100	442-444	ND	IC50 1.25 µM	ND	IC50 10.96 µM
2-(2-methoxy-phenylamino)-4-methyl-thiazole-5-carboxylic acid ((1R,2R)-2-benzyloxycyclopent-1-yl) amide	**31**		C	2.78	100	438	ND	IC50 2.91 µM	ND	IC50 25.34 µM
4-methyl-2-o-tolylamino-thiazole-5-carboxylic acid ((S)-1-naphthalen-2-yl-ethyl)-amide	**32**		C	2.46	97	402	ND	IC50 2.55 µM	ND	ND

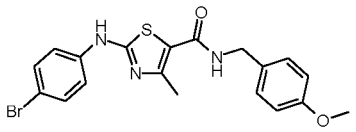
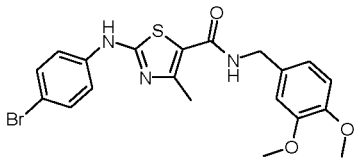
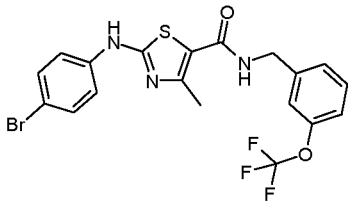
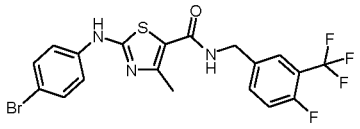
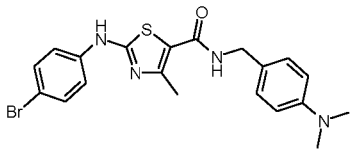
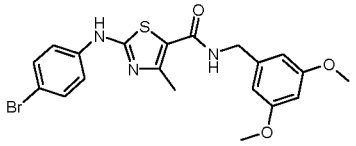
Name	Compound	Structure	P	Rt	Pu	ES+	m.p.	Kv4.3 charge	Kv4.3 peak	hERG
2-(2,5-dimethoxy-phenylamino)-4-methyl-thiazole-5-carboxylic acid ((1R,2R)-2-benzyloxycyclopent-1-yl) amide	**33**		C	2.76	98	468	ND	IC50 3.35 µM	ND	IC50 33.48 µM
2-(5-chloro-2-methoxy-phenylamino)-4-methyl-thiazole-5-carboxylic acid [(R)-1-(3-methoxy-phenyl)-ethyl]-amide	**34**		C	2.83	95	432	ND	IC50 1.62 µM	ND	IC50 8.73 µM
2-(5-chloro-2-methoxy-phenylamino)-4-methyl-thiazole-5-carboxylic acid ((1R,2R)-2-benzyloxycyclopent-1-yl) amide	**35**		C	3.05	98	472-474	ND	IC50 3.06 µM	ND	ND
2-(4-fluoro-phenylamino)-thiazole-4-carboxylic acid [(R)-1-(4-nitro-phenyl)-ethyl]amide	**36**		C	2.57	96	387	ND	ND	ND	ND
2-(4-fluoro-phenylamino)-thiazole-4-carboxylic acid ((1R,2R)-2-benzyloxycyclopent-1-yl) amide	**37**		C	2.81	94	412	ND	ND	ND	ND

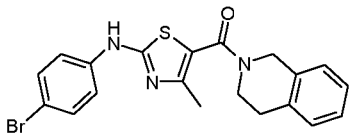
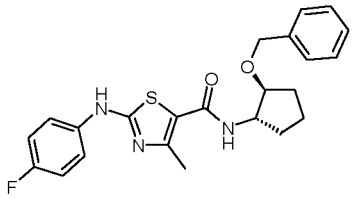
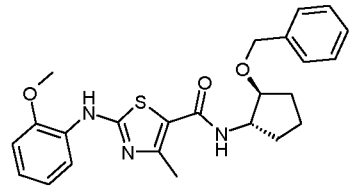
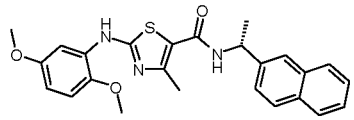
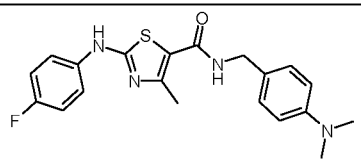
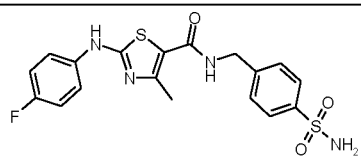
Name	Compound	Structure	P	Rt	Pu	ES+	m.p.	Kv4.3 charge	Kv4.3 peak	hERG
2-(4-fluoro-phenylamino)-thiazole-4-carboxylic acid ((1R,2R)-2-benzyloxycyclohex-1-yl) amide	**38**		C	2.85	93	426	ND	ND	ND	ND
2-(4-bromo-phenylamino)-thiazole-4-carboxylic acid ((1R,2R)-2-benzyloxycyclopent-1-yl) amide	**39**		C	2.98	96	472-474	ND	ND	ND	ND
2-(4-chloro-phenylamino)-thiazole-4-carboxylic acid ((1R,2R)-2-benzyloxycyclopent-1-yl) amide	**40**		C	2.91	95	428-430	ND	IC50 3.46 µM	ND	ND
2-(4-chloro-phenylamino)-thiazole-4-carboxylic acid ((1S,2S)-2-benzyloxycyclohex-1-yl) amide	**41**		C	3.01	95	442-444	ND	ND	ND	ND
2-(4-chloro-phenylamino)-thiazole-4-carboxylic acid (4-nitro-benzyl)-propyl -amide	**42**		C	2.92	95	431-433	ND	ND	ND	ND

Name	Compound	Structure	P	Rt	Pu	ES+	m.p.	Kv4.3 charge	Kv4.3 peak	hERG
2-(3,5-dimethyl-phenylamino)-thiazole-4-carboxylic acid [(R)-1-(4-nitro-phenyl)-ethyl]amide	**43**		C	2.84	100	397	ND	ND	ND	ND
2-(3,5-dimethyl-phenylamino)-thiazole-4-carboxylic acid ((S)-1-methoxymethyl-2-phenyl-ethyl)-amide	**44**		C	2.87	100	396	ND	ND	ND	ND
2-(3,5-dimethyl-phenylamino)-thiazole-4-carboxylic acid ((1R,2R)-2-benzyloxycyclopent-1-yl) amide	**45**		C	3.08	95	422	ND	ND	ND	ND
2-(3,5-dimethyl-phenylamino)-thiazole-4-carboxylic acid ((1S,2S)-2-benzyloxycyclohex-1-yl) amide	**46**		C	3.11	98	436	ND	ND	ND	ND
2-phenylamino-thiazole-4-carboxylic acid [(R)-1-(4-nitro-phenyl)-ethyl]amide	**47**		C	2.49	97	369	ND	IC50 1.80 µM	ND	ND

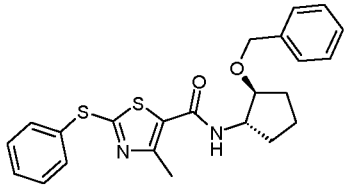
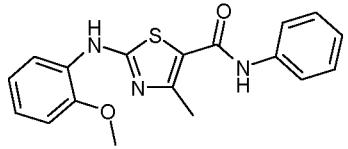
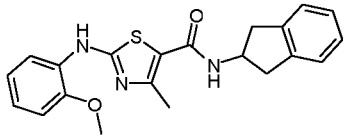
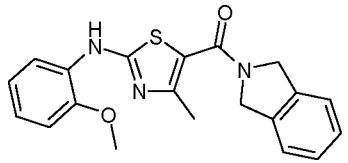
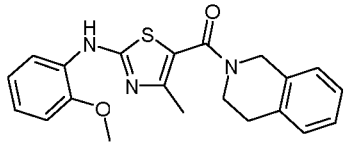
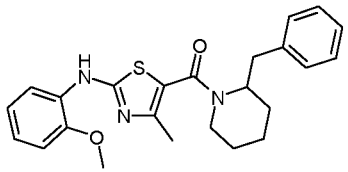
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3-phenylamino-thiazole-4-carboxylic acid ((1R,2R)-2-benzyloxycyclopent-1-yl) amide	**48**		C	2.75	95	394	ND	IC50 2.47 µM	ND	ND
3-phenylamino-thiazole-4-carboxylic acid ((1S,2S)-2-benzyloxycyclohex-1-yl) amide	**49**		C	2.79	98	408	ND	ND	ND	ND
2-(5-chloro-2-methoxy-phenylamino)-thiazole-4-carboxylic acid acid ((1S,2S)-2-benzyloxycyclohex-1-yl) amide	**50**		C	3.09	94	472-474	ND	ND	ND	ND
2-(5-chloro-2-methoxy-phenylamino)-thiazole-4-carboxylic acid acid ((1R,2R)-2-benzyloxycyclohex-1-yl) amide	**51**		C	3.07	95	472-474	ND	ND	ND	ND
2-(4-chloro-phenylamino)-4-methyl-thiazole-5-carboxylic acid ((R)-1-naphthalen-2-yl-ethyl)-amide	**52**		C	2.96	98	422-424	ND	IC50 0.34 µM	ND	IC50 24.20 µM

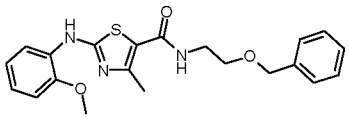
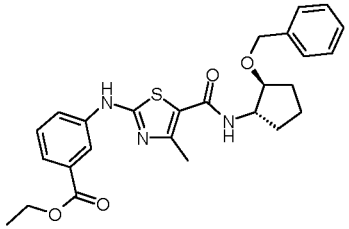
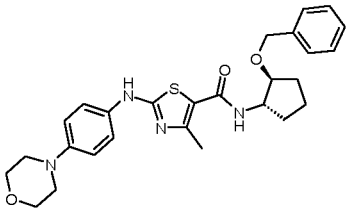
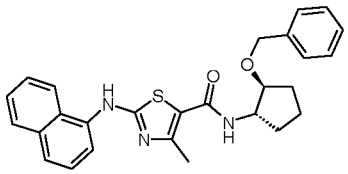
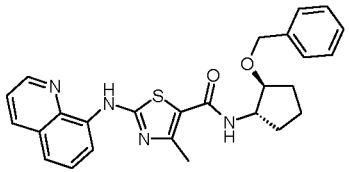
Name	Compound	Structure	P	Rt	Pu	ES+	m.p.	Kv4.3 charge	Kv4.3 peak	hERG
2-(2-methoxy-phenylamino)-4-methyl-thiazole-5-carboxylic acid ((R)-1-naphthalen-2-yl-ethyl)-amide	**53**		C	2.83	95	418	ND	IC50 3.95 µM	ND	ND
2-(4-chloro-phenylamino)-4-methyl-thiazole-5-carboxylic acid ((S)-1-naphthalen-2-yl-ethyl)-amide	**54**		C	2.95	100	422-424	ND	IC50 2.41 µM	ND	IC50 15.80 µM
2-(2-methoxy-phenylamino)-4-methyl-thiazole-5-carboxylic acid ((S)-1-naphthalen-2-yl-ethyl)-amide	**55**		C	2.84	100	418	ND	IC50 2.02 µM	ND	IC50 10.20 µM
2-(4-bromo-phenylamino)-4-methyl-thiazole-5-carboxylic acid (naphthalen-1-ylmethyl)-amide	**56**		C	6.15	98	452-454	ND	IC50 1.07 µM	ND	IC50 7.04 µM
2-(4-bromo-phenylamino)-4-methyl-thiazole-5-carboxylic acid (pyridin-4-ylmethyl)-amide	**57**		C	1.89	100	403-405	ND	IC50 11.20 µM	ND	ND
2-(4-bromo-phenylamino)-4-methyl-thiazole-5-carboxylic acid (pyridin-3-ylmethyl)-amide	**58**		C	1.94	71	403-405	ND	IC50 4.33 µM	ND	ND
2-(4-bromo-phenylamino)-4-methyl-thiazole-5-carboxylic acid (pyridin-2-ylmethyl)-amide	**59**		C	4.13	98	403-405	ND	IC50 3.06 µM	ND	ND

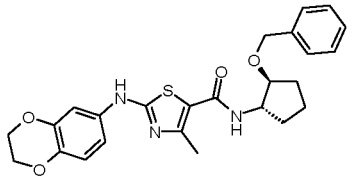
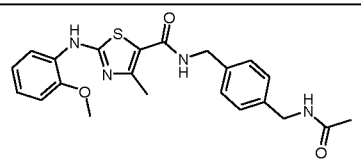
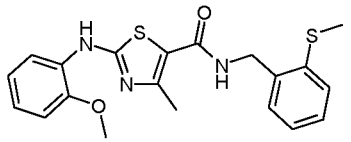
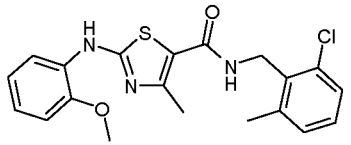
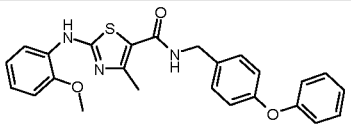
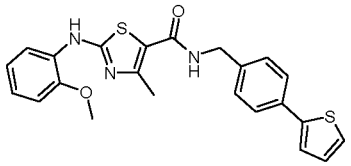
Name	Compound	Structure	P	Rt	Pu	ES+	m.p.	Kv4.3 charge	Kv4.3 peak	hERG
2-(4-bromo-phenylamino)-4-methyl-thiazole-5-carboxylic acid 4-methoxy-benzylamide	**60**		C	2.65	92	432-434	ND	IC50 0.39 µM	ND	IC50 3.00 µM
2-(4-bromo-phenylamino)-4-methyl-thiazole-5-carboxylic acid 3,4-dimethoxy-benzylamide	**61**		C	2.60	96	463-465	ND	IC50 1.53 µM	ND	ND
2-(4-bromo-phenylamino)-4-methyl-thiazole-5-carboxylic acid 3-trifluoromethoxy-benzylamide	**62**		C	6.19	95	486-488	ND	ND	ND	ND
2-(4-bromo-phenylamino)-4-methyl-thiazole-5-carboxylic acid 4-fluoro-3-trifluoromethyl-benzylamide	**63**		C	6.14	100	488-490	ND	IC50 0.16 µM	ND	IC50 5.29 µM
2-(4-bromo-phenylamino)-4-methyl-thiazole-5-carboxylic acid 4-dimethylamino-benzylamide	**64**		C	2.25	93	445-447	ND	IC50 0.83 µM	ND	IC50 > 100 µM
2-(4-bromo-phenylamino)-4-methyl-thiazole-5-carboxylic acid 3,5-dimethoxy-benzylamide	**65**		C	5.68	94	462-464	ND	IC50 0.18 µM	ND	IC50 1.63 µM

