OPHTHALMIC COMPOSITIONS FOR TREATING OCULAR HYPERTENSION

This application claims the benefit under 35 U.S.C. 119(e) of U.S. Provisional Application No. 60/500,095 filed 9/4/2003.

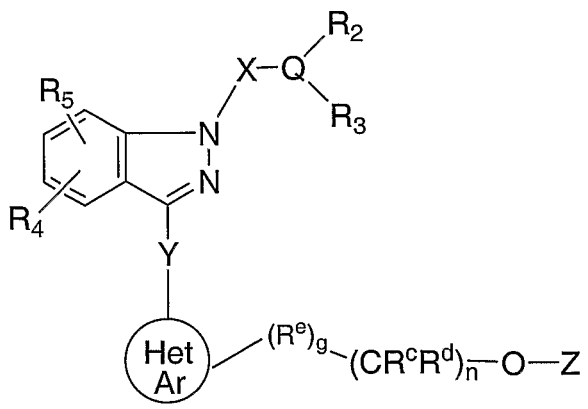
BACKGROUND OF THE INVENTION

Glaucoma is a degenerative disease of the eye wherein the intraocular pressure is too high to permit normal eye function. As a result, damage may occur to the optic nerve head and result in irreversible loss of visual function. If untreated, glaucoma may eventually lead to blindness. Ocular hypertension, i.e., the condition of elevated intraocular pressure without optic nerve head damage or characteristic glaucomatous visual field defects, is now believed by the majority of ophthalmologists to represent merely the earliest phase in the onset of glaucoma.

There are several therapies for treating glaucoma and elevated intraocular pressure, but the efficacy and the side effect profiles of these agents are not ideal. Recently potassium channel blockers were found to reduce intraocular pressure in the eye and therefore provide yet one more approach to the treatment of ocular hypertension and the degenerative ocular conditions related thereto. Blockage of potassium channels can diminish fluid secretion, and under some circumstances, increase smooth muscle contraction and would be expected to lower IOP and have neuroprotective effects in the eye. (see US Patent Nos. 5,573,758 and 5,925,342; Moore, et al., Invest. Ophthalmol. Vis. Sci 38, 1997; WO 89/10757, WO94/28900, and WO 96/33719).

SUMMARY OF THE INVENTION

This invention relates to the use of potent potassium channel blockers or a formulation thereof in the treatment of glaucoma and other conditions which are related to elevated intraocular pressure in the eye of a patient. This invention also relates to the use of such compounds to provide a neuroprotective effect to the eye of mammalian species, particularly humans. More particularly this invention relates to the treatment of glaucoma and/or ocular hypertension (elevated intraocular pressure) using novel phosphate containing indazole compounds having the structural formula I:



Formula I

or a pharmaceutically acceptable salt, *in vivo* hydrolysable ester, enantiomer, diastereomer or mixture thereof:
wherein,

R represents hydrogen, or C_{1-6} alkyl;

R^c and R^d independently represent hydrogen or halo;

R^e represents N or O;

X represents $-(CHR_7)_p-$, $-(CHR_7)_pCO-$;

Y represents $-CO(CH_2)_n-$, CH_2, or -CH(OR)-;

Q represents CR^y;

R^y represents H, or C_{1-6} alkyl;

R_w represents H, C_{1-6} alkyl, $-C(O)C_{1-6}$ alkyl, $-C(O)OC_{1-6}$ alkyl, $-SO_2N(R)_2$, $-SO_2C_{1-6}$ alkyl, $-SO_2C_{6-10}$ aryl, NO_2, CN or $-C(O)N(R)_2$;

R_2 represents hydrogen, C_{1-10} alkyl, OH, C_{2-6} alkenyl, C_{1-6} alkylSR, $-(CH_2)_nO(CH_2)_mOR$, $-(CH_2)_nC_{1-6}$ alkoxy, $-(CH_2)_nC_{3-8}$ cycloalkyl, $-(CH_2)_nC_{3-10}$ heterocyclyl, $-N(R)_2$, -COOR, or -

$(CH_2)_nC_{6-10}$ aryl, said alkyl, heterocyclyl, or aryl optionally substituted with 1-3 groups selected from R^a;

R_3 represents hydrogen, C_{1-10} alkyl, $-(CH_2)_nC_{3-8}$ cycloalkyl, $-(CH_2)_nC_{3-10}$ heterocyclyl, $-(CH_2)_nCOOR$, $-(CH_2)_nC_{6-10}$ aryl, $-(CH_2)_nNHR_8$, $-(CH_2)_nN(R)_2$, $-(CH_2)_nN(R_8)_2$, $-(CH_2)_nNHCOOR$, $-(CH_2)_nN(R_8)CO_2R$, $-(CH_2)_nN(R_8)COR$, $-(CH_2)_nNHCOR$, $-(CH_2)_nCONH(R_8)$, aryl, $-(CH_2)_nC_{1-6}$ alkoxy, CF_3, $-(CH_2)_nSO_2R$, $-(CH_2)_nSO_2N(R)_2$, $-(CH_2)_nCON(R)_2$, $-(CH_2)_nCONHC(R)_3$, $-(CH_2)_nCONHC(R)_2CO_2R$, $-(CH_2)_nCOR_8$, nitro, cyano or halogen, said alkyl, alkoxy, heterocyclyl, or aryl optionally substituted with 1-3 groups of R^a;

or, R_2 and R_3 taken together with the intervening Q form a 3-10 membered carbocyclic or heterocyclic carbon ring optionally interrupted by 1-2 atoms of O, S, C(O) or NR, and optionally having 1-4 double bonds, and optionally substituted by 1-3 groups selected from R^a;

R_4 and R_5 independently represent hydrogen, C_{1-6} alkoxy, OH, C_{1-6} alkyl, COOR, SO_3H, $-O(CH_2)_nN(R)_2$, $-O(CH_2)_nCO_2R$, $-OPO(OH)_2$, CF_3, OCF_3, $-N(R)_2$, nitro, cyano, C_{1-6} alkylamino, or halogen;



represents C_{6-10} aryl or C_{3-10} heterocyclyl, said aryl or heterocyclyl optionally substituted with 1-3 groups selected from R^a;

Z represents $(CH_2)_nPO(OR)(OR^*)$;

R* represents hydrogen, or C_{1-6} alkyl;

R_7 represents hydrogen, C_{1-6} alkyl, $-(CH_2)_nCOOR$ or $-(CH_2)_nN(R)_2$,

R_8 represents $-(CH_2)_nC_{3-8}$ cycloalkyl, $-(CH_2)_n$ 3-10 heterocyclyl, C_{1-6} alkoxy or $-(CH_2)_nC_{5-10}$ heteroaryl, $-(CH_2)_nC_{6-10}$ aryl said heterocyclyl, aryl or heteroaryl optionally substituted with 1-3 groups selected from R^a;

R^a represents F, Cl, Br, I, CF_3, $N(R)_2$, NO_2, CN, $-COR_8$, $-CONHR_8$, $-CON(R_8)_2$, $-O(CH_2)_nCOOR$, $-NH(CH_2)_nOR$, -COOR, $-OCF_3$, -NHCOR, $-SO_2R$, $-SO_2NR_2$, -SR, $(C_1\text{-}C_6$ alkyl)O-, $-(CH_2)_nO(CH_2)_mOR$, $-(CH_2)_nC_{1-6}$ alkoxy, (aryl)O-, $-(CH_2)_nOH$, $(C_1\text{-}C_6$ alkyl)$S(O)_m$-, H_2N-C(NH)-,

$(C_1$-C_6 alkyl)C(O)-, $(C_1$-C_6 alkyl)OC(O)NH-, -$(C_1$-C_6 alkyl)$NR_w(CH_2)_nC_{3-10}$ heterocyclyl-R_w, -$(C_1$-C_6 alkyl)$O(CH_2)_nC_{3-10}$ heterocyclyl-R_w, -$(C_1$-C_6 alkyl)$S(CH_2)_nC_{3-10}$ heterocyclyl-R_w, -$(C_1$-C_6 alkyl)-C_{3-10} heterocyclyl-R_w, -$(CH_2)_n$-Z^1-C(=Z^2)N(R)$_2$, -$(C_{2-6}$ alkenyl)$NR_w(CH_2)_nC_{3-10}$ heterocyclyl-R_w, -$(C_{2-6}$ alkenyl)$O(CH_2)_nC_{3-10}$ heterocyclyl-R_w, -$(C_{2-6}$ alkenyl)$S(CH_2)_nC_{3-10}$ heterocyclyl-R_w, -$(C_{2-6}$ alkenyl)-C_{3-10} heterocyclyl-R_w, -$(C_{2-6}$ alkenyl)-Z^1-C(=Z^2)N(R)$_2$, -$(CH_2)_nSO_2R$, -$(CH_2)_nSO_3H$, -$(CH_2)_nPO(OR)_2$, C_{3-10}cycloalkyl, C_{6-10} aryl, C_{3-10} heterocyclyl, C_{2-6} alkenyl, and C_1-C_{10} alkyl, said alkyl, alkenyl, alkoxy, heterocyclyl and aryl optionally substituted with 1-3 groups selected from C_1-C_6 alkyl, CN, NO_2, OH, CON(R)$_2$ and COOR;

Z^1 and Z^2 independently represents NR_w, O, CH_2, or S;

g is 0-1;
m is 0-3;
n is 0-3; and
p is 0-3.

This and other aspects of the invention will be realized upon inspection of the invention as a whole.

DETAILED DESCRIPTION OF THE INVENTION

The present invention is directed to novel potassium channel blockers of Formula I. It also relates to a method for decreasing elevated intraocular pressure or treating glaucoma by administration, preferably topical or intra-camaral administration, of a composition containing a potassium channel blocker of Formula I described hereinabove and a pharmaceutically acceptable carrier. This invention is also concerned with the use of a compound of formula I for the manufacture of a medicament for the treatment of ocular hypertension or glaucoma.

In an embodiment of the instant compounds are those compounds where p is 1-3.

One embodiment of this invention is realized when Y is -$CO(CH_2)_n$ and all other variables are as originally described. A subembodiment of this invention is realized when n is 0.

Another embodiment of this invention is realized when Y is CH(OR) and all other variables are as originally described.

Another embodiment of this invention is realized when Z is PO(OR)(OR*) and R and R* are H. A sub-embodiment of this invention is realized when R and R* are C_{1-6} alkyl.

In another embodiment R_w is selected from H, C_{1-6} alkyl, -C(O)C_{1-6} alkyl and -C(O)N(R)$_2$ and all other variables are as originally described..

In another embodiment X is –(CHR7)$_p$-, p is 1-3 and all other variables are as originally described.

In another embodiment X is –(CHR7)$_p$CO-, p is 1-3 and all other variables are as originally described.

In another embodiment 

is a 6 membered heteroaryl or phenyl optionally substituted with 1-3 groups selected from R^a. A sub-embodiment of this invention is realized when 

is a pyridyl.

Yet another embodiment of this invention is realized when R7 is hydrogen or C_{1-6} alkyl, and all other variables are as originally described.

Still another embodiment of this invention is realized when Z is $PO_3(OR)(OR^*)$, R_2 and and R_3 independently are hydrogen, C_{1-10} alkyl or C_{1-6} alkylOH, and Y is -CO$(CH_2)_n$

Another embodiment of the instant invention is realized when R^a is selected from F, Cl, Br, I, CF_3, N(R)$_2$, NO_2, CN, -CONHR$_8$, -CON(R$_8$)$_2$, -O$(CH_2)_n$COOR, -NH$(CH_2)_n$OR, -COOR, -OCF_3, -NHCOR, -SO_2R, -SO_2NR_2, -SR, (C_1-C_6 alkyl)O-, -$(CH_2)_n$O$(CH_2)_m$OR, -$(CH_2)_n$C$_{1-6}$ alkoxy, (aryl)O-, -$(CH_2)_n$OH, (C_1-C_6 alkyl)S(O)$_m$-, H_2N-C(NH)-, (C_1-C_6 alkyl)C(O)-, -$(CH_2)_n$PO(OR)$_2$, C_{2-6} alkenyl, and C_1-C_{10} alkyl, said alkyl and alkenyl, optionally substituted with 1-3 groups selected from C_1-C_6 alkyl, and COOR;

Examples of compounds of formula I of this invention are:

di-tert--butyl 4-{[1-(3,3-dimethyl-2-oxobutyl)-6-methoxy-1-H-indazole-3-yl]carbonyl}benzylphosphate;

4-{[1-(3,3-dimethyl-2-oxybutyl)-6-methoxy-1-H-indazol-3-yl]carbonyl}benzyl di-hydrogen phosphate;

2-[(5-{[1-(3,3-dimethyl-2-oxobutyl-6-methoxy-1-H-indazol-3-yl)carbonyl}pyridine-2-yl)oxy]ethyl di-hydrogen phosphate;

(5-{[1-3,3-dimethyl-2-oxobutyl)-6-methoxy-1H-indazol-3-yl]carbonyl}pyridine-2-yl)methyl dihydrogen phosphate;

2-(5-{[1-(3,3-dimethyl-2-oxobutyl)-6-methoxy-1H-indazol-3yl]carbonyl}pyridine-2-yl)-2,2-diflouroethyl di-hydrogen phosphate; and

2-(5-{[7-bromo-1-(3,3-dimethyl-2-oxobutyl)-6-methoxy-1H-indazol-3-yl]carbonyl}puyridin-2-yl)-2,2-difluoroethyl di-hydrogen phosphate,

or a pharmaceutically acceptable salt, *in vivo* hydrolysable ester, enantiomer, diastereomer or mixture thereof. A sub-embodiment of this invention is realized when the compounds are in the form of a mono-sodium or disodium salt.

The invention is described herein in detail using the terms defined below unless otherwise specified.

The compounds of the present invention may have asymmetric centers, chiral axes and chiral planes, and occur as racemates, racemic mixtures, and as individual diastereomers, with all possible isomers, including optical isomers, being included in the present invention. (See E.L. Eliel and S.H. Wilen *Stereochemistry of Carbon Compounds* (John Wiley and Sons, New York 1994), in particular pages 1119-1190)

When any variable (e.g. aryl, heterocycle, R^1, R^6 etc.) occurs more than one time in any constituent, its definition on each occurrence is independent at every other occurrence. Also, combinations of substituents/or variables are permissible only if such combinations result in stable compounds.

