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(54) **SUBSTITUTED POLYCYCLIC ARYL AND HETEROARYL $i(TERTIARY)-HETEROALKYLAMINES USEFUL FOR INHIBITING CHOLESTERYL ESTER TRANSFER PROTEIN ACTIVITY**

POLYCYCLISCHE ARYL UND HETEROARYL SUBSTITUIERTE TERTIÄRE HETEROALKYLAMINE, FÜR DIE HEMMUNG DER AKTIVITÄT DES CHOLESTERYL-ESTER-TRANSFER-PROTEINS

ARYL- ET HETEROARYL-HETEROALKYLAMINES TERTIAIRES POLYCYCLIQUES SUBSTITUEES, UTILES COMME INHIBITEURS DE L'ACTIVITE DE LA PROTEINE DE TRANSFERT DE L'ESTER DE CHOLESTERYLE

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Description

FIELD OF THE INVENTION

[0001] This invention is in the field of treating cardiovascular disease, and specifically relates to compounds, compositions and methods for treating atherosclerosis and other coronary artery disease. More particularly, the invention relates to substituted polycyclic aryl and heteroaryl *tertiary*-heteroalkylamine compounds that inhibit cholesteryl ester transfer protein (CETP), also known as plasma lipid transfer protein-I.

BACKGROUND OF THE INVENTION

[0002] Numerous studies have demonstrated that a low plasma concentration of high density lipoprotein (HDL) cholesterol is a powerful risk factor for the development of atherosclerosis (Barter and Rye, Atherosclerosis, 121, 1-12 (1996)). HDL is one of the major classes of lipoproteins that function in the transport of lipids through the blood. The major lipids found associated with HDL include cholesterol, cholesteryl ester, triglycerides, phospholipids and fatty acids. The other classes of lipoproteins found in the blood are low density lipoprotein (LDL) and very low density lipoprotein (VLDL). Since low levels of HDL cholesterol increase the risk of atherosclerosis, methods for elevating plasma HDL cholesterol would be therapeutically beneficial for the treatment of atherosclerosis and other diseases associated with accumulation of lipid in the blood vessels. These diseases include, but are not limited to, coronary heart disease, peripheral vascular disease, and stroke.

[0003] Atherosclerosis underlies most coronary artery disease (CAD), a major cause of morbidity and mortality in modem society. High LDL cholesterol (above 180 mg/dl) and low HDL cholesterol (below 35 mg/dl) have been shown to be important contributors to the development of atherosclerosis. Other diseases, such as peripheral vascular disease, stroke, and hypercholesterolaemia are negatively affected by adverse HDL/LDL ratios. Inhibition of CETP by the subject compounds is shown to effectively modify plasma HDL/LDL ratios, and to check the progress and/or formation of these diseases.

[0004] CETP is a plasma protein that facilitates the movement of cholesteryl esters and triglycerides between the various lipoproteins in the blood (Tall, J. Lipid Res., 34, 1255-74 (1993)). The movement of cholesteryl ester from HDL to LDL by CETP has the effect of lowering HDL cholesterol. It therefore follows that inhibition of CETP should lead to elevation of plasma HDL cholesterol and lowering of plasma LDL cholesterol, thereby providing a therapeutically beneficial plasma lipid profile (McCarthy, Medicinal Res. Revs., 13, 139-59 (1993); Sitori, Pharmac. Ther., 67,443-47 (1995)). This exact phenomenon was first demonstrated by Swenson et al., (J. Biol. Chem., 264, 14318 (1989)) with the use of a monoclonal antibody that specifically inhibited CETP. In rabbits, the antibody caused an elevation of the plasma HDL cholesterol and a decrease in LDL cholesterol. Son et al. (Biochim. Biophys. Acta 795, 743-480 (1984)), Morton et al. (J. Lipid Res. 35, 836-847 (1994)) and Tollefson et al. (Am. J. Physiol., 255, (Endocrinol. Metab. 18, E894-E902 (1988))) describe proteins from human plasma that inhibit CETP. U.S. Patent 5,519,001, issued to Kushwaha et al., describes a 36 amino acid peptide derived from baboon apo C-1 that inhibits CETP activity. Cho et al. (Biochim. Biophys. Acta 1391, 133-144 (1998)) describe a peptide from hog plasma that inhibits human CETP. Bonin et al. (J. Peptide Res., 51, 216-225 (1998)) disclose a decapeptide inhibitor of CETP. A depsipeptide fungal metabolite is disclosed as a CETP inhibitor by Hedge et al. in Bioorg. Med. Chem. Lett., 8, 1277-80 (1998).