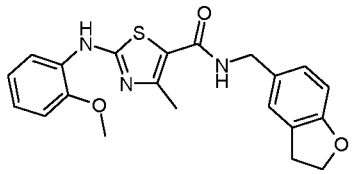
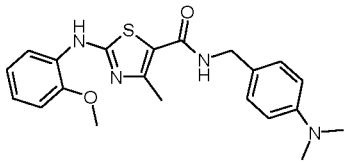
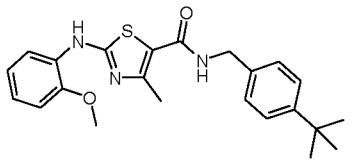
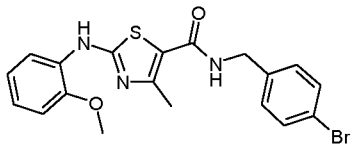
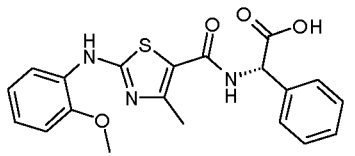
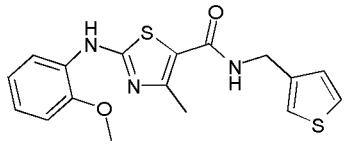
Name	Compound	Structure	P	Rt	Pu	ES+	m.p.	Kv4.3 charge	Kv4.3 peak	hERG
[2-(4-bromo-phenylamino)-4-methyl- thiazol-5-yl]-(3,4-dihydro-1H-isoquinolin-2-yl)-methanone	**66**		C	2.84	94	428-430	ND	IC50 0.34 µM	ND	IC50 9.88 µM
2-(4-fluoro-phenylamino)-4-methyl-thiazole-5-carboxylic acid ((1S,2S)-2-benzyloxycyclopent-1-yl) amide	**67**		C	2.72	100	426	ND	IC50 1.97 µM	ND	ND
2-(2-methoxy-phenylamino)-4-methyl-thiazole-5-carboxylic acid ((1S,2S)-2-benzyloxycyclopent-1-yl) amide	**68**		C	2.78	100	438	ND	IC50 0.54 µM	ND	IC50 7.95 µM
2-(2,5-dimethoxy-phenylamino)-4-methyl-thiazole-5-carboxylic acid ((R)-1-naphthalen-2-yl-ethyl)-amide	**69**		C	2.86	100	448	ND	ND	ND	ND
2-(4-fluoro-phenylamino)-4-methyl-thiazole-5-carboxylic acid 4-dimethylamino-benzylamide	**70**		C	1.93	100	385	ND	ND	ND	ND
2-(4-fluoro-phenylamino)-4-methyl-thiazole-5-carboxylic acid 4-sulfamoyl-benzylamide	**71**		C	1.97	100	421	ND	ND	ND	ND

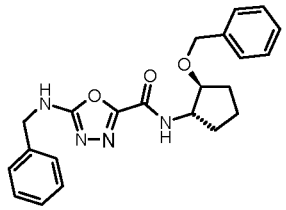
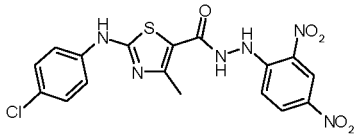
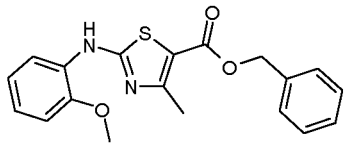
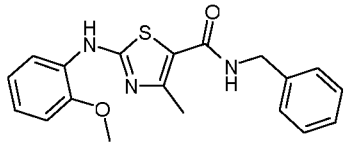
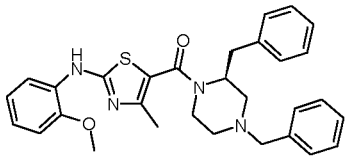
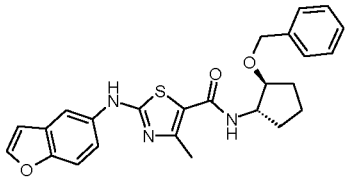
Name	Compound	Structure	P	Rt	Pu	ES+	m.p.	Kv4.3 charge	Kv4.3 peak	hERG
2-(4-chloro-phenylamino)-thiazole-4-carboxylic acid 4-dimethylamino-benzylamide	**72**		C	2.22	92	387-389	ND	ND	ND	ND
2-(2-methoxy-phenylamino)-thiophene-5-carboxylic acid ((1S,2S)-2-benzyloxycyclopent-1-yl) amide	**75**		E	2.71	100	423	69.7-71.6	41%	81%	76%
2-(2-methoxy-phenylamino)-pyrimidine-4-carboxylic acid ((1S,2S)-2-benzyloxycyclopent-1-yl) amide	**76**		J	2.82	100	419	97.3-99.8	62%	99%	34%
1-[2-(2-methoxy-phenylamino)-4-methyl-thiazol-5-yl]- 2-phenyl-ethanone	**79**		L	2.63	100	339	131.7-140.6	ND	ND	ND
4-methyl-2-phenoxy-thiazole-5-carboxylic acid ((1S,2S)-2-benzyloxycyclopent-1-yl) amide	**80**		C	2.70	100	409	93.4-95.8	ND	ND	ND

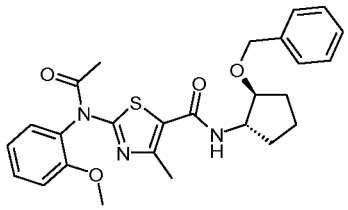
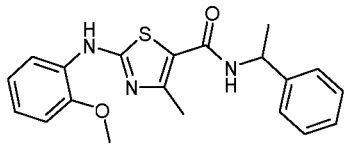
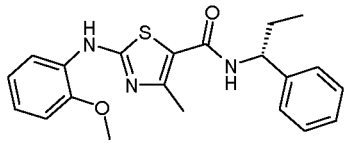
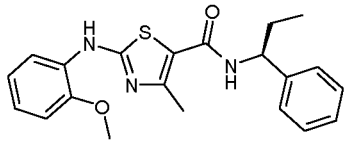
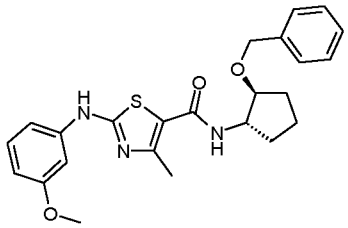
Name	Compound	Structure	P	Rt	Pu	ES+	m.p.	Kv4.3 charge	Kv4.3 peak	hERG
4-methyl-2-phenylsulfanyl-thiazole-5-carboxylic acid ((1S,2S)-2-benzyloxycyclopent-1-yl) amide	**81**		C	2.69	100	425	129.5-132.4	51%	90%	88%
2-(2-methoxy-phenylamino)-4-methyl-thiazole-5-carboxylic acid phenylamide	**82**		J	2.38	100	340	183.5-188.1	82%	91%	ND
2-(2-methoxy-phenylamino)-4-methyl-thiazole-5-carboxylic acid indan-2-ylamide	**83**		J	2.49	100	380	143.2 - 147.6	77%	97%	ND
(1,3-dihydro-isoindol-2-yl)-[2-(2-methoxy-phenylamino)-4-methyl-thiazol-5-yl]-methanone	**84**		C	2.41	100	366	147.6-149.6	87%	99%	ND
(3,4-dihydro-1H-isoquinolin-2-yl)-[2-(2-methoxy-phenylamino)-4-methyl-thiazol-5-yl]-methanone	**85**		J	2.50	97	380	159.3-163.5	82%	96%	ND
(2-benzyl-piperidin-1-yl)-[2-(2-methoxy-phenylamino)-4-methyl-thiazol-5-yl]-methanone	**86**		C	2.72	100	422	93.2-95.6	79%	102%	ND

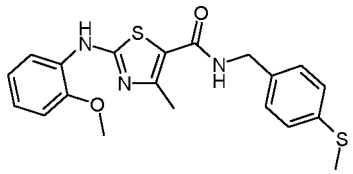
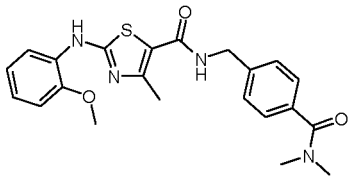
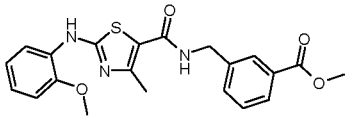
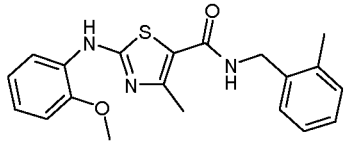
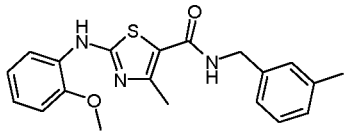
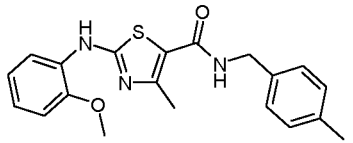
Name	Compound	Structure	P	Rt	Pu	ES+	m.p.	Kv4.3 charge	Kv4.3 peak	hERG
2-(2-methoxy-phenylamino)-4-methyl-thiazole-5-carboxylic acid (2-benzyloxy-ethyl)-amide	**88**		N	2.15	100	398	44.6-47.6	85%	95%	ND
3-[5-((1S,2S)-2-benzyloxy-cyclopent-1-ylcarbamoyl)-4-methyl-thiazol-2-ylamino]-benzoic acid ethyl ester	**89**		C	2.72	100	480	145.7-148.0	55%	93%	ND
4-methyl-2-(4-morpholin-4-yl-phenylamino)-thiazole-5-carboxylic acid ((1S,2S)-2-benzyloxycyclopent-1-yl) amide	**92**		C	2.40	100	493	192.5-194.9	ND	ND	ND
4-methyl-2-(naphtalen-1-ylamino)-thiazole-5-carboxylic acid ((1S,2S)-2-benzyloxycyclopent-1-yl) amide	**93**		J	2.85	94	458	102.4-108.2	62%	89%	59%
4-methyl-2-(quinolin-8-ylamino)-thiazole-5-carboxylic acid ((1S,2S)-2-benzyloxycyclopent-1-yl) amide	**94**		J	2.85	100	459	ND	49%	89%	69%

Name	Compound	Structure	P	Rt	Pu	ES+	m.p.	Kv4.3 charge	Kv4.3 peak	hERG
2-(2,3-dihydro-benzo[1,4]dioxin-6-ylamino-4-methyl-thiazole-5-carboxylic acid ((1S,2S)-2-benzyloxycyclopent-1-yl) amide	**95**		C	2.49	100	466	178.0-180.1	61%	91%	76%
2-(2-methoxy-phenylamino)-4-methyl-thiazole-5-carboxylic acid 4-(acetylamino-methyl)-benzylamide	**96**		S	1.88	98	425	199.7-200.3	85%	99%	ND
2-(2-methoxy-phenylamino)-4-methyl-thiazole-5-carboxylic acid 2-methyl sulfanyl-benzylamide	**97**		C	2.48	100	400	66.5	66%	96%	55%
2-(2-methoxy-phenylamino)-4-methyl-thiazole-5-carboxylic acid 2-chloro-6-methyl-benzylamide	**98**		C	2.65	98	402	105.4 - 107.6	59%	90%	38%
2-(2-methoxy-phenylamino)-4-methyl-thiazole-5-carboxylic acid 4-phenoxy-benzylamide	**102**		C	2.75	97	446	159.7 - 162.4	76%	89%	ND
2-(2-methoxy-phenylamino)-4-methyl-thiazole-5-carboxylic acid 4-thiophen-2-yl-benzylamide	**103**		C	2.71	100	436	195.6 - 198.6	64%	89%	ND

Name	Compound	Structure	P	Rt	Pu	ES+	m.p.	Kv4.3 charge	Kv4.3 peak	hERG
2-(2-methoxy-phenylamino)-4-methyl-thiazole-5-carboxylic acid (2,3-dihydro-benzofuran-5-ylmethyl)-amide	**104**		C	2.29	100	396	136.5 - 140.1	77%	93%	43%
2-(2-methoxy-phenylamino)-4-methyl-thiazole-5-carboxylic acid 4-dimethylamino-benzylamide	**105**		C	1.82	97	397	183.3-185.2	61%	77%	67%
2-(2-methoxy-phenylamino)-4-methyl-thiazole-5-carboxylic acid 4-tert-butyl-benzylamide	**106**		C	2.87	100	410	168.5-169.4	58%	98%	31%
2-(2-methoxy-phenylamino)-4-methyl-thiazole-5-carboxylic acid 4-bromo-benzylamide	**108**		C	2.56	100	433	150.7-154.2	59%	82%	19%
(S)-{[2-(2-methoxy-phenylamino)-4-methyl-thiazole-5-carbonyl]- amino}-phenyl-acetic acid	**114**		T	2.12	100	398	259.6 - 262.0	88%	87%	ND
2-(2-methoxy-phenylamino)-4-methyl-thiazole-5-carboxylic acid (thiophen-3-ylmethyl)-amide	**118**		C	2.65	100	360	153.4-154.8	85%	94%	ND

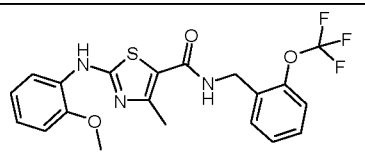
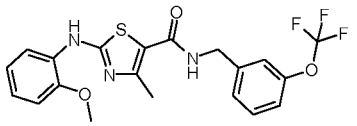
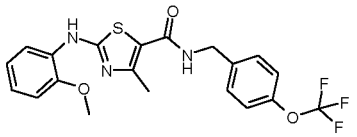
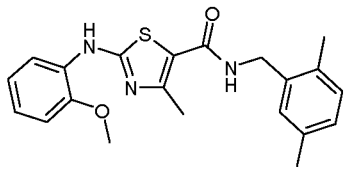
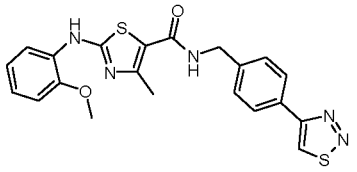
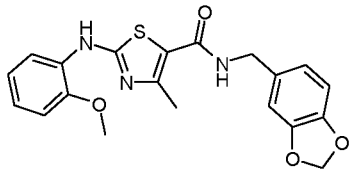
Name	Compound	Structure	P	Rt	Pu	ES+	m.p.	Kv4.3 charge	Kv4.3 peak	hERG
5-(benzylamino)-N-[(2S)-2-phenoxycyclopentyl]-1,3,4-oxadiazole-2-carboxamide	**119**							ND	ND	ND
2-(4-chloro-phenylamino)-4-methyl-thiazole-5-carboxylic acid N'-(2,4-dinitro-phenyl)-hydrazide	**121**		-	1.45	100	449	138.0-164.7	ND	ND	ND
2-(2-methoxy-phenylamino)-4-methyl-thiazole-5-carboxylic acid benzyl ester	**123**		N	2.82	100	355	98.4 - 100.0	31%	72%	ND
2-(2-methoxy-phenylamino)-4-methyl-thiazole-5-carboxylic acid benzylamide	**124**		C	2.31	100	354	153.6 - 156.2	90%	95%	ND
((S)-2,4-dibenzyl-piperazin-1-yl)-[2-(2-methoxy-phenylamino)-4-methyl-thiazol-5-yl]-methanone	**125**		C	2.41	100	513	89.3 - 92.5	74%	95%	ND
2-(benzofuran-5-ylamino)-4-methyl-thiazole-5-carboxylic acid ((1S,2S)-2-benzyloxycyclopent-1-yl) amide	**126**		C	2.62	100	448	164.4 - 169.3	58%	89%	74 at 1 µM

