NAPHTHYRIDINE DERIVATIVES AS POTASSIUM CHANNEL MODULATORS

Field of the Invention

This invention concerns novel compounds that modulate potassium channels. The compounds are useful for the treatment and prevention of diseases and disorders which are affected by activities of potassium ion channels. One such condition is seizure disorders.

Background of the Invention

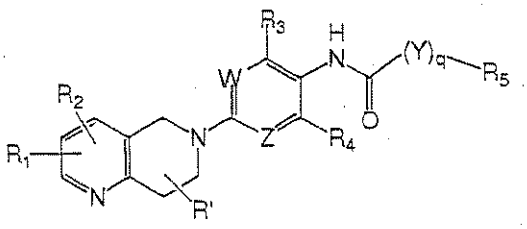
Retigabine (N-[2-amino-4-(4-fluorobenzylamino)phenyl]carbamic acid, ethyl ester] (United States Patent No. 5,384,330) has been found to be an effective treatment of seizure disorders in children. Bialer, M. et al., Epilepsy Research 1999, 34, 1-41. Retigabine has also been found to be useful in treating pain, including neuropathic pain. Blackburn-Munro and Jensen, Eur. J. Pharmacol. 2003, 460, 109-116; Wickenden, A.D. et al., Expert Opin.Ther. Patents 2004 14(4).

A form of epilepsy known as "benign familial neonatal convulsions" has been associated with mutations in the KCNQ2/3 channels. Biervert, C. *et al., Science* 1998, 27, 403-06; Singh, N.A. *et al., Nat. Genet. 1998,* 18, 25-29; Charlier, C. et al., *Nat. Genet.* 1998, 18, 53-55, Rogawski, *Trends in Neurosciences* 2000, 23, 393-398. Subsequent investigations have established that the primary site of retigabine action is the KCNQ2/3 channel. Wickenden, A.D. *et al., Mol. Pharmacol.* 2000, 58,591-600; Main, M.J. *et al., Mol. Pharmcol.* 2000, 58, 253-62. Retigabine has been shown to increase the conductance of the channels at the resting membrane potential and to bind the activation gate of the KCNQ 2/3 channel. Wuttke, T.V. *et al., Mol. Pharmacol.* 2005, 67, 1009-1017. With increased sophistication of research in this area, retigabine has also been shown to increase neuronal M currents and to increase the channel open probability of KCNQ 2/3 channels. Delmas, P. and Brown, D.A. *Nat. Revs Neurosci.,* vol. 6, 2005, 850-62; Tatulian, L. and Brown, D.A., J. Physiol., (2003) 549, *57-63.*

The recognition of retigabine as a potassium channel modulator has prompted numerous searches for other potassium channel modulators among compounds with various structural features in common with retigabine.

Summary

In a first aspect, there is provided a compound of formula I



I

where W and Z are, independently, CH or N; Y is CH_2, O or NH;

where R_1 and R_2, are, independently, H, halogen, CH_2F, CHF_2, CF_3, CF_2CF_3, C_1-C_6 alkyl, $C(=O)C_1$-C_6 alkyl, $CH_2C(=O)C_1$-C_6 alkyl, NH-C_1-C_6 alkyl, $NHC(=O)C_1$-C_6 alkyl, $C(=O)N(CH_3)_2$, $C(=O)N(Et)_2$, $C(=O)NH$-C_1-C_6 alkyl, $C(=O)OC_1$-C_6 alkyl, $OC(=O)C_1$-C_6 alkyl, OC_1-C_6 alkyl, SC_1-C_6 alkyl, C_3-C_6 cycloalkyl, $(CH_2)_mC_3$-C_6 cycloalkyl, C_3-C_6 cycloalkenyl, $(CH_2)_mC_3$-C_6 cycloalkenyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, Ar_1, $(CH_2)_mAr_1$, phenyl, pyridyl, pyrrolyl, $(CH_2)_m$imidazolyl, $(CH_2)_m$pyrazyl, furyl, thienyl, $(CH_2)_m$oxazolyl, $(CH_2)_m$isoxazolyl, $(CH_2)_m$thiazolyl, $(CH_2)_m$isothiazolyl, $(CH_2)_m$phenyl, $(CH_2)_m$pyrrolyl, $(CH_2)_m$pyridyl, or $(CH_2)_m$pyrimidyl, which cycloalkyl and said cycloalkenyl groups optionally contain one or two heteroatoms selected independently from O, N, and S, and which alkyl, cycloalkyl, cycloalkenyl, alkenyl, alkynyl, imidazolyl, pyrazyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, phenyl, pyrrolyl, pyridyl, or pyrimidyl groups are optionally substituted with one or two groups selected, independently, from OH, halogen, cyano, methyl, ethyl, or trifluoromethyl, where m is zero, 1, or 2;

or R_1 and R_2, together with the ring carbon atoms to which they are attached, form a 5- or 6-member fused ring, which ring may be saturated, unsaturated, or aromatic, which optionally contains one or two heteroatoms selected independently from O, N, and S, and which is optionally substituted with halogen, CF_3, or C_1-C_3 alkyl;

R' is H, halogen, CF_3, or C_1-C_3 alkyl;

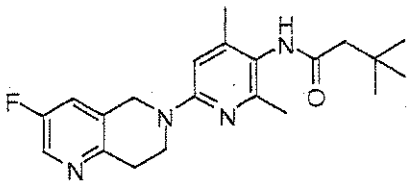
R_3 and R_4 are, independently, H, NH_2, (C_1-C_3 alkyl)NH, CN, halogen, CF_3, OCF_3, OC_1-C_3 alkyl, or C_1-C_3 alkyl, all said C_1-C_3 alkyl groups and said C_1-C_6 alkyl groups optionally

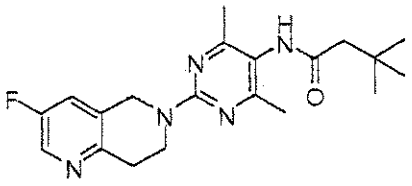
substituted with one or two groups selected, independently, from OH, halogen, C_1-C_3 alkyl, OC_1-C_3 alkyl, or trifluoromethyl;

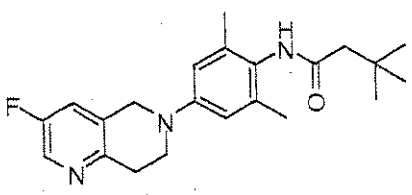
q = 1 or 0;

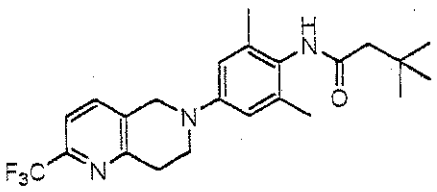
R_5 is C_1-C_6 alkyl, $(CHR_6)_wC_3$-C_6 cycloalkyl, $(CHR_6)_wCH_2C_3$-C_6 cycloalkyl, $CH_2(CHR_6)_wC_3$-C_6 cycloalkyl, CR_6=CH-C_3-C_6 cycloalkyl, CH=CR_6-C_3-C_6 cycloalkyl, $(CHR_6)_wC_5$-C_6 cycloalkenyl, $CH_2(CHR_6)_wC_5$-C_6 cycloalkenyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, Ar_1, $(CHR_6)_wAr_1$, $CH_2(CHR_6)_wAr_1$, or $(CHR_6)_wCH_2Ar_1$, where w = 0 – 3, Ar_1 is phenyl, pyridyl, furyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, or imidazolyl, wherein said C_1-C_6 alkyl group is optionally substituted with hydroxy, methoxy, methylthio, or halogen, and where said cycloalkyl and cycloalkenyl groups are optionally substituted with one or two groups selected, independently, from OH, halogen, cyano, methoxy, methyl, ethyl, or trifluoromethyl; R_6 is hydrogen, methyl, halogen, or methoxy; and pharmaceutically acceptable salts thereof.

