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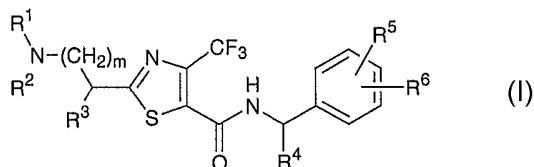
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(54) Title: AMINOALKYL THIAZOLE DERIVATIVES AS KCNQ MODULATORS



(57) Abstract: Novel aminoalkylthiazole derivatives of For-
mula I are described which are openers of KCNQ potassium
channels and are useful in the treatment of disorders respon-
sive to the opening of the KCNQ potassium channels, including
pain and migraine. (I)

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AMINOALKYL THIAZOLE DERIVATIVES AS KCNQ MODULATORS**REFERENCE TO RELATED APPLICATIONS**

5 This application claims the benefit of U.S. provisional application No. 60/435971, filed December 20, 2002.

BACKGROUND OF THE INVENTION

10 The present invention is directed to novel aminoalkylthiazole compounds which are modulators of KCNQ potassium channels and are useful in treating disorders responsive to the modulation of the potassium channels. The invention also provides pharmaceutical compositions and methods of treatment with the novel aminoalkylthiazol compounds.

15 Potassium (K^+) channels are a diverse class of ion channels and have several critical roles in cell function. One role is in neurons, where K^+ channels are responsible, in part, for determining cell excitability by contributing to membrane repolarization following depolarization, resting membrane potential, and regulation of neurotransmitter release. The M-current, measured by electrophysiology
20 recording methods and by pharmacology, has been described as a dominant conductance in controlling neuronal excitability. Pharmacological activation or suppression of M-currents by small molecules could have profound effects in controlling neuronal excitability. Recently, Wang reported that co-assembly of the
25 KCNQ2 and KCNQ3 potassium channels underlies the native M-current in neurons (Wang et al., *Science* **1998**, 282, 1890-1893).

 Activation or opening of the KCNQ channels, particularly the KCNQ2 or KCNQ2/3 channels, mutated or wild type, may be beneficial for increasing
30 hyperpolarization of neurons, thereby resulting in protection from abnormal synchronous firing during a migraine attack. This invention provides a solution to the problem of abnormal synchronous firing of neurons related to migraine headache by demonstrating that modulators, preferably openers, of KCNQ potassium channels

increase hyperpolarization of neurons. This leads to protection against abnormal synchronous neuron firing involved in migraine attacks.

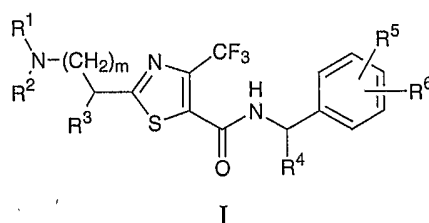
Although the symptom pattern varies among migraine sufferers, the severity
5 of migraine pain justifies a need for vigorous, yet safe and effective, treatments and
therapies for the great majority of cases. A need exists for agents that can be used to
combat and relieve migraine (and diseases similar to and mechanistically related to
migraine), as well as prevent the recurrence of migraine. Also needed are abortive
anti-migraine agents, effective in the treatment of acute migraine, as well as in the
10 prodrome phase of a migraine attack. Thus, a clear goal in the art is to discover new,
safe, nontoxic and effective anti-migraine compounds and their pharmaceutical
compositions for use in anti-migraine treatments.

Because migraine afflicts a large percentage of the population, there is a need
15 to discover compounds and agents that are useful in therapeutics and treatments, and
as components of pharmaceutical compositions, for treating the pain and discomfort
of migraine headache and other symptoms of migraine. This invention satisfies this
need by providing compounds that function as openers of the KCNQ family of
potassium ion channels and act as anti-migraine agents.

20
A number of thiazole derivatives have been disclosed. These references do
not teach or suggest the compounds of this invention. See the following: WO
01/40207 A1, JP 04128275 A2, US 5,244,867, US 4,980,363, US 5,846,990, JP
04049290 A2, WO 99/66925 A1, US 5,888,941, US 3,794,636, JP 57183768 A2, US
25 5,057,142, US 5,859,035, JP 02229190 A2, WO 98/28282 A2, WO 00/06085 A2, US
5,614,520, US 3,689,481, JP 01250379 A2, US 3,872,124, US 4,923886, WO
99/59570 A1, WO 01/10798 A1, and WO 95/19972 A1.

SUMMARY OF THE INVENTION

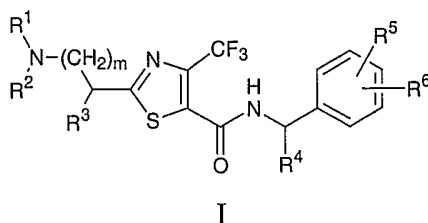
The invention encompasses novel aminoalkylthiazole compounds and related derivatives of Formula I.



The compounds are openers or activators of KCNQ potassium channels. The invention also describes pharmaceutical compositions methods of treatment of disorders sensitive to KCNQ potassium channel opening activity.

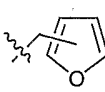
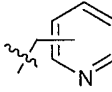
DETAILED DESCRIPTION OF THE INVENTION

The invention encompasses compounds of Formula I and related derivatives, including pharmaceutically acceptable salts and solvates,



where:

R^1 is C_{1-6} alkyl, C_{3-7} cycloalkyl, $-(CH_2)_{1-4}C_{3-7}$ cycloalkyl, $-(CH_2)_{2-4}N(C_{1-6}alkyl)_2$,

$-(CH_2)_{2-4}OC_{1-6}alkyl$, , or ;

R^2 is hydrogen, C_{1-6} alkyl, or $-(CH_2)_{2-4}OC_{1-6}alkyl$;

or where R¹ and R² taken together are -CH₂CH₂XCH₂CH₂-, where X is a chemical bond, CH₂, CHOH, NH, NCH₃, NCOCH₃, O, or S;

R³ is hydrogen or hydroxy, provided that where R³ is hydroxy, m is not 0;

5

R⁴ is hydrogen, C₁₋₆alkyl, -CH₂OH, or trifluoromethyl;

R⁵ is halogen, C₁₋₆alkyl, C₁₋₂perfluoroalkyl, C₁₋₆alkoxy, C₁₋₂perfluoroalkoxy, -N(R⁴)₂, N-morpholinyl, or pyridyl;

10

R⁶ is hydrogen, halogen, or C₁₋₆alkoxy;

m is 0 or 1.

15 “C₁₋₆ alkyl” means straight or branched chain alkyl groups such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, and *tert*-butyl. “C₁₋₆ alkoxy” means an oxygen substituted with straight or branched chain alkyl groups and includes groups such as methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, and *tert*-butoxy.

20 “KCNQ” means the family of polypeptides that have been described as KCNQ2, KCNQ3, KCNQ4, and KCNQ5 potassium channels as well as heteromultimers of different members. For example, KCNQ2/3, KCNQ2/5 and KCNQ3/5.

25 The term “pain” includes all types of acute and chronic pain, such as migraine or a migraine attack, cluster headaches, musculoskeletal pain, post-operative pain, surgical pain, inflammatory pain, neuropathic pain such as diabetic neuropathy and pain associated with cancer and fibromyalgias, chronic lower back pain, herpes neuralgia, phantom limb pain, central pain, dental pain, opioid-resistant pain, visceral
30 pain, surgical pain, bone injury pain, pain during labor and delivery, pain resulting from burns, including sunburn, post partum pain, migraine, angina pain, and genitourinary tract-related pain including cystitis. The term is also intended to include nociceptive pain or nociception.

“Therapeutically effective amount” means the amount of a compound required to elicit a meaningful patient benefit. For example, the amount of compound or composition necessary to improve a clinical parameter or ameliorate a symptom.

5

The invention includes all pharmaceutically acceptable salt forms of the compounds. Pharmaceutically acceptable salts are those in which the counter ions do not contribute significantly to the physiological activity or toxicity of the compounds and as such function as pharmacological equivalents. These salts can be made according to common organic techniques employing commercially available reagents. Some anionic salt forms include acetate, acistrate, besylate, bromide, chloride, citrate, fumarate, glucouronate, hydrobromide, hydrochloride, hydroiodide, iodide, lactate, maleate, mesylate, nitrate, pamoate, phosphate, succinate, sulfate, tartrate, tosylate, and xinofoate. Some cationic salt forms include ammonium, aluminum, benzathine, bismuth, calcium, choline, diethylamine, diethanolamine, lithium, magnesium, meglumine, 4-phenylcyclohexylamine, piperazine, potassium, sodium, tromethamine, and zinc.

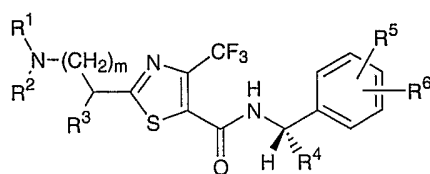
The invention also includes all solvated forms of the instant compounds, particularly hydrates. Solvates do not contribute significantly to the physiological activity or toxicity of the compounds and as such function as pharmacological equivalents. Solvates may form in stoichiometric amounts or may form from adventitious solvent or a combination of both. One type of solvate is hydrate, and some hydrated forms include monohydrate, hemihydrate, and dihydrate.

25

Some of the compounds of the invention possess asymmetric carbon atoms, such as the carbon atom bearing R¹ in Formula Id. The invention includes all stereoisomeric forms. Stereoisomeric mixtures of the compounds and related intermediates can be separated into individual isomers according to methods commonly known in the art.

30

6



Id

One aspect of the present invention are compounds of Formula I where m is

5 1.

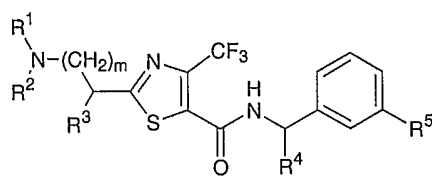
Another aspect of the invention are compounds of Formula I where R³ is hydrogen.

10 Another aspect of the invention are compounds of Formula I where R³ is hydroxy and m is 1.

Another aspect of the invention are compounds of Formula I where R⁴ is methyl.

15

Another aspect of the invention are compounds of Formula I where the structure is that of Formula Ie.



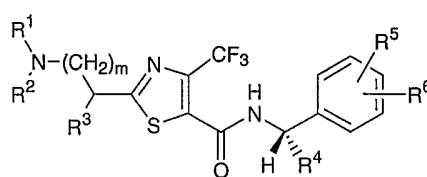
Ie

20

Another aspect of the invention are compounds of Formula I where the structure has the stereochemical configuration of Formula Id.

25

7



Id

Some compounds of the invention include the following:

5

(1) 2-[2-(4-morpholinyl)ethyl]-N-[1-[3-(3-pyridinyl)phenyl]ethyl]-4-(trifluoromethyl)-5-thiazolecarboxamide;

10

(2) N-[1-[3-(dimethylamino)phenyl]ethyl]-2-[2-(1-pyrrolidinyl)ethyl]-4-(trifluoromethyl)-5-thiazolecarboxamide;

(3) 2-[2-(1-pyrrolidinyl)ethyl]-4-(trifluoromethyl)-N-[1-[3-(trifluoromethyl)phenyl]ethyl]-5-thiazolecarboxamide;

15

(4) 2-[2-[(2-furanylmethyl)methylamino]ethyl]-N-[(1*S*)-1-[3-(4-morpholinyl)phenyl]ethyl]-4-(trifluoromethyl)-5-thiazolecarboxamide;

(5) 2-[2-[(2-furanylmethyl)methylamino]ethyl]-N-[1-[3-(3-pyridinyl)phenyl]ethyl]-4-(trifluoromethyl)-5-thiazolecarboxamide;

20

(6) 2-[2-(1-pyrrolidinyl)ethyl]-N-[1-[3-(trifluoromethoxy)phenyl]ethyl]-4-(trifluoromethyl)-5-thiazolecarboxamide;

25

(7) 2-[2-[(2-furanylmethyl)methylamino]ethyl]-N-[1-[3-(trifluoromethoxy)phenyl]ethyl]-4-(trifluoromethyl)-5-thiazolecarboxamide;

(8) 2-[2-(diethylamino)ethyl]-N-[1-[3-(trifluoromethoxy)phenyl]ethyl]-4-(trifluoromethyl)-5-thiazolecarboxamide;

- (9) 2-[2-(diethylamino)ethyl]-N-[1-[3-(dimethylamino)phenyl]ethyl]-4-(trifluoromethyl)-5-thiazolecarboxamide;
- (10) 2-[2-[ethyl(4-pyridinylmethyl)amino]ethyl]-4-(trifluoromethyl)-N-
5 [1-[3-(trifluoromethyl)phenyl]ethyl]-5-thiazolecarboxamide;
- (11) 2-[2-(4-thiomorpholinyl)ethyl]-4-(trifluoromethyl)-N-[1-[3-(trifluoromethyl)phenyl]ethyl]-5-thiazolecarboxamide;
- 10 (12) 2-[2-[[2-(dimethylamino)ethyl]methylamino]ethyl]-N-[1-[3-(trifluoromethoxy)phenyl]ethyl]-4-(trifluoromethyl)-5-thiazolecarboxamide;
- (13) 2-[2-[[2-(dimethylamino)ethyl]methylamino]ethyl]-4-(trifluoromethyl)-N-[1-[3-(trifluoromethyl)phenyl]ethyl]-5-
15 thiazolecarboxamide;
- (14) 2-[2-(4-methyl-1-piperazinyl)ethyl]-N-[1-[3-(trifluoromethoxy)phenyl]ethyl]-4-(trifluoromethyl)-5-thiazolecarboxamide;
- 20 (15) 2-[2-(1-piperidinyl)ethyl]-N-[1-[3-(trifluoromethoxy)phenyl]ethyl]-4-(trifluoromethyl)-5-thiazolecarboxamide;
- (16) N-[1-[3-(dimethylamino)phenyl]ethyl]-2-[2-(1-piperidinyl)ethyl]-4-(trifluoromethyl)-5-thiazolecarboxamide;
25
- (17) 2-[2-(1-piperidinyl)ethyl]-4-(trifluoromethyl)-N-[1-[3-(trifluoromethyl)phenyl]ethyl]-5-thiazolecarboxamide;
- (18) N-[(1S)-1-[3-(4-morpholinyl)phenyl]ethyl]-2-[2-(1-piperidinyl)ethyl]-4-(trifluoromethyl)-5-thiazolecarboxamide;
30
- (19) 2-[2-(4-hydroxy-1-piperidinyl)ethyl]-N-[1-[3-(trifluoromethoxy)phenyl]ethyl]-4-(trifluoromethyl)-5-thiazolecarboxamide;