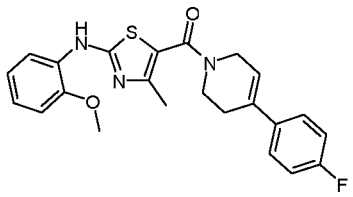
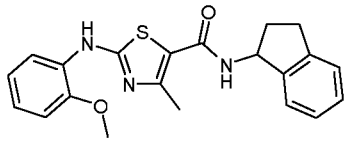
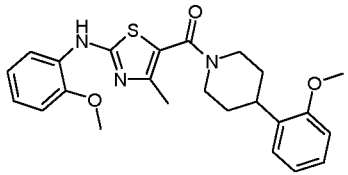
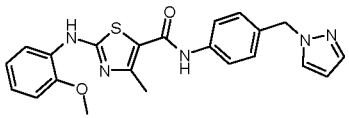
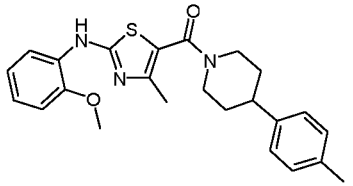
Name	Compound	Structure	P	Rt	Pu	ES^+	m.p.	Kv4.3 charge	Kv4.3 peak	hERG
2-[acetyl-(2-methoxy-phenyl)-amino]-4-methyl-thiazole-5-carboxylic acid ((1S,2S)-2-benzyloxycyclopent-1-yl) amide	**129**		R	2.58	100	480	145.8-149.0	ND	ND	ND
2-(2-methoxy-phenylamino)-4-methyl-thiazole-5-carboxylic acid (1-phenyl-ethyl)-amide	**130**		J	2.42	100	368	60.3-62.4	ND	ND	ND
2-(2-methoxy-phenylamino)-4-methyl-thiazole-5-carboxylic acid ((R)-1-phenyl-propyl)-amide	**131**		J	2.54	100	382	57.7-59.6	ND	ND	ND
2-(2-methoxy-phenylamino)-4-methyl-thiazole-5-carboxylic acid ((S)-1-phenyl-propyl)-amide	**132**		J	2.55	99	382	66.5-70.4	ND	ND	ND
2-(3-methoxy-phenylamino)-4-methyl-thiazole-5-carboxylic acid ((1S,2S)-2-benzyloxycyclopent-1-yl) amide	**133**		C	2.58	100	438	152.8-155.9	ND	ND	ND

Name	Compound	Structure	P	Rt	Pu	ES+	m.p.	Kv4.3 charge	Kv4.3 peak	hERG
2-(2-methoxy-phenylamino)-4-methyl-thiazole-5-carboxylic acid 4-methyl sulfanyl-benzylamide	**136**		C	2.47	100	400	142.1-144.9	ND	ND	ND
2-(2-methoxy-phenylamino)-4-methyl-thiazole-5-carboxylic acid 4-dimethylcarbamoyl-benzylamide	**137**		C	1.99	95	425	219.1 - 226.7	ND	ND	ND
[3-({[2-(2-methoxy-phenylamino)-4-methyl-thiazole-5-carbonyl]-amino}-methyl)-benzoic acid methyl ester	**138**		C	2.32	100	412	67.0 - 72.5	ND	ND	ND
2-(2-methoxy-phenylamino)-4-methyl-thiazole-5-carboxylic acid 2-methyl-benzylamide	**140**		C	2.46	100	368	118.3 - 121.7	ND	ND	ND
2-(2-methoxy-phenylamino)-4-methyl-thiazole-5-carboxylic acid 3-methyl-benzylamide	**141**		C	2.49	100	368	148.1-149.9	ND	ND	ND
2-(2-methoxy-phenylamino)-4-methyl-thiazole-5-carboxylic acid 4-methyl-benzylamide	**142**		C	2.47	100	368	166.8-168.3	74%	80%	ND

Name	Compound	Structure	P	Rt	Pu	ES+	m.p.	Kv4.3 charge	Kv4.3 peak	hERG
2-(2-methoxy-phenylamino)-4-methyl-thiazole-5-carboxylic acid (biphenyl-2-ylmethyl)- amide	**143**		C	2.75	100	430	128.4 - 132.0	ND	ND	ND
2-(2-methoxy-phenylamino)-4-methyl-thiazole-5-carboxylic acid (biphenyl-3-ylmethyl)- amide	**144**		C	2.75	100	430	126.6 - 128.3	ND	ND	ND
2-(2-methoxy-phenylamino)-4-methyl-thiazole-5-carboxylic acid (biphenyl-4-ylmethyl)- amide	**145**		C	2.75	100	430	189.6-191.2	ND	ND	ND
2-(2-methoxy-phenylamino)-4-methyl-thiazole-5-carboxylic acid 2-bromo-benzylamide	**146**		C	2.53	100	433	159.6 - 164.0	ND	ND	ND
2-(2-methoxy-phenylamino)-4-methyl-thiazole-5-carboxylic acid 3-bromo-benzylamide	**147**		C	2.56	97	433	161.3 - 164.1	ND	ND	ND
2-(2-methoxy-phenylamino)-4-methyl-thiazole-5-carboxylic acid ((S)-2-methoxy-1-phenyl-ethyl)-amide	**149**		C	2.41	100	398	118.8 - 129.6	ND	ND	ND

Name	Compound	Structure	P	Rt	Pu	ES+	m.p.	Kv4.3 charge	Kv4.3 peak	hERG
2-[(2-methoxy-phenyl)-methyl-amino]-4-methyl-thiazole-5-carboxylic acid ((S)-2-hydroxy-1-phenyl-ethyl)-amide	**150**		C	2.07	100	398	119.4	ND	ND	ND
(R)-{[2-(2-methoxy-phenylamino)-4-methyl-thiazole-5-carbonyl]-amino}-phenyl-acetic acid methyl ester	**151**		C	2.42	100	412	131.4-137.9	ND	ND	ND
(S)-{[2-(2-methoxy-phenylamino)-4-methyl-thiazole-5-carbonyl]-amino}-phenyl-acetic acid methyl ester	**152**		C	2.43	100	412	133.5-135.7	ND	ND	ND
4-methyl-2-(pyridin-4-ylamino)-thiazole-5-carboxylic acid ((1S,2S)-2-benzyloxycyclopent-1-yl) amide	**153**		C	2.17	100	409	78.1-81.7	ND	ND	ND
[4-({[2-(2-methoxy-phenylamino)-4-methyl-thiazole-5-carbonyl]-amino}-methyl)-benzoic acid methyl ester	**154**		C	2.40	100	412	68.1-71.3	ND	ND	ND
[3-({[2-(2-methoxy-phenylamino)-4-methyl-thiazole-5-carbonyl]-amino}-methyl)-benzoic acid	**156**		T	1.99	98	398	223.5 - 227.4	ND	ND	ND

Name	Compound	Structure	P	Rt	Pu	ES+	m.p.	Kv4.3 charge	Kv4.3 peak	hERG
2-(2-methoxy-phenylamino)-4-methyl-thiazole-5-carboxylic acid 2-trifluoromethoxy-benzylamide	**157**		C	2.65	100	438	76.1 - 80.2	ND	ND	ND
2-(2-methoxy-phenylamino)-4-methyl-thiazole-5-carboxylic acid 3-trifluoromethoxy-benzylamide	**158**		C	2.67	100	438	96.1 - 100.3	ND	ND	ND
2-(2-methoxy-phenylamino)-4-methyl-thiazole-5-carboxylic acid 4-trifluoromethoxy-benzylamide	**159**		C	2.69	100	438	135.2-138.9	ND	ND	ND
2-(2-methoxy-phenylamino)-4-methyl-thiazole-5-carboxylic acid 2,5-dimethyl-benzylamide	**160**		C	2.61	100	382	124.1 - 124.9	90%	99%	ND
2-(2-methoxy-phenylamino)-4-methyl-thiazole-5-carboxylic acid 4-[1,2,3]thiadiazol-4-yl-benzylamide	**161**		C	2.30	95	438	191.6 - 194.5	75%	89%	ND
2-(2-methoxy-phenylamino)-4-methyl-thiazole-5-carboxylic acid (benzo[1,3]dioxol-5-ylmethyl)-amide	**162**		C	2.26	100	398	166.0 - 167.4	ND	ND	ND

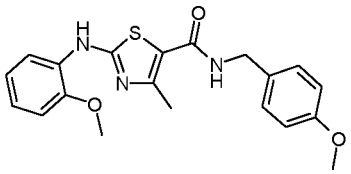
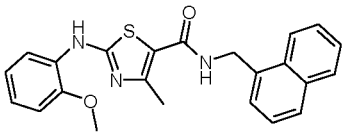
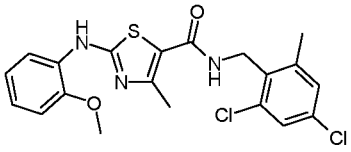
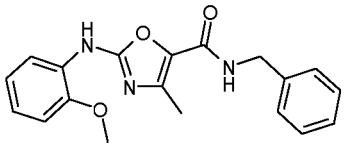
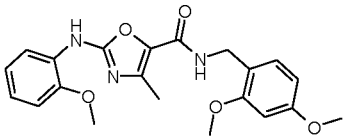
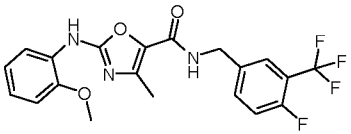
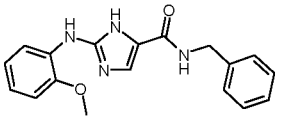
Name	Compound	Structure	P	Rt	Pu	ES+	m.p.	Kv4.3 charge	Kv4.3 peak	hERG
[4-(4-fluoro-phenyl)-3,6-dihydro-2H-pyridin-1-yl]-[2-(2-methoxy-phenylamino)-4-methyl-thiazol-5-yl]-methanone	**163**		C	2.67	97	424	144.4 - 149.2	ND	ND	ND
2-(2-methoxy-phenylamino)-4-methyl-thiazole-5-carboxylic acid indan-1-ylamide	**164**		C	2.54	100	380	146.2 - 148.0	ND	ND	ND
[2-(2-methoxy-phenylamino)-4-methyl-thiazol-5-yl]-[4-(2-methoxy-phenyl)-piperidin-1-yl]-methanone	**165**		C	2.71	95	438	134.5 - 139.0	80%	100%	ND
2-(2-methoxy-phenylamino)-4-methyl-thiazole-5-carboxylic acid (4-pyrazol-1-ylmethyl-phenyl)-amide	**166**		J	2.25	95	420	211.3 - 214.4	ND	ND	ND
[2-(2-methoxy-phenylamino)-4-methyl-thiazol-5-yl]-[4-p-tolyl- piperidin-1-yl]-methanone	**168**		C	2.84	95	422	187.7 - 191.5	ND	ND	ND

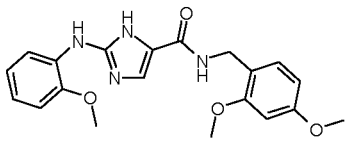
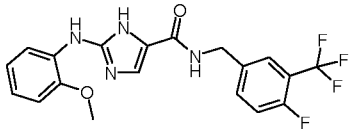
Name	Compound	Structure	P	Rt	Pu	ES+	m.p.	Kv4.3 charge	Kv4.3 peak	hERG
1-{1-[2-(2-methoxy-phenylamino)-4-methyl-thiazole-5-carbonyl]-piperidin-4-yl}-1,3-dihydro-benzoimidazol-2-one	**170**		C	2.10	95	464	>250	90%	97%	ND
2-o-tolylamino-thiazole-4-carboxylic acid ((1S,2S)-2-benzyloxycyclopent-1-yl) amide	**172**		C	2.68	100	408	ND	ND	ND	ND
2-(2-methoxy-phenylamino)-4-methyl-thiazole-5-carboxylic acid (1,2,3,4-tetrahydro-naphthalen-1-yl)-amide	**173**		C	2.63	96	394	129.4	ND	ND	ND
(4-benzyl-piperidin-1-yl)-[2-(2-methoxy-phenylamino)-4-methyl-thiazol-5-yl]-methanone	**174**		C	2.82	97	422	166.8-169.2	ND	ND	ND
[4-(4-fluoro-benzoyl)-piperidin-1-yl]-[2-(2-methoxy-phenylamino)-4-methyl-thiazol-5-yl]-methanone	**175**		C	2.50	100	454	92.6-99.6	ND	ND	ND

Name	Compound	Structure	P	Rt	Pu	ES+	m.p.	Kv4.3 charge	Kv4.3 peak	hERG
[2-(2-methoxy-phenylamino)-4-methyl-thiazol-5-yl]-(2-phenyl-pyrrolidin-1-yl)-methanone	**176**		C	2.46	100	394	113.5 - 117.6	ND	ND	ND
[2-(4-fluoro-phenyl)-pyrrolidin-1-yl]-[2-(2-methoxy-phenylamino)-4-methyl-thiazol-5-yl]-methanone	**177**		C	2.52	100	412	94.4 - 106.6	ND	ND	ND
2-benzoylamino-4-methyl-thiazole-5-carboxylic acid ((1S,2S)-2-benzyloxycyclopent-1-yl) amide	**179**		C	2.52	100	436	97.4 - 110.6	ND	ND	ND
2-(4-tert-butyl-benzoylamino)-4-methyl-thiazole-5-carboxylic acid ((1S,2S)-2-benzyloxycyclopent-1-yl) amide	**180**		C	2.98	100	492	88.7-90.0	73%	97%	64%