[0005] There have been several reports of non-peptidic compounds that act as CETP inhibitors. Barrett et al. (J. Am. Chem. Soc., 188, 7863-63 (1996)) and Kuo et al. (J. Am. Chem. Soc., 117, 10629-34 (1995)) describe cyclopropane-containing CETP inhibitors. Pietzonka et al. (Bioorg. Med. Chem. Lett, 6, 1951-54 (1996)) describe phosphonate-containing analogs of cholesteryl ester as CETP inhibitors. Coval et al. (Bioorg. Med. Chem. Lett., 5, 605-610 (1995)) describe Wiedendiol-A and -B, and related sesquiterpene compounds as CETP inhibitors. Japanese Patent Application No. 10287662-A describes polycyclic, non-amine containing, polyhydroxylic natural compounds possessing CETP inhibition properties. Lee et al. (J. Antibiotics, 49, 693-96 (1996)) describe CETP inhibitors derived from an insect fungus. Busch et al. (Lipids, 25, 216-220, (1990)) describe cholesteryl acetyl bromide as a CETP inhibitor. Morton and Zilversmit (J. Lipid Res., 35, 836-47 (1982)) describe that p-chloromercuriphenyl sulfonate, p-hydroxymercuribenzoate and ethyl mercurithiosalicylate inhibit CETP. Connolly et al. (Biochem. Biophys. Res. Comm. 223, 42-47 (1996)) describe other cysteine modification reagents as CETP inhibitors. Xia et al. describe 1,3,5-triazines as CETP inhibitors (Bioorg. Med. Chem. Lett., 6, 919-22 (1996)). Bisgaier et al. (Lipids, 29, 811-8 (1994)) describe 4-phenyl-5-tridecyl-4H-1,2,4-triazolethiol as a CETP inhibitor. Oomura et al. disclose non-peptidic tetracyclic and hexacyclic phenols as CETP inhibitors in Japanese Patent Application No. 10287662. In WO Patent Application No. 09914204, Sikorski describes 1,2,4-triazolylthiols useful as chlolesteryl ester transfer protein inhibitors.

[0006] Some substituted heteroalkylamine compounds are known. In European Patent Application No. 796846, Schmidt et al. describe 2-aryl-substituted pyridines as cholesteryl ester transfer protein inhibitors useful as cardiovascular agents. One substitutent at C3 of the pyridine ring can be an hydroxyalkyl group. In European Patent Application No.

801060, Dow and Wright describe heterocyclic derivatives substituted with an aldehyde addition product of an alkylamine to afford 1-hydroxy-1-amines. These are reported to be β3-adrenergic receptor agonists useful for treating diabetes and other disorders. In Great Britain Patent Application No. 2305665, Fisher et al. disclose 3-agonist secondary amino alcohol substituted pyridine derivatives useful for treating several disorders including cholesterol levels and atherosclerotic diseases. In European Patent Application No. 818448, Schmidt et al. describe tetrahydroquinoline derivatives as chlolesteryl ester transfer protein inhibitors. European Patent Application No. 818197, Schmek et al. describe pyridines with fused heterocycles as cholesteryl ester transfer protein inhibitors. Brandes et al. in German Patent Application No. 19627430 describe bicyclic condensed pyridine derivatives as cholesteryl ester transfer protein inhibitors. In WO Patent Application No. 09839299, Muller-Gliemann et al. describe quinoline derivatives as cholesteryl ester transfer protein inhibitors. U.S. Patent 2,700,686, issued to Dickey and Towne, describes N-(2-haloalkyl-2-hydroxyethyl)amines in which the amine is further substituted with either 1 to 2 aliphatic groups or one aromatic group and one aliphatic group. U.S. Patent 2,700,686 further describes a process to prepare the N-(2-haloalkyl-2-hydroxyethyl)amines by reacting halogenated-1,2-epoxyalkanes with the corresponding aliphatic amines and N-alkylanilines and their use as dye intermediates.

SUMMARY OF THE INVENTION

[0007] The present invention provides compounds that can be used to inhibit cholesteryl ester transfer protein (CETP) activity and that have the general structure defined in claim 1.

[0008] In another aspect , the present invention includes pharmaceutical compositions comprising a pharmaceutically effective amount of the compounds of this invention and a pharmaceutically acceptable carrier.

[0009] In another aspect, this invention relates to using these inhibitors for the manufacture of therapeutic agents in humans to inhibit cholesteryl ester transfer protein (CETP) activity, thereby decreasing the concentrations of low density lipoprotein (LDL) and raising the level of high density lipoprotein (HDL), resulting in a therapeutically beneficial plasma lipid profile. The compounds of this invention can also be used to treat dyslipidemia (hypoalphidipoproteinemia), hyperlipoproteinaemia (chylomicronemia and hyperapobetalipoproteinemia), peripheral vascular disease, hypercholesterolaemia, atherosclerosis, coronary artery disease and other CETP-mediated disorders. The compounds can also be used in prophylactic treatment of subjects who are at risk of developing such disorders. The compounds can be used to lower the risk of atherosclerosis. The compounds of this invention would be also useful in prevention of cerebral vascular accident (CVA) or stroke. Besides being useful for human treatment, these compounds are also useful for veterinary treatment of companion animals, exotic animals and farm animals such as primates, rabbits, pigs, horses, and the like.

