DERIVATIVES OF 4-(N-AZACYCLOALKYL) ANILIDES AS POTASSIUM CHANNEL MODULATORS

Field of the Invention

This invention concerns novel compounds that activate or otherwise modulate voltage-gated potassium channels. The compounds are useful for the treatment and prevention of diseases and disorders which are affected by modulation of potassium ion channels. One such condition is seizure disorders.

Background of the Invention

Epilepsy is a well-known neurological disease, found in about 3% of the population. Approximately 30% of patients with epilepsy do not respond to currently available therapies. Such unfortunate patients – who number hundreds of thousands of people world-wide – must contend with both uncontrolled seizures and the resulting narrowing of their options in such crucial areas of life as health insurance, employment, and driving.

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

"Benign familial neonatal convulsions," an inherited form of epilepsy, 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 one important site of action of retigabine 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

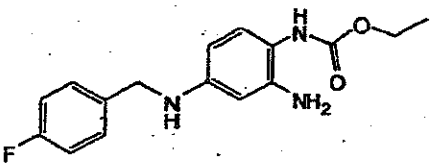
increase the conductance of the channels at the resting membrane potential, with a possible mechanism involving binding of the activation gate of the KCNQ 2/3 channel. Wuttke, T.V., *et al.*, *Mol. Pharmacol.* **2005**. Additionally, retigabine has been shown to increase neuronal M currents and to increase 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 seizure type that has been most resistant to therapy is the so-called "complex partial seizure." Retigabine is active in several seizure models, including, as indicated above, models for drug-refractory epilepsy. Because of retigabine's broad spectrum of activity and its unusual molecular mechanism, there is hope that retigabine will be effective in management of several seizure types, including the complex partial seizure, which have been resistant to treatment. Porter, R. J., Nohria, V., and Rundfeldt, C., *Neurotherapeutics*, **2007**, vol. 4, 149-154.

The recognition of retigabine as a potassium channel opener has inspired a search among compounds with structural features in common with retigabine for other compounds which can affect the opening of, or otherwise modulate, potassium ion channels.

Summary

In their efforts to design a potassium channel modulating compound that is superior to retigabine, shown below, which is a benzyl amine derivative,

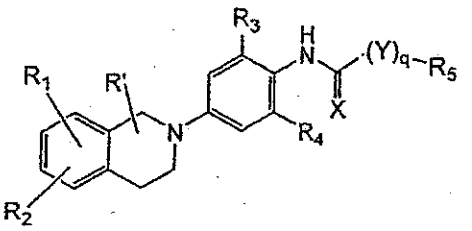


the present inventors have discovered surprising and exceptionally promising properties in a series of tetrahydroisoquinoline derivatives, specifically, para-*N*-(1,2,3,4-tetrahydro) isoquinolyl anilides and carbamates, and their several sulfur analogues, of the structure of formula IA below

These tetrahydroisoquinoline derivatives are, of course, benzyl amines which are restricted to particular conformations because the benzylic nitrogen is a member of a

second ring fused to the phenyl ring. Moreover, the present inventors have further discovered that replacement of the primary amino group of retigabine with substituents like halogen, C_1-C_3 alkyl, OC_1-C_3 alkyl, and trifluoromethyl also confers surprising and desirable properties.

In a first aspect, there is provided a compound of formula 1A

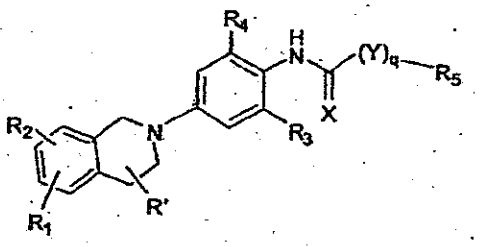


IA

where R_1 and R_2, are, independently, H, CN, halogen, CH_2CN, OH, CH_2F, CHF_2, CF_3, CF_2CF_3, C_1-C_6 alkyl, $C(=O)C_1$-C_6 alkyl; NH-C_1-C_6 alkyl; $N(C_1$-C_6 alkyl)-C_1-C_6 alkyl, $NHC(=O)C_1$-C_6 alkyl, $C(=O)N(CH_3)_2$, $C(=O)N(Et)_2$, $C(=O)NH_2$, $C(=O)NH$-C_1-C_6 alkyl, SO_2NH_2, $NHSO_2$-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, $(CH_2)_m$thienyl, $(CH_2)_m$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 $(CH_2)_m$pyrimidyl, where m = zero, 1, or 2, Ar is a 5- to 10- member mono- or bicyclic aromatic group, optionally containing 1 – 4 ring heteroatoms selected independently from N, O, and S; 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; R' is H, halogen, phenyl, 2-(N,N-dimethylamino)ethyl, CF_3, OC_1-C_3 alkyl or C_1-C_3 alkyl; R_3 and R_4 are, independently, H, CN, halogen, CF_3, OCF_3, OC_1-C_3 alkyl, or C_1-C_3 alkyl; X is O or S; Y is O or S; q = 1 or zero; 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, $(CHR_6)_w$Ar, $CH_2(CHR_6)_w$Ar, or $(CHR_6)_wCH_2$Ar, where w = zero, 1, 2, or 3, Ar is a 5- to 10- member mono- or bicyclic aromatic group, optionally containing 1 – 4 ring heteroatoms selected independently from N, O, and S; R_6 is H or C_1-C_3 alkyl; where all cycloalkyl and cycloalkenyl groups optionally contain one or two ring heteroatoms

selected independently from N, O, and S; where all alkyl, cycloalkyl, alkenyl, cycloalkenyl, heterocycloalkyl, heterocycloalkenyl, alkynyl, aryl, and heteroaryl groups in R_1, R_2, R', R_3, R_4, R_5, R_6, and Ar are optionally substituted with one or two substituents selected independently from C_1-C_3 alkyl, halogen, OH, OEt, OMe, CN, CH_2F, OCF_3, and CF_3; and where, additionally, all cycloalkyl and heterocycloalkyl groups are optionally substituted with a carbonyl group.

Thus, in one embodiment, this disclosure provides or contemplates a compound of formula IA



IA

where R_1 and R_2, are, independently, H, CN, halogen, CH_2CN, OH, NO_2, CH_2F, CHF_2, CF_3, CF_2CF_3, C_1-C_6 alkyl, C(=O)C_1-C_6 alkyl; NH_2, NH-C_1-C_6 alkyl; N(C_1-C_6 alkyl)-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_2, C(=O)NH-C_1-C_6 alkyl, SO_2NH_2, $NHSO_2$-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, $(CH_2)_m$thienyl, $(CH_2)_m$furyl, $(CH_2)_m$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 $(CH_2)_m$pyrimidyl, which cycloalkyl and said cycloalkenyl groups optionally contain one or two heteroatoms selected independently from O, N, and S, and which are optionally substituted as described below; where m is zero, 1, or 2, Ar is a 5- to 10- member mono- or bicyclic aromatic group, optionally containing 1 – 4 ring heteroatoms selected independently from N, O, and S; 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 as described below; R' is H, halogen, phenyl, 2-(N,N-dimethylamino)ethyl, CF_3, OC_1-C_3 alkyl or C_1-C_3 alkyl; R_3 and R_4 are, independently, H, CN, halogen, CF_3, OCF_3, OC_1-C_3 alkyl, or C_1-C_6 alkyl; X = O or S; Y is O or S; q = 1 or zero; 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, $(CHR_6)_wAr$, $CH_2(CHR_6)_wAr$, or $(CHR_6)_wCH_2Ar$, where w = zero, 1, 2, or 3, Ar is a 5- to 10- member mono- or bicyclic aromatic group, optionally containing 1 – 4 ring heteroatoms selected independently from N, O, and S; R_6 is H or C_1-C_3 alkyl; where all cycloalkyl and cycloalkenyl groups optionally contain one or two ring heteroatoms selected independently from N, O, and S; where all alkyl, cycloalkyl, alkenyl, cycloalkenyl, heterocycloalkyl, heterocycloalkenyl, alkynyl, aryl, and heteroaryl groups in R_1, R_2, R', R_3, R_4, R_5, R_6, and Ar are optionally substituted with one or two substituents selected independently from C_1-C_3 alkyl, halogen, CN, OH, OMe, OEt, CN, CH_2F, and trifluoromethyl; and where, additionally, all cycloalkyl and heterocycloalkyl groups are optionally substituted with a carbonyl group. Such compounds are potassium channel activators or modulators.

Essentially all combinations of the several variables in formula IA are contemplated by this invention.

In another embodiment, this disclosure provides or contemplates a composition comprising a pharmaceutically acceptable carrier or diluent and at least one of the following: a pharmaceutically effective amount of a compound of formula IA, a pharmaceutically acceptable salt of a compound of formula IA, a pharmaceutically acceptable solvate of a compound of formula IA, and a pharmaceutically acceptable ester of a compound of formula IA.

In yet another embodiment, this disclosure provides or contemplates a pediatric pharmaceutical composition comprising a pharmaceutically acceptable carrier or diluent, a syrup for pediatric use, and at least one of the following: a pharmaceutically effective amount of a compound of formula IA, a pharmaceutically acceptable salt of a compound of formula IA, a pharmaceutically acceptable ester of a compound of formula IA, and a pharmaceutically acceptable solvate of a compound of formula IA.

In yet another embodiment, this disclosure provides or contemplates a chewable tablet, suitable for pediatric pharmaceutical use, comprising a pharmaceutically acceptable carrier or diluent, and at least one of the following: a pharmaceutically

effective amount of a compound of formula IA, a pharmaceutically acceptable salt of a compound of formula IA, a pharmaceutically acceptable solvate of a compound of formula IA, and a pharmaceutically acceptable ester of a compound of formula IA.

In yet another embodiment, this disclosure provides or contemplates a method of preventing or treating a disease or disorder which is affected by activation voltage-gated potassium channels, comprising administering to a patient in need thereof a therapeutically effective amount of a compound of formula IA or a salt or ester or solvate thereof.

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

This disclosure provides or contemplates compounds of formula IA above where the group NH-C(=X)-$(Y)_q$-R_5 is each of the following: NHC(=O)R_5, NHC(=O)OR_5, NHC(=S)R_5, NHC(=S)SR_5, NHC(=S)OR_5, and NHC(=O)SR_5.

Thus, in one embodiment, this disclosure provides or contemplates a compound of formula IA, where NH-C(=X)-$(Y)_q$-R_5 is NHC(=O)R_5.

In another embodiment, this disclosure provides or contemplates a compound of formula IA, where NH-C(=X)-$(Y)_q$-R_5 is NHC(=S)R_5.

In another embodiment, this disclosure provides or contemplates a compound of formula IA, where NH-C(=X)-$(Y)_q$-R_5 is NHC(=S)SR_5.

In another embodiment, this disclosure provides or contemplates a compound of formula IA, where NH-C(=X)-$(Y)_q$-R_5 is each NHC(=O)OR_5.

In another embodiment, this disclosure provides or contemplates a compound of formula IA, where NH-C(=X)-$(Y)_q$-R_5 is NHC(=S)OR_5.

In another embodiment, this disclosure provides or contemplates a compound of formula IA, where NH-C(=X)-$(Y)_q$-R_5 is NHC(=O)SR_5.

In another generic embodiment, this disclosure provides or contemplates a compound of formula IA, where q is zero and R_5 is C_1-C_6 alkyl, or $(CHR_6)_w$$C_3$-$C_6$ cycloalkyl.

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

In another subgeneric embodiment, this disclosure provides or contemplates a compound of formula IA, where R' is phenyl.

In another subgeneric embodiment, this disclosure provides or contemplates a compound of formula IA, where R' is OC_1-C_3 alkyl.

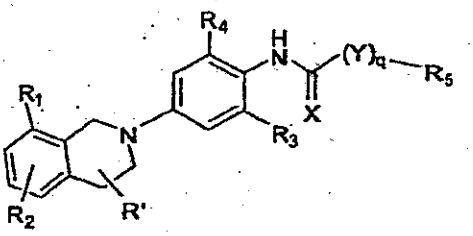
In another subgeneric embodiment, this disclosure provides or contemplates a compound of formula IA, where R' is 2-dimethylaminoethyl.

In another subgeneric embodiment, this disclosure provides or contemplates a compound of formula IA, where R' is H.

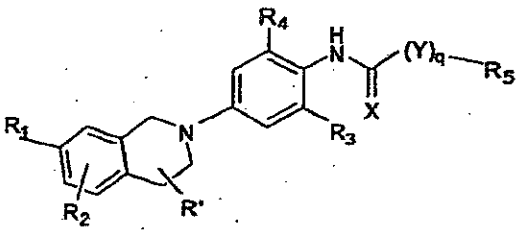
In another subgeneric embodiment, this disclosure provides or contemplates a compound of formula IA, where R' halogen.

In another subgeneric embodiment, this disclosure provides or contemplates a compound of formula IA, where R' is methyl or ethyl.

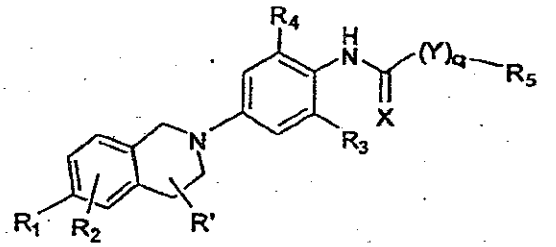
In another subgeneric embodiment, R_1 is located as shown below



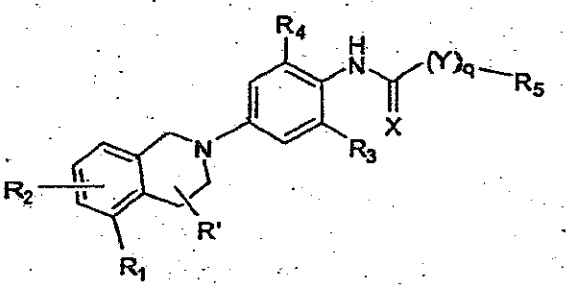
In another subgeneric embodiment, R_1 is located as shown below



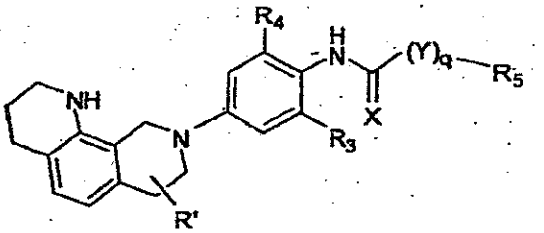
In another subgeneric embodiment, R_1 is located as shown below



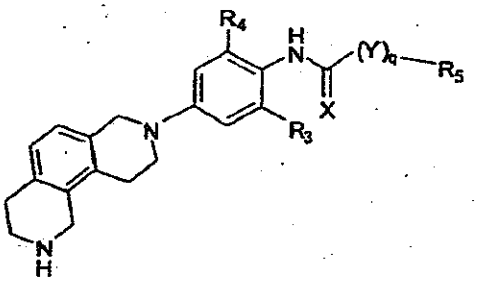
In another subgeneric embodiment, R_1 is located as shown below



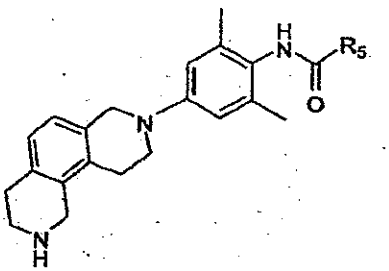
In another subgeneric embodiment, this disclosure provides or contemplates a compound of the structure shown below.



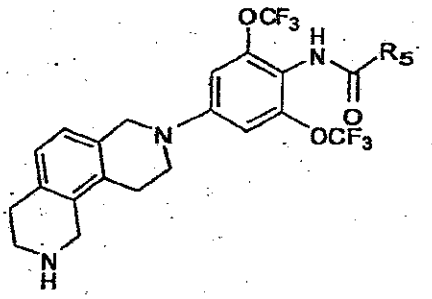
In another subgeneric embodiment, this disclosure provides or contemplates a compound of the structure shown below.



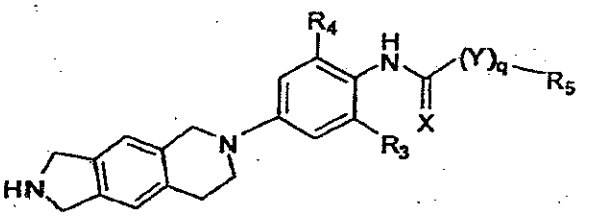
In a more specific subgeneric embodiment, this disclosure provides or contemplates a compound of the structure shown below, where R_5 is C_5-C_6 alkyl or $(CH_2)_wC_5$-C_6 cycloalkyl.



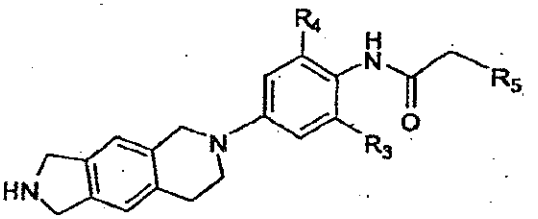
In another more specific subgeneric embodiment, this disclosure provides or contemplates a compound of the structure shown below, where R_5 is C_5-C_6 alkyl or $(CH_2)_wC_5$-C_6 cycloalkyl.



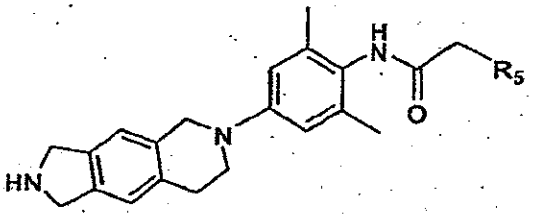
In another specific subgeneric embodiment, this disclosure provides or contemplates a compound of the structure shown below, where R_3 and R_4 are, independently, H, methyl, or methoxy.



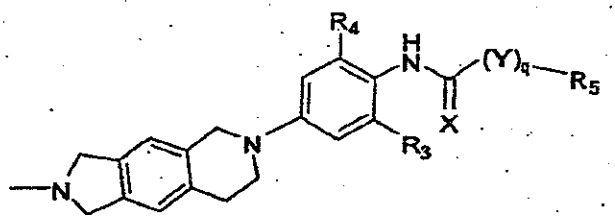
In a more specific subgeneric embodiment, this disclosure provides or contemplates a compound of the structure shown below, where R_3 and R_4 are, independently, H, methyl, or methoxy, and R_5 is C_5-C_6 alkyl or $(CH_2)_wC_5$-C_6 cycloalkyl.



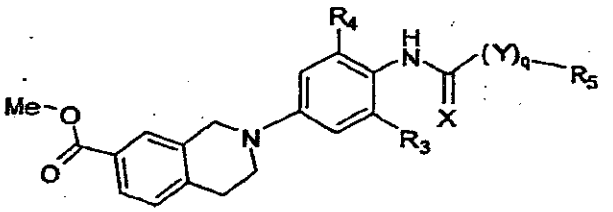
In a still more specific subgeneric embodiment, this disclosure provides or contemplates a compound of the structure shown below, where R_5 is C_5-C_6 alkyl or $(CH_2)_w$ C_5-C_6 cycloalkyl.



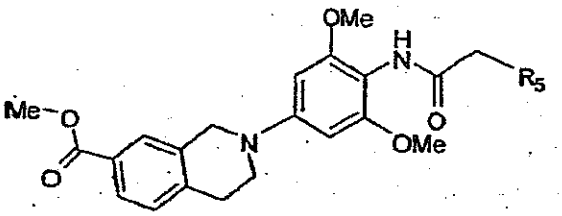
In another specific subgeneric embodiment, this disclosure provides or contemplates a compound of the structure shown below, where R_3 and R_4 are, independently, H, methyl, or methoxy.



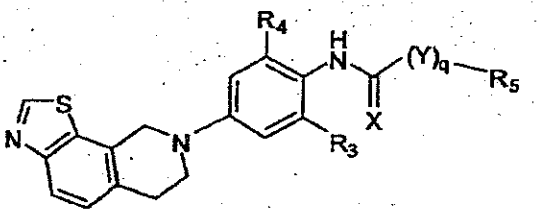
In another specific subgeneric embodiment, this disclosure provides or contemplates a compound of the structure shown below, where R_3 and R_4 are, independently, H, methyl, or methoxy.



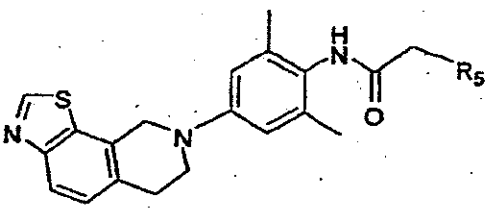
In a still more specific subgeneric embodiment, this disclosure provides or contemplates a compound of the structure shown below, where R_5 is C_5-C_6 alkyl or $(CH_2)_w$ C_5-C_6 cycloalkyl.



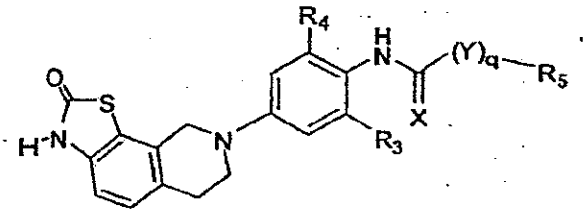
In another specific subgeneric embodiment, this disclosure provides or contemplates a compound of the structure shown below, where R_3 and R_4 are, independently, H, methyl, Cl, CF_3, OCF_3, or methoxy.



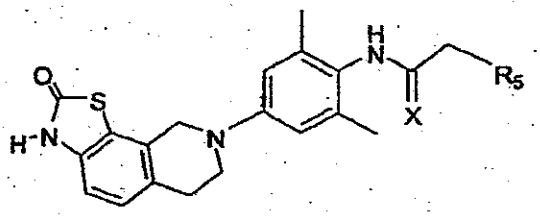
In a still more specific subgeneric embodiment, this disclosure provides or contemplates a compound of the structure shown below, where R_5 is C_5-C_6 alkyl or $(CH_2)_w$ C_5-C_6 cycloalkyl.



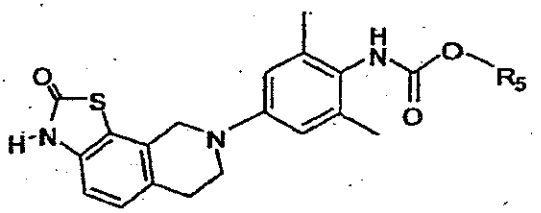
In another specific subgeneric embodiment, this disclosure provides or contemplates a compound of the structure shown below, where R_3 and R_4 are, independently, H, methyl, Cl, CF_3, OCF_3, or methoxy.



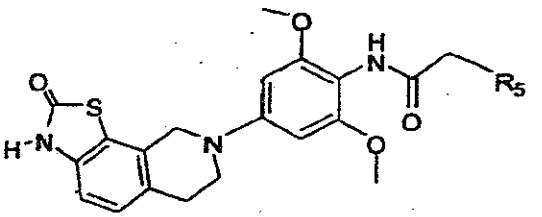
In a more specific subgeneric embodiment, this disclosure provides or contemplates a compound of the structure shown below, where R_5 is C_5-C_6 alkyl or $(CH_2)_w$ C_5-C_6 cycloalkyl.



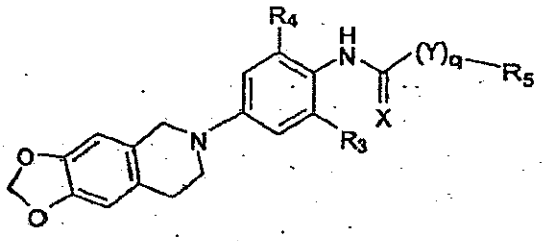
In another more specific subgeneric embodiment, this disclosure provides or contemplates a compound of the structure shown below, where R_5 is C_5-C_6 alkyl or $(CH_2)_w$ C_5-C_6 cycloalkyl.



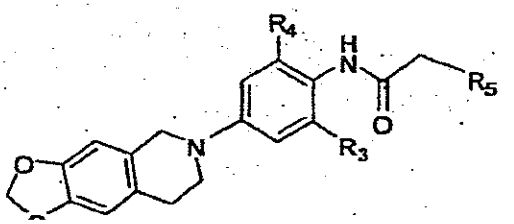
In yet another more specific subgeneric embodiment, this disclosure provides or contemplates a compound of the structure shown below, where R_5 is $(CH_2)_wAr$ or C_3-C_6 alkyl.



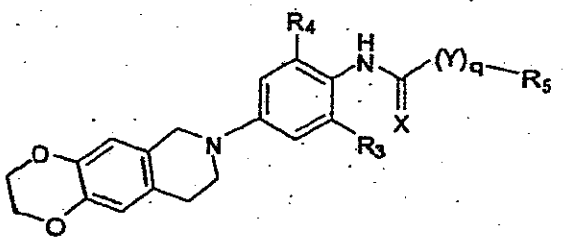
In another subgeneric embodiment, this disclosure provides or contemplates a compound of the structure shown below, where R_3 and R_4 are, independently, H, methyl, Cl, CF_3, OCF_3, or methoxy.



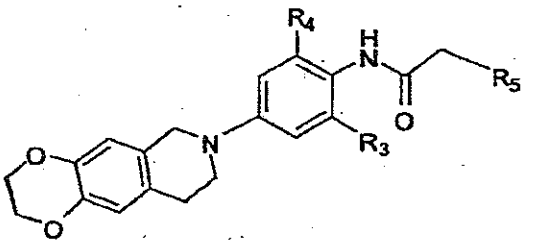
In a more specific subgeneric embodiment, this disclosure provides or contemplates a compound of the structure shown below, where R_3 and R_4 are, independently, H, methyl, Cl, CF_3, OCF_3, or methoxy and R_5 is $(CH_2)_wAr$ or C_3-C_6 alkyl.



In another subgeneric embodiment, this disclosure provides or contemplates a compound of the structure shown below, where R_5 is $(CH_2)_wAr$ or C_3-C_6 alkyl.



In yet another more specific subgeneric embodiment, this disclosure provides or contemplates a compound of the structure shown below, where R_3 and R_4 are, independently, H, methyl, Cl, CF_3, OCF_3, or methoxy and where R_5 is $(CH_2)_wAr$ or C_3-C_6 alkyl.



In another subgeneric embodiment, this disclosure provides or contemplates a compound of formula IA, where R_2 is H.

In another subgeneric embodiment, this disclosure provides or contemplates a compound of formula IA, where R_2 is halogen.

In another, more specific subgeneric embodiment, this disclosure provides or contemplates a compound of formula IA, where R_2 is Cl or F.

In another subgeneric embodiment, this disclosure provides or contemplates a compound of formula IA, where R_2 is trifluoromethyl.

In another subgeneric embodiment, this disclosure provides or contemplates a compound of formula IA, where R_3 and R_4 are, independently, H, Cl, methyl, ethyl, trifluoromethyl, or methoxy.

In another, more specific subgeneric embodiment, this disclosure provides or contemplates a compound of formula IA, where q is zero and R_3 and R_4 are Cl, ethyl, methoxy, or methyl.

In another, more specific subgeneric embodiment, this disclosure provides or contemplates a compound of formula IA, where q is zero and R_3 and R_4 are both methyl.

In another subgeneric embodiment, this disclosure provides or contemplates a compound of formula IA, where R' is methyl, halogen, or H; and R_3 and R_4 are, independently, H, Cl, ethyl, methoxy, or methyl.

In another subgeneric embodiment, this disclosure provides or contemplates a compound of formula IA, where R' is methoxy; and R_3 and R_4 are, independently, H, Cl, ethyl, methoxy, or methyl.

In another more specific subgeneric embodiment, this disclosure provides or contemplates a compound of formula IA, where R' is H; and R_3 and R_4 are, independently, H, Cl, ethyl, or methyl.

In another subgeneric embodiment, this disclosure provides or contemplates a compound of formula IA, where R' is H, q is zero, and R_5 is C_1-C_6 alkyl, or $(CHR_6)_wC_3$-C_6 cycloalkyl.

In another subgeneric embodiment, this disclosure provides or contemplates a compound of formula IA, where R' is H; q is 1; Y is O; and R_5 is C_1-C_6 alkyl, or $(CHR_6)_wC_3$-C_6 cycloalkyl.

In another subgeneric embodiment, this disclosure provides or contemplates a compound of formula IA, where R' is H; q is 1; Y is S; and R_5 is C_1-C_6 alkyl, or $(CHR_6)_wC_3$-C_6 cycloalkyl.

In a more specific subgeneric embodiment, this disclosure provides or contemplates a compound of formula IA, where R' and R_2 are H and R_5 is C_1-C_6 alkyl, or $(CHR_6)_wC_3$-C_6 cycloalkyl.

In a more specific subgeneric embodiment, this disclosure provides or contemplates a compound of formula IA, where R' and R_2 are H and R_5 is Ar, $(CHR_6)_wAr$, $CH_2(CHR_6)_wAr$, or $(CHR_6)_wCH_2Ar$.

In a more specific subgeneric embodiment, this disclosure provides or contemplates a compound of formula IA, where R' and R_2 are H and R_5 is $(CHR_6)_wC_5$-C_6 cycloalkenyl, $CH_2(CHR_6)_wC_5$-C_6 cycloalkenyl, C_2-C_6 alkenyl, or C_2-C_6 alkynyl.

In a more specific subgeneric embodiment, this disclosure provides or contemplates a compound of formula IA, where R' and R_2 are H and R_5 is CR_6=CH-C_3-C_6 cycloalkyl or CH=CR_6-C_3-C_6 cycloalkyl.

In another more specific subgeneric embodiment, this disclosure provides or contemplates a compound of formula IA, where R' is halogen; and R_3 and R_4 are H, Cl, ethyl, or methyl.

In another more specific subgeneric embodiment, this disclosure provides or contemplates a compound of formula IA, where R' is Cl or F; and R_3 and R_4 are H, Cl, ethyl, or methyl.

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

In another subgeneric embodiment, this disclosure provides or contemplates a compound of formula IA, where R' is phenyl, optionally substituted.

In another more specific subgeneric embodiment, this disclosure provides or contemplates a compound of formula IA, where R' is 1-phenyl, optionally substituted.

In another more specific subgeneric embodiment, this disclosure provides or contemplates a compound of formula IA, where R' is 4-phenyl, optionally substituted.

In another more specific subgeneric embodiment, this disclosure provides or contemplates a compound of formula IA, where R' is phenyl, optionally substituted, and R_5 is C_1-C_6 alkyl, or $(CHR_6)_wC_3$-C_6 cycloalkyl.

In another more specific subgeneric embodiment, this disclosure provides or contemplates a compound of formula IA, where R_1 is NH-C_1-C_6 alkyl, N(C_1-C_6 alkyl)-C_1-C_6 alkyl, C(=O)NH-C_1-C_6 alkyl, NH-C(=O)C_1-C_6 alkyl; O-C_1-C_6 alkyl, C(=O)-C_1-C_6 alkyl, C(=O)-OC_1-C_6 alkyl, or OC(=O)C_1-C_6 alkyl; R' is phenyl, optionally substituted, and R_5 is C_1-C_6 alkyl, or $(CHR_6)_wC_3$-C_6 cycloalkyl.

In another subgeneric embodiment, this disclosure provides or contemplates a compound of formula IA, where R' is H, methyl, or ethyl; and R_1 is NH-C_1-C_6 alkyl, N(C_1-C_6 alkyl)-C_1-C_6 alkyl, C(=O)NH-C_1-C_6 alkyl, or NH-C(=O)C_1-C_6 alkyl.

In yet another subgeneric embodiment, this disclosure provides or contemplates a compound of formula IA, where R' is H, methyl, or ethyl; and R_1 is C(=O)OC_1-C_6 alkyl, OC(=O)C_1-C_6 alkyl, or OC_1-C_6 alkyl.

In another specific subgeneric embodiment, this disclosure provides or contemplates a compound of formula IA, where R_1 is H, methyl, methoxy, or halogen, and R' is methyl or ethyl.

In another more specific subgeneric embodiment, this disclosure provides or contemplates a compound of formula IA, where R_1 is H, methyl, methoxy, or halogen, and R' is phenyl.

In another more specific subgeneric embodiment, this disclosure provides or contemplates a compound of formula IA, where R_1 is H, methyl, methoxy, or halogen, and R' is F.

In another subgeneric embodiment, this disclosure provides or contemplates a compound of formula IA, where R_1 is methoxy, methoxymethyl, ethoxymethyl, or methoxyethyl.

In a more specific subgeneric embodiment, this disclosure provides or contemplates a compound of formula IA, where R_1 is methoxy, methoxymethyl, ethoxymethyl, or methoxyethyl; R_2 is H, methyl, or halogen; and R_3 is methyl or Cl.

In another more specific subgeneric embodiment, this disclosure provides or contemplates a compound of formula IA, where R' is 4-phenyl, optionally substituted, and R_2 is H, methyl, methoxy, or halogen.

In another more specific subgeneric embodiment, this disclosure provides or contemplates a compound of formula IA, where R' is CF_3 or C_1-C_3 alkyl, and R_2 is H, methyl, methoxy, or halogen.

In another more specific subgeneric embodiment, this disclosure provides or contemplates a compound of formula IA, where R' is methoxy, and R_2 is H, methyl, methoxy, or halogen.

In another more specific subgeneric embodiment, this disclosure provides or contemplates a compound of formula IA, where R' is 2-dimethylamino ethyl, and R_2 is H, methyl, methoxy, or halogen.

In another more specific subgeneric embodiment, this disclosure provides or contemplates a compound of formula IA, where q is zero, R_2 is H, methyl, methoxy, or halogen, R' is 1-phenyl, optionally substituted; and R_3 and R_4 are H, Cl, ethyl, or methyl.

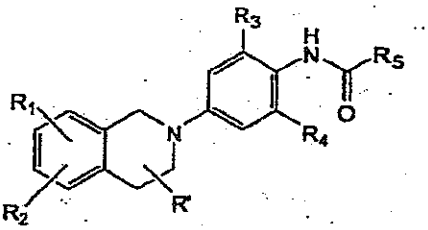
In another more specific subgeneric embodiment, this disclosure provides or contemplates a compound of formula IA, where q is zero, R_2 is H, methyl, methoxy, or halogen, R' is 4-phenyl, optionally substituted; and R_3 and R_4 are H, Cl, ethyl, or methyl.