Name	Compound	Structure	P	Rt	Pu	ES+	m.p.	Kv4.3 charge	Kv4.3 peak	hERG
2-(4-cyano-benzoylamino)-4-methyl-thiazole-5-carboxylic acid ((1S,2S)-2-benzyloxycyclopent-1-yl) amide	**181**		C	2.46	100	461	177.2 - 181.4	ND	ND	ND
2-(2-methoxy-phenylamino)-4-methyl-oxazole-5-carboxylic acid ((1S,2S)-2-benzyloxycyclopent-1-yl) amide	**210**		C	2.63	100	422	--	86%	99%	ND
2-benzylamino-4-methyl-thiazole-5-carboxylic acid ((1S,2S)-2-benzyloxycyclopent-1-yl) amide	**211**		C	2.48	100	422	185.1 - 185.8	86%	98%	ND
(R)-{[2-(2-methoxy-phenylamino)-4-methyl-thiazole-5-carbonyl]-amino}-phenyl-acetic acid	**212**		T	2.11	100	398	258.6 - 262.9	ND	ND	ND

Name	Compound	Structure	P	Rt	Pu	ES+	m.p.	Kv4.3 charge	Kv4.3 peak	hERG
N-[5-((1S,2S)-2-benzyloxy-cyclopentylcarbamoyl)-4-methyl-thiazol-2-yl]-terephthalamide	**213**		C	2.14	95	479	213.8-218.9	ND	ND	ND
[4-(2,5-dimethoxy-benzyl))-piperazin-1-yl]-[2-(2-methoxy-phenylamino)-4-methyl-thiazol-5-yl]-methanone	**214**		C	1.77	95	483	82.9 - 102.8	ND	ND	ND
2-(2-methoxy-phenylamino)-4-methyl-thiazole-5-carboxylic acid (1-benzyl-pyrrolidin-3-yl) amide	**215**		C	1.77	95	4.23	112.6-121.6	ND	ND	ND
2-(2-methoxy-phenylamino)-4-methyl-thiazole-5-carboxylic acid benzyl-phenyl-amide	**216**		J	2.78	100	430	167.2-170.0	ND	ND	ND
2-(2-methoxy-phenylamino)-4-methyl-thiazole-5-carboxylic acid (2,3-dihydro-benzo[1,4]dioxin-2-ylmethyl) amide	**217**		C	2.41	95	412	138.3-158.2	ND	ND	ND

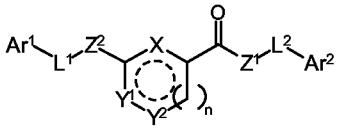
Name	Compound	Structure	P	Rt	Pu	ES+	m.p.	Kv4.3 charge	Kv4.3 peak	hERG
2-(2-methoxy-phenylamino)-4-methyl-thiazole-5-carboxylic acid 4-methoxybenzylamide	**218**		C	2.29	100	384	143.9-144.8	ND	ND	ND
2-(2-methoxy-phenylamino)-4-methyl-thiazole-5-carboxylic acid (naphtha-1-ylmethyl)-amide	**219**		C	2.61	100	404	150.4-156.7	ND	ND	ND
2-(2-methoxy-phenylamino)-4-methyl-thiazole-5-carboxylic acid 2,4-dichloro-6-methyl-benzylamide	**220**		C	2.89	100	437	142.0-147.7	ND	ND	ND
2-(2-methoxy-phenylamino)-4-methyl-oxazole-5-carboxylic acid benzylamide	**221**		C	2.28	97	338	125.9-130.2	ND	ND	ND
2-(2-methoxy-phenylamino)-4-methyl-oxazole-5-carboxylic acid 2,4-dimethoxy-benzylamide	**222**		C	2.37	100	398	68.7 - 82.4	ND	ND	ND
2-(2-methoxy-phenylamino)-4-methyl-oxazole-5-carboxylic acid 4-fluoro-3-trifluoromethyl-benzylamide	**223**		C	2.60	95	424	71.6-84.3	ND	ND	ND
2-(2-methoxy-phenylamino)-3H-imidazole-4-carboxylic acid benzylamide	**224**		C	1.59	100	323	212.5-213.9	ND	ND	ND

Name	Compound	Structure	P	Rt	Pu	ES+	m.p.	Kv4.3 charge	Kv4.3 peak	hERG
2-(2-methoxy-phenylamino)-3H-imidazole-4-carboxylic acid 2,4-dimethoxy-benzylamide	**225**		C	1.69	100	383	134.1-136.2	ND	ND	ND
2-(2-methoxy-phenylamino)-3H-imidazole-4-carboxylic acid 4-fluoro-3-trifluoromethyl-benzylamide	**226**		C	1.97	100	409	227.9 - 230.0	ND	ND	ND

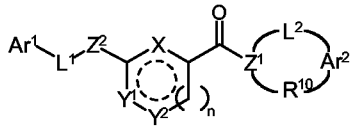
The present invention encompasses compounds of Formula I to , in particular compounds **15** to **181**, **210** to **226**. In a particular embodiment, the present invention encompasses compounds **16, 18, 19, 20, 21, 23, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 40, 47, 48, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 63, 64, 65, 66, 67, 68, 75, 76, 81, 82, 83, 84, 85, 86, 88, 89, 93, 94, 95, 96, 97, 98, 102, 103, 104, 105, 106, 108, 114, 118, 123, 124, 125, 126, 142**, **160, 161, 165**, **170**, **180**, **210, 211.**

Claims

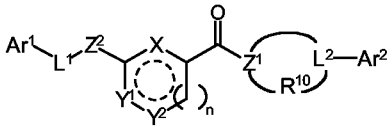
1. A compound having the structural Formula I, II, III or IV, stereoisomers, tautomers, racemics, prodrugs, metabolites thereof, or a pharmaceutically acceptable salt and/or solvate thereof,



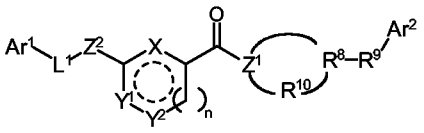
I



II



III



IV

wherein when X is O, Y^1 is selected from N or CH=, and n is 0,

wherein when X is N, Y^1 is selected from S, O, N or CH=, and n is 0or Y1 is selected from N or CH=and n is 1,

wherein when X is S, Y^1 is selected from N or CH=, and n is 0,

wherein when X is CH=, Y^1 is selected from O, N or S, and n is 0 or 1,

wherein Y^2 is selected from -C(R^2)- or N,

wherein n is an integer selected from 0 or 1,

wherein Z^1 is selected from -N(R^3)-, -O-, -N(R^3)-NH-, or -CH_2- in Formula I, and Z^1 is selected from N, or CH in Formula II, III or IV,

wherein Z^2 is selected from N(R^1)-, -O-, or S-,

wherein R^1 and R^3 are each independently selected from hydrogen, alkyl, alkylcarbonyl, cycloalkyl, alkenyl, alkynyl, aryl, heteroaryl, heterocyclyl, aralkyl, cycloalkylalkyl or acyl, optionally substituted by one or more substituents,

wherein R^2 is selected from hydrogen, alkyl, cycloalkyl, alkenyl or alkynyl, optionally substituted by one or more substituents,

wherein Ar^1 is selected from aryl, heterocyclyl or heteroaryl, optionally substituted by one or more substituents selected from halogen, hydroxy, nitro, amino, azide, cyano, alkyl, cycloalkyl, alkylamino, alkoxy, -SO_2-NH_2, aryl, heteroaryl, haloalkyl, haloalkoxy, haloaryl, carboxy, alkyloxycarbonyl, alkylaminocarbonyl, heteroarylalkyl, alkylsulfonamide, heterocyclyl, alkylcarbonylaminoalkyl, aryloxy, alkylcarbonyl, acyl,

arylcarbonyl, aminocarbonyl, alkylsulfoxide, $-SO_2R^{15}$, or alkylthio, wherein R^{15} is alkyl or cycloalkyl,

wherein Ar^2 is selected from aryl, heterocyclyl, or heteroaryl, optionally substituted by one or more substituents selected from halogen, hydroxy, nitro, amino, azide, cyano, alkyl, cycloalkyl, alkylamino, alkoxy, $-SO_2-NH_2$, $-SO_2R^{15}$, aryl, heteroaryl, heteroarylalkyl, haloalkyl, haloalkoxy, haloaryl, carboxy, alkyloxycarbonyl, alkylaminocarbonyl, alkylsulfonamide, heterocyclyl, alkylcarbonylaminoalkyl, aryloxy, alkylcarbonyl, acyl, arylcarbonyl, aminocarbonyl, alkylsulfoxide, or alkylthio, wherein R^{15} is alkyl or cycloalkyl

wherein L^2 is a linking group selected from a single bond, a group of Formula $-R^8-R^9-$, alkylyn, N, cycloalkylene, $-NH-(C(R^4)(R^4))_q-$, $-(C(R^4)(R^4))_q-$, $-C(R^4)=$, $-(C(R^4)(R^4))_v-O-(C(R^4)(R^4))_w-$, $-(C(R^4)(R^4))_v-(C(R^4))_w=$, $-(C(R^4)(R^4))_q-(C=O)-$, or cycloalkylenoxyalkylene, wherein $-(C(R^4)(R^4))_q-$, $(C(R^4)(R^4))_w$ and $-(C(R^4)(R^4))_v-$ are each independently aliphatic or form a cycloalkyl, wherein each R^4 is independently selected from hydrogen, alkyl, hydroxyl, alkylaminoalkyl, carboxy, hydroxyalkyl, alkoxyalkyl, alkylamino, or alkyloxycarbonyl; q is an integer between 0 and 6; v is an integer between 0 and 6 and w is an integer between 0 and 6,

wherein L^1 is a linking group selected from a single bond, $-(C(R^4)(R^4))_q-$, or $-(C(R^4)(R^4))_q-(C=O)-$, wherein each R^4 is independently selected from hydrogen, alkyl, hydroxyl, alkylaminoalkyl, carboxy, hydroxyalkyl, alkoxyalkyl, alkylamino, or alkyloxycarbonyl; q is an integer between 0 and 6;

wherein R^8 is alkylyn, $-(C(R^4)(R^4))_p-C(R^{14})$ or $-(C(R^4)(R^4))_p-C(R^4)=C$, wherein R^9 is selected from a single bond, $-(C(R^4)(R^4))_q-$, or C(=O)-, wherein R^{14} is selected from hydrogen, hydroxyl or alkyl, wherein p is an integer between 0 and 3,

wherein R^{10} is selected from $-(C(R^4)(R^4))_m-$, $-(C(R^4)(R^4))_m-C(=O)O-(C(R^4)(R^4))_q-$, or $-(C(R^4)(R^4))_m-N(R^{12})-(C(R^4)(R^4))_q-$, wherein m is an integer between 1 and 6, wherein R^{12} is selected from hydrogen, alkyl, aryl, arylalkyl or alkylcarbonyl, and

wherein the dotted ring represents one or several double bonds placed in any particular position of the bond forming the ring.

2. A compound according to claim 1, wherein X is nitrogen, Y^1 is sulfur, Y^2 is $C(R^2)-$, and n is 0, wherein R^2 has the same meaning as defined in claim 1.

3. A compound according to claim 1, wherein X is sulfur, Y^1 is nitrogen, Y^2 is $C(R^2)-$, and n is 0, wherein R^2 has the same meaning as defined in claim 1.

4. A compound according to claim 1, wherein X is oxygen, Y^1 is nitrogen, Y^2 is $C(R^2)$-, and n is 0, wherein R^2 has the same meaning as defined in claim 1.

5. A compound according to claim 1, wherein X is nitrogen, Y^1 is nitrogen, Y^2 is $C(R^2)$-, and n is 0, wherein R^2 has the same meaning as defined in claim 1.

6. A compound according to claim 1, wherein X is sulfur, Y^1 is CH-, Y^2 is $C(R^2)$-, and n is 0, wherein R^2 has the same meaning as defined in claim1.

7. A compound according to claim 1, wherein X is nitrogen, Y^1 is nitrogen, Y^2 is $C(R^2)$-, and n is 1, wherein R^2 has the same meaning as defined in claim 1.

8. A compound according to claim 1, wherein X is oxygen, Y^1 is nitrogen, Y^2 is nitrogen, and n is 0.

9. A compound according to any of claims 1 to 8, wherein Ar^1 is selected from 2- or 3-furyl, 2- or 3-thienyl, 1-, 2- or 3-pyrrolyl, 1-, 2-, 4- or 5-imidazolyl, 1-, 3-, 4- or 5-pyrazolyl, 3-, 4- or 5-isoxazolyl, 2-, 4- or 5-oxazolyl, 3-, 4- or 5-isothiazolyl, 2-, 4- or 5-thiazolyl, 1,2,3-triazol-1-, -2-, -4- or -5-yl, 1,2,4-triazol-1-, -3-, -4- or -5-yl, 1,2,3-oxadiazol-4- or -5-yl, 1,2,4-oxadiazol-3- or -5-yl, 1,2,3-thiadiazol-4- or -5-yl, 1,2,4-thiadiazol-3- or -5-yl, 1,2,5-thiadiazol-3- or -4-yl, 1- or 5-tetrazolyl, phenyl, 2-, 3- or 4-pyridyl, 3- or 4-pyridazinyl, 2-, 4-, 5- or 6-pyrimidinyl, 2-, 3-, 4-, 5- 6-2H-thiopyranyl, 2-, 3- or 4-4H-thiopyranyl, 2-, 3-, 4-, 5-, 6- or 7-benzofuryl, 2-, 3-, 4-, 5-, 6- or 7-benzothienyl, benzimidazolonyl, 1,3-benzodioxolyl, 1-, 2-, 3-, 4-, 5-, 6- or 7-indolyl, 1-, 2-, 4- or 5-benzimidazolyl, 1-, 3-, 4-, 5-, 6- or 7-benzopyrazolyl, 3-, 4-, 5-, 6- or 7-benzisoxazolyl, 2-, 4-, 5-, 6- or 7-benzoxazolyl, 3-, 4-, 5-, 6- or 7-benzisothiazolyl, 2-, 4-, 5-, 6- or 7-benzthiazolyl, 1- or 2- naphthyl, 2-, 3-, 4-, 5-, 6-, 7-, 8-quinolinyl, 2-, 4-, 5-, 6-, 7- or 8-quinazolyl, 1-, 3-, 4-, 5-, 6-, 7-, 8-isoquinolinyl, 2,3-dihydrobenzo[1,4]dioxin-2-yl, 2,3-dihydrobenzo[1,4]dioxin-6-yl, 2,3-dihydrobenzofurany-5-yl, indanyl, 1,3-dihydrobenzoimidazol2-one, 1, 2, 3, 4-tetrahydronapthtlanel-1-yl or 1-, 2-, 3-, 4- or 9-carbazolyl, optionally substituted by one or more substituents selected from halogen, hydroxy, nitro, amino, azido, cyano, alkyl, cycloalkyl, alkylamino, alkoxy, $-SO_2-NH_2$, aryl, heteroaryl, heteroarylalkyl, haloalkyl, haloalkoxy, haloaryl, carboxy, alkyloxycarbonyl, alkylaminocarbonyl, alkylsulfonamide, heterocyclyl, alkylcarbonylaminoalkyl, aryloxy, alkylcarbonyl, acyl, arylcarbonyl, aminocarbonyl, alkylsulfoxide, or alkylthio,

wherein Ar^2 is selected from 2- or 3-furyl, 2- or 3-thienyl, 1-, 2- or 3-pyrrolyl, 1-, 2-, 4- or 5-imidazolyl, 1-, 3-, 4- or 5-pyrazolyl, 3-, 4- or 5-isoxazolyl, 2-, 4- or 5-oxazolyl, 3-,