The term "alkyl" refers to a monovalent alkane (hydrocarbon) derived radical containing from 1 to 10 carbon atoms unless otherwise defined. It may be straight, branched or cyclic. Preferred alkyl groups include methyl, ethyl, propyl, isopropyl, butyl, t-butyl, cyclopropyl cyclopentyl and cyclohexyl. When the alkyl group is said to be substituted with an alkyl group, this is used interchangeably with "branched alkyl group".

Cycloalkyl is a specie of alkyl containing from 3 to 15 carbon atoms, unless otherwise defined, without alternating or resonating double bonds between carbon atoms. It may contain from 1 to 4 rings, which are fused. Examples of such cycloalkyl elements include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl.

Alkenyl is C_2-C_6 alkenyl.

Alkoxy refers to an alkyl group of indicated number of carbon atoms attached through an oxygen bridge, with the alkyl group optionally substituted as described herein. Said groups are those groups of the designated length in either a straight or branched configuration and if two or more carbon atoms in length, they may include a double or a triple bond. Exemplary of such alkoxy groups are methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, tertiary butoxy, pentoxy, isopentoxy, hexoxy, isohexoxy allyloxy, propargyloxy, and the like.

Halogen (halo) refers to chlorine, fluorine, iodine or bromine.

Aryl refers to aromatic rings e.g., phenyl, substituted phenyl and the like, as well as rings which are fused, e.g., naphthyl, phenanthrenyl and the like. An aryl group thus contains at least one ring having at least 6 atoms, with up to five such rings being present, containing up to 22 atoms therein, with alternating (resonating) double bonds between adjacent carbon atoms or suitable heteroatoms. Examples of aryl groups are phenyl, naphthyl, tetrahydronaphthyl, indanyl, biphenyl, phenanthryl, anthryl or acenaphthyl and phenanthrenyl, preferably phenyl, naphthyl or phenanthrenyl. Aryl groups may likewise be substituted as defined. Preferred substituted aryls include phenyl and naphthyl.

The term heterocyclyl or heterocyclic, as used herein, represents a stable 3- to 7-membered monocyclic or stable 8- to 11-membered bicyclic heterocyclic ring which is either saturated or unsaturated, and which consists of carbon atoms and from one to four heteroatoms selected from the group consisting of N, O, and S, and including any bicyclic group in which any of the above-defined heterocyclic rings is fused to a benzene ring. The heterocyclic ring may be attached at any heteroatom or carbon atom which results in the creation of a stable structure. A fused heterocyclic ring system may include carbocyclic rings and need include only one heterocyclic ring. The term heterocycle or heterocyclic includes heteroaryl moieties. Examples of such heterocyclic elements include, but are not limited to, azepinyl, benzimidazolyl, benzisoxazolyl, benzofurazanyl, benzopyranyl, benzothiopyranyl, benzofuryl, benzothiazolyl, benzothienyl, benzoxazolyl, chromanyl, cinnolinyl, dihydrobenzofuryl, dihydrobenzothienyl, dihydrobenzothiopyranyl, dihydrobenzothiopyranyl sulfone, dihydropyrrolyl, 1,3-dioxolanyl, furyl, imidazolidinyl, imidazolinyl, imidazolyl, indolinyl, indolyl, isochromanyl, isoindolinyl, isoquinolinyl, isothiazolidinyl, isothiazolyl, isothiazolidinyl, morpholinyl, naphthyridinyl, oxadiazolyl, 2-oxoazepinyl, oxazolyl, 2-oxopiperazinyl, 2-oxopiperdinyl, 2-oxopyrrolidinyl, piperidyl, piperazinyl, pyridyl, pyrazinyl, pyrazolidinyl, pyrazolyl, pyridazinyl, pyrimidinyl, pyrrolidinyl, pyrrolyl, quinazolinyl, quinolinyl, quinoxalinyl, tetrahydrofuryl, tetrahydroisoquinolinyl, tetrahydroquinolinyl, thiamorpholinyl, thiamorpholinyl sulfoxide, thiazolyl, thiazolinyl, thienofuryl, thienothienyl, and thienyl. Preferably, heterocycle is selected from 2-azepinonyl, benzimidazolyl, 2-diazapinonyl, dihydroimidazolyl, dihydropyrrolyl, imidazolyl, 2-imidazolidinonyl, indolyl, isoquinolinyl, morpholinyl, piperidyl, piperazinyl, pyridyl, pyrrolidinyl, 2-piperidinonyl, 2-pyrimidinonyl, 2-pyrollidinonyl, quinolinyl, tetrahydrofuryl, tetrahydroisoquinolinyl, and thienyl.

The term "heteroatom" means O, S or N, selected on an independent basis.

The term "heteroaryl" refers to a monocyclic aromatic hydrocarbon group having 5 or 6 ring atoms, or a bicyclic aromatic group having 8 to 10 atoms, containing at least one heteroatom, O, S or N, in which a carbon or nitrogen atom is the point of attachment, and in which one or two additional carbon atoms is optionally replaced by a heteroatom selected from O or S, and

in which from 1 to 3 additional carbon atoms are optionally replaced by nitrogen heteroatoms, said heteroaryl group being optionally substituted as described herein. Examples of such heterocyclic elements include, but are not limited to, benzimidazolyl, benzisoxazolyl, benzofurazanyl, benzopyranyl, benzothiopyranyl, benzofuryl, benzothiazolyl, benzothienyl, benzoxazolyl, chromanyl, cinnolinyl, dihydrobenzofuryl, dihydrobenzothienyl, dihydrobenzothiopyranyl, dihydrobenzothiopyranyl sulfone, furyl, imidazolyl, indolinyl, indolyl, isochromanyl, isoindolinyl, isoquinolinyl, isothiazolyl, naphthyridinyl, oxadiazolyl, pyridyl, pyrazinyl, pyrazolyl, pyridazinyl, pyrimidinyl, pyrrolyl, quinazolinyl, quinolinyl, quinoxalinyl, tetrahydroisoquinolinyl, tetrahydroquinolinyl, thiazolyl, thienofuryl, thienothienyl, thienyl and triazolyl. Additional nitrogen atoms may be present together with the first nitrogen and oxygen or sulfur, giving, e.g., thiadiazole.

This invention is also concerned with compositions and methods of treating ocular hypertension or glaucoma by administering to a patient in need thereof one of the compounds of formula I alone or in combination with one or more of the following active ingredients,in combination with a β-adrenergic blocking agent such as timolol, betaxolol, levobetaxolol, carteolol, levobunolol, a parasympathomimetic agent such as epinephrine, iopidine, brimonidine, clonidine, para-aminoclonidine, carbonic anhydrase inhibitor such as dorzolamide, acetazolamide, metazolamide or brinzolamide, an EP4 agonist (such as those disclosed in WO 02/24647, WO 02/42268, EP 1114816, WO 01/46140, PCT Appln. No. CA2004000471, and WO 01/72268), a prostaglandin such as latanoprost, travaprost, unoprostone, rescula, S1033 (compounds set forth in US Patent Nos. 5,889,052; 5,296,504; 5,422,368; and 5,151,444); a hypotensive lipid such as lumigan and the compounds set forth in US Patent No. 5,352,708; a neuroprotectant disclosed in US Patent No. 4,690,931, particularly eliprodil and R-eliprodil as set forth in WO 94/13275, including memantine; an agonist of 5-HT2 receptors as set forth in PCT/US00/31247, particularly 1-(2-aminopropyl)-3-methyl-1H-imdazol-6-ol fumarate and 2-(3-chloro-6-methoxy-indazol-1-yl)-1-methyl-ethylamine or a mixture thereof. An example of a hypotensive lipid (the carboxylic acid group on the α-chain link of the basic prostaglandin structure is replaced with electrochemically neutral substituents) is that in which the carboxylic acid group is replaced with a C_{1-6} alkoxy group such as OCH_3 (PGF_{2a} 1-OCH_3), or a hydroxy group (PGF_{2a} 1-OH).

Preferred potassium channel blockers are calcium activated potassium channel blockers. More preferred potassium channel blockers are high conductance, calcium activated potassium (Maxi-K) channel blockers. Maxi-K channels are a family of ion channels that are prevalent in neuronal, smooth muscle and epithelial tissues and which are gated by membrane potential and intracellular Ca^{2+}.

The present invention is based upon the finding that maxi-K channels, if blocked, inhibit aqueous humor production by inhibiting net solute and H_2O efflux and therefore lower IOP. This finding suggests that maxi-K channel blockers are useful for treating other ophthamological dysfunctions

such as macular edema and macular degeneration. It is known that lowering IOP promotes blood flow to the retina and optic nerve. Accordingly, the compounds of this invention are useful for treating macular edema and/or macular degeneration. This invention also relates to the use of a compound of formula I for the manufacture of a medicament for the treatment of these diseases.

It is believed that maxi-K channel blockers which lower IOP are useful for providing a neuroprotective effect. They are also believed to be effective for increasing retinal and optic nerve head blood velocity and increasing retinal and optic nerve oxygen by lowering IOP, which when coupled together benefits optic nerve health. As a result, this invention further relates to a method for increasing retinal and optic nerve head blood velocity, increasing retinal and optic nerve oxygen tension as well as providing a neuroprotective effect or a combination thereof. This invention also relates to the use of a compound of formula I for the manufacture of a medicament for the treatment of these diseases.

A number of marketed drugs function as potassium channel antagonists. The most important of these include the compounds Glyburide, Glipizide and Tolbutamide. These potassium channel antagonists are useful as antidiabetic agents. The compounds of this invention may be combined with one or more of these compounds to treat diabetes. This invention is also concerned with the use of a compound of formula I for the manufacture of a medicament for the treatment of diabetes.

Potassium channel antagonists are also utilized as Class 3 antiarrhythmic agents and to treat acute infarctions in humans. A number of naturally occuring toxins are known to block potassium channels including Apamin, Iberiotoxin, Charybdotoxin, Noxiustoxin, Kaliotoxin, Dendrotoxin(s), mast cell degranuating (MCD) peptide, and β-Bungarotoxin (β-BTX). The compounds of this invention may be combined with one or more of these compounds to treat arrhythmias. This invention is also concerned with the use of a compound of formula I in combination with these compounds for the manufacture of a medicament for the treatment of arrhythmias.

Depression is related to a decrease in neurotransmitter release. Current treatments of depression include blockers of neurotransmitter uptake, and inhibitors of enzymes involved in neurotransmitter degradation which act to prolong the lifetime of neurotransmitters.

Alzheimer's disease is also characterized by a diminished neurotransmitter release. Three classes of drugs are being investigated for the treatment of Alzheimer's disease cholinergic potentiators such as the anticholinesterase drugs (e.g., physostigmine (eserine), and Tacrine (tetrahydroaminocridine)); nootropics that affect neuron metabolism with little effect elsewhere (e.g., Piracetam, Oxiracetam; and those drugs that affect brain vasculature such as a mixture of ergoloid mesylates amd calcium channel blocking drugs including Nimodipine. Selegiline, a monoamine oxidase B inhibitor which increases brain dopamine and norepinephrine has reportedly caused mild improvement in some Alzheimer's patients. Aluminum chelating agents have been of interest to those who believe Alzheimer's disease is due to aluminum toxicity. Drugs that affect behavior, including neuroleptics, and

anxiolytics have been employed. Anxiolytics, which are mild tranquilizers, are less effective than neuroleptics The present invention is related to novel compounds which are useful as potassium channel antagonists. This invention also relates to the use of a compound of formula I for the manufacture of a medicament for the treatment of depression, and Alzheimer's.

The compounds of this invention may be combined with anticholinesterase drugs such as physostigmine (eserine) and Tacrine (tetrahydroaminocridine), nootropics such as Piracetam, Oxiracetam, ergoloid mesylates, selective calcium channel blockers such as Nimodipine, or monoamine oxidase B inhibitors such as Selegiline, in the treatment of Alzheimer's disease. The compounds of this invention may also be combined with Apamin, Iberiotoxin, Charybdotoxin, Noxiustoxin, Kaliotoxin, Dendrotoxin(s), mast cell degranuating (MCD) peptide, β-Bungarotoxin (β-BTX) or a combination thereof in treating arrythmias. The compounds of this invention may further be combined with Glyburide, Glipizide, Tolbutamide or a combination thereof to treat diabetes.

The herein examples illustrate but do not limit the claimed invention. Each of the claimed compounds are potassium channel antagonists and are thus useful in the described neurological disorders in which it is desirable to maintain the cell in a depolarized state to achieve maximal neurotransmitter release. The compounds produced in the present invention are readily combined with suitable and known pharmaceutically acceptable excipients to produce compositions which may be administered to mammals, including humans, to achieve effective potassium channel blockage.

For use in medicine, the salts of the compounds of formula I will be pharmaceutically acceptable salts. Other salts may, however, be useful in the preparation of the compounds according to the invention or of their pharmaceutically acceptable salts. When the compound of the present invention is acidic, suitable "pharmaceutically acceptable salts" refers to salts prepared form pharmaceutically acceptable non-toxic bases including inorganic bases and organic bases. Salts derived from inorganic bases include aluminum, ammonium, calcium, copper, ferric, ferrous, lithium, magnesium, manganic salts, manganous, potassium, sodium, zinc and the like. Particularly preferred are the ammonium, calcium, magnesium, potassium and sodium salts. Salts derived from pharmaceutically acceptable organic non-toxic bases include salts of primary, secondary and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines and basic ion exchange resins, such as arginine, betaine caffeine, choline, N,N^1-dibenzylethylenediamine, diethylamin, 2-diethylaminoethanol, 2-dimethylaminoethanol, ethanolamine, ethylenediamine, N-ethylmorpholine, N-ethylpiperidine, glucamine, glucosamine, histidine, hydrabamine, isopropylamine, lysine, methylglucamine, morpholine, piperazine, piperidine, polyamine resins, procaine, purines, theobromine, triethylamine, trimethylamine tripropylamine, tromethamine and the like. Preferred pharmaceutically acceptable salts are sodium and potassium salts. However, to facilitate isolation of the salt during preparation, salts which are less soluble in the chosen solvent may be preferred whether pharmaceutically acceptable or not.

When the compound of the present invention is basic, salts may be prepared from pharmaceutically acceptable non-toxic acids, including inorganic and organic acids. Such acids include acetic, benzenesulfonic, benzoic, camphorsulfonic, citric, ethanesulfonic, fumaric, gluconic, glutamic, hydrobromic, hydrochloric, isethionic, lactic, maleic, malic, mandelic, methanesulfonic, mucic, nitric, pamoic, pantothenic, phosphoric, succinic, sulfuric, tartaric, p-toluenesulfonic acid and the like. Particularly preferred are citric, hydrobromic, hydrochloric, maleic, phosphoric, sulfuric and tartaric acids.