- (20) 2-[2-(4-hydroxy-1-piperidiny)ethyl]-4-(trifluoromethyl)-N-[1-[3-(trifluoromethyl)phenyl]ethyl]-5-thiazolecarboxamide;
- (21) 2-[2-[(cyclopropylmethyl)propylamino]ethyl]-N-[1-[3-(trifluoromethoxy)phenyl]ethyl]-4-(trifluoromethyl)-5-thiazolecarboxamide;
- (22) 2-[2-[(cyclopropylmethyl)propylamino]ethyl]-N-[1-[3-(dimethylamino)phenyl]ethyl]-4-(trifluoromethyl)-5-thiazolecarboxamide;
- (23) 2-[2-[(cyclopropylmethyl)propylamino]ethyl]-4-(trifluoromethyl)-N-[1-[3-(trifluoromethyl)phenyl]ethyl]-5-thiazolecarboxamide;
- (24) 2-[2-(diethylamino)ethyl]-N-[(1*S*)-1-[3-(3-pyridinyl)phenyl]ethyl]-4-(trifluoromethyl)-5-thiazolecarboxamide;
- (25) 2-[2-(1-piperidiny)ethyl]-N-[(1*S*)-1-[3-(3-pyridinyl)phenyl]ethyl]-4-(trifluoromethyl)-5-thiazolecarboxamide;
- (26) 2-[2-[(1-ethylpropyl)amino]ethyl]-N-[1-[3-(trifluoromethoxy)phenyl]ethyl]-4-(trifluoromethyl)-5-thiazolecarboxamide;
- (27) 2-[2-[(1-ethylpropyl)amino]ethyl]-4-(trifluoromethyl)-N-[1-[3-(trifluoromethyl)phenyl]ethyl]-5-thiazolecarboxamide;
- (28) 2-[2-[(2-furanylmethyl)amino]ethyl]-N-[(1*S*)-1-[3-(3-pyridinyl)phenyl]ethyl]-4-(trifluoromethyl)-5-thiazolecarboxamide;
- (29) 2-[2-(cyclopentylamino)ethyl]-N-[1-[3-(trifluoromethoxy)phenyl]ethyl]-4-(trifluoromethyl)-5-thiazolecarboxamide;
- (30) 2-[2-(cyclopentylamino)ethyl]-N-[(1*S*)-1-[3-(3-pyridinyl)phenyl]ethyl]-4-(trifluoromethyl)-5-thiazolecarboxamide;

- (31) 2-[2-[bis(2-methoxyethyl)amino]ethyl]-N-[1-[3-(trifluoromethoxy)phenyl]ethyl]-4-(trifluoromethyl)-5-thiazolecarboxamide;
- (32) 2-[2-[bis(2-methoxyethyl)amino]ethyl]-4-(trifluoromethyl)-N-[1-[3-(trifluoromethyl)phenyl]ethyl]-5-thiazolecarboxamide;
- (33) 2-[2-[bis(2-methoxyethyl)amino]ethyl]-N-[(1*S*)-1-[3-(3-pyridinyl)phenyl]ethyl]-4-(trifluoromethyl)-5-thiazolecarboxamide;
- (34) 2-[2-(4-morpholinyl)ethyl]-N-[(1*S*)-1-[3-(4-morpholinyl)phenyl]ethyl]-4-(trifluoromethyl)-5-thiazolecarboxamide;
- (35) N-[1-[3-(dimethylamino)phenyl]ethyl]-2-[2-(4-thiomorpholinyl)ethyl]-4-(trifluoromethyl)-5-thiazolecarboxamide;
- (36) 2-[2-[[2-(dimethylamino)ethyl]methylamino]ethyl]-N-[1-[3-(dimethylamino)phenyl]ethyl]-4-(trifluoromethyl)-5-thiazolecarboxamide;
- (37) 2-[2-(4-methyl-1-piperazinyl)ethyl]-N-[(1*S*)-1-[3-(4-morpholinyl)phenyl]ethyl]-4-(trifluoromethyl)-5-thiazolecarboxamide;
- (38) 2-[2-(diethylamino)ethyl]-N-[1-[3-(trifluoromethoxy)phenyl]ethyl]-4-(trifluoromethyl)-5-thiazolecarboxamide;
- (39) 2-[2-(4-thiomorpholinyl)ethyl]-4-(trifluoromethyl)-N-[1-[3-(trifluoromethyl)phenyl]ethyl]-5-thiazolecarboxamide;
- (40) 2-[1-hydroxy-2-(1-piperidinyl)ethyl]-N-[1-[3-(trifluoromethoxy)phenyl]ethyl]-4-(trifluoromethyl)-5-thiazolecarboxamide;
- (41) 2-[1-hydroxy-2-(1-pyrrolidinyl)ethyl]-4-(trifluoromethyl)-N-[1-[3-(trifluoromethyl)phenyl]ethyl]-5-thiazolecarboxamide;

- (42) 2-[2-[(2-furanylmethyl)methylamino]-1-hydroxyethyl]-4-(trifluoromethyl)-N-[1-[3-(trifluoromethyl)phenyl]ethyl]-5-thiazolecarboxamide;
- 5 (43) 2-[2-[(cyclopropylmethyl)propylamino]-1-hydroxyethyl]-N-[1-[3-(trifluoromethoxy)phenyl]ethyl]-4-(trifluoromethyl)-5-thiazolecarboxamide;
- (44) 2-[2-(diethylamino)-1-hydroxyethyl]-N-[(1S)-1-[3-(4-morpholinyl)phenyl]ethyl]-4-(trifluoromethyl)-5-thiazolecarboxamide;
- 10 (45) 2-[2-(diethylamino)-1-hydroxyethyl]-N-[(1S)-1-[3-(3-pyridinyl)phenyl]ethyl]-4-(trifluoromethyl)-5-thiazolecarboxamide;
- (46) 2-[1-hydroxy-2-(4-morpholinyl)ethyl]-N-[1-[3-
- 15 (trifluoromethoxy)phenyl]ethyl]-4-(trifluoromethyl)-5-thiazolecarboxamide;
- (47) 2-[1-hydroxy-2-(4-morpholinyl)ethyl]-4-(trifluoromethyl)-N-[1-[3-(trifluoromethyl)phenyl]ethyl]-5-thiazolecarboxamide;
- (48) 2-[1-hydroxy-2-(4-methyl-1-piperazinyl)ethyl]-4-(trifluoromethyl)-N-[1-[3-(trifluoromethyl)phenyl]ethyl]-5-thiazolecarboxamide;
- 20 (49) 2-[1-hydroxy-2-(4-methyl-1-piperazinyl)ethyl]-N-[(1S)-1-[3-(4-morpholinyl)phenyl]ethyl]-4-(trifluoromethyl)-5-thiazolecarboxamide;
- 25 (50) 2-[1-hydroxy-2-(4-methyl-1-piperazinyl)ethyl]-N-[(1S)-1-[3-(3-pyridinyl)phenyl]ethyl]-4-(trifluoromethyl)-5-thiazolecarboxamide;
- (51) 2-[1-hydroxy-2-(1-piperidinyl)ethyl]-4-(trifluoromethyl)-N-[1-[3-
- 30 (trifluoromethyl)phenyl]ethyl]-5-thiazolecarboxamide;
- (52) 2-[1-hydroxy-2-(1-pyrrolidinyl)ethyl]-N-[1-[3-(trifluoromethoxy)phenyl]ethyl]-4-(trifluoromethyl)-5-thiazolecarboxamide;

(53) N-[1-[3-(dimethylamino)phenyl]ethyl]-2-[1-hydroxy-2-(1-pyrrolidinyl)ethyl]-4-(trifluoromethyl)-5-thiazolecarboxamide;

(54) 2-[1-hydroxy-2-(1-pyrrolidinyl)ethyl]-N-[(1S)-1-[3-(4-morpholinyl)phenyl]ethyl]-4-(trifluoromethyl)-5-thiazolecarboxamide;

(55) 2-[2-[(cyclopropylmethyl)propylamino]-1-hydroxyethyl]-4-(trifluoromethyl)-N-[1-[3-(trifluoromethyl)phenyl]ethyl]-5-thiazolecarboxamide; and

(56) 2-[2-(4-acetyl-1-piperazinyl)-1-hydroxyethyl]-4-(trifluoromethyl)-N-[1-[3-(trifluoromethyl)phenyl]ethyl]-5-thiazolecarboxamide;

and pharmaceutically acceptable salts and solvates of these compounds.

Synthetic Methods

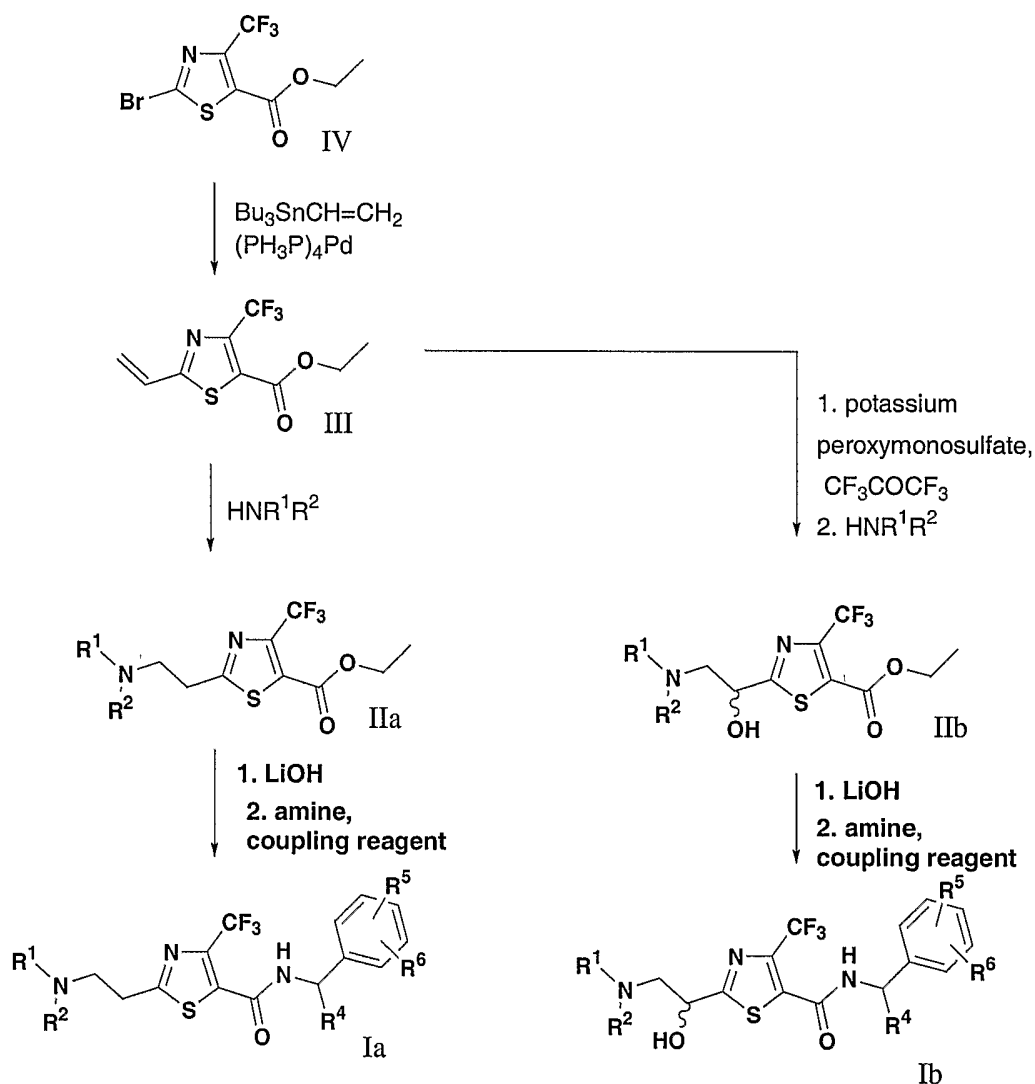
The general procedures used to synthesize intermediates and the compounds of Formula I are illustrated in Reaction Scheme 1-2 and are described in detail in the Specific Embodiments section. Reasonable variations of the described procedures, which would be evident to one skilled in the art, are intended to be within the scope of the present invention.

As illustrated in Scheme 1, 2-Bromothiazole **IV** is coupled with vinyltributyltin under Stille reaction conditions to form vinyl thiazole **III**. Treatment of **III** directly with various amines of Formula HNR^1R^2 provides a variety of aminoethylthiazoles of structure **IIa**. Hydrolysis of the ester moiety of **IIa** followed by amination provides phenylalkylamide compounds of structure **Ia**, which represent a subgenus of Formula I compounds.