In another more specific subgeneric embodiment, this disclosure provides or contemplates a compound of formula IA, where q is zero, R_2 is H, methyl, methoxy, or halogen; R' is CF_3 or C_1-C_3 alkyl; and R_3 and R_4 are H, Cl, ethyl, or methyl.

In another more specific subgeneric embodiment, this disclosure provides or contemplates a compound of formula IA, where q is zero, R_2 is H, methyl, methoxy, or halogen; R' is methoxy; and R_3 and R_4 are H, Cl, ethyl, or methyl.

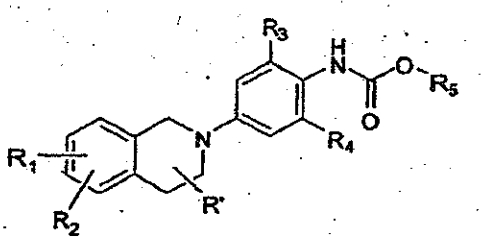
In another subgeneric embodiment, this disclosure provides or contemplates a compound of formula IA, where q is zero; R' is (2-dimethylamino) ethyl; R_2 is H, methyl, methoxy, or halogen; and R_3 and R_4 are H, Cl, ethyl, or methyl.

In a more specific sub-generic embodiment, the disclosure provides or contemplates a compound of formula IA-1 below.



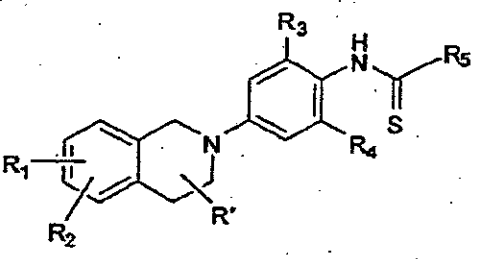
IA-1

In another more specific embodiment, this disclosure provides or contemplates a compound of formula IA-2 below.



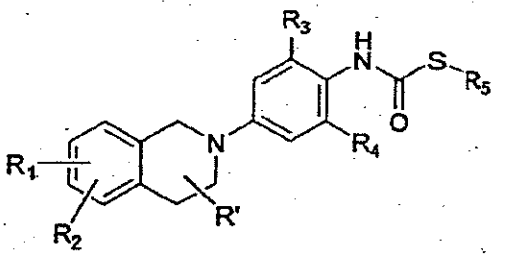
IA-2

In another more specific embodiment, this disclosure provides or contemplates a compound of formula IA-3 below.



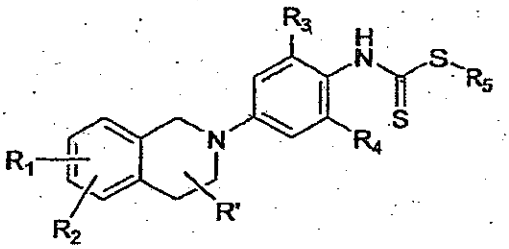
IA-3

In another more specific embodiment, this disclosure provides or contemplates a compound of formula IA-4 below.



IA-4

In another more specific embodiment, this disclosure provides or contemplates a compound of formula IA-5 below.



IA-5

In another subgeneric embodiment, this disclosure provides or contemplates a compound of formula IA-1 or formula IA-3, where R_2 is H, alkyl, or halogen; 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 $CH_2(CHR_6)_wC_3$-C_6 cycloalkyl.

In another more specific subgeneric embodiment, this disclosure provides or contemplates a compound of formula IA-1 or formula IA-3, where R_1 is $(CH_2)_mC_3$-C_6 cycloalkyl; R_2 is H, alkyl, or halogen; 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 $CH_2(CHR_6)_wC_3$-C_6 cycloalkyl.

In another more specific subgeneric embodiment, this disclosure provides or contemplates a compound of formula IA-1 or formula IA-3, where R_1 is methoxy, methoxymethyl, or methoxyethyl; R_2 is H, alkyl, or halogen; 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 $CH_2(CHR_6)_wC_3$-C_6 cycloalkyl.

In yet another more specific subgeneric embodiment, this disclosure provides or contemplates a compound of formula IA-2, where R_5 is C_1-C_6 alkyl, $(CHR_6)_wC_3$-C_6 cycloalkyl, $(CHR_6)_wCH_2C_3$-C_6 cycloalkyl, or $CH_2(CHR_6)_wC_3$-C_6 cycloalkyl.

In yet another more specific subgeneric embodiment, this disclosure provides or contemplates a compound of formula IA-2, where R_5 is Ar, $(CHR_6)_wAr$, $CH_2(CHR_6)_wAr$, or $(CHR_6)_wCH_2Ar$.

In yet another more specific subgeneric embodiment, this disclosure provides or contemplates a compound of formula IA-2, 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.

In yet another more specific subgeneric embodiment, this disclosure provides or contemplates a compound of formula IA-3, where R_2 and R' are H; R_3 is 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 $CH_2(CHR_6)_wC_3$-C_6 cycloalkyl.

In a still more specific subgeneric embodiment, this disclosure provides or contemplates a compound of formula IA-1, where R_1 is H, F, Cl, Br, methoxy, methoxymethyl, ethoxymethyl, methoxyethyl, or trifluoromethyl; R_3 is methyl; and R_5 is C_4-C_6 alkyl, $(CHR_6)_wCH_2C_5$-C_6 cycloalkyl, or $CH_2(CHR_6)_wC_5$-C_6 cycloalkyl.

In another still more specific subgeneric embodiment, this disclosure provides or contemplates a compound of formula IA-2, where R_5 is C_4-C_6 alkyl, $(CHR_6)_wC_5$-C_6 cycloalkyl, or $CH_2(CHR_6)_wC_5$-C_6 cycloalkyl; and R_1 is H, F, Cl, Br, methoxy, methoxymethyl, ethoxymethyl, methoxyethyl,or trifluoromethyl.

In another still more specific subgeneric embodiment, this disclosure provides or contemplates a compound of formula IA-3, where R_1 is H, F, Cl, Br, methoxy, methoxymethyl, ethoxymethyl, methoxyethyl, or trifluoromethyl; R_2 is H, methyl, or F; R' is H or methyl; R_3 is methyl; and R_5 is C_4-C_6 alkyl, $(CHR_6)_wC_5$-C_6 cycloalkyl, or $CH_2(CHR_6)_wC_5$-C_6 cycloalkyl.

In another more generic embodiment, this disclosure provides or contemplates a compound of formula IA-1, where R_1 is $(CH_2)_mC_3$-C_6 cycloalkyl, C_3-C_6 cycloalkenyl, or $(CH_2)_mC_3$-C_6 cycloalkenyl; R' is halogen; and R_3 is methyl or Cl.

In another more specific subgeneric embodiment, this disclosure provides or contemplates a compound of formula IA-1, where R_1 is $(CH_2)_mC_3$-C_6 cycloalkyl, C_3-C_6 cycloalkenyl, or $(CH_2)_mC_3$-C_6 cycloalkenyl; and R' is F or Cl.

In another more specific subgeneric embodiment, this disclosure provides or contemplates a compound of formula IA-1, where R_1 is methoxy, methoxymethyl, ethoxymethyl; or methoxyethyl; R_2 is H or F; R_3 is methyl; R_4 is methyl or Cl; and R_5 is $(CHR_6)_wC_5$-C_6 cycloalkenyl or $(CHR_6)_wAr$.

In another more specific subgeneric embodiment, this disclosure provides or contemplates a compound of formula IA-1, where R_1 is phenyl, optionally substituted.

In another subgeneric embodiment, this disclosure provides or contemplates a compound of formula IA-1, where R_1 is methyl, halomethyl, ethyl, or haloethyl.

In another subgeneric embodiment, this disclosure provides or contemplates a compound of formula IA-1, where R' is 2-(dimethylamino) ethyl.

In another subgeneric embodiment, this disclosure provides or contemplates a compound of formula IA-1, where R' is 1-methyl or 1-ethyl.

In another more specific subgeneric embodiment, this disclosure provides or contemplates a compound of formula IA-1, where R' is 1-fluoro, R_5 is C_4-C_6 alkyl, $(CHR_6)_wC_5$-C_6 cycloalkyl, or $CH_2(CHR_6)_wC_5$-C_6 cycloalkyl; and R_1 is H, F, Cl, Br, methoxy, or trifluoromethyl.

In another more specific subgeneric embodiment, this disclosure provides or contemplates a compound of formula IA-1, where R' is 4-fluoro, R_5 is C_4-C_6 alkyl, $(CHR_6)_wC_5$-C_6 cycloalkyl, or $CH_2(CHR_6)_wC_5$-C_6 cycloalkyl; and R_1 is H, F, Cl, Br, methoxy, or trifluoromethyl.

In another more specific subgeneric embodiment, this disclosure provides or contemplates a compound of formula IA-1, where R_1 is $(CH_2)_m$imidazolyl, $(CH_2)_m$pyrazyl, $(CH_2)_m$ furyl, $(CH_2)_m$ 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; and R_2 and R' are H.

In another more specific subgeneric embodiment, this disclosure provides or contemplates a compound of formula IA-1, where R_1 is $(CH_2)_m$imidazolyl, $(CH_2)_m$pyrazyl, $(CH_2)_m$ furyl, $(CH_2)_m$ 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; and R' is 4-phenyl, optionally substituted.

In another more specific subgeneric embodiment, this disclosure provides or contemplates a compound of formula IA-1, where R' is CF_3 or C_1-C_3 alkyl; R_5 is C_4-C_6 alkyl, $(CHR_6)_wC_5$-C_6 cycloalkyl, or $CH_2(CHR_6)_wC_5$-C_6 cycloalkyl; and R_1 is H, F, Cl, Br, methoxy, or trifluoromethyl.

In another more specific subgeneric embodiment, this disclosure provides or contemplates a compound of formula IA-1, where R' is 4-methyl or 4-ethyl; and R_5 is C_4-C_6 alkyl, $(CHR_6)_wC_5$-C_6 cycloalkyl, or $CH_2(CHR_6)_wC_5$-C_6 cycloalkyl; and R_1 is H, F, Cl, Br, methoxy, or trifluoromethyl.

In another more specific subgeneric embodiment, this disclosure provides or contemplates a compound of formula IA-1, where R' is methoxy or ethoxy; and R_5 is C_4-C_6 alkyl, $(CHR_6)_wC_5$-C_6 cycloalkyl, or $CH_2(CHR_6)_wC_5$-C_6 cycloalkyl; and R_1 is H, F, Cl, Br, methoxy, or trifluoromethyl.

In another more specific subgeneric embodiment, this disclosure provides or contemplates a compound of formula IA-1, where R' is 1-phenyl, optionally substituted; R_5 is C_4-C_6 alkyl, $(CHR_6)_wC_5$-C_6 cycloalkyl, or $CH_2(CHR_6)_wC_5$-C_6 cycloalkyl; and R_1 is H, F, Cl, Br, methoxy, or trifluoromethyl.

In another more specific subgeneric embodiment, this disclosure provides or contemplates a compound of formula IA-1, where R' is 4-phenyl, optionally substituted; R_5 is C_4-C_6 alkyl, $(CHR_6)_wC_5$-C_6 cycloalkyl, or $CH_2(CHR_6)_wC_5$-C_6 cycloalkyl; and R_1 is H, F, Cl, Br, methoxy, or trifluoromethyl.

In another more specific subgeneric embodiment, this disclosure provides or contemplates a compound of formula IA-1, where R' is CF_3 or C_1-C_3 alkyl; R_5 is C_4-C_6 alkyl, $(CHR_6)_wC_5$-C_6 cycloalkyl, or $CH_2(CHR_6)_wC_5$-C_6 cycloalkyl; and R_1 is H, F, Cl, Br, methoxy, or trifluoromethyl.

In another more specific subgeneric embodiment, this disclosure provides or contemplates a compound of formula IA-1, where R' is 4-methyl or 4-ethyl; R_5 is C_4-C_6 alkyl, $(CHR_6)_wC_5$-C_6 cycloalkyl, or $CH_2(CHR_6)_wC_5$-C_6 cycloalkyl; and R_1 is H, F, Cl, Br, methoxy, or trifluoromethyl.

In another more specific subgeneric embodiment, this disclosure provides or contemplates a compound of formula IA-1, where R' is methoxy or ethoxy, R_5 is C_4-C_6 alkyl, $(CHR_6)_wC_5$-C_6 cycloalkyl, or $CH_2(CHR_6)_wC_5$-C_6 cycloalkyl; and R_1 is H, F, Cl, Br, methoxy, or trifluoromethyl.

In another more specific subgeneric embodiment, this disclosure provides or contemplates a compound of formula IA-4, where R_1 is H, F, Cl, Br, methoxy, or trifluoromethyl; R_5 is C_4-C_6 alkyl, $(CHR_6)_wC_5$-C_6 cycloalkyl, or $CH_2(CHR_6)_wC_5$-C_6 cycloalkyl; and R_1 is H, F, Cl, Br, methoxy, or trifluoromethyl.

In another more specific subgeneric embodiment, this disclosure provides or contemplates a compound of formula IA-4, where R_2 is H, F, or methyl; R_5 is C_4-C_6 alkyl, $(CHR_6)_wC_5$-C_6 cycloalkyl, or $CH_2(CHR_6)_wC_5$-C_6 cycloalkyl; and R_1 is H, F, Cl, Br, methoxy, or trifluoromethyl.

In another more specific subgeneric embodiment, this disclosure provides or contemplates a compound of formula IA-2, where R' is H.

In another more specific subgeneric embodiment, this disclosure provides or contemplates a compound of formula IA-2, where R' is halogen.

In another subgeneric embodiment, this disclosure provides or contemplates a compound of formula IA-2, where R' is F.

In another still more specific subgeneric embodiment, this disclosure provides or contemplates a compound of formula IA-2, where R' is methyl or ethyl.

In another more specific subgeneric embodiment, this disclosure provides or contemplates a compound of formula IA-2, where R' is methyl or ethyl; R_5 is C_4-C_6 alkyl, $(CHR_6)_wC_5$-C_6 cycloalkyl, or $CH_2(CHR_6)_wC_5$-C_6 cycloalkyl; and R_1 is H, F, Cl, Br, methoxy, or trifluoromethyl.

In another more specific subgeneric embodiment, this disclosure provides or contemplates a compound of formula IA-2, where R' is halogen; R_5 is C_4-C_6 alkyl,

$(CHR_6)_wC_5$-C_6 cycloalkyl, or $CH_2(CHR_6)_wC_5$-C_6 cycloalkyl; and R_1 is H, F, Cl, Br, methoxy, or trifluoromethyl.

In another more specific subgeneric embodiment, this disclosure provides or contemplates a compound of formula IA-2, where R' is H; R_5 is C_4-C_6 alkyl, $(CHR_6)_wC_5$-C_6 cycloalkyl, or $CH_2(CHR_6)_wC_5$-C_6 cycloalkyl; and R_1 is H, F, Cl, Br, methoxy, or trifluoromethyl.

In another more specific subgeneric embodiment, this disclosure provides or contemplates a compound of formula IA-2, where R' is 1-phenyl, optionally substituted.

In another more specific subgeneric embodiment, this disclosure provides or contemplates a compound of formula IA-2, where R' is 4-phenyl, optionally substituted.

In another more specific subgeneric embodiment, this disclosure provides or contemplates a compound of formula IA-2, where R' is CF_3 or C_1-C_3 alkyl.

In another more specific subgeneric embodiment, this disclosure provides or contemplates a compound of formula IA-3, where R' is H; R_5 is C_4-C_6 alkyl, $(CHR_6)_wC_5$-C_6 cycloalkyl, or $CH_2(CHR_6)_wC_5$-C_6 cycloalkyl; and R_1 is H, F, Cl, Br, methoxy, or trifluoromethyl.

In another more specific subgeneric embodiment, this disclosure provides or contemplates a compound of formula IA-3, where R' is F; R_5 is C_4-C_6 alkyl, $(CHR_6)_wC_5$-C_6 cycloalkyl, or $CH_2(CHR_6)_wC_5$-C_6 cycloalkyl; and R_1 is H, F, Cl, Br, methoxy, or trifluoromethyl.

In another more specific subgeneric embodiment, this disclosure provides or contemplates a compound of formula IA-3, where R' is 1-phenyl, optionally substituted; R_5 is C_4-C_6 alkyl, $(CHR_6)_wC_5$-C_6 cycloalkyl, or $CH_2(CHR_6)_wC_5$-C_6 cycloalkyl; and R_1 is H, F, Cl, Br, methoxy, or trifluoromethyl.

In another more specific subgeneric embodiment, this disclosure provides or contemplates a compound of formula IA-3, where R' is 4-phenyl, optionally substituted; R_5 is C_4-C_6 alkyl, $(CHR_6)_wC_5$-C_6 cycloalkyl, or $CH_2(CHR_6)_wC_5$-C_6 cycloalkyl; and R_1 is H, F, Cl, Br, methoxy, or trifluoromethyl.

In another more specific subgeneric embodiment, this disclosure provides or contemplates a compound of formula IA-3, where R' is CF_3 or C_1-C_3 alkyl; R_5 is C_4-C_6•

alkyl, $(CHR_6)_wC_5$-C_6 cycloalkyl, or $CH_2(CHR_6)_wC_5$-C_6 cycloalkyl; and R_1 is H, F, Cl, Br, methoxy, or trifluoromethyl.

In another subgeneric embodiment, this disclosure provides or contemplates a compound of formula IA-1, where R_1 and R_2, are, independently, H, CN, F, Cl, Br, CH_2CN, OCH_3, CH_2OCH_3, CH_2 CH_2OCH_3, $CH_2OCH_2CH_3$, CH_2F, CHF_2, CF_3, CF_2CF_3, or C_1-C_6 alkyl and R_5 is C_1-C_6 alkyl or $CH_2(CHR_6)_wC_3$-C_6 cycloalkyl, where w = 0, 1, or 2.

In another more specific subgeneric embodiment, this disclosure provides or contemplates a compound of formula IA-1, R_1 is H, CN, F, Cl, Br, CH_2CN, OCH_3, CH_2OCH_3, $CH_2CH_2OCH_3$, $CH_2OCH_2CH_3$, CH_2F, CHF_2, CF_3, CF_2CF_3, or C_1-C_6 alkyl; R_2 is H, F, Cl, or methyl; R_3 is methyl or chloro; and R_5 is C_1-C_6 alkyl or $CH_2(CHR_6)_wC_3$-C_6 cycloalkyl, where R_6 is H or methyl and w = 1 or 2.

In another more specific subgeneric embodiment, this disclosure provides or contemplates a compound of formula IA, where R_5 is Ar, $(CHR_6)_wAr$, $CH_2(CHR_6)_wAr$, or $(CHR_6)_wCH_2Ar$.

In another subgeneric embodiment, this disclosure provides or contemplates a compound of formula IA-2, where R_5 is Ar, $(CHR_6)_wAr$, $CH_2(CHR_6)_wAr$, or $(CHR_6)_wCH_2Ar_1$.

In another subgeneric embodiment, this disclosure provides or contemplates a compound of formula IA-3, where R_5 is Ar, $(CHR_6)_wAr$, $CH_2(CHR_6)_wAr$, or $(CHR_6)_wCH_2Ar$.

In another more specific subgeneric embodiment, this disclosure provides or contemplates compounds of formula IA-1, IA-2, IA-3, IA-4, or IA-5, where R_1 and R_2, are, independently, methyl, ethyl, F, Cl, CF_3, methoxy or methoxymethyl, R' is methyl, and R_5 is C_4-C_6 alkyl, $(CHR_6)_wC_5$-C_6 cycloalkyl, or $CH_2(CHR_6)_wC_5$-C_6 cycloalkyl.

In another more specific subgeneric embodiment, this disclosure provides or contemplates a compound of formula IA, 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.

In another subgeneric embodiment, this disclosure provides or contemplates a compound of formula IA, where R_5 is haloalkyl.

In another subgeneric embodiment, this disclosure provides or contemplates a compound of formula IA-1, where R_5 is haloalkyl.

In another subgeneric embodiment, this disclosure provides or contemplates a compound of formula IA-2, where R_5 is haloalkyl.

In another subgeneric embodiment, this disclosure provides or contemplates a compound of formula IA-3, where R_5 is haloalkyl.

In another subgeneric embodiment, this disclosure provides or contemplates a compound of formula IA, where R_5 is methoxy alkyl.

In another subgeneric embodiment, this disclosure provides or contemplates a compound of formula IA, where R_5 is cyano alkyl.

In a more specific subgeneric embodiment, this disclosure provides or contemplates a compound of formula IA-4, where R_5 is halo alkyl.

In a more specific subgeneric embodiment, this disclosure provides or contemplates a compound of formula IA, where R_5 is CH_2-cycloalkyl or CH_2CH_2-cycloalkyl.

In a more specific subgeneric embodiment, this disclosure provides or contemplates a compound of formula IA-4, where R_5 is CH_2-cycloalkyl or CH_2CH_2-cycloalkyl.

In a more specific subgeneric embodiment, this disclosure provides or contemplates a compound of formula IA-5, where R_5 is CH_2-cycloalkyl or CH_2CH_2-cycloalkyl.

In another subgeneric embodiment, this disclosure provides or contemplates a compound of formula IA-1, where R_3 and R_4 are chloro, methoxy, or methyl and R_5 is CH_2-cycloalkyl.

In another subgeneric embodiment, this disclosure provides or contemplates a compound of formula IA-1, where R_3 and R_4 are chloro, methoxy, or methyl and R_5 is haloalkyl, hydroxyalkyl, or methoxyalkyl.

In a more specific subgeneric embodiment, this disclosure provides or contemplates a compound of formula IA-1, where R_3 and R_4 are chloro, methoxy, or methyl and R_5 is methoxy alkyl.

In another subgeneric embodiment, this disclosure provides or contemplates a compound of formula IA-2, where R_3 and R_4 are chloro, methoxy, or methyl and R_5 is chloroalkyl.

In another subgeneric embodiment, this disclosure provides or contemplates a compound of formula IA-2, where R_3 and R_4 are chloro, methoxy, or methyl and R_5 is methoxyalkyl.

In another subgeneric embodiment, this disclosure provides or contemplates a compound of formula IA-1, where R_3 and R_4 are both methyl and R_5 is 2-(2-halo cyclopentyl) ethyl.

In another subgeneric embodiment, this disclosure provides or contemplates a compound of formula IA-1, where R_3 and R_4 are both methyl and R_5 is 2-(2-furyl) ethyl.

In another subgeneric embodiment, this disclosure provides or contemplates a compound of formula IA-1, where R_3 and R_4 are both methyl and R_5 is 2-(2-tetrahydrofuryl) ethyl.

In another subgeneric embodiment, this disclosure provides or contemplates a compound of formula IA-1, where R_3 and R_4 are both methyl and R_5 is 2-phenyl ethyl.

In another subgeneric embodiment, this disclosure provides or contemplates a compound of formula IA-1, where R_3 and R_4 are both methyl and R_5 is 3-phenyl propyl.

In another subgeneric embodiment, this disclosure provides or contemplates a compound of formula IA-1, where R_3 and R_4 are both methyl and R_5 is 2-phenyl propyl.

In another more specific subgeneric embodiment, this disclosure provides or contemplates a compound of formula IA-1, where R_5 is C_1-C_6 alkyl, $(CHR_6)_wC_3$-C_6 cycloalkyl, $(CHR_6)_wCH_2C_3$-C_6 cycloalkyl, or $CH_2(CHR_6)_wC_3$-C_6 cycloalkyl; R' is halogen or C_1-C_3 alkyl; and R_1 is halogen.

In another more specific subgeneric embodiment, this disclosure provides or contemplates a compound of formula IA-1, where R_5 is C_1-C_6 alkyl, $(CHR_6)_wC_3$-C_6 cycloalkyl, $(CHR_6)_wCH_2C_3$-C_6 cycloalkyl, or $CH_2(CHR_6)_wC_3$-C_6 cycloalkyl; R' is halogen or C_1-C_3 alkyl; R_2 is H or halogen; and R_1 is halogen.

In another more specific subgeneric embodiment, this disclosure provides or contemplates a compound of formula IA-1, where R_5 is C_1-C_6 alkyl, $(CHR_6)_wC_3$-C_6

cycloalkyl, $(CHR_6)_wCH_2C_3$-C_6 cycloalkyl, or $CH_2(CHR_6)_wC_3$-C_6 cycloalkyl; R' is phenyl, optionally substituted; R_2 is H or halogen; and R_1 is halogen.

In another more specific subgeneric embodiment, this disclosure provides or contemplates a compound of formula IA-1, where R_5 is C_1-C_6 alkyl, $(CHR_6)_wC_3$-C_6 cycloalkyl, $(CHR_6)_wCH_2C_3$-C_6 cycloalkyl, or $CH_2(CHR_6)_wC_3$-C_6 cycloalkyl; R' is halogen or C_1-C_3 alkyl; R_2 is H or halogen; and R_1 is halogen.

In another more specific subgeneric embodiment, this disclosure provides or contemplates a compound of formula IA-2, where R_5 is C_1-C_6 alkyl, $(CHR_6)_wC_3$-C_6 cycloalkyl, $(CHR_6)_wCH_2C_3$-C_6 cycloalkyl, or $CH_2(CHR_6)_wC_3$-C_6 cycloalkyl; R' is halogen or C_1-C_3 alkyl; and R_1 is halogen.

In another more specific subgeneric embodiment, this disclosure provides or contemplates a compound of formula IA-3, where R_5 is C_1-C_6 alkyl, $(CHR_6)_wC_3$-C_6 cycloalkyl, $(CHR_6)_wCH_2C_3$-C_6 cycloalkyl, or $CH_2(CHR_6)_wC_3$-C_6 cycloalkyl; R' is halogen or C_1-C_3 alkyl; and R_1 is halogen.

In another more specific subgeneric embodiment, this disclosure provides or contemplates a compound of formula IA, 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.

In another more specific subgeneric embodiment, this disclosure provides or contemplates a compound of formula IA, where R_5 is Ar, $(CHR_6)_wAr$, $CH_2(CHR_6)_wAr$, or $(CHR_6)_wCH_2Ar_1$.

In another more specific subgeneric embodiment, this disclosure provides or contemplates a compound of formula IA-3, where R_1 is haloalkyl; R_2 is H or F; R_3 and R_4 are Cl, methoxy, or 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 $CH_2(CHR_6)_wC_3$-C_6 cycloalkyl.

In another more specific subgeneric embodiment, this disclosure provides or contemplates a compound of formula IA, where R_1 is C_1-C_3 alkyl, halogen, or haloalkyl; R_2 is H or F; R_3 and R_4 are H, methyl, or Cl; and R_5 is CH_2CR_6-C_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_4-C_6 alkyl, C_2-C_6 alkenyl, or C_2-C_6 alkynyl.

In another more specific subgeneric embodiment, this disclosure provides or contemplates a compound of formula IA-1, where R_1 is C_1-C_3 alkyl, halogen, or haloalkyl; R_2 is H or F; R_3 and R_4 are H, methyl, or Cl; and R_5 is CH_2CR_6-C_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_4-C_6 alkyl, C_2-C_6 alkenyl, or C_2-C_6 alkynyl.

In another more specific subgeneric embodiment, this disclosure provides or contemplates a compound of formula IA-3, where R_1 is C_1-C_3 alkyl, halogen, or haloalkyl; R_2 is H or F; R_3 and R_4 are H, methyl, or Cl; and R_5 is CH_2CR_6-C_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_4-C_6 alkyl, C_2-C_6 alkenyl, or C_2-C_6 alkynyl.

In another more specific subgeneric embodiment, this disclosure provides or contemplates a compound of formula IA-1, where R_1 is C_1-C_3 alkyl, halogen, or haloalkyl; R_2 is H or F; R_3 and R_4 are H, methyl, or Cl; and R_5 is CH_2CR_6-C_3-C_6 cycloalkyl, or C_2-C_6 alkyl.

In another more specific subgeneric embodiment, this disclosure provides or contemplates a compound of formula IA-3, where R_1 is C_1-C_3 alkyl, halogen, or haloalkyl; R_2 is H or F; R_3 and R_4 are H, methyl, or Cl; and R_5 is CH_2CR_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.

In another more specific subgeneric embodiment, this disclosure provides or contemplates a compound of formula IA-3, where R_1 is halogen or haloalkyl; R_2 is H or F; and 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.

In another more specific subgeneric embodiment, this disclosure provides or contemplates a compound of formula IA-3, where R_1 is halogen or haloalkyl; R_2 is H or F; and 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.

In another more specific subgeneric embodiment, this disclosure provides or contemplates a compound of formula IA-3, where R_1 is halogen or haloalkyl; R_2 is H or

F; R_3 and R_4 are Cl, methoxy, or 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 $CH_2(CHR_6)_wC_3$-C_6 cycloalkyl.

In another more specific subgeneric embodiment, this disclosure provides or contemplates a compound of formula IA-3, where R_1 is halogen or haloalkyl; R_2 is H or F; and 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.

In another more specific subgeneric embodiment, this disclosure provides or contemplates a compound of formula IA-3, where R_1 is methyl, fluoro, or fluoroalkyl; R_2 is H or F; 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 $CH_2(CHR_6)_wC_3$-C_6 cycloalkyl.

In another more specific subgeneric embodiment, this disclosure provides or contemplates a compound of formula IA-3, where R_1 is Cl, F, or CF_3; R_2 is H or F; R' is H or CH_3; and 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.

In another more specific subgeneric embodiment, this disclosure provides or contemplates a compound of formula IA-3, where R_1 is Cl, F, or CF_3; R_2 is H or F; R' is H or CH_3; and R_5 is Ar, $(CHR_6)_wAr$, $CH_2(CHR_6)_wAr$, or $(CHR_6)_wCH_2Ar$.

In another more specific subgeneric embodiment, this disclosure provides or contemplates a compound of formula IA-4, where R_3 and R_4 are H, methyl, or Cl; 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 $CH_2(CHR_6)_wC_3$-C_6 cycloalkyl.

In another more specific subgeneric embodiment, this disclosure provides or contemplates a compound of formula IA-5, where R_3 and R_4 are H, methyl, or Cl; and 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.

In another more specific subgeneric embodiment, this disclosure provides or contemplates a compound of formula IA-1, where R_3 and R_4 are H, methyl, or Cl; and where R_1 and R_2, on adjacent carbons, form a six-membered ring.

In another more specific subgeneric embodiment, this disclosure provides or contemplates a compound of formula IA-1, where R_3 and R_4 are H, methyl, or Cl; where

R_5 is C_2-C_6 alkyl, CH_2-C_5-C_6 cycloalkyl, CH_2CH_2-C_5-C_6 cycloalkyl, CR_6=CH-C_3-C_6 cycloalkyl, CH=CR_6-C_3-C_6 cycloalkyl, or C_2-C_6 alkenyl; and where R_1 and R_2, are on adjacent carbons, and are both other than H.

In another more specific subgeneric embodiment, this disclosure provides or contemplates a compound of formula IA-1, where R_3 and R_4 are H, methyl, or Cl; where R_5 is C_2-C_6 alkyl, CH_2-C_5-C_6 cycloalkyl, CH_2CH_2-C_5-C_6 cycloalkyl, CR_6=CH-C_3-C_6 cycloalkyl, CH=CR_6-C_3-C_6 cycloalkyl, or C_2-C_6 alkenyl; and where R_1 and R_2, on adjacent carbons, are both halogen.

In a more specific subgeneric embodiment, this disclosure provides or contemplates a compound of formula IA-1, where R_3 and R_4 are H, methyl, or Cl; where R_5 is C_2-C_6 alkyl, CH_2-C_5-C_6 cycloalkyl, CH_2CH_2-C_5-C_6 cycloalkyl, CR_6=CH-C_3-C_6 cycloalkyl, CH=CR_6-C_3-C_6 cycloalkyl, or C_2-C_6 alkenyl; and where R_1 and R_2, on adjacent carbons, are both fluorine.

In a more specific subgeneric embodiment, this disclosure provides or contemplates a compound of formula IA-1, where R' is F, methyl, or H; R_3 and R_4 are H, methyl, or Cl; and R_5 is C_1-C_6 alkyl, $(CHR_6)_w$$C_3$-$C_6$ cycloalkyl, $(CHR_6)_w$$CH_2$$C_3$-$C_6$ cycloalkyl, or $CH_2(CHR_6)_w$$C_3$-$C_6$ cycloalkyl.

In another more specific subgeneric embodiment, this disclosure provides or contemplates a compound of formula IA-1, where R' is F, methyl, or H; R_5 is CR_6=CH-C_3-C_6 cycloalkyl, CH=CR_6-C_3-C_6 cycloalkyl, $(CHR_6)_w$$C_5$-$C_6$ cycloalkenyl, $CH_2(CHR_6)_w$$C_5$-$C_6$ cycloalkenyl, C_2-C_6 alkenyl, or C_2-C_6 alkynyl.

In another more specific subgeneric embodiment, this disclosure provides or contemplates a compound of formula IA-1, where R' is halogen and R_5 is Ar, $(CHR_6)_w$Ar, $CH_2(CHR_6)_w$Ar, or $(CHR_6)_w$$CH_2$$Ar_1$.

In another subgeneric embodiment, this disclosure provides or contemplates a compound of formula IA-1, where R_1 and R_2 are on adjacent carbon atoms and are both other than H.

In a more specific subgeneric embodiment, this disclosure provides or contemplates a compound of formula IA-1, where R_1 and R_2, on adjacent carbon atoms

are, independently trifluoromethyl or halogen; and where R_5 is C_1-C_6 alkyl, $(CHR_6)_wC_3$-C_6 cycloalkyl, $(CHR_6)_wCH_2C_3$-C_6 cycloalkyl, or $CH_2(CHR_6)_wC_3$-C_6 cycloalkyl.

In another subgeneric embodiment, this disclosure provides or contemplates a compound of formula IA-1, where R_5 is $(CHR_6)_wC_5$-C_6 cycloalkenyl, $CH_2(CHR_6)_wC_5$-C_6 cycloalkenyl, C_2-C_6 alkenyl, or C_2-C_6 alkynyl.

In another more specific subgeneric embodiment, this disclosure provides or contemplates a compound of formula IA-1, where R_1 is halogen and R_2 is H, or R_1 and R_2, on adjacent carbon atoms are, independently trifluoromethyl or halogen; and 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.