4- or 5-isothiazolyl, 2-, 4- or 5-thiazolyl, 1,2,3-triazol-1-, -2-, -4- or -5-yl, 1,2,4-triazol-1-, -3-, -4- or -5-yl, 1,2,3-oxadiazol-4- or -5-yl, 1,2,4-oxadiazol-3- or -5-yl, 1,2,3-thiadiazol-4- or -5-yl, 1,2,4-thiadiazol-3- or -5-yl, 1,2,5-thiadiazol-3- or -4-yl, 1- or 5-tetrazolyl, phenyl, 2-, 3- or 4-pyridyl, 3- or 4-pyridazinyl, 2-, 4-, 5- or 6-pyrimidinyl, 2,3-dihydrobenzo[1,4]dioxin-2-yl, 2,3-dihydrobenzo[1,4]dioxin-6-yl, 2,3-dihydrobenzofurany-5-yl, indanyl, 1,3-dihydrobenzoimidazol2-one, 1, 2, 3, 4-tetrahydronapthtlanel-1-yl, 2-, 3-, 4-, 5- 6-2H-thiopyranyl, 2-, 3- or 4-4H-thiopyranyl, 2-, 3-, 4-, 5-, 6- or 7-benzofuryl, 2-, 3-, 4-, 5-, 6- or 7-benzothienyl, benzimidazolonyl, 1,3-benzodioxolyl, 1-, 2-, 3-, 4-, 5-, 6- or 7-indolyl, 1-, 2-, 4- or 5-benzimidazolyl, 1-, 3-, 4-, 5-, 6- or 7-benzopyrazolyl, 3-, 4-, 5-, 6- or 7-benzisoxazolyl, 2-, 4-, 5-, 6- or 7-benzoxazolyl, 3-, 4-, 5-, 6- or 7-benzisothiazolyl, 2-, 4-, 5-, 6- or 7-benzthiazolyl, 1- or 2- naphthyl, 2-, 3-, 4-, 5-, 6-, 7-, 8-quinolinyl, 2-, 4-, 5-, 6-, 7- or 8-quinazolyl, 1-, 3-, 4-, 5-, 6-, 7-, 8-isoquinolinyl, or 1-, 2-, 3-, 4- or 9-carbazolyl, optionally substituted by one or more substituents selected from halogen, hydroxy, nitro, amino, azido, cyano, alkyl, cycloalkyl, alkylamino, alkoxy, $-SO_2-NH_2$, aryl, heteroaryl, heteroarylalkyl, haloalkyl, haloalkoxy, haloaryl, carboxy, alkyloxycarbonyl, alkylaminocarbonyl, alkylsulfonamide, heterocyclyl, alkylcarbonylaminoalkyl, aryloxy, alkylcarbonyl, acyl, arylcarbonyl, aminocarbonyl, alkylsulfoxide, or alkylthio,

wherein L^2 is a linking group selected from a single bond, a group of Formula $-R^8-R^9-$, alkylyn, N, cycloalkylene, $-NH-(C(R^4)(R^4))_q-$, $-(C(R^4)(R^4))_q-$, $-C(R^4)=$, $-(C(R^4)(R^4))_v-O-(C(R^4)(R^4))_w-$, $-(C(R^4)(R^4))_v-(C(R^4))_w=$, $-(C(R^4)(R^4))_q-(C=O)-$, or cycloalkylenoxyalkylene, wherein $-(C(R^4)(R^4))_q-$, $(C(R^4)(R^4))_w$ and $-(C(R^4)(R^4))_v-$ are each independently aliphatic or form a cycloalkyl, wherein each R^4 is independently selected from hydrogen, alkyl, hydroxyl, alkylaminoalkyl, carboxy, hydroxyalkyl, alkoxyalkyl, alkylamino, or alkyloxycarbonyl; q is an integer between 0 and 6; v is an integer between 0 and 6 and w is an integer between 0 and 6,

wherein L^1 is a linking group selected from a single bond, $-(C(R^4)(R^4))_q-$, or $-(C(R^4)(R^4))_q-(C=O)-$, wherein each R^4 is independently selected from hydrogen, alkyl, hydroxyl, alkylaminoalkyl, carboxy, hydroxyalkyl, alkoxyalkyl, alkylamino, or alkyloxycarbonyl; q is an integer between 0 and 6;

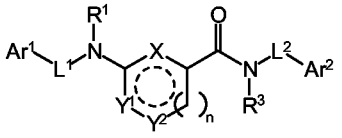
wherein R^8 is alkylyn, $-(C(R^4)(R^4))_p-C(R^{14})$ or $-(C(R^4)(R^4))_p-C(R^4)=C$, wherein R^9 is selected from a single bond, $-(C(R^4)(R^4))_q-$, or C(=O)-, wherein R^{14} is selected from hydrogen, hydroxyl or alkyl, wherein p is an integer between 0 and 3,

wherein R^{10} is selected from $-(C(R^4)(R^4))_m-$, $-(C(R^4)(R^4))_m-C(=O)O-(C(R^4)(R^4))_q-$, or $-(C(R^4)(R^4))_m-N(R^{12})-(C(R^4)(R^4))_q-$, wherein m is an integer between 1 and 6, wherein R^{12} is selected from hydrogen, alkyl, aryl, arylalkyl, or alkylcarbonyl,

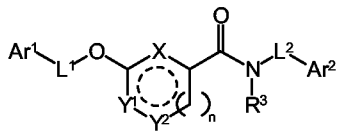
wherein R^1 and R^3 are each independently selected from hydrogen, C_1-C_8 alkyl, aryl, aralkyl, C_3-C_8 cycloalkyl, alkylcarbonyl, or acyl, and

wherein R^2 is selected from hydrogen, C_1-C_8 alkyl or C_3-C_8 cycloalkyl.

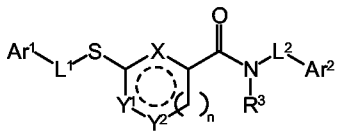
10. A compound according to any of claims 1 to 9, having the structural Formula V to XIII,



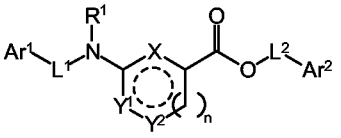
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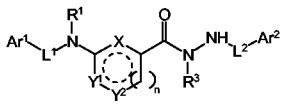
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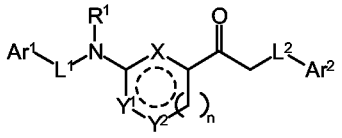
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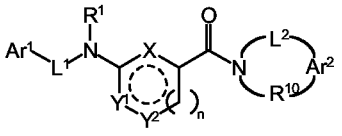
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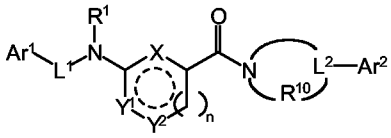
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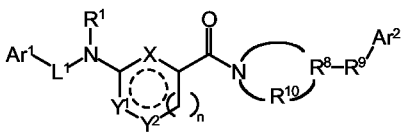
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XI



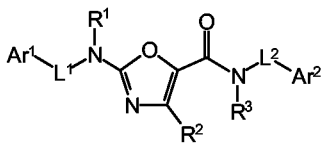
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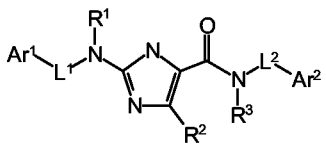
XIII

wherein X, Y^1, Y^2, R^1, n, R^3, R^8, R^9, R^{10}, L^1, L^2, Ar^1 and Ar^2 have the same meaning as that defined in any of the previous claims.

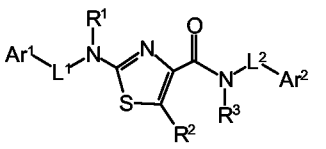
11. A compound according to any of claims 1 to 10, having the structural Formula XIV to XXIX,



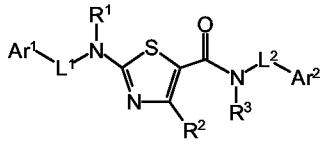
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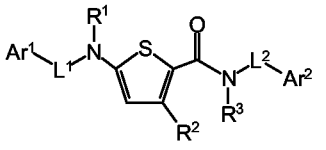
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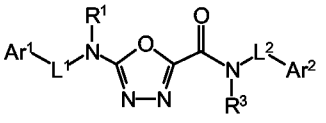
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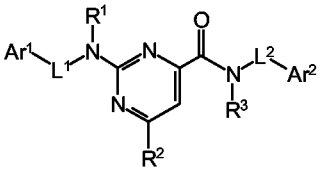
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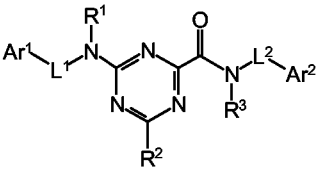


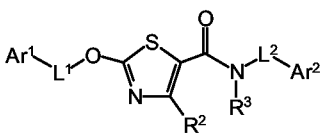
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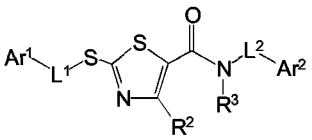
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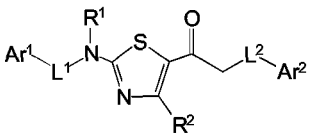




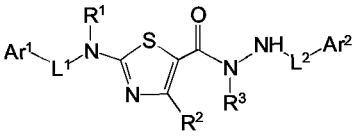
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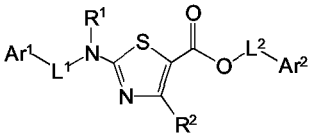
XXI



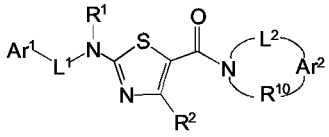
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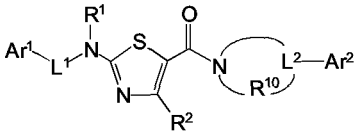
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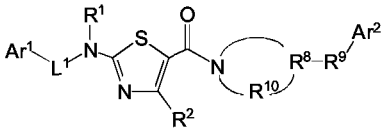
XXIV



XXV



XXVI XXVII XXVIII



XXIX

wherein Ar^1 is selected from 2- or 3-furyl, 2- or 3-thienyl, 1-, 2- or 3-pyrrolyl, 1-, 2-, 4- or 5-imidazolyl, 1-, 3-, 4- or 5-pyrazolyl, 3-, 4- or 5-isoxazolyl, 2-, 4- or 5-oxazolyl, 3-, 4- or 5-isothiazolyl, 2-, 4- or 5-thiazolyl, 1,2,3-triazol-1-, -2-, -4- or -5-yl, 1,2,4-triazol-1-, -3-, -4- or -5-yl, 1,2,3-oxadiazol-4- or -5-yl, 1,2,4-oxadiazol-3- or -5-yl, 1,2,3-thiadiazol-4- or -5-yl, 1,2,4-thiadiazol-3- or -5-yl, 1,2,5-thiadiazol-3- or -4-yl, 1- or 5-tetrazolyl, phenyl, 2-, 3- or 4-pyridyl, 3- or 4-pyridazinyl, 2-, 4-, 5- or 6-pyrimidinyl, 2-, 3-, 4-, 5- 6-2H-thiopyranyl, 2-, 3- or 4-4H-thiopyranyl, 2-, 3-, 4-, 5-, 6- or 7-benzofuryl, 2-, 3-, 4-, 5-, 6- or 7-benzothienyl, benzimidazolonyl, 1,3-benzodioxolyl, 1-, 2-, 3-, 4-, 5-, 6- or 7-indolyl, 1-, 2-, 4- or 5-benzimidazolyl, 1-, 3-, 4-, 5-, 6- or 7-benzopyrazolyl, 3-, 4-, 5-, 6- or 7-benzisoxazolyl, 2-, 4-, 5-, 6- or 7-benzoxazolyl, 3-, 4-, 5-, 6- or 7-benzisothiazolyl, 2-, 4-, 5-, 6- or 7-benzthiazolyl, 1- or 2- naphthyl, 2-, 3-, 4-, 5-, 6-, 7-, 8-quinolinyl, 2-, 4-, 5-, 6-, 7- or 8-quinazolyl, 1-, 3-, 4-, 5-, 6-, 7-, 8-isoquinolinyl, 2,3-dihydrobenzo[1,4]dioxin-2-yl, 2,3-dihydrobenzo[1,4]dioxin-6-yl, 2,3-dihydrobenzofurany-5-yl, indanyl, 1,3-dihydrobenzoimidazol2-one, 1, 2, 3, 4-tetrahydronapthtlanel-1-yl or 1-, 2-, 3-, 4- or 9-carbazolyl, optionally substituted by one or more substituents selected from halogen, hydroxy, nitro, amino, azido, cyano, alkyl, cycloalkyl, alkylamino, alkoxy, $-SO_2-NH_2$, aryl, heteroaryl, heteroarylalkyl, haloalkyl, haloalkoxy, haloaryl, carboxy, alkyloxycarbonyl, alkylaminocarbonyl, alkylsulfonamide, heterocyclyl, alkylcarbonylaminoalkyl, aryloxy, alkylcarbonyl, acyl, arylcarbonyl, aminocarbonyl, alkylsulfoxide, or alkylthio,

wherein Ar^2 is selected from 2- or 3-furyl, 2- or 3-thienyl, 1-, 2- or 3-pyrrolyl, 1-, 2-, 4- or 5-imidazolyl, 1-, 3-, 4- or 5-pyrazolyl, 3-, 4- or 5-isoxazolyl, 2-, 4- or 5-oxazolyl, 3-, 4- or 5-isothiazolyl, 2-, 4- or 5-thiazolyl, 1,2,3-triazol-1-, -2-, -4- or -5-yl, 1,2,4-triazol-1-,