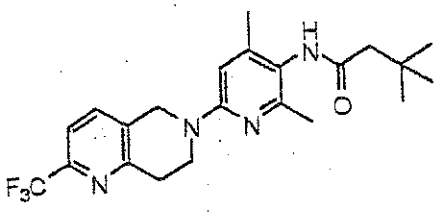
In a second aspect, there is provided a compound selected from the group consisting of:

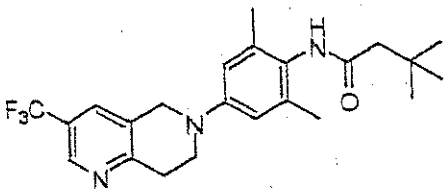


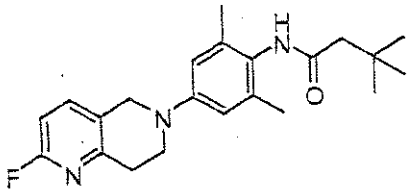


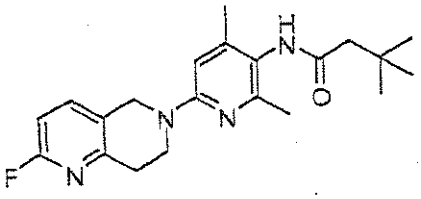


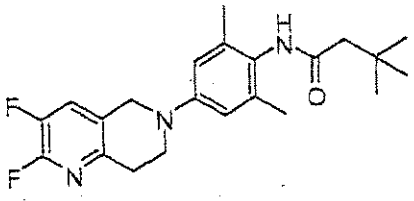


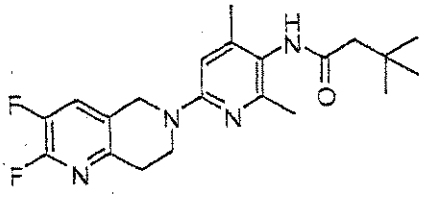












In a third aspect, there is provided a composition comprising a pharmaceutically acceptable carrier and at least one of the following: i) a pharmaceutically effective amount of a compound of formula I; ii) a pharmaceutically acceptable salt of a compound of formula I; iii) a pharmaceutically acceptable ester of a compound of formula I; iv) a pharmaceutically solvate of a compound of formula I.

In a fourth aspect, there is provided the use of a therapeutically effective amount of a compound of formula I as defined above or a pharmaceutically acceptable salt, solvate, or ester thereof in the manufacture of a medicament for preventing or treating a disease or disorder which is affected by activation of voltage-gated potassium channels.

In a fifth aspect, there is provided the use of a compound of formula I or a salt, solvate, or a ester thereof in the manufacture of a medicament for increasing the channel open probability of KCNQ2/3 channels in a mammal.

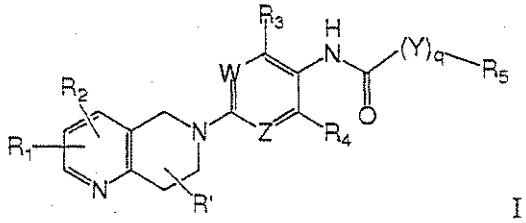
In a sixth aspect, there is provided the use of a compound of formula IA or a salt, solvate, or ester thereof in the manufacture of a medicament for increasing neuronal M currents in a mammal.

In a seventh aspect, there is provided a tablet for oral dosing comprising a pharmaceutically acceptable carrier and from approximately 100 to approximately 700 mg of a compound of formula IA or a salt, solvate, or ester thereof.

In an eighth aspect, there is provided a pharmaceutical syrup for pediatric use, comprising from approximately 100 to approximately 700 mg per dose of a compound of formula IA or a salt, solvate, or ester thereof.

Brief Description

In one embodiment, this disclosure provides a compound of formula I



I

where W and Z are, independently, CH or N; Y is CH_2, O or NH;

where R_1 and R_2, are, independently, H, halogen, CH_2F, CHF_2, CF_3, CF_2CF_3, C_1-C_6 alkyl, $C(=O)C_1$-C_6 alkyl, $CH_2C(=O)C_1$-C_6 alkyl, NH-C_1-C_6 alkyl, $NHC(=O)C_1$-C_6 allcyl, $C(=O)N(CH_3)_2$, $C(=O)N(Et)_2$, C(=O)NH-C_1-C_6 alkyl, $C(=O)OC_1$-C_6 alkyl, $OC(=O)C_1$-C_6 allcyl, OC_1-C_6 alkyl, SC_1-C_6 alkyl, C_3-C_6 Cycloalkyl, $(CH_2)mC_3$-C_6 cycloalkyl, C_3-C_6,cycloalkenyl, $(CH_2)_mC_3$-C_6 cycloalkenyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, Ari, (CH_2)n,Ari, phenyl, pyridyl, pyrrolyl, $(CH_2)_m$imidazolyl, $(CH_2)_m$pyrazyl, furyl, thienyl, $(CH_2)_m$oxazolyl, $(CH_2)_m$isoxazolyl, $(CH_2)_m$thiazolyl, $(CH_2)_m$isothiazolyl, $(CH_2)_m$phenyl, $(CH_2)_m$pyrrolyl, $(CH_2)_m$pyridyl, or $(CH_2)_m$pyrimidyl, which cycloalkyl and said cycloalkenyl groups optionally contain one or two heteroatoms selected independently from O, N, and S, and which alkyl, cycloalkyl, cycloalkenyl, alkenyl, alkynyl, imidazolyl, pyrazyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, phenyl, pyrrolyl, pyridyl, or pyrimidyl groups are optionally substituted with one or two groups selected, independently, from OH, halogen, cyano, methyl, ethyl, or trifluoromethyl, where m is zero, 1, or 2; or R_1 and R_2, together with the ring carbon atoms to which they are attached, form a 5- or 6- member fused ring, which ring. may be saturated, unsaturated, or aromatic, which optionally contains one or two heteroatoms selected independently from O, N, and S, and which is optionally substituted with halogen, CF_3, or C_1-C_3 alkyl; R' is H, halogen, CF_3, or C_1-C_3 alkyl; R_3 and R_4 are, independently, H, NH_2, (C_1-C_3 alkyl)NH, CN, halogen, CF_3, OCF_3, OC_1-C_3 alkyl, or C_1-C_3 alkyl, all said C_1-C_3 alkyl groups and said C_1-C_6 alkyl groups optionally substituted with one or two groups selected, independently, from OH, halogen, C_1-C_3 alkyl, OC_1-C_3 alkyl, or trifluoromethyl; q=1 or 0; R_5 is C_1-C_6 alkyl, $(CHR_6)_wC_3$-C_6 cycloalkyl, $(CHR_6)o,,CH_2C_3$-C_6 cycloalkyl, CH_2 $(CHR_6)_wC_3$-C_6 cycloalkyl, CR_6=CH-C_3-C_6 cycloalkyl, CH=CR_6-C_3-C6 cycloalkyl, $(CHR_6)_wC_5$-C6 cycloalkenyl, CH_2 $(CHR_6)_wC_5$-C_6 cycloalkenyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, Ar_1, $(CHRAr_1$, $CH_2(CHR_6)_wAr_1$, or $(CHR_6)_wCH2Ar_1$, where w=0-3, Ar_1 is phenyl, pyridyl, furyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, or imidazolyl where the C_1-C_6 alkyl group is optionally substituted with hydroxy,

methoxy, methylthio, or halogen, and where the cycloalkyl and cycloalkenyl groups are optionally substituted with one or two groups selected, independently, from OH, halogen, cyano, methyl, ethyl, or trifluoromethyl; R_6 is hydrogen, methyl, halogen, or methoxy; and pharmaceutically acceptable salts thereof. Such compounds are potassium channel modulators.

In another embodiment, this disclosure provides or contemplates a composition comprising a pharmaceutically acceptable carrier, excipient or diluent and at least one of the following: i) a pharmaceutically effective amount of a compound of formula I; ii) a pharmaceutically acceptable salt thereof; iii) a pharmaceutically acceptable ester thereof; iv) and a pharmaceutically acceptable solvate thereof.

In another embodiments, this disclosure provides or contemplates a method of treating or preventing a disease or disorder which is affected by enhancement of neural M currents comprising administering to a patient in need thereof one or more of the following: i) a pharmaceutically effective amount of a compound of formula I; ii) a pharmaceutically acceptable salt thereof; iii) a pharmaceutically acceptable ester thereof; iv) and a pharmaceutically acceptable solvate thereof.

In yet another embodiment, this disclosure provides a method of preventing or treating a disease or disorder which is affected by activation of voltage-gated potassium channels, comprising administering to a patient in need thereof one or more of the following: a pharmaceutically effective amount of a compound of formula I; ii) a pharmaceutically acceptable salt thereof; iii) a pharmaceutically acceptable ester thereof; and iv) a pharmaceutically acceptable solvate thereof.

In yet another embodiment, this disclosure provides or contemplates a method of treating or preventing a seizure disorder in a human comprising administering to a patient afflicted or potentially afflicted with such disorder one or more of the following: a pharmaceutically effective amount of a compound of formula I; ii) a pharmaceutically acceptable salt thereof; iii) a pharmaceutically acceptable ester thereof; iv) and a pharmaceutically acceptable solvate thereof.

In another embodiment, this disclosure provides or contemplates a pharmaceutical formulation for oral administration comprising a therapeutically effective amount of a compound of formula I and either an appropriate tabletting agent or an appropriate syrup for pediatric use.

In another embodiment, this disclosure provides or contemplates a tablet for oral administration comprising a therapeutically effective amount of a compound of formula I and an

appropriate tabletting agent.

In another appropriate embodiment, this disclosure provides or contemplates a syrup for pediatric use comprising a solution or dispersion or suspension of a compound of formula I and an appropriate syrup.