In another subgeneric embodiment, this disclosure provides or contemplates a compound of formula IA-1, where R_5 is Ar, $(CHR_6)_wAr$, $CH_2(CHR_6)_wAr$, or $(CHR_6)_wCH_2Ar_1$.

In another more specific subgeneric embodiment, this disclosure provides or contemplates a compound of formula IA-1, where R_1 is halogen or trifluoromethyl and R_2 is H, or R_1 and R_2, on adjacent carbon atoms are, independently trifluoromethyl or halogen; and where R_5 is Ar, $(CHR_6)_wAr$, $CH_2(CHR_6)_wAr$, or $(CHR_6)_wCH_2Ar$.

In another more specific subgeneric embodiment, this disclosure provides or contemplates a compound of formula IA, where X is S, q =1, Y is O, and R_5 is C_1-C_6 alkyl, $(CHR6)_wC_3$-C_6 cycloalkyl, $(CHR6)_wCH_2C_3$-C_6 cycloalkyl, or $CH_2(CHR6)_wC_3$-C_6 cycloalkyl.

In another more specific subgeneric embodiment, this disclosure provides or contemplates a compound of formula IA, where X is S, q =1, Y is O, and R_5 is CR6=CH-C_3-C_6 cycloalkyl, CH=CR6-C_3-C_6 cycloalkyl, $(CHR6)_wC_5$-C_6 cycloalkenyl, $CH_2(CHR6)_wC_5$-C_6 cycloalkenyl, C_2-C_6 alkenyl, or C_2-C_6 alkynyl.

In another more specific subgeneric embodiment, this disclosure provides or contemplates a compound of formula IA, where X is S, q =1, Y is O, and R_5 is Ar, $(CHR6)_wAr$, $CH_2(CHR6)_wAr$, or $(CHR6)_wCH_2Ar$.

In another more specific subgeneric embodiment, this disclosure provides or contemplates a compound of formula IA, where X is S, q = zero, and R_5 is C_1-C_6 alkyl,

$(CHR6)_wC_3$-C_6 cycloalkyl, $(CHR6)_wCH_2C_3$-C_6 cycloalkyl, or $CH_2(CHR6)_wC_3$-C_6 cycloalkyl.

In another more specific subgeneric embodiment, this disclosure provides or contemplates a compound of formula IA, where X is S, q = zero, and 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.

In another subgeneric embodiment, this disclosure provides or contemplates a compound of formula IA-2 where R_5 is C_1-C_6 alkyl or $(CHR_6)_wC_3$-C_6 cycloalkyl.

In another subgeneric embodiment, this disclosure provides or contemplates a compound of formula IA-3, where R_5 is C_1-C_6 alkyl or $(CHR_6)_wC_3$-C_6 cycloalkyl.

In another subgeneric embodiment, this disclosure provides or contemplates a compound of formula IA-2, where R_1 is halogen or trifluoromethyl and R_2 is H or R_1 and R_2, on adjacent carbon atoms, are, independently, halogen or trifluoromethyl; and R_5 is C_1-C_6 alkyl or $(CHR_6)_wC_3$-C_6 cycloalkyl.

In another subgeneric embodiment, this disclosure provides or contemplates a compound of formula IA-3, where R_1 is halogen or trifluoromethyl and R_2 is H or R_1 and R_2, on adjacent carbon atoms, are, independently, halogen or trifluoromethyl; and R_5 is C_1-C_6 alkyl or $(CHR_6)_wC_3$-C_6 cycloalkyl.

In another more specific subgeneric embodiment, this disclosure provides or contemplates a compound of formula IA-2, where R_1 and R_2 are, independently, methyl, methoxy, trifluoromethyl, F, Cl, or H; and R_5 is C_1-C_6 alkyl or $(CHR_6)_wC_3$-C_6 cycloalkyl.

In another more specific subgeneric embodiment, this disclosure provides or contemplates a compound of formula IA-3, where R_1 and R_2 are, independently, methyl, methoxy, trifluoromethyl, F, Cl, or H; R' is H; and R_5 is C_1-C_6 alkyl or $(CHR_6)_wC_3$-C_6 cycloalkyl.

In another subgeneric embodiment, this disclosure provides or contemplates a compound of formula IA-1 or IA-2 or IA-3, where R_1 is halogen, C_1-C_6 alkyl, mono-halo C_1-C_6 alkyl, CN, di-halo C_1-C_6 alkyl, CF_3, CN, or O-C_1-C_6 alkyl; R' is methyl or ethyl; and R_5 is C_5-C_6 alkyl or CH_2-C_3-C_6 cycloalkyl.

In another more specific subgeneric embodiment, this disclosure provides or contemplates a compound of formula IA-1 or IA-2 or IA-3, where R_1 is H, halogen, cyano, CF_3, or methoxy, R_2 is H, F, or methyl, R' is H, halogen, methyl, ethyl, or methoxy, and R_5 is C_5-C_6 alkyl or CH_2-C_3-C_6 cycloalkyl.

In another subgeneric embodiment, this disclosure provides or contemplates a compound of formula IA, where R_1 is F, Cl, or CF_3; R_2 is H; and R' is halogen, methyl, ethyl, or methoxy; R_3 and R_4 are H, methyl, or Cl; and R_5 is C_5-C_6 alkyl or CH_2-C_3-C_6 cycloalkyl.

In another subgeneric embodiment, this disclosure provides or contemplates a compound of formula IA, where R_1 is halogen or CF_3; R_2 is H, F, or methyl, R' is phenyl; R_3 and R_4 are H, methyl, or Cl; and R_5 is C_5-C_6 alkyl or CH_2-C_5-C_6 cycloalkyl.

In another subgeneric embodiment, this disclosure provides or contemplates a compound of formula IA, where R_1 is halogen or CF_3; R_2 is H, F, or methyl, R' is halophenyl; R_3 and R_4 are H, methyl, or Cl; and R_5 is C_5-C_6 alkyl or CH_2-C_5-C_6 cycloalkyl.

In another subgeneric embodiment, this disclosure provides or contemplates a compound of formula IA, where R_1 is NH_2, NH-C_1-C_6 alkyl; N(C_1-C_6 alkyl)-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_2, C(=O)NH-C_1-C_6 alkyl, SO_2NH_2, $NHSO_2$-C_1-C_6 alkyl.

In a more specific subgeneric embodiment, this disclosure provides or contemplates a compound of formula IA where R_1 is NH_2, NH-C_1-C_6 alkyl; or N(C_1-C_6 alkyl)-C_1-C_6 alkyl; and R_2 is H or halogen.

In another more specific subgeneric embodiment, this disclosure provides or contemplates a compound of formula IA where R_1 is NHC(=O)C_1-C_6 alkyl, C(=O)N(CH_3)$_2$, C(=O)N(Et)$_2$, C(=O)NH_2, or C(=O)NH-C_1-C_6 alkyl.

In another more specific subgeneric embodiment, this disclosure provides or contemplates a compound of formula IA-1 where R_1 is NHC(=O)C_1-C_6 alkyl, C(=O)N(CH_3)$_2$, C(=O)N(Et)$_2$, C(=O)NH_2, or C(=O)NH-C_1-C_6 alkyl.

In another more specific subgeneric embodiment, this disclosure provides or contemplates a compound of formula IA-1 where R_1 is SO_2NH_2 or $NHSO_2$-C_1-C_6 alkyl.

In another more specific subgeneric embodiment, this disclosure provides or contemplates a compound of formula IA-2 where R_1 is SO_2NH_2 or $NHSO_2$-C_1-C_6 alkyl.

In another subgeneric embodiment, this disclosure provides or contemplates a compound of formula IA, where R_1 is $C(=O)OC_1$-C_6 alkyl, $OC(=O)C_1$-C_6 alkyl, OC_1-C_6 alkyl, or SC_1-C_6 alkyl.

In another subgeneric embodiment, this disclosure provides or contemplates a compound of formula IA, where R_1 is $(CH_2)_mC_3$-C_6 cycloalkenyl, C_2-C_6 alkenyl, or C_2-C_6 alkynyl.

In another subgeneric embodiment, this disclosure provides or contemplates a compound of formula IA, where R_1 is CH_2OCH_3, $CH_2OCH_2CH_3$, OC_1-C_6 alkyl, or SC_1-C_6 alkyl.

In another more specific subgeneric embodiment, this disclosure provides or contemplates a compound of formula IA-1, where R_1 is $C(=O)OC_1$-C_6 alkyl, $OC(=O)C_1$-C_6 alkyl, OC_1-C_6 alkyl, or SC_1-C_6 alkyl.

In another subgeneric embodiment, this disclosure provides or contemplates a compound of formula IA-1, where R_1 is CH_2OCH_3, $CH_2OCH_2CH_3$, OC_1-C_6 alkyl, or SC_1-C_6 alkyl.

In another more specific subgeneric embodiment, this disclosure provides or contemplates a compound of formula IA-1, where R_1 is $C(=O)OC_1$-C_6 alkyl, $OC(=O)C_1$-C_6 alkyl, OC_1-C_6 alkyl, or SC_1-C_6 alkyl; R_2 is H, F, or methyl, R' is halogen or methyl; and R_5 is C_5-C_6 alkyl or CH_2-C_5-C_6 cycloalkyl.

In another more specific subgeneric embodiment, this disclosure provides or contemplates a compound of formula IA-1, where R_1 is NH_2, NH-C_1-C_6 alkyl; or N(C_1-C_6 alkyl)-C_1-C_6 alkyl; R_2 is H, F, or methyl, R' is halogen or methyl; and R_5 is C_5-C_6 alkyl or CH_2-C_5-C_6 cycloalkyl.

In another more specific subgeneric embodiment, this disclosure provides or contemplates a compound of formula IA-1, where R_1 is $NHC(=O)C_1$-C_6 alkyl, $C(=O)N(CH_3)_2$, $C(=O)N(Et)_2$, $C(=O)NH_2$, $C(=O)NH$-C_1-C_6 alkyl, SO_2NH_2, or $NHSO_2$-C_1-C_6 alkyl; R_2 is H, F, or methyl, R' is halogen or methyl; and R_5 is C_5-C_6 alkyl or CH_2-C_5-C_6 cycloalkyl.

In another subgeneric embodiment, this disclosure provides or contemplates a **compound of formula IA, where R_1 is C_2–C_6 alkynyl, optionally substituted.**

In another subgeneric embodiment, this disclosure provides or contemplates a **compound of formula IA, where R_1 and R_2 form a fused, nitrogen-containing ring.**

In another subgeneric embodiment, this disclosure provides or contemplates a **compound of formula IA, where R_1 and R_2 form a fused, oxygen-containing ring.**

In another subgeneric embodiment, this disclosure provides or contemplates a **compound of formula IA, where R_1 and R_2 form a fused thiazolo or isothiazolo group.**

In another subgeneric embodiment, this disclosure provides or contemplates a **compound of formula IA, where R_1 and R_2 form a fused cyclopentane, optionally substituted.**

In another subgeneric embodiment, this disclosure provides or contemplates a **compound of formula IA, where R_1 and R_2 form a fused cyclohexane, optionally substituted.**

In another subgeneric embodiment, this disclosure provides or contemplates a **compound of formula IA-1 or IA-2, where R_1 and R_2 form a fused, nitrogen-containing ring.**

In another subgeneric embodiment, this disclosure provides or contemplates a **compound of formula IA-1 or IA-2, where R_1 and R_2 form a fused, oxygen-containing ring.**

In another subgeneric embodiment, this disclosure provides or contemplates a **compound of formula IA-1 or IA-2, where R_1 and R_2 form a fused thiazolo or isothiazolo group.**

In another subgeneric embodiment, this disclosure provides or contemplates a **compound of formula IA-1 or IA-2, where R_1 and R_2 form a fused cyclopentane, optionally substituted.**

In another subgeneric embodiment, this disclosure provides or contemplates a **compound of formula IA-1 or IA-2, where R_1 and R_2 form a fused cyclohexane, optionally substituted.**

In another subgeneric embodiment, this disclosure provides or contemplates a compound of formula IA-1 or IA-2, where R_1 and R_2 form a fused, nitrogen-containing ring; and R_5 is C_5-C_6 alkyl or CH_2-C_5-C_6 cycloalkyl.

In another subgeneric embodiment, this disclosure provides or contemplates a compound of formula IA-1 or IA-2, where R_1 and R_2 form a fused, oxygen-containing ring; and R_5 is C_5-C_6 alkyl or CH_2-C_5-C_6 cycloalkyl.

In another subgeneric embodiment, this disclosure provides or contemplates a compound of formula IA-1 or IA-2, where R_1 and R_2 form a fused thiazolo or isothiazolo group; and R_5 is C_5-C_6 alkyl or CH_2-C_5-C_6 cycloalkyl.

In another subgeneric embodiment, this disclosure provides or contemplates a compound of formula IA-1 or IA-2, where R_1 and R_2 form a fused cyclopentane, optionally substituted; and R_5 is C_5-C_6 alkyl or CH_2-C_5-C_6 cycloalkyl.

In another subgeneric embodiment, this disclosure provides or contemplates a compound of formula IA-1 or IA-2, where R_1 and R_2 form a fused cyclohexane, optionally substituted; and R_5 is C_5-C_6 alkyl or CH_2-C_5-C_6 cycloalkyl.

In another more specific subgeneric embodiment, this disclosure provides or contemplates a compound of formula IA-1, where R_1 is halogen; R_2 is H, F, or methyl, R' is halogen or methyl; and R_5 is C_5-C_6 alkyl or CH_2-C_5-C_6 cycloalkyl.

In another more specific subgeneric embodiment, this disclosure provides or contemplates a compound of formula IA-1, where R_1 is halogen; R_2 is H, F, or methyl, R' is 2-(dimethylamino) ethyl; and R_5 is C_5-C_6 alkyl or CH_2-C_5-C_6 cycloalkyl.

In another more specific subgeneric embodiment, this disclosure provides or contemplates a compound of formula IA-1, where R_1 is halogen; R_2 is H, halogen, or methyl, R' is H; and R_5 is C_5-C_6 alkyl or CH_2-C_5-C_6 cycloalkyl.

In another more specific subgeneric embodiment, this disclosure provides or contemplates a compound of formula IA-2, where R_1 is halogen; R_2 is H or methyl, R' is halogen or methyl; and R_5 is C_5-C_6 alkyl or CH_2-C_5-C_6 cycloalkyl.

$C(=O)OC_1$-C_6 alkyl, $OC(=O)C_1$-C_6 alkyl, OC_1-C_6 alkyl In another more specific subgeneric embodiment, this disclosure provides or contemplates a compound of formula IA-1. In another more specific subgeneric embodiment, this disclosure provides or

contemplates a compound of formula IA-1, where R_1 is trifluoromethyl; R_2 is H or methyl, R' is halogen or methyl; and R_5 is C_5-C_6 alkyl or CH_2-C_5-C_6 cycloalkyl.

In another more specific subgeneric embodiment, this disclosure provides or contemplates a compound of formula IA-2, where R_1 where R_1 is trifluoromethyl; R_2 is H or methyl, R' is halogen or methyl; and R_5 is C_5-C_6 alkyl or CH_2-C_5-C_6 cycloalkyl.

In another more specific subgeneric embodiment, this disclosure provides or contemplates a compound of formula IA-3, where R_1 where R_1 is trifluoromethyl; R_2 is H or methyl, R' is halogen or methyl; and R_5 is C_5-C_6 alkyl or CH_2-C_5-C_6 cycloalkyl.

In another more specific subgeneric embodiment, this disclosure provides or contemplates a compound of formula IA-4 or IA-5, where R_1 where R_1 is trifluoromethyl; R_2 is H or methyl, R' is halogen or methyl; and R_5 is C_5-C_6 alkyl or CH_2-C_5-C_6 cycloalkyl.

In another more specific subgeneric embodiment, this disclosure provides or contemplates a compound of formula IA-2, where R_1 is trifluoromethyl; R_2 is F; R' is halogen or methyl; and R_5 is C_5-C_6 alkyl or CH_2-C_5-C_6 cycloalkyl.

In another subgeneric embodiment, this disclosure provides or contemplates a compound of formula IA, where R_1 or R_5 is CH_2Ar or CH_2CH_2-Ar, where Ar is phenyl, pyridyl, pyrrolyl, imidazolyl, oxazolyl, or thiazolyl.

In another subgeneric embodiment, this disclosure provides or contemplates a compound of formula IA, where R_1 is F.

In another subgeneric embodiment, this disclosure provides or contemplates a compound of formula IA, where R_1 is Cl.

In another subgeneric embodiment, this disclosure provides or contemplates a compound of formula IA, where R_1 is Br.

In another subgeneric embodiment, this disclosure provides or contemplates a compound of formula IA-1, where R_1 is F.

In another subgeneric embodiment, this disclosure provides or contemplates a compound of formula IA-1, where R_1 is Cl.

In another subgeneric embodiment, this disclosure provides or contemplates a compound of formula IA-1, where R_1 is Br.

In another subgeneric embodiment, this disclosure provides or contemplates a compound of formula IA-1, where R_1 is F and R_2 is H, OCH_3, or F.

In another subgeneric embodiment, this disclosure provides or contemplates a compound of formula IA-1, where R_1 is F; R_3 and R_4 are both methyl; and R' is H.

In another subgeneric embodiment, this disclosure provides or contemplates a compound of formula IA-1, where R_1 is CF_3; R_3 and R_4 are both methyl; and R' is H.

In another subgeneric embodiment, this disclosure provides or contemplates a compound of formula IA, where R_1 and R_2 are both F.

In another subgeneric embodiment, this disclosure provides or contemplates a compound of formula IA, where R_1 is mono-, di-, or tri-halomethyl.

In another subgeneric embodiment, this disclosure provides or contemplates a compound of formula IA, where R_1 is CH_2F, CHF_2, or CF_3.

In another subgeneric embodiment, this disclosure provides or contemplates a compound of formula IA, where R_1 is CH_2Cl.

In another subgeneric embodiment, this disclosure provides or contemplates a compound of formula IA, where R_1 is CH_2Br.

In another subgeneric embodiment, this disclosure provides or contemplates a compound of formula IA-1, where R_1 and R_2 are both F; R_3 and R_4 are both methyl; and R' is H.

In another subgeneric embodiment, this disclosure provides or contemplates a compound of formula IA-2, where R_1 is F.

In another subgeneric embodiment, this disclosure provides or contemplates a compound of formula IA-2, where R_1 and R_2 are both F.

In another subgeneric embodiment, this disclosure provides or contemplates a compound of formula IA-3, where R_1 is F.

In another subgeneric embodiment, this disclosure provides or contemplates a compound of formula IA-3, where R_1 and R_2 are both F.

In another subgeneric embodiment, this disclosure provides or contemplates a compound of formula IA, where R_1 or R_5 is CH_2Ar or CH_2CH_2-Ar, where Ar is isoxazolyl or isothiazolyl.

In another subgeneric embodiment, this disclosure provides or contemplates a compound of formula IA, where R_1 or R_5 is CH_2Ar or CH_2CH_2-Ar, where Ar is quinolyl or isoquinolyl.

In another subgeneric embodiment, this disclosure provides or contemplates a compound of formula IA, where R_1 or R_5 is CH_2Ar or CH_2CH_2-Ar, where Ar is pyrimidyl or purinyl.

In another subgeneric embodiment, this disclosure provides or contemplates a compound of formula IA, where R_1 or R_5 is CH_2Ar or CH_2CH_2-Ar, where Ar is indolyl, isoindolyl, or benzimidazolyl.

In a more specific embodiment, this disclosure provides or contemplates a compound of formula IA, where R_1 or R_5 is CH_2Ar or CH_2CH_2-Ar, where Ar is halo phenyl.

In another more specific embodiment, this disclosure provides or contemplates a compound of formula IA, where R_1 or R_5 is CH_2Ar or CH_2CH_2-Ar, where Ar is dihalophenyl or dihalopyridyl.

In another more specific embodiment, this disclosure provides or contemplates a compound of formula IA, where R_1 or R_5 is CH_2Ar or CH_2CH_2-Ar, where Ar is mono- or di-halothienyl, mono- or di-halofuryl, mono- or di-halobenzothienyl, or mono- or di-halobenzofuryl.

In another more specific embodiment, this disclosure provides or contemplates a compound of formula IA, where R_1 or R_5 is CH_2Ar or CH_2CH_2-Ar, where Ar is *o*-, *m*-, or *p*- xylyl or *o*-, *m*-, or *p*-anisyl.

In another more specific embodiment, this disclosure provides or contemplates a compound of formula IA, where R_1 or R_5 is CH_2Ar or CH_2CH_2-Ar, where Ar is *m*- or *p*-cyanophenyl or *m*- or *p*-cyanomethyl phenyl.

In another subgeneric embodiment, this disclosure provides or contemplates a compound of formula IA, in which R_3 and R_4 are halogen, CF_3, or C_1-C_3 alkyl and R_5 is C_1-C_6 alkyl, where the alkyl group is substituted with one or two groups selected, independently, from OH, OMe, OEt, F, CF_3, Cl, or CN.

In another subgeneric embodiment, this disclosure provides or contemplates a compound of formula IA, in which R_3 and R_4 are halogen, CF_3, OCF_3, C_1-C_3 alkyl, or OC_1-C_3 alkyl, and R_5 is $(CH_2)_wC_3$-C_6 cycloalkyl, where w is 1 or 2, where the cycloalkyl group is substituted with Me, OH, OMe, OEt, F, CF_3, Cl, or CN.

In a more specific subgeneric embodiment, this disclosure provides or contemplates a compound of formula IA-1, in which R_3 and R_4 are halogen, CF_3, or C_1-C_3 alkyl, and R_5 is $(CH_2)_w$-C_5-C_6 cycloalkyl, optionally substituted, or $(CH_2)_w$-C_5-C_6 heterocycloalkyl, optionally substituted.

In another more specific embodiment, this disclosure provides or contemplates a compound of formula IA-1, where R_1 is CH_2phenyl or CH_2CH_2-phenyl.

In another more specific embodiment, this disclosure provides or contemplates a compound of formula IA-1, where R_1 is Ar, CH_2Ar or CH_2CH_2-Ar, where Ar is 3,5-dichlorophenyl or 3,5-difluorophenyl.

In a more specific embodiment, this disclosure provides or contemplates a compound of formula IA-1, where R_5 is Ar, $(CHR_6)_wAr$, $CH_2(CHR_6)_wAr$, or $(CHR_6)_wCH_2Ar$, where Ar is phenyl or pyridyl; R_3 and R_4 are H or C_1-C_6 alkyl, unsubstituted or substituted with one or two groups selected from OH, OMe; and R_6 is CN, CH_2CN, or halogen.

In another subgeneric embodiment, this disclosure provides or contemplates a compound of formula IA-1, where R_5 is Ar, $(CHR_6)_wAr$, $CH_2(CHR_6)_wAr$, or $(CHR_6)_wCH_2Ar$, where Ar is phenyl or pyridyl; and R_1 is F, CH_2F, CHF_2, CF_3, or CF_2CF_3.

In a more specific embodiment, this disclosure provides or contemplates a compound of formula IA-1, where R_5 is Ar, $(CHR_6)_wAr$, $CH_2(CHR_6)_wAr$, or $(CHR_6)_wCH_2Ar$, where Ar is phenyl or pyridyl, and R_1 is OC_1-C_6 alkyl or $C(=O)C_1$-C_6 alkyl.

In a more specific embodiment, this disclosure provides or contemplates a compound of formula IA-1, where R_5 is Ar, $(CHR_6)_wAr$, $CH_2(CHR_6)_wAr$, or $(CHR6)_wCH_2Ar$, where Ar is phenyl or pyridyl, and R_1 is $C(=O)OC_1$-C_6 alkyl or $OC(=O)C_1$-C_6 alkyl.

In a more specific embodiment, this disclosure provides or contemplates a compound of formula IA-1, where R_5 is Ar, $(CHR_6)_wAr$, $CH_2(CHR_6)_wAr$, or $(CHR_6)_wCH_2Ar$, where Ar is phenyl or pyridyl, R_1 is C_2-C_6 alkenyl or C_2-C_6 alkynyl, q is 1, and X and Y are both O.

In a more specific embodiment, this disclosure provides or contemplates a compound of formula IA-1, where R_5 is Ar, $(CHR_6)_wAr$, $CH_2(CHR_6)_wAr$, or $(CHR_6)_wCH_2Ar$, Ar is phenyl or pyridyl, and R_1 is SC_1-C_6 alkyl.

In a more specific embodiment, this disclosure provides or contemplates a compound of formula IA-1, where R_5 is Ar, $(CHR_6)_wAr$, $CH_2(CHR_6)_wAr$, or $(CHR_6)_wCH_2Ar$, where Ar is phenyl or pyridyl, R_3 and R_4 are H, Cl, methoxy, or C_1-C_3 alkyl, and R_1 is C_1-C_6 alkyl.

In a more specific embodiment, this disclosure provides or contemplates a compound of formula IA-2, where R_5 is Ar, $(CHR_6)_wAr$, $CH_2(CHR_6)_wAr$, or $(CHR_6)_wCH_2Ar$, where Ar is phenyl or pyridyl; R_3 and R_4 are H, Cl, methoxy, or C_1-C_2 alkyl, unsubstituted or substituted with one or two groups selected from OH, OMe; and R_1 is CN, CH_2CN, or halogen.

In another subgeneric embodiment, this disclosure provides or contemplates a compound of formula IA-2, where R_5 is Ar, $(CHR_6)_wAr$, $CH_2(CHR_6)_wAr$, or $(CHR_6)_wCH_2Ar$, where Ar is phenyl or pyridyl; and R_1 is F, CH_2F, CHF_2, CF_3, or CF_2CF_3.

In a more specific embodiment, this disclosure provides or contemplates a compound of formula IA-1, where R_5 is Ar, $(CHR_6)_wAr$, $CH_2(CHR_6)_wAr$, or $(CHR_6)_wCH_2Ar$, where Ar is phenyl or pyridyl, and R_1 is OC_1-C_6 alkyl or $C(=O)C_1$-C_6 alkyl.

In a more specific embodiment, this disclosure provides or contemplates a compound of formula IA-2, where R_5 is Ar, $(CHR_6)_wAr$, $CH_2(CHR_6)_wAr$, or $(CHR_6)_wCH_2Ar$, where Ar is phenyl or pyridyl, and R_1 is OC_1-C_6 alkyl or $C(=O)C_1$-C_6 alkyl.

In a more specific embodiment, this disclosure provides or contemplates a compound of formula IA-3, where R_5 is Ar, $(CHR_6)_wAr$, $CH_2(CHR_6)_wAr$, or

$(CHR_6)_wCH_2Ar$, where Ar is phenyl or pyridyl, and R_1 is OC_1-C_6 alkyl or $C(=O)C_1$-C_6 alkyl.

In a more specific embodiment, this disclosure provides or contemplates a compound of formula IA-3, where R' is phenyl or methoxy, R_2 is H, and R_5 is Ar, $(CHR_6)_wAr$, $CH_2(CHR_6)_wAr$, or $(CHR_6)_wCH_2Ar$, where Ar is phenyl or pyridyl, and R_1 is $C(=O)OC_1$-C_6 alkyl or $OC(=O)C_1$-C_6 alkyl.

In a more specific embodiment, this disclosure provides or contemplates a compound of formula IA-2, where R_5 is Ar, $(CHR_6)_wAr$, $CH_2(CHR_6)_wAr$, or $(CHR_6)_wCH_2Ar$, Ar is phenyl or pyridyl, and R_1 is SC_1-C_6 alkyl.

In a more specific embodiment, this disclosure provides or contemplates a compound of formula IA-2, where R_5 is Ar, $(CHR_6)_wAr$, $CH_2(CHR_6)_wAr$, or $(CHR_6)_wCH_2Ar$, where Ar is phenyl or pyridyl, R_3 and R_4 are H or C_1-C_3 alkyl, and R_1 is C_1-C_6 alkyl.

In the second aspect, there is provided a compound which is one of the following:

N-(2-chloro-4-(3,4-dihydroisoquinolin-2(*1H*)-yl)-6-(trifluoromethyl)phenyl)-3,3-dimethylbutanamide

N-(4-(3,4-dihydroisoquinolin-2(*1H*)-yl)-2,6-dimethylphenyl)-3,3-dimethylbutanamide

N-(2-chloro-4-(3,4-dihydroisoquinolin-2(*1H*)-yl)-6-(trifluoromethyl)phenyl)-3-cyclopentylpropanamide

N-(2-chloro-4-(6-fluoro-3,4-dihydroisoquinolin-2(*1H*)-yl)-6-(trifluoromethylphenyl)-3,3-dimethylbutanamide

N-[2-chloro-4-(3,4-dihydro-*1H*-isoquinolin-2-yl)-6-methyl phenyl]-3,3-dimethylbutanamide

N-[2-chloro-4-(6-fluoro-3,4-dihydro-*1H*-isoquinolin-2-yl)-6-trifluoromethyl phenyl]-3-cyclopentylpropionamide

N-[2,6-dimethyl-4-(6-trifluoromethyl-3,4-dihydro-*1H*-isoquinolin-2-yl)-phenyl]-3,3-dimethylbutanamide

N-[2-chloro-6-trifluoromethyl-4-(6-trifluoromethyl-3,4-dihydro-*1H*-isoquinolin-2-yl)-phenyl]-3,3-dimethylbutanamide

N-[2-chloro-4-(6-chloro-3,4-dihydro-*1H*-isoquinolin-2-yl)-6-trifluoromethyl phenyl]-3,3-dimethylbutanamide

N-[4-(6-chloro-3,4-dihydro-*1H*-isoquinolin-2-yl)-2,6-dimethyl-phenyl]-3,3-dimethylbutanamide

N-[4-(6-fluoro-3,4-dihydro-*1H*-isoquinolin-2-yl)-2,6-dimethyl phenyl]-3,3-dimethylbutanamide

N-[2-chloro-4-(7-fluoro-3,4-dihydro-*1H*-isoquinolin-2-yl)-6-trifluoromethyl-phenyl]-3,3-dimethylbutanamide

N-[4-(7-fluoro-3,4-dihydro-*1H*-isoquinolin-2-yl)-2,6-dimethyl-phenyl]-3,3-dimethylbutanamide

N-[2-chloro-4-(6-fluoro-3,4-dihydro-*1H*-isoquinolin-2-yl)-6-methylphenyl]-3,3-dimethylbutanamide

N-[2-chloro-4-(7-fluoro-3,4-dihydro-*1H*-isoquinolin-2-yl)-6-methylphenyl]-3,3-dimethylbutanamide

N-[2-chloro-6-methyl-4-(6-trifluoromethyl-3,4-dihydro-*1H*-isoquinolin-2-yl)-phenyl]-3,3-dimethylbutanamide

N-[2-chloro-4-(6-chloro-3,4-dihydro-*1H*-isoquinolin-2-yl)-6-methyl-phenyl]-3,3-dimethylbutanamide

N-[2-chloro-4-(6-fluoro-3,4-dihydro-*1H*-isoquinolin-2-yl)-phenyl]-3,3-dimethylbutanamide

N-[4-(6-fluoro-3,4-dihydro-*1H*-isoquinolin-2-yl)-2-methyl-phenyl]-3,3-dimethylbutanamide

N-[4-(6-fluoro-3,4-dihydro-*1H*-isoquinolin-2-yl)-2-trifluoromethylphenyl]-3,3-dimethylbutanamide

N-[2-chloro-4-(6-trifluoromethyl-3,4-dihydro-*1H*-isoquinolin-2-yl)-phenyl]-3,3-dimethylbutanamide

N-[4-(7-fluoro-3,4-dihydro-*1H*-isoquinolin-2-yl)-2-trifluoromethyl-phenyl]-3,3-dimethylbutanamide

3,3-dimethyl-N-[2-trifluoromethyl-4-(7-trifluoromethyl-3,4-dihydro-*1H*-isoquinolin-2-yl)-phenyl]butanamide

N-[4-(6-methoxy-3,4-dihydro-*1H*-isoquinolin-2-yl)-2,6-dimethyl-phenyl]-3,3-dimethylbutanamide

N-[4-(3,4-dihydro-*1H*-isoquinolin-2-yl)-2-methoxy-6-methyl-phenyl]-3,3-dimethylbutanamide

N-[2-chloro-4-(3,4-dihydro-*1H*-isoquinolin-2-yl)-6-trifluoromethoxy-phenyl]-3,3-dimethylbutanamide, and

N-[4-(3,4-dihydro-*1H*-isoquinolin-2-yl)-2,6-dimethoxy-phenyl]-3,3-dimethylbutanamide.

In the third aspect, there is provided a composition comprising a pharmaceutically acceptable carrier and one or more of the following:

i. a compound of formula IA;

ii. a pharmaceutically acceptable solvate of a compound of formula IA;

iii. a pharmaceutically acceptable salt of a compound of formula IA; and

iv. a pharmaceutically acceptable ester of a compound of formula IA.

In the fourth aspect, there is provided the use of compound of formula IA or a salt or solvate thereof in the manufacture of medicament for the treatment of a disease or disorder which is affected by modulation of potassium channels.

In another embodiment, this disclosure provides or contemplates a method of treating **or preventing a disease, disorder, or condition that is affected by modulation of potassium ion channels in a patient comprising administration of a compound of formula IA in an amount of up to 2000 mg per day.**

In another embodiment, this disclosure provides or contemplates a method of treating **or preventing a disease, disorder, or condition that is affected by modulation of potassium ion channels in a patient comprising administration of a compound of formula IA in an amount of from about 10 mg to about 2000 mg per day.**

In a more specific embodiment, this disclosure provides or contemplates a method of **treating or preventing a disease, disorder, or condition that is affected by modulation of potassium ion channels in a patient comprising administration of a compound of formula IA-1 in an amount of up to about 2000 mg per day.**

In the fifth aspect, there is provided the use of compound of formula IA or a salt or ester or solvate thereof in the manufacture of medicament for the treatment of a disease or disorder which is affected by activation of voltage-gated potassium channels.

In the sixth aspect, there is provided the use of compound of formula IA, a salt of compound IA or a solvate of compound of formula IA in the manufacture of medicament for the treatment of a seizure or seizure disorder.

In a more specific embodiment, this disclosure provides or contemplates a method of **treating or preventing a seizure disorder in a patient comprising administration of a compound of formula IA in an amount of up to about 2000 mg per day.**

In the seventh aspect, there is provided the use of compound of formula IA or a salt or solvate thereof in the manufacture of medicament for the treatment or prevention of a disorder characterized by hyperexcitability of the nervous system.