DESCRIPTION OF THE INVENTION

[0010] The present invention relates to a class of compounds comprising substituted polycyclic aryl and heteroaryl *tertiary*-heteroalkylamines which are beneficial in the therapeutic and prophylactic treatment of coronary artery disease as defined in claim 1 (also referred to herein as generic substituted polycyclic heteroaryl tertiary 2-heteroalkylamines) or a pharmaceutically acceptable salt thereof. Preferred compounds are set forth in claims 2-24.

[0011] R_5, R_6, R_7, R_{10}, R_{11}, and R_{12} are independently selected from the group consisting of perhaloaryloxy, N-aryl-N-alkylamino, heterocyclylalkoxy, heterocyclylthio, hydroxyalkoxy, aralkanoylalkoxy, aralkenoyl, cycloalkylcarbonyl, cyanoalkoxy, heterocyclylcarbonyl, hydrido, alkyl, halo, haloalkyl, haloalkoxy, aryl, alkylthio, arylamino, arylthio, aroyl, arylsulfonyl, aryloxy, aralkoxy, heteroaryloxy, alkoxy, aralkyl, cycloalkoxy, cycloalkylalkoxy, cycloalkylalkanoyl, heteroaryl, cycloalkyl, haloalkylthio, hydroxyhaloalkyl, heteroaralkoxy, and heteroaryloxyalkyl.

[0012] In an embodiment of compounds of the invention,

[0013] R_1 is selected from the group consisting of trifluoromethyl, chloromethyl, fluoromethyl, difluoromethyl, chlorodifluoromethyl, pentafluoroethyl, 2,2,3,3,3-pentafluoropropyl, and heptafluoropropyl;

[0014] R_2 is selected from the group consisting of hydrido, methyl, ethyl, propyl, butyl, isopropyl, isobutyl, phenyl, trifluoromethyl, chloromethyl, fluoromethyl, difluoromethyl, chlorodifluoromethyl, pentafluoroethyl, 2,2,3,3,3-pentafluoropropyl, and heptafluoropropyl;

[0015] R_3 is selected from the group consisting of hydrido, methyl, ethyl, propyl, trifluoromethyl, chloromethyl, fluoromethyl, difluoromethyl, chlorodifluoromethyl, pentafluoroethyl, 2,2,3,3,3-pentafluoropropyl, and heptafluoropropyl.

[0016] In a preferred embodiment of compounds of the invention,

[0017] R_1 is selected from the group consisting of trifluoromethyl, difluoromethyl, chlorodifluoromethyl, and pentafluoroethyl;

[0018] R_2 is selected from the group consisting of hydrido, methyl, ethyl, propyl, butyl, phenyl, trifluoromethyl, difluoromethyl, chlorodifluoromethyl, pentafluoroethyl, 2,2,3,3,3-pentafluoropropyl, and heptafluoropropyl;

[0019] R_3 is selected from the group consisting of hydrido, methyl, ethyl, vinyl, trifluoromethyl, difluoromethyl, chlorodifluoromethyl, and pentafluoroethyl.

[0020] In a even more preferred embodiment of compounds of the invention,

[0021] R_1 is selected from the group consisting of trifluoromethyl, difluoromethyl, chlorodifluoromethyl, and pentafluoroethyl;

[0022] R_2 is selected from the group consisting of hydrido, methyl, ethyl, phenyl, trifluoromethyl, difluoromethyl, chlorodifluoromethyl, pentafluoroethyl, 2,2,3,3,3-pentafluoropropyl, and heptafluoropropyl;

[0023] R_3 is selected from the group consisting of hydrido, methyl, trifluoromethyl, difluoromethyl, and chlorodifluoromethyl.

[0024] In a most preferred embodiment of compounds of the invention,

[0025] R_1 is selected from the group consisting of trifluoromethyl and pentafluoroethyl;

[0026] R_2 is selected from the group consisting of hydrido, phenyl, and trifluoromethyl;

[0027] R_3 is selected from the group consisting of hydrido, methyl, trifluoromethyl, and difluoromethyl.

