acceptable acid. Pharmaceutically acceptable acids commonly employed to form such acid addition salts include inorganic acids, such as hydrochloric, hydrobromic, nitric, sulphuric or phoshoric acids, and organic acids such as acetic, citric, esylic, fumaric, glycolic, glucuronic, glutaric, lactic, maleic, malic, mandelic, mesylic, napadisylic, oxalic, succinic, tartaric, salicyclic, *o*-acetoxybenzoic, or p-toluene-sulphonic. Pharmaceutically acceptable salts that are base addition are formed when a compound of formula I and the intermediates described herein containing a acidic functionality are reacted with a pharmaceutically acceptable base. Pharmaceutically acceptable bases commonly employed to form base addition salts include organic bases such as ammonia, arginine, benethamine, benzathine, benzylamine, betaine, butylamine, choline, dicyclohexylamine, diethanolamine, diethylamine, ethylenediamine, glucosamine, imidazole, lysine, piperazine, procaine, and inorganic bases such as calcium, potassium, sodium and zinc salts of hydroxide, carbonate or bicarbonate and the like.

In addition to pharmaceutically acceptable salts, other salts are included in the invention. They may serve as intermediates in the purification of compounds or in the preparation of other, for example pharmaceutically-acceptable, acid addition salts, or are useful for identification, characterization or purification.

The term "protecting group or Pg," as used herein, refers to those groups intended to protect or block functional groups against undesirable reactions during synthetic procedures. In the case of an amino or hydroxyl functional group, the suitable protecting group used will depend upon the conditions that will be employed in subsequent reaction steps wherein protection is required. For example, it may be desirable to employ the protection of multiple functional groups, such as amino and hydroxyl, and control their protection and deprotection independently. Commonly used amino and hydroxyl protecting groups are disclosed in *Protective Groups In Organic Synthesis*, T.W. Greene and P.G.M. Wuts 3rd Ed. (John Wiley & Sons, New York (1999)). Suitable amino protecting groups include acyl groups such as formyl, acetyl, propionyl, pivaloyl, t-butylacetyl, 2-chloroacetyl, 2-bromoacetyl, trifluoroacetyl, trichloroacetyl, phthalyl, o-nitrophenoxyacetyl, alpha-chlorobutyryl, benzoyl, 4-chlorobenzoyl, 4-bromobenzoyl, 4-nitrobenzoyl, and the like; sulfonyl groups such as benzenesulfonyl, *p*-toluenesulfonyl and the like, carbamate forming groups such as benzyloxycarbonyl, *p*-chlorobenzyloxycarbonyl, *p*-methoxybenzyloxycarbonyl, *p*-nitrobenzyloxycarbonyl,

2-nitrobenzyloxycarbonyl, *p*-bromobenzyloxycarbonyl, 3,4-dimethoxybenzyloxycarbonyl, 3,5-dimethoxybenzyloxycarbonyl, 2,4-dimethoxybenzyloxycarbonyl, 4-methoxybenzyloxycarbonyl, 2-nitro-4,5-dimethoxybenzyloxycarbonyl, 3,4,5-trimethoxybenzyloxycarbonyl, 1-(*p*-biphenylyl)-1-methylethoxycarbonyl, alpha, alpha-dimethyl-3,5-dimethoxybenzyloxycarbonyl, benzhydryloxycarbonyl, *t*-butyloxycarbonyl, diisopropylmethoxycarbonyl, isopropyloxycarbonyl, ethoxycarbonyl, methoxycarbonyl, allyloxycarbonyl, 2,2,2-trichloroethoxycarbonyl, phenoxycarbonyl, 4-nitrophenoxycarbonyl, fluorenyl-9-methoxycarbonyl, cyclopentyloxycarbonyl, adamantyloxycarbonyl, cyclohexyloxycarbonyl, phenylthiocarbonyl and the like; alkyl groups such as benzyl, triphenylmethyl, benzyloxymethyl and the like; and silyl groups such as trimethylsilyl and the like. Preferred suitable amino protecting groups are acetyl, methyloxycarbonyl, benzoyl, pivaloyl, allyloxycarbonyl, *t*-butylacetyl, benzyl, *t*-butyloxycarbonyl (Boc) and benzyloxycarbonyl (Cbz). Suitable hydroxyl protecting groups include ethers such as methoxymethyl, 1-ethoxyethyl, *tert*-butyl, allyl, benzyl, tetrahydropyranyl and the like; silyl ethers such as trimethylsilyl, triethylsilyl, triisopropylsilyl, *tert*-butyldimethylsilyl and the like; esters such as formate, acetate, pivaloate, benzoate and the like; and sulfonates such as mesylate, benzylsulfonate, tosylate and the like. Preferred suitable hydroxyl protecting groups are acetyl, trimethylsilyl, triisopropylsilyl, *tert*-butyldimethylsilyl and benzyl.