-3-, -4- or -5-yl, 1,2,3-oxadiazol-4- or -5-yl, 1,2,4-oxadiazol-3- or -5-yl, 1,2,3-thiadiazol-4- or -5-yl, 1,2,4-thiadiazol-3- or -5-yl, 1,2,5-thiadiazol-3- or -4-yl, 1- or 5-tetrazolyl, phenyl, 2-, 3- or 4-pyridyl, 3- or 4-pyridazinyl, 2-, 4-, 5- or 6-pyrimidinyl, 2,3-dihydrobenzo[1,4]dioxin-2-yl, 2,3-dihydrobenzo[1,4]dioxin-6-yl, 2,3-dihydrobenzofurany-5-yl, indanyl, 1,3-dihydrobenzoimidazol2-one, 1, 2, 3, 4-tetrahydronapthtlanel-1-yl, 2-, 3-, 4-, 5- 6-2H-thiopyranyl, 2-, 3- or 4-4H-thiopyranyl, 2-, 3-, 4-, 5-, 6- or 7-benzofuryl, 2-, 3-, 4-, 5-, 6- or 7-benzothienyl, benzimidazolonyl, 1,3-benzodioxolyl, 1-, 2-, 3-, 4-, 5-, 6- or 7-indolyl, 1-, 2-, 4- or 5-benzimidazolyl, 1-, 3-, 4-, 5-, 6- or 7-benzopyrazolyl, 3-, 4-, 5-, 6- or 7-benzisoxazolyl, 2-, 4-, 5-, 6- or 7-benzoxazolyl, 3-, 4-, 5-, 6- or 7-benzisothiazolyl, 2-, 4-, 5-, 6- or 7-benzthiazolyl, 1- or 2- naphthyl, 2-, 3-, 4-, 5-, 6-, 7-, 8-quinolinyl, 2-, 4-, 5-, 6-, 7- or 8-quinazolyl, 1-, 3-, 4-, 5-, 6-, 7-, 8-isoquinolinyl, or 1-, 2-, 3-, 4- or 9-carbazolyl, optionally substituted by one or more substituents selected from halogen, hydroxy, nitro, amino, azido, cyano, alkyl, cycloalkyl, alkylamino, alkoxy, $-SO_2-NH_2$, aryl, heteroaryl, heteroarylalkyl, haloalkyl, haloalkoxy, haloaryl, carboxy, alkyloxycarbonyl, alkylaminocarbonyl, alkylsulfonamide, heterocyclyl, alkylcarbonylaminoalkyl, aryloxy, alkylcarbonyl, acyl, arylcarbonyl, aminocarbonyl, alkylsulfoxide, or alkylthio,

wherein L^2 is a linking group selected from a single bond, a group of Formula $-R^8-R^9-$, alkylyn, N, cycloalkylene, $-NH-(C(R^4)(R^4))_q-$, $-(C(R^4)(R^4))_q-$, $-C(R^4)=$, $-(C(R^4)(R^4))_v-O-(C(R^4)(R^4))_w-$, $-(C(R^4)(R^4))_v-(C(R^4))_w=$, $-(C(R^4)(R^4))_q-(C=O)-$, or cycloalkylenoxyalkylene, wherein $-(C(R^4)(R^4))_q-$, $(C(R^4)(R^4))_w$ and $-(C(R^4)(R^4))_v-$ are each independently aliphatic or form a cycloalkyl, wherein each R^4 is independently selected from hydrogen, alkyl, hydroxyl, alkylaminoalkyl, carboxy, hydroxyalkyl, alkoxyalkyl, alkylamino, or alkyloxycarbonyl; q is an integer between 0 and 6; v is an integer between 0 and 6 and w is an integer between 0 and 6,

wherein L^1 is a linking group selected from a single bond, $-(C(R^4)(R^4))_q-$, or $-(C(R^4)(R^4))_q-(C=O)-$, wherein each R^4 is independently selected from hydrogen, alkyl, hydroxyl, alkylaminoalkyl, carboxy, hydroxyalkyl, alkoxyalkyl, alkylamino, or alkyloxycarbonyl; q is an integer between 0 and 6;

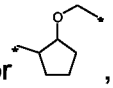
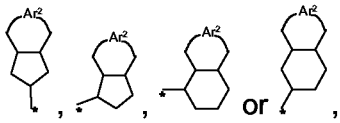
wherein R^8 is alkylyn, $-(C(R^4)(R^4))_p-C(R^{14})$ or $-(C(R^4)(R^4))_p-C(R^4)=C$, wherein R^9 is selected from a single bond, $-(C(R^4)(R^4))_q-$, or C(=O)-, wherein R^{14} is selected from hydrogen, hydroxyl or alkyl, wherein p is an integer between 0 and 3,

wherein R^{10} is selected from $-(C(R^4)(R^4))_m-$, $-(C(R^4)(R^4))_m-C(=O)O-(C(R^4)(R^4))_q-$, or $-(C(R^4)(R^4))_m-N(R^{12})-(C(R^4)(R^4))_q-$, wherein m is an integer between 1 and 6, wherein R^{12} is selected from hydrogen, alkyl, aryl, arylalkyl, or alkylcarbonyl,

wherein R^1 and R^3 are each independently selected from hydrogen, C_1-C_8 alkyl, aryl, aralkyl, C_3-C_8 cycloalkyl, alkylcarbonyl, or acyl, and

wherein R^2 is selected from hydrogen, C_1-C_8 alkyl or C_3-C_8 cycloalkyl.

12. A compound according to claim 11, having a structural Formula selected from Formula XIV to XXVI, wherein Ar^1 is selected from phenyl, 6-indolyl, 1-napthyl, 2-naphtly, 2,3-dihydrobenzo[1,4]dioxin-2-yl, 2,3-dihydrobenzo[1,4]dioxin-6-yl, indanyl, 1,3-dihydrobenzoimidazol2-one, 1, 2, 3, 4-tetrahydronapthtlanel-1-yl, 2-benzofuran-5-yl, pyridin-4-yl, 1,3-benzodioxolyl, benzimidazolonyl, 3-thienyl, or 5-(2,3-dihydro)benzofuranyl, optionally substituted with one to 4 substituent selected from F, Cl, Br, $-CH_3$, t-bu, $-OCH_3$, $-NO_2$, $-CO_2H$, $-C(=O)-N(CH_3)_2$, $-O-C(=O)-CH_3$, , , , $-CH_2-CH_3$, phenyl, morpholino, $-SO_2-CH_3$, $-CF_3$, $-OCF_3$, $-CH_2-NH-C(=O)-CH_3$, $-S-CH_3$, $-C(=O)-CH_3$, $-C(=O)O-CH_3$, $-C(=O)NH_2$, $-N(CH_3)_2$, $-SO_2-N(CH_3)_2$, phenoxyl, benzoyl, $-C(CH_3)_3$, $-O-(CH_2)_2-CH_3$, -OH or CN,

wherein L^2 is selected from single bond, $-CH_2-$, $-(CH_2)_2-$, $-(CH_2)_3-$, $-CH(CH_2OH)-$, $-CH(CH_2-O-CH_3)-$, $-CH(CH_3)-$, $-CH(CH_2-CH_3)-$, $-CH(CO_2H)-$, $-CH(CO_2CH_3)-$, $-(CH_2)_2-O-CH_2-$, $-CH(,CH_2-N(CH_3)_2)-$, $-(CH_2)_2-CH=$, or , or wherein L^2-Ar^2 is , or ,

wherein Ar^2 is selected from phenyl, 1-naphthyl or 2-naphthyl, pyridin-4-yl, 1,3-benzodioxolyl, benzimidazolonyl, pyridin-3-yl, pyridin-2-yl, 5-indolyl, 8-quinolinyl, 2-thiophenyl, 2,3-dihydrobenzofuran-5-yl, 2-thienyl, 3-thienyl, 2,3-dihydrobenzo[1,4]dioxin-2-yl, 2,3-dihydrobenzo[1,4]dioxin-6-yl, indanyl, 1,3-dihydrobenzoimidazol-2-one, benzo(1,3)dioxo-5-yl, indan-1-yl, 1, 2, 3, 4-tetrahydronapthtlanel-1-yl, 2-benzofuran-5-yl, pyridin-4-yl, 2-benzoxazolyl, or 5-benzofuranyl, optionally substituted by one or more substituents selected from nitro, $-SO_2-NH_2$, F, Cl, Br, OH, $-CH_3$, $-OCH_3$, $-NO_2$, $-CO_2H$, $-C(=O)-N(CH_3)_2$, $-O-C(=O)-CH_3$, , , , , -N-morpholino, $-CH_2-CH_3$, phenyl, $-SO_2-CH_3$, $-CF_3$, -

OCF_3, $-CH_2-NH-C(=O)-CH_3$, $-S-CH_3$, $-C(=O)-CH_3$, $-C(=O)O-CH_3$, $-C(=O)O-CH_2-CH_3$, $-C(=O)NH_2$, $-N(CH_3)_2$, $-SO_2-N(CH_3)_2$, phenoxyl, benzoyl, $-C(CH_3)_3$, $-O-(CH_2)_2-CH_3$, or CN,

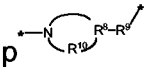
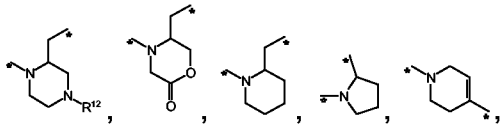
wherein L^1 is single bond or C(=O)-,

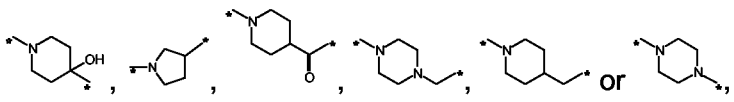
wherein R^1 is selected from hydrogen, $-CH_3$, or $-C(=O)-CH_3$,

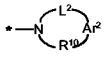
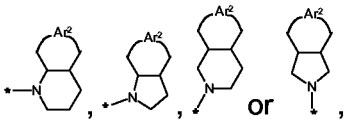
wherein R^3 is selected from hydrogen, $-CH_3$, phenyl, benzyl or $-C(=O)-CH_3$, and

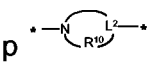
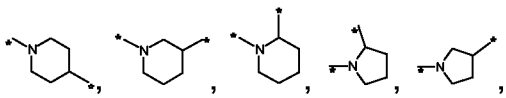
wherein R^2 is selected from hydrogen, $-CH_3$, or $-C(=O)-CH_3$.

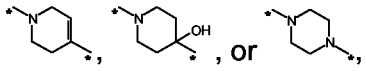
13. A compound according to claim 11, having a structural Formula selected from Formula XXVII to XXIX,

wherein the group  is selected from 



wherein the group  is selected from 

wherein the group  is selected from 



wherein R^{12} is selected from hydrogen, $CH_3-C(=O)-$, CH_3- or benzyl,

wherein Ar^1 is selected from phenyl, 6-indolyl, 3-thiophenyl, 1,3-benzodioxolyl, benzimidazolonyl, or 5-(2,3-dihydro)benzofuranyl, optionally substituted with one to 4 substituent selected from F, Cl, Br, OH, $-CH_3$, t-bu, $-OCH_3$, $-NO_2$, $-CO_2H$, $-C(=O)-N(CH_3)_2$, $-O-C(=O)-CH_3$, , , - N-morpholino, $-CH_2-CH_3$, phenyl, $-SO_2-CH_3$, $-CF_3$, $-OCF_3$, $-CH_2-NH-C(=O)-CH_3$, $-S-CH_3$, $-C(=O)-CH_3$, $-C(=O)O-CH_3$, $-C(=O)NH_2$, $-N(CH_3)_2$, $-SO_2-N(CH_3)_2$, phenoxyl, benzoyl, $-C(CH_3)_3$, $-O-(CH_2)_2-CH_3$, -OH or CN,

wherein Ar^2 is selected from phenyl, 1-naphthyl or 2-naphthyl, pyridin-4-yl, pyridin-3-yl, pyridin-2-yl, 5-indolyl, 8-quinolinyl, 2-thiophenyl, 2-benzoxazolyl, 1,3-benzodioxolyl, 2,3-dihydrobenzofuran-5-yl, 2-thienyl, 3-thienyl, 2,3-dihydrobenzo[1,4]dioxin-2-yl, 2,3-

dihydrobenzo[1,4]dioxin-6-yl, indanyl, 1,3-dihydrobenzoimidazol-2-one, benzo(1,3)dioxo-5-yl, indan-1-yl, 1, 2, 3, 4-tetrahydronapthtlanel-1-yl, 2-benzofuran-5-yl, pyridin-4-yl, benzimidazolonyl, or 5-benzofuranyl, optionally substituted by one or more substituents selected from nitro, $-SO_2-NH_2$, F, Cl, Br, OH, $-CH_3$, $-OCH_3$, $-NO_2$, $-CO_2H$, $-C(=O)-N(CH_3)_2$, $-O-C(=O)-CH_3$, , , , , N-morpholino, $-CH_2-CH_3$, phenyl, $-SO_2-CH_3$, $-CF_3$, $-OCF_3$, $-CH_2-NH-C(=O)-CH_3$, $-S-CH_3$, $-C(=O)-CH_3$, $-C(=O)O-CH_3$, $-C(=O)O-CH_2-CH_3$, $-C(=O)NH_2$, $-N(CH_3)_2$, $-SO_2-N(CH_3)_2$, phenoxyl, benzoyl, $-C(CH_3)_3$, $-O-(CH_2)_2-CH_3$, or CN, wherein R^1 is selected from hydrogen, $-CH_3$, or $-C(=O)-CH_3$,

wherein L^1 is single bond or C(=O)-,

wherein R^3 is selected from hydrogen, $-CH_3$, phenyl, benzyl or $-C(=O)-CH_3$, and

wherein R^2 is selected from hydrogen, $-CH_3$, or $-C(=O)-CH_3$.