In the eighth aspect, there is provided the use of compound of formula IA-1 or salt or solvate thereof in the manufacture of medicament for increasing the channel open probability of KCNQ2/3 channels in a mammal.

In another embodiment, this disclosure provides or contemplates a method of treating **or preventing a seizure disorder in a patient comprising administration of a compound of formula IA in an amount of from about 10 mg per day to about 2000 mg per day.**

In another embodiment, this disclosure provides or contemplates a method of treating **or preventing a seizure disorder in a patient comprising administration of a compound of formula IA in an amount of from about 300 mg per day to about 2000 mg per day.**

In another embodiment, this disclosure provides or contemplates a method of treating **or preventing a seizure disorder in a patient comprising administration of a compound of formula IA in an amount of from about 300 mg per day to about 1200 mg per day.**

In another more specific embodiment, this disclosure provides or contemplates a **method of treating or preventing a seizure disorder in a patient comprising administration of a compound of formula IA-1 in an amount of up to 2000 mg per day.**

In another embodiment, this disclosure provides or contemplates a method of treating **or preventing a seizure disorder in a patient comprising administration of a compound of formula IA-1 in an amount of from about 10 mg per day to about 2000 mg per day.**

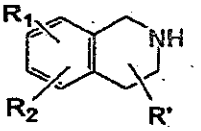
In another embodiment, this disclosure provides or contemplates a method of treating **or preventing a seizure disorder in a patient comprising administration of a compound of formula IA-1 in an amount of from about 300 mg per day to about 2000 mg per day.**

In another embodiment, this disclosure provides or contemplates a method of treating **or preventing a seizure disorder in a patient comprising administration of a compound of formula IA-1 in an amount of from about 300 mg per day to about 1200 mg per day.**

In the ninth aspect, there is provided the use of compound of formula IA-1 or salt, solvate, or ester thereof in the manufacture of medicament for increasing neuronal M currents in a mammal.

In the tenth aspect, there is provided the use of compound of formula IA or a salt or solvate thereof in the manufacture of medicament for the treatment or prevention of a disease or disorder which is affected by modulation of potassium channels.

In the eleventh aspect, there is provided the product resulting from the reaction of **N-(4-bromo-2,6-dimethyl-phenyl)-3,3-dimethyl-butanamide with a tetrahydroisoquinoline derivative of formula Q below, in**



Q

where R_1 and R_2, are, independently, H, CN, halogen, CH_2CN, OH, NO_2, CH_2F, CHF_2, CF_3, CF_2CF_3, C_1-C_6 alkyl, $C(=O)C_1$-C_6 alkyl; NH_2, NH-C_1-C_6 alkyl; N(C_1-C_6 alkyl)-C_1-C_6 alkyl, $NHC(=O)C_1$-C_6 alkyl, $C(=O)N(CH_3)_2$, $C(=O)N(Et)_2$, $C(=O)NH_2$, $C(=O)NH$-C_1-C_6 alkyl, SO_2NH_2, $NHSO_2$-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, $(CH_2)_m$thienyl, $(CH_2)_m$furyl, $(CH_2)_m$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 $(CH_2)_m$pyrimidyl, which cycloalkyl and said cycloalkenyl groups optionally contain one or two heteroatoms selected independently from O, N, and S; 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; R' is H, halogen, phenyl, 2-(N,N-dimethylamino)ethyl, CF_3, OC_1-C_3 alkyl or C_1-C_3 alkyl; where all alkyl, cycloalkyl, alkenyl, cycloalkenyl, heterocycloalkyl, heterocycloalkenyl, alkynyl, aryl, and heteroaryl groups in R_1, R_2, and R' are optionally substituted with one or two substituents selected independently from C_1-C_3 alkyl, halogen, CN, OH, OMe, OEt, CN, CH_2F, and trifluoromethyl; and where, additionally, all cycloalkyl and heterocycloalkyl groups are optionally substituted with a carbonyl group; in the presence of bis(dibenzylidineacetone)palladium, (2'-dicyclohexyl phosphanyl-biphenyl-2-yl)-dimethylamine, and potassium t-butoxide in dry toluene.

In the twelfth aspect, there is provided a composition comprising a pharmaceutically acceptable carrier or diluent, a syrup for pediatric use, and a pharmaceutically effective amount of at least one of the following: a compound of formula 1A, a pharmaceutically acceptable salt of a compound of formula 1A, and a pharmaceutically acceptable solvate of a compound of formula 1.

In the thirteenth aspect, there is provided a tablet comprising a pharmaceutically acceptable carrier or diluent, and a pharmaceutically effective amount of at least one of the following: a compound of formula 1A-1, a pharmaceutically acceptable salt of a compound of formula 1A-1, and a pharmaceutically acceptable solvate of a compound of formula 1A-1.

In the fourteenth aspect, there is provided a capsule comprising a pharmaceutically acceptable carrier or diluent, and a pharmaceutically effective amount of at least one of the following: a compound of formula 1A-1, a pharmaceutically acceptable salt of a compound of formula 1A-1, and a pharmaceutically acceptable solvate of a compound of formula 1A-1.

In the fifteenth aspect, there is provided the use of compound of formula IA in an amount of from about 10 mg to about 2000 mg per day in the manufacture of medicament for the treatment or prevention of a disease, disorder, or condition that is affected by modulation of potassium ion channels .

Detailed Description of Invention

As contemplated by this invention, compounds of formula IA are designed for oral or intravenous dosing of up to 2000 mg per day. Yet the high activities of many of these compounds indicate that dosing of less than 1200 mg per day – the current anticipated dosing level of retigabine in adults – is possible. Thus, this invention comprises tablets, capsules, solutions, and suspensions of compounds of formula IA which are formulated for oral administration. Similarly, solutions and suspensions suitable for oral pediatric administration, comprising, in addition to compounds of formula IA, a syrup such as

sorbitol or propylene glycol, among many other examples, are also contemplated. More specifically, solutions and suspensions comprising, in addition to compounds of formula IA, a syrup such as sorbitol or propylene glycol, along with colorants and flavorings suitable for oral pediatric administration, are also contemplated. Additionally, both chewable and non-chewable tablets comprising compounds of formula IA, 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, disintegrants, preservatives, anti-oxidants, flavours and colourants as are typically used in the art of formulation of pharmaceuticals. Examples of such agents include – but are not limited to – starch, calcium carbonate, dibasic calcium phosphate, dicalcium phosphate, microcrystalline cellulose, hydroxypropylcellulose, hydroxypropylmethylcellulose lactose, polyethylene glycols, polysorbates, glycols, safflower oil, sesame oil, soybean oil, and Povidone. Additionally, disintegrants such as sodium starch glycolate; lubricants such as magnesium stearate, stearic acid, and SiO_2; and solubility enhancers such as cyclodextrins, among a great 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.

As used herein, the term "pharmaceutically acceptable acid salts" refers to acid addition salts formed from acids which provide non-toxic anions. The pharmaceutically acceptable anions include, but are not limited to, acetate, aspartate, benzoate, bicarbonate, carbonate, bisulfate, sulfate, chloride, bromide, benzene sulfonate, methyl sulfonate, phosphate, acid phosphate, lactate, maleate, malate, malonate, fumarate, lactate, tartrate, borate, camsylate, citrate, edisylate, esylate, formate, fumarate, gluceptate, glucuronate, gluconate oxalate, palmitate, pamoate, saccharate, stearate, succinate, tartrate, tosylate and trifluoroacetate salts, among a great many other examples. Hemi-salts, including but not limited to hemi-sulfate salts, are likewise contemplated.

For a review on suitable salts, see "Handbook of Pharmaceutical Salts: Properties, Selection, and Use" by Stahl and Wermuth (Wiley-VCH, Weinheim, Germany, 2002).

As is well known, pharmaceutically acceptable salts of compounds of formula I may be prepared by reaction of a compound of formula I with the desired acid; by removal of a protecting group from a suitable precursor of the compound of formula I or by ring-opening a suitable cyclic precursor, for example, a lactone or lactam, using the desired acid or base; and by conversion of one salt of the compound of formula I to another by reaction with an appropriate acid or base or by passage through an appropriate ion-exchange column.

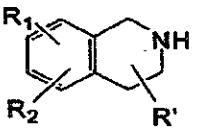
As used herein, the term "pharmaceutically acceptable solvate" refers to describe a molecular complex comprising the compound of the invention and a stoichiometric amount of one or more pharmaceutically acceptable solvent molecules, including but not limited to water and ethanol. Thus, the term solvate includes a hydrate as one example and an ethanolate as another example.

As used herein, modulation of ion channels refers to activating the ion channels, to affecting the kinetics of opening and closing of the ion channels, or to causing any change in the channel open probability of the ion channels.

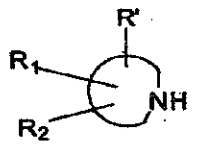
Preparation of compounds

General Strategy

Section I. The preparation of compounds of formula VI is outlined in Scheme 1, in which, for convenience, a substituted tetrahydroisoquinoline,



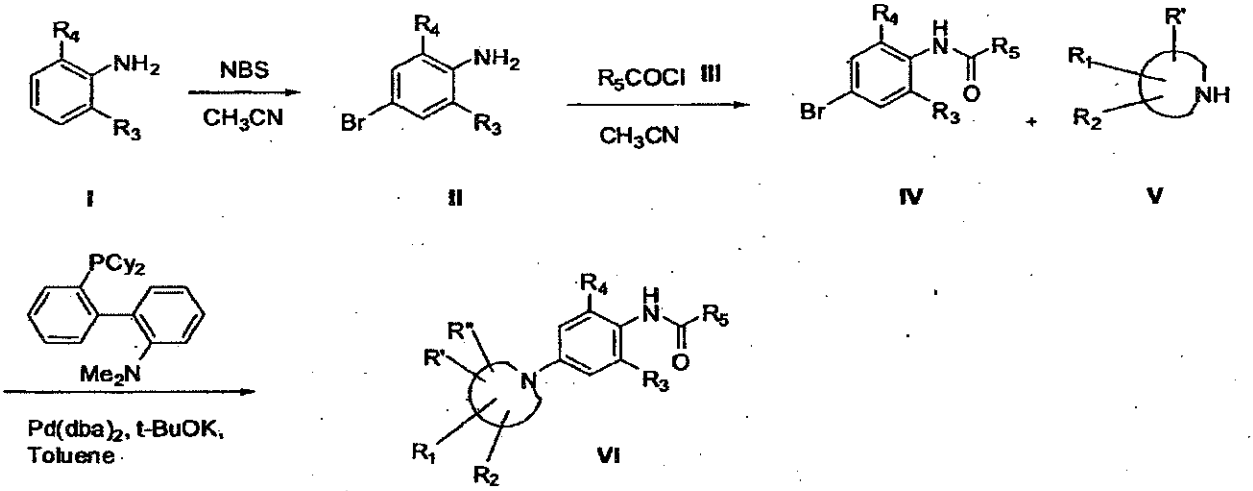
is symbolized by structure V.



V

Such substituted tetrahydroisoquinolines are either commercially available or are prepared from commercially available materials. A great many substituted tetrahydroisoquinolines are known, including many fused isothiazole, piperidino and pyrrolidino derivatives. Thus, for example, compounds of formula IA where R_1 is 5-fluoro- can be prepared starting with 5-fluoro-1,2,3,4-tetrahydroisoquinoline. Similarly, as another among many examples, compounds of formula IA where R_1 or R_2 is 6-methyl- can be prepared starting with 6-methyl-1,2,3,4-tetrahydroisoquinoline. and, again, in two more examples among many, compounds of formula IA where R_1 and R_2 are 6- and 7-chloro, respectively, can be prepared starting with 6-, 7- dichloro-1,2,3,4-tetrahydroisoquinoline; and compounds with a substituent in the 9-position can be prepared starting with the appropriate 9-substitued tetrahydroisoquinoline. Analogously, compounds with R' other than H can be prepared starting with the appropriate 1-, 3-, or 4-substituted tetrahydroisoquinolines. For examples, compounds in which, in the 1- and 4-positions, R' is phenyl, methoxy, ethyl, methyl, F, or 2-(N-, N-dimethylamino)ethyl are accessible *via* the commercially available 1- and 4-substituted tetrahydroisoquinolines.

Scheme 1:



In this procedure the aromatic amine I is brominated according to standard procedures, including but not limited to the reaction with such reagents as N-bromosuccinimide in an aprotic solvent such as acetonitrile. The reaction mixture is typically heated under reflux for a period of from approximately 8 to approximately 48 hours.

In a typical procedure, the resulting bromo derivative II is purified by filtration of the crude reaction mixture through Celite. If desired, other standard purification techniques, including flash chromatography, can be used.

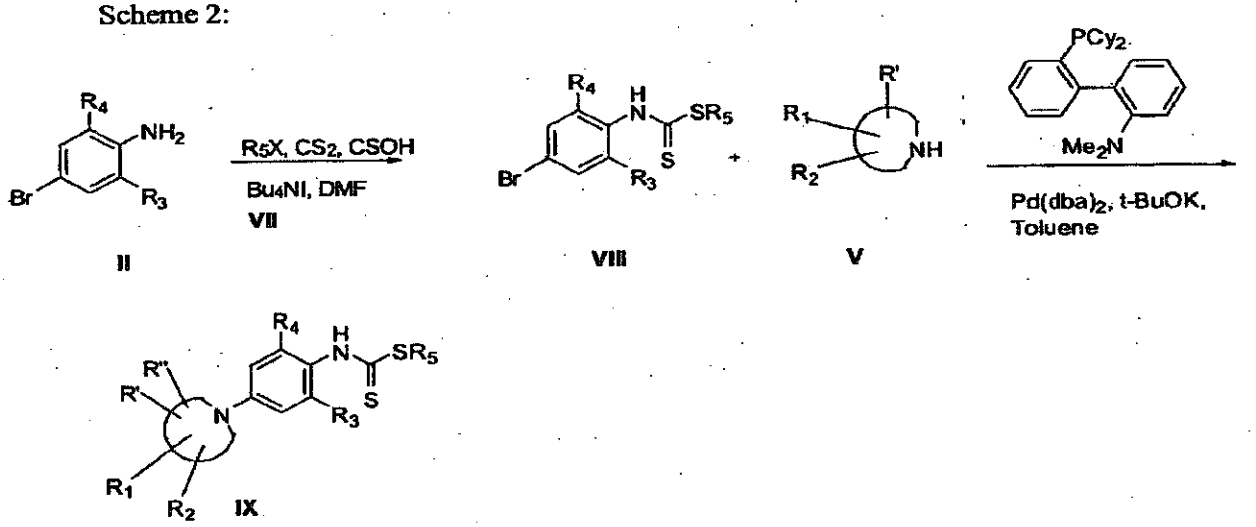
In the following step, the reaction of a compound II with the appropriate acyl chloride III in an aprotic solvent such as acetonitrile produces the amide of general formula IV. This reaction is typically conducted at room temperature for a period of from approximately 4 to approximately 48 hours. The resulting amide of general formula IV can be purified by a standard chromatographic technique such as flash chromatography or thin layer chromatography.

The next step of the reaction sequence is to prepare the desired product of general Formula VI using the well-known palladium coupling reaction, employing a phosphine ligand such as the commercially available dicyclohexyl phosphino-2'-(*N,N,*-dimethylamino)biphenyl. Thus, the amine of general formula V can be coupled to the bromine derivative of general formula IV using a palladium derivative such as, for

example, bis(dibenzylidineacetone)palladium, a base such as potassium *tert*-butoxide and the ligand dicyclohexyl phosphino-2'-(*N,N,*-dimethyl amino)biphenyl in an aprotic solvent. The reaction mixture is typically heated in an oil bath at 90°C for a period of from approximately 8 to approximately 48 hours, or it can be heated using a microwave apparatus (Horizon unit, Biotage) at a temperature range of from approximately 90° to approximately 250°C. The desired compound of general formula VI is purified by standard chromatographic techniques, such as flash chromatography or thin layer chromatography. It can also be recrystallized from toluene.

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

Scheme 2:

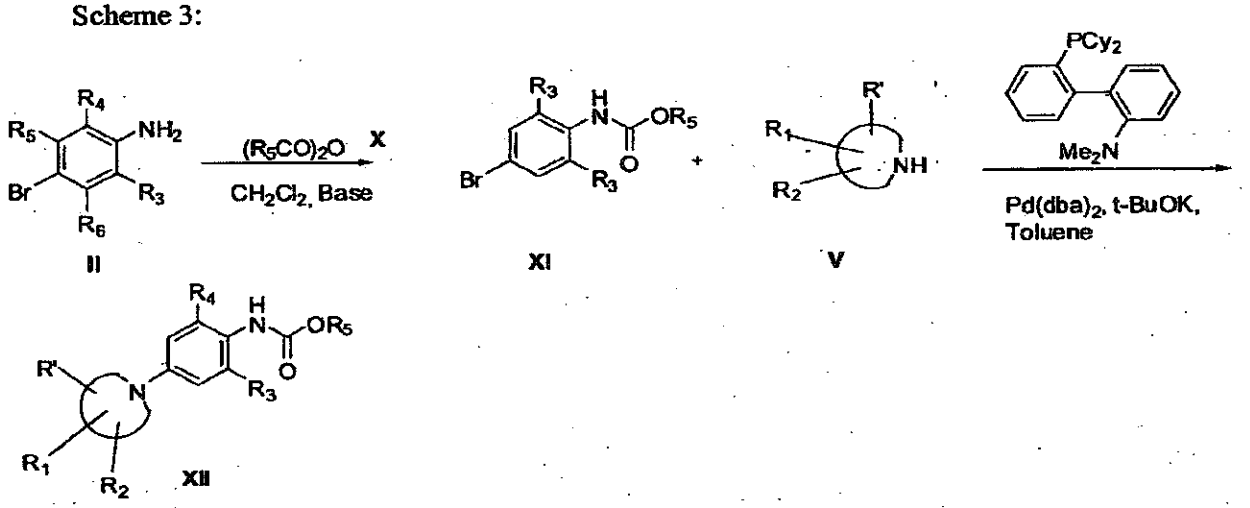


In reactions in section II, the compounds of general Formula IX are prepared in a way similar to that employed in section I. The aniline derivative II (section I) is combined with the haloalkyl compound VII under standard conditions to produce the desired thioester of general formula VIII. The reaction is typically conducted at a temperature of from approximately 20° to approximately 90°C for a period of from approximately 8 to approximately 48 hours, or in a microwave apparatus (Horizon unit, Biotage) at a temperature range of from approximately 90° to approximately 250°C. As in the previous sequence, the thioester can be purified by standard chromatographic techniques such as flash chromatography or thin layer chromatography. The final step, a

palladium coupling reaction to produce the compound of general Formula IX, is identical to that described in the corresponding step in Section I.

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

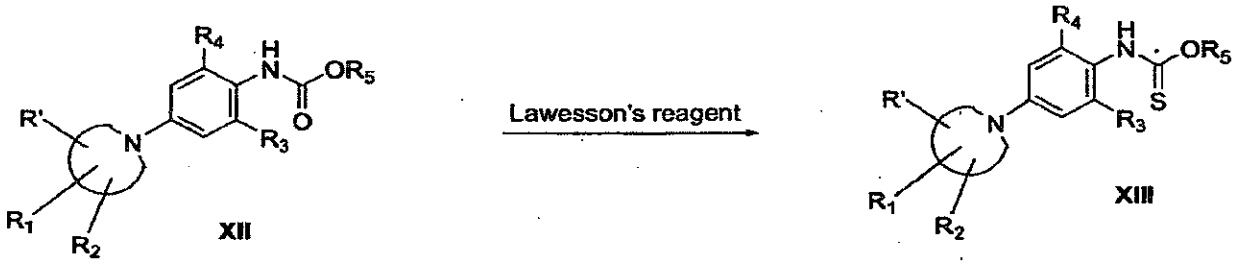
Scheme 3:



In section III, the carbamate derivative of general Formula XI is obtained from the aniline derivative of general Formula II (see section I) using standard conditions. Typically, the aniline is allowed to react with an anhydride derivative of general Formula X in the presence of a base such as triethylamine or diisopropyl ethylamine in an aprotic solvent such as methylene chloride. The reaction is conducted at a temperature in the range of from approximately -20° to approximately 40°C for a period of from approximately 30 min to approximately 48 hours, depending on the particular substrates. The resulting carbamate derivative of general Formula XI can be purified by the usual chromatographic techniques, such as flash chromatography or thin layer chromatography. As in sections I and II, the final step is a palladium coupling.

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

Scheme 4:

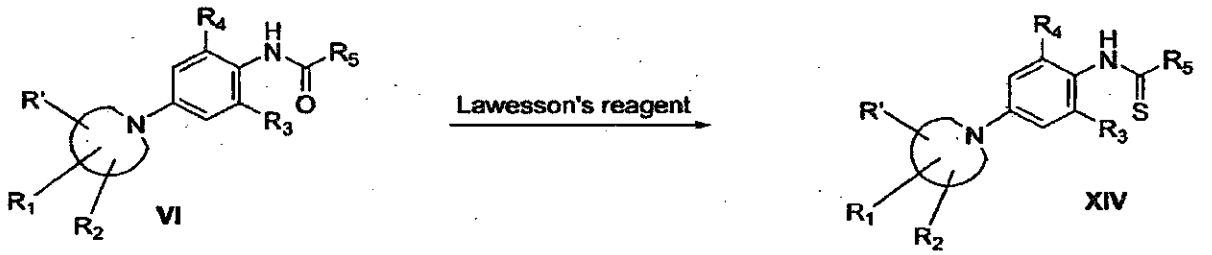


XII XIII

Here, a compound of general Formula XII, obtained as in section III, reacts with Lawesson's reagent in an aprotic solvent such as methylene chloride to produce the thiocarbamate. Depending on the substrates involved, the reaction is stirred at room temperature or is heated under reflux for a period of from approximately 2 to approximately 48 hours. The resulting compound XIII can be purified by the usual chromatographic techniques, such as flash chromatography or thin layer chromatography.

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

Scheme 5:



VI XIV

The compound of general Formula XIV is obtained under the same conditions described in section IV. The reaction is typically heated under reflux or stirred at room temperature for a period of from approximately 2 to approximately 48 hours. The resulting derivative of general Formula XIV can be purified by the usual chromatographic techniques, such as flash chromatography or thin layer chromatography.

Exemplary Compounds

Starting materials: bromodimethylaniline was obtained from either Alfa Aesar or Sigma Aldrich.

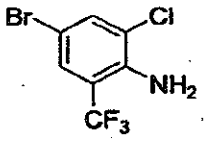
Substituted tetrahydroisoquinolines commercially available; those used in exemplary reactions here were obtained from ASW MedChem Inc., of New Brunswick,

NJ. Other substituted tetrahydroisoquinolines may be synthesized from commercially available starting materials *via* standard synthetic techniques.

Example 1

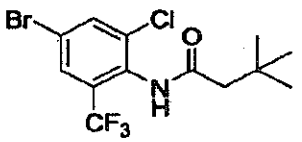
N-(2-chloro-4-(3,4-dihydroisoquinolin-2(*1H*)-yl)-6-(trifluoromethyl)phenyl)-3,3-dimethylbutanamide

Step A: 4-bromo-2-chloro-6-(trifluoromethyl)aniline



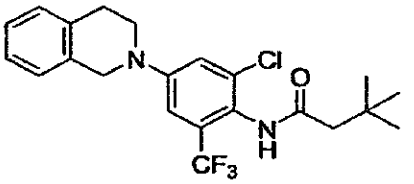
N-bromo succinimide (910 mg, 5.1 mmol) was added to a solution of 2-chloro-6-(trifluoromethyl)aniline (1.0 g, 5.1 mmol) and acetic acid (3 mL) in acetonitrile (10 mL) at room temperature. The mixture was heated at reflux, with stirring, for18h. The reaction mixture was then filtered through Celite and concentrated to give the title compound, which was used in the next step without further purification.

Step B: N-(4-bromo-2-chloro-6-(trifluoromethyl)phenyl)-3,3-dimethylbutanamide:



3,3-Dimethylbutanoyl chloride (1.08 g, 8.0 mmol) was added to a solution of 4-bromo-2-chloro-6-(trifluoromethyl)aniline (2.0 g, 7.3 mmol) in acetonitrile (10 mL). The reaction mixture was stirred at room temperature overnight. Water was added, and the mixture was then extracted with ethyl acetate. The organic layer was dried over sodium sulfate and concentrated. Purification by column chromatography in dichloromethane afforded the title compound as a powder (1.22 g, 65% over the two steps).

Step C: N-(2-chloro-4-(3,4-dihydroisoquinolin-2(*1H*)-yl)-6-(trifluoromethyl)phenyl)-3,3-dimethylbutanamide:

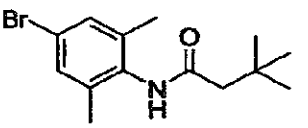


Bis(dibenzylidineacetone)palladium (2 mg, 0.0035mmol) and (2'-dicyclohexyl phosphanyl-biphenyl-2-yl)-dimethylamine (3.3 mg, 0.0084 mmol) were added to dry toluene (10 mL purged with argon), and the solution was stirred for 15 minutes under argon. Potassium *tert*-butoxide (122 mg, 1.08 mmol), 1,2,3,4-tetrahydroisoquinoline (87 mg, 0.65 mmol), and N-(2-chloro-4-(3,4-dihydroisoquinolin-2(*1H*)-yl)-6-(trifluoromethyl)phenyl)-3,3-dimethylbutanamide (200 mg, 0.54 mmol) were then added, and the reaction mixture was stirred at 90 °C overnight. The reaction mixture was then cooled to room temperature, concentrated, and purified by thin layer chromatography (dichloromethane:methanol 5%) to afford the title compound as a solid. (106 mg, 47%). ^{1}H NMR (DMSO-d_6, 300 MHz) δ 1.02 (s, 9H), 2.07 (s, 3H), 2.17 (s, 2H), 2.92 (t, J = 5.4 Hz, 2H), 3.62(t, J = 6 Hz, 2H), 4.48 (s, 2H), 7.33 (m, 6H), 9.30 (s, 1H).

Example 2

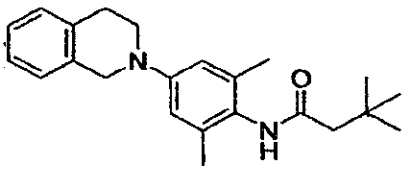
N-(4-(3,4-dihydroisoquinolin-2(*1H*)-yl)-2,6-dimethylphenyl)-3,3-dimethyl butanamide

Step A: N-(4-Bromo-2,6-dimethyl-phenyl)-3,3-dimethyl-butanamide:



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-2,6-dimethyl-phenylamine (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 which formed was collected to give the title compound as a powder (7.46 g, 100% yield).

Step B: N-(4-(3,4-dihydroisoquinolin-2(*1H*)-yl)-2,6-dimethylphenyl)-3,3-dimethylbutanamide:



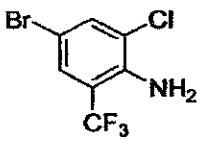
Bis(dibenzylidineacetone)palladium (2 mg, 0.0035mmol) and (2'-dicyclohexyl phosphanyl-biphenyl-2-yl)-dimethylamine (3.3 mg, 0.0084 mmol) were added to dry toluene (10 mL purged with argon) and stirred for 15 minutes under argon. Potassium *tert*-butoxide (150 mg, 1.34 mmol), 1,2,3,4-tetrahydroisoquinoline (107 mg, 0.8 mmol) and N-(4-bromo-2,6-dimethyl-phenyl)-3,3-dimethyl-butanamide (200 mg, 0.67 mmol) were then added, and the reaction mixture was stirred at 90 °C overnight. The reaction mixture was then cooled to room temperature, concentrated, and purified by thin layer chromatography (dichloromethane:methanol 5%) to afford the title compound as a solid. (113.20 mg, 50%).

^{1}H NMR (DMSO-d_6, 300 MHz) δ 1.03 (s, 9H), 2.08 (s, 6H), 2.15 (s, 2H), 2.89 (t, J = 5.7 Hz, 2H), 3.49 (t, J = 5.7 Hz, 2H), 4.31 (s, 2H), 6.68 (s, 2H), 7.2 (m, 4H), 8.86 (s, 1H).

Example 3

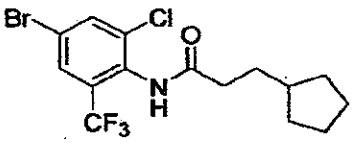
N-(2-chloro-4-(3,4-dihydroisoquinolin-2(*1H*)-yl)-6-(trifluoromethyl)phenyl)-3-cyclopentyl propanamide

Step A: 4-bromo-2-chloro-6-(trifluoromethyl)aniline:



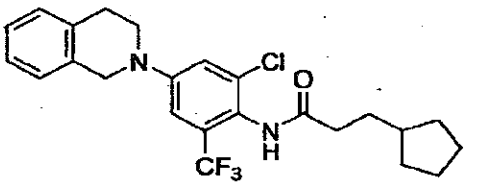
N-bromosuccinimide (910 mg, 5.1 mmol) was added to a solution of 2-chloro-6-(trifluoromethyl)aniline (1.0 g, 5.1 mmol) and acetic acid (3 mL) in acetonitrile (10 mL) at room temperature. The mixture was stirred at reflux for 18h. The reaction mixture was then filtered through Celite and concentrated to give the title compound, which was used in the next step without further purification.

Step B: N-(4-Bromo-2-chloro-6-trifluoromethyl-phenyl)-3-cyclopentyl-propionamide:



3-Cyclopentyl propionyl chloride (1.28 g, 8.0 mmol) was added to a solution of 4-bromo-2-chloro-6-(trifluoromethyl)aniline (2.0 g, 7.3 mmol) in acetonitrile (10 mL). The reaction mixture was stirred at room temperature overnight. Water was added, and the mixture was then extracted with ethyl acetate. The organic layer was dried over sodium sulfate and concentrated. Purification by column chromatography (100% DCM) afforded the title compound as a powder.

Step C: N-(2-chloro-4-(3,4-dihydroisoquinolin-2(*1H*)-yl)-6-(trifluoromethyl)phenyl)-3-cyclopentyl propanamide:



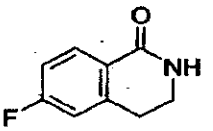
Bis(dibenzylidineacetone)palladium (2 mg, 0.0035mmol) and (2'-dicyclohexyl phosphanyl-biphenyl-2-yl)-dimethylamine (3.3 mg, 0.0084 mmol) were added to dry toluene (10 mL purged with argon) and stirred for 15 minutes under argon. Potassium *tert*-butoxide (150 mg, 1.34 mmol), 1,2,3,4-tetrahydroisoquinoline (107 mg, 0.8 mmol), and N-(4-bromo-2-chloro-6-trifluoromethyl phenyl)-3-cyclopentyl propionamide (200 mg, 0.5 mmol) were then added, and the reaction mixture was stirred at 90 °C overnight. The reaction mixture was then cooled to room temperature, concentrated, and purified by thin layer chromatography (dichloromethane: methanol 5%) to afford the title compound as a solid.

Yield: 28%. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.15 (m, 2H), 1.65 (m, 4H), 1.85 (m, 4H), 2.44 (t, J = 7.5 Hz, 2H), 3.01 (t, J = 5.7. Hz, 2H), 3.6 (t, J = 5.7. Hz, 2H), 4.43 (s, 2H), 6.72 (s, 1H), 7.10 (m, 2H), 7.24 (m, 4H).

Example 4

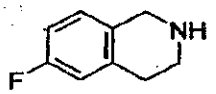
N-(2-chloro-4-(6-fluoro-3,4-dihydroisoquinolin-2(*1H*)-yl)-6-(trifluoromethyl)phenyl)-3,3-dimethylbutanamide:

Step A: 6-fluoro-3,4-dihydroisoquinolin-1(*2H*)-one:



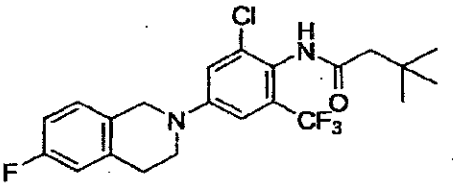
Sodium azide (0.870 g, 13.33 mmol) was added in portions to a stirred solution of 5-fluoro-1-indanone (1.0 g, 6.67 mmol) and methanesulfonic acid (4 mL) in dichloromethane (4 mL) at 0 °C. The reaction mixture was stirred at room temperature for 18 h. The mixture was then cooled to 0 °C and neutralized with 2N NaOH. The layers were separated, the aqueous layer extracted with dichloromethane, and the combined organic layers were dried over Na_2SO_4 and concentrated to give the title compound as a white powder. The crude product was used in the next step.

Step B: 6-fluoro-1,2,3,4-tetrahydroisoquinoline:



Diborane (1M, THF, 24 mL) was added at 0 °C to a solution of 6-fluoro-3,4-dihydro isoquinolin-1(*2H*)-one (1.14g, 6.9 mmol) in THF (8 mL). The mixture was stirred at reflux for 18 h. It was cooled to room temperature and water was added. The mixture was extracted with dichloromethane, and the organic layer was dried over sodium sulfate and concentrated. Purification by column chromatography (hexanes: ethyl acetate 1:1) afforded the title compound.

Step C: N-(2-chloro-4-(6-fluoro-3,4-dihydroisoquinolin-2(*1H*)-yl)-6-(trifluoromethyl)phenyl)-3,3-dimethylbutanamide:

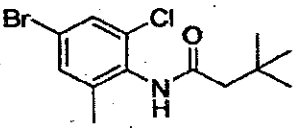


Bis(dibenzylidineacetone)palladium (2 mg, 0.0035mmol) and (2'-dicyclohexyl phosphanyl biphenyl-2-yl) dimethylamine (3.3 mg, 0.0084 mmol) were added to dry toluene (10 mL purged with argon) and stirred for 15 minutes under argon. Potassium *tert*-butoxide (122 mg, 1.08 mmol), 6-fluoro-1,2,3,4-tetrahydroisoquinoline (96 mg, 0.65 mmol), and N-(4-bromo-2-chloro-6-(trifluoromethyl)phenyl)-3,3-dimethylbutanamide (200 mg, 0.54 mmol) were then added, and the reaction mixture was stirred at 90 °C overnight. The reaction mixture was then cooled to room temperature, concentrated, and purified by thin layer chromatography (dichloromethane:methanol 5%) to afford the title compound as a solid. m/z = 441 [M-1]$^-$.