The preparation of the pharmaceutically acceptable salts described above and other typical pharmaceutically acceptable salts is more fully described by Berg *et al.*, "Pharmaceutical Salts," *J. Pharm. Sci.*, 1977:66:1-19.

In vivo hydrolysable esters are those pharmaceutically acceptable esters that hydrolyze in the human body to produce the parent compound. Such esters can be identified by administering, eg. Intravenously to a test animal, the compound under test and subsequently examining the test animal's body fluids.

As used herein, the term "composition" is intended to encompass a product comprising the specified ingredients in the specific amounts, as well as any product which results, directly or indirectly, from combination of the specific ingredients in the specified amounts.

When a compound according to this invention is administered into a human subject, the daily dosage will normally be determined by the prescribing physician with the dosage generally varying according to the age, weight, sex and response of the individual patient, as well as the severity of the patient's symptoms.

The maxi-K channel blockers used can be administered in a therapeutically effective amount intravaneously, subcutaneously, topically, transdermally, parenterally or any other method known to those skilled in the art.

Ophthalmic pharmaceutical compositions are preferably adapted for topical administration to the eye in the form of solutions, suspensions, ointments, creams or as a solid insert. Ophthalmic formulations of this compound may contain from 0.01 ppm to 1% and especially 0.1 ppm to 1% of medicament. Higher dosages as, for example, about 10% or lower dosages can be employed provided the dose is effective in reducing intraocular pressure, treating glaucoma, increasing blood flow velocity or oxygen tension. For a single dose, from between 0. 1 ng to 5000 ug, preferably 1 ng to 500 ug, and especially 10 ng to 100 ug of the compound can be applied to the human eye.

The pharmaceutical preparation which contains the compound may be conveniently admixed with a non-toxic pharmaceutical organic carrier, or with a non-toxic pharmaceutical inorganic carrier. Typical of pharmaceutically acceptable carriers are, for example, water, mixtures of water and water-miscible solvents such as lower alkanols or aralkanols, vegetable oils, polyalkylene glycols,

petroleum based jelly, ethyl cellulose, ethyl oleate, carboxymethyl-cellulose, polyvinylpyrrolidone, isopropyl myristate and other conventionally employed acceptable carriers. The pharmaceutical preparation may also contain non-toxic auxiliary substances such as emulsifying, preserving, wetting agents, bodying agents and the like, as for example, polyethylene glycols 200, 300, 400 and 600, carbowaxes 1,000, 1,500, 4,000, 6,000 and 10,000, antibacterial components such as quaternary ammonium compounds, phenylmercuric salts known to have cold sterilizing properties and which are non-injurious in use, thimerosal, methyl and propyl paraben, benzyl alcohol, phenyl ethanol, buffering ingredients such as sodium borate, sodium acetates, gluconate buffers, and other conventional ingredients such as sorbitan monolaurate, triethanolamine, oleate, polyoxyethylene sorbitan monopalmitylate, dioctyl sodium sulfosuccinate, monothioglycerol, thiosorbitol, ethylenediamine tetracetic acid, and the like. Additionally, suitable ophthalmic vehicles can be used as carrier media for the present purpose including conventional phosphate buffer vehicle systems, isotonic boric acid vehicles, isotonic sodium chloride vehicles, isotonic sodium borate vehicles and the like. The pharmaceutical preparation may also be in the form of a microparticle formulation. The pharmaceutical preparation may also be in the form of a solid insert. For example, one may use a solid water soluble polymer as the carrier for the medicament. The polymer used to form the insert may be any water soluble non-toxic polymer, for example, cellulose derivatives such as methylcellulose, sodium carboxymethyl cellulose, (hydroxyloweralkyl cellulose), hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropylmethyl cellulose; acrylates such as polyacrylic acid salts, ethylacrylates, polyactylamides; natural products such as gelatin, alginates, pectins, tragacanth, karaya, chondrus, agar, acacia; the starch derivatives such as starch acetate, hydroxymethyl starch ethers, hydroxypropyl starch, as well as other synthetic derivatives such as polyvinyl alcohol, polyvinyl pyrrolidone, polyvinyl methyl ether, polyethylene oxide, neutralized carbopol and xanthan gum, gellan gum, and mixtures of said polymer.

Suitable subjects for the administration of the formulation of the present invention include primates, man and other animals, particularly man and domesticated animals such as cats and dogs.

The pharmaceutical preparation may contain non-toxic auxiliary substances such as antibacterial components which are non-injurious in use, for example, thimerosal, benzalkonium chloride, methyl and propyl paraben, benzyldodecinium bromide, benzyl alcohol, or phenylethanol; buffering ingredients such as sodium chloride, sodium borate, sodium acetate, sodium citrate, or gluconate buffers; and other conventional ingredients such as sorbitan monolaurate, triethanolamine, polyoxyethylene sorbitan monopalmitylate, ethylenediamine tetraacetic acid, and the like.

The ophthalmic solution or suspension may be administered as often as necessary to maintain an acceptable IOP level in the eye. It is contemplated that administration to the mamalian eye will be about once or twice daily.

For topical ocular administration the novel formulations of this invention may take the form of solutions, gels, ointments, suspensions or solid inserts, formulated so that a unit dosage comprises a therapeutically effective amount of the active component or some multiple thereof in the case of a combination therapy.

The following examples given by way of illustration is demonstrative of the present invention.

Definitions of the terms used in the examples are as follows:

SM - Starting material,

DMSO – dimethyl sulfoxide,

TLC – thin layer chromatography,

SGC – silica gel chromatography,

PhMgBr – phenylmagnesiumbromide

h = hr = hour,

THF – tetrahydrofuran,

DMF – dimethylformamide,

min – minute,

LC/MS – liquid chromatography/mass spectrometry,

HPLC – high performance liquid chromatography,

PyBOP – Benzotriazol-1-yloxytris-(dimethyl amino)phosphonium hexafluorophosphate,

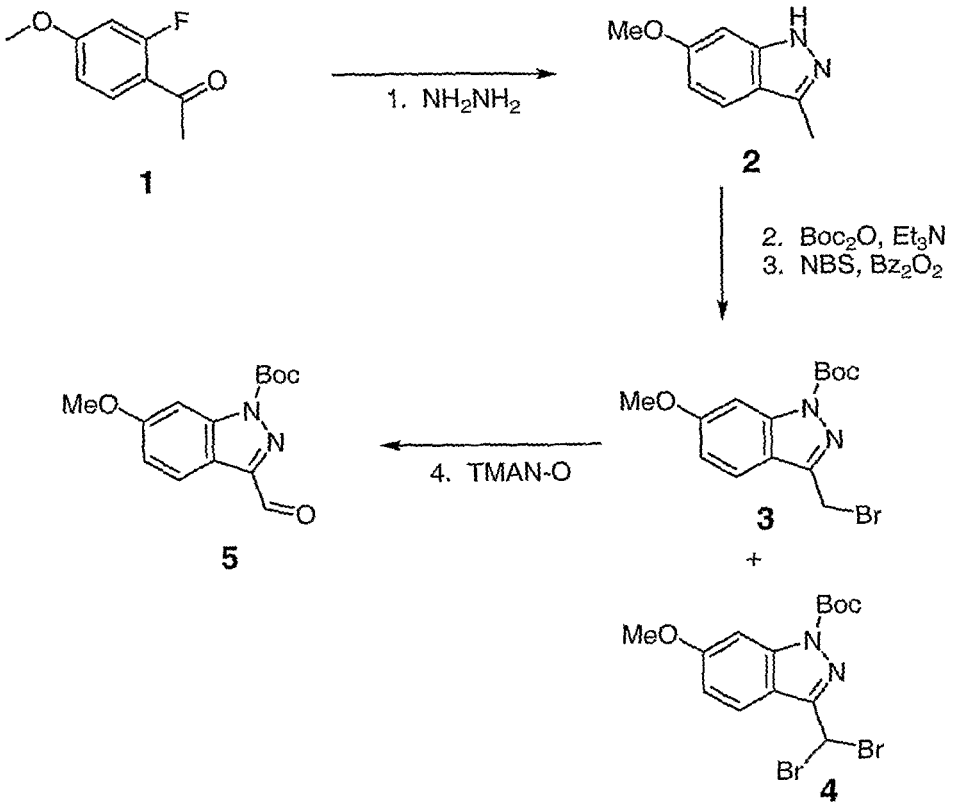
equiv = eq = equivalent,

NBS – N-Bromosuccinamide and

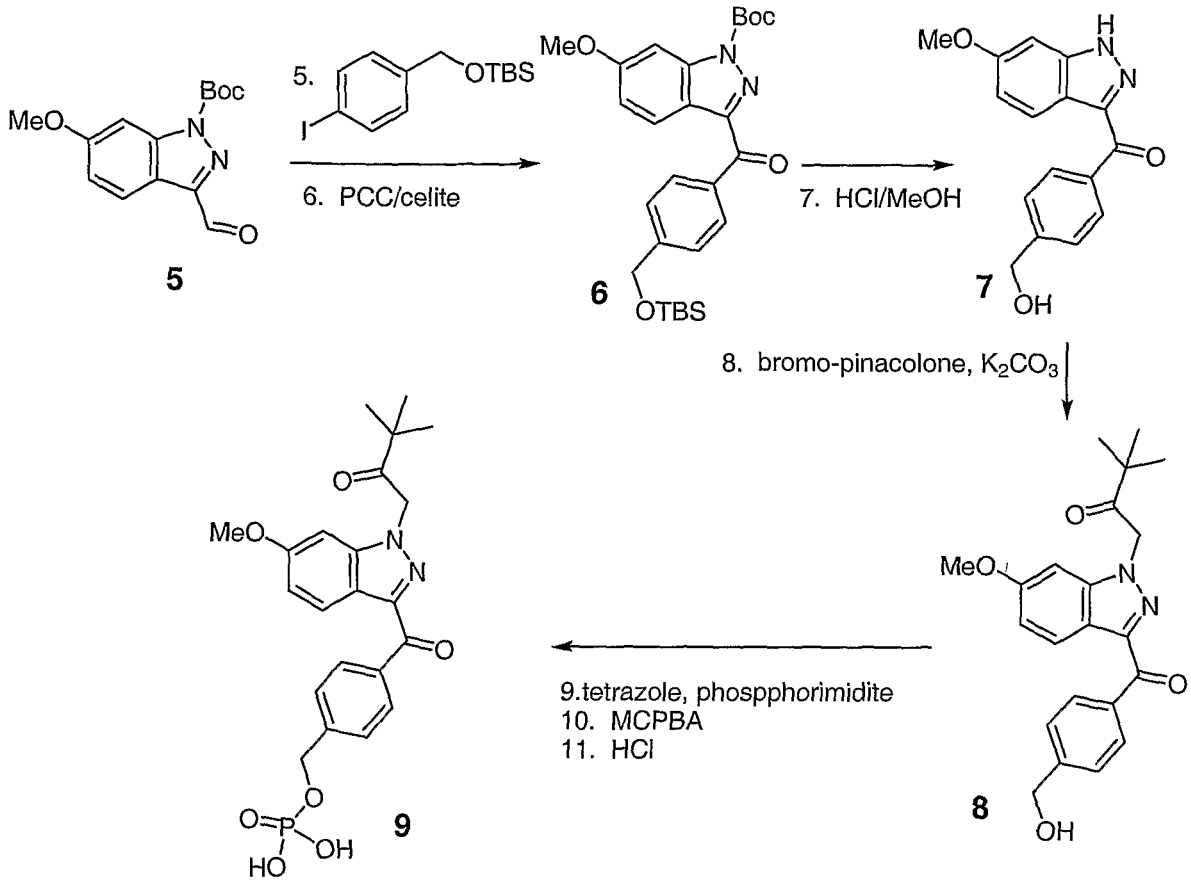
AIBN – 2,2'-azobisisobutyronitrile.

The compounds of this invention can be made, with modification where appropriate, in accordance with Schemes 1 through 5.

Scheme 1

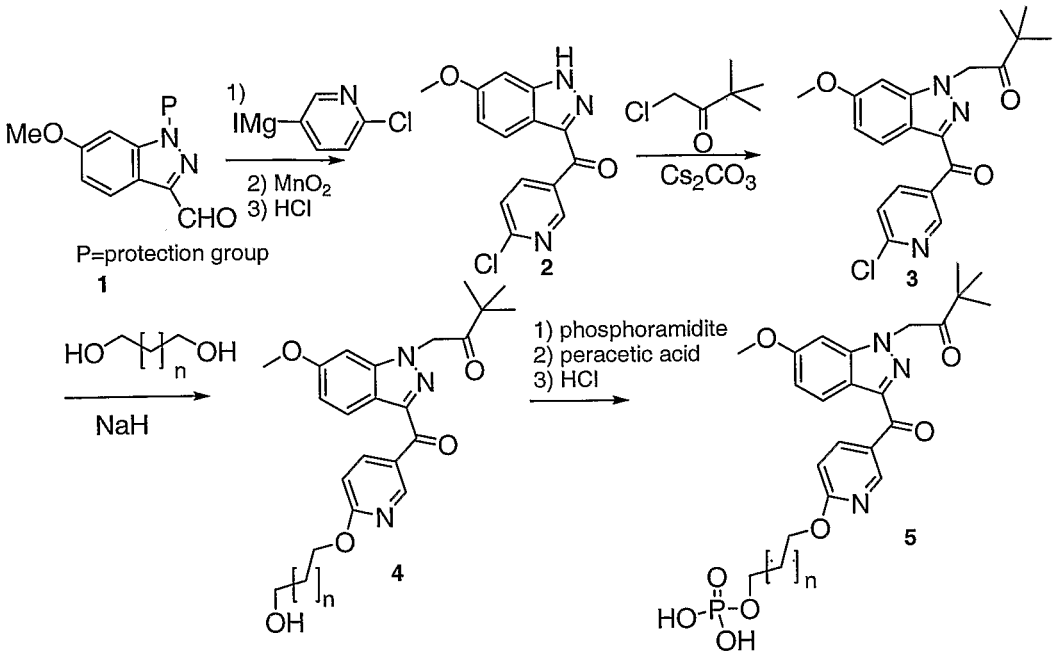

MeO
F
O
1
1. NH_2NH_2
MeO
H
N
N
2
2. Boc_2O, Et_3N
3. NBS, Bz_2O_2
MeO
Boc
N
N
Br
3
+
MeO
Boc
N
N
Br
Br
4
4. TMAN-O
MeO
Boc
N
N
O
5