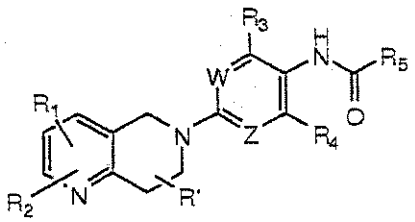
In another embodiment, this disclosure contemplates a pharmaceutical formulation for administration to animals, including companion animals (dogs and cats), and livestock comprising a therapeutically effective amount of a compound of formula I and a veterinary acceptable carrier.

In another embodiment, this disclosure contemplates a method of preventing or treating a disease or disorder which is affected by activation of voltage-gated potassium channels comprising administering to an animal in need thereof one or more of the following: i) a pharmaceutically effective amount of a compound of formula I; ii) a pharmaceutically acceptable salt thereof; iii) a pharmaceutically acceptable ester thereof; iv) and a pharmaceutically acceptable solvate thereof.

In another embodiment, this disclosure contemplates a method of treating a seizure disorder in an animal comprising administering to an animal afflicted or potentially afflicted with such a disorder one or more of the following: i) a pharmaceutically effective amount of a compound of formula I; ii) a pharmaceutically acceptable salt thereof; iii) a pharmaceutically acceptable ester thereof; iv) and a pharmaceutically acceptable solvate thereof.

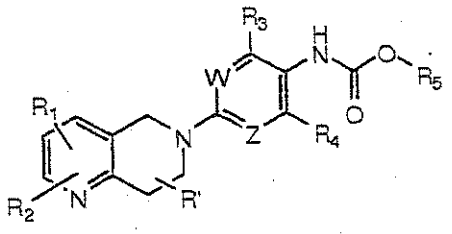
This disclosure includes all tautomers, salts and stereoistomeric forms of compounds of formula I. This disclosure also includes all compounds of this disclosure where one or more atoms are replaced by a radioactive isotope thereof.

In a more specific subgeneric embodiment, the disclosure provides a compound of formula IA



IA

In another more specific subgeneric embodiment, this disclosure provides a compound of formula IB.



IB

In a still more specific subgeneric embodiment, this disclosure provides a compound of formula IA, where W and Z are both N.

In another still more specific subgeneric embodiment, this disclosure provides a compound of formula IA, where W is N and Z is CH.

In another still more specific subgeneric embodiment, this disclosure provides a compound of formula IA, where W is CH and Z is N.

In another more specific subgeneric embodiment, this disclosure provides a compound of formula IA, where R' is H, halogen, CF_3, or methyl.

In another more specific subgeneric embodiment, this disclosure provides a compound of formula IA, where W and Z are both N and R' is H, F, or methyl.

In another more specific subgeneric embodiment, this disclosure provides a compound of formula IB, where W and Z are both N.

In another more specific subgeneric embodiment, this disclosure provides a compound of formula IB, where W is N and Z is CH.

In another more specific subgeneric embodiment, this disclosure provides a compound of formula IB, where W is CH and Z is N.

In another more specific subgeneric embodiment, this disclosure provides a compound of formula IB, where R' is H, halogen, CF_3, or methyl.

In another more specific subgeneric embodiment, this disclosure provides a compound of formula IB, where W and Z are both N and R' is H, F, or methyl.

In a more specific subgeneric embodiment, this disclosure provides or contemplates a compound of formula IA, where R_5 is C_1-C_6 alkyl, (CHR_6),NC_3-C_6 cycloalkyl, $(CHR_6)_wCH_2C_3$-C_6 cycloalkyl, or CH_2 $(CHR_6)_wC_3$-C_6 cycloalkyl.

In a more specific subgeneric embodiment, this disclosure provides or contemplates a compound of formula IB, where R_5 is C_1-C_6 alkyl, (CHR_6)a,C_3-C_6 cycloalkyl, $(CHR_6)_wCH_2C_3$-C_6 cycloalkyl, or CH_2 $(CHR_6)_wC_3$-C_6 cycloalkyl.

In a still more specific subgeneric embodiment, this disclosure provides or contemplates a compound of formula IA, where R_5 is C_1-C_6 alkyl, $(CHR_6)C_3$-C_6 cycloalkyl, $(CHR_6)_wCH_2C_3$-C_6 cycloalkyl, or CH_2 $(CHR_6)_wC_3$-C_6 cycloalkyl; and R_1 is H, CF_3, or halogen.

In a more specific subgeneric embodiment, this disclosure provides or contemplates a compound of formula IA, where R5 is C_1-C_6 alkyl, substituted with methoxy, methylthio, or halogen; R' is methyl or H; and R_1 is H, CF_3, or halogen.

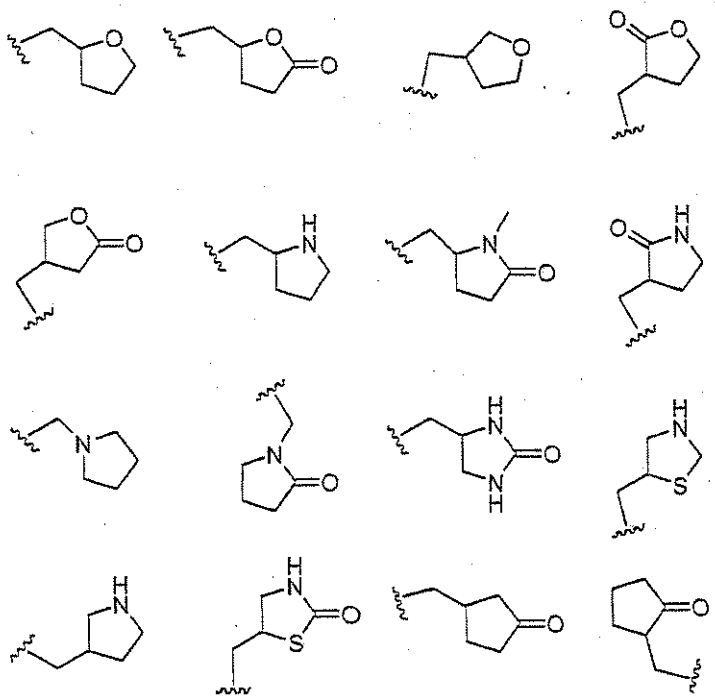
In another subgeneric embodiment, this disclosure provides or contemplates a compound of formula I, where R_5 is CR_6=CH-C_3-C_6 cycloalkyl, CH=CR_6-C_3-C_6 cycloalkyl, $(CHR_6)_wC_5$-C_6 cycloalkenyl, CH_2 (CHR_6) $_wC_5$-C_6 cycloalkenyl, C_2-C_6 alkenyl, or C_2-C_6 alkynyl; R' is methyl or H; and R_1 is H, CF_3, or halogen.

In another more specific subgeneric embodiment, this disclosure provides or contemplates a compound of formula IA, where R' is methyl or H; R_1 is H, CF_3, or halogen; R_3 and R_4 are methyl, aminomethyl, or chloro; and R_5 is Ar_1, $(CHR_6)_wArl$, CH_2 $(CHR_6)_wAr_1$, or $(CHR_6)_wCH_2Ar_1$.

In another more specific subgeneric embodiment, this disclosure provides or contemplates a compound of formula IA, where R' is methyl or H; R_1 is H, CF_3, or halogen; R_3 and R_4 are methyl; and R_5 is C_1-C_6 alkyl, $(CHR_6)_wC_3$-C_6 cycloalkyl, $(CHR_6)CH_2C3$-C_6 cycloalkyl, or CH_2 $(CHR_6)C3$-C_6 cycloalkyl.

In another more specific subgeneric embodiment, this disclosure provides or contemplates a compound of either of formulas IA or IB, where R_2 is H or F; R' is H or halogen; R_3 and R_4 are methyl; and R_5 is C_1-C_6 alkyl, $(CHR_6)_wC_3$-C_6 cycloalkyl, $(CHR_6)_wCH_2C_3$-C_6 cycloalkyl, or CH_2 $(CHR_6)_wC3$-C_6 cycloalkyl.