14. A compound according to any of claims 1 to 13 selected from the group comprising 2-(4-fluoro-phenylamino)-4-methyl-thiazole-5-carboxylic acid ((S)-1-naphthalen-2-yl-ethyl)-amide; 2-(4-fluoro-phenylamino)-4-methyl-thiazole-5-carboxylic acid ((R)-1-naphthalen-2-yl-ethyl)-amide; 2-(4-fluoro-phenylamino)-4-methyl-thiazole-5-carboxylic acid (4-nitro-benzyl)-propyl-amide; 2-(4-bromo-phenylamino)-4-methyl-thiazole-5-carboxylic acid ((S)-1-naphthalen-2-yl-ethyl)-amide; 2-(4-bromo-phenylamino)-4-methyl-thiazole-5-carboxylic acid ((R)-1-naphthalen-2-yl-ethyl)-amide; 2-(4-bromo-phenylamino)-4-methyl-thiazole-5-carboxylic acid benzylamide; 2-(4-bromo-phenylamino)-4-methyl-thiazole-5-carboxylic acid [(R)-1-(3-methoxy-phenyl)-ethyl]amide; 2-(4-bromo-phenylamino)-4-methyl-thiazole-5-carboxylic acid [(R)-1-(4-nitro-phenyl)-ethyl]amide; 2-(4-bromo-phenylamino)-4-methyl-thiazole-5-carboxylic acid 4-nitro-benzylamide; 2-(4-bromo-phenylamino)-4-methyl-thiazole-5-carboxylic acid 3,5-bis-trifluoromethyl-benzylamide; 2-(4-bromo-phenylamino)-4-methyl-thiazole-5-carboxylic acid ((1R,2R)-2-benzyloxycyclopent-1-yl) amide; 2-(4-bromo-phenylamino)-4-methyl-thiazole-5-carboxylic acid ((1S,2S)-2-benzyloxycyclopent-1-yl) amide; 2-(4-bromo-phenylamino)-4-methyl-thiazole-5-carboxylic acid methyl-naphthalen-1-ylmethyl-amide; 2-(4-bromo-phenylamino)-4-methyl-thiazole-5-carboxylic acid (4-nitro-benzyl)-propyl-amide; 2-[(4-bromo-phenyl)-methyl-amino)-4-methyl-thiazole-5-carboxylic acid ((1R,2R)-2-benzyloxycyclopent-1-yl) amide; 2-(4-chloro-phenylamino)-4-methyl-thiazole-5-carboxylic acid ((1R,2R)-2-benzyloxycyclopent-1-yl) amide; 2-(2-methoxy-phenylamino)-4-methyl-thiazole-5-

carboxylic acid ((1R,2R)-2-benzyloxycyclopent-1-yl) amide; 4-methyl-2-o-tolylamino-thiazole-5-carboxylic acid ((S)-1-naphthalen-2-yl-ethyl)-amide; 2-(2,5-dimethoxy-phenylamino)-4-methyl-thiazole-5-carboxylic acid ((1R,2R)-2-benzyloxycyclopent-1-yl) amide; 2-(5-chloro-2-methoxy-phenylamino)-4-methyl-thiazole-5-carboxylic acid [(R)-1-(3-methoxy-phenyl)-ethyl]-amide; 2-(5-chloro-2-methoxy-phenylamino)-4-methyl-thiazole-5-carboxylic acid ((1R,2R)-2-benzyloxycyclopent-1-yl) amide; 2-(4-fluoro-phenylamino)-thiazole-4-carboxylic acid [(R)-1-(4-nitro-phenyl)-ethyl]amide; 2-(4-fluoro-phenylamino)-thiazole-4-carboxylic acid ((1R,2R)-2-benzyloxycyclopent-1-yl) amide; 2-(4-fluoro-phenylamino)-thiazole-4-carboxylic acid ((1R,2R)-2-benzyloxycyclohex-1-yl) amide; 2-(4-bromo-phenylamino)-thiazole-4-carboxylic acid ((1R,2R)-2-benzyloxycyclopent-1-yl) amide; 2-(4-chloro-phenylamino)-thiazole-4-carboxylic acid ((1R,2R)-2-benzyloxycyclopent-1-yl) amide; 2-(4-chloro-phenylamino)-thiazole-4-carboxylic acid ((1S,2S)-2-benzyloxycyclohex-1-yl) amide; and 2-(4-chloro-phenylamino)-thiazole-4-carboxylic acid (4-nitro-benzyl)-propylamide.

15. A compound according to any of claims 1 to 13, selected from the group comprising 2-(3,5-dimethyl-phenylamino)-thiazole-4-carboxylic acid [(R)-1-(4-nitro-phenyl)-ethyl]amide; 2-(3,5-dimethyl-phenylamino)-thiazole-4-carboxylic acid ((S)-1-methoxymethyl-2-phenyl-ethyl)-amide; 2-(3,5-dimethyl-phenylamino)-thiazole-4-carboxylic acid ((1R,2R)-2-benzyloxycyclopent-1-yl) amide; 2-(3,5-dimethyl-phenylamino)-thiazole-4-carboxylic acid ((1S,2S)-2-benzyloxycyclohex-1-yl) amide; 2-phenylamino-thiazole-4-carboxylic acid [(R)-1-(4-nitro-phenyl)-ethyl]amide; 3-phenylamino-thiazole-4-carboxylic acid ((1R,2R)-2-benzyloxycyclopent-1-yl) amide; 3-phenylamino-thiazole-4-carboxylic acid ((1S,2S)-2-benzyloxycyclohex-1-yl) amide; 2-(5-chloro-2-methoxy-phenylamino)-thiazole-4-carboxylic acid acid ((1S,2S)-2-benzyloxycyclohex-1-yl) amide; 2-(5-chloro-2-methoxy-phenylamino)-thiazole-4-carboxylic acid acid ((1R,2R)-2-benzyloxycyclohex-1-yl) amide; 2-(4-chloro-phenylamino)-4-methyl-thiazole-5-carboxylic acid ((R)-1-naphthalen-2-yl-ethyl)-amide; 2-(2-methoxy-phenylamino)-4-methyl-thiazole-5-carboxylic acid ((R)-1-naphthalen-2-yl-ethyl)-amide; 2-(4-chloro-phenylamino)-4-methyl-thiazole-5-carboxylic acid ((S)-1-naphthalen-2-yl-ethyl)-amide; 2-(2-methoxy-phenylamino)-4-methyl-thiazole-5-carboxylic acid ((S)-1-naphthalen-2-yl-ethyl)-amide; 2-(4-bromo-phenylamino)-4-methyl-thiazole-5-carboxylic acid (naphthalen-1-ylmethyl)-amide; 2-(4-bromo-phenylamino)-4-methyl-thiazole-5-carboxylic acid (pyridin-4-ylmethyl)-amide; 2-(4-bromo-phenylamino)-4-methyl-thiazole-5-carboxylic acid (pyridin-3-ylmethyl)-amide; 2-(4-bromo-phenylamino)-4-methyl-thiazole-5-carboxylic acid (pyridin-2-ylmethyl)-amide;

2-(4-bromo-phenylamino)-4-methyl-thiazole-5-carboxylic acid 4-methoxy-benzylamide; 2-(4-bromo-phenylamino)-4-methyl-thiazole-5-carboxylic acid 3,4-dimethoxy-benzylamide; 2-(4-bromo-phenylamino)-4-methyl-thiazole-5-carboxylic acid 3-trifluoromethoxy-benzylamide; and 2-(4-bromo-phenylamino)-4-methyl-thiazole-5-carboxylic acid 4-fluoro-3-trifluoromethyl-benzylamide.

16. A compound according to any of claims 1 to 13, selected from the group comprising 2-(4-bromo-phenylamino)-4-methyl-thiazole-5-carboxylic acid 4-dimethylamino-benzylamide; 2-(4-bromo-phenylamino)-4-methyl-thiazole-5-carboxylic acid 3,5-dimethoxy-benzylamide; [2-(4-bromo-phenylamino)-4-methyl- thiazol-5-yl]-(3,4-dihydro-1H-isoquinolin-2-yl)-methanone; 2-(4-fluoro-phenylamino)-4-methyl-thiazole-5-carboxylic acid ((1S,2S)-2-benzyloxycyclopent-1-yl) amide; 2-(2-methoxy-phenylamino)-4-methyl-thiazole-5-carboxylic acid ((1S,2S)-2-benzyloxycyclopent-1-yl) amide; 2-(2,5-dimethoxy-phenylamino)-4-methyl-thiazole-5-carboxylic acid ((R)-1-naphthalen-2-yl-ethyl)-amide; 2-(4-fluoro-phenylamino)-4-methyl-thiazole-5-carboxylic acid 4-dimethylamino-benzylamide; 2-(4-fluoro-phenylamino)-4-methyl-thiazole-5-carboxylic acid 4-sulfamoyl-benzylamide; 2-(4-chloro-phenylamino)-thiazole-4-carboxylic acid 4-dimethylamino-benzylamide; 2-(2-methoxy-phenylamino)-4-methyl-oxazole-5-carboxylic acid ((1S,2S)-2-benzyloxycyclopent-1-yl) amide; 2-(2-methoxy-phenylamino)-thiophene-5-carboxylic acid ((1S,2S)-2-benzyloxycyclopent-1-yl) amide; 2-(2-methoxy-phenylamino)-pyrimidine-4-carboxylic acid ((1S,2S)-2-benzyloxycyclopent-1-yl) amide; 1-[2-(2-methoxy-phenylamino)-4-methyl-thiazol-5-yl]-2-phenyl-ethanone; 4-methyl-2-phenoxy-thiazole-5-carboxylic acid ((1S,2S)-2-benzyloxycyclopent-1-yl) amide; 4-methyl-2-phenylsulfanyl-thiazole-5-carboxylic acid ((1S,2S)-2-benzyloxycyclopent-1-yl) amide; 2-(2-methoxy-phenylamino)-4-methyl-thiazole-5-carboxylic acid phenylamide; 2-(2-methoxy-phenylamino)-4-methyl-thiazole-5-carboxylic acid indan-2-ylamide; (1,3-dihydro-isoindol-2-yl)-[2-(2-methoxy-phenylamino)-4-methyl-thiazol-5-yl]-methanone; (3,4-dihydro-1H-isoquinolin-2-yl)-[2-(2-methoxy-phenylamino)-4-methyl-thiazol-5-yl]-methanone; (2-benzyl-piperidin-1-yl)-[2-(2-methoxy-phenylamino)-4-methyl-thiazol-5-yl]-methanone.

17. A compound according to any of claims 1 to 13, selected from the group comprising 2-(2-methoxy-phenylamino)-4-methyl-thiazole-5-carboxylic acid (2-benzyloxy-ethyl)-amide; 3-[5-((1S,2S)-2-benzyloxy-cyclopent-1-ylcarbamoyl)-4-methyl-thiazol-2-ylamino]-benzoic acid ethyl ester ; 4-methyl-2-(4-morpholin-4-yl-phenylamino)-thiazole-5-carboxylic acid ((1S,2S)-2-benzyloxycyclopent-1-yl) amide; 4-methyl-2-

(naphtalen-1-ylamino)-thiazole-5-carboxylic acid ((1S,2S)-2-benzyloxycyclopent-1-yl) amide; 4-methyl-2-(quinolin-8-ylamino)-thiazole-5-carboxylic acid ((1S,2S)-2-benzyloxycyclopent-1-yl) amide; 2-(2,3-dihydro-benzo[1,4]dioxin-6-ylamino-4-methyl-thiazole-5-carboxylic acid ((1S,2S)-2-benzyloxycyclopent-1-yl) amide; 2-(2-methoxy-phenylamino)-4-methyl-thiazole-5-carboxylic acid 4-(acetylamino-methyl)-benzylamide; 2-(2-methoxy-phenylamino)-4-methyl-thiazole-5-carboxylic acid 2-methyl sulfanyl-benzylamide; 2-(2-methoxy-phenylamino)-4-methyl-thiazole-5-carboxylic acid 2-chloro-6-methyl-benzylamide; 2-(2-methoxy-phenylamino)-4-methyl-thiazole-5-carboxylic acid 4-phenoxy-benzylamide; 2-(2-methoxy-phenylamino)-4-methyl-thiazole-5-carboxylic acid 4-thiophen-2-yl-benzylamide; 2-(2-methoxy-phenylamino)-4-methyl-thiazole-5-carboxylic acid (2,3-dihydro-benzofuran-5-ylmethyl)-amide; 2-(2-methoxy-phenylamino)-4-methyl-thiazole-5-carboxylic acid 4-dimethylamino-benzylamide; 2-(2-methoxy-phenylamino)-4-methyl-thiazole-5-carboxylic acid 4-tert-butyl-benzylamide; 2-(2-methoxy-phenylamino)-4-methyl-thiazole-5-carboxylic acid 4-bromo-benzylamide; (S)-{[2-(2-methoxy-phenylamino)-4-methyl-thiazole-5-carbonyl]-amino}-phenyl-acetic acid; 2-(2-methoxy-phenylamino)-4-methyl-thiazole-5-carboxylic acid (thiophen-3-ylmethyl)-amide; 2-(4-chloro-phenylamino)-4-methyl-thiazole-5-carboxylic acid N -(2,4-dinitrophenyl)-hydrazide; 2-(2-methoxy-phenylamino)-4-methyl-thiazole-5-carboxylic acid benzyl ester; 2-(2-methoxy-phenylamino)-4-methyl-thiazole-5-carboxylic acid benzylamide; ((S)-2,4-dibenzyl-piperazin-1-yl)-[2-(2-methoxy-phenylamino)-4-methyl-thiazol-5-yl]-methanone; 2-(benzofuran-5-ylamino)-4-methyl-thiazole-5-carboxylic acid ((1S,2S)-2-benzyloxycyclopent-1-yl) amide; 2-benzylamino-4-methyl-thiazole-5-carboxylic acid ((1S,2S)-2-benzyloxycyclopent-1-yl) amide; 2-[acetyl-(2-methoxy-phenyl)-amino]-4-methyl-thiazole-5-carboxylic acid ((1S,2S)-2-benzyloxycyclopent-1-yl) amide; 2-(2-methoxy-phenylamino)-4-methyl-thiazole-5-carboxylic acid (1-phenyl-ethyl)-amide; 2-(2-methoxy-phenylamino)-4-methyl-thiazole-5-carboxylic acid ((R)-1-phenyl-propyl)-amide; 2-(2-methoxy-phenylamino)-4-methyl-thiazole-5-carboxylic acid ((S)-1-phenyl-propyl)-amide; 2-(3-methoxy-phenylamino)-4-methyl-thiazole-5-carboxylic acid ((1S,2S)-2-benzyloxycyclopent-1-yl) amide ; 2-(2-methoxy-phenylamino)-4-methyl-thiazole-5-carboxylic acid 4-methyl sulfanyl-benzylamide; 2-(2-methoxy-phenylamino)-4-methyl-thiazole-5-carboxylic acid 4-dimethylcarbamoyl-benzylamide.