As with any group of pharmaceutically active compounds, some groups are preferred in their end use application. Preferred embodiments for a compound of formula I of the present invention are given below.

Compounds in which R^1 is C3-C7 cycloalkyl or C4-C8 cycloalkylalkyl are preferred. Compounds in which R^1 is C1-C5 alkyl are more preferred. Compounds in which R^1 is methyl are even more preferred.

Compounds in which R^2 is phenyl, substituted phenyl, thiophenyl, substituted thiophenyl, thiazolyl, substituted thiazolyl, pyridinyl, or substituted pyridinyl are preferred. Compounds in which R^2 is C1-C5 alkyl, halo or C1-C3 fluoroalkyl are more preferred. Compounds in which R^2 is methyl, propyl, trifluoromethyl, or chloro are even more preferred.

Compounds in which X is $S(O)_m$ where m is 0, 1 or 2 are preferred. Compounds in which X is O are more preferred.

Compounds in which Y is C1-C3 alkanediyl are preferred. Compounds in which Y is methylene are more preferred.

Compounds in which Ar_1 is substituted phenylene, 1,2,4-oxadiazol-3,5-diyl or substituted pyridinediyl are preferred. Compounds in which Ar_1 is phenylene or pyridinediyl, either attached in the 1-3 position, are more preferred. Compounds in which Ar_1 is phenylene or pyridinediyl, either ring attached in the 1-4 position, are even more preferred.

Compounds in which Ar_2 is substituted phenylene or substituted pyridinediyl are preferred. Compounds in which Ar_2 is phenylene or pyridinediyl are more preferred. Compounds in which Ar_2 is pyridinediyl attached in the 1-4 or 1-3 position are even more preferred.

Compounds in which Ar_1 and Ar_2 are independently phenylene or pyridinediyl are preferred.

Compounds in which Ar_1 is phenylene are preferred.

Compounds in which Ar_2 is pyridinediyl are preferred.

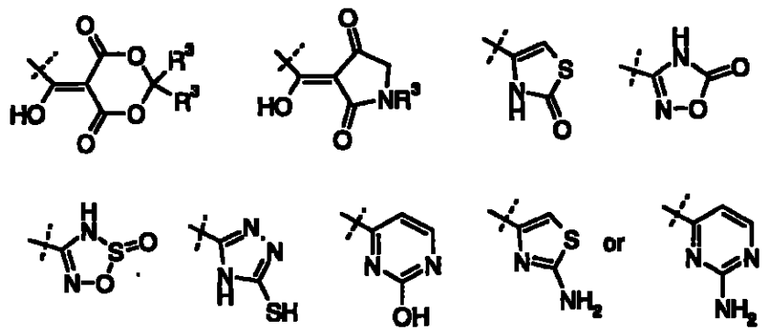
Compounds in which Ar_2 is attached at the 1-4 position are preferred.

Compounds in which Ar_2 is attached at the 1-3 position are preferred.

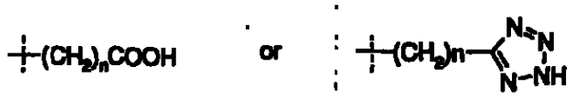
Compounds in which Ar_1 is attached at the 1-3 position or 1-4 position are preferred.

Compounds in which L is S(O)p are preferred. Compounds in which L is S are more preferred. Compounds in which L is O are more preferred.

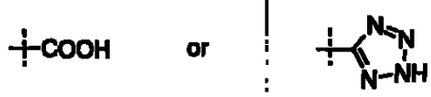
Compounds in which Z is



are preferred. Compounds in which Z is



are more preferred. Compounds in which Z is



are even more preferred.