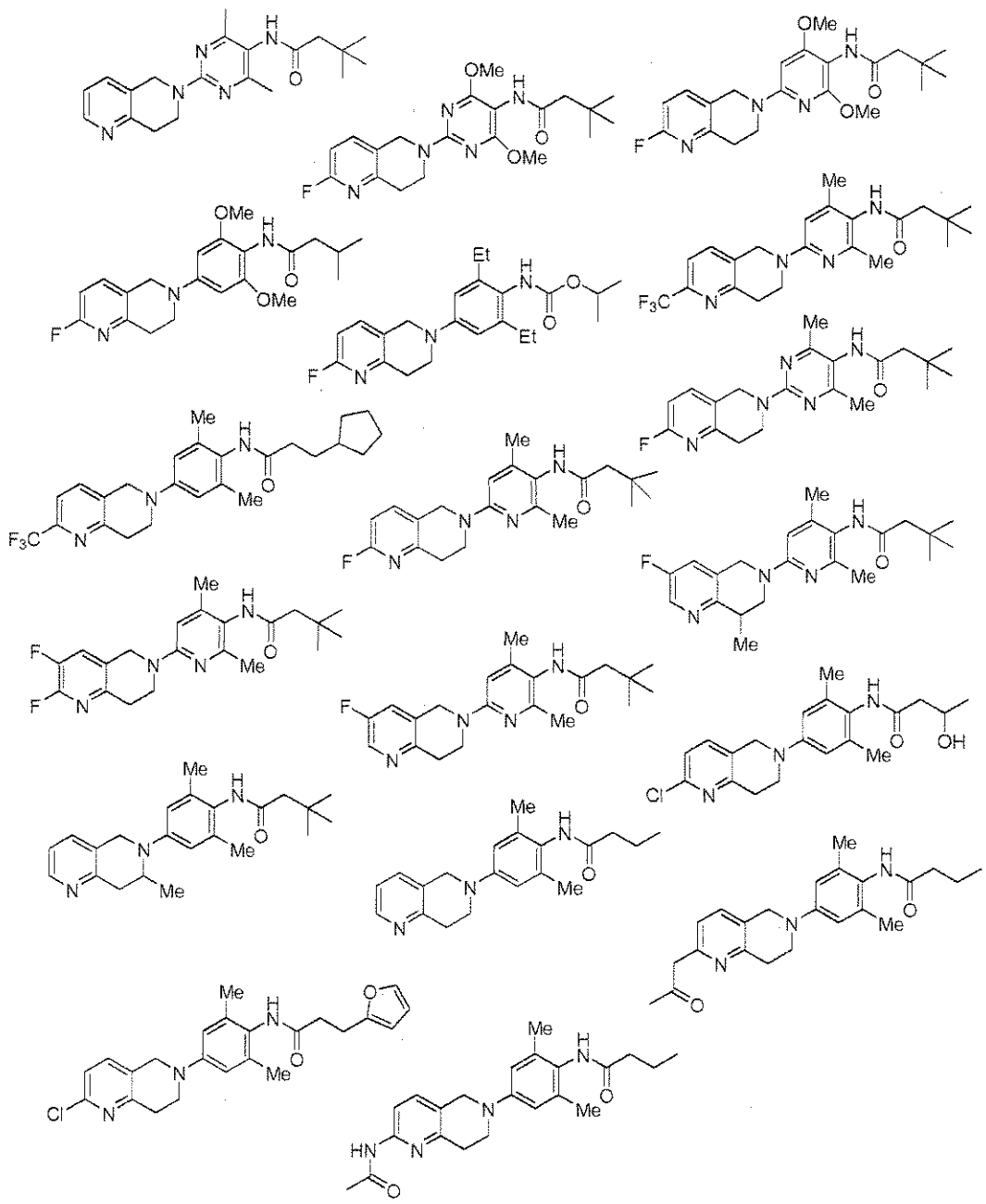
In another more specific subgeneric embodiment, this disclosure provides or contemplates a compound of formula IA or formula IB, where RS is CHZCHZcyclopentyl or one of the groups below:



In another more specific subgeneric embodiment, this disclosure provides or contemplates a compound of formula IA or IB where R_1 is halogen or halomethyl; R_2 is H, or halogen; and R_5 is one of the groups above.

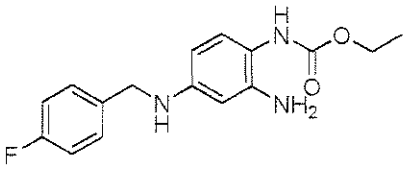
In another more specific subgeneric embodiment, this disclosure provides or contemplates a compound of formula IA or IB, where R_1 is phenyl, pyridyl, pyrrolyl, $(CH_2)_m$imidazolyl, $(CH_2)_m$pyrazyl, $(CH_2)_m$oxazolyl, $(CH_2)_m$isoxazolyl, $(CH_2)_m$thiazolyl, $(CH_2)_m$isothiazolyl, $(CH_2)_m$phenyl, $(CH_2)_m$pyrrolyl, $(CH_2)_m$pyridyl, or $(CH_2)_n$pyrimidyl, and R_5 is C_5-C_6 alkyl or CH_2-C_3-C_6 cycloalkyl.

The examples below are provided to show - but not to limit in any way - the variety of possible embodiments of this disclosure



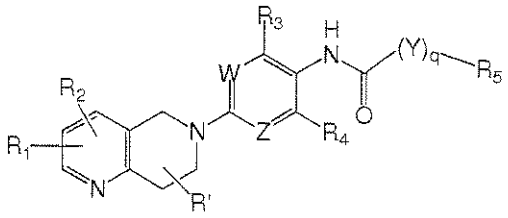
Detailed Description of the Invention

In designing compounds with therapeutic properties superior to those of retigabine,



retigabine

the present inventors have discovered that para N-1,2,3,4-tetrahydro isoquinolyl anilides and carbamates of the structure of formula I



I

have surprising and exceptional activity toward potassium channels, as evidenced by their potent activities, as measured in the rubidium efflux assay described below.

As used herein the term "potassium channel modulator" refers to a compound capable of causing an increase in potassium channel currents. It also refers to a compound capable of increasing the KCNQ2/3 channel open probability. For preliminary testing of compounds for potassium channel modulating ability, the inventors have employed the rubidium ion efflux test described below.

As contemplated by this invention, compounds of formula I are designed for oral or intravenous dosing of up to approximately 1200 mg per day. Thus, this invention contemplates solutions and suspensions of compounds of formula I formulated for intravenous administration. Similarly, solutions and suspensions comprising a syrup such as sorbitol or propylene glycol, among many other examples, in addition to compounds of formula I, suitable for oral pediatric administration, are also contemplated. Additionally, both chewable and non-chewable tablets comprising' compounds of formula I, along with pharmaceutically acceptable tabletting agents and other pharmaceutically acceptable carriers and excipients, are also contemplated. As used herein,

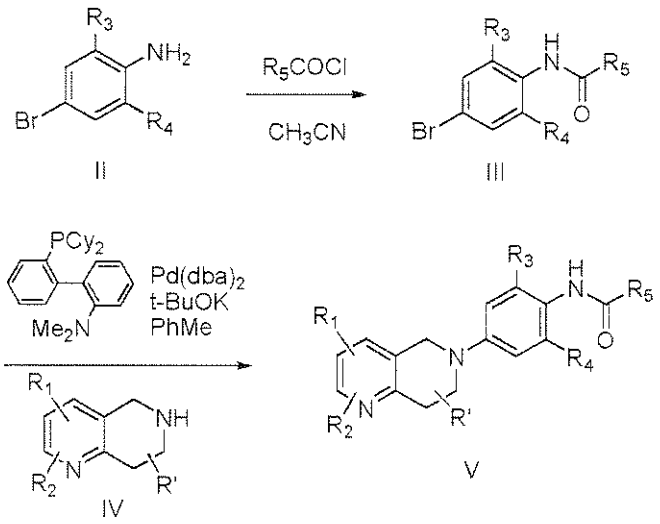
the term pharmaceutically acceptable carrier comprises such excipients, binders, lubricants, tabletting agents and disintegrants as are typically used in the art of formulation of pharmaceuticals. Examples of such agents include — but are not limited to — microcrystalline cellulose, lactose, starch, and dicalcium phosphate, and Providone. Additionally, disintegrants such as sodium starch glycolate, lubricants such as stearic acid and SiO_2, and solubility enhancers such as cyclodextrins, among many other examples for each group, are contemplated. Such materials and the methods of using them are well known in the pharmaceutical art. Additional examples are provided in Kibbe, Handbook of Pharmaceutical Excipients, London, Pharmaceutical Press, 2000.

The invention also contemplates pharmaceutical formulations, including vaccine formulations, for administration to animals, including companion animals (dogs and cats) and livestock, such as cattle, pigs, sheep and horses comprising a therapeutically effective amount of a compound of formula I and a veterinary acceptable carrier. However, any animal that is susceptible to seizure disorders is included within the scope of this invention. The typical mode of administration will be intramuscular, oral or subcutaneous injection of between about 0.05 ml and 25 ml of vaccine formulation. However, as indicated above, the compounds of formula I are designed to be dosed up to approximately 1200 mg per day. Vaccination can be accomplished by a single inoculation or via several inoculations. The contemplated vaccine compositions utilized in the methods of the present invention can include one or more veterinary-acceptable carriers. A "veterinary-acceptable carrier" includes any and all solvents, dispersion media, coatings adjuvants, stabilizing agents; diluents, excipients, preservatives, isotonic agents. Diluents can include water, saline, dextrose, ethanol, glycerol and the like. Isotonic agents can include sodium chloride, dextrose, mannitol, serbitol and lactose, for example. Adjuvants contemplated by the present invention include, saponin, cholesterol, aluminum hydroxide gel, Freund's complete and incomplete adjuvants. The present invention also contemplates vaccine formulations comprising from about 1 mg/ml to about 2000 mg of adjuvant/dose of the vaccine composition.