Example 5

N-[2-Chloro-4-(3,4-dihydro-*1H*-isoquinolin-2-yl)-6-methyl-phenyl]-3,3-dimethyl-butanamide

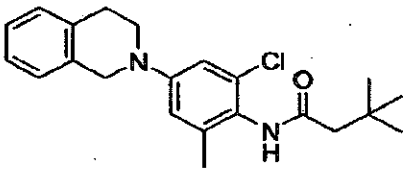
Step A: N-(4-Bromo-2-chloro-6-methylphenyl)-3,3-dimethyl butanamide:



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-methyl-phenylamine (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 that formed was collected to give the title compound as a powder (7.46 g, 100% yield).

Step B: N-[2-Chloro-4-(3,4-dihydro-*1H*-isoquinolin-2-yl)-6-methyl-phenyl]-3,3-dimethyl-butanamide:

The synthesis of this compound was performed as described in example 4, step C.

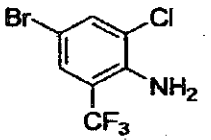


^{1}H NMR (DMSO-d_6, 300 MHz) δ 1.03 (s, 9H), 2.12 (s, 3H), 2.15 (s, 2H), 2.89 (t, J = 5.7 Hz, 2H), 3.53 (t, J = 5.7 Hz, 2H), 4.36 (s, 2H), 6.87 (d, J = 9.6, 2H), 7.2 (m, 4H), 9.08 (s, 1H).

Example 6

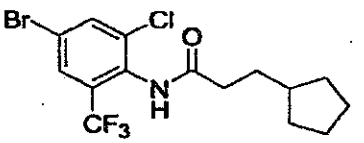
N-[2-Chloro-4-(6-fluoro-3,4-dihydro-*1H*-isoquinolin-2-yl)-6-trifluoromethyl-phenyl]-3-cyclopentyl-propionamide

Step A: 4-bromo-2-chloro-6-(trifluoromethyl)aniline:



N-bromosuccinimide (910 mg, 5.1 mmol) was added at room temperature to a solution of 2-chloro-6-(trifluoromethyl)aniline (1.0 g, 5.1 mmol) and acetic acid (3 mL) in acetonitrile (10 mL). The mixture was stirred at reflux to 18h. The reaction mixture was then filtered through celite and concentrated to give the title compound, which was used in the next step without further purification.

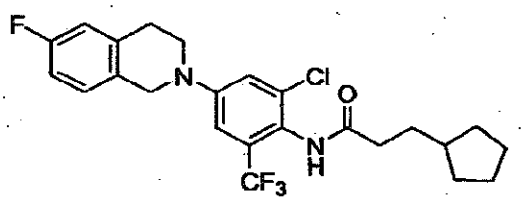
Step B: N-(4-Bromo-2-chloro-6-trifluoromethyl-phenyl)-3-cyclopentyl propionamide:



3-Cyclopentyl propionyl chloride (1.28 g, 8.0 mmol) was added to a solution of 4-bromo-2-chloro-6-(trifluoromethyl)aniline (2.0 g, 7.3 mmol) in acetonitrile (10 mL). The reaction mixture was stirred at room temperature overnight. Water was added to the

mixture, which was then extracted with ethyl acetate. The organic layer was dried over sodium sulfate and concentrated. Purification by column chromatography (100% DCM) afforded the title compound as a powder.

Step C: N-[2-Chloro-4-(6-fluoro-3,4-dihydro-*1H*-isoquinolin-2-yl)-6-trifluoromethyl-phenyl]-3-cyclopentyl propionamide:

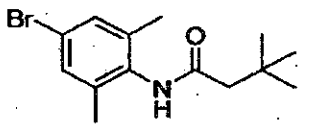


Bis(dibenzylidineacetone)palladium (2 mg, 0.0035mmol) and (2'-dicyclohexyl phosphanyl-biphenyl-2-yl)-dimethylamine (3.3 mg, 0.0084 mmol) were added to dry toluene (10 mL purged with argon) and stirred for 15 minutes under argon. Potassium *tert*-butoxide (140 mg, 1.25 mmol), 6-fluoro-1,2,3,4-tetrahydroisoquinoline hydrochloride salt (150 mg, 0.8 mmol) and N-(4-Bromo-2-chloro-6-trifluoromethyl-phenyl)-3-cyclopentyl-propionamide (200 mg, 0.5 mmol) were then added and the reaction mixture was stirred at 90 °C overnight. The reaction mixture was then cooled to room temperature, concentrated, and purified by thin layer chromatography (dichloromethane:methanol 5%) to afford the title compound as a solid.
^{1}H NMR (DMSO-d_6, 300 MHz) δ 1.07 (m, 2H), 1.57 (m, 6H), 1.75 (m, 3H), 2.31 (m, 2H), 2.93 (t, J = 5.1 Hz, 2H), 3.60 (t, J = 5.4 Hz, 2H), 4.45 (s, 2H), 7.06 (m, 2H), 7.15 (s, 1H), 7.32 (m, 2H), 9.39 (s, 1H).

Example 7

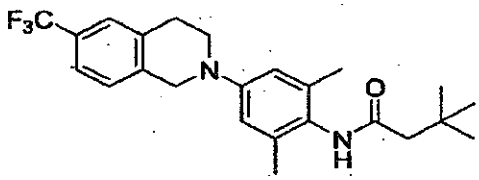
N-[2,6-Dimethyl-4-(6-trifluoromethyl-3,4-dihydro-*1H*-isoquinolin-2-yl)-phenyl]-3,3-dimethyl butanamide

Step A: N-(4-Bromo-2,6-dimethyl-phenyl)-3,3-dimethyl-butanamide:



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-2,6-dimethyl-phenylamine (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 which formed was collected to give the title compound as a powder (7.46 g, 100% yield).

Step B: N-[2,6-Dimethyl-4-(6-trifluoromethyl-3,4-dihydro-*1H*-isoquinolin-2-yl)-phenyl]-3,3-dimethyl butanamide:



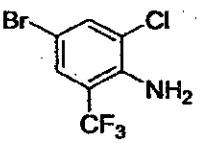
Bis(dibenzylidineacetone)palladium (390 mg, 0.68 mmol) and (2'-dicyclohexyl phosphanyl-biphenyl-2-yl)-dimethylamine (800 mg, 2.0 mmol) were added to dry toluene (150 mL purged with argon) and stirred for 30 minutes under argon. Potassium *tert*-butoxide (4.75 mg, 42.3 mmol), 6-Trifluoromethyl-1,2,3,4-tetrahydro-isoquinoline hydrochloride salt (4.82 g, 20.3 mmol) and N-(4-bromo-2,6-dimethyl-phenyl)-3,3-dimethyl-butanamide (5 g, 16.8 mmol) were then added, and the reaction mixture was stirred at 80 °C overnight. The reaction mixture was then cooled to room temperature and recrystallized from toluene to afford the title compound as a solid. (5.55 g, 79%).

^{1}H NMR (DMSO-d_6, 500 MHz) δ 1.03 (s, 9H), 2.09 (s, 6H), 2.15 (s, 2H), 2.98 (t, J = 5.0 Hz, 2H), 3.52 (t, J = 6.0 Hz, 2H), 4.40 (s, 2H), 6.71 (s, 2H), 7.45 (d, J = 8.0, 1H), 7.52 (m, 2H), 8.87 (s, 1H).

Example 8

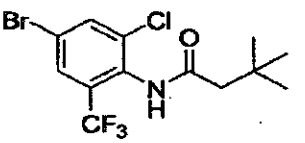
N-[2-Chloro-6-trifluoromethyl-4-(6-trifluoromethyl-3,4-dihydro-*1H*-isoquinolin-2-yl)-phenyl]-3,3-dimethyl butanamide

Step A: 4-bromo-2-chloro-6-(trifluoromethyl)aniline:



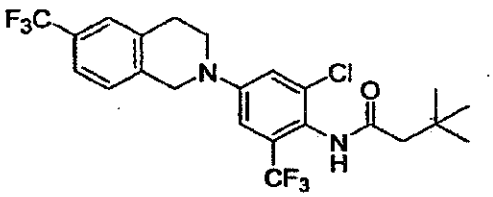
N-bromosuccinimide (910 mg, 5.1 mmol) was added to a solution of 2-chloro-6-(trifluoromethyl)aniline (1.0 g, 5.1 mmol) in acetonitrile (10 mL) and acetic acid (3 mL) at room temperature. The mixture was stirred at reflux to 18h. The reaction mixture was then filtered through celite and concentrated to give the title compound which was used in the next step without further purification.

Step B: N-(4-bromo-2-chloro-6-(trifluoromethyl)phenyl)-3,3-dimethylbutanamide:



3,3-dimethylbutanoyl chloride (1.08 g, 8.0 mmol) was added to a solution of 4-bromo-2-chloro-6-(trifluoromethyl)aniline (2.0 g, 7.3 mmol) in acetonitrile (10 mL). The reaction mixture was stirred at room temperature overnight. Water was added to the mixture and then extracted with ethyl acetate. The organic layer was dried over sodium sulfate and concentrated. Purification by column chromatography (100% DCM) afforded the title compound as a powder (1.22 g, 65%) over the two steps.

Step C: N-[2-Chloro-6-trifluoromethyl-4-(6-trifluoromethyl-3,4-dihydro-*1H*-isoquinolin-2-yl)-phenyl]-3,3-dimethyl butanamide:



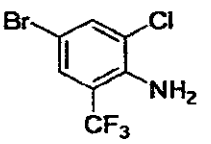
Bis(dibenzylidineacetone)palladium (2 mg, 0.0035mmol) and (2'-dicyclohexyl phosphanyl-biphenyl-2-yl)-dimethylamine (3.3 mg, 0.0084 mmol) were added to dry toluene (10 mL purged with argon) and stirred for 15 minutes under argon. Potassium *tert*-butoxide (197 mg, 1.75 mmol), 6-trifluoro-1,2,3,4-tetrahydroisoquinoline (154 mg, 0.65 mmol) and N-(4-bromo-2-chloro-6-(trifluoromethyl)phenyl)-3,3-dimethylbutanamide (200 mg, 0.54 mmol) were then added, and the reaction mixture was stirred at 90 °C overnight. The reaction mixture was then cooled to room temperature, concentrated, and purified by thin layer chromatography (dichloromethane:methanol 5%) to afford the title compound as a solid

^{1}H NMR (DMSO-d_6, 500 MHz) δ 1.03 (s, 9H), 2.17 (s, 2H), 3.02 (t, J = 5.35 Hz, 2H), 3.65 (t, J = 5.0 Hz, 2H), 4.61 (s, 2H), 7.19 (d, J = 2.0 Hz, 1H), 7.38 (d, J = 1.9 Hz, 1H), 7.49 (d, J = 8.0 Hz, 1H), 7.56 (d, J = 8.1 Hz, 1H), 7.59 (s, 1H), 9.32 (s, 1H).

Example 9

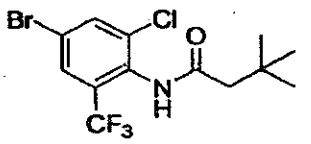
N-[2-Chloro-4-(6-chloro-3,4-dihydro-*1H*-isoquinolin-2-yl)-6-trifluoromethyl-phenyl]-3,3-dimethyl butanamide

Step A: 4-bromo-2-chloro-6-(trifluoromethyl)aniline:



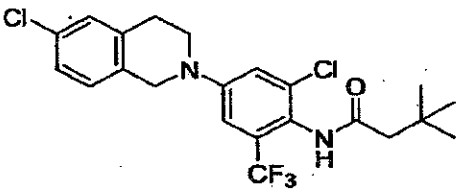
N-bromosuccinimide (910 mg, 5.1 mmol) was added to a solution of 2-chloro-6-(trifluoromethyl)aniline (1.0 g, 5.1 mmol) in acetonitrile (10 mL) and acetic acid (3 mL) at room temperature. The mixture was stirred at reflux to 18h. The reaction mixture was then filtered through Celite and concentrated to give the title compound which was used in the next step without further purification.

Step B: N-(4-bromo-2-chloro-6-(trifluoromethyl)phenyl)-3,3-dimethylbutanamide:



3,3-Dimethylbutanoyl chloride (1.08 g, 8.0 mmol) was added to a solution of 4-bromo-2-chloro-6-(trifluoromethyl)aniline (2.0 g, 7.3 mmol) in acetonitrile (10 mL). The reaction mixture was stirred at room temperature overnight. Water was added to the mixture and then extracted with ethyl acetate. The organic layer was dried over sodium sulfate and concentrated. Purification by column chromatography (100% DCM) afforded the title compound as a powder (1.22 g, 65%) over the two steps.

Step C: N-[2-Chloro-4-(6-chloro-3,4-dihydro-*1H*-isoquinolin-2-yl)-6-trifluoromethyl-phenyl]-3,3-dimethyl-butanamide:



Bis(dibenzylidineacetone)palladium (2 mg, 0.0035mmol) and (2'-dicyclohexyl phosphanyl-biphenyl-2-yl)-dimethylamine (3.3 mg, 0.0084 mmol) were added to dry toluene (10 mL purged with argon) and stirred for 15 minutes under argon. Potassium *tert*-butoxide (151 mg, 1.35 mmol), 6-chloro-1,2,3,4-tetrahydroisoquinoline

hydrochloride (133 mg, 0.65 mmol) and N-(4-bromo-2-chloro-6-(trifluoromethyl)phenyl)-3,3-dimethylbutanamide (200 mg, 0.54 mmol) were then added and the reaction mixture was stirred at 90 °C overnight. The reaction mixture was then cooled to room temperature, concentrated and purified by thin layer chromatography (dichloromethane:methanol 5%) to afford the title compound as a solid

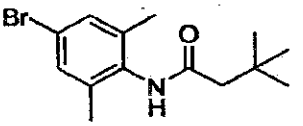
^{1}H NMR (DMSO-d_6, 500 MHz) δ 1.02 (s, 9H), 2.17 (s, 2H), 2.92 (t, J = 5.35 Hz, 2H), 3.61

(t, J = 5.6 Hz, 2H), 4.47 (s, 2H), 7.16 (s, 1H), 7.29 (m, 3H), 7.34 (s, 1H), 9.31(s, 1H).

Example 10

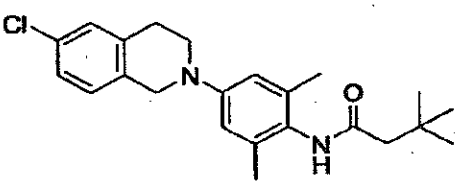
N-[4-(6-Chloro-3,4-dihydro-*1H*-isoquinolin-2-yl)-2,6-dimethyl-phenyl]-3,3-dimethyl-butanamide

Step A: N-(4-Bromo-2,6-dimethyl-phenyl)-3,3-dimethyl-butanamide:



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-2,6-dimethyl phenylamine (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).

Step B: N-[4-(6-Chloro-3,4-dihydro-*1H*-isoquinolin-2-yl)-2,6-dimethyl-phenyl]-3,3-dimethyl butanamide:



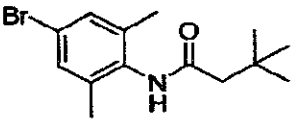
Bis(dibenzylidineacetone)palladium (2 mg, 0.0035mmol) and (2'-dicyclohexyl phosphanyl-biphenyl-2-yl)-dimethylamine (3.3 mg, 0.0084 mmol) were added to dry toluene (5 mL purged with argon) and stirred for 15 minutes under argon. Potassium *tert*-butoxide (188 mg, 1.7 mmol), 6-chloro-1,2,3,4-tetrahydro isoquinoline hydrochloride salt (165 mg, 0.8 mmol), and N-(4-bromo-2,6-dimethylphenyl)-3,3-dimethylbutanamide (200 mg, 0.67 mmol) were then added, and the reaction mixture was stirred at 80 °C overnight. The reaction mixture was then cooled to room temperature and filtered through silica gel. Purification by preparative thin layer chromatography afforded the title compound as a solid.

^{1}H NMR (DMSO-d_6, 500 MHz) δ 1.03 (s, 9H), 2.08 (s, 6H), 2.15 (s, 2H), 2.89 (t, J = 5.25 Hz, 2H), 3.47 (t, J = 5.6 Hz, 2H), 4.30 (s, 2H), 6.68 (s, 2H), 7.25 (m, 3H), 8.85 (s, 1H).

Example 11

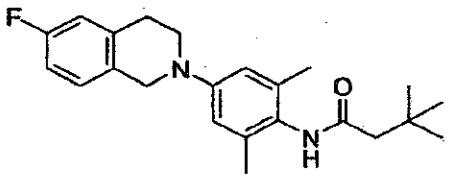
N-[4-(6-fluoro-3,4-dihydro-*1H*-isoquinolin-2-yl)-2,6-dimethyl phenyl]-3,3-dimethyl butanamide

Step A: N-(4-Bromo-2,6-dimethyl-phenyl)-3,3-dimethyl-butanamide:



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-2,6-dimethyl-phenylamine (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 which formed was collected to give the title compound as a powder (7.46 g, 100% yield).

Step B: N-[4-(6-Fluoro-3,4-dihydro-*1H*-isoquinolin-2-yl)-2,6-dimethylphenyl]-3,3-dimethyl butanamide:

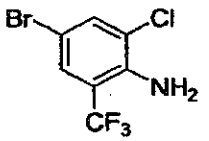


Bis(dibenzylidineacetone)palladium (390 mg, 0.68 mmol) and (2'-dicyclohexyl phosphanyl-biphenyl-2-yl)-dimethylamine (800 mg, 2.0 mmol) were added to dry toluene (150 mL purged with argon for 30 minutes) and stirred for 30 minutes under argon. Potassium *tert*-butoxide (4.75 mg, 42.3 mmol), 6-fluoro-1,2,3,4-tetrahydro-isoquinoline hydrochloride salt (3.2 g, 17.0 mmol), and N-(4-bromo-2,6-dimethyl-phenyl)-3,3-dimethyl-butanamide (5 g, 16.8 mmol) were then added, and the reaction mixture was stirred at 80 °C overnight. The reaction mixture was then cooled to room temperature and recrystallized from toluene to afford the title compound as a solid. (5.11 g, 83%). ^{1}H NMR (DMSO-d_6, 500 MHz) δ 1.03 (s, 9H), 2.08 (s, 6H), 2.15 (s, 2H), 2.89 (t, J = 5.25 Hz, 2H), 3.47 (t, J = 5.6 Hz, 2H), 4.30 (s, 2H), 6.68 (s, 2H), 6.99 (m, 2H), 7.25 (m, 1H), 8.84 (s, 1H).

Example 12

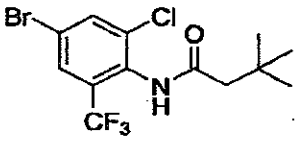
N-[2-Chloro-4-(7-fluoro-3,4-dihydro-*1H*-isoquinolin-2-yl)-6-trifluoromethyl-phenyl]-3,3-dimethylbutanamide

Step A: 4-bromo-2-chloro-6-(trifluoromethyl)aniline:



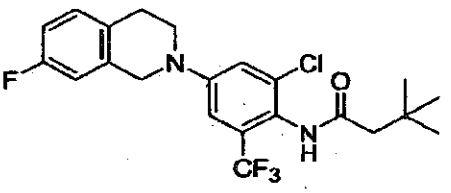
N-bromosuccinimide (910 mg, 5.1 mmol) was added to a solution of 2-chloro-6-(trifluoromethyl)aniline (1.0 g, 5.1 mmol) in acetonitrile (10 mL) and acetic acid (3 mL) at room temperature. The mixture was stirred at reflux for 18h. The reaction mixture was then filtered through Celite and concentrated to give the title compound, which was used in the next step without further purification.

Step B: N-(4-bromo-2-chloro-6-(trifluoromethyl)phenyl)-3,3-dimethylbutanamide:



3,3-Dimethylbutanoyl chloride (1.08 g, 8.0 mmol) was added to a solution of 4-bromo-2-chloro-6-(trifluoromethyl)aniline (2.0 g, 7.3 mmol) in acetonitrile (10 mL). The reaction mixture was stirred at room temperature overnight. Water was added to the mixture and then extracted with ethyl acetate. The organic layer was dried over sodium sulfate and concentrated. Purification by column chromatography (100% DCM) afforded the title compound as a powder (1.22 g, 65%) over the two steps.

Step C: N-[2-Chloro-4-(7-fluoro-3,4-dihydro-*1H*-isoquinolin-2-yl)-6-trifluoromethyl-phenyl]-3,3-dimethylbutanamide:



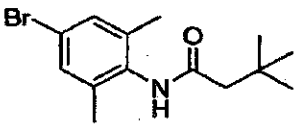
Bis(dibenzylidineacetone)palladium (2 mg, 0.0035mmol) and (2'-dicyclohexyl phosphanyl-biphenyl-2-yl)-dimethylamine (3.3 mg, 0.0084 mmol) were added to dry toluene (10 mL purged with argon) and stirred for 15 minutes under argon. Potassium *tert*-butoxide (151 mg, 1.35 mmol), 7-fluoro-1,2,3,4-tetrahydroisoquinoline hydrochloride (122 mg, 0.65 mmol) and N-(4-bromo-2-chloro-6-(trifluoromethyl)phenyl)-3,3-dimethylbutanamide (200 mg, 0.54 mmol) were then added, and the reaction mixture was stirred at 90 °C overnight. The reaction mixture was then cooled to room temperature, concentrated, and purified by thin layer chromatography (dichloromethane:methanol 5%) to afford the title compound as a solid.

^{1}H NMR (DMSO-d_6, 500 MHz) δ 1.02 (s, 9H), 2.17 (s, 2H), 2.89 (t, J = 5.1 Hz, 2H), 3.61 (t, J = 5.7 Hz, 2H), 4.49 (s, 2H), 7.03 (dd, J = 8.6, 2,3 Hz, 1H), 7.12 (m, 2H), 7.16 (d, J = 2.2 Hz, 1H), 7.23 (m, 1H), 7.33 (d, J = 2.6, 1H), 9.30 (s, 1H).

Example 13

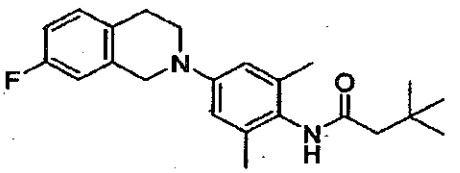
N-[4-(7-Fluoro-3,4-dihydro-*1H*-isoquinolin-2-yl)-2,6-dimethyl-phenyl]-3,3-dimethyl-butanamide

Step A: N-(4-Bromo-2,6-dimethyl-phenyl)-3,3-dimethyl-butanamide:



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-2,6-dimethyl-phenylamine (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).

Step B: N-[4-(7-Fluoro-3,4-dihydro-*1H*-isoquinolin-2-yl)-2,6-dimethyl-phenyl]-3,3-dimethyl-butanamide:



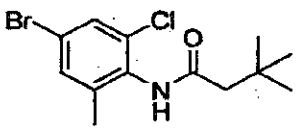
Bis(dibenzylidineacetone)palladium (156 mg, 0.28 mmol) and (2'-dicyclohexyl phosphanyl-biphenyl-2-yl)-dimethylamine (320 mg, 0.8 mmol) were added to dry toluene (60 mL purged with argon) and stirred for 15 minutes under argon. Potassium *tert*-butoxide (1.9 g, 16.25 mmol), 7-fluoro-1,2,3,4-tetrahydro-isoquinoline hydrochloride salt (1.28 g, 6.8 mmol), and N-(4-bromo-2,6-dimethyl-phenyl)-3,3-dimethyl-butanamide (5 g, 6.8 mmol) were then added, and the reaction mixture was stirred at 80 °C overnight. The reaction mixture was then cooled to room temperature and recrystallized from toluene to afford the title compound as a solid. (1.9 g, 76%).

^{1}H NMR (DMSO-d_6, 400 MHz) δ 1.05 (s, 9H), 2.10 (s, 6H), 2.17 (s, 2H), 2.89 (t, J = 5.1 Hz, 2H), 3.49 (t, J = 5.7 Hz, 2H), 4.34 (s, 2H), 6.70 (s, 2H), 7.0 (m, 1H), 7.1 (m, 1H), 7.2 (m, 1H), 8.9 (s, 1H).

Example 14

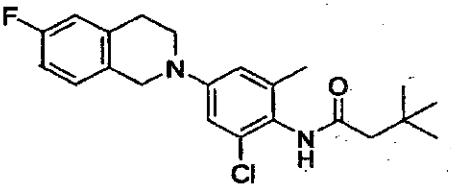
N-[2-Chloro-4-(6-fluoro-3,4-dihydro-*1H*-isoquinolin-2-yl)-6-methylphenyl]-3,3-dimethylbutanamide

Step A: N-(4-Bromo-2-chloro-6-methyl-phenyl)-3,3-dimethyl-butanamide:



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-methyl-phenylamine (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).

Step B: N-[2-Chloro-4-(6-fluoro-3,4-dihydro-*1H*-isoquinolin-2-yl)-6-methylphenyl]-3,3-dimethylbutanamide:



Bis(dibenzylidineacetone)palladium (2 mg, 0.0035mmol) and (2'-dicyclohexyl phosphanyl-biphenyl-2-yl)-dimethylamine (3.3 mg, 0.0084 mmol) were added to dry toluene (10 mL purged with argon) and stirred for 15 minutes under argon. Potassium *tert*-butoxide (197 mg, 1.75 mmol), 6-fluoro-1,2,3,4-tetrahydroisoquinoline hydrochloride salt (121 mg, 0.65 mmol) and N-(4-bromo-2-chloro-6-methyphenyl)-3,3-dimethylbutanamide (200 mg, 0.63 mmol) were then added and the reaction mixture was stirred at 90 °C overnight. The reaction mixture was then cooled to room temperature,

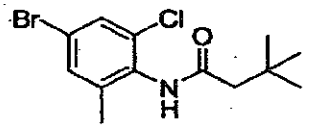
concentrated and purified by thin layer chromatography (dichloromethane:methanol 5%) to afford the title compound as a solid.

^{1}H NMR (DMSO-d_6, 400 MHz) δ 1.05 (s, 9H), 2.14 (s, 3H), 2.17 (s, 2H), 2.91 (t, J = 5.25 Hz, 2H), 3.52 (t, J = 5.6 Hz, 2H), 4.37 (s, 2H), 6.85 (s, 1H), 6.9 (s, 1H), 7.0 (m, 2H), 7.3 (m, 1H), 9.10 (s, 1H).

Example 15

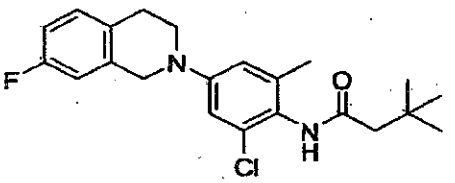
N-[2-Chloro-4-(7-fluoro-3,4-dihydro-*1H*-isoquinolin-2-yl)-6-methylphenyl]-3,3-dimethylbutanamide

Step A: N-(4-Bromo-2-chloro-6-methyl-phenyl)-3,3-dimethyl-butanamide:



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-methyl-phenylamine (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).

Step B: N-[2-Chloro-4-(7-fluoro-3,4-dihydro-*1H*-isoquinolin-2-yl)-6-methylphenyl]-3,3-dimethylbutanamide:



Bis(dibenzylidineacetone)palladium (2 mg, 0.0035mmol) and (2'-dicyclohexyl phosphanyl-biphenyl-2-yl)-dimethylamine (3.3 mg, 0.0084 mmol) were added to dry toluene (10 mL purged with argon) and stirred for 15 minutes under argon. Potassium *tert*-butoxide (197 mg, 1.75 mmol), 7-fluoro-1,2,3,4-tetrahydroisoquinoline hydrochloride salt (121 mg, 0.65 mmol) and N-(4-bromo-2-chloro-6-methyphenyl)-3,3-

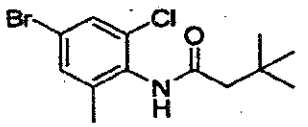
dimethylbutanamide (200 mg, 0.63 mmol) were then added and the reaction mixture was stirred at 90 °C overnight. The reaction mixture was then cooled to room temperature, concentrated, and purified by thin layer chromatography (dichloromethane:methanol 5%) to afford the title compound as a solid.

^{1}H NMR (DMSO-d_6, 400 MHz) δ 1.04 (s, 9H), 2.14 (s, 3H), 2.18 (s, 2H), 2.88 (t, J = 5.25 Hz, 2H), 3.55 (t, J = 5.6 Hz, 2H), 4.4 (s, 2H), 6.88 (s, 1H), 6.9 (s, 1H), 7.0 (m, 1H), 7.1 (m, 1H), 7.2 (m, 1H), 9.10 (s, 1H).

Example 16

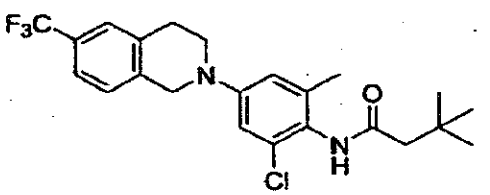
N-[2-Chloro-6-methyl-4-(6-trifluoromethyl-3,4-dihydro-*1H*-isoquinolin-2-yl)-phenyl]-3,3-dimethylbutanamide

Step A: N-(4-Bromo-2-chloro-6-methyl-phenyl)-3,3-dimethyl-butanamide:



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-methyl-phenylamine (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).

Step B: N-[2-Chloro-6-methyl-4-(6-trifluoromethyl-3,4-dihydro-*1H*-isoquinolin-2-yl)-phenyl]-3,3-dimethylbutanamide:



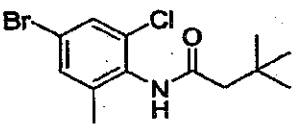
Bis(dibenzylidineacetone)palladium (2 mg, 0.0035mmol) and (2'-dicyclohexyl phosphanyl-biphenyl-2-yl)-dimethylamine (3.3 mg, 0.0084 mmol) were added to dry toluene (10 mL purged with argon) and stirred for 15 minutes under argon. Potassium *tert*-butoxide (197 mg, 1.75 mmol), 6-trifluoromethyl-1,2,3,4-tetrahydroisoquinoline hydrochloride salt (154 mg, 0.65 mmol) and N-(4-bromo-2-chloro-6-methyphenyl)-3,3-dimethylbutanamide (200 mg, 0.63 mmol) were then added and the reaction mixture was stirred at 90 °C overnight. The reaction mixture was then cooled to room temperature, concentrated and purified by thin layer chromatography (dichloromethane:methanol 5%) to afford the title compound as a solid.

^{1}H NMR (DMSO-d_6, 400 MHz) δ 1.08 (s, 9H), 2.17(s, 3H), 2.21 (s, 2H), 3.0 (t, J = 5.25 Hz, 2H), 3.6 (t, J = 5.6 Hz, 2H), 4.5 (s, 2H), 6.9 (s, 1H), 6.95 (s, 1H), 7.3 (m, 1H), 7.5 (m, 2H), 9.13 (s, 1H).

Example 17

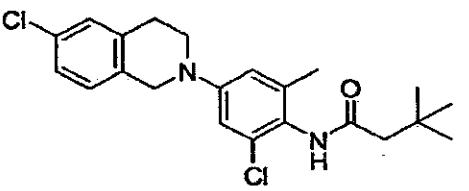
N-[2-Chloro-4-(6-chloro-3,4-dihydro-*1H*-isoquinolin-2-yl)-6-methyl-phenyl]-3,3-dimethylbutanamide

Step A: N-(4-Bromo-2-chloro-6-methyl-phenyl)-3,3-dimethylbutanamide:



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-methyl-phenylamine (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).

Step: N-[2-Chloro-4-(6-chloro-3,4-dihydro-*1H*-isoquinolin-2-yl)-6-methyl-phenyl]-3,3-dimethylbutanamide:



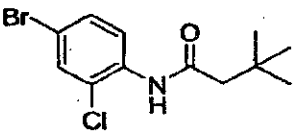
Bis(dibenzylidineacetone)palladium (2 mg, 0.0035mmol) and (2'-dicyclohexyl phosphanyl-biphenyl-2-yl)-dimethylamine (3.3 mg, 0.0084 mmol) were added to dry toluene (10 mL purged with argon) and stirred for 15 minutes under argon. Potassium *tert*-butoxide (197 mg, 1.75 mmol), 6-chloro-1,2,3,4-tetrahydroisoquinoline hydrochloride salt (133 mg, 0.65 mmol), and N-(4-bromo-2-chloro-6-methyphenyl)-3,3-dimethylbutanamide (200 mg, 0.63 mmol) were then added, and the reaction mixture was stirred at 90 °C overnight. The reaction mixture was then cooled to room temperature, concentrated, and purified by thin layer chromatography (dichloromethane:methanol 5%) to afford the title compound as a solid.

^{1}H NMR (DMSO-d_6, 400 MHz) δ 1.06 (s, 9H), 2.14 (s, 3H), 2.18 (s, 2H), 2.9 (t, J = 5.25 Hz, 2H), 3.5 (t, J = 5.6 Hz, 2H), 4.4 (s, 2H), 6.85 (s, 1H), 6.9 (s, 1H), 7.25 (m, 3H), 9.1 (s, 1H).

Example 18

N-[2-Chloro-4-(6-fluoro-3,4-dihydro-*1H*-isoquinolin-2-yl)-phenyl]-3,3-dimethylbutanamide

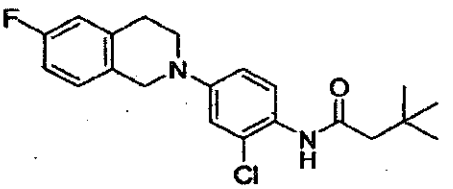
Step A: N-(4-Bromo-2-chloro-phenyl)-3,3-dimethyl-butanamide:



3,3-Dimethylbutanoyl chloride (717 mg, 0.74 mL, 5.32 mmol) was added to a solution of 4-Bromo-2-chloro-phenylamine (1.0 g, 4.84 mmol) in acetonitrile (10 mL). The reaction mixture was stirred at room temperature overnight. Water was added to the mixture and the precipitate formed collected to give the title compound as a powder (1.04 g, 72% yield).