Alternatively, **III** can be epoxidized with potassium peroxymonosulfate (OXONE) followed by treatment with an amine of Formula HNR^1R^2 to form aminoethylthiazoles of structure **IIb**. Hydrolysis of the ester moiety of **IIb** followed

by amination in the same manner as that for converting **IIa** provides phenylalkylamide compounds of structure **Ib**, which represent a second subgenus of Formula I compounds.

5 Scheme 1.

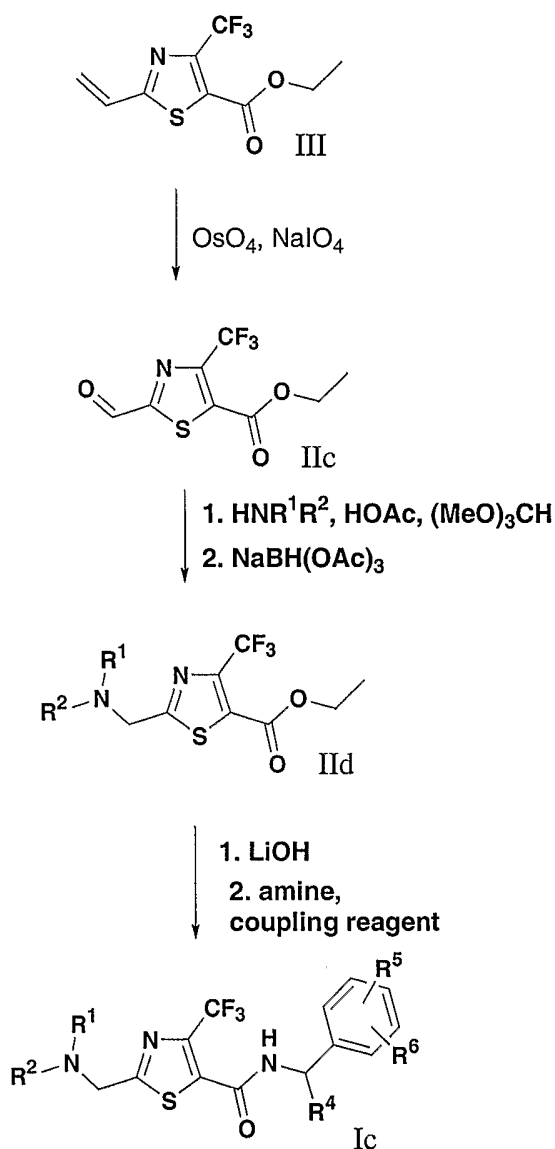


Scheme 2 illustrates a method for preparing other compounds of Formula I.

- 10 Vinyl thiazole **III** can be converted to aldehyde **IIc** by ozonolysis. Reductive amination generates compounds of structure **IId**. Transformation of the ester moiety into an amide as described above produces Formula **Ic** compounds.

14

Scheme 2.



Biological Methods

5

KCNQPotassium (K⁺) channels are structurally and functionally diverse families of K⁺-selective channel proteins which are ubiquitous in cells, indicating their central importance in regulating a number of key cell functions [Rudy, B., Neuroscience, 25: 729-749 (1988)]. While widely distributed as a class, K⁺ channels are differentially distributed as individual members of this class or as families. [Gehlert, D.R., et al., Neuroscience, 52: 191-205 (1993)]. In general, activation of K⁺ channels in cells, and particularly in excitable cells such as neurons and muscle

10

cells, leads to hyperpolarization of the cell membrane, or in the case of depolarized cells, to repolarization. In addition to acting as an endogenous membrane voltage clamp, K⁺ channels can respond to important cellular events such as changes in the intracellular concentration of ATP or the intracellular concentration of calcium

5 (Ca²⁺). The central role of K⁺ channels in regulating numerous cell functions makes them particularly important targets for therapeutic development. [Cook, N.S., Potassium channels: Structure, classification, function and therapeutic potential. Ellis Horwood, Chichester (1990)]. One class of K⁺ channels, the KCNQ family exemplified by KCNQ2, KCNQ2/3 heteromultimers, and KCNQ5, is regulated by

10 transmembrane voltage and plays a potentially important role in the regulation of neuronal excitability [Biervert, C., et al., Science, 279: 403-406 (1998); Lerche, C. et al., J. Biol. Chem. 275:22395-22400 (2000); Wang, H. et al., Science, 282:1890-1893 (1998)].

15 An opener of KCNQ channels, such as the KCNQ2 and KCNQ2/3 channel opener retigabine, exerts its cellular effects by increasing the open probability of these channels [Main J., Mol Pharmacol 58(2):253-62 (2000); Wickenden, A. et al., Mol. Pharm. 58:591-600 (2000)]. This increase in the opening of individual KCNQ channels collectively results in the hyperpolarization of cell membranes, particularly

20 in depolarized cells, produced by significant increases in whole-cell KCNQ-mediated conductance.

Thallium Flux Assay for KCNQ channel Openers. The thallium assay is a modification of that published by Weaver and is referenced in its entirety (Weaver,

25 C. D. WO 02/31508, 2002).

Approximately 20,000 cells/well of an HEK-293 cell line stably transfected with one of the members of the KCNQ family were plated into clear-bottom, black-walled, poly-D-lysine coated, 384 well assay plates in 20 µl/well of low chloride

30 plating medium. Low chloride plating medium was composed of the following: sodium gluconate, 109 mM; potassium gluconate, 5.4 mM; hemi-calcium gluconate, 3.6 mM; magnesium sulfate, 0.8 mM; sodium bicarbonate, 26.2 mM; sodium

phosphate monobasic, 1.2 mM; glutamine, 2 mM; glucose, 5 mM; 4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid (HEPES) (pH 7.3) 10 mM, MEM vitamin solution (10 x concentration of vitamins, Gibco/LifeTechnologies 11120-052) and MEM amino acid solution (1 x concentration of amino acids,
5 Gibco/LifeTechnologies 11130-051).

Following overnight incubation in a 5% CO₂ incubator at 37 °C, the cells in the plates were loaded with 20 µl/well of a dye loading solution containing the commercially available thallium-sensitive fluorescent dye BTC-AM, the
10 acetomethoxy ester of BTC (see US Patent 5,501,980) (2 µM) and pluronic acid F-127 (Molecular Probes P 6867) (0.02% w/v) in chloride free assay buffer. Chloride free assay buffer was composed of the following: sodium gluconate, 140 mM; potassium gluconate, 2.5 mM; hemi-calcium gluconate, 6 mM; hemi-magnesium gluconate, 2 mM; glucose, 5 mM; HEPES (pH 7.3), 10 mM.

15

Following incubation in the dye loading solution for from 45-90 min at room temperature, the dye loading solution was removed by aspiration and replaced with 40 µl/well of chloride free assay buffer.

20 Prior to addition to cell plates, test compound and standard compounds were dissolved in DMSO to 3 mM concentration. Compounds were then diluted from the 3 mM stock to 100-fold over the final assay concentration in DMSO. Finally, compounds in DMSO were diluted from 100-fold over the final assay concentration to 5-fold over the final assay concentration in chloride free assay buffer.

25

Ten µl/well of compounds at 5-fold over the final assay concentration were then added to the cell plates. This represents a 1:5 dilution, yielding the final test concentration. The wells used for test compounds were A1-P20. Wells A21-P22 contained a standard opener and a maximally efficacious concentration (positive
30 control). Wells A23-P24 contained chloride free assay buffer containing 1% DMSO (negative control).

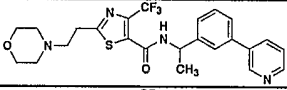
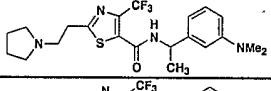
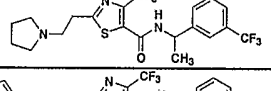
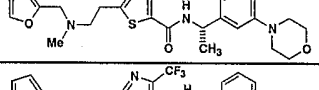
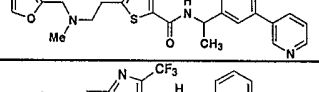
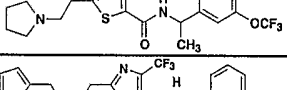
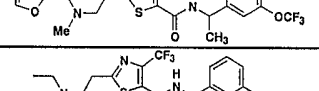
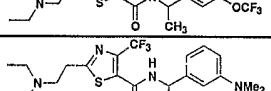
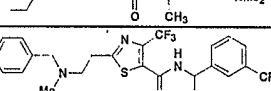
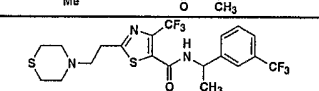
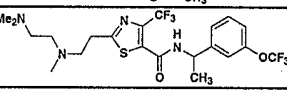
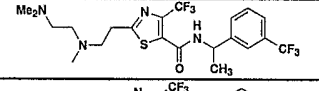
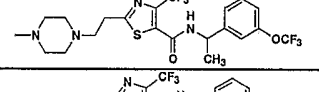
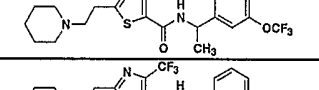
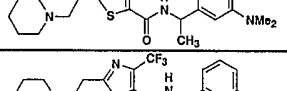
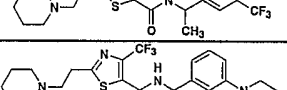
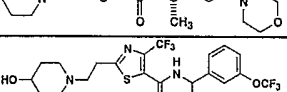
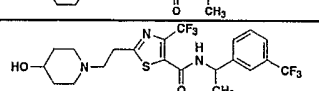
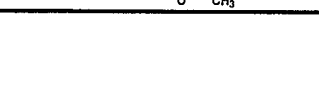
Following addition of test compounds, the plates were loaded onto the Molecular Devices FLIPR. The 488 nm line of the argon laser was used to excite the BTC and the emission filter was a 540(+/-30) nm. Images were collected at 1Hz. Ten seconds of baseline were collected and then the FLIPR was used to add 13 μ l/well of a stimulus buffer composed of 7.5 mM Ti_2SO_4 in chloride free assay buffer. Images were collected for an additional 60 seconds.

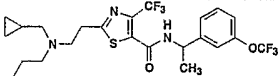
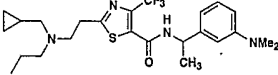
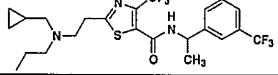
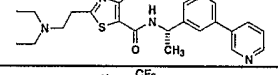
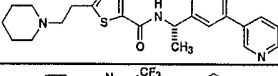
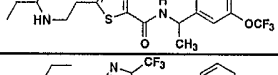
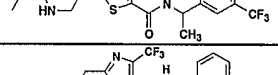
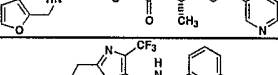
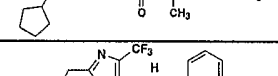
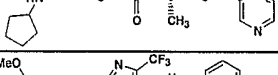
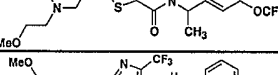
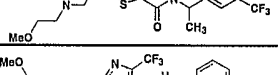
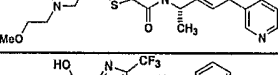
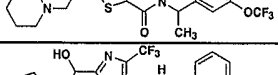
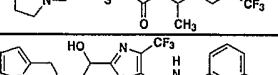
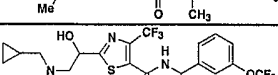
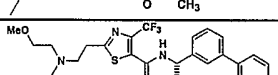
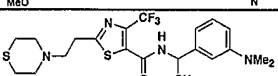
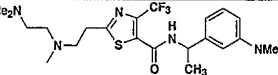
For data analysis, the amplitude of the average of the negative controls was subtracted from all wells. The amplitudes of the test compounds were then compared to the value of four standard deviations of the negative control wells. The lowest concentration of a test compound sufficient to generate a signal amplitude greater than or equal to four standard deviations from the amplitude of the negative controls was defined as the minimal active concentration.

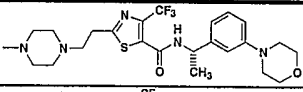
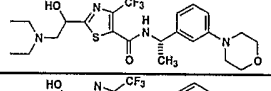
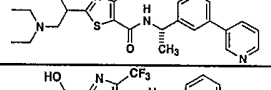
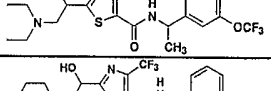
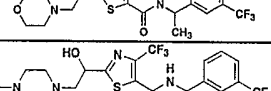
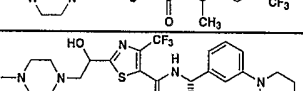
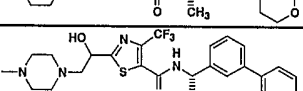
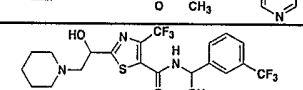
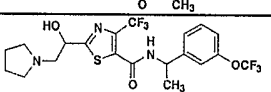
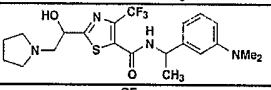
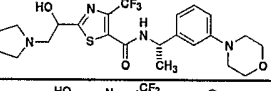
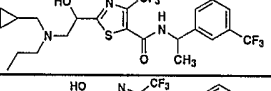
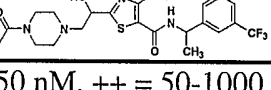
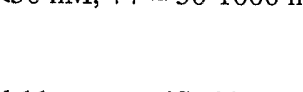
For generating EC_{50} values, compounds were serially diluted in 1:3 volume increments to produce a 10 point concentration series. EC_{50} values were calculated by fitting the resulting amplitudes to a single-site logistic equation. EC_{50} was defined as the concentration of test compound required to yield 50% of the maximal response. Maximal response (Maximal opening) was the largest signal amplitude divided by the negative control amplitude generated by any concentration of a test compound.