A compound of formula I as described above wherein

R^1 is methyl or ethyl;

R^2 is selected from the group consisting of hydrogen, methyl, ethyl, propyl, fluoro, chloro, trifluoromethyl, and COOH;

X is O;

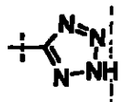
Y is methylene;

Ar_1 is phenylene or pyridinediyl;

Ar_2 is selected from the group consisting of phenylene, trifluoromethylphenylene, and pyridinediyl;

L is selected from the group consisting of O, S, SO, SO_2 and NH; and

Z is COOH or



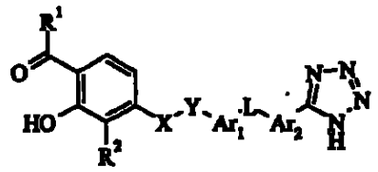
is preferred.

A compound of formula I selected from the group consisting of 1-(2-hydroxy-3-methyl-4-{4-[4-(1*H*-tetrazol-5-yl)-pyridin-2-yloxy]-benzyloxy}-phenyl)-ethanone, 1-(2-hydroxy-3-methyl-4-{4-[3-(1*H*-tetrazol-5-yl)-phenoxy]-benzyloxy}-phenyl)-ethanone and 1-(2-hydroxy-4-{3-[4-(2*H*-tetrazol-5-yl)-pyridin-2-yloxy]-benzyloxy}-3-trifluoromethyl-phenyl)-ethanone is preferred.

A compound of formula I which is 6-(3-((4-acetyl-3-hydroxy-2-propyl-phenoxy)methyl)phenylthio)isonicotinic acid is more preferred.

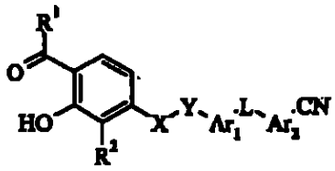
Further embodiments of the invention include a process for preparing the compound of formula I, or a pharmaceutically acceptable salt thereof, comprising

(A) for a compound of formula I where Z is tetrazolyl,



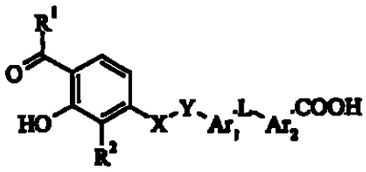
I, Z is tetrazolyl

cycloaddition of a compound of formula II where R^{10} is cyano with an azide reagent;



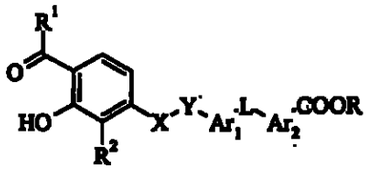
II, R^{10} is cyano

(B) for a compound of formula I where Z is COOH,



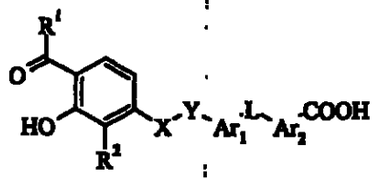
I, Z is COOH

hydrolysis of a compound of formula II where R^{10} is carboxylic acid ester;



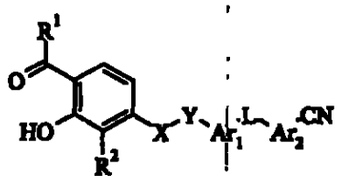
II, R^{10} is COOR

(C) for a compound of formula I where Z is COOH,



I, Z is COOH

hydrolysis of a compound of formula II where R^{10} is cyano; and

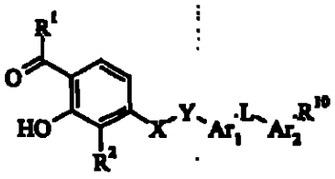


II, R^{10} is cyano

whereafter, when a pharmaceutically acceptable salt of the compound of formula I is required, it is obtained by reacting the acid of formula I with a physiologically acceptable base or by reacting a basic compound of formula I with a physiologically acceptable acid or by any other conventional procedure.

Chemical Abstracts discloses 5-[[6-[(4-acetyl-3-hydroxy-2-propylphenoxy)-methyl]-2-pyridinyl]methoxy]-2-butoxybenzoic acid ethyl ester.

A further embodiment of the present invention provides intermediate compounds useful for the preparation of a compound of formula I. More specifically, the present invention provides a compound of formula II



II

wherein

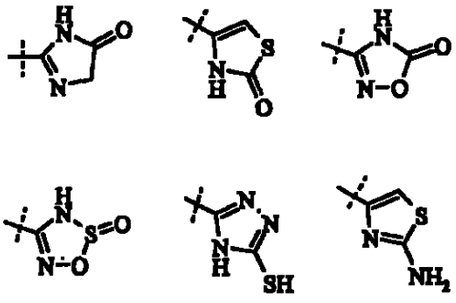
R^1, R^2, X, Y, Ar_1, Ar_2 and L are defined as above; and

R^{10} is CN or $COOR^{14}$ in which R^{14} is selected from the group consisting of C1-C5 alkyl, phenyl and benzyl; other than 5-[[6-[(4-acetyl-3-hydroxy-2-propylphenoxy)-

methyl]-2-pyridinyl]methoxy]-2-butoxybenzoic acid ethyl ester. A particular value of R^{14} is methyl.