[0028] In a most preferred embodiment of compounds of the invention,

[0029] Y is methylene;

[0030] R_4, R_8, R_9, and R_{13} are independently selected from the group consisting of hydrido and fluoro;

[0031] R_5 is selected from the group consisting of 5-bromo-2-fluorophenoxy, 4-chloro-3-ethylphenoxy, 2,3-dichlorophenoxy, 3,4-dichlorophenoxy, 3-difluoromethoxyphenoxy, 3,5-dimethylphenoxy, 3,4-dimethylphenoxy, 3-ethylphenoxy, 3-ethyl-5-methylphenoxy, 4-fluoro-3-methylphenoxy, 4-fluorophenoxy, 3-isopropylphenoxy, 3-methylphenoxy, 3-pentafluoroethylphenoxy, 3-tert -butylphenoxy, 3-(1,1,2,2-tetrafluoroethoxy)phenoxy, 2-(5,6,7,8-tetrahydronaphthyloxy), 3-trifluoromethoxybenzyloxy,3-trifluoromethoxyphenoxy, 3-trifluoromethylbenzyloxy, and 3-trifluoromethylthiophenoxy;

[0032] R_{10} is selected from the group consisting of cyclopentyl, 1,1,2,2-tetrafluoroethoxy, 2-furyl, 1,1-bis-trifluoromethyl-1-hydroxymethyl, pentafluoroethyl, trifluoromethoxy, trifluoromethyl, and trifluoromethylthio;

[0033] R_6 and R_{11} are independently selected from the group consisting of fluoro and hydrido;

[0034] R_7 and R_{12} are independently selected from the group consisting of hydrido and fluoro.

DEFINITIONS

[0035] The use of generic terms in the description of the compounds are herein defined for clarity.

[0036] Standard single letter elemental symbols are used to represent specific types of atoms unless otherwise defined. The symbol "C" represents a carbon atom. The symbol "O" represents an oxygen atom. The symbol "N" represents a nitrogen atom. The symbol "P" represents a phosphorus atom. The symbol "S" represents a sulfur atom. The symbol "H" represents a hydrogen atom. Double letter elemental symbols are used as defined for the elements of the periodical table (i.e., Cl represents chlorine, Se represents selenium, etc.).

[0037] As utilized herein, the term "alkyl", either alone or within other terms such as "haloalkyl" and "alkylthio", means an acyclic alkyl radical containing from I to about 10, preferably from 1 to about 8 carbon atoms and more preferably 1 to about 6 carbon atoms. Said alkyl radicals may be optionally substituted with groups as defined below. Examples of such radicals include methyl, ethyl, chloroethyl, hydroxyethyl, n-propyl, oxopropyl, isopropyl, n-butyl, cyanobutyl, isobutyl, sec-butyl, tert-butyl, pentyl, aminopentyl, iso-amyl, hexyl, octyl and the like.

[0038] The term "alkenyl" refers to an unsaturated, acyclic hydrocarbon radical in so much as it contains at least one double bond. Such alkenyl radicals contain from about 2 to about 10 carbon atoms, preferably from about 2 to about 8 carbon atoms and more preferably 2 to about 6 carbon atoms. Said alkenyl radicals may be optionally substituted with groups as defined below. Examples of suitable alkenyl radicals include propenyl, 2-chloropropenyl, buten-1-yl, isobutenyl, penten-1-yl, 2-2-methylbuten-1-yl, 3-methylbuten-1-yl, hexen-1-yl, 3-hydroxyhexen-1-yl, hepten-1-yl, and octen-1-yl, and the like.

[0039] The term "alkynyl" refers to an unsaturated, acyclic hydrocarbon radical in so much as it contains one or more triple bonds, such radicals containing about 2 to about 10 carbon atoms, preferably having from about 2 to about 8 carbon atoms and more preferably having 2 to about 6 carbon atoms. Said alkynyl radicals may be optionally substituted with groups as defined below. Examples of suitable alkynyl radicals include ethynyl, propynyl, hydroxypropynyl, butyn-1-yl, butyn-2-yl, pentyn-1-yl, pentyn-2-yl, 4-methoxypentyn-2-yl, 3-methylbutyn-1-yl, hexyn-1-yl, hexyn-2-yl, hexyn-3-yl, 3,3-dimethylbutyn-1-yl radicals and the like.

[0040] The term "hydrido" denotes a single hydrogen atom (H). This hydrido radical may be attached, for example, to an oxygen atom to form a "hydroxyl" radical, one hydrido radical may be attached to a carbon atom to form a "methine" radical (=CH-), or two hydrido radicals may be attached to a carbon atom to form a "methylene" ($-CH_2-$) radical.

[0041] The term "carbon" radical denotes a carbon atom without any covalent bonds and capable of forming four covalent bonds.

[0042] The term "cyano" radical denotes a carbon radical having three of four covalent bonds shared by a nitrogen atom.

[0043] The term "hydroxyalkyl" embraces radicals wherein any one or more of the alkyl carbon atoms is substituted with a hydroxyl as defined above. Specifically embraced are monohydroxyalkyl, dihydroxyalkyl and polyhydroxyalkyl radicals.

[0044] The term "alkanoyl" embraces radicals wherein one or more of the terminal alkyl carbon atoms are substituted

with one or more carbonyl radicals as defined below. Specifically embraced are monocarbonylalkyl and dicarbonylalkyl radicals. Examples of monocarbonylalkyl radicals include formyl, acetyl, and pentanoyl. Examples of dicarbonylalkyl radicals include oxalyl, malonyl, and succinyl.