Synthetic Chemistry
General Schemes

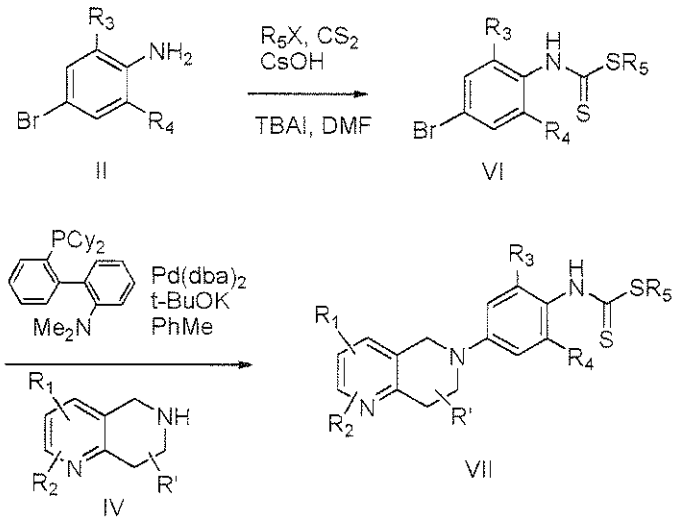
Section I. The preparation of compounds of formula V is outlined in Scheme 1.

Scheme 1:



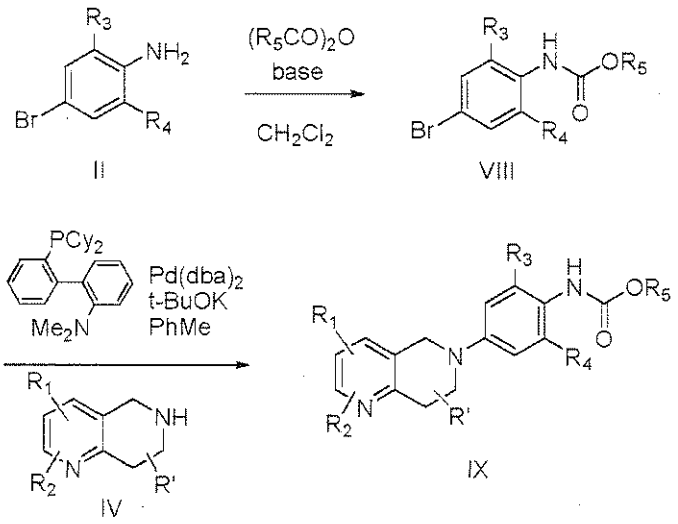
Section II. The preparation of compounds of formula VII is outlined in Scheme 2.

Scheme 2:



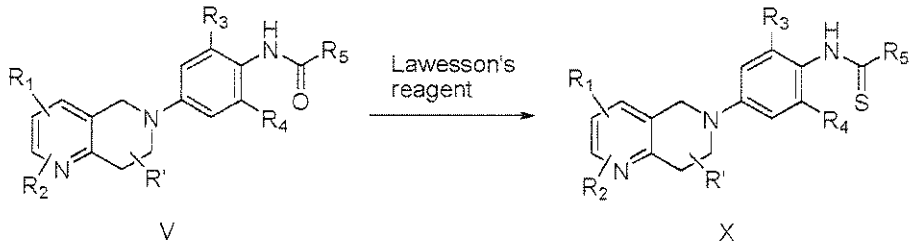
Section III. The preparation of compound of formula IX is outlined in Scheme 3.

Scheme 3:



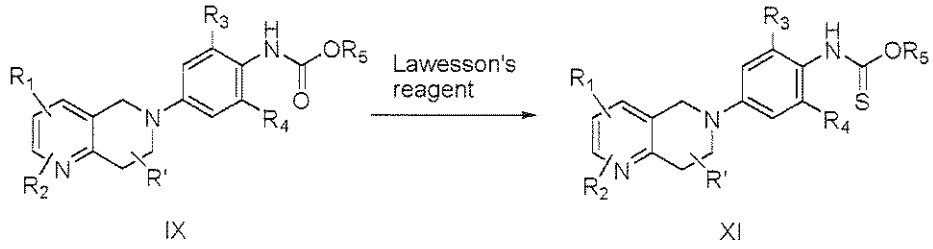
Section IV. The preparation of compound of formula X is outlined in Scheme 4.

Scheme 4:



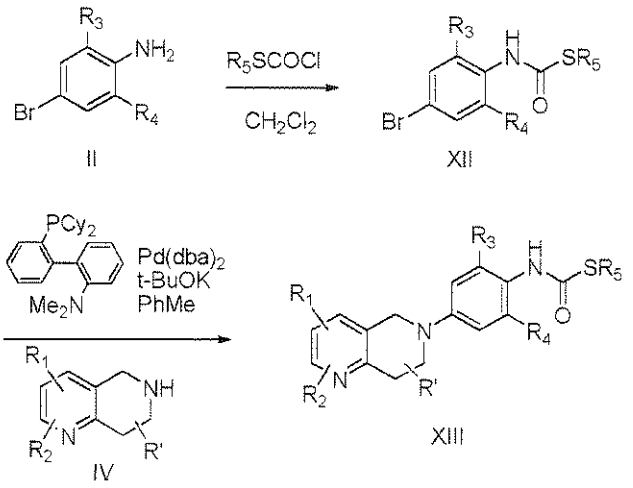
Section V. The preparation of compound of formula XI is outlined in Scheme 5.

Scheme 5:



Section VI. The preparation of compound of formula XIII is outlined in Scheme 6.

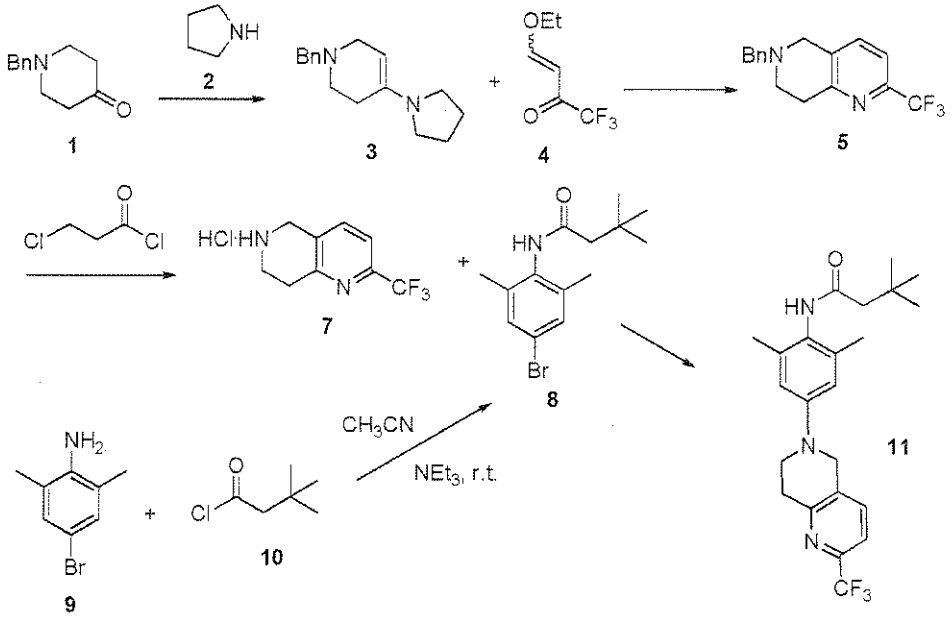
Scheme 6:



Preparation of particular compounds

Synthesis of N-[2,6-dimethyl-4-(2-trifluoromethyl-7,8-dihydro-5H-[1,6]naphthyridin-6-yl)-phenyl]-3,3-dimethyl-butyramide (11)

Scheme I



1-Benzyl-4-pyrrolidin-1-yl-1,2,3,6-tetrahydropyridine (3)

A solution containing N-benzyl piperidone 1 (5g, 26.4 mmol) and pyrrolidine 2 (2.82g, 39.6 mmol) in toluene (60 mL) was heated to reflux with azeotropic removal of water. The reaction mixture was then cooled and concentrated under reduced pressure. The resulting oil was dissolved in ether, dried over magnesium sulfate, and concentrated under reduced pressure. The crude enamine 3 was used in the next step.