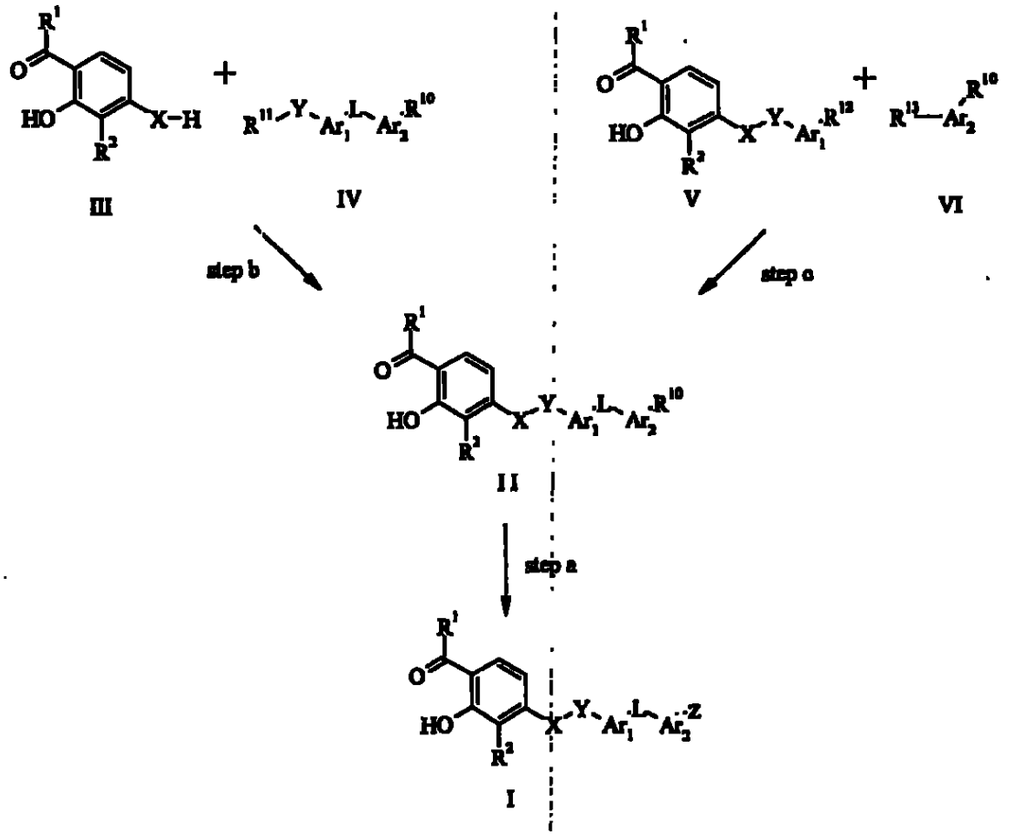
Compounds of the present invention may be made by a process which is analogous to one known in the chemical art for the production of structurally analogous compounds or by a novel process described herein. Such processes useful for the manufacture of a compound of formula I as defined above are provided as further features of the invention and are illustrated by the following procedures in which, unless otherwise specified, the meanings of the generic radicals are as defined above and all reagents are well known and appreciated in the art.

Generally, a compound of formula I may be prepared from a compound of formula II where R^{10} represents a precursor to Z (Reaction Scheme A, step a). More specifically, a compound of formula II where R^{10} is carboxylic acid ester or nitrile is reacted with a suitable base such as potassium hydroxide in a suitable solvent such as water to provide a compound of formula I where Z is carboxylic acid. Additionally, a compound of formula II where R^{10} is cyano is reacted with an azide reagent to provide a compound of formula I where Z is tetrazolyl. Azide reagents include HN_3 wherein HN_3 is provided from the reaction of sodium azide and a protic acid such as triethylamine hydrochloride and ammonium chloride. The reaction is conveniently in a solvent such solutions of water and an organic co-solvent wherein the organic cosolvent is an alcohol such as isopropyl alcohol or a tertiary amide such as N-methyl pyrrolidinone. Other examples of azide reagents include transition metal azide complexes such as provided from the reaction of zinc bromide and sodium azide, as well as the trialkylsilylazides such as trimethylsilylazide. A compound of formula II where R^{10} is an acid halide is reacted in one or more steps with cyclocondensating agents to provide a compound of formula I where Z is