[0045] The term "alkylene" radical denotes linear or branched radicals having from 1 to about 10 carbon atoms and having attachment points for two or more covalent bonds. Examples of such radicals are methylene, ethylene, ethylidene, methylethylene, and isopropylidene.

[0046] The term "alkenylene" radical denotes linear or branched radicals having from 2 to about 10 carbon atoms, at least one double bond, and having attachment points for two or more covalent bonds. Examples of such radicals are 1,1-vinylidene (CH_2=C), 1,2-vinylidene (-CH=CH-), and 1,4-butadienyl (-CH=CH-CH=CH-).

[0047] The term "halo" means halogens such as fluorine, chlorine, bromine or iodine atoms.

[0048] The term "haloalkyl" embraces radicals wherein any one or more of the alkyl carbon atoms is substituted with halo as defined above. Specifically embraced are monohaloalkyl, dihaloalkyl and polyhaloalkyl radicals. A monohaloalkyl radical, for one example, may have either a bromo, chloro or a fluoro atom within the radical. Dihalo radicals may have two or more of the same halo atoms or a combination of different halo radicals and polyhaloalkyl radicals may have more than two of the same halo atoms or a combination of different halo radicals. More preferred haloalkyl radicals are "lower haloalkyl" radicals having one to about six carbon atoms. Examples of such haloalkyl radicals include fluoromethyl, difluoromethyl, trifluoromethyl, chloromethyl, dichloromethyl, trichloromethyl, trifluoroethyl, pentafluoroethyl, heptafluoropropyl, difluorochloromethyl, dichlorofluoromethyl, difluoroethyl, difluoropropyl, dichloroethyl and dichloropropyl.

[0049] The term "hydroxyhaloalkyl" embraces radicals wherein any one or more of the haloalkyl carbon atoms is substituted with hydroxy as defined above. Examples of "hydroxyhaloalkyl" radicals include hexafluorohydoxypropyl.

[0050] The term "haloalkylene radical" denotes alkylene radicals wherein any one or more of the alkylene carbon atoms is substituted with halo as defined above. Dihalo alkylene radicals may have two or more of the same halo atoms or a combination of different halo radicals and polyhaloalkylene radicals may have more than two of the same halo atoms or a combination of different halo radicals. More preferred haloalkylene radicals are "lower haloalkylene" radicals having one to about six carbon atoms. Examples of "haloalkylene" radicals include difluoromethylene, tetrafluoroethylene, tetrachloroethylene, alkyl substituted monofluoromethylene, and aryl substituted trifluoromethylene.

[0051] The term "haloalkenyl" denotes linear or branched radicals having from 1 to about 10 carbon atoms and having one or more double bonds wherein any one or more of the alkenyl carbon atoms is substituted with halo as defined above. Dihaloalkenyl radicals may have two or more of the same halo atoms or a combination of different halo radicals and polyhaloalkenyl radicals may have more than two of the same halo atoms or a combination of different halo radicals.

[0052] The terms "alkoxy" and "alkoxyalkyl" embrace linear or branched oxy-containing radicals each having alkyl portions of one to about ten carbon atoms, such as methoxy radical. The term "alkoxyalkyl" also embraces alkyl radicals having one or more alkoxy radicals attached to the alkyl radical, that is, to form monoalkoxyalkyl and dialkoxyalkyl radicals. More preferred alkoxy radicals are "lower alkoxy" radicals having one to six carbon atoms. Examples of such radicals include methoxy, ethoxy, propoxy, butoxy, isopropoxy and *tert*-butoxy alkyls. The "alkoxy" radicals may be further substituted with one or more halo atoms, such as fluoro, chloro or bromo, to provide "haloalkoxy" and "haloalkoxyalkyl" radicals. Examples of such haloalkoxy radicals include fluoromethoxy, chloromethoxy, trifluoromethoxy, difluoromethoxy, trifluoroethoxy, fluoroethoxy, tetrafluoroethoxy, pentafluoroethoxy, and fluoropropoxy. Examples of such haloalkoxyalkyl radicals include fluoromethoxymethyl, chloromethoxyethyl, trifluoromethoxymethyl, difluoromethoxyethyl, and trifluoroethoxymethyl.

[0053] The terms "alkenyloxy" and "alkenyloxyalkyl" embrace linear or branched oxy-containing radicals each having alkenyl portions of two to about ten carbon atoms, such as ethenyloxy or propenyloxy radical. The term "alkenyloxyalkyl" also embraces alkenyl radicals having one or more alkenyloxy radicals attached to the alkyl radical, that is, to form monoalkenyloxyalkyl and dialkenyloxyalkyl radicals. More preferred alkenyloxy radicals are "lower alkenyloxy" radicals having two to six carbon atoms. Examples of such radicals include ethenyloxy, propenyloxy, butenyloxy, and isopropenyloxy alkyls. The "alkenyloxy" radicals may be further substituted with one or more halo atoms, such as fluoro, chloro or bromo, to provide "haloalkenyloxy" radicals. Examples of such radicals include trifluoroethenyloxy, fluoroethenyloxy, difluoroethenyhloxy, and fluoropropenyloxy.