Step B: N-[2-Chloro-4-(6-fluoro-3,4-dihydro-*1H*-isoquinolin-2-yl)-phenyl]-3,3-dimethylbutanamide:

The synthesis of this compound was performed as described in example 4, step C.

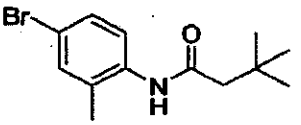


^{1}H NMR (DMSO-d_6, 400 MHz) δ 1.04 (s, 9H), 2.19 (s, 2H), 2.93 (t, J = 8 Hz, 2H), 3.54 (t, J = 8 Hz, 2H), 4.37 (s, 2H), 6.96 (dd, J = 4, 12 Hz, 1H), 7.04 (m, 3H), 7.27 (m, 1H), 7.34 (d, J = 8 Hz, 1H), 9.17 (s, 1H).

Example 19

N-[4-(6-Fluoro-3,4-dihydro-*1H*-isoquinolin-2-yl)-2-methyl-phenyl]-3,3-dimethylbutanamide

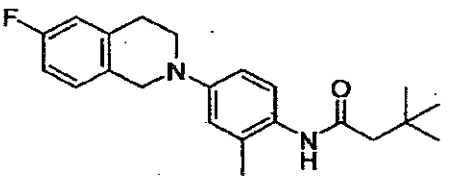
Step A: N-(4-Bromo-2-methyl-phenyl)-3,3-dimethylbutanamide:



3,3-Dimethylbutanoyl chloride (724 mg, 0.75 mL, 5.4 mmol) was added to a solution of 4-Bromo-2-methyl-phenylamine (1.0 g, 5.4 mmol) in acetonitrile (10 mL). The reaction mixture was stirred at room temperature overnight. Water was added to the mixture and the precipitate formed collected to give the title compound as a powder (830 mg, 56% yield).

Step B: N-[4-(6-Fluoro-3,4-dihydro-*1H*-isoquinolin-2-yl)-2-methyl-phenyl]-3,3-dimethylbutanamide:

The synthesis of this compound was performed as described in example 4, step C.

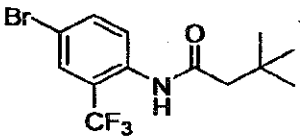


^{1}H NMR (DMSO-d_6, 400 MHz) δ 1.04 (s, 9H), 2.14 (s, 3H), 2.16 (s, 2H), 2.91 (t, J = 8 Hz, 2H), 3.48 (t, J = 8 Hz, 2H), 4.31 (s, 2H), 6.8 (dd, J = 4, 12 Hz, 1H), 6.85 (s, 1H), 7.0 (m, 2H), 7.09 (d, J = 8 Hz, 1H), 7.3 (m, 1H), 8.98 (s, 1H).

Example 20

N-[4-(6-Fluoro-3,4-dihydro-*1H*-isoquinolin-2-yl)-2-trifluoromethylphenyl]-3,3-dimethylbutanamide

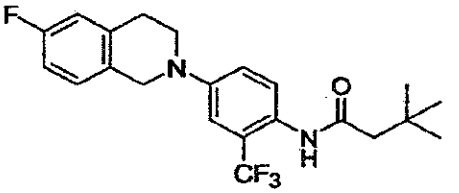
Step A: N-(4-Bromo-2-trifluoromethyl-phenyl)-3,3-dimethylbutanamide:



3,3-Dimethylbutanoyl chloride (617 mg, 0.64 mL, 4.6 mmol) was added to a solution of 4-Bromo-2-trifluoromethyl-phenylamine (1.0 g, 4.16 mmol) in acetonitrile (10 mL). The reaction mixture was stirred at room temperature overnight. Water was added to the mixture and the precipitate formed collected to give the title compound as a powder (1.1 g, 79% yield).

Step B: N-[4-(6-Fluoro-3,4-dihydro-*1H*-isoquinolin-2-yl)-2-trifluoromethyl-phenyl]-3,3-dimethylbutanamide:

The synthesis of this compound was performed as described in example 4, step C.

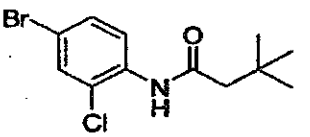


^{1}H NMR (DMSO-d_6, 400 MHz) δ 1.02 (s, 9H), 2.18 (s, 2H), 2.94 (t, J = 8 Hz, 2H), 3.59 (t, J = 8 Hz, 2H), 4.43 (s, 2H), 7.0 (m, 2H), 7.17 (m, 3H), 7.3 (m, 1H), 9.18 (s, 1H).

Example 21

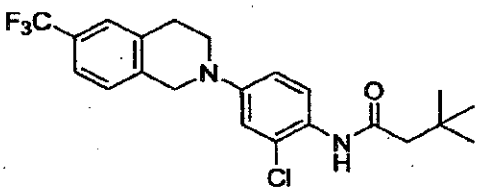
N-[2-Chloro-4-(6-trifluoromethyl-3,4-dihydro-*1H*-isoquinolin-2-yl)-phenyl]-3,3-dimethylbutanamide

Step A: N-(4-Bromo-2-chloro-phenyl)-3,3-dimethylbutanamide:



3,3-Dimethylbutanoyl chloride (717 mg, 0.74 mL, 5.32 mmol) was added to a solution of 4-Bromo-2-chloro-phenylamine (1.0 g, 4.84 mmol) in acetonitrile (10 mL). The reaction mixture was stirred at room temperature overnight. Water was added to the mixture and the precipitate formed collected to give the title compound as a powder (1.04 g, 72% yield).

Step B: N-[2-Chloro-4-(6-trifluoromethyl-3,4-dihydro-*1H*-isoquinolin-2-yl)-phenyl]-3,3-dimethylbutanamide:



Bis(dibenzylidineacetone)palladium (2 mg, 0.0035mmol) and (2'-dicyclohexyl phosphanyl-biphenyl-2-yl)-dimethylamine (3.3 mg, 0.0084 mmol) were added to dry toluene (10 mL purged with argon) and stirred for 15 minutes under argon. Potassium

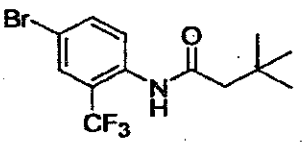
tert-butoxide (197 mg, 1.75 mmol), 6-trifluoromethyl-1,2,3,4-tetrahydroisoquinoline hydrochloride salt (154 mg, 0.65 mmol) and N-(4-bromo-2-chloro)-3,3-dimethylbutanamide (200 mg, 0.66 mmol) were then added and the reaction mixture was stirred at 90 °C overnight. The reaction mixture was then cooled to room temperature, concentrated, and purified by thin layer chromatography (dichloromethane:methanol 5%) to afford the title compound as a solid.

^{1}H NMR (DMSO-d_6, 400 MHz) δ 1.03 (s, 9H), 2.19 (s, 2H), 2.99 (t, J = 8 Hz, 2H), 3.58 (t, J = 8 Hz, 2H), 4.48 (s, 2H), 6.99 (dd, J = 4, 8 Hz, 1H), 7.08 (d, J = 4 Hz, 1H), 7.35 (dd, J = 4, 8 Hz, 1H), 7.48 (dd, J = 4, 8 Hz, 1H), 7.56 (m, 2H), 9.19 (s, 1H).

Example 22

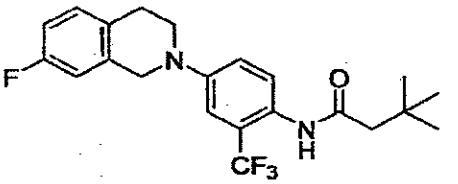
N-[4-(7-Fluoro-3,4-dihydro-*1H*-isoquinolin-2-yl)-2-trifluoromethyl-phenyl]-3,3-dimethylbutanamide

Step A: N-(4-Bromo-2-trifluoromethyl-phenyl)-3,3-dimethyl-butanamide:



3,3-Dimethylbutanoyl chloride (617 mg, 0.64 mL, 4.6 mmol) was added to a solution of 4-Bromo-2-trifluoromethyl-phenylamine (1.0 g, 4.16 mmol) in acetonitrile (10 mL). The reaction mixture was stirred at room temperature overnight. Water was added to the mixture and the precipitate formed collected to give the title compound as a powder (1.1 g, 79% yield).

Step B: N-[4-(7-Fluoro-3,4-dihydro-*1H*-isoquinolin-2-yl)-2-trifluoromethyl-phenyl]-3,3-dimethylbutanamide:



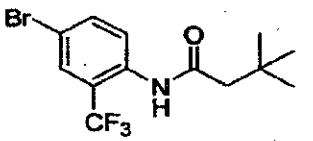
Bis(dibenzylidineacetone)palladium (2 mg, 0.0035mmol) and (2'-dicyclohexyl phosphanyl-biphenyl-2-yl)-dimethylamine (3.3 mg, 0.0084 mmol) were added to dry toluene (10 mL purged with argon) and stirred for 15 minutes under argon. Potassium *tert*-butoxide (197 mg, 1.75 mmol), 7-Fluoro-1,2,3,4-tetrahydroisoquinoline hydrochloride salt (122 mg, 0.65 mmol) and N-(4-bromo-2-trifluoromethyl)-3,3-dimethylbutanamide (200 mg, 0.59 mmol) were then added and the reaction mixture was stirred at 90 °C overnight. The reaction mixture was then cooled to room temperature, concentrated and purified by thin layer chromatography (dichloromethane 100%) to afford the title compound as a solid.

^{1}H NMR (DMSO-d_6, 400 MHz) δ 1.02 (s, 9H), 2.18 (s, 2H), 2.90 (t, J = 8 Hz, 2H), 3.60 (t, J = 8 Hz, 2H), 4.46 (s, 2H), 7.0 (m, 1H), 7.23 (m, 5H), 9.17(s, 1H).

Example 23

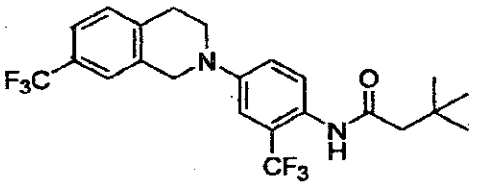
3,3-Dimethyl-N-[2-trifluoromethyl-4-(7-trifluoromethyl-3,4-dihydro-*1H*-isoquinolin-2-yl)-phenyl]-butanamide

Step A: N-(4-Bromo-2-trifluoromethyl-phenyl)-3,3-dimethylbutanamide:



3,3-Dimethylbutanoyl chloride (617 mg, 0.64 mL, 4.6 mmol) was added to a solution of 4-Bromo-2-trifluoromethyl-phenylamine (1.0 g, 4.16 mmol) in acetonitrile (10 mL). The reaction mixture was stirred at room temperature overnight. Water was added to the mixture and the precipitate formed collected to give the title compound as a powder (1.1 g, 79% yield).

Step B: 3,3-Dimethyl-N-[2-trifluoromethyl-4-(7-trifluoromethyl-3,4-dihydro-*1H*-isoquinolin-2-yl)-phenyl]-butanamide:



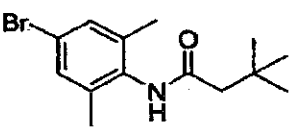
Bis(dibenzylidineacetone)palladium (2 mg, 0.0035mmol) and (2'-dicyclohexyl phosphanyl-biphenyl-2-yl)-dimethylamine (3.3 mg, 0.0084 mmol) were added to dry toluene (10 mL purged with argon) and stirred for 15 minutes under argon. Potassium *tert*-butoxide (197 mg, 1.75 mmol), 7-trifluoromethyl-1,2,3,4-tetrahydroisoquinoline hydrochloride salt (154 mg, 0.65 mmol) and N-(4-bromo-2-trifluoromethyl)-3,3-dimethylbutanamide (200 mg, 0.59 mmol) were then added and the reaction mixture was stirred at 90 °C overnight. The reaction mixture was then cooled to room temperature, concentrated and purified by thin layer chromatography (Dichloromethane 100%) to afford the title compound as a solid.

^{1}H NMR (DMSO-d_6, 400 MHz) δ 1.02 (s, 9H), 2.18 (s, 2H), 3.01 (t, J = 8 Hz, 2H), 3.62 (t, J = 8 Hz, 2H), 4.56 (s, 2H), 7.24 (m, 3H), 7.44 (d, J = 4 Hz, 1H), 7.52 (d, J = 4 Hz, 1H), 7.67 (s, 1H), 9.18 (s, 1H).

Example 24

N-[4-(6-Methoxy-3,4-dihydro-*1H*-isoquinolin-2-yl)-2,6-dimethyl-phenyl]-3,3-dimethyl butanamide

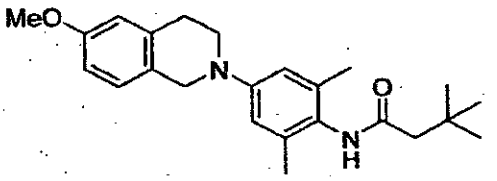
Step A: N-(4-Bromo-2,6-dimethyl-phenyl)-3,3-dimethyl-butanamide:



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-2,6-dimethyl-

phenylamine (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).

Step B: N-[4-(6-Methoxy-3,4-dihydro-*1H*-isoquinolin-2-yl)-2,6-dimethyl-phenyl]-3,3-dimethylbutanamide:



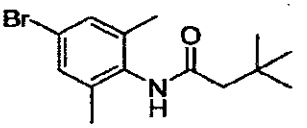
Bis(dibenzylidineacetone)palladium (2 mg, 0.0035mmol) and (2'-dicyclohexyl phosphanyl-biphenyl-2-yl)-dimethylamine (3.3 mg, 0.0084 mmol) were added to dry toluene (10 mL purged with argon) and stirred for 15 minutes under argon. Potassium *tert*-butoxide (197 mg, 1.75 mmol), 6-methoxy-1,2,3,4-tetrahydroisoquinoline hydrochloride salt (134 mg, 0.67 mmol) and N-(4-bromo-2,6-dimethyphenyl)-3,3-dimethylbutanamide (200 mg, 0.67 mmol) were then added and the reaction mixture was stirred at 80 °C overnight. The reaction mixture was then cooled to room temperature, concentrated, filtered through a pad of silica gel, and recrystallized from toluene to afford the title compound as a solid.

^{1}H NMR (DMSO-d_6, 400 MHz) δ 1.05 (s, 9H), 2.10 (s, 6H), 2.14 (s, 2H), 2.87 (t, J = 8 Hz, 2H), 3.48 (t, J = 8 Hz, 2H), 3.72 (s, 3H), 4.26 (s, 2H), 6.68 (s, 2H), 6.79 (m, 2H), 7.14 (m, 1H), 8.85 (s, 1H).

Example 25

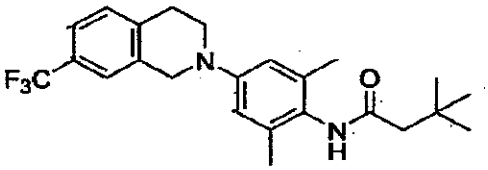
N-[2,6-Dimethyl-4-(7-trifluoromethyl-3,4-dihydro-*1H*-isoquinolin-2-yl)-phenyl]-3,3-dimethyl butanamide

Step A: N-(4-Bromo-2,6-dimethyl-phenyl)-3,3-dimethylbutanamide:



3,3-Dimethylbutanoyl chloride (3.37 g, 3.5 mL, 25 mmol) and triethylamine (2.53 g, 3.5 mL, 25 mmol) were added to a solution of 4-bromo-2,6-dimethyl-phenylamine (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 that formed was collected to give the title compound as a powder (7.46 g, 100% yield).

Step B: N-[2,6-Dimethyl-4-(7-trifluoromethyl-3,4-dihydro-*1H*-isoquinolin-2-yl)-phenyl]-3,3-dimethyl-butanamide:



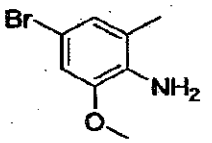
Bis(dibenzylidineacetone)palladium (390 mg, 0.68 mmol) and (2'-dicyclohexyl phosphanyl-biphenyl-2-yl)-dimethylamine (800 mg, 2.0 mmol) were added to dry toluene (150 mL purged with argon) and stirred for 15 minutes under argon. Potassium *tert*-butoxide (4.75 g, 42.3 mmol), 7-trifluoromethyl-1,2,3,4-tetrahydro-isoquinoline hydrochloride salt (4.82 g, 20.3 mmol) and N-(4-Bromo-2,6-dimethyl-phenyl)-3,3-dimethyl-butanamide (5 g, 16.8 mmol) were then added and the reaction mixture was stirred at 80 °C overnight. The reaction mixture was then cooled to room temperature, filtered through silica gel, and recrystallized from toluene to afford the title compound as a solid. (5.94 g, 85%).

^{1}H NMR (DMSO-d_6, 400 MHz) δ 1.06 (s, 9H), 2.11 (s, 6H), 2.18 (s, 2H), 2.89 (t, J = 4 Hz, 2H), 3.54 (t, J = 4 Hz, 2H), 4.44 (s, 2H), 6.73 (s, 2H), 7.40 (d, J = 8 Hz, 1H), 7.51 (d, J = 8 Hz, 1H), 7.62 (s, 1H), 8.87 (s, 1H).

Example 26

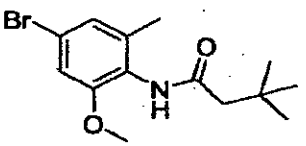
N-[4-(3,4-Dihydro-*1H*-isoquinolin-2-yl)-2-methoxy-6-methyl-phenyl]-3,3-dimethyl-butanamide

Step A: 4-bromo-2-methoxy-6-methyl-aniline:



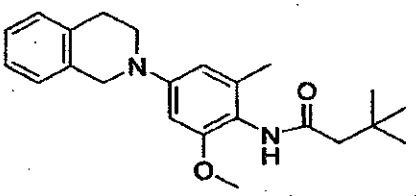
To an ice-water cooled solution of 2-methoxy-6-methylaniline (10 g, 72.9 mmol) in 30 mL of methanol and 10 mL of acetic acid was added dropwise bromine (3.75 mL, 72.9 mmol). The reaction mixture was allowed to stand for overnight. The solvent was removed under reduced pressure and the residue was suspended in 60 mL of 1N NaOH and extracted with ethyl acetate and dried over sodium sulfate and evaporated to dryness to give reddish crude product, which was recrystallized from hexane to give pure product (14.3 g, 91%).

Step B: (4-Bromo-2-methoxy-6-methyl-phenyl)-3,3-dimethyl butanamide:



To a solution of 4-bromo-2-methoxy-6-methyl-aniline (2.2 g, 10mmol) and triethylamine (1.5 g, 15 mmol) in anhydrous dichloromethane (50 mL) was added dropwise *tert*-butylacetyl chloride (1.6g, 12mmol) with stirring at room temperature. The reaction mixture was stirred for 3 hours at room temperature, than the reaction mixture was diluted with dichloromethane and washed with water and dried over anhydrous sodium sulfate and evaporated to dryness under reduced pressure. The residue was purified by silica gel column (ISCO, hexane/EtOAc, 0-40%, 40 min) to give a white solid (2.8 g, 89%).

Step C: N-[4-(3,4-Dihydro-*1H*-isoquinolin-2-yl)-2-methoxy-6-methyl-phenyl]-3,3-dimethyl-butanamide:



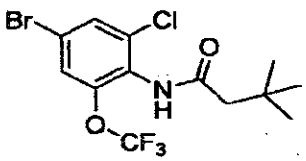
Toluene (6ml) was degassed with nitrogen for 15 min in a 10 mL of microwave tube, then (4-bromo-2-methoxy-6-methyl-phenyl)-3,3-dimethyl-butanamide (188mg, 0.6mmol) and 1,2,3,4-tetrahydroisoquinoline (96 mg, 0.72 mmol) was added, followed by potassium tert-butoxide (101mg, 0.9mmol), bis(dibenzylidene acetone)palladium (17 mg, 0.03 mmol), and 2-dicyclohexyphosphino-2-(N,N-dimethylamino)biphenyl (24 mg, 0.06 mmol). The reaction tube was sealed and reacted in microwave at 100 °C for 2 hours. The reaction mixture was purified by silica gel column (ISCO, hexane/EtOAc, 0-40%, 40 min) to give pure compound as a white solid.

^{1}H-NMR (DMSO-d_6, 400MHz): δ 8.64 (brs, 1H, exchangeable with D_2O), 7.20 (m, 4H), 6.48 (s, 1H), 6.43 (s, 1H), 4.37 (s, 2H), 3.73 (s, 3H), 3.52 (t, J=6.0Hz, 2H), 2.92 (t, J=6.0Hz, 2H), 2.13 (s, 2H), 2.08 (S, 3H), 1.04 (s, 9H). MS: 367 (M+1).

Example 27

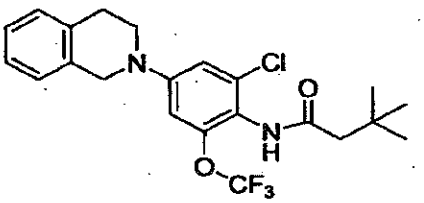
N-[2-Chloro-4-(3,4-dihydro-*1H*-isoquinolin-2-yl)-6-trifluoromethoxy-phenyl]-3,3-dimethyl-butanamide

Step A: N-(4-Bromo-2-chloro-6-trifluoromethoxy-phenyl)-3,3-dimethyl-butanamide:



To a solution of 4-bromo-2-chloro-6-trifluoromethoxy-aniline (2.9 g, 10 mmol) and triethylamine (1.5 g, 15 mmol) in anhydrous dichloromethane (50 mL) was added dropwise *tert*-butylacetyl chloride (1.6 g, 12 mmol) with stirring at room temperature. The reaction mixture was stirred for 3 hours at room temperature, than the reaction mixture was diluted with dichloromethane and washed with water and dried over anhydrous sodium sulfate and evaporated to dryness under reduced pressure. The residue was purified by silica gel column (ISCO, hexane/EtOAc, 0-40%, 40 min) to give a white solid (3.6 g, 93%).

Step B: N-[2-Chloro-4-(3,4-dihydro-*1H*-isoquinolin-2-yl)-6-trifluoromethoxy-phenyl]-3,3-dimethylbutanamide:

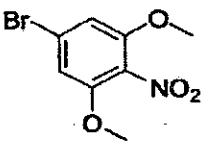


Synthesized according to example 26: ^{1}H-NMR (DMSO-d_6, 400MHz): δ 9.28 (brs, 1H, exchangeable with D_2O), 7.20 (m, 4H), 7.10 (s, 1H), 6.89 (s, 1H), 4.45 (s, 2H), 3.57 (t, J=6.0Hz, 2H), 2.92 (t, J=6.0Hz, 2H), 2.18 (s, 2H), 1.04 (s, 9H). MS: 441 (M+1).

Example 28

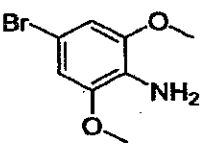
N-[4-(3,4-Dihydro-*1H*-isoquinolin-2-yl)-2,6-dimethoxy-phenyl]-3,3-dimethyl-butanamide

Step A: 5-Bromo-1,3-dimethoxy-2-nitro-benzene:



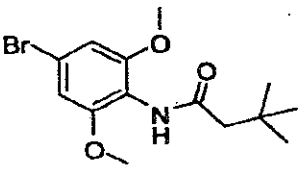
1-Bromo-3,5-dimethoxybenzene (10.9 g, 50 mmol) was dissolved in 100 mL of acetic anhydride and cooled to 0 °C. A cooled solution of 70% HNO_3 (6.4 mL, 100 mmol) in 20 mL of acetic anhydride was added dropwise and the resulting mixture was stirred for 1 hour at 0 °C and for 3 hours at room temperature. The reaction mixture was poured into ice-water with strong stirring and the yellow solid was filtered and washed with water. The solid as a mixture of two isomers was separated by silica gel column (ISCO, hexane/EtOAc, 0-30%, 40 min) to give 3.3 g (25%) of pure 5-bromo-1,3-dimethoxy-2-nitro-benzene as an yellow solid. ^{1}H-NMR (DMSO-d_6, 400MHz): δ 7.17 (s, 2H), 3.89 (s, 6H).

Step B: 5-Bromo-1,3-dimethoxy-2-amino-benzene:



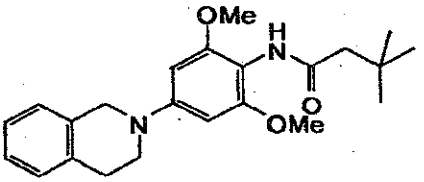
5-Bromo-1,3-dimethoxy-2-nitro-benzene (2.6 g, 10 mmol) was dissolved in 200 mL of methanol and 40 mL of water was added, followed by 2.5 g of Fe powder and 2.5 g of ammonium chloride. The mixture was heated to reflux at 80 °C for 2 hours and the cooled reaction mixture was filtered and washed with methanol. The filtrate was evaporated under reduce pressure to give the crude product, which was used for next step without further purification.

Step C: N-(4-Bromo-2,6-dimethoxy-phenyl)-3,3-dimethyl-butanamide:



To a solution of the crude 5-bromo-1,3-dimethoxy-2-amino-benzene from above and triethylamine (1.5 g, 15 mmol) in anhydrous dichloromethane (50 mL) was added dropwise *tert*-butyl acetyl chloride (1.6 g, 12 mmol) with stirring at room temperature. The reaction mixture was stirred for 3 hours at room temperature. Then the reaction mixture was diluted with dichloromethane, washed with water, dried over anhydrous sodium sulfate, and evaporated to dryness under reduced pressure. The residue was purified by silica gel column (ISCO, hexane/EtOAc, 0-40%, 40 min) to give a white solid (3.0 g, 91%). ^{1}H-NMR (DMSO-d_6, 400MHz): δ 8.69 (brs, 1H, exchangeable with D_2O), 6.87 (s, 2H), 3.73 (s, 6H), 2.11 (s, 2H), 1.02 (s, 9H).

Step D: N-[4-(3,4-Dihydro-*1H*-isoquinolin-2-yl)-2,6-dimethoxy-phenyl]-3,3-dimethyl-butanamide:

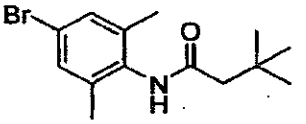


Toluene (6 mL) was degassed with nitrogen for 15 min in a 10 mL of microwave tube, then N-(4-bromo-2,6-dimethoxy phenyl)-3,3-dimethyl butanamide (200 mg, 0.6 mmol) and 1,2,3,4-tetrahydroisoquinoline (96 mg, 0.72 mmol) was added, followed by potassium *tert*-butoxide (101 mg, 0.9 mmol), bis(dibenzylidene acetone)palladium (17 mg, 0.03 mmol), and 2-dicyclohexyphosphino-2-(N,N-dimethylamino)biphenyl (24 mg, 0.06 mmol). The reaction tube was sealed and reacted in microwave at 100 °C for 2 hours. The reaction mixture was purified by silica gel column (ISCO, hexane/EtOAc, 0-40%, 40 min) to give pure compound as a white solid. ^{1}H-NMR (DMSO-d_6, 400MHz): δ 8.36 (brs, 1H, exchangeable with D_2O), 7.20 (m, 4H), 6.25 (s, 2H), 4.41 (s, 2H), 3.72 (s, 6H), 3.55 (t, J=6.0Hz, 2H), 2.95 (t, J=6.0Hz, 2H), 2.07 (s, 2H), 1.03 (s, 9H). MS: 383 (M+1).

Example 28

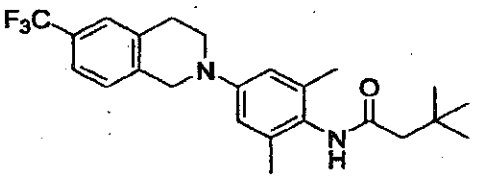
N-[2,6-Dimethyl-4-(6-trifluoromethyl-3,4-dihydro-*1H*-isoquinolin-2-yl)-phenyl]-3,3-dimethyl-thiobutanamide

Step A: N-(4-Bromo-2,6-dimethyl-phenyl)-3,3-dimethyl-butyramide:



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-2,6-dimethyl-phenylamine (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).

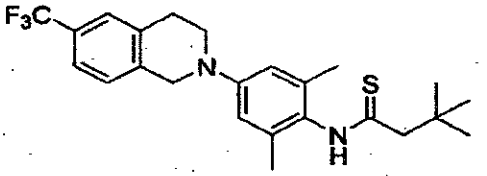
Step B: N-[2,6-Dimethyl-4-(6-trifluoromethyl-3,4-dihydro-1H-isoquinolin-2-yl)-phenyl]-3,3-dimethyl-butanamide:



Bis(dibenzylidineacetone)palladium (390 mg, 0.68 mmol) and (2'-dicyclohexylphosphanyl-biphenyl-2-yl)-dimethylamine (800 mg, 2.0 mmol) were added to dry toluene (150 mL purged with argon) and stirred for 15 minutes under argon. Potassium *tert*-butoxide (4.75 mg, 42.3 mmol), 6-Trifluoromethyl-1,2,3,4-tetrahydro-isoquinoline hydrochloride salt (4.82 g, 20.3 mmol) and N-(4-Bromo-2,6-dimethyl-phenyl)-3,3-dimethyl-butyramide (5 g, 16.8 mmol) were then added and the reaction mixture was stirred at 80 °C over night. The reaction mixture was then cooled to room temperature and recrystallized from toluene to afford the title compound as a solid. (5.55 g, 79%).

^{1}H NMR (DMSO-d_6, 500 MHz) δ 1.03 (s, 9H), 2.09 (s, 6H), 2.15 (s, 2H), 2.98 (t, J = 5.0 Hz, 2H), 3.52 (t, J = 6.0 Hz, 2H), 4.40 (s, 2H), 6.71 (s, 2H), 7.45 (d, J = 8.0, 1H), 7.52 (m, 2H), 8.87 (s, 1H).

Step C: N-[2,6-Dimethyl-4-(6-trifluoromethyl-3,4-dihydro-*1H*-isoquinolin-2-yl)-phenyl]-3,3-dimethyl-thiobutanamide:



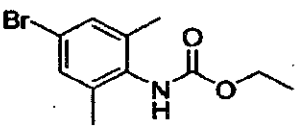
To a solution of N-[2,6-Dimethyl-4-(6-trifluoromethyl-3,4-dihydro-1H-isoquinolin-2-yl)-phenyl]-3,3-dimethyl-butyramide (200 mg, 0.48 mmol) in dichloroethane (10 mL) was added Lawesson's reagent (193 mg, 0.48 mmol) and the reaction mixture was stirred at reflux for 2h. The mixture was then cooled to room temperature and concentrate. Purification by preparative thin layer chromatography (dichloromethane 100%) afforded the desired compound as a solid.

^{1}H NMR (DMSO-d_6, 400 MHz) δ 1.12 (s, 9H), 2.11 (s, 6H), 2.73 (s, 2H), 3.0 (t, J = 5.0 Hz, 2H), 3.57 (t, J = 4.0 Hz, 2H), 4.46 (s, 2H), 6.75 (s, 2H), 7.47 (d, J = 8.0, 1H), 7.56 (m, 2H), 10.7 (s, 1H).

Example 29

[2,6-Dimethyl-4-(6-trifluoromethyl-3,4-dihydro-*1H*-isoquinolin-2-yl)-phenyl]-carbamic acid ethyl ester:

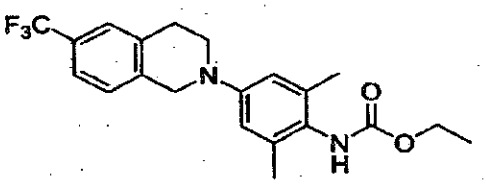
Step A: (4-Bromo-2,6-dimethyl-phenyl)-carbamic acid ethyl ester:



Ethyl chloroformate (0.55g, 0.48 mL, 5 mmol) was added to a solution of 4-bromo-2,6-dimethyl-phenylamine (1.0 g, 5 mmol) in acetonitrile (20 mL). The reaction

mixture was stirred at reflux for 16 hours. Water was added to the mixture and the precipitate formed collected to give the title compound as a powder (1.32 g, 97% yield).

Step B: [2,6-Dimethyl-4-(6-trifluoromethyl-3,4-dihydro-1H-isoquinolin-2-yl)-phenyl]-carbamic acid ethyl ester:



Bis(dibenzylidineacetone)palladium (17 mg, 0.03 mmol) and (2'-dicyclohexylphosphanyl-biphenyl-2-yl)-dimethylamine (35 mg, 0.09 mmol) were added to dry toluene (5 mL purged with argon) and stirred for 15 minutes under argon. Potassium *tert*-butoxide (166 mg, 1.48 mmol), 6-Trifluoromethyl-1,2,3,4-tetrahydro-isoquinoline hydrochloride salt (176 mg, 0.74 mmol) and (4-Bromo-2,6-dimethyl-phenyl)-carbamic acid ethyl ester (200 mg, 0.74 mmol) were then added and the reaction mixture was stirred at 80 °C overnight. The reaction mixture was then cooled to room temperature filtered through silica gel and purified by preparative thin layer chromatography (DCM 100%) to give the desired compound as a solid.
^{1}H NMR (DMSO-d_6, 400 MHz) δ 1.23 (t, J = 7.2 Hz, 3H), 2.12 (s, 6H), 3.0 (t, J = 6.4 Hz, 2H), 3.52 (t, J = 6.3 Hz, 2H), 4.08 (q, J = 13.6, 8.3 Hz, 2H), 4.42 (s, 2H) 6.73 (s, 2H), 7.46 (d, J = 7.4, 1H), 7.54 (m, 2H), 8.32 (s, 1H).

Biological Results

Compounds of this invention formula were evaluated for activity toward potassium channels in a cell-based Rb^+ efflux assay This cellular bioassay is believed to faithfully represent the M current channel activities identified with KCNQ2/3 heteromultimers. The most active compounds of this invention have EC_{50}s in the single-digit nM range, which represents a 40- to 400-fold improvement over retigabine. Additionally, antiseizure activity *in vivo* was evaluated in a mouse maximal electroshock

seizure (MES) model, and neurotoxicities were determined from a rotorod neurocognitive motor impairment model.