6-Benzyl-2-trifluoromethyl-5,6,7,8-tetrahydro-[1,6]naphthyridine (5)

To a solution of the crude enamine 3(500mg, 2.1 mmol) in dioxane (5 mL) was added compound 4(0.3 mL, 2.1 mmol), and the mixture was stirred at room temperature overnight. Ammonium acetate (20 mg) was then added, and the mixture was heated at reflux for 18 h. The reaction mixture was then cooled to room temperature, acidified with 10% HCl, extracted with dichloromethane, and concentrated. Purification by preparative thin layer chromatography (DCM/MeOH 5%) afforded compound 5.

2-Trifluoromethyl-5,6,7,8-tetrahydro-[1,6]naphthyridine (7)

To a solution of 5 (500mg, 1.7 mmol) in dichoromethane (8 mL) was added compound 6, 3-chloro propionyl chloride (0.22 mL, 2.1 mmol) and the reaction mixture was stirred at 40 °C for 18h. The reaction was then cooled to room temperature and concentrated. The resulting residue was dissolved in methanol (16 mL) and stirred at 40°C for 3h. The mixture was then cooled to room temperature and concentrated.

N-(4-Bromo-2,6-dimethyl-phenyl)-3,3-dimethyl-butyramide (8)

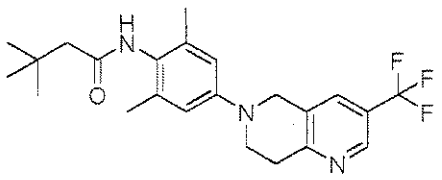
3,3-dimethylbutanoyl chloride (3.37 g, 3.5 mL, 25 mmol) and triethylamine (2.53g, 3.5 mL, 25 mmol) were added to a solution of 4-bromo-2-chloro-6- (trifluoromethyl)aniline (5.0 g, 25 mmol) in acetonitrile (30 mL). The reaction mixture was stirred at room temperature for 4 hours. Water was added to the mixture, and the precipitate formed collected to give the title compound as a powder (7.46 g, 100% yield).

N-[2,6-Dimethyl-4-(2-trifluoromethyl-7,8-dihydro-5H-[1,6]naphthyridin-6-yl)-phenyl]-3,3-dimethyl-butyramide (11)

Bis(dibenzylidineacetone)palladium (15mg, 0.026 mmol) and (2'- dicyclohexyl phosphanyl-biphenyl-2-yl)-dimethylamine (40 mg, 0.1 mmol) were added to dry toluene (5 mL

purged with argon for 30 min), and the mixture was stirred for an additional 30 minutes at room temperature under argon. Potassium *tert*-butoxide (188 g, 71 mmol), compound 7 (191mg, 0.8 mmol), aid compound **8** (200 mg, 0.67 mmol) were then added; the reaction mixture was stirred at 80°C overnight. The reaction mixture was then cooled to room temperature, filtered through a pad of silica gel, and purified by preparative TLC (DCM/MeOH 5%) to afford compound **11**.

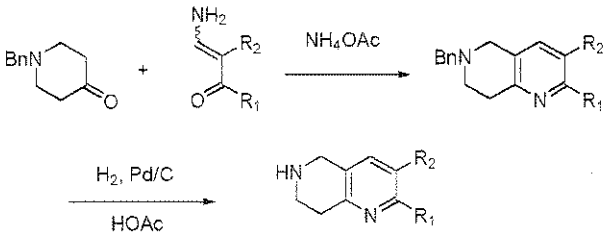
N-(2,6-dimethyl-4-(3-(trifluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)phenyl)-3,3-dimethylbutanamide



Bis(dibenzylidineacetone)palladium (4 mg, 0.069mmol) and (2'-dicyclohexylphosphanyl-biphenyl-2-yl)-dimethylamine (7 mg, 0.015 mmol) were added to dry toluene (1 mL purged with argon) and stirred for 15 minutes under argon. Potassium *tert*-butoxide (36 mg, 0.32 mmol), N-(4-bromo-2,6-dimethylphenyl)-3,3-dimethylbutanamide (52 mg, 0.17 mmol) and 3-(trifluoromethyl)-5,6,7,8-tetrahydro-1,6-naphthyridine (WO/04069162) (40 mg, 0.15 mmol) were then added and the reaction mixture was stirred at 80 °C over night. The reaction mixture was then cooled to room temperature, concentrated and purified by biotage (75% Ethyl acetate:Hexanes) to afford the desired compound as a solid. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 1.05 (s, 9H), 2.11 (s, 6H), 2.17 (s, 2H), 3.08 (t, J = 5.6 Hz, 2H), 3.64 (t, J = 5.9 Hz, 2H), 4.48 (s, 2H), 6.76 (s, 2H), 8.08 (s, 1H), 8.75 (s, 1H), 8.90 (s, 1H).**Synthesis of other substituted tetrahydro-1,6-naphthyridines**

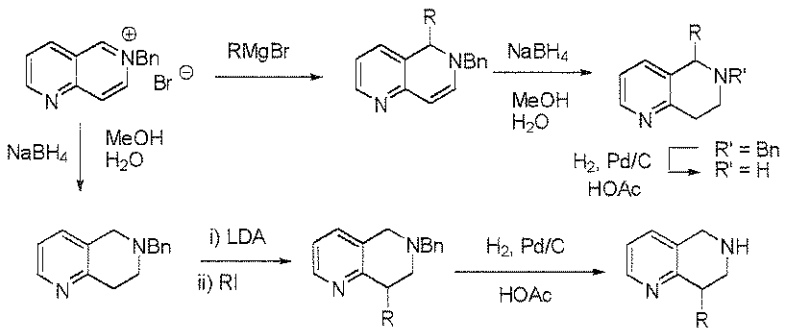
Substitution at positions 2 and 3 of tetrahydro-1,6-naphthyridines can be accomplished by the condensation of 1-benzyl-4-piperidinone with the corresponding 3-amino-enones followed by debenzylation. (Scheme II)

Scheme II



Alkylation at the 5- or 8- position of tetrahydro-1,6-naphthyridines can be accomplished by chemical modification of pyridine derivatives. (See Scheme III)

Scheme III



Biological Results

Compounds of this invention formula were evaluated as potassium channel modulators by measuring rhubidium ion release in the following assay.

Methods: PC-12 cells were grown at 37 °C and 5 % CO_2 in DMEM/F12 Medium supplemented with 10 % horse serum, 5% fetal bovine serum, 2 mM glutamine, 100 U/ml penicillin, 100 U/mi streptomycin. They were plated in poly- D-lysine-coated 96-well cell culture microplates at a density of 40,000 cells/well and differentiated with 100 ng/ml NGF-7s for 2-5 days. For the assay, the medium was aspirated, and the cells were washed once with 0.2 ml in wash buffer (25 mM HEPES, pH 7.4, 150 mM NaCl, 1 mM $MgCl_2$, 0.8 mM NaH_2PO_4, 2 mM $CaCl_2$). The cells were then loaded with 0.2 ml Rb^+ loading buffer (wash buffer plus 5.4 mM $RbCl_2$, 5 mM glucose) and incubated at 37 °C for 2 h. Attached cells were quickly washed three times with buffer (same as Rb^+ loading buffer, but containing 5.4 mM KCl instead of RbCl) to remove extracellular Rb^+. Immediately following the wash, 0.2 ml of depolarization buffer (wash buffer plus 15 mM KCl) with or without compounds was added to the cells to activate efflux of potassium ion channels. After incubation for 10 min at room temperature, the supernatant was carefully removed and collected. Cells were lysed by the addition of 0.2 ml of lysis buffer (depolarization buffer plus 0.1 % Triton X- 100) and the cell lysates were also collected. If collected samples were not immediately analyzed for Rb^+ contents by atomic absorption spectroscopy (see below), they were stored at 4°C without any negative effects on subsequent Rb^+ analysis.