[0054] The term "haloalkoxyalkyl" also embraces alkyl radicals having one or more haloalkoxy radicals attached to the alkyl radical, that is, to form monohaloalkoxyalkyl and dihaloalkoxyalkyl radicals. The term "haloalkenyloxy" also embraces oxygen radicals having one or more haloalkenyloxy radicals attached to the oxygen radical, that is, to form monohaloalkenyloxy and dihaloalkenyloxy radicals. The term "haloalkenyloxyalkyl" also embraces alkyl radicals having one or more haloalkenyloxy radicals attached to the alkyl radical, that is, to form monohaloalkenyloxyalkyl and dihaloalkenyloxyalkyl radicals.

[0055] The term "alkylenedioxy" radicals denotes alkylene radicals having at least two oxygens bonded to a single alkylene group. Examples of "alkylenedioxy" radicals include methylenedioxy, ethylenedioxy, alkylsubstituted methylenedioxy, and arylsubstituted methylenedioxy. The term "haloalkylenedioxy" radicals denotes haloalkylene radicals having at least two oxy groups bonded to a single haloalkyl group. Examples of "haloalkylenedioxy" radicals include

difluoromethylenedioxy, tetrafluoroethylenedioxy, tetrachloroethylenedioxy, alkylsubstituted monofluoromethylenedioxy, and arylsubstituted monofluoromethylenedioxy.

[0056] The term "aryl", alone or in combination, means a carbocyclic aromatic system containing one, two or three rings wherein such rings may be attached together in a pendant manner or may be fused. The term "fused" means that a second ring is present (ie, attached or formed) by having two adjacent atoms in common (ie, shared) with the first ring. The term "fused" is equivalent to the term "condensed". The term "aryl" embraces aromatic radicals such as phenyl, naphthyl, tetrahydronaphthyl, indane and biphenyl.

[0057] The term "perhaloaryl" embraces aromatic radicals such as phenyl, naphthyl, tetrahydronaphthyl, indane and biphenyl wherein the aryl radical is substituted with 3 or more halo radicals as defined below.

[0058] The term "heterocyclyl" embraces saturated, partially saturated and unsaturated heteroatom-containing ring-shaped radicals having from 5 through 15 ring members selected from carbon, nitrogen, sulfur and oxygen, wherein at least one ring atom is a heteroatom. Heterocyclyl radicals may contain one, two or three rings wherein such rings may be attached in a pendant manner or may be fused. Examples of saturated heterocyclic radicals include saturated 3 to 6-membered heteromonocylic group containing 1 to 4 nitrogen atoms[e.g. pyrrolidinyl, imidazolidinyl, piperidino, piperazinyl, etc.]; saturated 3 to 6-membered heteromonocyclic group containing 1 to 2 oxygen atoms and 1 to 3 nitrogen atoms [e.g. morpholinyl, etc.]; saturated 3 to 6-membered heteromonocyclic group containing 1 to 2 sulfur atoms and 1 to 3 nitrogen atoms [e.g., thiazolidinyl, etc.]. Examples of partially saturated heterocyclyl radicals include dihydrothiophene, dihydropyran, dihydrofuran and dihydrothiazole. Examples of unsaturated heterocyclic radicals, also termed "heteroaryl" radicals, include unsaturated 5 to 6 membered heteromonocyclyl group containing 1 to 4 nitrogen atoms, for example, pyrrolyl, pyrrolinyl, imidazolyl, pyrazolyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, pyrimidyl, pyrazinyl, pyridazinyl, triazolyl [e.g., 4H-1,2,4-triazolyl, 1H-1,2,3-triazolyl, 2H-1,2,3-triazolyl, etc.] tetrazolyl [e.g. 1H-tetrazolyl, 2H-tetrazolyl, etc.], etc.; unsaturated condensed heterocyclic group containing 1 to 5 nitrogen atoms, for example, indolyl, isoindolyl, indolizinyl, benzimidazolyl, quinolyl, isoquinolyl, indazolyl, benzotriazolyl, tetrazolopyridazinyl [e.g., tetrazolo [1,5-b]pyridazinyl, etc.], etc.; unsaturated 3 to 6-membered heteromonocyclic group containing an oxygen atom, for example, pyranyl, 2-furyl, 3-furyl, etc.; unsaturated 5 to 6-membered heteromonocyclic group containing a sulfur atom, for example, 2-thienyl, 3-thienyl, etc.; unsaturated 5- to 6-membered heteromonocyclic group containing 1 to 2 oxygen atoms and 1 to 3 nitrogen atoms, for example, oxazolyl, isoxazolyl, oxadiazolyl [e.g., 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,5-oxadiazolyl, etc. 1 etc.; unsaturated condensed heterocyclic group containing 1 to 2 oxygen atoms and 1 to 3 nitrogen atoms [e.g. benzoxazolyl, benzoxadiazolyl, etc.]: unsaturated 5 to 6-membered heteromonocyclic group containing 1 to 2 sulfur atoms and 1 to 3 nitrogen atoms, for example, thiazolyl, thiadiazolyl [e.g., 1,2,4- thiadiazolyl, 1,3,4-thiadiazolyl, 1,2,5-thiadiazolyl, etc.] etc.; unsaturated condensed heterocyclic group containing 1 to 2 sulfur atoms and 1 to 3 nitrogen atoms [e.g., benzothiazolyl, benzothiadiazolyl, etc.] and the like. The term also embraces radicals where heterocyclic radicals are fused with aryl radicals. Examples of such fused bicyclic radicals include benzofuran, benzothiophene, and the like. Said "heterocyclyl" group may have 1 to 3 substituents as defined below. Preferred heterocyclic radicals include five to twelve membered fused or unfused radicals. Non-limiting examples of heterocyclic radicals include pyrrolyl, pyridinyl, pyridyloxy, pyrazolyl, triazolyl, pyrimidinyl, pyridazinyl, oxazolyl, thiazolyl, imidazolyl, indolyl, thiophenyl, furanyl, tetrazolyl, 2-pyrrolinyl, 3-pyrrolinyl, pyrrolindinyl, 1,3-dioxolanyl, 2-imidazolinyl, imidazolidinyl, 2-pyrazolinyl, pyrazolidinyl, isoxazolyl, isothiazolyl, 1,2,3-oxadiazolyl, 1,2,3-triazolyl, 1,3,4-thiadiazolyl, 2H-pyranyl, 4H-pyranyl, piperidinyl, 1,4-dioxanyl, morpholinyl, 1,4-dithianyl, thiomorpholinyl, pyrazinyl, piperazinyl, 1,3,5-triazinyl, 1,3,5-trithianyl, benzo(b)thiophenyl, benzimidazoyl, quinolinyl, tetraazolyl, and the like.