Table 1 describes the effect of representative Formula I compounds on KCNQ channels. Example numbers refer to the examples described in the specific embodiments section. Examples 62 and 63 refer to 2-[2-(diethylamino)ethyl]-4-(trifluoromethyl)-N-[1-[3-(trifluoromethoxy)phenyl]ethyl]-5-thiazolecarboxamide and 2-[2-(4-thiomorpholinyl)ethyl]-4-(trifluoromethyl)-N-[1-[3-(trifluoromethyl)phenyl]ethyl]-5-thiazolecarboxamide.

Table 1.

Example	Structure	Min conc. response (μM)	EC ₅₀ (μM)
8		10	+
9		10	+
10		30	+
11		30	+
12		3	+++
13		10	+
14		3	+++
15		0.3	++
16		0.3	+
17		3	+
18		3	++
19		3	+
20		30	+
21		0.3	+
22		0.3	++
23		0.3	+
24		0.3	+
25		3	+
26		10	+
27		30	+

Example	Structure	Min conc. response (μM)	EC ₅₀ (μM)
28		0.3	+++
29		3	+
30		3	+++
31		0.3	+
32		3	+
33			+
34		3	+
35		10	+
36		30	+
37		30	+
38		3	+
39		3	+
40		30	++
41		30	+
42		3	++
43		3	++
44		3	++
45		3	na
46		3	na
47		0.3	na

Example	Structure	Min conc. response (μM)	EC ₅₀ (μM)
48		3	na
49		30	na
50		0.3	na
51		0.3	na
52		10	na
53		30	na
54		0.3	na
55		0.3	na
56		30	na
57		3	na
58		0.3	na
59		30	na
60		3	na
61		10	na

EC₅₀ values: +++ = <50 nM, ++ = 50-1000 nM, + = 1000-20000 nM.

Examples 8 and 11 were verified in a patch-clamp assay measuring the effect of compounds on the current of KCNQ channels.

5

KCNQ Patch-clamp. Whole-cell patch-clamp recordings were made from an HEK 293 stable cell line expressing mKCNQ2 channels, maintained in culture for 1-2 days. Patch pipettes had initial resistances of 2.5-4 M Ω . Currents were recorded with an EPC-9 amplifier (HEKA, Lambrecht, Germany) controlled with software (Pulse, HEKA) run on a standard lab PC. Series resistance compensation was used

10

during current recording, and set at 80%. The series resistance (R) and cell capacitance (C) were determined electronically by subtracting the capacitive currents at the onset and offset of a 5mV voltage step. The cancellation of whole-cell capacitive transients was virtually complete in all cells. Analog current signals were
5 low-pass filtered at 2.9kHz using a four-pole Bessel filter -3dB) and stored on a local network server computer at a sampling rate of 1.5kHz. All recordings were performed at room temperature (20-22°C). The pipette solution contained (mM) : KCl, 150; CaCl₂, 2.5; EGTA, 5; MgCl₂, 1; HEPES, 10; pH to 7.3 with KOH, and Osmolality of 290-300 mOsm. The extracellular solution contained (mM) : NaCl,
10 140; KCl, 2.5; CaCl₂, 2.5; MgCl₂, 1; glucose, 10; HEPES, 10; pH to 7.3 with NaOH, and Osmolality of 305-310 mOsm.

For analysis of agents effects on mKCNQ2 currents, the raw current records were displayed on the digital oscilloscope of the Pulse software application.
15 Concentration response data were generated by measuring the difference in the steady-state amplitude of current in the presence of compound at the end of a 600 ms voltage-clamp step from a holding potential of -80mV. The concentration-response data were fitted with Hill-type equations:

20
$$I = I_{\max}/(1+EC_{50}/[A]^{nH}),$$

where I is the steady-state current at a given concentration of agonist [A]; and I_{max}, EC₅₀ and nH are parameters estimated from the curve fit. In some cases the concentration-response data were fitted with equations consisting of the sum of two
25 Hill-type components. Current-voltage (I/V) relationships for agonist-evoked currents were obtained by performing 600 ms voltage steps (-110 mV to +40 mV) in the absence and presence of agonist. The EC₅₀ example 15 was 3.56 μM; the EC₅₀ of example 18 was 1.23 μM.

Pharmaceutical composition and methods of treatment

Another aspect of this invention includes pharmaceutical compositions comprising at least one compound of Formula I in combination with a
5 pharmaceutical adjuvant, carrier or diluent.

A further aspect of this invention relates to a method of treatment or prevention of disorders responsive to opening of KCNQ potassium channels in a mammal in need thereof, which comprises administering to said mammal a
10 therapeutically effective amount of a compound of Formula I. The compounds of Formula I should be useful in the treatment of treatment of migraine or a migraine attack, cluster headaches, bipolar disorder, convulsions, mania, acute mania, epilepsy, anxiety, depression, schizophrenia, functional bowel disorders, stroke, traumatic brain injury, multiple sclerosis, neurodegenerative disorders or alleviating pain such
15 as musculoskeletal pain, post operative pain, surgical pain, inflammatory pain, neuropathic pain such as diabetic neuropathy and pain associated with cancer and fibromyalgia.

For therapeutic use, the compounds of Formula I will normally be
20 administered as pharmaceutical compositions comprising as an active ingredient at least one compound in association with a pharmaceutically acceptable solid or liquid carrier and, optionally, with pharmaceutically acceptable adjuvants and excipients employing standard and conventional techniques.

25 The pharmaceutical compositions include suitable dosage forms for oral, parenteral (including subcutaneous, intramuscular, intradermal and intravenous) bronchial or nasal administration. If a solid carrier is used, the preparation may be tableted, placed in a hard gelatin capsule in powder or pellet form, or in the form of a troche or lozenge. The solid carrier may contain conventional excipients such as
30 binding agents, fillers, tableting lubricants, disintegrants, wetting agents and the like. The tablet may, if desired, be film coated by conventional techniques. If a liquid carrier is employed, the preparation may be in the form of a syrup, emulsion, soft gelatin capsule, sterile vehicle for injection, an aqueous or non-aqueous liquid

suspension, or may be a dry product for reconstitution with water or other suitable vehicle before use. Liquid preparations may contain conventional additives such as suspending agents, emulsifying agents, wetting agents, non-aqueous vehicle (including edible oils), preservatives, as well as flavoring and/or coloring agents. For
5 parenteral administration, a vehicle normally will comprise sterile water, at least in large part, although saline solutions, glucose solutions and like may be utilized. Injectable suspensions also may be used, in which case conventional suspending agents may be employed. Conventional preservatives, buffering agents and the like also may be added to the parenteral dosage forms. Aerosol compositions can be
10 formed with pharmaceutically accepted propellants. The pharmaceutical compositions are prepared by conventional techniques and are normally formulated in unit doses. The unit dose depends on the composition and can range from about 0.01 mg to about 1000 mg. Some unit doses for solid compositions are 1 mg, 10, mg, 100 mg, and 1000 mg. Some unit doses for liquid compositions are 0.01 mg/mL, 0.1
15 mg/mL, 1 mg/mL, 10 mg/mL, and 100 mg/mL.

A suitable dose of a compound of Formula I or a related pharmaceutical composition for a mammal, including man, is about 0.01 mg/kg to about 100 mg/kg body weight daily of active ingredient. For parenteral administration, the dose may
20 be in the range of about 0.1 mg/kg to about 10 mg/kg body weight for intravenous administration. For oral administration, the dose may be in the range about 0.1 mg/kg to about 100 mg/kg body weight. The active ingredient can be administered continuously or in equal doses from one to four times a day. Usually a small dose is administered, and the dosage is gradually increased until the optimal dosage for the
25 patient is determined. The specific dosing regimen, however, must be carefully monitored and adjusted using sound medical judgement.

DESCRIPTION OF SPECIFIC EMBODIMENTS

30 Unless otherwise stated, solvents and reagents were used directly as obtained from commercial sources, and reactions were performed under a nitrogen atmosphere. Flash chromatography was conducted on Silica gel 60 (0.040-0.063 particle size; EM Science supply). ¹H NMR spectra were recorded on a Bruker

DRX-500f at 500 MHz; a Bruker DPX-300B at 300 MHz; or a Varian Gemini 300 at 300 MHz. The chemical shifts were reported in ppm on the δ scale relative to δ TMS = 0. The following internal references were used for the residual protons in the following solvents: CDCl_3 (δ_{H} 7.26), CD_3OD (δ_{H} 3.30) and $\text{DMSO}-d_6$ (δ_{H} 2.50).

5 Standard acronyms were employed to describe the multiplicity patterns: s (singlet), d (doublet), t (triplet), q (quartet), quint (quintuplet), m (multiplet), br (broad), app (apparent). The coupling constant (J) is in hertz. LC/MS was performed on a Shimadzu LC-10AS liquid chromatograph using a SPD-10AV UV-VIS detector with Mass Spectrometry data determined using a Micromass LC Platform in positive
10 electrospray ionization mode (ESI+). Mass Spectrometry (MS) data was obtained using a standard flow injection technique on a Micromass LC Platform in positive electrospray ionization mode (ESI+) unless otherwise noted. High resolution mass spectrometry (HRMS) data was obtained using a standard flow injection technique on a Finnigan MAT 900 mass spectrometer in electrospray ionization (ESI) mode. The
15 analytical reverse phase HPLC method is as follows unless otherwise noted:
Method: 3 min run is 2 min gradient from 100%A to 100%B followed by 1 min at 100%B; solvent A: 10% MeOH/90% H_2O /0.1 % TFA; solvent B: 90% MeOH/10% H_2O /0.1 % TFA; Column: XTERRA 3.0 x 50 mm S7. Preparative reverse phase HPLC was performed on a Shimadzu LC-8A automated preparative HPLC system
20 with detector (SPD-10AV UV-VIS) wavelength and solvent systems (A and B) the same as above except where otherwise noted.

EXAMPLE 1

Preparation of Intermediate IV

25 **2-Amino-4-Trifluoromethyl-thiazole-5-carboxylic acid ethyl ester.** To a solution of ethyl 2-chloro-4,4,4-trifluoroacetoacetate (50.0 g, 230 mmol) in ethanol (250 mL) was added thiourea (17.5 g, 230 mmol). The resulting mixture was heated at reflux for 3 h, at which time TLC indicated a complete reaction. The mixture was
30 concentrated *in vacuo*, and the residue dissolved in ether. The organic layer was successively washed with aqueous sodium bicarbonate, and brine, then dried over magnesium sulfate and concentrated *in vacuo*. The resulting solid was recrystallized

with ethyl acetate and hexanes to give white crystals (41.64 g, 75% yield). ¹H NMR (MeOD-d₄, 300MHz): δ 4.26 (q, *J* = 7.1 Hz, 2H), 1.31 (t, *J* = 7.1 Hz, 3H).

2-Bromo-4-Trifluoromethyl-thiazole-5-carboxylic acid ethyl ester (IV). To a
5 solution of the aminothiazole (40.0 g, 167 mmol) in 48% HBr (300 mL) at 0 °C was
added a 0 °C solution of sodium nitrite (17.0 g, 250 mmol) in water (200 mL)
dropwise over 1 h. The mixture was stirred at 0 °C for an additional 0.5 h, at which
time a 0 °C solution of CuBr (23.9 g, 167 mmol) in 48% HBr (200 mL) over 0.5 h.
The mixture was stirred for an additional 0.5 h at 0 °C, then for 2 h at room
10 temperature. The mixture was then extracted three times with methylene chloride.
The combined organic extracts were then dried over magnesium sulfate, filtered, and
concentrated *in vacuo*. The product was purified by chromatography (SiO₂, Hexane
to 2.5 % EtOAc/Hexane) to yield pure **IV** (47.0 g, 93 % yield). ¹H NMR (CDCl₃,
300MHz): δ 4.40 (q, *J* = 7.1 Hz, 2H), 1.38 (t, *J* = 7.1 Hz, 3H).

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EXAMPLE 2

Preparation of Intermediates of Formula III

20 **4-Trifluoromethyl-2-vinyl-thiazole-5-carboxylic acid ethyl ester (III).** To a
solution of thiazole **IV** (17.4 g, 57.3 mmol) in toluene (150 mL) was added
tetrakis(triphenylphosphine)palladium(0) (1.32 g, 1.14 mmol), tributyl(vinyl)tin (18.4
mL, 63.0 mmol), and 2,6-di-*t*-butyl-4-methyl phenol (catalytic). This mixture was
stirred at 120 °C in a sealed tube for 25 min. The mixture was then allowed to come
25 to 25 °C. Ethyl acetate (250 mL) was added and the mixture was washed with 1 N
aqueous NaOH (2 x 150 mL), saturated aqueous NaCl (1 x 150 mL), dried over
MgSO₄ and concentrated *in vacuo* to give a brown oil. Purification by flash
chromatography (silica, 0-10% ethyl acetate/hexane) gave the 2-vinyl thiazole **III**
(11.0 g, 76%) as a yellow oil. ¹H NMR (CDCl₃, 300 MHz): δ 6.88 (dd, *J* = 11.0,
30 17.6 Hz, 1H), 6.20 (d, *J* = 17.6 Hz, 1H), 5.74 (d, *J* = 11.0 Hz, 1H), 4.38 (q, *J* = 7.2
Hz, 2H), 1.37 (t, *J* = 7.1 Hz, 3H).