Scheme 2

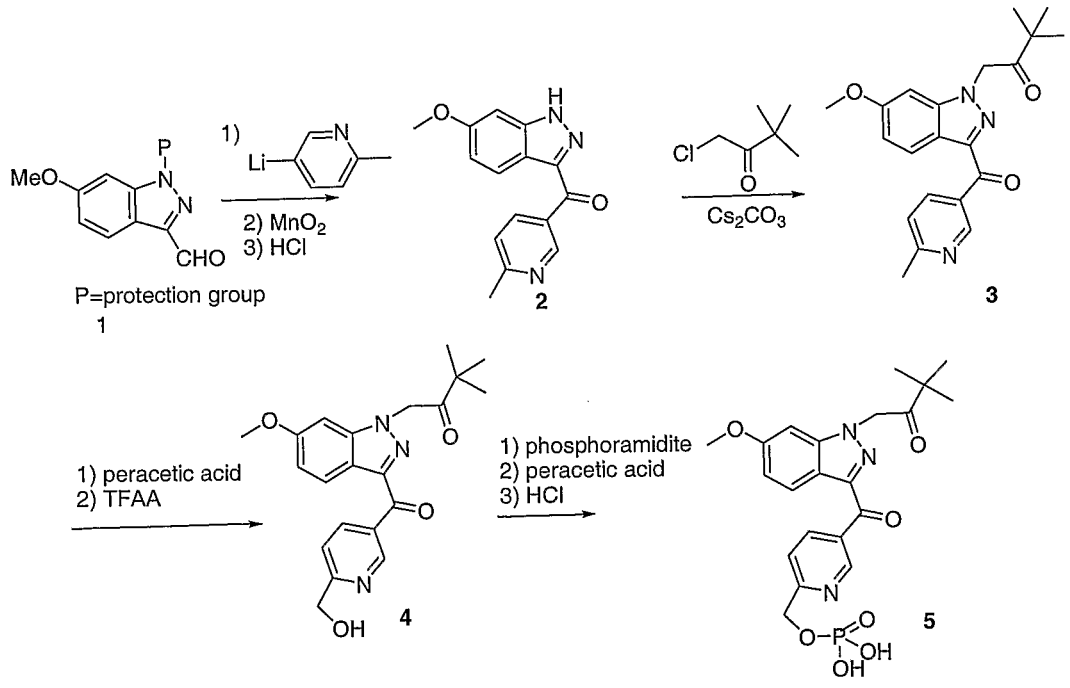


In Schemes 1 and 2 nitroanisole is brominated using NBS, AIBN and benzoyl peroxide. Treatment of the bromonitroanisole with potassium cyanide yielded the cyanonitroanisole. Conversion of the nitro group to an amine is accomplished by hydrogenation. The amine is then treated with sodium nitrite and HCl to yield the indazole ring. In this reaction as soon as the diazonium is generated by nitrosation of the aniline moiety it is trapped intramolecularily by the acidic benzyl cyanide. Tautomerization of the resultant derivative gives the indazole nucleus. Treatment of the nitrile with a Gringard followed by hydrolysis of the resultant imino-magnesium complex gives the desired alkyl/aryl ketone.

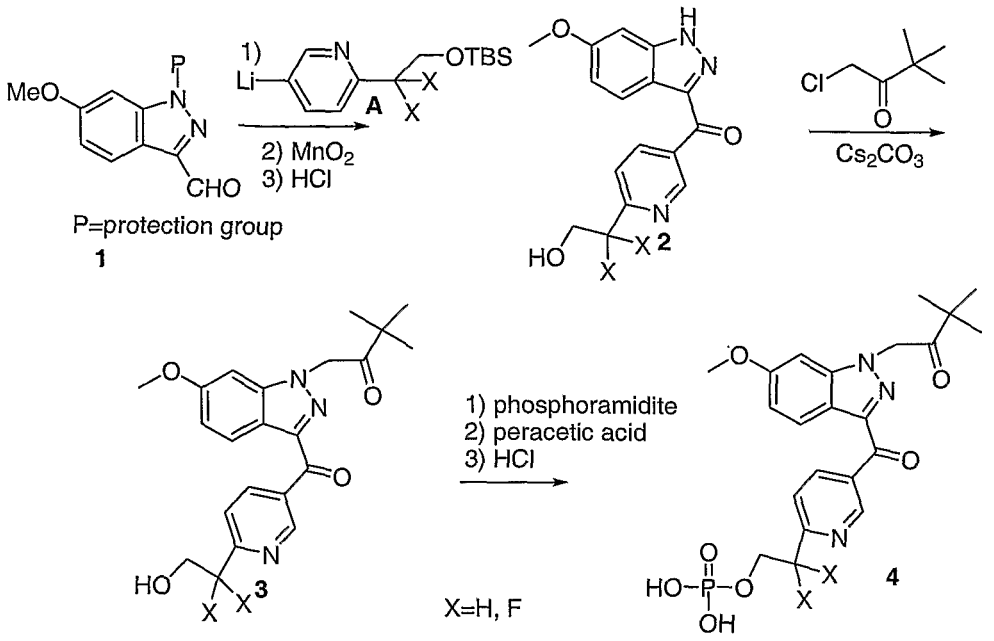
Scheme 3



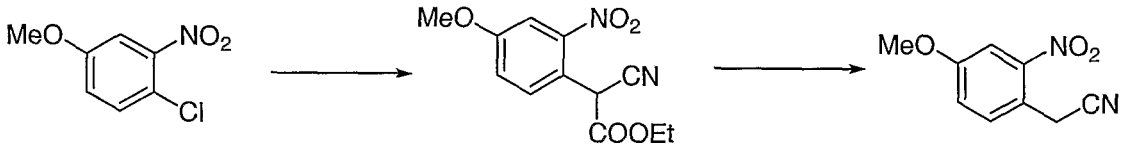
Scheme 4



Scheme 5



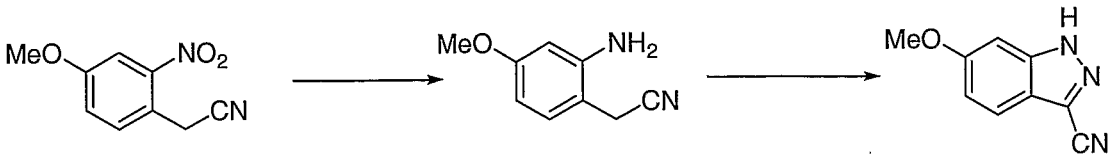
Preparative Example 1



In a 500 mL flask was charged 336 mmoles (13.44g; 60%) of NaH. Under argon 150 mL of DMSO was added, followed by dropwise addition of 32 mL of ethyl cyanoacetate (2.2 equiv.; 352 mmloes) at 5o C. After all the addition the reaction was warmed upto room temperature over 1h. 30 g of starting nitro benzene derivative was added (160 mmoles) as a powder. The reaction mixture was heated in a closed system at 90oC for 8hours. Acidification and standard work-up gave a crude oily residue which was purified over a silica-gel column to give 39 g of desired crystalline product which was decarboxylated to give the benzyl nitrile as follows. Thirty eight grams of SM obtained above was dissolved in 400 mL of 1N sodium carbonate. The homogenous solution was stirred at rt for two days. TLC analysis indicated competion of reaction. The reaction mixture was acidified and extratced with ethyl acetate (100 mL X 4). The combined organic phases was dried over sodium sulphate and concentrated and residue was subjected to SGC to give the desired product.

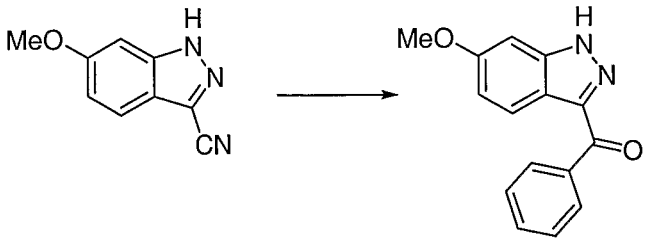
1H NMR CDCL3: 7.72 (1H, d, J = 3 Hz); 7.61 (1H, d, J = 8.5 Hz); 7,25 (1H, dd, J = 3 and 8.5 Hz); 4.17 (2H, s); 3.94 (3H, s). LCMS [M+H] = 193.

Preparative Example 2



10g of benzylnitrile derivative was dissolved in THF 20 mL followed by dilution with 50 mL of methanol. The reaction mixture was taken in a pressure tube, Pd-C (10% wt/ 10 mole %) was added and the reaction mixture was hydrogenated at 40 psi. After the requisite amount of hydrogen for the reduction of the NO_2 group was consumed the reaction was stopped. TLC analysis indicated a spot to spot conversion. The reaction mixture was filtered over a pad of celite and the filtrate was concentrated to a solid and used in the next step directly. Crude aniline derivative (52 mmoles was dissloved/suspended in 2N HCl (150 mL), cooled to 5 ^oC followed by the addition of 5.4g of sodium nitrite in 10 mL of water. The reaction mixture was allowed to stir for 1h with gradual warming to room temperature. TLC analysis indicated complete consumption of SM and the formation of a new spot. The reaction mixture was extratced with ethyl acetate (100 mL X 4); organic phase was collected, dried and concentrated. The residue was purified by SGC to give desired product. LCMS [M+H] = 174

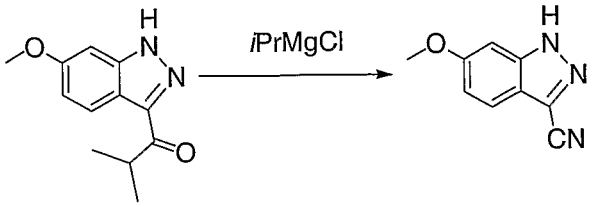
Preparative Example 3



Nitrile (1.5 g) obtained from Preparative Example 2 was dissolved in 20 mL of dry THF and under argon 3 equiv. of PhMgBr (1M in THF) was added at 5°C. The reaction mixture was stirred at room temperature for 1h. The reaction was carefully quenched by addition of water and 1N HCl (15 mL). The quenched reaction mixture was stirred at room temperature for 1hour then extracted with ethyl

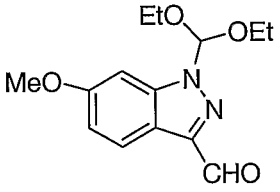
acetate (20 mL X3); combined organic phases were dried over sodium sulfate and concentrated to a solid residue which was azeotroped with toluene three times. LCMS [M+H] = 253

Preparative Example 4

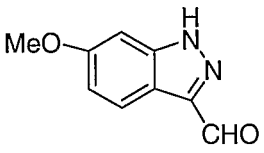


Weighed out 4.15 g of indazole and azeoptroped water with 2 toluene (100 ml) washings, pulling off toluene azeotrope by rotovap. Dried thoroughly under high vaccuum and performed argon purges. Dissolved in 40 ml dry THF and 92 ml dry ether under argon. Cooled to 5°C in ice water bath. Charged 3 eq of isopropylmagnesium chloride ((6 ml of a 2M solution in THF) and stired for 0.5 hr at room temp. Carefully charged 1N HCl (240 ml) and stired for 1 h. Monitored reaction by TLC. Extracted with EtOAc, rotovaped and produced desired product.
LCMS [M+H] = 219

Preparative Example 5

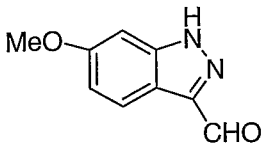


Step A:



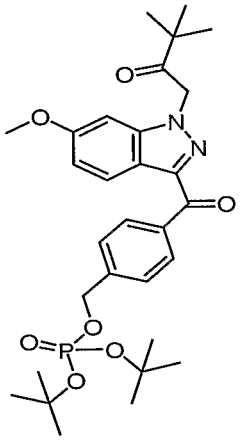
To a solution of dibromide (23.2g, by-product of Example 1, step-3) in acetic acid was added sodium acetate (22.5g). The mixture was placed in oil bath and refluxed for a couple of hours until reaction completed. The mixture was cooled to room temperature and then poured into ice/water to give desired compound as an off-white solid. The solid was isolated by filtration and dried over nitrogen atmosphere. ^{1}H NMR ($CDCl_3$) : δ 10.23 (1H, s); 8.19 (1H, d); 7.02 (1H, dd); 6.96 (1H, d); 3.90 (3H, s).

Step B:



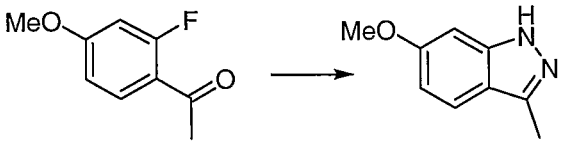
To the intermediate from Step A was added triethyl orthoformate (40ml) and heated to 130°C for a couple of hours. The resulting mixture was concentrated to dry to give title compound as a brown solid. ^{1}H NMR (DMSO) : δ 10.08 (1H, s); 7.98 (1H, d); 7.25 (1H, d); 7.02 (1H, dd); 6.81 (1H, s); 3.82 (3H, s); 3.52 (4H, q); 1.11 (6H, t).

Example 1



di-tert--butyl 4-{[1-(3,3-dimethyl-2-oxobutyl)-6-methoxy-1-H-indazole-3-yl]carbonyl}benzylphosphate

Step 1



100 g of fluoro-acetophenone in 400 mL of ethylene glycol was stirred at room temperature with hydrazine (0.624 mol, 20 g) for 4h after which the reaction mixture was heated to 150 C for 48h. TLC analysis indicated complete reaction. Partitioned the reaction mixture into dichloromethane and brine.

Dried organic phase over sodium sulphate and evaporated to a solid. Re-crystallized from hexane/dicholomethane gave indazole.

1H NMR (CDCL3): 7.5 (1H, d, 7.5 Hz); 6.8 (2H, m); 3.8 (3H, s); 2.55 (3H, s)
LCMS [M+H] = 163

Step 2

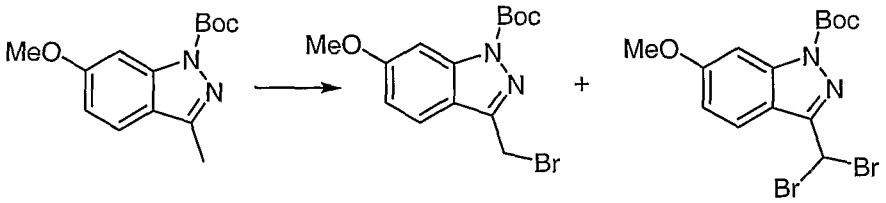


6-methoxy-3-methyl-1-H tert-butyl-6-methoxy-3-methyl-indazole 1-indazole-carboxylate

78g of indazole was dissolved in 1L of MeCN containing 1.1 equiv of tri-ethyl amine, 0.2 equiv of DMAP was cooled to -5 C; followed by slow addition of Boc2O (1.1 equiv) in 200 mL of MeCN. After 2h of stirring the reaction at rt the reaction mixture was evaporated to an oil which was partitioned between EtOAc and brine, dried over sodium sulphate and evaporated. The residue was applied to a short SGC and eluted with 15% EtOAc in hexane. Evaporation gave product.