A compound of formula of II may be prepared from a compound of formula III (Reaction Scheme A, step b) or, alternatively, from a compound of formula V (Reaction Scheme A, step c). More specifically in step b, a compound of formula III where X is O is reacted under Mitsunobu conditions with a compound of formula IV where R^{11} is OH in the presence of an organophosphine such as tributylphosphine and an appropriate azodicarbonyl reagent such as 1,1'-(azodicarbonyl)dipiperidine to provide a compound of formula II. Suitable solvents include toluene and dichloromethane. In step b, a compound of formula II may also be prepared by reacting a compound of formula III where X is O, S, NH with a compound of formula IV where R^{11} is a leaving group in the presence of a suitable base such as cesium carbonate and a suitable solvent such as acetone. Suitable leaving groups include halides such as iodide, and sulfonate esters such as methanesulfonate ester.

Reaction Scheme A



Alternatively, a compound of formula of II may be prepared from a compound of formula V (Reaction Scheme A, step c) where R^{12} is an appropriate precursor to the group L. More specifically, a compound of formula V where Ar_1 is pyridinediyl and R^{12} is a leaving group is reacted with a compound of formula VI where R^{13} is thiol in a solvent such dimethylformamide to provide a compound of formula II where L is S. Suitable leaving groups include a halide such as chloride.

A compound of formula III where R^2 is halo, phenyl, substituted phenyl, thiophenyl, substituted thiophenyl and the like maybe prepared from a compound of formula VII (Reaction Scheme B). More specially, a compound of formula VII where X is O is reacted under the appropriate halogenation conditions to provide a compound of formula III where X is O and R^2 is a halogen such as chloro, bromo or iodo. A compound of formula III where X is O and R^2 is a halogen such as chloro, bromo or iodo is reacted with a boronic acid of phenyl, substituted phenyl, thiophenyl, substituted thiophenyl and the like in the presence of a transition metal catalyst such as $Pd(dppf)_2Cl_2$ and a base such as cesium hydroxide to provide a compound of formula III where R^2 is the corresponding phenyl, substituted phenyl, thiophenyl, substituted thiophenyl and the like. The reaction is conveniently carried out in a solvent such as solutions of tetrahydrofuran and water.

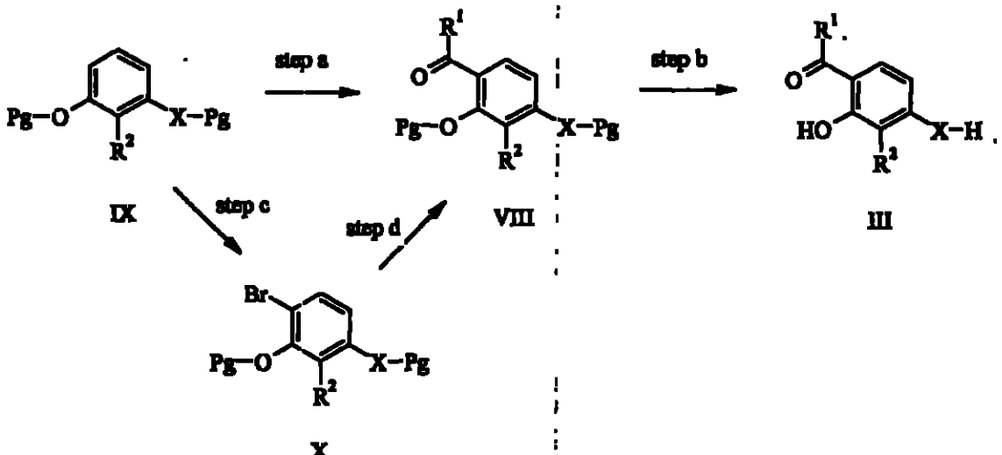
Reaction Scheme B

VII III

A compound of formula III where X is S may be prepared from a compound of formula III where X is O. More specifically, a compound of formula III where X is O is reacted with dimethylthiocarbamoyl chloride in a suitable solvent such as dichloromethane. The resulting thiocarbamate is heated in a suitable solvent such as dodecane and treated with sodium hydroxide to provide a compound of formula III where X is S.