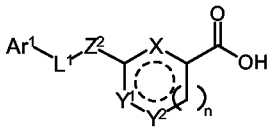
18. A compound according to any of claims 1 to 13, selected from the group comprising [3-({[2-(2-methoxy-phenylamino)-4-methyl-thiazole-5-carbonyl]-amino}-methyl)-benzoic acid methyl ester; 2-(2-methoxy-phenylamino)-4-methyl-thiazole-5-carboxylic

acid 2-methyl-benzylamide; 2-(2-methoxy-phenylamino)-4-methyl-thiazole-5-carboxylic acid 3-methyl-benzylamide; 2-(2-methoxy-phenylamino)-4-methyl-thiazole-5-carboxylic acid 4-methyl-benzylamide; 2-(2-methoxy-phenylamino)-4-methyl-thiazole-5-carboxylic acid (biphenyl-2-ylmethyl)- amide; 2-(2-methoxy-phenylamino)-4-methyl-thiazole-5-carboxylic acid (biphenyl-3-ylmethyl)- amide; 2-(2-methoxy-phenylamino)-4-methyl-thiazole-5-carboxylic acid (biphenyl-4-ylmethyl)- amide; 2-(2-methoxy-phenylamino)-4-methyl-thiazole-5-carboxylic acid 2-bromo-benzylamide; 2-(2-methoxy-phenylamino)-4-methyl-thiazole-5-carboxylic acid 3-bromo-benzylamide; 2-(2-methoxy-phenylamino)-4-methyl-thiazole-5-carboxylic acid ((S)-2-methoxy-1-phenyl-ethyl)-amide; 2-[(2-methoxy-phenyl)-methyl-amino]-4-methyl-thiazole-5-carboxylic acid ((S)-2-hydroxy-1-phenyl-ethyl)-amide; (R)-{[2-(2-methoxy-phenylamino)-4-methyl-thiazole-5-carbonyl]-amino}-phenyl-acetic acid methyl ester; (S)-{[2-(2-methoxy-phenylamino)-4-methyl-thiazole-5-carbonyl]-amino}-phenyl-acetic acid methyl ester; 4-methyl-2-(pyridin-4-ylamino)-thiazole-5-carboxylic acid ((1S,2S)-2-benzyloxycyclopent-1-yl) amide; [4-({[2-(2-methoxy-phenylamino)-4-methyl-thiazole-5-carbonyl]-amino}-methyl)-benzoic acid methyl ester; [3-({[2-(2-methoxy-phenylamino)-4-methyl-thiazole-5-carbonyl]-amino}-methyl)-benzoic acid; 2-(2-methoxy-phenylamino)-4-methyl-thiazole-5-carboxylic acid 2-trifluoromethoxy-benzylamide; 2-(2-methoxy-phenylamino)-4-methyl-thiazole-5-carboxylic acid 3-trifluoromethoxy-benzylamide; 2-(2-methoxy-phenylamino)-4-methyl-thiazole-5-carboxylic acid 4-trifluoromethoxy-benzylamide; (R)-{[2-(2-methoxy-phenylamino)-4-methyl-thiazole-5-carbonyl]-amino}-phenyl-acetic acid; 2-(2-methoxy-phenylamino)-4-methyl-thiazole-5-carboxylic acid 2,5-dimethyl-benzylamide; 2-(2-methoxy-phenylamino)-4-methyl-thiazole-5-carboxylic acid 4-[1,2,3]thiadiazol-4-yl-benzylamide; 2-(2-methoxy-phenylamino)-4-methyl-thiazole-5-carboxylic acid (benzo[1,3]dioxol-5-ylmethyl)-amide; [4-(4-fluoro-phenyl)-3,6-dihydro-2H-pyridin-1-yl]-[2-(2-methoxy-phenylamino)-4-methyl-thiazol-5-yl]-methanone; 2-(2-methoxy-phenylamino)-4-methyl-thiazole-5-carboxylic acid indan-1-ylamide; [2-(2-methoxy-phenylamino)-4-methyl-thiazol-5-yl]-[4-(2-methoxy-phenyl)-piperidin-1-yl]-methanone; 2-(2-methoxy-phenylamino)-4-methyl-thiazole-5-carboxylic acid (4-pyrazol-1-ylmethyl-phenyl)-amide; [2-(2-methoxy-phenylamino)-4-methyl-thiazol-5-yl]-[4-p-tolyl- piperidin-1-yl]-methanone; 1-{1-[2-(2-methoxy-phenylamino)-4-methyl-thiazole-5-carbonyl]-piperidin-4-yl}-1,3-dihydro-benzoimidazol-2-one.

19. A compound according to any of claims 1 to 13, selected from the group comprising 2-o-tolylamino-thiazole-4-carboxylic acid ((1S,2S)-2-benzyloxycyclopent-1-yl) amide; 2-(2-methoxy-phenylamino)-4-methyl-thiazole-5-carboxylic acid (1,2,3,4-tetrahydro-

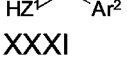
naphthalen-1-yl)-amide; (4-benzyl-piperidin-1-yl)-[2-(2-methoxy-phenylamino)-4-methyl-thiazol-5-yl]-methanone; [4-(4-fluoro-benzoyl)-piperidin-1-yl]-[2-(2-methoxy-phenylamino)-4-methyl-thiazol-5-yl]-methanone; [2-(2-methoxy-phenylamino)-4-methyl-thiazol-5-yl]-(2-phenyl-pyrrolidin-1-yl)-methanone; [2-(4-fluoro-phenyl)-pyrrolidin-1-yl]-[2-(2-methoxy-phenylamino)-4-methyl-thiazol-5-yl]-methanone; 2-benzoylamino-4-methyl-thiazole-5-carboxylic acid ((1S,2S)-2-benzyloxycyclopent-1-yl) amide; 2-(4-tert-butyl-benzoylamino)-4-methyl-thiazole-5-carboxylic acid ((1S,2S)-2-benzyloxycyclopent-1-yl) amide; 2-(4-cyano-benzoylamino)-4-methyl-thiazole-5-carboxylic acid ((1S,2S)-2-benzyloxycyclopent-1-yl) amide; N-[5-((1S,2S)-2-benzyloxy-cyclopentylcarbamoyl)-4-methyl-thiazol-2-yl]-terephthalamide; [4-(2,5-dimethoxy-benzyl))-piperazin-1-yl]-[2-(2-methoxy-phenylamino)-4-methyl-thiazol-5-yl]-methanone; 2-(2-methoxy-phenylamino)-4-methyl-thiazole-5-carboxylic acid (1-benzyl-pyrrolidin-3-yl) amide; 2-(2-methoxy-phenylamino)-4-methyl-thiazole-5-carboxylic acid benzyl-phenyl-amide; 2-(2-methoxy-phenylamino)-4-methyl-thiazole-5-carboxylic acid (2,3-dihydro-benzo[1,4]dioxin-2-ylmethyl) amide; 2-(2-methoxy-phenylamino)-4-methyl-thiazole-5-carboxylic acid 4-methoxybenzylamide; 2-(2-methoxy-phenylamino)-4-methyl-thiazole-5-carboxylic acid (naphtha-1-ylmethyl)-amide; 2-(2-methoxy-phenylamino)-4-methyl-thiazole-5-carboxylic acid 2,4-dichloro-6-methyl-benzylamide; 2-(2-methoxy-phenylamino)-4-methyl-oxazole-5-carboxylic acid benzylamide; 2-(2-methoxy-phenylamino)-4-methyl-oxazole-5-carboxylic acid 2,4-dimethoxy-benzylamide; 2-(2-methoxy-phenylamino)-4-methyl-oxazole-5-carboxylic acid 4-fluoro-3-trifluoromethyl-benzylamide; 2-(2-methoxy-phenylamino)-3H-imidazole-4-carboxylic acid benzylamide; 2-(2-methoxy-phenylamino)-3H-imidazole-4-carboxylic acid 2,4-dimethoxy-benzylamide; 2-(2-methoxy-phenylamino)-3H-imidazole-4-carboxylic acid 4-fluoro-3-trifluoromethyl-benzylamide.

20. Method for synthesizing a compound having the structural Formula I, II, III or IV comprising the step of condensing a compound of Formula XXX:

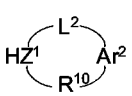


XXX

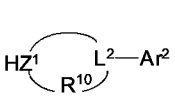
with a compound of Formula XXXI, XXXII, XXXIII or XXXIV :



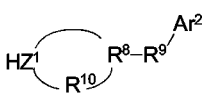
XXXI



XXXII

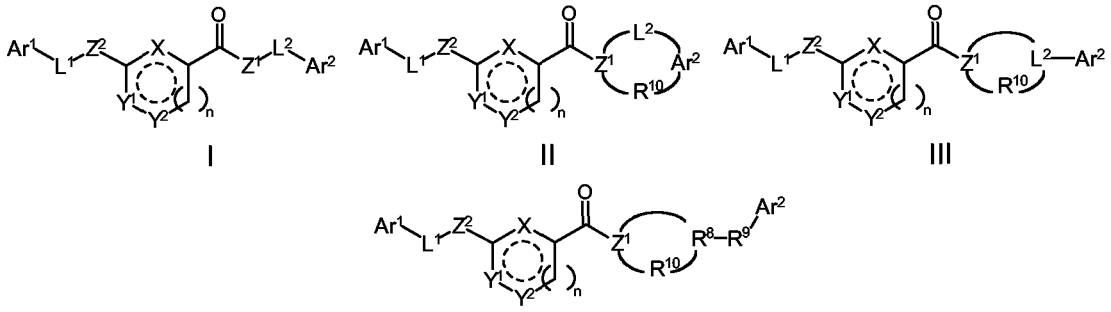


XXXIII



XXXIV

hereby obtaining a compound of Formula I, II, III or IV,



I II III

IV

wherein Ar^1, Ar^2, L^1, L^2, X, Y^1, Y^2, R^{10}, R^8 and R^9 have the same meaning as that defined in any of claims 1 to 13.

21. A method according to claim 20, wherein the condensation is performed via the formation of the acyl chloride of the compound of Formula XXX and then by the coupling of said acyl chloride with the compound of Formula XXXI, XXXII, XXXIII or XXXIV.

22. A method according to claim 20, wherein the condensation is performed using a suitable coupling agent, in a suitable solvent, in the presence of suitable base.

23. A method according to claim 22, wherein the suitable coupling agent is selected from the group comprising hydroxybenzotriazole, o-benzotriazol-1-yl-N,N,N',N'-tetramethyluronium hexafluorophosphate and the like.

24. A method according to claim 22 or 23, wherein the suitable solvent is selected from the group comprising dichloromethane, dimethylformamide and the like or mixture thereof.

25. A method according to any of claims 22 to 24, wherein the suitable base is selected from the group comprising potassium carbonate, diisopropylethylamine, triethylamine, triisopropylamine and the like.

26. A method according to any of claims 22 to 25, wherein said base is used in an amount between 0.1 and 5.0 equivalents.

27. A compound obtainable by the method of any of claims 20 to 26.

28. A compound according to any of claims 1 to 19 and 27 for use as a medicament.

29. Use of a compound according to any of claims 1 to 19 and 27 as an ion channel blocker.

30. Use of a compound according to claim 29 as a blocker of an ion channel of the Kv4 family of ion-channels.

31. Use of a compound according to claim 29 as a blocker of an ion channel of the Kv1 family of ion channels.

32. Use of a compound according to claim 29 or 30 as a blocker of an ion channel of the Kv4.3 family of ion-channels.

33. Use of a compound according to claim 29 or 31 as a blocker of an ion-channel of the Kv1.5 family of ion channels.

34. Use of a compound according to any of claims 1 to 19 and 27 for the preparation of a medicament for the prevention and/or treatment of conditions or diseases associated with ion channels of the Kv4 family.

35. Use according to claim 34, wherein said conditions or diseases associated with ion channels of the Kv4 family, preferably Kv4.3 ion channels is selected from the group comprising cardiac disorders including arrhythmia, hypertension-induced heart disorders including hypertension-induced cardiac hypertrophy, disorders of the nervous system including epilepsy, stroke, spinal cord injury, traumatic brain injury, anxiety, insomnia, encephalomyelitis, Alzheimer's disease, multiple sclerosis, demyelinating disease and Parkinson's syndrome.

36. Use of a compound according to any of claims 1 to 19 and 27 for the preparation of a medicament for the prevention and/or treatment of conditions or diseases associated with ion channels of the Kv1 family.

37. Use according to claim 36, wherein said conditions or diseases associated with ion channels of the Kv1 family, preferably Kv1.5 ion channels, is selected from the group comprising cardiac disorders including arrhythmia, hypertension-induced heart disorders including hypertension-induced cardiac hypertrophy, disorders of the nervous system including epilepsy, stroke, spinal cord injury, traumatic brain injury, encephalomyelitis, anxiety, insomnia, Alzheimer's disease, multiple sclerosis, demyelinating disease and Parkinson's syndrome.

38. Use according to claim 34 or 37 for the preparation of a medicament for treating cardiac disorders.

39. Use according to claim 34 or 37 for the preparation of a medicament for treating disorders of the nervous system.

40. A pharmaceutical composition comprising a pharmaceutically acceptable excipient and a therapeutically effective amount of a compound according to any of claims 1 to 19 and 27.

41. Use of a pharmaceutical composition according to claim 40 for the treatment of conditions or diseases associated with ion channels of the Kv4 family, preferably the Kv4.3 ion channel.

42. Use according to claim 37, wherein said conditions or diseases associated with ion channels of the Kv4 family is selected from the group comprising cardiac disorders including arrhythmia, hypertension-induced heart disorders including hypertension-induced cardiac hypertrophy, disorders of the nervous system including epilepsy, stroke, spinal cord injury, traumatic brain injury, encephalomyelitis, anxiety, insomnia, Alzheimer's disease, multiple sclerosis, demyelinating disease and Parkinson's syndrome.

43. Use of a pharmaceutical composition according to claim 40 for the treatment of conditions or diseases associated with ion channels of the Kv1 family, preferably the Kv1.5 ion channel.

44. Use of a pharmaceutical composition according to claim 40 for the treatment of cardiac disorders.

45. Use of a pharmaceutical composition according to claim 40 for the treatment of disorders of the nervous system.

46. Method of treating cardiac disorders comprising administrating to an individual in need of such treatment a pharmaceutical composition according to claim 40.

47. Method of treating disorders of the nervous system comprising administrating to an individual in need of such treatment a pharmaceutical composition according to claim 40.