1H NMR (CDCL3): 7.6 (1H, bs); 7.42 (1H, d, J = 7.5 Hz); 6.85 (1H, dd); 3.8 (3H, s); 2.5 (3H, s); 1.7 (9H, s)
LCMS [M+H] = 263

Step 3

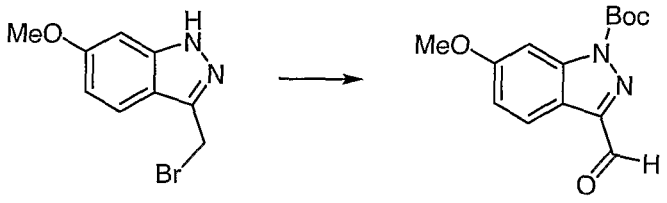


100 g of indazole was dissolved in 600 mL of CCl4, followed by addition of 1.1 equiv of NBS and 0.2 equiv of Bz2O. Reaction mix was vac-purged with argon and set to reflux for 5h in presence of light from a sun lamp. Reaction mixture was filtered over a pad of SG and concentrated. Residual oil was purified over a short SGC. 85 g of pure bromide was obtained. Mixed fractions yielded di-bromo derivative

mono-bromide: 1H NMR (CDCL3): 7.7 (1H, d, 7.5 Hz); 7.6 (1H, bs); 6.95 (1H, dd); 4.7 (2H, s); 3.9 (3H, s); 1.7 (9H, s);

di-bromide: 1H NMR (CDCL3): 8.05 (1H, d, J = 7.5 Hz); 7.6 (1H, bs); 7.0 (1H,dd); 6.85 (1H, s); 3.9 (3H, s); 1.7 (9H, s);

Step 4

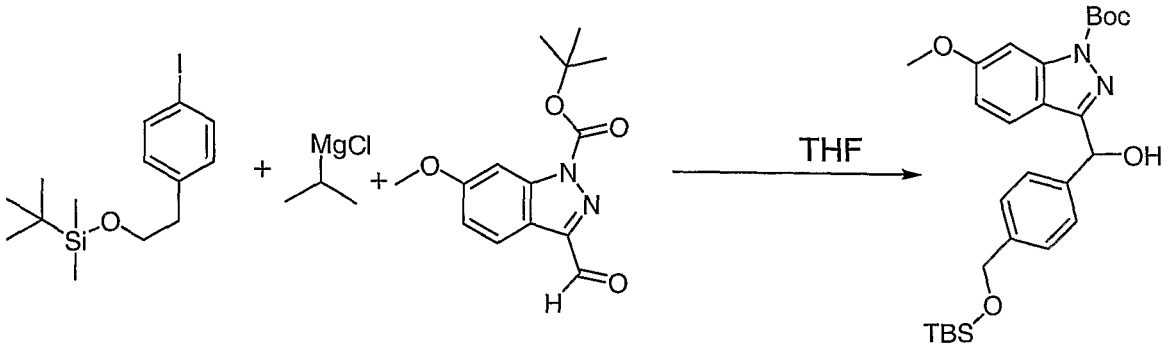


3-(bromomethyl)-6-methoxy-t-butyl-3-formyl-6-methoxy-1-H-indazole 1-H-indazole-1-carboxylate

5 g of bromide was dissolved in 10 mL of DMSO, cooled to 0 Cfollowed by addition of 2.5 equiv of TMANO (trimethyl amine N-oxide). Reaction was stirred for 0.5h then a standard work-up and SG pad filteration gave desired product quantitatively. LCMS [M+H] = 277

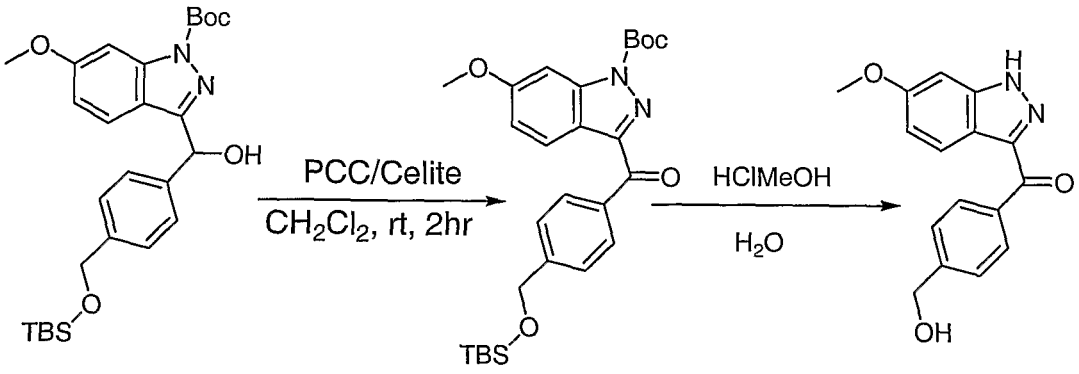
1H NMR (CDCL3): 10.2 (1H, s); 8.1 (1H, d, J = 7.5 Hz); 7.6 (1H, bs); 7.0 (1H, dd); 3.9 (3H, s); 1.7 (9H, s);

Step 5



Glasswares were flame dried under high vacuum To neat iodo-benzyl alcohol derivative (3.6 g, 10 mmol) in the flask was slowly added isopropylMgCl (5 mL, 2M solution). After stirring at rt for 2 hr, indazole derivative (1.1g, 4 mmol) in 15 mL THF was added. The reaction mixture was stirred at rt for 2 hr. LC-MS showed the reaction was complete. Pour the reaction mixture into 30 mL saturated NH4Cl, followed by adding 40 mL ether. The organic layer was separated, the aqueous layer was extracted by ether (40 mL). The combined organic layers were washed with saturated K2CO3 (2x30 mL), water (40 mL) and brine (20 mL). The solvent was removed, the residue was used for next step reaction without further purification. LCMS [M+H] = 499

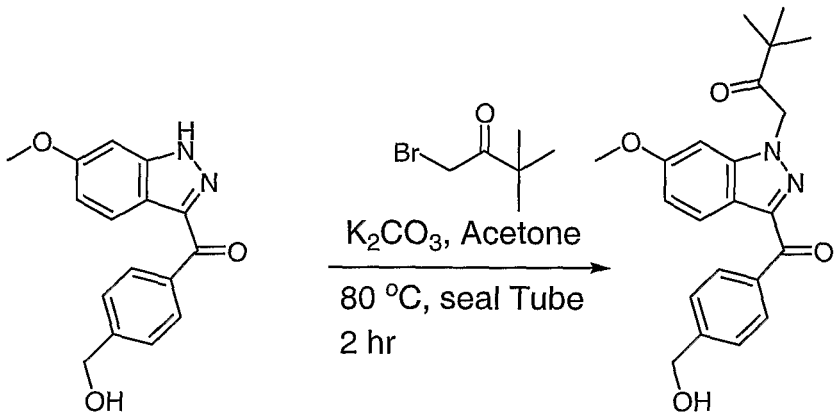
Steps 6 and 7



To a solution of indazole (crude from step 5) in 20 mL dichloromethane was added 5 g celite and 4.3 g of PCC (MW 215.56, ~2 eq). The reaction mixture was stirred at rt for 2 hr. LC-MS showed the reaction was completed LCMS [M+H] = 497. The reaction mixture was filtered. The solvent was removed, the

residue was dissolved in 10 mL MeOH, and added 20 mL 2N HCl. After stirring for 1 hr at rt LCMS and TLC analysis indicated complete reaction. The reaction mixture was extracted with EtOAc (2x30 mL). The solvent was removed, the residue was used for next step reaction without further purification. LCMS [M+H] = 283

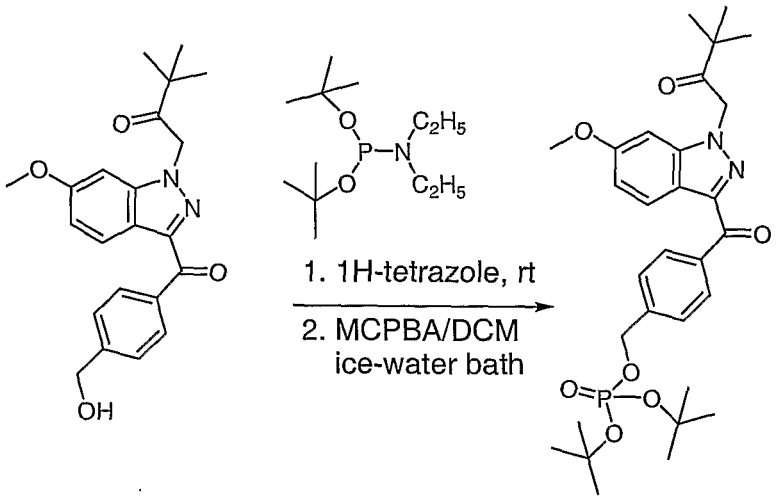
Step 8



To a solution of indazole (342 mg crude prod from step 7, ~10 mmol)) in 15 mL acetone was added 1.5 g of K2CO3 and 1.5 mL Bromopinacolone (Mw179.06, d1.326, 2.0 g, 11mmol). The reaction mixture was stirred at 80 oC in a seal tube for 2 hr. After filtered off salts, the solvent was removed, the residue was purified by HPFC to give white solid product.

1H NMR (CDCL3) = 8.3 (3H, m); 7.5 (1H, d, J = 7.5 Hz); 7.05 (1H, dd); 7.6 (1H, bs); 5.4 (2H, s); 4.8 (2H, bs); 3.9 (3H, s); 1.38 (9H, s)
LCMS [M+H] = 381

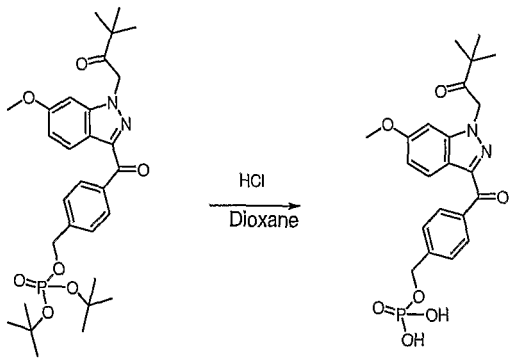
Steps 9, and 10



di-t-butyl-4-{[1-(3,3-dimethyl-2-oxobutyl)-6-methoxy-1-H- indazol-3-yl]carbonyl}benzyl phosphate

To a solution of indazole-benzyl alcohol derivative (1.02g, 2.68 mmol) in 20 mL CHCl3 was added 15 mL 0.45 M 1H-tetrazole in CH3CN, followed by addition of di-tert-butyl N,N-diethylphosphoramidite (0.8 mL, d0.896, Mw 249.34, 2.87mmol, 1.1 eq). After stirred for 30 min., cooled the reaction mixture to -40 oC, and a solution of MCPBA (85%, 2 g, Mw 172.57, 9.8 mmol) in 5 mL DCM was added. The reaction mixture was warmed to rt and stirred for 10 min. 10 mL 10% NaHSO3 solution was added to quench excess MCPBA. Stirred at rt for 15 min. The reaction mixture was worked up with ether and water. The organic layer was separated and washed with water. The solvent was removed, the product (residue) was used for next step reaction (Example 2) without further purification.

Example 2



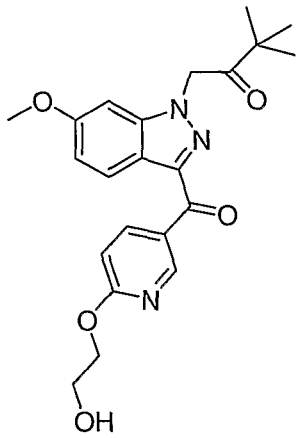
di-tert--butyl 4-{[1-(3,3-dimethyl-2-oxobutyl)-6-methoxy-1-H-indazol-3-yl]carbonyl}benzyl phosphate

4-{[1-(3,3-dimethyl-2-oxobutyl)-6-methoxy-1-H-indazol-3-yl]carbonyl}benzyl dihydrogen phosphate

To the crude product obtained in Step 10 of Example 1 was added HCL in EtOAc (HCl passed through EtOAc at 0 C for 5 min) and stirred at room temperature for 4 hours. The solvent was removed. The residue was purified by reverse phase HPLC to yield the desired compound as a white solid product.

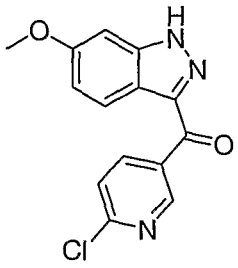
1H NMR (CD3OD): 8.25 (2H, d, J=7.5 Hz); 8.18 (1H, d, J=7.5 Hz); 7.6 (2H, d, J=7.5 Hz); 7.0 (1H, dd); 6.9 (1H, bs); 5.65 (2H, s); 5.1 (2H, bs); 3.9 (3H, s); 1.35 (9H, s);
LCMS [M+H] = 460

Example 3



1-(3-{[6-(2-hydroxyethoxy)pyridin-3-yl]carbonyl-6-methoxy-1-H-indazol-1-yl)-3,3-dimethylbutan-2-one

Step A:

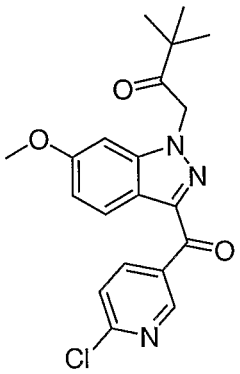


6-chloropyridin-3-yl)-6-methoxy-1-H-indazol-3-yl)-methanone

To a solution of 5-iodo-2-chloropyridine (2.56 g, 10.78 mmol) in THF (10 mL) was added *i*PrMgBr dropwise at -78 °C. The reaction stirred for 1 h before Intermediate 1 (1.71 g, 6.10 mmol) was added as a solution in THF (5 mL). After 2 h and the reaction was quenched with 1N NaOH and extracted with

EtOAc. The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. To a solution of the crude product in toluene (50 mL) was added MnO_2 (2.173 g, 25.0 mmol) and the reaction mixture was heated to 130 °C. After 1h the reaction was complete, filtered through a celite pad, and concentrated *in vacuo*. The crude product was dissolved in THF (10 mL) and 4 mL of 1N HCl was added dropwise. The reaction stirred at RT until TLC analysis indicated completion. The reaction mixture was cooled to 0°C and the solid precipitate was collected. ^{1}H NMR (CD_3OD) δ : 3.900 (3H, s), 7.013 (1H, d), 7.062 (1H, s), 7.627 (1H, d), 8.672 (1H, d), 9.306 (1H, s).