EXAMPLE 3Preparation of Intermediates of Formula IIa

General procedure for amination of intermediate III into intermediate IIa. To a solution of 2-vinyl thiazole **III** (400 mg, 1.59 mmol) in ethanol (4mL) was added amine (167 μ L, 1.91 mmol). This mixture was stirred at 25 °C for 1 h. The mixture was then concentrated *in vacuo*. Purification by flash chromatography (silica, 0-10% methanol/chloroform) gave thiazole **IIa**.

EXAMPLE 4

2-(2-Morpholin-4-yl-ethyl)-4-trifluoromethyl-thiazole-5-carboxylic acid ethyl ester. Prepared according to the method of example 3. Isolated as a brown oil (50%). ^1H NMR (CDCl_3 , 300 MHz): δ 4.38 (q, $J = 7.2$ Hz, 2H), 3.80 (t, $J = 4.8$ Hz, 4H), 3.18 (t, $J = 6.4$ Hz, 2H), 2.72 (t, $J = 6.2$ Hz, 2H), 2.55 (t, $J = 4.4$ Hz, 4H), 1.37 (t, $J = 7.0$ Hz, 3H).

EXAMPLE 5Preparation of Intermediates of Formula IIb

General procedure for converting intermediate III into intermediates of structure IIb. To a solution of 2-vinyl thiazole **III** (5.14 g, 20.5 mmol) in acetonitrile (150 mL) was added 4×10^{-4} M aqueous NaEDTA (100 mL). This mixture was cooled to 0 °C and trifluoroacetone was added. A mixture of solid sodium bicarbonate (13.3 g, 158.7 mmol) and solid oxone (63 g, 102.4 mmol) was then added portionwise over 1 h. After the addition was complete, the mixture was stirred at 0 °C for an additional 30 min. The mixture was quenched with water (250 mL) and extracted with CH_2Cl_2 (3 x 150 mL). The combined organic extracts were washed with saturated aqueous NaCl (1 x 150 mL), dried over MgSO_4 , and concentrated *in vacuo*. Purification by flash chromatography (silica, 0-10% methanol/chloroform) gave the epoxide (3.914 g, 72%) as a white solid.

To a solution of 2-oxiranyl-4-trifluoromethyl-thiazole-5-carboxylic acid ethyl ester (390 mg, 1.46 mmol) in ethanol (4 mL) was added amine (1.75 mmol). This mixture was brought to reflux and stirred for 2 h. The mixture was then concentrated *in vacuo*. Purification of the resulting oil by flash chromatography (silica, 0-5% methanol/chloroform) gave thiazole **Iib**.

EXAMPLE 6

2-(2-Diethylamino-1-hydroxy-ethyl)-4-trifluoromethyl-thiazole-5-carboxylic acid ethyl ester. Prepared by the method of example 5. Isolated as a yellow oil. ¹H NMR (CDCl₃, 300 MHz): δ 7.37 (app d, *J* = 1.8 Hz, 1H), 6.31 (dd, *J* = 2.0, 2.7 Hz, 1H), 6.20 (d, *J* = 3.3 Hz, 1H), 4.92 (dd, *J* = 4.6, 9.0 Hz, 1H), 4.37 (q, *J* = 7.2 Hz, 2H), 3.67 (AB q, *J* = 8.8 Hz, Δ*v* = 14.3 Hz, 2H), 2.96 (dd, *J* = 4.4, 12.8 Hz, 1H), 2.68 (dd, *J* = 9.2, 12.8 Hz, 1H), 2.34 (s, 3H), 1.36 (t, *J* = 7.2 Hz, 3H).

EXAMPLE 7

Preparation of Formula I Compounds

General procedure for converting intermediate II into compounds of Formula I.

To a solution of thiazole **II** (0.8 mmol) in THF (2 mL) was added 1 N aqueous LiOH (1 mL). This mixture was heated to reflux and stirred vigorously for 1 h. The mixture was allowed to come to 25 °C. 1 N aqueous HCl (1 mL) was added and the resulting mixture was concentrated *in vacuo*. The crude residue was used as is.

To a solution of the resulting carboxylic acid (0.145 mmol) in DMF (1 mL) was added DEPBT (54 mg, 0.18 mmol). A solution of [3-(1-Amino-ethyl)-phenyl]-dimethyl-amine (24 mg, 0.145mmol) in DMF (0.5 mL) was then added, followed by Et₃N (81 μL, 0.58 mmol). This mixture was stirred at 25 °C for 18 h. The reaction mixture was filtered and applied directly to a preparatory HPLC column for purification (C18, 10-100% methanol/water/0.1% trifluoroacetic acid). The resulting residue was taken up in methanol (3 mL) and applied to an SAX column (United Chemical Technologies CHQAX12M6) having hydroxide as the counter ion. The

product was eluted with methanol (10 mL). The methanol solution was concentrated *in vacuo* to give thiazole I.

Compounds which needed further purification were purified by flash
5 chromatography (silica, 0-10% methanol/chloroform).

Examples of Formula I compounds

EXAMPLE 8

10

2-[2-[(4-morpholinyl)ethyl]-N-[1-[3-(3-pyridinyl)phenyl]ethyl]-4-(trifluoromethyl)-5-thiazolecarboxamide. ¹H NMR (CDCl₃, 300 MHz): δ 8.80 (s, 1H), 8.57 (s, 1H), 7.85 (d, *J* = 8.1 Hz, 1H), 7.53-7.35 (m, 5H), 6.52 (br d, *J* = 7.0 Hz, 1H), 5.31 (app quint, *J* = 7.1 Hz, 1H), 3.80-3.70 (m, 4H), 3.22-3.08 (m, 4H),
15 2.76-2.65 (m, 2H), 2.60-2.48 (m, 2H), 1.63 (d, *J* = 6.9 Hz, 3H); LCMS (M⁺) 490, RT = 0.773.

EXAMPLE 9

20 **N-[1-[3-(dimethylamino)phenyl]ethyl]-2-[2-(1-pyrrolidinyl)ethyl]-4-(trifluoromethyl)-5-thiazolecarboxamide.** ¹H NMR (CDCl₃, 300 MHz): δ 7.26-7.17 (m, 1H), 6.70-6.61 (m, 3H), 6.35 (br d, *J* = 7.3 Hz, 1H), 5.17 (app quint, *J* = 7.1 Hz, 1H), 3.21 (t, *J* = 6.9 Hz, 2H), 2.97-2.85 (m, 8H), 2.74-2.61 (m, 4H), 1.90-1.78 (m, 4H), 1.57 (d, *J* = 6.9 Hz, 3H); LCMS (M⁺) 440, T = 0.603.

25

EXAMPLE 10

2-[2-(1-pyrrolidinyl)ethyl]-4-(trifluoromethyl)-N-[1-[3-(trifluoromethyl)phenyl]ethyl]-5-thiazolecarboxamide. ¹H NMR (CDCl₃, 300
30 MHz): δ 7.58-7.44 (m, 4H), 6.45 (br d, *J* = 6.6 Hz, 1H), 5.25 (app quint, *J* = 7.1 Hz, 1H), 3.18 (t, *J* = 6.4 Hz, 2H), 2.86 (t, *J* = 6.3 Hz, 2H), 2.70-2.58 (m, 4H), 1.88-1.74 (m, 4H), 1.58 (d, *J* = 6.9 Hz, 3H); LCMS (M⁺) 465, RT = 1.280.

EXAMPLE 11

2-[2-[(2-furanylmethyl)methylamino]ethyl]-N-[1-[3-(4-morpholinyl)phenyl]ethyl]-4-(trifluoromethyl)-5-thiazolecarboxamide. ¹H NMR (CDCl₃, 300 MHz): δ 7.34 (dd, J = 0.7, 1.8 Hz, 1H), 7.30-7.22 (m, 1H), 6.91-6.79 (m, 3H), 6.34-6.25 (m, 2H), 6.19 (d, J = 2.9 Hz, 1H), 5.19 (app quint, J = 7.1 Hz, 1H), 3.84 (t, J = 4.8 Hz, 4H), 3.65 (s, 2H), 3.20-3.09 (m, 6H), 2.76 (t, J = 6.6 Hz, 2H), 2.31 (s, 3H), 1.57 (d, J = 6.9 Hz, 3H); LCMS (M+) 522, RT = 0.993.

10

EXAMPLE 12

2-[2-[(2-furanylmethyl)methylamino]ethyl]-N-[1-[3-(3-pyridinyl)phenyl]ethyl]-4-(trifluoromethyl)-5-thiazolecarboxamide. ¹H NMR (CDCl₃, 300 MHz): δ 8.81 (s, 1H), 8.58 (d, J = 4.2 Hz, 1H), 7.86 (dt, J = 1.9, 7.9 Hz, 1H), 7.54-7.32 (m, 6H), 6.45 (d, 1H), 6.29 (m, 1H), 6.19 (m, 1H), 5.32 (m, 1H), 3.65 (s, 2H), 3.14 (t, J = 6.6 Hz, 2H), 2.77 (t, J = 6.3 Hz, 2H), 2.31 (s, 3H), 1.63 (d, J = 6.9 Hz, 3H); LCMS (M+) 514, RT = 0.877.

20

EXAMPLE 13

2-[2-(1-pyrrolidinyl)ethyl]-4-(trifluoromethyl)-N-[1-[3-(trifluoromethoxy)phenyl]ethyl]-5-thiazolecarboxamide. ¹H NMR (CDCl₃, 300 MHz): δ 7.41-7.12 (m, 4H), 6.32 (br d, J = 6.2 Hz, 1H), 5.24 (app quint, J = 7.1 Hz, 1H), 3.15 (t, J = 6.3 Hz, 2H), 2.82 (t, J = 6.3 Hz, 2H), 2.64-2.54 (m, 4H), 1.86-1.75 (m, 4H), 1.57 (d, J = 6.9 Hz, 3H); LCMS (M+) 481, RT = 1.320.

25

EXAMPLE 14

2-[2-[(2-furanylmethyl)methylamino]ethyl]-4-(trifluoromethyl)-N-[1-[3-(trifluoromethoxy)phenyl]ethyl]-5-thiazolecarboxamide. ¹H NMR (CDCl₃, 300 MHz): δ 7.38-7.13 (m, 5H), 6.31-6.18 (m, 3H), 5.25 (app quint, J = 7.1 Hz, 1H),

30

3.64 (s, 2H), 3.13 (t, $J = 6.3$ Hz, 2H), 2.76 (d, $J = 6.3$ Hz, 2H), 2.31 (s, 3H), 1.57 (d, $J = 6.9$ Hz, 3H); LCMS (M+) 521, RT = 1.380.

EXAMPLE 15

5

2-[2-[(2-diethylamino)ethyl]-4-(trifluoromethyl)-N-[1-[3-(trifluoromethoxy)phenyl]ethyl]-5-thiazolecarboxamide. ^1H NMR (CDCl_3 , 300 MHz): δ 7.4-7.1 (m, 4H), 6.36 (br d, $J = 6.6$ Hz, 1H), 5.23 (app quint, $J = 7.1$ Hz, 1H), 3.20 (t, $J = 6.2$ Hz, 2H), 2.81 (t, $J = 6.2$ Hz, 2H), 2.65 (q, $J = 7.2$ Hz, 4H), 1.57 (d, $J = 7.0$ Hz, 3H), 1.05 (t, $J = 7.1$ Hz, 6H); LCMS (M+) 483, RT = 1.393.

10

EXAMPLE 16

2-[2-(diethylamino)ethyl]-N-[1-[3-(dimethylamino)phenyl]ethyl]-4-(trifluoromethyl)-5-thiazolecarboxamide. ^1H NMR (CDCl_3 , 300 MHz): δ 7.27-7.17 (m, 1H), 6.7-6.61 (m, 3H), 6.31 (br d, $J = 5.9$ Hz, 1H), 5.17 (app quint, $J = 7.1$ Hz, 1H), 3.10 (t, $J = 6.4$ Hz, 2H), 2.95 (s, 6H), 2.76 (t, $J = 6.4$ Hz, 2H), 2.60 (q, $J = 7.2$ Hz, 4H), 1.58 (d, $J = 6.6$ Hz, 3H), 1.02 (t, $J = 7.1$ Hz, 6H); LCMS (M+) 442, RT = 0.613.

20

EXAMPLE 17

2-[2-[(4-pyridylmethyl)methylamino]ethyl]-4-(trifluoromethyl)-N-[1-[3-(trifluoromethyl)phenyl]ethyl]-5-thiazolecarboxamide. ^1H NMR (CDCl_3 , 300 MHz): δ 8.45 (d, $J = 5.9$ Hz, 2H), 7.63-7.43 (m, 4H), 7.18 (d, $J = 5.9$ Hz, 2H), 6.68 (br d, $J = 7.3$ Hz, 1H), 5.28 (app quint, $J = 7.1$ Hz, 1H), 3.61 (s, 2H), 3.10 (t, $J = 6.4$ Hz, 2H), 2.84 (t, $J = 6.4$ Hz, 2H), 2.58 (q, $J = 7.0$ Hz, 2H), 1.61 (d, $J = 7.0$ Hz, 3H), 1.03 (t, $J = 7.0$ Hz, 3H); LCMS (M+) 530, RT = 1.263.

30

EXAMPLE 18

2-[2-(4-thiomorpholinyl)ethyl]-4-(trifluoromethyl)-N-[1-[3-(trifluoromethyl)phenyl]ethyl]-5-thiazolecarboxamide. ¹H NMR (CDCl₃, 300 MHz): δ 7.62-7.43 (m, 4H), 6.36 (br d, *J* = 6.2 Hz, 1H), 5.28 (app quint, *J* = 7.1 Hz, 1H), 3.13 (t, *J* = 6.2 Hz, 2H), 2.84-2.75 (m, 4H), 2.75-2.64 (m, 6H), 1.60 (d, *J* = 7.0 Hz, 3H); LCMS (M+) 497, RT = 1.350.