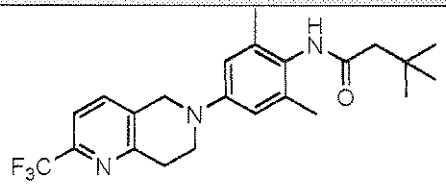
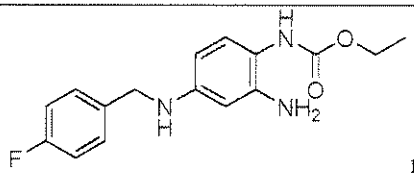
The concentration of Rb^+ in the supernatants (Rb^+_{sup}) and cell lysates (Rb^+_{Lys}) was quantified using an ICR8000 flame atomic absorption spectrometer (Aurora Biomed Inc., Vancouver, B.C.) under conditions defined by the manufacturer. One 0.05 ml samples were processed automatically from microtiter plates by dilution with an equal volume of Rb^+ sample analysis buffer and injection into an air-acetylene flame. The amount of Rb^+ in the sample was measured by absorption at 780 nm using a hollow cathode lamp as light source and a PMT detector. A calibration curve covering the range 0-5 mg/L Rb in sample analysis buffer was generated with each set of plates. The percent Rb^+ efflux (F) was defined by

$$F = [Rb^+_{sup} / (Rb^+_{sup} + Rb^+_{Lys})] \text{ X } 100\ \%$$

The effect (E) of a compound was defined by: $E = [(F_c - F_b)/(F_s - F_b)]$ x 100 % where the F_c is the efflux in the presence of compound in depolarization buffer, F_b is the efflux in basal buffer, and F_s is the efflux in depolarization buffer, and F is the efflux in the presence of compound in depolarization buffer. The effect (E) and compound concentration relationship was plotted to calculate an EC_{50} value, a compound's concentration for 50% of maximal Rb+ efflux. The results are shown below. Legend: A: EC_{50} = 1 nM - 50 nM; B: EC_{50} = 50 nM - 100 nM; C: EC_{50} = 100 - 500 nM

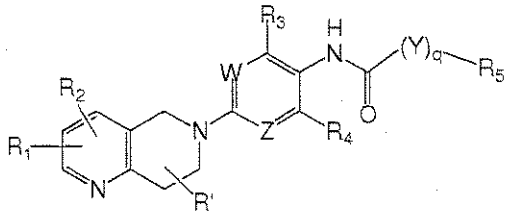
TABLE 1

ACTIVITY OF EXEMPLARY COMPOUND

COMPOUND	ACTIVITY
	A
 retigabine	C

What is claimed:

1. A compound of formula I



I

where W and Z are, independently, CH or N; Y is CH_2, O or NH;

where R_1 and R_2, are, independently, H, halogen, CH_2F, CHF_2, CF_3, CF_2CF_3, C_1-C_6 alkyl, $C(=O)C_1$-C_6 alkyl, $CH_2C(=O)C_1$-C_6 alkyl, NH-C_1-C_6 alkyl, $NHC(=O)C_1$-C_6 alkyl, $C(=O)N(CH_3)_2$, $C(=O)N(Et)_2$, $C(=O)NH$-C_1-C_6 alkyl, $C(=O)OC_1$-C_6 alkyl, $OC(=O)C_1$-C_6 alkyl, OC_1-C_6 alkyl, SC_1-C_6 alkyl, C_3-C_6 cycloalkyl, $(CH_2)_mC_3$-C_6 cycloalkyl, C_3-C_6 cycloalkenyl, $(CH_2)_mC_3$-C_6 cycloalkenyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, Ar_1, $(CH_2)_mAr_1$, phenyl, pyridyl, pyrrolyl, $(CH_2)_m$imidazolyl, $(CH_2)_m$pyrazyl, furyl, thienyl, $(CH_2)_m$oxazolyl, $(CH_2)_m$isoxazolyl, $(CH_2)_m$thiazolyl, $(CH_2)_m$isothiazolyl, $(CH_2)_m$phenyl, $(CH_2)_m$pyrrolyl, $(CH_2)_m$pyridyl, or $(CH_2)_m$pyrimidyl, which cycloalkyl and said cycloalkenyl groups optionally contain one or two heteroatoms selected independently from O, N, and S, and which alkyl, cycloalkyl, cycloalkenyl, alkenyl, alkynyl, imidazolyl, pyrazyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, phenyl, pyrrolyl, pyridyl, or pyrimidyl groups are optionally substituted with one or two groups selected, independently, from OH, halogen, cyano, methyl, ethyl, or trifluoromethyl, where m is zero, 1, or 2;

or R_1 and R_2, together with the ring carbon atoms to which they are attached, form a 5- or 6-member fused ring, which ring may be saturated, unsaturated, or aromatic, which optionally contains one or two heteroatoms selected independently from O, N, and S, and which is optionally substituted with halogen, CF_3, or C_1-C_3 alkyl;

R' is H, halogen, CF_3, or C_1-C_3 alkyl;

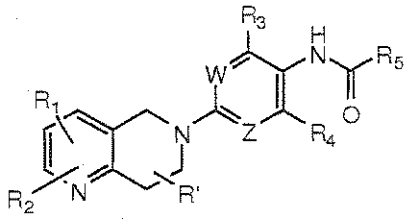
R_3 and R_4 are, independently, H, NH_2, (C_1-C_3 alkyl)NH, CN, halogen, CF_3, OCF_3, OC_1-C_3 alkyl, or C_1-C_3 alkyl, all said C_1-C_3 alkyl groups and said C_1-C_6 alkyl groups optionally

substituted with one or two groups selected, independently, from OH, halogen, C_1-C_3 alkyl, OC_1-C_3 alkyl, or trifluoromethyl;

q = 1 or 0;

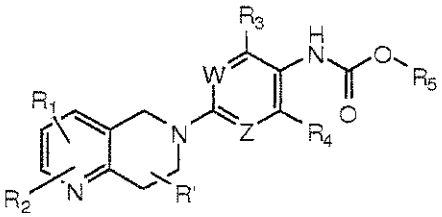
R_5 is C_1-C_6 alkyl, $(CHR_6)_wC_3$-C_6 cycloalkyl, $(CHR_6)_wCH_2C_3$-C_6 cycloalkyl, $CH_2(CHR_6)_wC_3$-C_6 cycloalkyl, CR_6=CH-C_3-C_6 cycloalkyl, CH=CR_6-C_3-C_6 cycloalkyl, $(CHR_6)_wC_5$-C_6 cycloalkenyl, $CH_2(CHR_6)_wC_5$-C_6 cycloalkenyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, Ar_1, $(CHR_6)_wAr_1$, $CH_2(CHR_6)_wAr_1$, or $(CHR_6)_wCH_2Ar_1$, where w = 0 – 3, Ar_1 is phenyl, pyridyl, furyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, or imidazolyl, wherein said C_1-C_6 alkyl group is optionally substituted with hydroxy, methoxy, methylthio, or halogen, and where said cycloalkyl and cycloalkenyl groups are optionally substituted with one or two groups selected, independently, from OH, halogen, cyano, methoxy, methyl, ethyl, or trifluoromethyl; R_6 is hydrogen, methyl, halogen, or methoxy; and pharmaceutically acceptable salts thereof.

2. The compound of claim 1 which is a compound of formula IA



IA

3. The compound of claim 1 which is a compound of formula IB.



IB

4. The compound of claim 2, where W and Z are CH and R' is halogen, C_1-C_3 alkyl, or H.

5. The compound of claim 3, where W and Z are CH and R' is halogen, C_1-C_3 alkyl, or H.

6. The compound of claim 2, where W and Z are both N and R' is halogen, C_1-C_3 alkyl, or H.

7. The compound of claim 3, where W and Z are both N, and R' is halogen, C_1-C_3 alkyl, or H.

8. The compound of claim 2, where W is N, Z is CH, and R' is halogen, C_1-C_3 alkyl, or H.

9. The compound of claim 3, where W is N, Z is CH, and R' is halogen, C_1-C_3 alkyl, or H.

10. The compound of claim 4, where R_3 and R_4 are, independently, methyl, amino, aminomethyl, methoxy, trifluoromethyl, or chloro.

11. The compound of claim 5, where R_3 and R_4 are, independently, methyl, amino, aminomethyl, methoxy, trifluoromethyl, or chloro.

12. The compound of claim 10, where R_3 and R_4 are, independently chloro, trifluoromethyl, methoxy, or methyl, R_5 is C_5-C_6 alkyl, $(CHR_6)_wCH_2C_3$-C_6 cycloalkyl, or $CH_2(CHR_6)_wC_3$-C_6 cycloalkyl, said C_5-C_6 alkyl group optionally substituted methoxy or halogen, and said cycloalkyl groups optionally substituted with one or two groups selected, independently, from OH, halogen, cyano, methoxy, methyl, ethyl, or trifluoromethyl.

13. The compound of claim 11, where R_3 and R_4 are, independently chloro, trifluoromethyl, methoxy, or methyl, and R_5 is C_5-C_6 alkyl, $(CHR_6)_wCH_2C_3$-C_6 cycloalkyl, or $CH_2(CHR_6)_wC_3$-C_6 cycloalkyl, said C_5-C_6 alkyl group optionally substituted methoxy or halogen, and said cycloalkyl groups optionally substituted with one or two groups selected, independently, from OH, halogen, cyano, methoxy, methyl, ethyl, or trifluoromethyl.

14. The compound of claim 12, where R_3 and R_4 are, independently chloro, trifluoromethyl, or methyl, and R_5 is C_5-C_6 alkyl, $(CHR_6)_wCH_2C_3$-C_6 cycloalkyl, or $CH_2(CHR_6)_wC_3$-C_6 cycloalkyl, said C_5-C_6 alkyl group optionally substituted methoxy or halogen, and said cycloalkyl groups optionally substituted with one or two groups selected, independently, from OH, halogen, cyano, methoxy, methyl, ethyl, or trifluoromethyl.