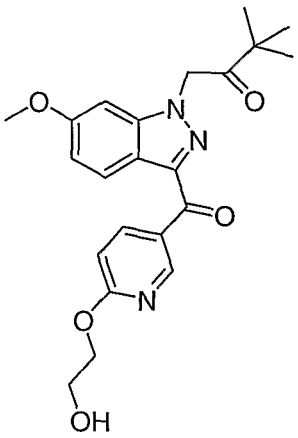
Step B:



1-{3-[6-chloropyridin-3-yl)carbonyl]-6-methoxy-1-H-indazol-1-yl)-3,3-dimethylbutan-2-one

To a solution of the intermediate from Step A (1.00 g, 3.48 mmol) and Cs_2CO_3 (3.396 g, 10.45 mmol) in DMF (14 mL) was added 1-chloropinacolone (0.681 mL, 5.22 mmol). After 40 min the reaction was complete and quenched with H_2O. The reaction mixture was extracted with EtOAc and the combined organic layers were washed with H_2O, brine, dried over $MgSO_4$, and concentrated *in vacuo* to yield the desired product. ^{1}H NMR (CD_3OD) δ : 1.344 (9H, s), 3.888 (3H, s), 6.947 (1H, s), 7.043 (1H, d), 7.625 (1H, d), 8.221 (1H, d), 8.624 (1H, d), 9.257 (1H, d).

Step C:

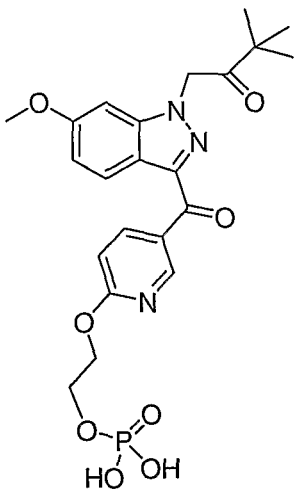


1-{3-[6-(2-hydroxyethoxy)pyridin-3-yl)carbonyl]-6-methoxy-1-H-indazol-1-yl)-3,3-dimethylbutan-2-one

40.6 mg (1.036 mmol) of NaH (60% dispersion in mineral oil) was washed 3x with hexane and dried under nitrogen. Ethylene glycol (1mL) was added to the dry NaH and the reaction stirred for 20 min at 60 °C. To the reaction mixture was added the intermediate from Step B (100 mg, 0.259 mmol) as a solution in THF (1.5 mL). The reaction continued to stir overnight at 60 °C. Upon completion, the THF was removed *in vacuo*, diluted with EtOAc, washed with H_2O, brine, dried over $MgSO_4$, and concentrated *in vacuo*. The crude residue was purified via silica gel chromatography.

1.376 (9H, s), 3.889 (3H, s), 4.021 (2H, m), 4.608 (2H, m), 5.429 (2H, s), 6.543 (1H, s), 6.223 (1H, d), 7.054 (1H, d), 8.336 (1H, d), 8.541 (1H, d), 9.310 (1H, s).

Example 4

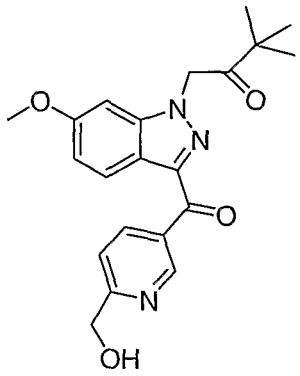


2-[(5-{[1-(3,3-dimethyl-2-oxobutyl-6-methoxy-1-H-indazol-3-yl)carbonyl}pyridine-2-yl)oxy]ethyl di-hydrogen phosphate

To a solution of the intermediate from Example 3, Step C (160 mg, 0.388 mmol) in $CHCl_3$ (5 mL) was added tetrazole (1.29 mL, 0.582 mmol, 0.45 M/CH_3CN) and di–*tert*-butyl diethylphosphoramidite (0.129mL, 0.465 mmol) at RT. After 0.5 h the reaction was complete and peracetic acid (0.072 mL, 0.582 mmol) was added at 0 °C. The reaction mixture was quenched with saturated sodium bisulfite, diluted with EtOAc, washed with saturated sodium bicarbonate, H_2O, and saturated NaCl, dried over $MgSO_4$, and evaporated to dryness *in vacuo*. The crude residue was chromatographed on SiO_2. A solution of the phosphate ester in EtOAc was cooled to 0 °C and 99 % HCl gas was bubbled into the mixture until saturation occurred. The solid precipitate was collected and recrystallized from EtOAc/ether to yield the final product.

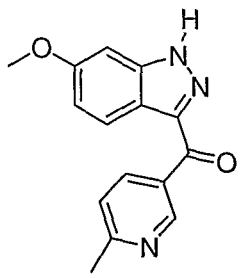
^{1}H NMR (CD_3OD) δ : 1.350 (9H, s), 3.887 (3H, s), 4.353 (2H, m), 4.652 (2H, m), 5.696 (2H, s), 6.929 (1H, s), 7.024 (1H, d), 7.072 (1H, d), 8.199 (1H, d), 8.638 (1H, d), 9.217 (1H, s).

Example 5



1-(3-{[6-(hydroxymethyl)pyridin-3-yl)carbonyl}-6-methoxy-1H-indazol-1-yl)-3,3-dimethylbutan-2-one

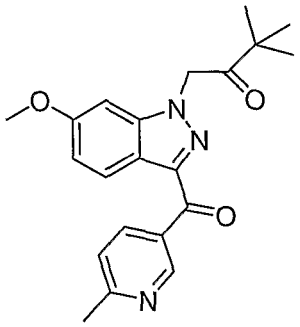
Step A:



(6-methoxy-1H-indazol-3-yl)6-methylpyridin-3-yl)methanone

To a solution of 5-bromo-2-methylpyridine (736 mg, 4.31 mmol) in THF (15 mL) was added *n*BuLi dropwise (2.156 mL, 5.39 mmol, 2.5 M in hexanes) at –78 °C. The reaction stirred for 1 h before Intermediate 1 (1.00 g, 3.59 mmol) was added as a solution in THF (5 mL). The starting material was consumed after 2 h and the reaction was quenched with 1N NaOH and extracted with EtOAc. The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. A solution of the crude product in toluene (20 mL) was added MnO_2 (0.414 g, 4.77 mmol) and the reaction mixture was heated to 130 °C. After 1h the reaction was complete, filtered through a celite pad, and concentrated *in vacuo*. The crude product was dissolved in THF and 4 mL of 1N HCl was added dropwise. After 1h reaction mixture was cooled to 0 °C and the solid precipitate was collected. ^{1}H NMR (DMSO) δ : 2.553 (3H, s), 3.832 (3H, s), 7.000 (1H, d), 7.089 (1H, s), 7.451 (1H, d), 8.100 (1H, d), 8.430 (1H, d), 9.220 (1H, s).

Step B:

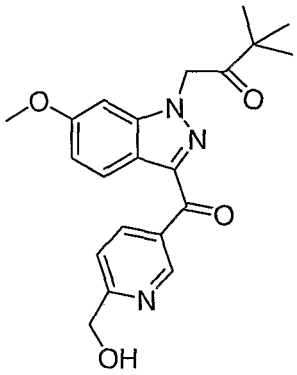


1-{6-methoxy-3-[6-methylpyridin-3-yl)carbonyl]-1H-indazol-1-yl)-3,3-dimethylbutan-2-one

This compound was made as described in Step B of Example 3.

^{1}H NMR ($CDCl_3$) δ : 1.38 (9H, s), 2.65 (3H, s), 3.85 (3H, s), 5.22 (2H, s), 6.56 (1H, s), 7.05 (1H, d), 7.32 (1H, d), 8.34 (1H, d), 8.45 (1H, d), 9.50 (1H, s).

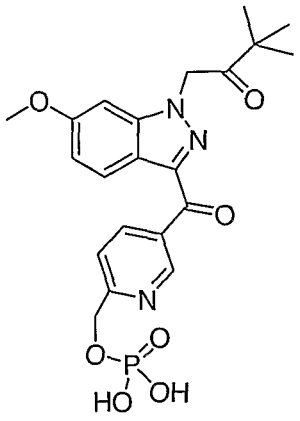
Step C:



1-(3-{[6-(hydroxymethyl)pyridin-3-yl)carbonyl]-1H-indazol-1-yl)-3,3-dimethylbutan-2-one

To a stirring solution of the intermediate from Step B (74 mg, 0.202 mmol) in CH_2Cl_2 was added MCPBA (67 mg, 0.303 mmol) at 0 °C. TLC indicated the reaction was complete after 1.5 h and the reaction mixture was concentrated *in vacuo*. The crude residue was dissolved in EtOAc and washed with saturated sodium bisulfite, H_2O, brine, dried over $MgSO_4$, and concentrated *in vacuo*. Purified via silica gel chromatography. The N-oxide was dissolved in CH_2Cl_2 and TFAA was added dropwise at 0 °C. After 2h the reaction was concentrated *in vacuo* and purified via silica gel chromatography. ^1H NMR ($CDCl_3$) δ :1.373 (9H, s), 3.898 (3H, s), 4.882 (2H, s), 5.428 (2H, s), 6.564 (1H, s), 7.066 (1H, d), 7.429 (1H, d), 8.352 (1H, d), 8.581 (1H, d), 9.541 (1H, s).

Example 6

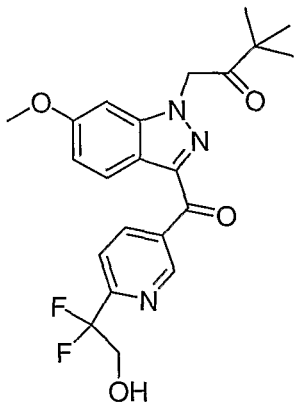


(5-{[1-3,3-dimethyl-2-oxobutyl)-6-methoxy-1H-indazol-3-yl]carbonyl}pyridine-2-yl)methyl dihydrogen phosphate

This compound was prepared as described in Example 4 and the product was recrystallized from EtOAc and hexane.

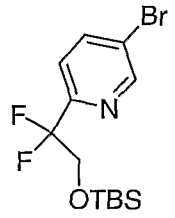
^{1}H NMR (CD_3OD) δ : 1.340 (9H, s), 3.884 (3H, s), 5.235 (2H, d), 5.687 (2H, s), 6.937 (1H, s), 7.036 (1H, d), 7.840 (1H, d), 8.210 (1H, d), 8.797 (1H, d), 9.430 (1H, s).

Example 7



1-(3-{[6-(1,1-difluoro-2-hydroxyethyl)pyridin-3-yl]carbonyl}-6-methoxy-1-indazol-1-yl)-3,3-dimethylbutan-2-one

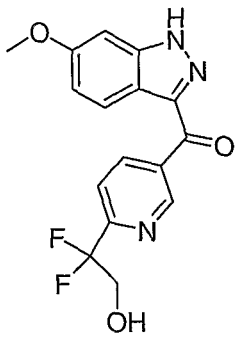
Step A:



To a solution of 2-pyridineacetic acid, 5-bromo-α,α-difluoro-, ethyl ester (13.4g; prepared according to "Ero, H.; Haneko, Y.; Sakamoto, T. *Chem Pharm. Bull.* 2000,*48*, 982.") in ethanol was added sodium borohydride (2.3g) portion-wise at 0 °C. After stirring at 0 °C for 1 hour, the mixture was poured into water and extracted with ethyl acetate. The organic layer was washed with 1N $NaOH_{aq}$, brine, dried ($MgSO_4$), and concentrated under reduced pressure to afford crude alcohol. The crude alcohol in methylene chloride was added imidazole (4.1g) and TBS-Cl (8.3g) at 0 °C. The mixture was stirred for 1 hour. The reaction was poured into 0.1 N HCl_{aq} extracted with methylene chloride. The organic layer was washed with brine, dried ($MgSO_4$) and evaporated. The residue was purified by silica gel (100% methylene chloride) to give desired compound as a colorless oil.

^{1}H NMR ($CDCl_3$) : δ 8.75 (1H, d); 7.95 (1H, dd); 7.57 (1H, d); 4.20 (2H, t); 0.82 (9H, s); 0.02 (6H, s).

Step B:

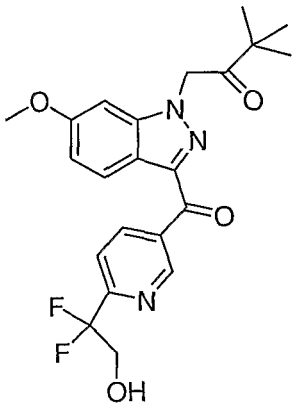


The desired compound was prepared by a procedure similar to the one described for Example 3, Step A.

^{1}H NMR (DMSO) : δ 9.35 (1H, d); 8.65 (1H, dd); 8.14 (1H, d); 7.88 (1H, d); 7.10 (1H, d); 7.03 (1H, dd); 4.05 (2H, t); 3.85 (3H, s).

LC-MS (M+H)=334.2.

Step C:

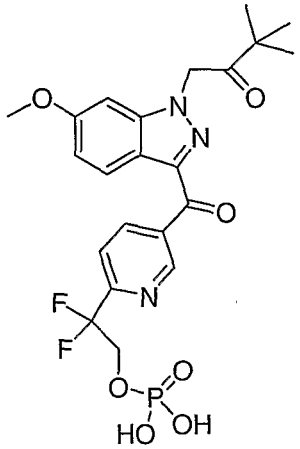


The desired compound was prepared by a procedure similar to the one described for Example 3, Step B. This compound was purified by silica gel (hexanes/ ethyl acetate=1/1) and crystalized from hexanes/ ethyl acetate.

^{1}H NMR ($CHCl_3$) : δ 9.53 (1H, d); 8.71 (1H, dd); 8.35 (1H, d); 7.88 (1H, d); 7.08 (1H, dd); 6.57 (1H, d); 5.44 (2H, s); 4.32 (2H, t); 3.91 (3H, s); 1.38 (9H, s).

LC-MS (M+H)=432.3.