A compound of formula III may also be prepared from a compound of formula IX where the group Pg represents a suitable protecting group (Reaction Scheme C). More specifically in step a, a compound of formula IX where R^2 is a halogen such iodo or bromo and Pg is methyl, is reacted with a boronic acid of phenyl, substituted phenyl, thiophenyl, substituted thiophenyl and the like in the presence of a transition metal catalyst such as $Pd(dppf)_2Cl_2$ and a base such as cesium hydroxide to provide a compound of formula IX where R^2 is phenyl, substituted phenyl, thiophenyl, substituted thiophenyl and the like, and Pg is methyl. The reaction is conveniently carried out in a solvent such as a solution of tetrahydrofuran and water. Further in step a, a compound of formula IX where R^2 is phenyl, substituted phenyl, thiophenyl, substituted thiophenyl and the like is reacted with an R^1 acyl halide such as acetyl chloride and a Lewis acid such as aluminum chloride in a suitable solvent to provide a compound of formula VIII where R^1 is methyl and R^2 is phenyl, substituted phenyl, thiophenyl, substituted thiophenyl and the like. Suitable solvents include dichloromethane. In step b, a compound of formula VIII where the group Pg is methyl is reacted with deprotection agents such as pyridine hydrochloride in the presence of microwave radiation to provide a compound of formula III where R^2 is phenyl, substituted phenyl, thiophenyl, substituted thiophenyl and the like.

Reaction Scheme C

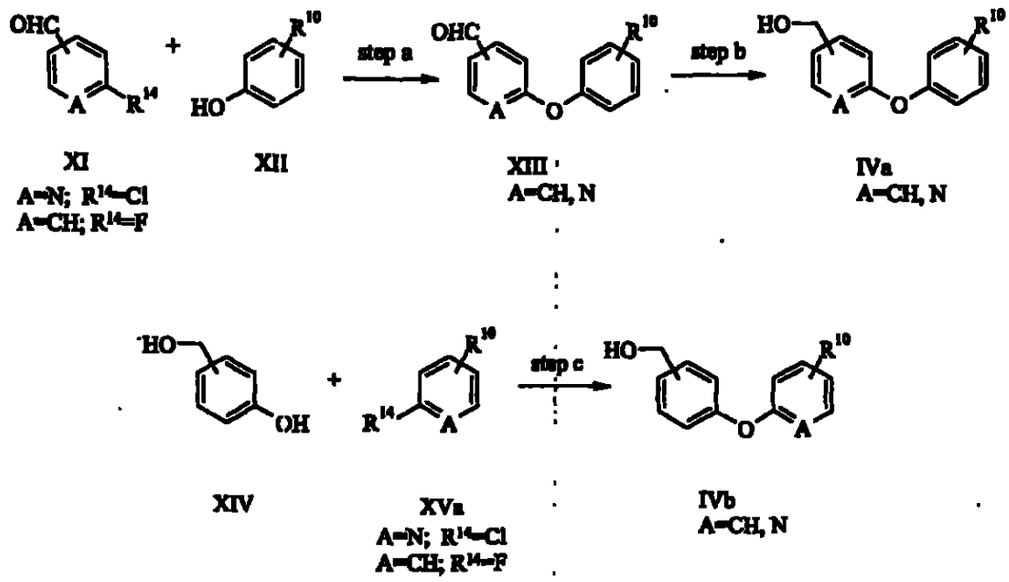


Additionally in Reaction Scheme C, a compound of formula III where R^2 is C1-C3 fluoroalkyl may be prepared from a compound of formula IX where R^2 is a halogen. More specifically, a compound of formula IX where R^2 is iodo, X is O and Pg is

a suitable protecting group such as benzyl is reacted with an alkyl ester of difluoro-fluorosulfonyl-acetic acid in the presence of hexamethylphosphoramide and a transistion metal catalyst such as copper iodide in a suitable solvent to provide a compound of formula IX where R^2 is trifluoromethyl, X is O, and Pg is benzyl. Suitable solvents include dimethylformamide. In step c, a compound of formula IX where R^2 is trifluoromethyl, X is O, and Pg is benzyl is reacted *N*-bromosuccinimide in a suitable solvent such as dimethylformamide to provide a compound of formula X. In step d, a compound of formula X is reacted with tributyl-(1-ethoxy-vinyl)-stannane and a transition metal catalyst such as tetrakis(triphenylphosphine)palladium in a solvent such as dioxane followed by acid hydrolysis to provide a compound of formula VIII where R^1 is methyl, R^2 is trifluoromethyl, X is O, and Pg is benzyl. In step b, a compound of formula VIII where R^1 is methyl, R^2 is trifluoromethyl, X is O, and Pg is benzyl is reacted with a transistion metal catalyst such as palladium hydroxide in the presence of an effective hydrogen source such as cyclohexene to provide a compound of formula III where R^1 is methyl, R^2 is trifluoromethyl, and X is O. Suitable solvents include ethanol.