Methods:

Rubidium Efflux Test

PC-12 cells were grown at 37 °C and 5 % CO_2 in DMEM/F12 Medium (Dulbecco's Modified Eagle Medium with Nutrient Mix F-12, available from Invitrogen of Carlsbad, CA), supplemented with 10 % horse serum, 5 % fetal bovine serum, 2 mM glutamine, 100 U/ml penicillin, and 100 U/ml 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 concentrations of Rb^+ in the supernatants (Rb^+_{Sup}) and the cell lysates (Rb^+_{Lys}) were quantified using an ICR8000 flame atomic absorption spectrometer (Aurora Biomed Inc., Vancouver, B.C.) under conditions defined by the manufacturer. Samples 0.05 ml in volume 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

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

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_c is the efflux in the presence of compound in depolarization buffer. The efflux (F) 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.

Maximal Electroshock Seizure (MES) and Acute Toxicity Tests

MES Test

The MES testing protocol is based on procedures established at the National Institute of Neurological Disorders and Stroke in conjunction with the Anticonvulsant Screening Program (ASP) at the University of Utah (White, H.S., Woodhead, J.H., Wilcox, K.S., Stables, J.P., Kupferberg, H.J and Wolf, H.H. 2002. "General Principles: Discovery and Preclinical Development of Antiepileptic Drugs," in *Antiepileptic Drugs*, 5th Edition, R.H. Levy, ed.; R.H. Mattson, B.S. Meldrum, and E. Perucca. Philadelphia, Lippincott Williams & Wilkins.), The goal of the test rapid identification and characterization of the *in vivo* anticonvulsant activity of any compounds that have been shown active in PC-12 cellular based Rb^+ efflux assay.

Adult male CF-1 albino mice (18-25 g, Charles River Laboratories) are exclusively used for in-house MES screen of compounds. Male Sprague-Dawley albino rats (100-125g, Charles River Laboratories) are also used to test anticonvulsant compounds. Variability of test outcomes is reduced by using animals of the same sex, age, and weight. Animals are permitted to rest and recover from transit for at least 48 hr prior to experimentation. Animals are used for AED testing only once. In some instances, the animals may be anesthetized prior to blood collection and/or whole brain extraction for pharmacokinetic assay. All animals are maintained and handled as outlined in standard animal care guidelines.

In the experiments, testing compounds are prepared as suspensions in 0.5% methyl cellulose (Sigma, Cat # M0512, Viscosity 4000 cP at 20°C) in water, regardless of solubility. Dry powder compounds are initially ground with a glass rod in a test tube in several drops of methyl cellulose to create a paste and to break down any large chunks. After several minutes of grinding, the volume of the suspension is increased to the final concentration desired. The suspension is then sonicated using a Branson sonicator model 3510 in a water bath at room temperature for 15 minutes. Compound suspensions are further vortexed prior to animal dosing. In some of the cases, DMSO is used to initially solubilize compounds in small volumes and then this solution is added to the 0.5% methyl cellulose solution, in order to create more even and less aggregated compound suspensions. The final concentration of DMSO is 3.75%, an amount with no apparent toxicity or neuroprotective effects in our usual rotarod and MES tests. Methyl cellulose/DMSO compound suspensions are identically prepared for intraperitoneally (i.p.) to mice or orally (p.o.) to rat dosing.

Initially the animals are weighed with an electronic scale and then marked. Data recording sheets are generated for each compound assessment. Mice or rats are dosed with the compound suspension at 0.01 mL/g of body weight. The typical injection volume range is between 180-250 µl for mice. Compounds are dosed by i.p. to mice using a 25 or 22 gauge needle, depending on the viscosity of the suspension. Rats are p.o. dosed using a flexible feeding tube, typically starting at a compound dose of 5 mg/kg.

A Rodent Electroconvulsive Stimulator (Model 200, Hamit-Darvin-Freesh, Snow Canyon Clinic, Ivins, UT) is used for MES testing. A 60-Hz alternating current (50 mA for mice; 150 mA for rats) is delivered for 0.2 seconds through corneal electrodes to the mice. A drop of 0.5% tetracaine (Sigma, Cat. # T-7508) solution is placed on the eye prior to current delivery. The electrodes are subsequently placed gently onto the eyes of the animal and the electrical shock is initiated by triggering through a foot-pedal activator. The animals are restrained by hand and gently released as the shock is delivered and the seizure commences. Animals are monitored for hind limb tonic extension as the end point for this test. Current delivery is recorded as a measure of overall seizure-induction potential. Electrical current delivery can vary from

approximately 30-55 mA (mice) or 90-160 mA (rats) depending on impedance in the animal and quality of the current delivery (ie. correct placement of the electrodes on the cornea). Seizures will be successfully induced in control animals throughout this current range. Tonic extension is considered abolished if the hind limbs fail to become fully extended at 180° with the plane of the body. Lack of tonic extension suggests that the test compound has prevented the spread of seizure discharge through neural tissue. Although unnecessary in mice, the rats are pre-screened for seizure induction potential using the MES 24hr prior to compound dosing and the subsequent MES test. A success rate of 92-100% has been determined for the rat seizure induction potential. Rats that fail to develop tonic/clonic seizures during the pre-screening are not used for drug testing.

For a compound testing, time-to-peak effect studies are initially performed using 0.5, 1, 2, 4, 8 and 24 hr time points, typically using a single 5 or 25 mg/kg dose. The determined time-to-peak effect is used for further titration of a compound's potency (ED_{50}, the dose of a drug that protects 50% of animals from electrical induced seizure) in both mouse and rat models. For titrations, 8 animals are used per concentration and dose (normal 5 concentrations) is varied until a full dose response curve can be obtained. Probit analysis (ASP method) or non-linear regression analysis on Graph Pad (constraining the lower dose/effect value) is used to calculate an ED_{50} value for the test compound.

Rotarod Test

Prior to MES testing, compound dosed mice are scrutinized for abnormal neurologic status as defined by motor impairment on a slowly turning (6 rpm) rotarod apparatus (Model 755, Series 8, HTC Life Sciences, Woodland Hills, CA). The inability of a mouse to maintain its balance on the rotarod over a period of one minute (three falls = failure) signifies motor impairment and hence acute toxicity. These measurements are done at the same time points as the MES assay. Untreated normal mice are able to maintain balance on the rotarod for at least one minute without falling. Median toxicity of a compound (TD_{50}, the dose of a drug that results in motor impairment in 50% of animals) is determined.

Open Field Test

Before MES test, compound treated rats are visually observed for acute toxicity signs for approximately one minute in the open field test. Here, rats are gently placed into a plexiglass enclosure and are monitored for behavior consistent with toxicity including ataxia, trembling, hypoactivity (including failure to seek the walls), hypersensitivity, lack of exploratory behavior and lack of avoidance of the open area. Typically if the rats exhibits two or more of these abnormal behaviors they are scored as toxic.

TABLE 1

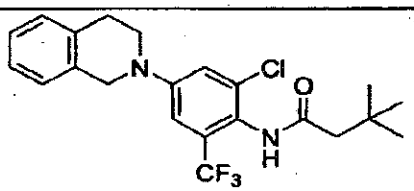
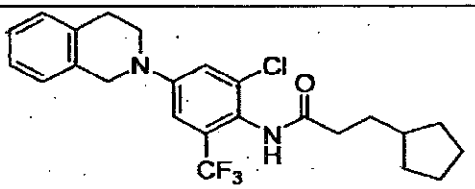
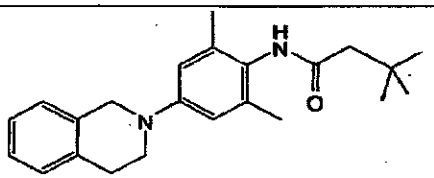
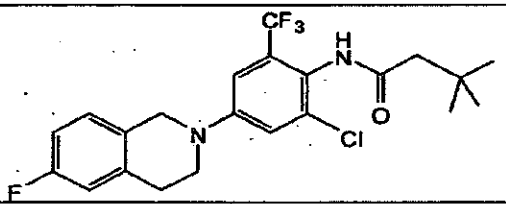
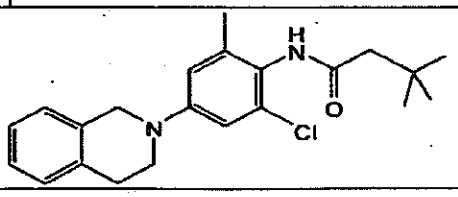
ACTIVITIES OF EXEMPLARY COMPOUNDS

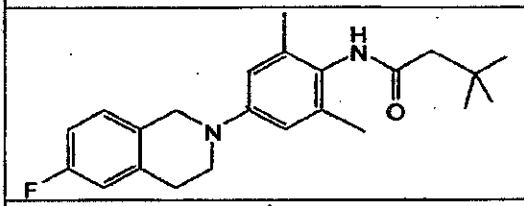
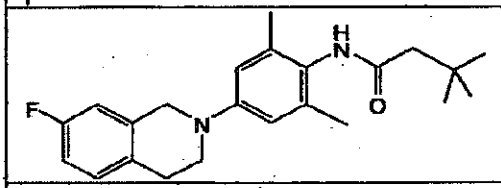
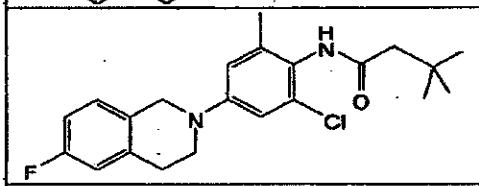
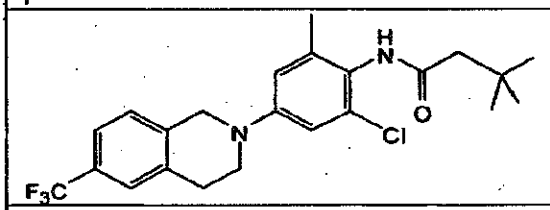
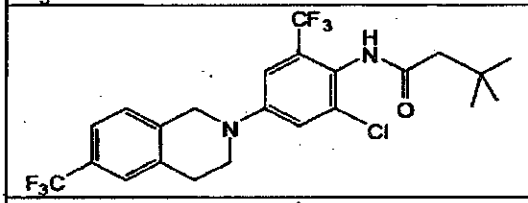
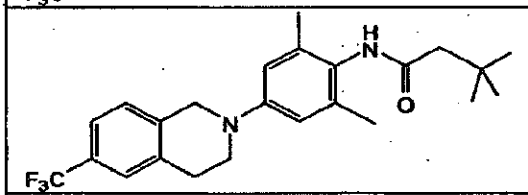
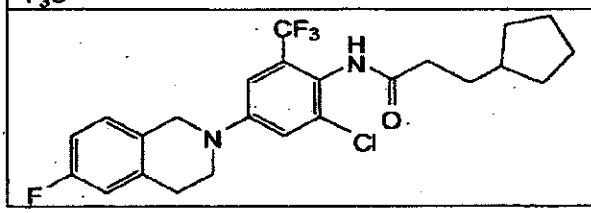
Legend: A: $EC_{50} \leq 1$ nM; B: = 1 nM < $EC_{50} \leq 10$ nM;
C:10 nM <$EC_{50} \leq 50$ nM; D: 50 nM <$EC_{50} \leq 500$ nM

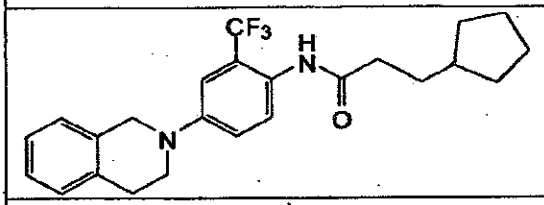
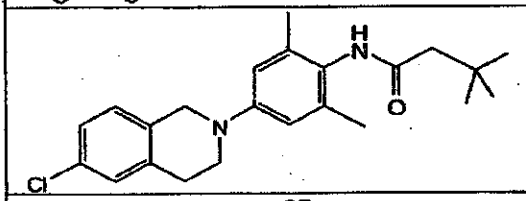
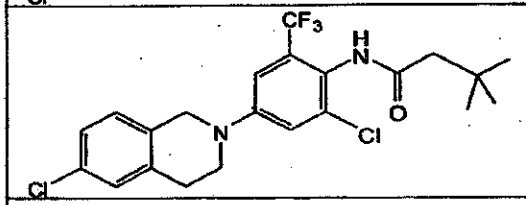
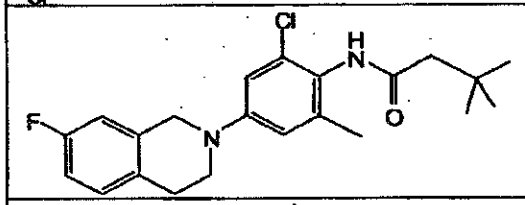
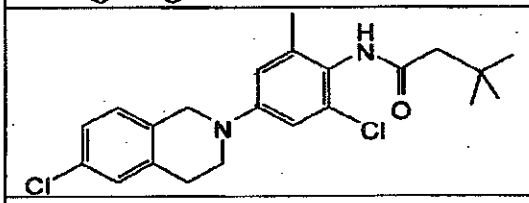
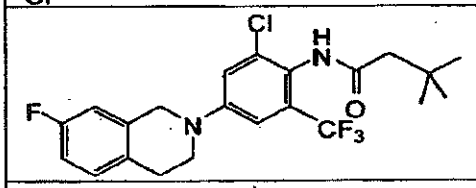
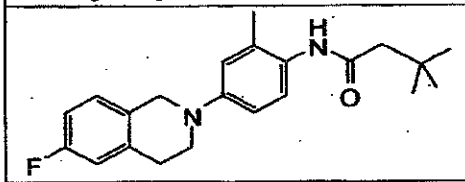
α: 0.12< ED50 ≤ 1.2

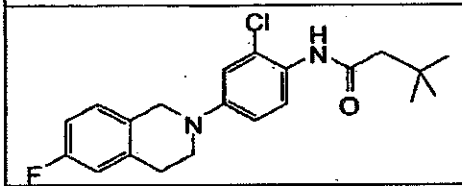
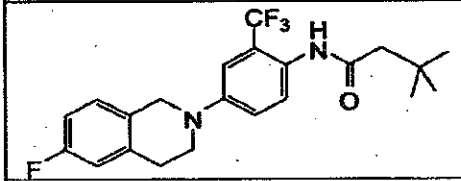
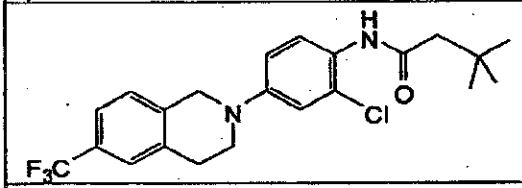
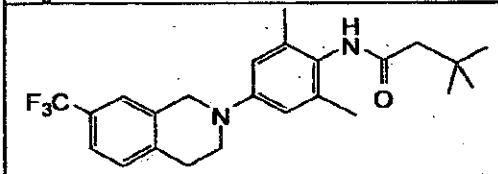
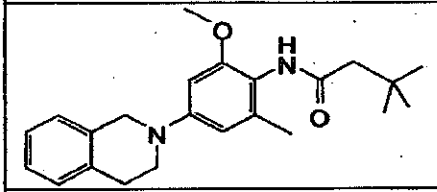
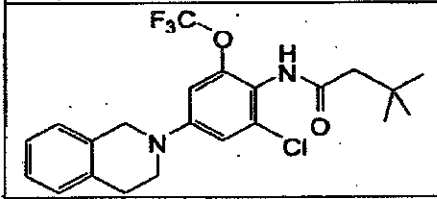
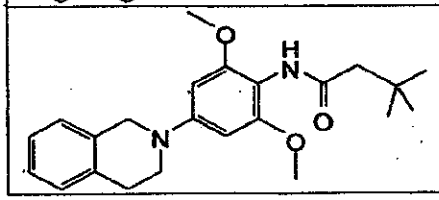
β: 1.2 < ED50 ≤ 12

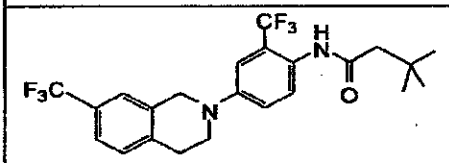
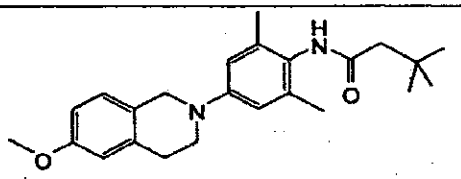
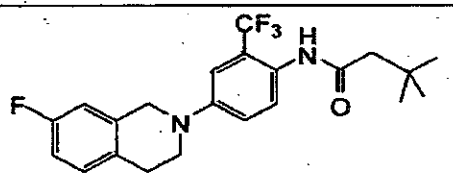
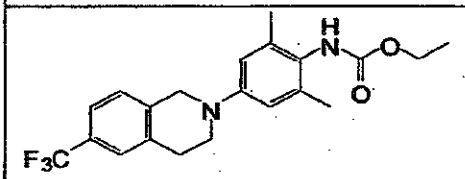
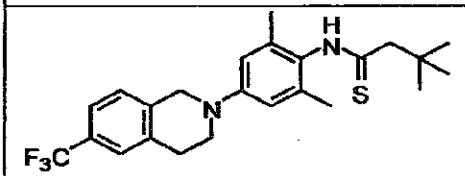
γ: 12 < ED50

COMPOUND	Mouse ED_{50} (mg/kg)	Rat ED_{50} (mg/kg)	ACTIVITY EC_{50}
	γ	NA	B
	γ	NA	B
	β	NA	C
	γ	NA	C
	β	NA	B

COMPOUND	Mouse ED_{50} (mg/kg)	Rat ED_{50} (mg/kg)	ACTIVITY EC_{50}
	β	α	C
	β	NA	B
	γ	NA	B
	γ	NA	B
	γ	NA	B
	α	α	B
	γ	NA	A

COMPOUND	Mouse ED_{50} (mg/kg)	Rat ED_{50} (mg/kg)	ACTIVITY EC_{50}
	NA	NA	C
	β	NA	C
	γ	NA	C
	β	NA	B
	β	NA	C
	γ	NA	B
	NA	NA	D

COMPOUND	Mouse ED_{50} (mg/kg)	Rat ED_{50} (mg/kg)	ACTIVITY EC_{50}
	γ	NA	D
	β	NA	D
	γ	NA	D
	α	α	B
	β	NA	B
	γ	NA	B
	α	α	C

COMPOUND	Mouse ED_{50} (mg/kg)	Rat ED_{50} (mg/kg)	ACTIVITY EC_{50}
	β	NA	D
	γ	NA	D
	NA	NA	D
	NA	NA	C
	NA	NA	D

Studies of KCNQ2/3 opening activity and KCNQ subtype selectivity using electrophysiological patch clamp in Xenopus oocytes

Expression in Xenopus laevis oocytes

Female Xenopus laevis extracted ovaries were purchased from eNASCO (LM00935MX, eNASCO Fort Atkinson, WI). Following manual dissection of the oocytes into smaller groups, the oocytes were defolliculated by enzymatic treatment with collagenase type 2 (LS004177, Worthington, Lakewood, NJ) for 1-1/2 hour in the presence of calcium-free Culture Bath solution (88 mM NaCl, 1 mM KCl, 0.82 mM $MgSO_4$, 2.4 mM $NaHCO_3$, and 5 mM HEPES, pH 7.5). Oocytes were then kept in

supplemented Culture Bath solution (88 mM NaCl, 1 mM KCl, 0.82 mM $MgSO_4$, 0.9 mM $CaCl_2$, 2.4 mM $NaHCO_3$, 1 mM sodium pyruvate, 0.05 mg/ml Geneticin, 100 U/ml penicillin, 0.1 mg/ml streptomycin and 5 mM HEPES, pH 7.5) at 19°C for 24 hours before injection of cRNA. Approximately 50 nl cRNA (about 50 ng) was injected for KCNQ1, KCNQ4, and KCNQ5 using a Nanoject microinjector (Drummond, Broomall, PA, USA). For co-expression of KCNQ2 and KCNQ3 and of KCNQ1 and KCNE1, cRNA's were mixed in equal molar ratios before injection of approximately 50 nl. The mixtures contained about 10 + 10 ng and 12.5 + 2.5 ng cRNA, respectively. The smaller amounts are needed because larger currents arise when KCNQ2/KCNQ3 and KCNQ1/KCNE1 are co-expressed. Oocytes were kept in Culture Barth solution at 19°C which was changed daily and currents were recorded after 3 to 5 days.

Electrophysiology

KCNQ channel currents expressed in Xenopus laevis oocytes were recorded using a two-electrode voltage-clamp. The recordings were made at room temperature in recording solution (96 mM NaCl, 2 mM KCl, 1 mM $MgCl_2$, 1.8 mM $CaCl_2$, and 5 mM HEPES, pH 7.5) using a two-electrode voltage-clamp amplifier (OC-725C, Warner Instrument, Hamden, CT, USA). The oocytes were placed in custom built perfusion chambers connected to a continuous flow system and impaled with a current electrode and a voltage-clamp electrode pulled from borosilicate glass on a Flaming/Brown Micropipette Puller (Sutter Instruments Co, Novato, CA, USA). Recording electrodes were filled with 3 M KCl and had a resistance of 0.5 to 2.5 MΩ.

Compounds

All compounds were dissolved in DMSO to obtain concentrated stock solutions. On the day of electrophysiological experiments the stock solutions were thawed and diluted in recording solution to their final concentrations. The final DMSO concentration never exceeded 0.1%. Compound delivery was performed using a custom built multi-barrel apparatus connected to the flow system.

Calculations

Data were acquired by means of an Axograph X software (Axograph Scientific, Sydney, AU) and analyzed using Graph Pad Prism (GraphPad Software Inc., CA, USA).

Concentration - response curves were constructed by plotting the increase in steady-state current expressed in percentages as a function of drug concentration. During the course of the experiment, while various concentrations of the drug were being dosed, the resting voltage was held at -90 mV and pulsed to -60 mV, -40 mV, and -50 mV for 5 s for KCNQ2/KCNQ3, KCNQ4 and KCNQ5 channels respectively. The plot was then fitted to a Hill function:

$$\text{Response} = R2 + (R1-R2)/[1+(C/EC_{50})^{\wedge}nH]$$

where R1 is the initial response, R2 is the maximum response, C is the drug concentration and nH is the slope (Hill coefficient) of the curve.

The efficacy of compounds of this invention in comparison with Retigabine (as a positive control) was determined by recording the steady current using the above voltage protocol for the channels in the presence of the EC_{75} of the drugs. After steady channel current was recorded in the presence of Retigabine at its EC75, recorded oocyte was washed with the recording solution until its steady current returned to its normal level without the presence of any drugs. Then the channel steady current was recorded in the presence of the test compound at its EC_{75}. The percent efficacy was then expressed as:

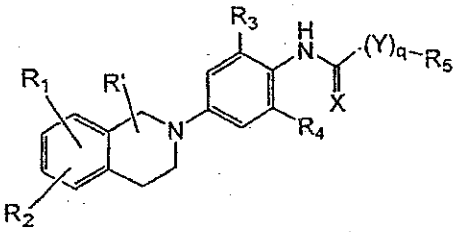
$$\% \text{ efficacy} = (C2/C1) \text{ X } 100\ \%$$

where C2 is the recorded steady current in the presence of follow-on compound at its EC_{75} and C1 is the recorded steady current in the presence of Retigabine at its EC_{75}.

AMENDED CLAIMS
received by the International Bureau on 24 June 2008

What is claimed is:

1. A compound of formula IA



IA

where R_1 and R_2, are, independently, H, CN, halogen, CH_2CN, OH, CH_2F, CHF_2, CF_3, CF_2CF_3, C_1-C_6 alkyl, $C(=O)C_1$-C_6 alkyl; NH-C_1-C_6 alkyl; $N(C_1$-C_6 alkyl)-C_1-C_6 alkyl, $NHC(=O)C_1$-C_6 alkyl, $C(=O)N(CH_3)_2$, $C(=O)N(Et)_2$, $C(=O)NH_2$, $C(=O)NH$-C_1-C_6 alkyl, SO_2NH_2, $NHSO_2$-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, $(CH_2)_m$thienyl, $(CH_2)_m$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 $(CH_2)_m$pyrimidyl, where m = zero, 1, or 2, Ar is a 5- to 10- member mono- or bicyclic aromatic group, optionally containing 1 – 4 ring heteroatoms selected independently from N, O, and S; 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; R' is H, halogen, phenyl, 2-(N,N-dimethylamino)ethyl, CF_3, OC_1-C_3 alkyl or C_1-C_3 alkyl; R_3 and R_4 are, independently, H, CN, halogen, CF_3, OCF_3, OC_1-C_3 alkyl, or C_1-C_3 alkyl; X is O or S; Y is O or S; q = 1 or zero; 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, $(CHR_6)_wAr$, $CH_2(CHR_6)_wAr$, or $(CHR_6)_wCH_2Ar$, where w = zero, 1, 2, or 3, Ar is a 5- to 10- member mono- or bicyclic aromatic group, optionally containing 1 – 4 ring heteroatoms selected independently from N, O, and S; R_6 is H or C_1-C_3 alkyl; where all cycloalkyl and cycloalkenyl groups optionally contain one or two ring heteroatoms

selected independently from N, O, and S; where all alkyl, cycloalkyl, alkenyl, cycloalkenyl, heterocycloalkyl, heterocycloalkenyl, alkynyl, aryl, and heteroaryl groups in R_1, R_2, R', R_3, R_4, R_5, R_6, and Ar are optionally substituted with one or two substituents selected independently from C_1-C_3 alkyl, halogen, OH, OEt, OMe, CN, CH_2F, OCF_3, and CF_3; and where, additionally, all cycloalkyl and heterocycloalkyl groups are optionally substituted with a carbonyl group.

2. The compound of claim 1, where R_1 and R_2, are, independently, H, halogen, CF_3, C_1-C_6 alkyl, $C(=O)C_1$-C_6 alkyl, $C(=O)OC_1$-C_6 alkyl, $OC(=O)C_1$-C_6 alkyl, OC_1-C_6 alkyl, SCH_3, C_3-C_6 cycloalkyl, $(CH_2)_mC_3$-C_6 cycloalkyl, phenyl, pyridyl, pyrrolyl, thienyl, $(CH_2)_m$phenyl, $(CH_2)_m$pyrrolyl, or $(CH_2)_m$pyridyl, said cycloalkyl groups optionally containing one or two heteroatoms selected independently from O, N, and S, and said alkyl, cycloalkyl, phenyl, pyrrolyl, and pyridyl groups optionally substituted with one or two groups selected, independently, from halogen, methyl, ethyl, or trifluoromethyl, where m is zero, 1, or 2; R' is H, halogen, phenyl, 2-(N,N-dimethylamino)ethyl, CF_3, OC_1-C_3 alkyl or C_1-C_3 alkyl; where R_3 and R_4 are, independently, H, halogen, CF_3, OCF_3, OC_1-C_3 alkyl, or C_1-C_3 alkyl; X = O or S; Y is O or S; 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, $(CHR_6)_w$Ar, $CH_2(CHR_6)_w$Ar, or $(CHR_7)_wCH_2$Ar, where w = 0 – 3, Ar is phenyl, pyrimidyl, or pyridyl, or a 5- member heteroaromatic ring, containing 1 or 2 ring heteroatoms selected independently from N, O, and S; R_6 is H or methyl; where all cycloalkyl and cycloalkenyl groups in R_5 optionally contain one or two ring heteroatoms selected independently from N, O, and S; and where all alkyl, cycloalkyl, alkenyl, cycloalkenyl, heterocycloalkyl, heterocycloalkenyl, alkynyl, aryl, and heteroaryl groups in R_1, R_2, R_3, R_4, R_5, R_6, and Ar are optionally substituted with one or two substituents selected independently from C_1-C_3 alkyl, halogen, OEt, OMe, and trifluoromethyl.

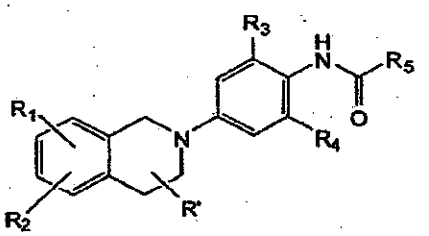
3. The compound of claim 1, where R_1 and R_2, are, independently, H, halogen, CF_3, C_1-C_6 alkyl, C(=O)C_1-C_6 alkyl, C(=O)OC_1-C_6 alkyl, OC(=O)C_1-C_6 alkyl, OC_1-C_6 alkyl, SCH_3, $(CH_2)_m$ cyclopropyl, $(CH_2)_m$cyclobutyl, $(CH_2)_m$ cyclopentyl, $(CH_2)_m$ cyclohexyl, $(CH_2)_m$oxazolyl, $(CH_2)_m$isoxazolyl, $(CH_2)_m$thiazolyl, $(CH_2)_m$isothiazolyl, $(CH_2)_m$phenyl, $(CH_2)_m$pyrrolyl, $(CH_2)_m$pyridyl, or $(CH_2)_m$pyrimidyl, said cyclopentyl and said cyclohexyl groups optionally containing one or two ring heteroatoms selected independently from O, N, and S, and said alkyl, cycloalkyl, phenyl, pyrrolyl, and pyridyl groups optionally substituted with one or two groups selected, independently, from halogen, CH_3, ethyl, or CF_3, where m is zero, 1, or 2; R' is H, halogen, CF_3, or C_1-C_3 alkyl; R_3 and R_4 are, independently, H, halogen, CF_3, OCF_3, OC_1-C_3 alkyl, or C_1-C_3 alkyl; X = O or S; Y is O; 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, $(CHR_6)_w$Ar, $CH_2(CHR_6)_w$Ar, or $(CHR_6)_wCH_2$Ar, where w = 0 – 3, Ar is phenyl, pyridyl, or a 5-member heteroaromatic ring, containing 1 or 2 ring heteroatoms selected independently from N, O, and S; R_6 is H or methyl; where all cycloalkyl and cycloalkenyl groups optionally contain one or two ring heteroatoms selected independently from N, O, and S; where all alkyl, cycloalkyl, alkenyl, cycloalkenyl, heterocycloalkyl, heterocycloalkenyl, alkynyl, aryl, and heteroaryl groups in R_1, R_2, R_3, R_4, R_5, R_6, and Ar are optionally substituted with one or two substituents selected independently from C_1-C_3 alkyl, halogen, OMe, OEt, and CF_3.

4. The compound of claim 2, where R_1 and R_2, are, independently, H, halogen, CF_3, OC_1-C_3 alkyl, C_1-C_6 alkyl, C(=O)OC_1-C_3 alkyl, OC(=O)C_1-C_3 alkyl, or C(=O)C_1-C_3 alkyl; R' is H, F, CH_3, or ethyl; R_3 and R_4 are, independently, H, F, Cl, CF_3, OCF_3, OC_1-C_3 alkyl, or C_1-C_3 alkyl; and 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, or $(CHR_6)_w$Ar, $CH_2(CHR_6)_w$Ar, or $(CHR_6)_wCH_2$Ar.

5. The compound of claim 1, where R_2 is H or F; R' is H; R_3 is H, CH_3, OCH_3, CF_3, OCF_3, or Cl; R_4 is CH_3, OCH_3, CF_3, OCF_3, or Cl; and R_5 is C_3-C_6 alkyl or $(CH_2)_wC_3$-C_6 cycloalkyl.

6. The compound of claim 1 or claim 2, where R_1 is halogen or CF_3; R_2 is H or F; R' is H; R_3 and R_4 are, independently, H, CH_3, OCH_3, CF_3, OCF_3, or Cl; and 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, $(CHR_6)_wAr$, $CH_2(CHR_6)_wAr$, or $(CHR_6)_wCH_2Ar$.

7. The compound of claim 1 which is a compound of formula IA-1

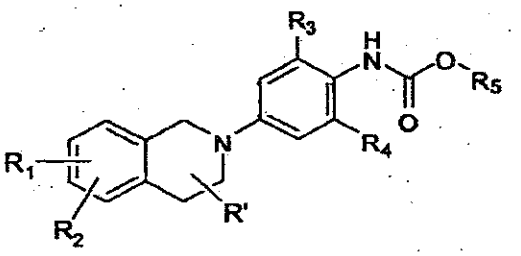


IA-1

where R_1 is H, halogen, CN, CH_2CN, CF_3, C_1-C_6 alkyl, OCH_3, (C=O)OCH_3, O(C=O)CH_3, OCF_3, $(CH_2)_mC_3$-C_6 cycloalkyl, phenyl, or pyridyl; R_2 is H, F, OCH_3, CH_3, or CF_3; R_3 and R_4 are, independently, H, F, Cl, CF_3, OCF_3, OC_1-C_3 alkyl, or C_1-C_3; and 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, $(CHR_6)_wAr$, $CH_2(CHR_6)_wAr$, or $(CHR_6)_wCH_2Ar$, where w = 0 – 3, Ar is phenyl, furyl, pyrrolyl, oxazolyl, thiazolyl, thienyl, or pyridyl; and R_6 is C_1-C_3 alkyl; where all alkyl, cycloalkyl, aryl, and heteroaryl groups in R_1, R_2, R_3, R_4, R_5, R_6, and Ar are optionally substituted with one or two substituents selected independently from C_1-C_3 alkyl, halogen, OCH_3, OCH_2CH_3, CN, and CF_3.

8. The compound of claim 7, where R_1 is H, F, Cl, Br, CF_3, C_1-C_6 alkyl, OCH_3, CH_2OCH_3, $CH_2CH_2OCH_3$, $CH_2OCH_2CH_3$, OCH_2CH_3, or CH_2OCH_3; R' is H, CH_3, CH_2CH_3, or halogen; R_3 and R_4 are, independently, H, F, Cl, CF_3, OCF_3, OCH_3, or CH_3; and R_5 is C_1-C_6 alkyl, CH_2C_3-C_6 cycloalkyl, $CH_2CH_2C_3$-C_6 cycloalkyl, CH=CH-C_3-C_6 cycloalkyl, CH=CH-C_5-C_6 cycloalkenyl, CH_2C_5-C_6 cycloalkenyl, $CH_2CH_2C_5$-C_6 cycloalkenyl, C_2-C_6 alkenyl, or $(CH_2)_wAr$, where w = 1 or 2; Ar is phenyl, oxazolyl, thiazolyl, isoxazolyl, isothiazolyl, furyl, thienyl, pyrrolyl, or pyridyl; where all alkyl, cycloalkyl, aryl, and heteroaryl groups in R_1, R_2, R_3, R_4, R_5, R_6, and Ar are optionally substituted with one or two substituents selected independently from CH_3, halogen, OCH_3, OCH_2CH_3, CN, and CF_3.