Example 8

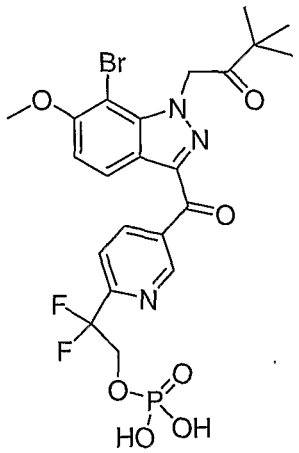


2-(5-{[1-(3,3-dimethyl-2-oxobutyl)-6-methoxy-1H-indazol-3yl]carbonyl}pyridine-2-yl)-2,2-diflouroethyl di-hydrogen phosphate

This compound was prepared as described in Example 4. The final product was purified via reverse phase liquid chromatography (20-90% acetonitrile in H_2O).

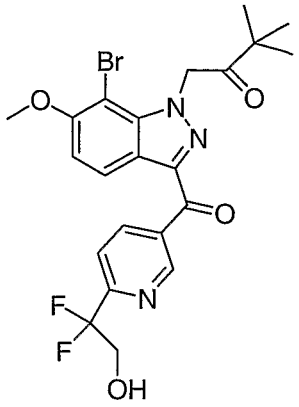
^{1}H NMR (CD_3OD) δ : 1.341 (9H, s), 3.888 (3H, s), 4.586 (2H, m), 5.704 (2H, s), 6.938 (1H, s), 7.046 (1H, d), 7.897 (1H, d), 8.215 (1H, d), 8.727 (1H, d), 9.457 (1H, s).

Example 9



2-(5-{[7-bromo-1-(3,3-dimethyl-2-oxobutyl)-6-methoxy-1H-indazol-3-yl]carbonyl}puyridin-2-yl)-2,2-difluoroethyl di-hydrogen phosphate

Step A:

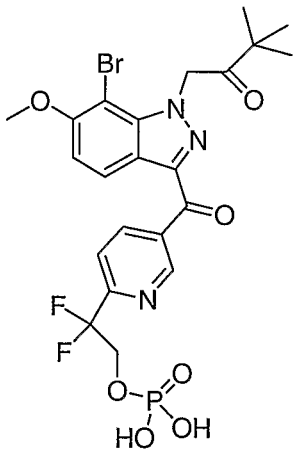


To the intermediate from Example 7, Step C in chloroform was added bromine at 0 °C slowly. The reaction was stirred at 0 °C for 5 min and poured into sodium bisulfite solution. The mixture was extracted with methylene chloride. The organic layer was dried over $MgSO_4$ and concentrated. The residue was purified by crystallization (hexanes/ ethyl acetate).

^{1}H NMR ($CHCl_3$) : δ 9.51 (1H, d); 8.69 (1H, dd); 8.45 (1H, d); 7.88 (1H, d); 7.14 (1H, d); 5.97 (2H, s); 4.31 (2H, t); 4.04 (3H, s); 1.38 (9H, s).

LC-MS (M+H)=512.1.

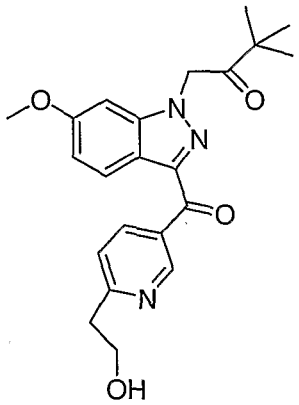
Step B:



The desired compound was prepared by a procedure similar to the one described for Example 4. This compound was crystalized from ethyl acetate.

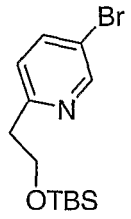
1H NMR (CD3OD) : δ 9.44 (1H, d); 8.74 (1H, dd); 8.39 (1H, d); 7.92 (1H, d); 7.28 (1H, d); 6.57 (1H, d); 6.08 (2H, s); 4.61 (2H, m); 4.01 (3H, s); 1.33 (9H, s).

Example 10



1-(3-{[6-(2 hydroxyethyl)pyridine-3-yl]carbonyl}-6-methoxy-1H-indazol-1-yl)-3,3-dimethylbutan-2-one

Step A:

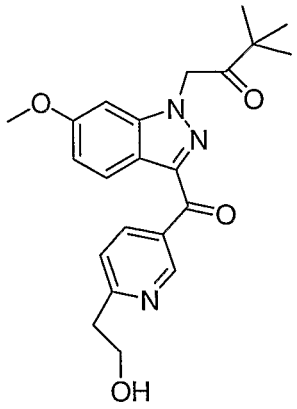


To a solution of 2,5-dibromopyridine (2.4g) in toluene was added tributylallyltin (3.4 ml) and dichlorobis(triphenylphosphine) palladium (0.7g) under nitrogen atmosphere. The mixture was refluxed for a couple of hours and concentrated under reduced pressure. The residue was re-dissolved in "wet ether" and added DBU (3ml) slowly to give a cloudy solution. The mixture was filtered over a pad of silica gel and concentrated. The residue was dissolved in methylene chloride/methanol=1/1 solution and cooled to –78 °C. To this solution was bubbled though ozone until the reaction mixture became a blue color. The reaction was warmed to 0 °C and added sodium borohydride (0.5g) portion-wise. After stirring at 0 °C for 1 hour, the mixture was poured into water and extracted with ethyl acetate. The organic layer was washed with 1N $NaOH_{aq}$, brine, dried ($MgSO_4$), and concentrated under reduced pressure to afford crude alcohol. The alcohol was purified by silica gel (methylene chloride/ ethyl acetate=1/1) to give desired alcohol. To a solution of alcohol in methylene chloride was added imidazole (0.4g) and TBS-Cl (0.8g) at 0 °C. The mixture was stirred for 1 hour. The reaction was poured into 0.1

N HCl_{aq} extracted with methylene chloride. The organic layer was washed with brine, dried ($MgSO_4$) and evaporated. The residue was purified by silica gel (100% methylene chloride) to give desired compound.

^1H NMR ($CDCl_3$) : δ 8.61 (1H, d); 7.73 (1H, dd); 7.14 (1H, d); 3.97 (2H, t); 2.96 (2H, t); 0.86 (9H, s); -0.02 (6H, s).

Step B:



The desired compound was prepared by a procedure similar to the one described for Example 5, Steps A and B. This compound was purified by silica gel (hexanes/ ethyl acetate=1/3).

^1H NMR ($CHCl_3$) : δ 9.53 (1H, d); 8.54 (1H, dd); 8.35 (1H, d); 7.37 (1H, d); 7.07 (1H, dd); 6.56 (1H, d); 5.45 (2H, s); 4.11 (2H, t); 3.90 (3H, s); 3.18 (2H, t); 1.38 (9H, s).

LC-MS (M+H)=396.2.

FUNCTIONAL ASSAYS

A. Maxi-K Channel

The activity of the compounds can also be quantified by the following assay.

The identification of inhibitors of the Maxi-K channel is based on the ability of expressed Maxi-K channels to set cellular resting potential after transfection of both alpha and beta1 subunits of the channel in HEK-293 cells and after being incubated with potassium channel blockers that selectively eliminate the endogenous potassium conductances of HEK-293 cells. In the absence of maxi-K channel inhibitors, the transfected HEK-293 cells display a hyperpolarized membrane potential, negative inside, close to E_K (-80 mV) which is a consequence of the activity of the maxi-K channel. Blockade of the Maxi-K channel by incubation with maxi-K channel blockers will cause cell depolarization. Changes in membrane potential can be determined with voltage-sensitive fluorescence resonance energy transfer (FRET) dye pairs that use two components, a donor coumarin (CC_2DMPE) and an acceptor oxanol ($DiSBAC_2(3)$).

Oxanol is a lipophilic anion and distributes across the membrane according to membrane potential. Under normal conditions, when the inside of the cell is negative with respect to the outside, oxanol is accumulated at the outer leaflet of the membrane and excitation of coumarin will cause FRET to occur. Conditions that lead to membrane depolarization will cause the oxanol to redistribute to the inside of the cell, and, as a consequence, to a decrease in FRET. Thus, the ratio change (donor/acceptor) increases after membrane depolarization, which determines if a test compound actively blocks the maxi-K channel.

The HEK-293 cells were obtained from the American Type Culture Collection , 12301 Parklawn Drive, Rockville, Maryland, 20852 under accession number ATCC CRL-1573. Any restrictions relating to public access to the microorganism shall be irrevocably removed upon patent issuance.

Transfection of the alpha and beta1 subunits of the maxi-K channel in HEK-293 cells was carried out as follows: HEK-293 cells were plated in 100 mm tissue culture treated dishes at a density of $3x10^6$ cells per dish, and a total of five dishes were prepared. Cells were grown in a medium consisting of Dulbecco's Modified Eagle Medium (DMEM) supplemented with 10% Fetal Bovine serum, 1X L-Glutamine, and 1X Penicillin/Streptomycin, at 37°C, 10% CO_2. For transfection with Maxi-K hα(pCIneo) and Maxi-K hβ1(pIRESpuro) DNAs, 150 µl FuGENE6™ was added dropwise into 10 ml of serum free/phenol-red free DMEM and allowed to incubate at room temperature for 5 minutes. Then, the FuGENE6™ solution was added dropwise to a DNA solution containing 25 µg of each plasmid DNA, and incubated at room temperature for 30 minutes. After the incubation period, 2 ml of the FuGENE6™/DNA solution was added dropwise to each plate of cells and the cells were allowed to grow two days under the same conditions as described above. At the end of the second day, cells were put under selection media which consisted of DMEM supplemented with both 600 µg/ml G418 and 0.75 µg/ml puromycin. Cells were grown until separate colonies were formed. Five colonies were collected and transferred to a 6 well tissue culture treated dish. A total of 75 colonies were collected. Cells were allowed to grow until a confluent monolayer was obtained. Cells were then tested for the presence of maxi-K channel alpha and beta1 subunits using an assay that monitors binding of ^{125}I-iberiotoxin-D19Y/Y36F to the channel. Cells expressing ^{125}I-iberiotoxin-D19Y/Y36F binding activity were then evaluated in a functional assay that monitors the capability of maxi-K channels to control the membrane potential of transfected HEK-293 cells using fluorescence resonance energy transfer (FRET) ABS technology with a VIPR instrument. The colony giving the largest signal to noise ratio was subjected to limiting dilution. For this, cells were resuspended at approximately 5 cells/ml, and 200 µl were plated in individual wells in a 96 well tissue culture treated plate, to add ca. one cell per well. A total of two 96 well plates were made. When a confluent monolayer was formed, the cells were transferred to 6 well tissue culture treated plates. A total of 62 wells were transferred. When a confluent monolayer was

obtained, cells were tested using the FRET-functional assay. Transfected cells giving the best signal to noise ratio were identified and used in subsequent functional assays.

For functional assays:

The transfected cells (2E+06 Cells/mL) are then plated on 96-well poly-D-lysine plates at a density of about 100,000 cells/well and incubated for about 16 to about 24 hours. The medium is aspirated of the cells and the cells washed one time with 100 µl of Dulbecco's phosphate buffered saline (D-PBS). One hundred microliters of about 9 µM coumarin (CC_2DMPE)-0.02% pluronic-127 in D-PBS per well is added and the wells are incubated in the dark for about 30 minutes. The cells are washed two times with 100 µl of Dulbecco's phosphate-buffered saline and 100 µl of about 4.5 µM of oxanol ($DiSBAC_2(3)$) in (mM) 140 NaCl, 0.1 KCl, 2 $CaCl_2$, 1 $MgCl_2$, 20 Hepes-NaOH, pH 7.4, 10 glucose is added. Three micromolar of an inhibitor of endogenous potassium conductance of HEK-293 cells is added. A maxi-K channel blocker is added (about 0.01 micromolar to about 10 micromolar) and the cells are incubated at room temperature in the dark for about 30 minutes.

The plates are loaded into a voltage/ion probe reader (VIPR) instrument, and the fluorescence emission of both CC_2DMPE and $DiSBAC_2(3)$ are recorded for 10 sec. At this point, 100 µl of high-potassium solution (mM): 140 KCl, 2 $CaCl_2$, 1 $MgCl_2$, 20 Hepes-KOH, pH 7.4, 10 glucose are added and the fluorescence emission of both dyes recorded for an additional 10 sec. The ratio $CC_2DMPE/DiSBAC_2(3)$, before addition of high-potassium solution equals 1. In the absence of maxi-K channel inhibitor, the ratio after addition of high-potassium solution varies between 1.65-2.0. When the Maxi-K channel has been completely inhibited by either a known standard or test compound, this ratio remains at 1. It is possible, therefore, to titrate the activity of a Maxi-K channel inhibitor by monitoring the concentration-dependent change in the fluorescence ratio.

The compounds of this invention were found to cause concentration-dependent inhibition of the fluorescence ratio with IC_{50}'s in the range of about 1nM to about 20 µM, more preferably from about 10 nM to about 500 nM.

B. <u>Electrophysiological assays of compound effects on high-conductance calcium-activated potassium channels</u>

<u>Methods:</u>

Patch clamp recordings of currents flowing through large-conductance calcium-activated potassium (maxi-K) channels were made from membrane patches excised from CHO cells constitutively expressing the α-subunit of the maxi-K channel or HEK293 cells constitutively expressing both α- and β-subunits using conventional techniques (Hamill et al., 1981, Pflügers Archiv. 391, 85-100) at room temperature. Glass capillary tubing (Garner #7052 or Drummond custom borosilicate glass 1-014-1320) was pulled in two stages to yield micropipettes with tip diameters of approximately 1-2 microns.

Pipettes were typically filled with solutions containing (mM): 150 KCl, 10 Hepes (4-(2-hydroxyethyl)-1-piperazine methanesulfonic acid), 1 Mg, 0.01 Ca, and adjusted to pH 7.20 with KOH. After forming a high resistance (>10^9 ohms) seal between the plasma membrane and the pipette, the pipette was withdrawn from the cell, forming an excised inside-out membrane patch. The patch was excised into a bath solution containing (mM): 150 KCl, 10 Hepes, 5 EGTA (ethylene glycol bis(ß-aminoethyl ether)-N,N,N',N'-tetraacetic acid), sufficient Ca to yield a free Ca concentration of 1-5 μM, and the pH was adjusted to 7.2 with KOH. For example, 4.193 mM Ca was added to give a free concentration of 1 μM at 22 °C. An EPC9 amplifier (HEKA Elektronic, Lambrect, Germany) was used to control the voltage and to measure the currents flowing across the membrane patch. The input to the headstage was connected to the pipette solution with a Ag/AgCl wire, and the amplifier ground was connected to the bath solution with a Ag/AgCl wire covered with a tube filled with agar dissolved in 0.2 M KCl. The identity of maxi-K currents was confirmed by the sensitivity of channel open probability to membrane potential and intracellular calcium concentration.