A compound of formula IV where L is O may be prepared under aryl ether forming conditions as outlined in Reaction Scheme D. More specifically in step a, a compound of formula XII where R^{10} represents a precursor to Z is reacted with a compound of formula XI where A is N and R^{14} is chloro in the presence of a suitable base such as potassium carbonate to provide a compound of formula XIII where A is N. The reaction is conveniently carried out in a solvent such as dimethylacetamide. Analogously, a compound of formula XII where R^{10} represents a precursor to Z is reacted with a compound of formula XI where A is CH and R^{14} is fluoro in the presence of a suitable base such as potassium carbonate to provide a compound of formula XIII where A is CH. The reaction is conveniently carried out in a solvent such as dimethylacetamide.

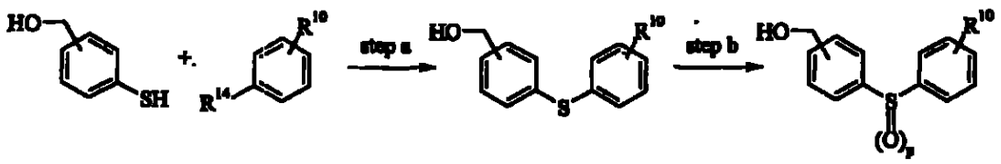
Reaction Scheme D



In Reaction Scheme D, step b, a compound of formula XIII where A is CH or N is reacted with a reducing agent such as sodium borohydride in a suitable solvent such as methanol to provide a compound of formula IVa where A is CH or N. In step c, a compound of formula XVa where A is N and R^{14} is chloro or alternatively a compound where A is CH and R^{14} is fluoro is reacted with a compound of formula XIV in the presence of a suitable base such as potassium carbonate to provide a compound of formula IVb where A is N or CH. The reaction is conveniently carried out in a solvent such as dimethylacetamide.

A compound of formula IV where L is $S(O)_p$ and p is 0,1 or 2 may be prepared from a compound of formula XVb as outlined in Reaction Scheme E. More specifically in step a, a compound of formula XVb where $R^{14'}$ is a halogen such as iodo is reacted with a compound of formula XVI, copper (I) chloride and a suitable base such as cesium carbonate to provide a compound of formula IVc. The reaction is conveniently carried out in a solvent such as *N*-methylpyrrolidinone. In step b, a compound of formula IVc is reacted with a suitable oxidizing agent such as potassium peroxymonosulfate in a solvent such as methanol to provide a compound of formula IVd where p is 1 or 2.

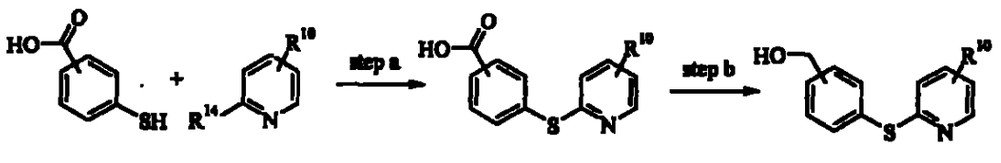
Reaction Scheme E



XVI XVb IVc IVd

In Reaction Scheme F step a, a compound of formula XIV is reacted sequentially with a suitable base such as sodium hydride and a compound of formula XVc where R^{14} is a halogen such as chloro in a suitable solvent such as dimethylformamide to provide a compound of formula XVI. In step b, a compound of formula XVI is reacted with an acyl halide forming agent such as thionyl chloride to form an intermediate acid chloride which is reacted with a suitable reducing agent such as sodium borohydride in suitable solvent such as dioxane to provide a compound of formula IVe.

Reaction Scheme F



XIV XVc XVI IVe

The compounds of the present invention can be administered alone or in the form of a pharmaceutical composition, that is, combined with pharmaceutically acceptable carriers or excipients, the proportion and nature of which are determined by the solubility and chemical properties of the compound selected, the chosen route of administration, and standard pharmaceutical practice. The compounds of the present invention, while effective themselves, may be formulated and administered in the form of their pharmaceutically acceptable salts, for purposes of stability, convenience of crystallization, increased solubility, and the like.