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



IA-2

where R_1 and R_2, are, independently, H, halogen, CH_2CN, CF_3, C_1-C_6 alkyl, $(CH_2)_mC_3$-C_6 cycloalkyl, or phenyl, said alkyl and cycloalkyl groups optionally substituted with one or two groups selected, independently, from OH, halogen, CN, CH_3, CH_2CH_3, or CF_3, where m is zero, 1, or 2; R' is H, F, Cl, or C_1-C_3 alkyl; where R_3 and R_4 are, independently, H, F, Cl, CF_3, OCF_3, OCH_3, or C_1-C_3 alkyl, all said 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 CF_3; 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, $(CHR_6)_wAr$, $CH_2(CHR_6)_wAr$, or $(CHR_6)_wCH_2Ar$, where w = 0 – 3, Ar is phenyl, furyl, pyrrolyl, or pyridyl; R_6 is C_1-C_3 alkyl; where all alkyl, cycloalkyl, aryl, and heteroaryl

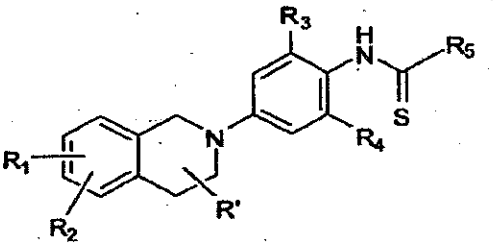
groups in R_4, R_5, R_6, and Ar are optionally substituted with one or two substituents selected independently from C_1-C_3 alkyl, halogen, OMe, OEt, CN, and CF_3.

10. The compound of claim 8, where R_1 is F, CF_3, Cl, CH_3, CH_2CH_3, SCH_3, OCH_3, CH_2OCH_3, $CH_2OCH_2CH_3$, OCF_3, phenyl, thienyl, or H; R_2 is H, F, Cl, or OCH_3; R' is H, F, CH_2CH_3, or CH_3; R_3 and R_4 are, independently, H, Cl, CH_3, CF_3, OCH_3, or OCF_3; and R_5 is C_4-C_6 alkyl, $(CH_2)_wAr$, or $(CH_2)_wC_5$-C_6 cycloalkyl, where w is 1, 2, or 3.

11. The compound of claim 10, where R_1 is F, CF_3, Cl, CH_3, OCH_3, CH_2OCH_3, or H; R_2 is H, F, CH_3, or Cl; R' is H; R_3 is H, Cl, CH_3, CF_3, OCH_3, or OCF_3; R_4 is Cl, OCH_3, or CH_3; and R_5 is C_4-C_6 alkyl or 2-cyclopentyl ethyl.

12. The compound of claim 11, where R_3 and R_4 are both CH_3 or both OCH_3; and R_5 is C_5-C_6 alkyl.

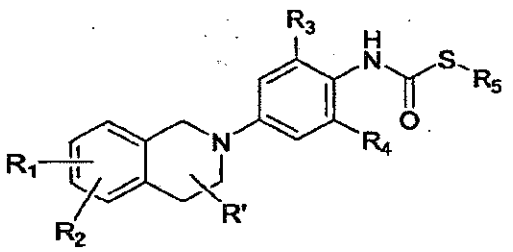
13. The compound of claim 1 which is a compound of formula IA-3



IA-3

where R_1 is F, CF_3, Cl, CH_3, CH_2CH_3, SCH_3, OCH_3, CH_2OCH_3, $CH_2OCH_2CH_3$, OCF_3, phenyl, thienyl, or H; R_2 is H, F, Cl, or methyl; R' is H, F, ethyl, or methyl; R_3 and R_4 are, independently, H, Cl, CH_3, CF_3, OCH_3, or OCF_3; and R_5 is C_4-C_6 alkyl, $(CH_2)_wAr$, or $(CH_2)_wC_5$-C_6 cycloalkyl, where w is 1, 2, or 3.

14. The compound of claim 1 which is a compound of formula IA-4



IA-4

where R_1 is F, CF_3, Cl, CH_3, CH_2CH_3, SCH_3, OCH_3, CH_2OCH_3, $CH_2OCH_2CH_3$, OCF_3, phenyl, thienyl, or H; R_2 is H, F, Cl, or methyl; R' is H, F, ethyl, or methyl; R_3 and R_4 are, independently, H, Cl, CH_3, CF_3, OCH_3, or OCF_3; and R_5 is C_4-C_6 alkyl, $(CH_2)_wAr$ or $(CH_2)_wC_5$-C_6 cycloalkyl, where w is 1, 2, or 3.

15. The compound of claim 3, where R' and R_2 are H; R_3 and R_4 are both methyl; and R_5 is C_5-C_6 alkyl or $(CH_2)_wC_5$-C_6 cycloalkyl, where w is 1, 2, or 3.

16. A composition comprising a pharmaceutically acceptable carrier and one or more of the following:

i. a compound of formula IA;

ii. a pharmaceutically acceptable solvate of a compound of formula IA;

iii. a pharmaceutically acceptable salt of a compound of formula IA; and

iv. a pharmaceutically acceptable ester of a compound of formula IA.

17. The composition of claim 16, wherein the compound of formula IA is a compound of formula IA-1.

18. The composition according to either of claims 16 or 17, where R_1 is F, CF_3, Cl, or H; R_2 is H; R' is H; R_3 and R_4 are CH_3 or OCH_3; and R_5 is C_4-C_6 alkyl or 2-cyclopentyl ethyl.

19. A compound which is one of the following:

N-(2-chloro-4-(3,4-dihydroisoquinolin-2(*1H*)-yl)-6-(trifluoromethyl)phenyl)-3,3-dimethylbutanamide

N-(4-(3,4-dihydroisoquinolin-2(*1H*)-yl)-2,6-dimethylphenyl)-3,3-dimethylbutanamide

N-(2-chloro-4-(3,4-dihydroisoquinolin-2(*1H*)-yl)-6-(trifluoromethyl)phenyl)-3-cyclopentylpropanamide

N-(2-chloro-4-(6-fluoro-3,4-dihydroisoquinolin-2(*1H*)-yl)-6-(trifluoromethylphenyl)-3,3-dimethylbutanamide

N-[2-chloro-4-(3,4-dihydro-*1H*-isoquinolin-2-yl)-6-methyl phenyl]-3,3-dimethylbutanamide

N-[2-chloro-4-(6-fluoro-3,4-dihydro-*1H*-isoquinolin-2-yl)-6-trifluoromethyl phenyl]-3-cyclopentylpropionamide

N-[2,6-dimethyl-4-(6-trifluoromethyl-3,4-dihydro-*1H*-isoquinolin-2-yl)-phenyl]-3,3-dimethylbutanamide

N-[2-chloro-6-trifluoromethyl-4-(6-trifluoromethyl-3,4-dihydro-*1H*-isoquinolin-2-yl)-phenyl]-3,3-dimethylbutanamide

N-[2-chloro-4-(6-chloro-3,4-dihydro-*1H*-isoquinolin-2-yl)-6-trifluoromethyl phenyl]-3,3-dimethylbutanamide

N-[4-(6-chloro-3,4-dihydro-*1H*-isoquinolin-2-yl)-2,6-dimethyl-phenyl]-3,3-dimethylbutanamide

N-[4-(6-fluoro-3,4-dihydro-*1H*-isoquinolin-2-yl)-2,6-dimethyl phenyl]-3,3-dimethylbutanamide

N-[2-chloro-4-(7-fluoro-3,4-dihydro-*1H*-isoquinolin-2-yl)-6-trifluoromethyl-phenyl]-3,3-dimethylbutanamide

N-[4-(7-fluoro-3,4-dihydro-*1H*-isoquinolin-2-yl)-2,6-dimethyl-phenyl]-3,3-dimethylbutanamide

N-[2-chloro-4-(6-fluoro-3,4-dihydro-*1H*-isoquinolin-2-yl)-6-methylphenyl]-3,3-dimethylbutanamide

N-[2-chloro-4-(7-fluoro-3,4-dihydro-*1H*-isoquinolin-2-yl)-6-methylphenyl]-3,3-dimethylbutanamide

N-[2-chloro-6-methyl-4-(6-trifluoromethyl-3,4-dihydro-*1H*-isoquinolin-2-yl)-phenyl]-3,3-dimethylbutanamide

N-[2-chloro-4-(6-chloro-3,4-dihydro-*1H*-isoquinolin-2-yl)-6-methyl-phenyl]-3,3-dimethylbutanamide

N-[2-chloro-4-(6-fluoro-3,4-dihydro-*1H*-isoquinolin-2-yl)-phenyl]-3,3-dimethylbutanamide

N-[4-(6-fluoro-3,4-dihydro-*1H*-isoquinolin-2-yl)-2-methyl-phenyl]-3,3-dimethylbutanamide

N-[4-(6-fluoro-3,4-dihydro-*1H*-isoquinolin-2-yl)-2-trifluoromethylphenyl]-3,3-dimethylbutanamide

N-[2-chloro-4-(6-trifluoromethyl-3,4-dihydro-*1H*-isoquinolin-2-yl)-phenyl]-3,3-dimethylbutanamide

N-[4-(7-fluoro-3,4-dihydro-*1H*-isoquinolin-2-yl)-2-trifluoromethyl-phenyl]-3,3-dimethylbutanamide

3,3-dimethyl-N-[2-trifluoromethyl-4-(7-trifluoromethyl-3,4-dihydro-*1H*-isoquinolin-2-yl)-phenyl]butanamide

N-[4-(6-methoxy-3,4-dihydro-*1H*-isoquinolin-2-yl)-2,6-dimethyl-phenyl]-3,3-dimethylbutanamide

N-[4-(3,4-dihydro-*1H*-isoquinolin-2-yl)-2-methoxy-6-methyl-phenyl]-3,3-dimethylbutanamide

N-[2-chloro-4-(3,4-dihydro-*1H*-isoquinolin-2-yl)-6-trifluoromethoxy-phenyl]-3,3-dimethylbutanamide, and

N-[4-(3,4-dihydro-*1H*-isoquinolin-2-yl)-2,6-dimethoxy-phenyl]-3,3-dimethylbutanamide.

20. The composition of claim 16, where the compound of formula IA is chosen from the following:

N-(2-chloro-4-(3,4-dihydroisoquinolin-2(*1H*)-yl)-6-(trifluoromethyl)phenyl)-3,3-dimethyl butanamide

N-(4-(3,4-dihydroisoquinolin-2(*1H*)-yl)-2,6-dimethylphenyl)-3,3-dimethylbutanamide

N-(2-chloro-4-(3,4-dihydroisoquinolin-2(*1H*)-yl)-6-(trifluoromethyl)phenyl)-3-cyclopentylpropanamide

N-(2-chloro-4-(6-fluoro-3,4-dihydroisoquinolin-2(*1H*)-yl)-6-(trifluoromethyl phenyl)-3,3-dimethylbutanamide

N-[2-chloro-4-(3,4-dihydro-*1H*-isoquinolin-2-yl)-6-methyl phenyl]-3,3-dimethylbutanamide

N-[2-chloro-4-(6-fluoro-3,4-dihydro-*1H*-isoquinolin-2-yl)-6-trifluoromethyl phenyl]-3-cyclopentylpropionamide

N-[2,6-dimethyl-4-(6-trifluoromethyl-3,4-dihydro-*1H*-isoquinolin-2-yl)-phenyl]-3,3-dimethylbutanamide

N-[2-chloro-6-trifluoromethyl-4-(6-trifluoromethyl-3,4-dihydro-*1H*-isoquinolin-2-yl)-phenyl]-3,3-dimethylbutanamide

N-[2-chloro-4-(6-chloro-3,4-dihydro-*1H*-isoquinolin-2-yl)-6-trifluoromethyl phenyl]-3,3-dimethylbutanamide

N-[4-(6-chloro-3,4-dihydro-*1H*-isoquinolin-2-yl)-2,6-dimethyl-phenyl]-3,3-dimethylbutanamide

N-[4-(6-fluoro-3,4-dihydro-*1H*-isoquinolin-2-yl)-2,6-dimethyl phenyl]-3,3-dimethylbutanamide

N-[2-chloro-4-(7-fluoro-3,4-dihydro-*1H*-isoquinolin-2-yl)-6-trifluoromethyl-phenyl]-3,3-dimethylbutanamide

N-[4-(7-fluoro-3,4-dihydro-*1H*-isoquinolin-2-yl)-2,6-dimethylphenyl]-3,3-dimethylbutanamide

N-[2-chloro-4-(6-fluoro-3,4-dihydro-*1H*-isoquinolin-2-yl)-6-methylphenyl]-3,3-dimethylbutanamide

N-[2-chloro-4-(7-fluoro-3,4-dihydro-*1H*-isoquinolin-2-yl)-6-methylphenyl]-3,3-dimethylbutanamide

N-[2-chloro-6-methyl-4-(6-trifluoromethyl-3,4-dihydro-*1H*-isoquinolin-2-yl)phenyl]-3,3-dimethylbutanamide

N-[2-chloro-4-(6-chloro-3,4-dihydro-*1H*-isoquinolin-2-yl)-6-methylphenyl]-3,3-dimethylbutanamide

N-[2-chloro-4-(6-fluoro-3,4-dihydro-*1H*-isoquinolin-2-yl)phenyl]-3,3-dimethylbutanamide

N-[4-(6-fluoro-3,4-dihydro-*1H*-isoquinolin-2-yl)-2-methylphenyl]-3,3-dimethylbutanamide

N-[4-(6-fluoro-3,4-dihydro-*1H*-isoquinolin-2-yl)-2-trifluoromethylphenyl]-3,3-dimethylbutanamide

N-[2-chloro-4-(6-trifluoromethyl-3,4-dihydro-*1H*-isoquinolin-2-yl)phenyl]-3,3-dimethylbutanamide

N-[4-(7-fluoro-3,4-dihydro-*1H*-isoquinolin-2-yl)-2-trifluoromethylphenyl]-3,3-dimethylbutanamide

3,3-dimethyl-N-[2-trifluoromethyl-4-(7-trifluoromethyl-3,4-dihydro-*1H*-isoquinolin-2-yl)-phenyl]butanamide

N-[4-(6-methoxy-3,4-dihydro-*1H*-isoquinolin-2-yl)-2,6-dimethylphenyl]-3,3-dimethylbutanamide

N-[4-(3,4-dihydro-*1H*-isoquinolin-2-yl)-2-methoxy-6-methylphenyl]-3,3-dimethyl-butanamide

N-[2-chloro-4-(3,4-dihydro-*1H*-isoquinolin-2-yl)-6-trifluoromethoxyphenyl]-3,3-dimethyl-butanamide, and

N-[4-(3,4-dihydro-*1H*-isoquinolin-2-yl)-2,6-dimethoxy-phenyl]-3,3-dimethylbutanamide.

21. The use of compound of formula IA or a salt or solvate thereof in the manufacture of medicament for the treatment of a disease or disorder which is affected by modulation of potassium channels.

22. The method of claim 20, where the compound of formula IA is a compound of formula IA-1.

23. The method of claim 20, where the compound of formula IA is chosen from the following:

N-(2-chloro-4-(3,4-dihydroisoquinolin-2(*1H*)-yl)-6-(trifluoromethyl)phenyl)-3,3-dimethylbutanamide

N-(4-(3,4-dihydroisoquinolin-2(*1H*)-yl)-2,6-dimethylphenyl)-3,3-dimethylbutanamide

N-(2-chloro-4-(3,4-dihydroisoquinolin-2(*1H*)-yl)-6-(trifluoromethyl)phenyl)-3-cyclopentylpropanamide

N-(2-chloro-4-(6-fluoro-3,4-dihydroisoquinolin-2(*1H*)-yl)-6-(trifluoromethylphenyl)-3,3-dimethylbutanamide

N-[2-chloro-4-(3,4-dihydro-*1H*-isoquinolin-2-yl)-6-methylphenyl]-3,3-dimethyl-butanamide

N-[2-chloro-4-(6-fluoro-3,4-dihydro-*1H*-isoquinolin-2-yl)-6-trifluoromethylphenyl]-3-cyclopentylpropionamide

N-[2,6-dimethyl-4-(6-trifluoromethyl-3,4-dihydro-*1H*-isoquinolin-2-yl)phenyl]-3,3-dimethylbutanamide

N-[2-chloro-6-trifluoromethyl-4-(6-trifluoromethyl-3,4-dihydro-*1H*-isoquinolin-2-yl)-phenyl]-3,3-dimethylbutanamide

N-[2-chloro-4-(6-chloro-3,4-dihydro-*1H*-isoquinolin-2-yl)-6-trifluoromethylphenyl]-3,3-dimethyl butanamide

N-[4-(6-chloro-3,4-dihydro-*1H*-isoquinolin-2-yl)-2,6-dimethylphenyl]-3,3-dimethylbutanamide

N-[4-(6-fluoro-3,4-dihydro-*1H*-isoquinolin-2-yl)-2,6-dimethylphenyl]-3,3-dimethylbutanamide

N-[2-chloro-4-(7-fluoro-3,4-dihydro-*1H*-isoquinolin-2-yl)-6-trifluoromethylphenyl]-3,3-dimethylbutanamide

N-[4-(7-fluoro-3,4-dihydro-*1H*-isoquinolin-2-yl)-2,6-dimethylphenyl]-3,3-dimethylbutanamide

N-[2-chloro-4-(6-fluoro-3,4-dihydro-*1H*-isoquinolin-2-yl)-6-methylphenyl]-3,3-dimethylbutanamide

N-[2-chloro-4-(7-fluoro-3,4-dihydro-*1H*-isoquinolin-2-yl)-6-methylphenyl]-3,3-dimethylbutanamide

N-[2-chloro-6-methyl-4-(6-trifluoromethyl-3,4-dihydro-*1H*-isoquinolin-2-yl)phenyl]-3,3-dimethylbutanamide

N-[2-chloro-4-(6-chloro-3,4-dihydro-*1H*-isoquinolin-2-yl)-6-methylphenyl]-3,3-dimethylbutanamide

N-[2-chloro-4-(6-fluoro-3,4-dihydro-*1H*-isoquinolin-2-yl)phenyl]-3,3-dimethylbutanamide

N-[4-(6-fluoro-3,4-dihydro-*1H*-isoquinolin-2-yl)-2-methylphenyl]-3,3-dimethylbutanamide

N-[4-(6-fluoro-3,4-dihydro-*1H*-isoquinolin-2-yl)-2-trifluoromethylphenyl]-3,3-dimethylbutanamide

N-[2-chloro-4-(6-trifluoromethyl-3,4-dihydro-*1H*-isoquinolin-2-yl)phenyl]-3,3-dimethylbutanamide

N-[4-(7-fluoro-3,4-dihydro-*1H*-isoquinolin-2-yl)-2-trifluoromethylphenyl]-3,3-dimethylbutanamide

3,3-dimethyl-N-[2-trifluoromethyl-4-(7-trifluoromethyl-3,4-dihydro-*1H*-isoquinolin-2-yl)-phenyl]butanamide

N-[4-(6-methoxy-3,4-dihydro-*1H*-isoquinolin-2-yl)-2,6-dimethylphenyl]-3,3-dimethylbutanamide

N-[4-(3,4-dihydro-*1H*-isoquinolin-2-yl)-2-methoxy-6-methylphenyl]-3,3-dimethylbutanamide

N-[2-chloro-4-(3,4-dihydro-*1H*-isoquinolin-2-yl)-6-trifluoromethoxyphenyl]-3,3-dimethylbutanamide, and

N-[4-(3,4-dihydro-*1H*-isoquinolin-2-yl)-2,6-dimethoxyphenyl]-3,3-dimethylbutanamide.

24. The use of compound of formula IA or a salt or ester or solvate thereof in the manufacture of medicament for the treatment of a disease or disorder which is affected by activation of voltage-gated potassium channels.

25. The use of compound of formula IA, a salt of compound 1A or a solvate of compound of formula IA in the manufacture of medicament for the treatment of a seizure or seizure disorder.

26. The use of compound of formula IA or a salt or solvate thereof in the manufacture of medicament for the treatment or prevention of a disorder characterized by hyperexcitability of the nervous system.

27. The use of compound of formula IA-1 or salt or solvate thereof in the manufacture of medicament for increasing the channel open probability of KCNQ2/3 channels in a mammal.

28. The use of compound of formula IA-1 or salt, solvate, or ester thereof in the manufacture of medicament for increasing neuronal M currents in a mammal.

29. The use of any of claims 24, 25, and 26, where the compound of formula IA is a compound of formula IA-I.

30. The use of any of claims 24, 25, 26, 27, or 28 where the compound used is a compound chosen from the following:

N-(2-chloro-4-(3,4-dihydroisoquinolin-2(*1H*)-yl)-6-(trifluoromethyl)phenyl)-3,3-dimethylbutanamide

N-(4-(3,4-dihydroisoquinolin-2(*1H*)-yl)-2,6-dimethylphenyl)-3,3-dimethylbutanamide

N-(2-chloro-4-(3,4-dihydroisoquinolin-2(*1H*)-yl)-6-(trifluoromethyl)phenyl)-3-cyclopentylpropanamide

N-(2-chloro-4-(6-fluoro-3,4-dihydroisoquinolin-2(*1H*)-yl)-6-(trifluoromethylphenyl)-3,3-dimethylbutanamide

N-[2-chloro-4-(3,4-dihydro-*1H*-isoquinolin-2-yl)-6-methylphenyl]-3,3-dimethylbutanamide

N-[2-chloro-4-(6-fluoro-3,4-dihydro-*1H*-isoquinolin-2-yl)-6-trifluoromethylphenyl]-3-cyclopentylpropionamide

N-[2,6-dimethyl-4-(6-trifluoromethyl-3,4-dihydro-*1H*-isoquinolin-2-yl)-phenyl]-3,3-dimethylbutanamide

N-[2-chloro-6-trifluoromethyl-4-(6-trifluoromethyl-3,4-dihydro-*1H*-isoquinolin-2-yl)-phenyl]-3,3-dimethylbutanamide

N-[2-chloro-4-(6-chloro-3,4-dihydro-*1H*-isoquinolin-2-yl)-6-trifluoromethylphenyl]-3,3-dimethylbutanamide

N-[4-(6-chloro-3,4-dihydro-*1H*-isoquinolin-2-yl)-2,6-dimethylphenyl]-3,3-dimethylbutanamide

N-[4-(6-fluoro-3,4-dihydro-*1H*-isoquinolin-2-yl)-2,6-dimethylphenyl]-3,3-dimethylbutanamide

N-[2-chloro-4-(7-fluoro-3,4-dihydro-*1H*-isoquinolin-2-yl)-6-trifluoromethylphenyl]-3,3-dimethylbutanamide

N-[4-(7-fluoro-3,4-dihydro-*1H*-isoquinolin-2-yl)-2,6-dimethylphenyl]-3,3-dimethylbutanamide

N-[2-chloro-4-(6-fluoro-3,4-dihydro-*1H*-isoquinolin-2-yl)-6-methylphenyl]-3,3-dimethylbutanamide

N-[2-chloro-4-(7-fluoro-3,4-dihydro-*1H*-isoquinolin-2-yl)-6-methylphenyl]-3,3-dimethylbutanamide

N-[2-chloro-6-methyl-4-(6-trifluoromethyl-3,4-dihydro-*1H*-isoquinolin-2-yl)phenyl]-3,3-dimethylbutanamide

N-[2-chloro-4-(6-chloro-3,4-dihydro-*1H*-isoquinolin-2-yl)-6-methylphenyl]-3,3-dimethylbutanamide

N-[2-chloro-4-(6-fluoro-3,4-dihydro-*1H*-isoquinolin-2-yl)phenyl]-3,3-dimethylbutanamide

N-[4-(6-fluoro-3,4-dihydro-*1H*-isoquinolin-2-yl)-2-methylphenyl]-3,3-dimethylbutanamide

N-[4-(6-fluoro-3,4-dihydro-*1H*-isoquinolin-2-yl)-2-trifluoromethylphenyl]-3,3-dimethylbutanamide

N-[2-chloro-4-(6-trifluoromethyl-3,4-dihydro-*1H*-isoquinolin-2-yl)phenyl]-3,3-dimethylbutanamide

N-[4-(7-fluoro-3,4-dihydro-*1H*-isoquinolin-2-yl)-2-trifluoromethylphenyl]-3,3-dimethylbutanamide

3,3-dimethyl-N-[2-trifluoromethyl-4-(7-trifluoromethyl-3,4-dihydro-*1H*-isoquinolin-2-yl)-phenyl]butanamide

N-[4-(6-methoxy-3,4-dihydro-*1H*-isoquinolin-2-yl)-2,6-dimethylphenyl]-3,3-dimethylbutanamide

N-[4-(3,4-dihydro-*1H*-isoquinolin-2-yl)-2-methoxy-6-methylphenyl]-3,3-dimethylbutanamide

N-[2-chloro-4-(3,4-dihydro-*1H*-isoquinolin-2-yl)-6-trifluoromethoxyphenyl]-3,3-dimethyl-butanamide, and

N-[4-(3,4-dihydro-*1H*-isoquinolin-2-yl)-2,6-dimethoxyphenyl]-3,3-dimethylbutanamide.

31. The use of compound of formula IA or a salt or solvate thereof in the manufacture of medicament for the treatment or prevention of a disease or disorder which is affected by modulation of potassium channels.

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

33. The method of claim 20, where the compound of formula IA is chosen from the following:

N-(2-chloro-4-(3,4-dihydroisoquinolin-2(*1H*)-yl)-6-(trifluoromethyl)phenyl)-3,3-dimethylbutanamide

N-(4-(3,4-dihydroisoquinolin-2(*1H*)-yl)-2,6-dimethylphenyl)-3,3-dimethylbutanamide

N-(2-chloro-4-(3,4-dihydroisoquinolin-2(*1H*)-yl)-6-(trifluoromethyl)phenyl)-3-cyclopentylpropanamide

N-(2-chloro-4-(6-fluoro-3,4-dihydroisoquinolin-2(*1H*)-yl)-6-(trifluoromethylphenyl)-3,3-dimethylbutanamide

N-[2-chloro-4-(3,4-dihydro-*1H*-isoquinolin-2-yl)-6-methylphenyl]-3,3-dimethyl-butanamide

N-[2-chloro-4-(6-fluoro-3,4-dihydro-*1H*-isoquinolin-2-yl)-6-trifluoromethylphenyl]-3-cyclopentylpropionamide

N-[2,6-dimethyl-4-(6-trifluoromethyl-3,4-dihydro-*1H*-isoquinolin-2-yl)phenyl]-3,3-dimethylbutanamide

N-[2-chloro-6-trifluoromethyl-4-(6-trifluoromethyl-3,4-dihydro-*1H*-isoquinolin-2-yl)-phenyl]-3,3-dimethylbutanamide

N-[2-chloro-4-(6-chloro-3,4-dihydro-*1H*-isoquinolin-2-yl)-6-trifluoromethylphenyl]-3,3-dimethylbutanamide

N-[4-(6-chloro-3,4-dihydro-*1H*-isoquinolin-2-yl)-2,6-dimethylphenyl]-3,3-dimethylbutanamide

N-[4-(6-fluoro-3,4-dihydro-*1H*-isoquinolin-2-yl)-2,6-dimethylphenyl]-3,3-dimethylbutanamide

N-[2-chloro-4-(7-fluoro-3,4-dihydro-*1H*-isoquinolin-2-yl)-6-trifluoromethylphenyl]-3,3-dimethylbutanamide

N-[4-(7-fluoro-3,4-dihydro-*1H*-isoquinolin-2-yl)-2,6-dimethylphenyl]-3,3-dimethylbutanamide

N-[2-chloro-4-(6-fluoro-3,4-dihydro-*1H*-isoquinolin-2-yl)-6-methylphenyl]-3,3-dimethylbutanamide

N-[2-chloro-4-(7-fluoro-3,4-dihydro-*1H*-isoquinolin-2-yl)-6-methylphenyl]-3,3-dimethylbutanamide

N-[2-chloro-6-methyl-4-(6-trifluoromethyl-3,4-dihydro-*1H*-isoquinolin-2-yl)phenyl]-3,3-dimethylbutanamide

N-[2-chloro-4-(6-chloro-3,4-dihydro-*1H*-isoquinolin-2-yl)-6-methylphenyl]-3,3-dimethylbutanamide

N-[2-chloro-4-(6-fluoro-3,4-dihydro-*1H*-isoquinolin-2-yl)phenyl]-3,3-dimethylbutanamide

N-[4-(6-fluoro-3,4-dihydro-*1H*-isoquinolin-2-yl)-2-methylphenyl]-3,3-dimethylbutanamide

N-[4-(6-fluoro-3,4-dihydro-*1H*-isoquinolin-2-yl)-2-trifluoromethylphenyl]-3,3-dimethylbutanamide

N-[2-chloro-4-(6-trifluoromethyl-3,4-dihydro-*1H*-isoquinolin-2-yl)phenyl]-3,3-dimethylbutanamide

N-[4-(7-fluoro-3,4-dihydro-*1H*-isoquinolin-2-yl)-2-trifluoromethylphenyl]-3,3-dimethylbutanamide

3,3-dimethyl-N-[2-trifluoromethyl-4-(7-trifluoromethyl-3,4-dihydro-*1H*-isoquinolin-2-yl)-phenyl]butanamide

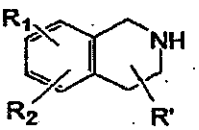
N-[4-(6-methoxy-3,4-dihydro-*1H*-isoquinolin-2-yl)-2,6-dimethylphenyl]-3,3-dimethylbutanamide

N-[4-(3,4-dihydro-*1H*-isoquinolin-2-yl)-2-methoxy-6-methy-phenyl]-3,3-dimethylbutanamide

N-[2-chloro-4-(3,4-dihydro-*1H*-isoquinolin-2-yl)-6-trifluoromethoxyphenyl]-3,3-dimethylbutanamide, and

N-[4-(3,4-dihydro-*1H*-isoquinolin-2-yl)-2,6-dimethoxyphenyl]-3,3-dimethylbutanamide.

34. The product resulting from the reaction of N-(4-bromo-2,6-dimethyl-phenyl)-3,3-dimethyl-butanamide with a tetrahydroisoquinoline derivative of formula Q below, in



Q

where R_1 and R_2, are, independently, H, CN, halogen, CH_2CN, OH, NO_2, CH_2F, CHF_2, CF_3, CF_2CF_3, C_1-C_6 alkyl, C(=O)C_1-C_6 alkyl; NH_2, NH-C_1-C_6 alkyl; N(C_1-C_6 alkyl)-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_2, C(=O)NH-C_1-C_6 alkyl, SO_2NH_2, $NHSO_2$-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)_m$$C_3$-$C_6$ cycloalkyl, C_3-C_6 cycloalkenyl, $(CH_2)_m$$C_3$-$C_6$ cycloalkenyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, $(CH_2)_m$thienyl, $(CH_2)_m$furyl, $(CH_2)_m$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 $(CH_2)_m$pyrimidyl, which cycloalkyl and said cycloalkenyl groups optionally contain one or two heteroatoms selected independently from O, N, and S; 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; R' is H, halogen, phenyl, 2-(N,N-dimethylamino)ethyl, CF_3, OC_1-C_3 alkyl or C_1-C_3 alkyl; where all alkyl, cycloalkyl, alkenyl, cycloalkenyl, heterocycloalkyl, heterocycloalkenyl, alkynyl, aryl, and heteroaryl groups in R_1, R_2, and R' are optionally substituted with one or two substituents selected independently from C_1-C_3 alkyl, halogen, CN, OH, OMe, OEt, CN, CH_2F, and trifluoromethyl; and where, additionally, all cycloalkyl and heterocycloalkyl groups are optionally substituted with a carbonyl group; in the presence of bis(dibenzylidineacetone)palladium, (2'-dicyclohexyl phosphanyl-biphenyl-2-yl)-dimethylamine, and potassium t-butoxide in dry toluene.

35. The product of claim 31, where R' is H, halogen, CF_3, OC_1-C_3 alkyl or C_1-C_3 alkyl.

36. A composition comprising a pharmaceutically acceptable carrier or diluent, a syrup for pediatric use, and a pharmaceutically effective amount of at least one of the following: a compound of formula IA, a pharmaceutically acceptable salt of a compound of formula IA, and a pharmaceutically acceptable solvate of a compound of formula I.

37. A tablet comprising a pharmaceutically acceptable carrier or diluent, and a pharmaceutically effective amount of at least one of the following: a compound of

formula IA-1, a pharmaceutically acceptable salt of a compound of formula IA-1, and a pharmaceutically acceptable solvate of a compound of formula IA-1.

38. The tablet of claim 32, where the tablet is chewable.

39. A capsule comprising a pharmaceutically acceptable carrier or diluent, and a pharmaceutically effective amount of at least one of the following: a compound of formula IA-1, a pharmaceutically acceptable salt of a compound of formula IA-1, and a pharmaceutically acceptable solvate of a compound of formula IA-1.

40. The compound of claim 1 which is a compound of formula IA-1, where R_1 and R_2 form a fused 5- or 6- member ring, optionally substituted with methyl or halogen, and where R_3 and R_4 are, independently, H, F, Cl, CF_3, OCF_3, OC_1-C_3 alkyl, or C_1-C_3; and 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, $(CHR_6)_wAr$, $CH_2(CHR_6)_wAr$, or $(CHR_6)_wCH_2Ar$, where $w = 0-3$, Ar is phenyl, furyl, pyrrolyl, oxazolyl, thiazolyl, thienyl, or pyridyl; and R_6 is C_1-C_3 alkyl; where all alkyl, cycloalkyl, aryl, and heteroaryl groups in R_3, R_4, R_5, R_6, and Ar are optionally substituted with one or two substituents selected independently from C_1-C_3 alkyl, halogen, OCH_3, OCH_2CH_3, CN, and CF_3.

41. The use of compound of formula IA in an amount of from about 10 mg to about 2000 mg per day in the manufacture of medicament for the treatment or prevention of a disease, disorder, or condition that is affected by modulation of potassium ion channels .