EXAMPLE 19

10

2-[2-[[3-(dimethylamino)propyl]methylamino]ethyl]-N-[1-[3-(3-trifluoromethoxy)phenyl]ethyl]-4-(trifluoromethyl)-5-thiazolecarboxamide. ¹H NMR (CDCl₃, 300 MHz): δ 7.40-7.20 (m, 4H), 7.11 (br d, *J* = 6.6 Hz, 1H), 5.23 (app quint, *J* = 7.1 Hz, 1H), 3.13 (t, *J* = 6.2 Hz, 2H), 2.79 (t, *J* = 6.2 Hz, 2H), 2.67-2.55 (m, 4H), 2.35 (s, 6H), 2.30 (s, 3H), 1.58 (d, *J* = 7.0 Hz, 3H); LCMS (M+) 512, RT = 1.227.

EXAMPLE 20

2-[2-[[3-(dimethylamino)propyl]methylamino]ethyl]-N-[1-[3-(3-trifluoromethyl)phenyl]ethyl]-4-(trifluoromethyl)-5-thiazolecarboxamide. ¹H NMR (CDCl₃, 300 MHz): δ 7.65-7.40 (m, 4H), 7.14 (br s, 1H), 5.26 (app quint, *J* = 7.1 Hz, 1H), 3.14 (t, *J* = 6.4 Hz, 2H), 2.79 (t, *J* = 6.4 Hz, 2H), 2.69-2.53 (m, 4H), 2.34 (s, 6H), 2.30 (s, 3H), 1.69 (d, *J* = 7.0 Hz, 3H); LCMS (M+) 496, RT = 1.183.

25

EXAMPLE 21

2-[2-(4-methyl-1-piperazinyl)ethyl]-N-[1-[3-(3-trifluoromethoxy)phenyl]ethyl]-4-(trifluoromethyl)-5-thiazolecarboxamide. ¹H NMR (CDCl₃, 300 MHz): δ 7.42-7.08 (m, 4H), 6.38 (br d, *J* = 7.0 Hz, 1H), 5.23 (app quint, *J* = 7.1 Hz, 1H), 3.13 (t, *J* = 6.2 Hz, 2H), 2.68 (t, *J* = 6.4 Hz, 2H), 2.64-2.43 (m, 8H), 2.31 (s, 3H), 1.57 (d, *J* = 7.0 Hz, 3H); LCMS (M+) 510, RT = 1.307.

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EXAMPLE 22

2-[2-(1-piperidinyl)ethyl]-N-[1-[3-(3-trifluoromethoxy)phenyl]ethyl]-4-(trifluoromethyl)-5-thiazolecarboxamide. ¹H NMR (CDCl₃, 300 MHz): δ 7.42-7.10 (m, 4H), 6.34 (br d, *J* = 6.6 Hz, 1H), 5.24 (app quint, *J* = 7.1 Hz, 1H), 3.15 (t, *J* = 6.4 Hz, 2H), 2.64 (t, *J* = 6.2 Hz, 2H), 2.54-2.39 (m, 4H), 1.69-1.52 (m, 7H), 1.52-1.40 (m, 2H); LCMS (M⁺) 495, RT = 1.353.

EXAMPLE 23

10

N-[1-[3-(dimethylamino)phenyl]ethyl]-2-[2-(1-piperidinyl)ethyl]-4-(trifluoromethyl)-5-thiazolecarboxamide. ¹H NMR (CDCl₃, 300 MHz): δ 7.26-7.18 (m, 1H), 6.71-6.62 (m, 3H), 5.17 (app quint, *J* = 7.1 Hz, 1H), 3.15 (t, *J* = 6.2 Hz, 2H), 2.95 (s, 6H), 2.65 (t, *J* = 6.4 Hz, 2H), 2.55-2.40 (m, 4H), 1.69-1.53 (m, 7H), 1.52-1.41 (m, 2H); LCMS (M⁺) 455, RT = 0.687.

EXAMPLE 24

2-[2-(1-piperidinyl)ethyl]-N-[1-[3-(3-trifluoromethyl)phenyl]ethyl]-4-(trifluoromethyl)-5-thiazolecarboxamide. ¹H NMR (CDCl₃, 300 MHz): δ 7.61-7.42 (m, 4H), 6.38 (br d, *J* = 6.6 Hz, 1H), 5.27 (app quint, *J* = 7.1 Hz, 1H), 3.14 (t, *J* = 6.4 Hz, 2H), 2.63 (t, *J* = 6.4 Hz, 2H), 2.54-2.40 (m, 4H), 1.69-1.53 (m, 7H), 1.53-1.40 (m, 2H); LCMS (M⁺) 479, RT = 1.317.

25

EXAMPLE 25

N-[1-[3-(4-morpholinyl)phenyl]ethyl]-2-[2-(1-piperidinyl)ethyl]-4-(trifluoromethyl)-5-thiazolecarboxamide. ¹H NMR (CDCl₃, 300 MHz): δ 7.31-7.20 (m, 1H), 6.91-6.79 (m, 3H), 6.32 (br d, *J* = 7.0 Hz, 1H), 5.18 (app quint, *J* = 7.1 Hz, 1H), 3.84 (t, *J* = 4.8 Hz, 4H), 3.19-3.09 (m, 6H), 2.64 (t, *J* = 6.2 Hz, 2H), 2.54-2.40 (m, 4H), 1.69-1.52 (m, 7H), 1.52-1.41 (m, 2H); LCMS (M⁺) 496, RT = 0.943.

EXAMPLE 26

2-[2-(4-hydroxy-1-piperidiny)ethyl]-4-(trifluoromethyl)-N-[1-[3-(trifluoromethoxy)phenyl]ethyl]-5-thiazolecarboxamide. ¹H NMR (CDCl₃, 300 MHz): δ 7.46-7.09 (m, 4H), 6.37 (br d, *J* = 5.5 Hz, 1H), 5.23 (app quint, *J* = 7.1 Hz, 1H), 3.74 (s, 1H), 3.14 (t, *J* = 6.2 Hz, 2H), 2.89-2.75 (m, 2H), 2.67 (t, *J* = 5.9 Hz, 2H), 2.40-2.20 (m, 2H), 2.02-1.85 (m, 2H), 1.74-1.49 (m, 6H); LCMS (M+) 511, RT = 1.353.

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EXAMPLE 27

2-[2-(4-hydroxy-1-piperidiny)ethyl]-4-(trifluoromethyl)-N-[1-[3-(trifluoromethyl)phenyl]ethyl]-5-thiazolecarboxamide. ¹H NMR (CDCl₃, 300 MHz): δ 7.62-7.41 (m, 4H), 6.41 (br d, *J* = 6.2 Hz, 1H), 5.27 (app quint, *J* = 7.1 Hz, 1H), 3.80-3.67 (m, 1H), 3.14 (t, *J* = 6.2 Hz, 2H), 2.86-2.75 (m, 2H), 2.67 (t, *J* = 6.2 Hz, 2H), 2.37-2.19 (m, 2H), 1.97-1.85 (m, 2H), 1.70-1.51 (m, 6H); LCMS (M+) 495, RT = 1.313.

20

EXAMPLE 28

2-[2-[(cyclopropylmethyl)propylamino]ethyl]-N-[1-[3-(trifluoromethoxy)phenyl]ethyl]-4-(trifluoromethyl)-5-thiazolecarboxamide. ¹H NMR (CDCl₃, 300 MHz): δ 7.41-7.10 (m, 4H), 6.34 (br d, *J* = 6.2 Hz, 1H), 5.23 (app quint, *J* = 7.1 Hz, 1H), 3.15 (t, *J* = 6.2 Hz, 2H), 2.91 (t, *J* = 5.7 Hz, 2H), 2.59 (t, *J* = 7.7 Hz, 2H), 2.46 (d, *J* = 6.2 Hz, 2H), 1.61-1.42 (m, 5H), 0.93-0.81 (m, 4H), 0.55-0.45 (m, 2H), 0.15-0.05 (m, 2H); LCMS (M+) 523, RT = 1.497.

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EXAMPLE 29

2-[2-[(cyclopropylmethyl)propylamino]ethyl]-N-[1-[3-(dimethylamino)phenyl]ethyl]-4-(trifluoromethyl)-5-thiazolecarboxamide. ¹H NMR (CDCl₃, 300 MHz): δ 7.26-7.17 (m, 1H), 6.71-6.61 (m, 3H), 6.32 (br d, *J* = 7.0

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Hz, 1H), 5.17 (app quint, $J = 7.1$ Hz, 1H), 3.15 (br t, 2H), 2.99-2.85 (m, 8H), 2.58 (br t, 2H), 2.45 (d, $J = 5.1$ Hz, 2H), 1.62-1.43 (m, 5H), 0.93-0.80 (m, 4H), 0.56-0.45 (m, 2H), 0.15-0.05 (m, 2H); LCMS (M+) 482, RT = 0.823.

5

EXAMPLE 30

2-[2-[(cyclopropylmethyl)propylamino]ethyl]-N-[1-[3-

(trifluoromethyl)phenyl]ethyl]-4-(trifluoromethyl)-5-thiazolecarboxamide. ^1H

10 NMR (CDCl_3 , 300 MHz): δ 7.66-7.42 (m, 4H), 6.36 (br d, $J = 6.2$ Hz, 1H), 5.27 (app quint, $J = 7.1$ Hz, 1H), 3.15 (br t, 2H), 2.90 (br t, 2H), 2.59 (br t, 2H), 2.45 (d, $J = 6.2$ Hz, 2H), 1.67-1.41 (m, 5H), 0.98-0.78 (m, 4H), 0.60-0.42 (m, 2H), 0.20-0.03 (m, 2H); LCMS (M+) 507, RT = 1.267.

EXAMPLE 31

15

2-[2-[(diethylamino)ethyl]-N-[1-[3-(3-pyridinyl)phenyl]ethyl]-4-

(trifluoromethyl)-5-thiazolecarboxamide. ^1H NMR (CDCl_3 , 300 MHz): δ 8.78 (d, $J = 1.83$ Hz, 1H), 8.55 (dd, $J = 1.7, 4.9$ Hz, 1H), 7.85 (dt, $J = 2.0, 7.7$ Hz, 1H), 7.56-7.51 (m, 1H), 7.51-7.42 (m, 2H), 7.42-7.30 (m, 2H), 6.85 (br d, $J = 6.2$ Hz, 1H), 5.30 (app quint, $J = 7.1$ Hz, 1H), 3.25 (br t, 2H), 3.03 (br t, 2H), 2.81 (q, $J = 7.1$ Hz, 4H), 1.62 (d, $J = 7.0$ Hz, 3H), 1.13 (t, $J = 7.1$ Hz, 6H); LCMS (M+) 476, RT = 0.780.

EXAMPLE 32

25 **2-[2-(1-piperidiny)ethyl]-N-[1-[3-(3-pyridinyl)phenyl]ethyl]-**

4-(trifluoromethyl)-5-thiazolecarboxamide. ^1H NMR (CDCl_3 , 300 MHz): δ 8.78

(d, $J = 2.2$ Hz, 1H), 8.50 (dd, $J = 1.7, 4.9$ Hz, 1H), 7.85 (dt, $J = 1.9, 7.9$ Hz, 1H), 7.53 (s, 1H), 7.50-7.43 (m, 2H), 7.43-7.31 (m, 2H), 6.66 (br d, $J = 6.6$ Hz, 1H), 5.30 (app quint, $J = 7.1$ Hz, 1H), 3.17 (t, $J = 6.4$ Hz, 2H), 2.71 (t, $J = 6.4$ Hz, 2H), 2.60-2.46 (m, 4H), 1.70-1.57 (m, 7H), 1.53-1.38 (m, 2H); LCMS (M+) 488, RT = 0.810.

30

EXAMPLE 33

2-[2-(3-pentylamino)ethyl]-N-[1-[3-(trifluoromethoxy)phenyl]ethyl]-4-

(trifluoromethyl)-5-thiazolecarboxamide. ¹H NMR (CDCl₃, 300 MHz): δ 7.41-

5 7.09 (m, 4H), 6.51 (br d, *J* = 7.0 Hz, 1H), 5.21 (app quint, *J* = 7.1 Hz, 1H), 3.17 (t, *J* = 6.2 Hz, 2H), 3.01 (t, *J* = 6.2 Hz, 2H), 2.64 (br s, 1H), 2.48 (quint, *J* = 5.9 Hz, 1H), 1.55 (d, *J* = 7.0 Hz, 3H), 1.47 (app quint, *J* = 7.1 Hz, 4H), 0.88 (t, *J* = 7.5 Hz, 6H); LCMS (M⁺) 497, RT = 1.590.

10

EXAMPLE 34

2-[2-(3-pentylamino)ethyl]-N-[1-[3-(trifluoromethyl)phenyl]ethyl]-4-

(trifluoromethyl)-5-thiazolecarboxamide. ¹H NMR (CDCl₃, 300 MHz): δ 7.59-

7.41 (m, 4H), 6.54 (br d, *J* = 7.0 Hz, 1H), 5.25 (app quint, *J* = 7.1 Hz, 1H), 3.18 (t, *J* = 6.2 Hz, 2H), 3.02 (t, *J* = 6.0 Hz, 2H), 2.68 (br s, 1H), 2.49 (quint, *J* = 5.9 Hz, 1H), 1.58 (d, *J* = 7.0 Hz, 3H), 1.53-1.41 (m, 4H), 0.88 (t, *J* = 7.3 Hz, 6H); LCMS (M⁺) 481, RT = 1.540.