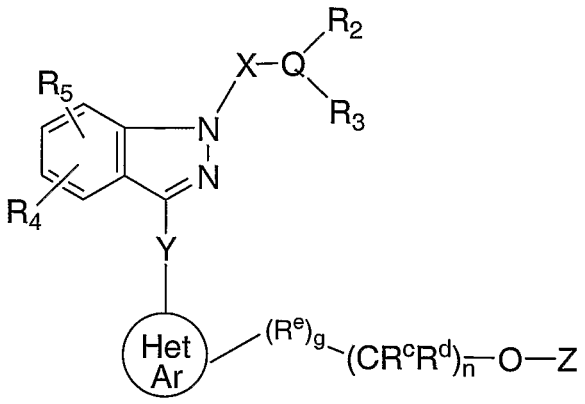
Data acquisition was controlled by PULSE software (HEKA Elektronic) and stored on the hard drive of a MacIntosh computer (Apple Computers) for later analysis using PULSEFIT (HEKA Elektronic) and Igor (Wavemetrics, Oswego, OR) software.

Results:

The effects of the compounds of the present invention on maxi-K channels was examined in excised inside-out membrane patches with constant superfusion of bath solution. The membrane potential was held at –80 mV and brief (100-200 ms) voltage steps to positive membrane potentials (typically +50 mV) were applied once per 15 seconds to transiently open maxi-K channels. As a positive control in each experiment, maxi-K currents were eliminated at pulse potentials after the patch was transiently exposed to a low concentration of calcium (<10 nM) made by adding 1 mM EGTA to the standard bath solution with no added calcium. The fraction of channels blocked in each experiment was calculated from the reduction in peak current caused by application of the specified compound to the internal side of the membrane patch. Compound was applied until a steady state level of block was achieved. K_I values for channel block were calculated by fitting the fractional block obtained at each compound concentration with a Hill equation. The K_I values for channel block by the compounds described in the present invention range from 0.01 nM to greater than 10 μM.

WHAT IS CLAIMED IS:

1. A compound of the structural formula I:



Formula I

or a pharmaceutically acceptable salt, *in vivo* hydrolysable ester, enantiomer, diastereomer or mixture thereof:

wherein,

R represents hydrogen, or C_{1-6} alkyl;

R^c and R^d independently represent hydrogen or halo;

R^e represents N or O;

X represents $-(CHR_7)_p-$, $-(CHR_7)_pCO-$;

Y represents $-CO(CH_2)_n-$, CH_2, or $-CH(OR)-$;

Q represents CR_Y;

R_Y represents H, or C_{1-6} alkyl;

R_w represents H, C_{1-6} alkyl, $-C(O)C_{1-6}$ alkyl, $-C(O)OC_{1-6}$ alkyl, $-SO_2N(R)_2$, $-SO_2C_{1-6}$ alkyl, $-SO_2C_{6-10}$ aryl, NO_2, CN or $-C(O)N(R)_2$;

R_2 represents hydrogen, C_{1-10} alkyl, OH, C_{2-6} alkenyl, C_{1-6} alkylSR, $-(CH_2)_nO(CH_2)_mOR$, $-(CH_2)_nC_{1-6}$ alkoxy, $-(CH_2)_nC_{3-8}$ cycloalkyl, $-(CH_2)_nC_{3-10}$ heterocyclyl, $-N(R)_2$, -COOR, or $-(CH_2)_nC_{6-10}$ aryl, said alkyl, heterocyclyl, or aryl optionally substituted with 1-3 groups selected from R^a;

R_3 represents hydrogen, C_{1-10} alkyl, $-(CH_2)_nC_{3-8}$ cycloalkyl, $-(CH_2)_nC_{3-10}$ heterocyclyl, $-(CH_2)_nCOOR$, $-(CH_2)_nC_{6-10}$ aryl, $-(CH_2)_nNHR_8$, $-(CH_2)_nN(R)_2$, $-(CH_2)_nN(R_8)_2$, $-(CH_2)_nNHCOOR$, $-(CH_2)_nN(R_8)CO_2R$, $-(CH_2)_nN(R_8)COR$, $-(CH_2)_nNHCOR$, $-(CH_2)_nCONH(R_8)$, aryl, $-(CH_2)_nC_{1-6}$ alkoxy, CF_3, $-(CH_2)_nSO_2R$, $-(CH_2)_nSO_2N(R)_2$, $-(CH_2)_nCON(R)_2$, $-(CH_2)_nCONHC(R)_3$, $-(CH_2)_nCONHC(R)_2CO_2R$, $-(CH_2)_nCOR_8$, nitro, cyano or halogen, said alkyl, alkoxy, heterocyclyl, or aryl optionally substituted with 1-3 groups of R^a;

or, R_2 and R_3 taken together with the intervening Q form a 3-10 membered carbocyclic or heterocyclic carbon ring optionally interrupted by 1-2 atoms of O, S, C(O) or NR, and optionally having 1-4 double bonds, and optionally substituted by 1-3 groups selected from R^a;

R_4 and R_5 independently represent hydrogen, C_{1-6} alkoxy, OH, C_{1-6} alkyl, COOR, SO_3H, $-O(CH_2)_nN(R)_2$, $-O(CH_2)_nCO_2R$, $-OPO(OH)_2$, CF_3, OCF_3, $-N(R)_2$, nitro, cyano, C_{1-6} alkylamino, or halogen;



represents C_{6-10} aryl or C_{3-10} heterocyclyl, said aryl or heterocyclyl optionally substituted with 1-3 groups selected from R^a;

Z represents $(CH_2)_nPO(OR)(OR^*)$;

R* represents hydrogen, or C_{1-6} alkyl;

R_7 represents hydrogen, C_{1-6} alkyl, $-(CH_2)_nCOOR$ or $-(CH_2)_nN(R)_2$,

R_8 represents $-(CH_2)_nC_{3-8}$ cycloalkyl, $-(CH_2)_n$ 3-10 heterocyclyl, C_{1-6} alkoxy or $-(CH_2)_nC_{5-10}$ heteroaryl, $-(CH_2)_nC_{6-10}$ aryl said heterocyclyl, aryl or heteroaryl optionally substituted with 1-3 groups selected from R^a;

R^a represents F, Cl, Br, I, CF_3, $N(R)_2$, NO_2, CN, $-COR_8$, $-CONHR_8$, $-CON(R_8)_2$, $-O(CH_2)_nCOOR$, $-NH(CH_2)_nOR$, -COOR, $-OCF_3$, -NHCOR, $-SO_2R$, $-SO_2NR_2$, -SR, (C_1-C_6 alkyl)O-, $-(CH_2)_nO(CH_2)_mOR$, $-(CH_2)_nC_{1-6}$ alkoxy, (aryl)O-, $-(CH_2)_nOH$, (C_1-C_6 alkyl)$S(O)_m$-, H_2N-C(NH)-, (C_1-C_6 alkyl)C(O)-, (C_1-C_6 alkyl)OC(O)NH-, -(C_1-C_6 alkyl)$NR_w(CH_2)_nC_{3-10}$ heterocyclyl-R_w, -(C_1-C_6 alkyl)$O(CH_2)_nC_{3-10}$ heterocyclyl-R_w, -(C_1-C_6 alkyl)$S(CH_2)_nC_{3-10}$ heterocyclyl-R_w, -(C_1-C_6 alkyl)-C_{3-10} heterocyclyl-R_w, $-(CH_2)_n$-Z^1-C(=Z^2)$N(R)_2$, -(C_{2-6} alkenyl)$NR_w(CH_2)_nC_{3-10}$ heterocyclyl-R_w, -(C_{2-6} alkenyl)$O(CH_2)_nC_{3-10}$ heterocyclyl-R_w, -(C_{2-6} alkenyl)$S(CH_2)_nC_{3-10}$ heterocyclyl-R_w, -(C_{2-6} alkenyl)-C_{3-10} heterocyclyl-R_w, -(C_{2-6} alkenyl)-Z^1-C(=Z^2)$N(R)_2$, $-(CH_2)_nSO_2R$, $-(CH_2)_nSO_3H$, $-(CH_2)_nPO(OR)_2$, C_{3-10}cycloalkyl, C_{6-10} aryl, C_{3-10} heterocyclyl, C_{2-6} alkenyl, and C_1-C_{10} alkyl, said alkyl, alkenyl, alkoxy, heterocyclyl and aryl optionally substituted with 1-3 groups selected from C_1-C_6 alkyl, CN, NO_2, OH, $CON(R)_2$ and COOR;

Z^1 and Z^2 independently represents NR_w, O, CH_2, or S;

g is 0-1;
m is 0-3;
n is 0-3; and
p is 0-3.

2. The compound according to claim 1 wherein Y is $-CO(CH_2)_n$, p is 1-3 and X is $-(CHR_7)_p$ or $-(CHR_7)_pCO$-.

3. The compound according to claim 2 wherein Z is PO(OR)(OR*), R_2 and R_3 are independently hydrogen, C_{1-10} alkyl or C_{1-6} alkylOH, Y is $-CO(CH_2)_n$.

4. The compound according to claim 3 wherein 

is a 6 membered heteroaryl or phenyl optionally substituted with 1-3 groups selected from R^a.

5. A compound according to claim 4 wherein 

is pyridyl optionally substituted with 1-3 groups selected from R^a.

6. A compound which is:
di-tert--butyl 4-{[1-(3,3-dimethyl-2-oxobutyl)-6-methoxy-1-H-indazole-3-yl]carbonyl}benzylphosphate;

4-{[1-(3,3-dimethyl-2-oxybutyl)-6-methoxy-1-H-indazol-3-yl]carbonyl}benzyl di-hydrogen phosphate;

2-[(5-{[1-(3,3-dimethyl-2-oxobutyl-6-methoxy-1-H-indazol-3-yl)carbonyl}pyridine-2-yl)oxy]ethyl di-hydrogen phosphate;

(5-{[1-3,3-dimethyl-2-oxobutyl)-6-methoxy-1H-indazol-3-yl]carbonyl}pyridine-2-yl)methyl dihydrogen phosphate;

2-(5-{[1-(3,3-dimethyl-2-oxobutyl)-6-methoxy-1H-indazol-3yl]carbonyl}pyridine-2-yl)-2,2-diflouroethyl di-hydrogen phosphate; and

2-(5-{[7-bromo-1-(3,3-dimethyl-2-oxobutyl)-6-methoxy-1H-indazol-3-yl]carbonyl}puyridin-2-yl)-2,2-difluoroethyl di-hydrogen phosphate,
or a pharmaceutically acceptable salt, *in vivo* hydrolysable ester, enantiomer, diastereomer or mixture thereof.

7. A compound which is:
di-tert--butyl 4-{[1-(3,3-dimethyl-2-oxobutyl)-6-methoxy-1-H-indazole-3-yl]carbonyl}benzylphosphate in the form of a monosodium or disodium salt;

4-{[1-(3,3-dimethyl-2-oxybutyl)-6-methoxy-1-H-indazol-3-yl]carbonyl}benzyl di-hydrogen phosphate in the form of a monosodium or disodium salt;

2-[(5-{[1-(3,3-dimethyl-2-oxobutyl-6-methoxy-1-H-indazol-3-yl)carbonyl}pyridine-2-yl)oxy]ethyl di-hydrogen phosphate in the form of a monosodium or disodium salt;

(5-{[1-3,3-dimethyl-2-oxobutyl)-6-methoxy-1H-indazol-3-yl]carbonyl}pyridine-2-yl)methyl dihydrogen phosphate in the form of a monosodium or disodium salt;

2-(5-{[1-(3,3-dimethyl-2-oxobutyl)-6-methoxy-1H-indazol-3yl]carbonyl}pyridine-2-yl)-2,2-diflouroethyl di-hydrogen phosphate in the form of a monosodium or disodium salt; and

2-(5-{[7-bromo-1-(3,3-dimethyl-2-oxobutyl)-6-methoxy-1H-indazol-3-yl]carbonyl}puyridin-2-yl)-2,2-difluoroethyl di-hydrogen phosphate in the form of a monosodium or disodium salt.

8. Use of a compound of formula I in claim 1 for the manufacture of a medicament for the treatment of ocular hypertension or glaucoma.

9. Use of a compound of formula I in claim 1 for the manufacture of a medicament for the treatment of macular edema, macular degeneration, increasing retinal and optic nerve head blood velocity, increasing retinal and optic nerve oxygen tension, and/or a neuroprotective effect.

10. Use of a compound of formula I in claim 1 for the manufacture of a medicament for preventing repolarization or hyperpolarization of a mammalian cell containing potassium channel or for treating Alzheimer's Disease, depression, cognitive disorders, and/or arrhythmia disorders.

11. Use of a compound of formula I in claim 1 for the manufacture of a medicament for treating diabetes.

12. A composition comprising a compound of formula I of claim 1 and a pharmaceutically acceptable carrier.

13. The composition according to Claim 12 wherein the compound of formula I is applied as a topical formulation, said topical formulation administered as a solution or suspension and optionally containing xanthan gum or gellan gum.

14. A composition according to claim 13 wherein one or more of an active ingredient belonging to the group consisting of: β-adrenergic blocking agent, parasympatho-mimetic agent, sympathomimetic agent, carbonic anhydrase inhibitor, EP4 agonist, a prostaglandin or derivative thereof, hypotensive lipid, neuroprotectant, and/or 5-HT2 receptor agonist is optionally added.

15. A composition according to claim 14 wherein the β-adrenergic blocking agent is timolol, betaxolol, levobetaxolol, carteolol, or levobunolol; the parasympathomimetic agent is pilocarpine; the sympathomimetic agent is epinephrine, brimonidine, iopidine, clonidine, or para-aminoclonidine, the carbonic anhydrase inhibitor is dorzolamide, acetazolamide, metazolamide or brinzolamide; the prostaglandin is latanoprost, travaprost, unoprostone, rescula, or S1033, the hypotensive lipid is lumigan, the neuroprotectant is eliprodil, R-eliprodil or memantine; and the 5-HT2 receptor agonist is 1-(2-aminopropyl)-3-methyl-1H-imdazol-6-ol fumarate or 2-(3-chloro-6-methoxy-indazol-1-yl)-1-methyl-ethylamine.