[0059] The term "sulfonyl", whether used alone or linked to other terms such as alkylsulfonyl, denotes respectively divalent radicals -SO_2-. "Alkylsulfonyl", embraces alkyl radicals attached to a sulfonyl radical, where alkyl is defined as above. "Alkylsulfonylalkyl", embraces alkylsulfonyl radicals attached to an alkyl radical, where alkyl is defined as above. "Haloalkylsulfonyl", embraces haloalkyl radicals attached to a sulfonyl radical, where haloalkyl is defined as above. "Haloalkylsulfonylalkyl", embraces haloalkylsulfonyl radicals attached to an alkyl radical, where alkyl is defined as above. The term "aminosulfonyl" denotes an amino radical attached to a sulfonyl radical.

[0060] The term "sulfinyl", whether used alone or linked to other terms such as alkylsulfinyl, denotes respectively divalent radicals -S(O)-. "Alkylsulfinyl", embraces alkyl radicals attached to a sulfinyl radical, where alkyl is defined as above. "Alkylsulfinylalkyl", embraces alkylsulfinyl radicals attached to an alkyl radical, where alkyl is defined as above. "Haloalkylsulfinyl", embraces haloalkyl radicals attached to a sulfinyl radical, where haloalkyl is defined as above. "Haloalkylsulfinylalkyl", embraces haloalkylsulfinyl radicals attached to an alkyl radical, where alkyl is defined as above.

[0061] The term "aralkyl" embraces aryl-substituted alkyl radicals. Preferable aralkyl radicals are "lower aralkyl" radicals having aryl radicals attached to alkyl radicals having one to six carbon atoms. Examples of such radicals include benzyl, diphenylmethyl, triphenylmethyl, phenylethyl and diphenylethyl. The terms benzyl and phenylmethyl are interchangeable.

[0062] The term "heteroaralkyl" embraces heteroaryl-substituted alkyl radicals wherein the heteroaralkyl radical may be additionally substituted with three or more substituents as defined above for aralkyl radicals. The term "perhaloaralkyl" embraces aryl-substituted alkyl radicals wherein the aralkyl radical is substituted with three or more halo radicals as defined above.

[0063] The term "aralkylsulfinyl", embraces aralkyl radicals attached to a sulfinyl radical, where aralkyl is defined as above. "Aralkylsulfinylalkyl", embraces aralkylsulfinyl radicals attached to an alkyl radical, where alkyl is defined as above.

[0064] The term "aralkylsulfonyl", embraces aralkyl radicals attached to a sulfonyl radical, where aralkyl is defined as above. "Aralkylsulfonylalkyl", embraces aralkylsulfonyl radicals attached to an alkyl radical, where alkyl is defined as above.