15. The compound of claim 13, where R_1 is H, halogen, CH_2F, CHF_2, CF_3, CF_2CF_3, C_1-C_6 alkyl, $C(=O)C_1$-C_6 alkyl.

16. The compound of claim 14, where R_1 is H, halogen, CH_2F, CHF_2, CF_3, CF_2CF_3, C_1-C_6 alkyl, $C(=O)C_1$-C_6 alkyl.

17. The compound of claim 15, where R_5 is C_5-C_6 alkyl or $CH_2(CHR_6)_wC_3$-C_6 cycloalkyl, where w = 1 and R_6 is H, methyl, or methoxy.

18. The compound of claim 16, where R_5 is C_5-C_6 alkyl or $CH_2(CHR_6)_wC_3$-C_6 cycloalkyl, where w = 1 and R_6 is H, methyl, or methoxy.

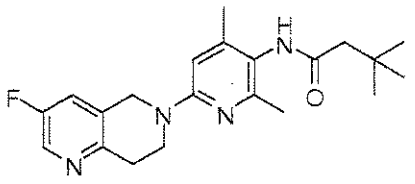
19. The compound of claim 17, where R_3 and R_4 are both methyl, and R_5 is neopentyl or 2-cyclohexyl ethyl.

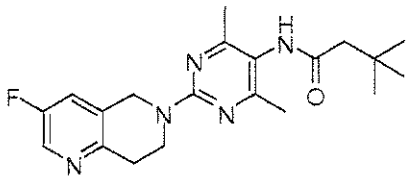
20. The compound of claim 18, where R_3 and R_4 are both methyl, and R_5 is neopentyl or 2-cyclohexyl ethyl.

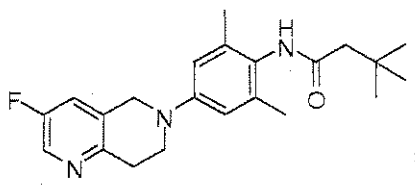
21. The compound of claim 19, where R_1 is F or CF_3, and R_2 is H or F.

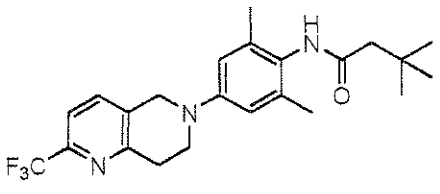
22. The compound of claim 20, where R_1 is F or CF_3, and R_2 is H or F.

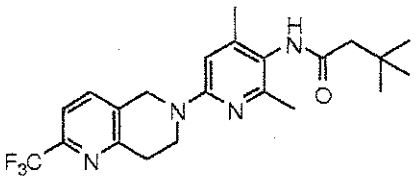
23. A compound selected from the group consisting of:

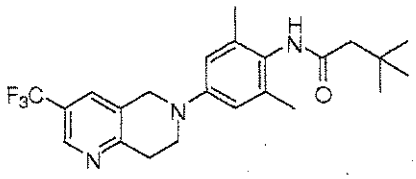


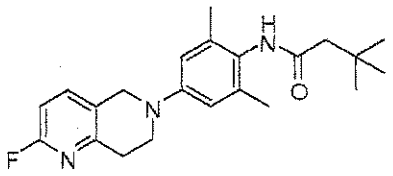


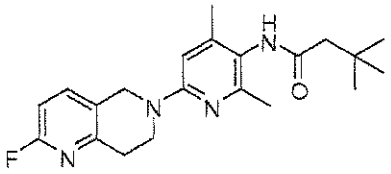


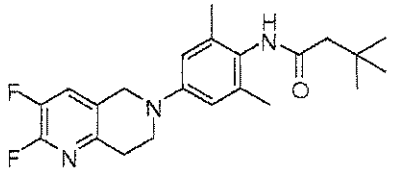


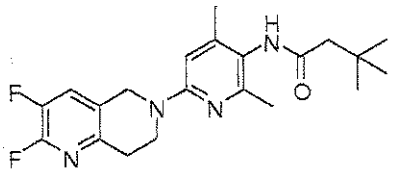












24. A composition comprising a pharmaceutically acceptable carrier and at least one of the following: i) a pharmaceutically effective amount of a compound of formula I; ii) a pharmaceutically acceptable salt of a compound of formula I; iii) a pharmaceutically acceptable ester of a compound of formula I; iv) a pharmaceutically solvate of a compound of formula I.

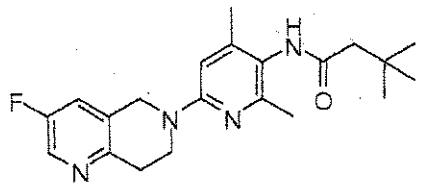
25. The composition of claim 24, in which the pharmaceutically acceptable carrier is microcrystalline cellulose.

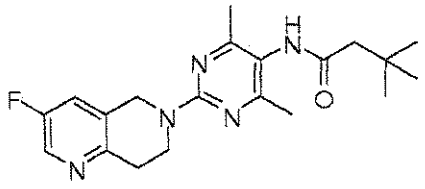
26. Use of a therapeutically effective amount of a compound of formula I according to claim 1 or a pharmaceutically acceptable salt, solvate, or ester thereof in the manufacture of a medicament for preventing or treating a disease or disorder which is affected by activation of voltage-gated potassium channels.

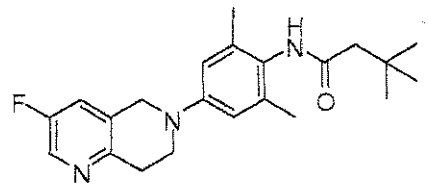
27. The use of claim 26. wherein the disease or disorder is a seizure disorder.

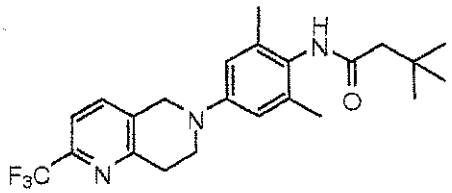
28. The use of claim 27. wherein the compound of formula I is a compound of formula IA.

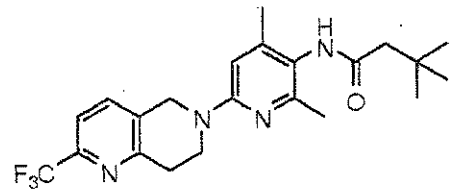
29. The use of claim 26, wherein the compound of formula I is selected from the group consisting of:

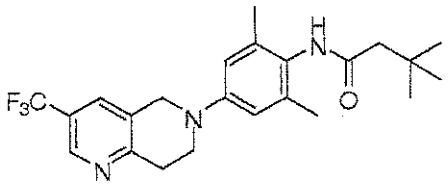


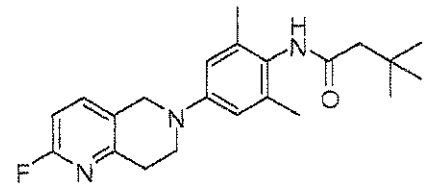


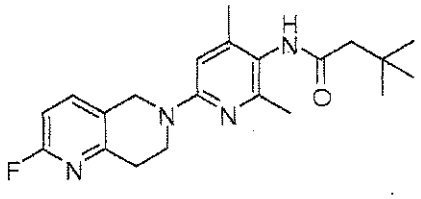


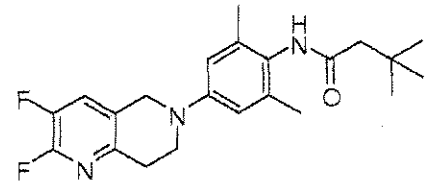


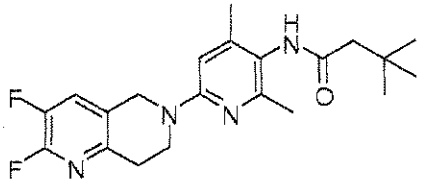












30. The use of any of claims 27-29, wherein the therapeutically effective amount is from approximately 300 mg to approximately 2000 mg per day.

31. Use of a compound of formula I or a salt, solvate, or a ester thereof in the manufacture of a medicament for increasing the channel open probability of KCNQ2/3 channels in a mammal.

32. The use of claim 31, where the compound of formula I is a compound of formula IA.

33. Use of a compound of formula IA or a salt, solvate, or ester thereof in the manufacture of a medicament for increasing neuronal M currents in a mammal.

34. A tablet for oral dosing comprising a pharmaceutically acceptable carrier and from approximately 100 to approximately 700 mg of a compound of formula IA or a salt, solvate, or ester thereof.

35. The tablet of claim 34, further comprising a lubricant.

36. The tablet of claim 34, further comprising a disintegrant.

37. The tablet of claim 34, wherein the tablet is chewable.

38. A pharmaceutical syrup for pediatric use, comprising from approximately 100 to approximately 700 mg per dose of a compound of formula IA or a salt, solvate, or ester thereof.