20

EXAMPLE 35

2-[2-[(2-furanylmethyl)amino]ethyl]-N-[1-[3-(3-pyridinyl)phenyl]ethyl]-4-

(trifluoromethyl)-5-thiazolecarboxamide. ¹H NMR (CDCl₃, 300 MHz): δ 8.79 (d,

J = 1.8 Hz, 1H), 8.56 (dd, *J* = 1.8, 4.8 Hz, 1H), 7.85 (dt, *J* = 2.0, 8.0 Hz, 1H), 7.55-

7.43 (m, 3H), 7.43-7.30n (m, 3H), 6.57 (br d, *J* = 7.0 Hz, 1H), 6.3 (dd, *J* = 2.0, 3.1

25 Hz, 1H), 6.18 (d, *J* = 3.3 Hz, 1H), 5.30 (app quint, *J* = 7.1 Hz, 1H), 3.81 (s, 2H), 3.12 (t, *J* = 6.0 Hz, 2H), 2.99 (t, *J* = 6.0 Hz, 2H), 1.96 (s, 1H), 1.62 (d, *J* = 7.0 Hz, 3H); LCMS (M⁺) 500, RT = 0.983.

30

EXAMPLE 36

2-[2-(cyclopentylamino)ethyl]-N-[1-[3-(trifluoromethoxy)phenyl]ethyl]-4-

(trifluoromethyl)-5-thiazolecarboxamide. ¹H NMR (CDCl₃, 300 MHz): δ 7.42-

7.08 (m, 4H), 6.66 (br d, $J = 6.6$ Hz, 1H), 5.21 (app quint, $J = 7.1$ Hz, 1H), 3.26-3.11 (m, 3H), 3.06 (t, $J = 6.4$ Hz, 2H), 2.92 (br s, 1H), 1.94-1.79 (m, 2H), 1.79-1.63 (m, 2H), 1.63-1.50 (m, 5H), 1.50-1.36 (m, 2H); LCMS (M^+) 495, RT = 1.530.

5

EXAMPLE 37

2-[2-(3-pentylamino)ethyl]-N-[1-[3-(3-pyridinyl)phenyl]ethyl]-4-

(trifluoromethyl)-5-thiazolecarboxamide. ^1H NMR (CDCl_3 , 300 MHz): δ 8.77 (d, $J = 1.8$ Hz, 1H), 8.54 (dd, $J = 1.5, 4.8$ Hz, 1H), 7.84 (dt, $J = 2.0, 8.2$ Hz, 1H), 7.53 (s, 1H), 7.50-7.41 (m, 2H), 7.41-7.30 (m, 2H), 6.87 (br d, $J = 7.3$ Hz, 1H), 5.28 (app quint, $J = 7.1$ Hz, 1H), 3.26-3.141 (m, 3H), 3.11-2.88 (m, 3H), 1.94-1.77 (m, 2H), 1.77-1.64 (m, 2H), 1.61 (d, $J = 7.0$ Hz, 3H), 1.57-1.36 (m, 4H); LCMS (M^+) 488, RT = 1.043.

15

EXAMPLE 38

2-[2-(cyclopentylamino)ethyl]-N-[1-[3-(trifluoromethoxy)phenyl]ethyl]-4-

(trifluoromethyl)-5-thiazolecarboxamide. ^1H NMR (CDCl_3 , 300 MHz): δ 7.41-7.33 (m, 1H), 7.31-7.23 (m, 1H), 7.20-7.09 (m, 2H), 6.39 (br d, $J = 7.0$ Hz, 1H), 5.24 (app quint, $J = 7.1$ Hz, 1H), 3.45 (t, $J = 5.7$ Hz, 4H), 3.28 (s, 6H), 3.11 (t, $J = 6.4$ Hz, 2H), 2.93 (t, $J = 6.4$ Hz, 2H), 2.78 (t, $J = 5.7$ Hz, 4H), 1.57 (d, $J = 7.0$ Hz, 3H); LCMS (M^+) 543, RT = 1.490.

25

EXAMPLE 39

2-[2-(cyclopentylamino)ethyl]-N-[1-[3-(trifluoromethyl)phenyl]ethyl]-4-

(trifluoromethyl)-5-thiazolecarboxamide. ^1H NMR (CDCl_3 , 300 MHz): δ 7.61-7.43 (m, 4H), 6.42 (br d, $J = 7.0$ Hz, 1H), 5.27 (app quint, $J = 7.1$ Hz, 1H), 3.45 (t, $J = 5.7$ Hz, 4H), 3.28 (s, 6H), 3.11 (t, $J = 6.4$ Hz, 2H), 2.93 (t, $J = 6.4$ Hz, 2H), 2.78 (t, $J = 5.7$ Hz, 4H), 1.58 (d, $J = 7.0$ Hz, 3H); LCMS (M^+) 527, RT = 1.430.

30

EXAMPLE 40

2-[2-(cyclopentylamino)ethyl]-N-[1-[3-(3-pyridinyl)phenyl]ethyl]-4-

(trifluoromethyl)-5-thiazolecarboxamide. ¹H NMR (CDCl₃, 300 MHz): δ 8.79-

5 8.69 (m, 1H), 8.52 (d, *J* = 4.4 Hz, 1H), 7.82 (d, *J* = 7.7 Hz, 1H), 7.51 (s, 1H), 7.48-
7.27 (m, 4H), 6.84 (br d, *J* = 7.3 Hz, 1H), 5.29 (app quint, *J* = 7.1 Hz, 1H), 3.42 (t, *J*
= 5.7 Hz, 4H), 3.25 (s, 6H), 3.08 (t, *J* = 6.4 Hz, 2H), 2.90 (t, *J* = 6.4 Hz, 2H), 2.75 (t,
J = 5.7 Hz, 4H), 1.61 (d, *J* = 7.0 Hz, 3H); LCMS (M⁺) 536, RT = 0.947.

10

EXAMPLE 41

2-[1-hydroxy-2-(1-piperidinyl)ethyl]-N-[1-[3-(trifluoromethoxy)phenyl]ethyl]- 4-

(trifluoromethyl)-5-thiazolecarboxamide. ¹H NMR (CDCl₃, 300 MHz): δ 7.42-

7.09 (m, 4H), 6.48 (br d, *J* = 7.0 Hz, 1H), 5.22 (app quint, *J* = 7.1 Hz, 1H), 4.97 (dd,
15 *J* = 4.4, 9.2 Hz, 1H), 4.48 (br s, 1H), 2.91 (dd, *J* = 4.6, 12.6 Hz, 1H), 2.73-2.61 (m,
2H), 2.56 (ddd, *J* = 2.3, 9.3, 12.0 Hz, 1H), 2.51-2.39 (m, 2H), 1.69-1.51 (m, 7H),
1.51-1.40 (m, 2H); LCMS (M⁺) 511, RT = 1.440.

EXAMPLE 42

20

2-[1-hydroxy-2-(1-pyrrolidinyl)ethyl]-N-[1-[3-(trifluoromethyl)phenyl]ethyl]- 4-

(trifluoromethyl)-5-thiazolecarboxamide. ¹H NMR (CDCl₃, 300 MHz): δ 7.60-

7.42 (m, 4H), 6.60 (br d, *J* = 7.0 Hz, 1H), 5.25 (app quint *J* = 7.1 Hz, 1H), 4.99 (dd, *J*
= 4.4, 8.4 Hz, 1H), 4.51 (br s, 1H), 3.05 (dd, *J* = 4.0, 12.4 Hz, 1H), 2.91 (ddd, *J* = 2.2,
25 8.8, 12.4 Hz, 1H), 2.84-2.73 (m, 2H), 2.73-2.60 (m, 2H), 1.88-1.74 (m, 4H), 1.57 (d,
J = 7.0 Hz, 3H); LCMS (M⁺) 481, RT = 1.373.

EXAMPLE 43

30 2-[1-hydroxy-[2-(2-furanylmethyl)methylamino]ethyl]-N-[1-[3-

(trifluoromethyl)phenyl]ethyl]- 4-(trifluoromethyl)-5-thiazolecarboxamide. ¹H

NMR (CDCl₃, 300 MHz): δ 7.60-7.42 (m, 4H), 7.39-7.33 (m, 1H), 6.46 (br d, *J* = 7.0

Hz, 1H), 6.33-6.28 (m, 1H), 6.21 (d, $J = 3.3$ Hz, 1H), 5.26 (app quint, $J = 7.1$ Hz, 1H), 4.91 (dd, $J = 4.4, 9.2$ Hz, 1H), 3.68 (ABR q, $J = 14.6$ Hz, $\Delta\nu = 23.7$ Hz, 2H), 2.93 (ddd, $J = 1.1, 4.4, 12.8$ Hz, 1H), 2.68 (ddd, $J = 2.6, 9.2, 12.8$ Hz, 1H), 2.34 (s, 3H), 1.58 (d, $J = 7.0$ Hz, 3H); LCMS (M^+) 521, RT = 1.447.

5

EXAMPLE 44

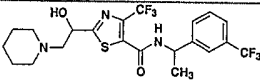
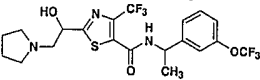
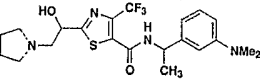
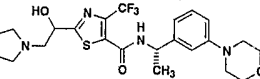
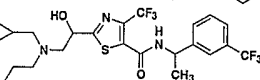
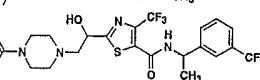
2-[1-hydroxy-[2-(cyclopropylmethyl)propylamino]ethyl]-N-[1-[3-(trifluoromethoxy)phenyl]ethyl]-4-(trifluoromethyl)-5-thiazolecarboxamide. ^1H

10 NMR (CDCl_3 , 300 MHz): δ 7.42-7.09 (m, 4H), 6.44 (br d, $J = 7.3$ Hz, 1H), 5.23 (app quint, $J = 7.1$ Hz, 1H), 4.91 (dd, $J = 4.4, 9.2$ Hz, 1H), 3.10 (dd, $J = 4.4, 12.8$ Hz, 1H), 2.80-2.51 (m, 3H), 2.47 (d, $J = 6.6$ Hz, 2H), 1.61-1.41 (m, 5H), 0.94-0.81 (m, 4H), 0.62-0.46 (m, 2H), 0.20-0.06 (m, 2H); LCMS (M^+) 539, RT = 1.510.

15

The following examples were also made by the above methods.

Example	Structure	Retention time (min)	MS (M^+)
45		0.840	498
46		0.637	472
47		0.517	471
48		0.847	511
49		1.000	500
50		0.900	492
51		1.420	513
52		1.363	497
53		1.340	510
54		0.920	527
55		0.840	519

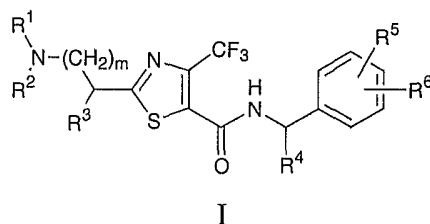
Example	Structure	Retention time (min)	MS (M+)
56		1.393	495
57		1.423	497
58		0.657	456
59		0.953	498
60		1.477	523
61		1.363	538

Method: 3 min run is 2 min gradient from 100%A to 100%B followed by 1 min at 100%B; solvent A: 10% MeOH/90% H₂O/0.1 % TFA; solvent B: 90% MeOH/10% H₂O/0.1 % TFA; Column: XTERRA 3.0 x 50 mm S7.

CLAIMS

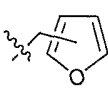
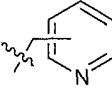
We claim:

- 5 1. A compound of Formula I or a pharmaceutically acceptable salt thereof



- 10 wherein

R^1 is C_{1-6} alkyl, C_{3-7} cycloalkyl, $-(CH_2)_{1-4}C_{3-7}$ cycloalkyl, $-(CH_2)_{2-4}N(C_{1-6}alkyl)_2$,

$-(CH_2)_{2-4}OC_{1-6}alkyl$, , or  ;

- 15 R^2 is hydrogen, C_{1-6} alkyl, or $-(CH_2)_{2-4}OC_{1-6}alkyl$;

or where R^1 and R^2 taken together are $-CH_2CH_2XCH_2CH_2-$, where X is a chemical bond, CH_2 , $CHOH$, NH , NCH_3 , $NCOCH_3$, O, or S;

- 20 R^3 is hydrogen or hydroxy, provided that where R^3 is hydroxy, m is not 0;

R^4 is hydrogen, C_{1-6} alkyl, hydroxymethyl, or trifluoromethyl;

R^5 is halogen, C_{1-6} alkyl, C_{1-2} perfluoroalkyl, C_{1-6} alkoxy, C_{1-2} perfluoroalkoxy, $-N(R^4)_2$,

- 25 N-morpholinyl, or pyridyl;

R^6 is hydrogen, halogen, or C_{1-6} alkoxy;

m is 0 or 1.