In practice, the compounds of formula I are usually administered in the form of pharmaceutical compositions, that is, in admixture with pharmaceutically acceptable carriers or diluents, the proportion and nature of which are determined by the chemical

properties of the selected compound of formula I, the chosen route of administration, and standard pharmaceutical practice.

Thus, the present invention provides pharmaceutical compositions comprising a compound of the formula I and a pharmaceutically acceptable carrier, diluent or excipient.

The compounds of formula I can be administered by a variety of routes. In effecting treatment of a patient afflicted with disorders described above, a compound of formula I can be administered in any form or mode which makes the compound bioavailable in an effective amount, including oral and parenteral routes. For example, compounds of formula I can be administered orally, by inhalation, subcutaneously, intramuscularly, intravenously, transdermally, intranasally, rectally, ocularly, topically, sublingually, buccally, and the like. Oral administration is generally preferred for treatment of the neurological and psychiatric disorders described herein.

One skilled in the art of preparing formulations can readily select the proper form and mode of administration depending upon the particular characteristics of the compound selected, the disorder or condition to be treated, the stage of the disorder or condition, and other relevant circumstances. (*Remington's Pharmaceutical Sciences*, 18th Edition, Mack Publishing Co. (1990)).

The pharmaceutical compositions of the present invention are prepared in a manner well known in the pharmaceutical art. The carrier or excipient may be a solid, semi-solid, or liquid material which can serve as a vehicle or medium for the active ingredient. Suitable carriers or excipients are well known in the art. The pharmaceutical composition may be adapted for oral, inhalation, parenteral, or topical use and may be administered to the patient in the form of tablets, capsules, aerosols, inhalants, suppositories, solution, suspensions, or the like.

The compounds of the present invention may be administered orally, for example, with an inert diluent or capsules or compressed into tablets. For the purpose of oral therapeutic administration, the compounds may be incorporated with excipients and used in the form of tablets, troches, capsules, elixirs, suspensions, syrups, wafers, chewing gums and the like. These preparations should contain at least 4% of the compound of the present invention, the active ingredient, but may be varied depending upon the particular form and may conveniently be between 4% to about 70% of the weight of the unit. The

amount of the compound present in compositions is such that a suitable dosage will be obtained. A person skilled in the art may determine preferred compositions and preparations according to the present invention.

The tablets, pills, capsules, troches, and the like may also contain one or more of the following adjuvants: binders such as microcrystalline cellulose, gum tragacanth or gelatin; excipients such as starch or lactose, disintegrating agents such as alginic acid, Primogel, corn starch and the like; lubricants such as magnesium stearate or Sterotex; glidants such as colloidal silicon dioxide; and sweetening agents such as sucrose or saccharin may be added or a flavoring agent such as peppermint, methyl salicylate or orange flavoring. When the dosage unit form is a capsule, it may contain, in addition to materials of the above type, a liquid carrier such as polyethylene glycol or a fatty oil. Other dosage unit forms may contain other various materials which modify the physical form of the dosage unit, for example, as coatings. Thus, tablets or pills may be coated with sugar, shellac, or other coating agents. A syrup may contain, in addition to the present compounds, sucrose as a sweetening agent and certain preservatives, dyes and colorings and flavors. Materials used in preparing these various compositions should be pharmaceutically pure and non-toxic in the amounts used.

For the purpose of parenteral therapeutic administration, the compounds of the present invention may be incorporated into a solution or suspension. These preparations typically contain at least 0.1% of a compound of the invention, but may be varied to be between 0.1 and about 90% of the weight thereof. The amount of the compound of formula I present in such compositions is such that a suitable dosage will be obtained. The solutions or suspensions may also include one or more of the following adjuvants: sterile diluents such as water for injection, saline solution, fixed oils, polyethylene glycols, glycerine, propylene glycol or other synthetic solvents; antibacterial agents such as benzyl alcohol or methyl paraben; antioxidants such as ascorbic acid or sodium bisulfite; chelating agents such as ethylene diaminetetraacetic acid; buffers such as acetates, citrates or phosphates and agents for the adjustment of tonicity such as sodium chloride or dextrose. The parenteral preparation can be enclosed in ampoules, disposable syringes or multiple dose vials made of glass or plastic. Preferred compositions and preparations are able to be determined by one skilled in the art.