2. A compound of claim 1 where R^3 is hydrogen and m is 1.
3. A compound of claim 2 where R^4 is methyl.
- 5 4. A compound of claim 3 selected from the following group:

2-[2-(4-morpholinyl)ethyl]-N-[1-[3-(3-pyridinyl)phenyl]ethyl]-4-(trifluoromethyl)-5-thiazolecarboxamide;

10 N-[1-[3-(dimethylamino)phenyl]ethyl]-2-[2-(1-pyrrolidinyl)ethyl]-4-(trifluoromethyl)-5-thiazolecarboxamide;

2-[2-(1-pyrrolidinyl)ethyl]-4-(trifluoromethyl)-N-[1-[3-(trifluoromethyl)phenyl]ethyl]-5-thiazolecarboxamide;

15 2-[2-[(2-furanylmethyl)methylamino]ethyl]-N-[(1S)-1-[3-(4-morpholinyl)phenyl]ethyl]-4-(trifluoromethyl)-5-thiazolecarboxamide;

2-[2-[(2-furanylmethyl)methylamino]ethyl]-N-[1-[3-(3-pyridinyl)phenyl]ethyl]-4-(trifluoromethyl)-5-thiazolecarboxamide;

20 2-[2-(1-pyrrolidinyl)ethyl]-N-[1-[3-(trifluoromethoxy)phenyl]ethyl]-4-(trifluoromethyl)-5-thiazolecarboxamide;

2-[2-[(2-furanylmethyl)methylamino]ethyl]-N-[1-[3-(trifluoromethoxy)phenyl]ethyl]-4-(trifluoromethyl)-5-thiazolecarboxamide;

25 2-[2-(diethylamino)ethyl]-N-[1-[3-(trifluoromethoxy)phenyl]ethyl]-4-(trifluoromethyl)-5-thiazolecarboxamide;

2-[2-(diethylamino)ethyl]-N-[1-[3-(dimethylamino)phenyl]ethyl]-4-(trifluoromethyl)-5-thiazolecarboxamide;

30

- 2-[2-[ethyl(4-pyridinylmethyl)amino]ethyl]-4-(trifluoromethyl)-N-[1-[3-(trifluoromethyl)phenyl]ethyl]-5-thiazolecarboxamide;
- 2-[2-(4-thiomorpholinyl)ethyl]-4-(trifluoromethyl)-N-[1-[3-(trifluoromethyl)phenyl]ethyl]-5-thiazolecarboxamide;
- 5 2-[2-[[2-(dimethylamino)ethyl]methylamino]ethyl]-N-[1-[3-(trifluoromethoxy)phenyl]ethyl]-4-(trifluoromethyl)-5-thiazolecarboxamide;
- 10 2-[2-[[2-(dimethylamino)ethyl]methylamino]ethyl]-4-(trifluoromethyl)-N-[1-[3-(trifluoromethyl)phenyl]ethyl]-5-thiazolecarboxamide;
- 2-[2-(4-methyl-1-piperazinyl)ethyl]-N-[1-[3-(trifluoromethoxy)phenyl]ethyl]-4-(trifluoromethyl)-5-thiazolecarboxamide;
- 15 2-[2-(1-piperidinyl)ethyl]-N-[1-[3-(trifluoromethoxy)phenyl]ethyl]-4-(trifluoromethyl)-5-thiazolecarboxamide;
- N-[1-[3-(dimethylamino)phenyl]ethyl]-2-[2-(1-piperidinyl)ethyl]-4-(trifluoromethyl)-5-thiazolecarboxamide;
- 20 2-[2-(1-piperidinyl)ethyl]-4-(trifluoromethyl)-N-[1-[3-(trifluoromethyl)phenyl]ethyl]-5-thiazolecarboxamide;
- 25 N-[(1*S*)-1-[3-(4-morpholinyl)phenyl]ethyl]-2-[2-(1-piperidinyl)ethyl]-4-(trifluoromethyl)-5-thiazolecarboxamide;
- 2-[2-(4-hydroxy-1-piperidinyl)ethyl]-N-[1-[3-(trifluoromethoxy)phenyl]ethyl]-4-(trifluoromethyl)-5-thiazolecarboxamide;
- 30 2-[2-(4-hydroxy-1-piperidinyl)ethyl]-4-(trifluoromethyl)-N-[1-[3-(trifluoromethyl)phenyl]ethyl]-5-thiazolecarboxamide;

- 2-[2-[(cyclopropylmethyl)propylamino]ethyl]-N-[1-[3-(trifluoromethoxy)phenyl]ethyl]-4-(trifluoromethyl)-5-thiazolecarboxamide;
- 2-[2-[(cyclopropylmethyl)propylamino]ethyl]-N-[1-[3-(dimethylamino)phenyl]ethyl]-4-(trifluoromethyl)-5-thiazolecarboxamide;
- 5 4-(trifluoromethyl)-5-thiazolecarboxamide;
- 2-[2-[(cyclopropylmethyl)propylamino]ethyl]-4-(trifluoromethyl)-N-[1-[3-(trifluoromethyl)phenyl]ethyl]-5-thiazolecarboxamide;
- 10 2-[2-(diethylamino)ethyl]-N-[(1*S*)-1-[3-(3-pyridinyl)phenyl]ethyl]-4-(trifluoromethyl)-5-thiazolecarboxamide;
- 2-[2-(1-piperidinyl)ethyl]-N-[(1*S*)-1-[3-(3-pyridinyl)phenyl]ethyl]-4-(trifluoromethyl)-5-thiazolecarboxamide;
- 15 2-[2-[(1-ethylpropyl)amino]ethyl]-N-[1-[3-(trifluoromethoxy)phenyl]ethyl]-4-(trifluoromethyl)-5-thiazolecarboxamide;
- 2-[2-[(1-ethylpropyl)amino]ethyl]-4-(trifluoromethyl)-N-[1-[3-(trifluoromethyl)phenyl]ethyl]-5-thiazolecarboxamide;
- 20 (trifluoromethyl)phenyl]ethyl]-5-thiazolecarboxamide;
- 2-[2-[(2-furanylmethyl)amino]ethyl]-N-[(1*S*)-1-[3-(3-pyridinyl)phenyl]ethyl]-4-(trifluoromethyl)-5-thiazolecarboxamide;
- 25 2-[2-(cyclopentylamino)ethyl]-N-[1-[3-(trifluoromethoxy)phenyl]ethyl]-4-(trifluoromethyl)-5-thiazolecarboxamide;
- 2-[2-(cyclopentylamino)ethyl]-N-[(1*S*)-1-[3-(3-pyridinyl)phenyl]ethyl]-4-(trifluoromethyl)-5-thiazolecarboxamide;
- 30 2-[2-[bis(2-methoxyethyl)amino]ethyl]-N-[1-[3-(trifluoromethoxy)phenyl]ethyl]-4-(trifluoromethyl)-5-thiazolecarboxamide;

2-[2-[bis(2-methoxyethyl)amino]ethyl]-4-(trifluoromethyl)-N-[1-[3-(trifluoromethyl)phenyl]ethyl]-5-thiazolecarboxamide;

2-[2-[bis(2-methoxyethyl)amino]ethyl]-N-[(1S)-1-[3-(3-pyridinyl)phenyl]ethyl]-4-(trifluoromethyl)-5-thiazolecarboxamide;

2-[2-(4-morpholinyl)ethyl]-N-[(1S)-1-[3-(4-morpholinyl)phenyl]ethyl]-4-(trifluoromethyl)-5-thiazolecarboxamide;

10 N-[1-[3-(dimethylamino)phenyl]ethyl]-2-[2-(4-thiomorpholinyl)ethyl]-4-(trifluoromethyl)-5-thiazolecarboxamide;

2-[2-[[2-(dimethylamino)ethyl]methylamino]ethyl]-N-[1-[3-(dimethylamino)phenyl]ethyl]-4-(trifluoromethyl)-5-thiazolecarboxamide; and

2-[2-(4-methyl-1-piperazinyl)ethyl]-N-[(1S)-1-[3-(4-morpholinyl)phenyl]ethyl]-4-(trifluoromethyl)-5-thiazolecarboxamide.

5. A compound of claim 1 where R³ is hydroxy and m is 1.

6. A compound of claim 5 where R⁴ is methyl.

7. A compound of claim 6 selected from the following group:

25 2-[1-hydroxy-2-(1-piperidinyl)ethyl]-N-[1-[3-(trifluoromethoxy)phenyl]ethyl]-4-(trifluoromethyl)-5-thiazolecarboxamide;

2-[1-hydroxy-2-(1-pyrrolidinyl)ethyl]-4-(trifluoromethyl)-N-[1-[3-(trifluoromethyl)phenyl]ethyl]-5-thiazolecarboxamide;

30 2-[2-[(2-furanylmethyl)methylamino]-1-hydroxyethyl]-4-(trifluoromethyl)-N-[1-[3-(trifluoromethyl)phenyl]ethyl]-5-thiazolecarboxamide;

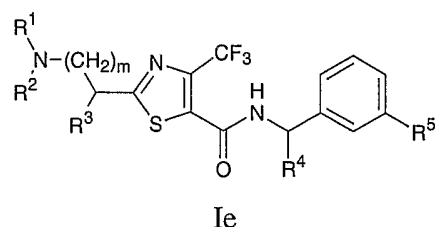
- 2-[2-[(cyclopropylmethyl)propylamino]-1-hydroxyethyl]-N-[1-[3-(trifluoromethoxy)phenyl]ethyl]-4-(trifluoromethyl)-5-thiazolecarboxamide;
- 2-[2-(diethylamino)-1-hydroxyethyl]-N-[(1*S*)-1-[3-(4-morpholinyl)phenyl]ethyl]-4-(trifluoromethyl)-5-thiazolecarboxamide;
- 5 2-[2-(diethylamino)-1-hydroxyethyl]-N-[(1*S*)-1-[3-(3-pyridinyl)phenyl]ethyl]-4-(trifluoromethyl)-5-thiazolecarboxamide;
- 10 2-[1-hydroxy-2-(4-morpholinyl)ethyl]-N-[1-[3-(trifluoromethoxy)phenyl]ethyl]-4-(trifluoromethyl)-5-thiazolecarboxamide;
- 2-[1-hydroxy-2-(4-morpholinyl)ethyl]-4-(trifluoromethyl)-N-[1-[3-(trifluoromethyl)phenyl]ethyl]-5-thiazolecarboxamide;
- 15 2-[1-hydroxy-2-(4-methyl-1-piperazinyl)ethyl]-4-(trifluoromethyl)-N-[1-[3-(trifluoromethyl)phenyl]ethyl]-5-thiazolecarboxamide;
- 2-[1-hydroxy-2-(4-methyl-1-piperazinyl)ethyl]-N-[(1*S*)-1-[3-(4-morpholinyl)phenyl]ethyl]-4-(trifluoromethyl)-5-thiazolecarboxamide;
- 20 2-[1-hydroxy-2-(4-methyl-1-piperazinyl)ethyl]-N-[(1*S*)-1-[3-(3-pyridinyl)phenyl]ethyl]-4-(trifluoromethyl)-5-thiazolecarboxamide;
- 25 2-[1-hydroxy-2-(1-piperidinyl)ethyl]-4-(trifluoromethyl)-N-[1-[3-(trifluoromethyl)phenyl]ethyl]-5-thiazolecarboxamide;
- 2-[1-hydroxy-2-(1-pyrrolidinyl)ethyl]-N-[1-[3-(trifluoromethoxy)phenyl]ethyl]-4-(trifluoromethyl)-5-thiazolecarboxamide;
- 30 N-[1-[3-(dimethylamino)phenyl]ethyl]-2-[1-hydroxy-2-(1-pyrrolidinyl)ethyl]-4-(trifluoromethyl)-5-thiazolecarboxamide;

2-[1-hydroxy-2-(1-pyrrolidinyl)ethyl]-N-[(1*S*)-1-[3-(4-morpholinyl)phenyl]ethyl]-4-(trifluoromethyl)-5-thiazolecarboxamide;

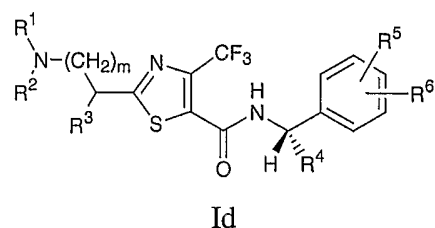
2-[2-[(cyclopropylmethyl)propylamino]-1-hydroxyethyl]-4-(trifluoromethyl)-N-[1-
5 [3-(trifluoromethyl)phenyl]ethyl]-5-thiazolecarboxamide; and

2-[2-(4-acetyl-1-piperazinyl)-1-hydroxyethyl]-4-(trifluoromethyl)-N-[1-[3-(trifluoromethyl)phenyl]ethyl]-5-thiazolecarboxamide.

10 8. A compound of claim 1 where the structure is that of Formula Ie.



15 9. A compound of claim 1 where the structure has the stereochemical configuration of Formula Id.



20

10. A pharmaceutical composition comprising a compound of Formula I and a pharmaceutically acceptable carrier.

11. A method for the treatment of disorders responsive to opening of the KCNQ
25 potassium channels in a mammal in need thereof, which comprises administering to said mammal a therapeutically effective amount of the compound of claim 1.

12. The method of claim 11 wherein said disorders are acute and chronic pain, migraine, neuropathic pain, bipolar disorders, convulsions, mania, epilepsy, anxiety, depression and neurodegenerative disorders.
- 5 13. The method of claim 11 wherein said disorder is migraine.
14. The method of claim 11 wherein said disorder is bipolar disorders.
15. The method of claim 11 wherein said disorder is neuropathic pain.
- 10 16. The method of claim 11 wherein said disorder is anxiety.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US03/39352

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : C07D 277/20, 417/12; A61K 31/426, 31/427; A61P 25/06, 25/08, 25/18, 25/22
 US CL : 548/200; 544/106; 546/187, 268.1; 514/365, 231.5, 317, 336

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 548/333

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

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
 CAS ONLINE, EAST

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5,045,554 A (ALT et al) 03 September 1991 (03.09.1991). See entire document.	1-9
A	US 5,330,995 A (EICKEN et al) 19 July 1994 (19.07.1994). See entire document.	1-9
A	US 6,319,940 B1 (ELBE et al) 20 November 2001 (20.11.2001). See entire document.	1-9

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

☐ See patent family annex.
*** Special categories of cited documents:**

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