[0065] The term "cycloalkyl" embraces radicals having three to ten carbon atoms. More preferred cycloalkyl radicals are "lower cycloalkyl" radicals having three to seven carbon atoms. Examples include radicals such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl. The term "cycloalkylalkyl" embraces cycloalkyl-substituted alkyl radicals. Preferable cycloalkylalkyl radicals are "lower cycloalkylalkyl" radicals having cycloalkyl radicals attached to alkyl radicals having one to six carbon atoms. Examples of such radicals include cyclohexylhexyl. The term "cycloalkenyl" embraces radicals having three to ten carbon atoms and one or more carbon-carbon double bonds. Preferred cycloalkenyl radicals are "lower cycloalkenyl" radicals having three to seven carbon atoms. Examples include radicals such as cyclobutenyl, cyclopentenyl, cyclohexenyl and cycloheptenyl. The term "halocycloalkyl" embraces radicals wherein any one or more of the cycloalkyl carbon atoms is substituted with halo as defined above. Specifically embraced are monohalocycloalkyl, dihalocycloalkyl and polyhalocycloalkyl radicals. A monohalocycloalkyl radical, for one example, may have either a bromo, chloro or a fluoro atom within the radical. Dihalo radicals may have two or more of the same halo atoms or a combination of different halo radicals and polyhalocycloalkyl radicals may have more than two of the same halo atoms or a combination of different halo radicals. More preferred halocycloalkyl radicals are "lower halocycloalkyl" radicals having three to about eight carbon atoms. Examples of such halocycloalkyl radicals include fluorocyclopropyl, difluorocyclobutyl, trifluorocyclopentyl, tetrafluorocyclohexyl, and dichlorocyclopropyl. The term "halocycloalkenyl" embraces radicals wherein any one or more of the cycloalkenyl carbon atoms is substituted with halo as defined above. Specifically embraced are monohalocycloalkenyl, dihalocycloalkenyl and polyhalocycloalkenyl radicals.

[0066] The term "cycloalkoxy" embraces cycloalkyl radicals attached to an oxy radical. Examples of such radicals includes cyclohexoxy and cyclopentoxy. The term "cycloalkoxyalkyl" also embraces alkyl radicals having one or more cycloalkoxy radicals attached to the alkyl radical, that is, to form monocycloalkoxyalkyl and dicycloalkoxyalkyl radicals. Examples of such radicals include cyclohexoxyethyl. The "cycloalkoxy" radicals may be further substituted with one or more halo atoms, such as fluoro, chloro or bromo, to provide "halocycloalkoxy" and "halocycloalkoxyalkyl" radicals.

[0067] The term "cycloalkylalkoxy" embraces cycloalkyl radicals attached to an alkoxy radical. Examples of such radicals includes cyclohexylmethoxy and cyclopentylmethoxy.

[0068] The term "cycloalkenyloxy" embraces cycloalkenyl radicals attached to an oxy radical. Examples of such radicals includes cyclohexenyloxy and cyclopentenyloxy. The term "cycloalkenyloxyalkyl" also embraces alkyl radicals having one or more cycloalkenyloxy radicals attached to the alkyl radical, that is, to form monocycloalkenyloxyalkyl and dicycloalkenyloxyalkyl radicals. Examples of such radicals include cyclohexenyloxyethyl. The "cycloalkenyloxy" radicals may be further substituted with one or more halo atoms, such as fluoro, chloro or bromo, to provide "halocycloalkenyloxy" and "halocycloalkenyloxyalkyl" radicals.

[0069] The term "cycloalkylenedioxy" radicals denotes cycloalkylene radicals having at least two oxygens bonded to a single cycloalkylene group. Examples of "alkylenedioxy" radicals include 1,2-dioxycyclohexylene.

[0070] The term "cycloalkylsulfinyl", embraces cycloalkyl radicals attached to a sulfinyl radical, where cycloalkyl is defined as above. "Cycloalkylsulfinylalkyl", embraces cycloalkylsulfinyl radicals attached to an alkyl radical, where alkyl is defined as above. The term "Cycloalkylsulfonyl", embraces cycloalkyl radicals attached to a sulfonyl radical, where cycloalkyl is defined as above. "Cycloalkylsulfonylalkyl", embraces cycloalkylsulfonyl radicals attached to an alkyl radical, where alkyl is defined as above.

[0071] The term "cycloalkylalkanoyl" embraces radicals wherein one or more of the cycloalkyl carbon atoms are substituted with one or more carbonyl radicals as defined below. Specifically embraced are monocarbonylcycloalkyl and dicarbonylcycloalkyl radicals. Examples of monocarbonylcycloalkyl radicals include cyclohexylcarbonyl, cyclohexylacetyl, and cyclopentylcarbonyl. Examples of dicarbonylcycloalkyl radicals include 1,2-dicarbonylcyclohexane..

[0072] The term "alkylthio" embraces radicals containing a linear or branched alkyl radical, of one to ten carbon atoms, attached to a divalent sulfur atom. More preferred alkylthio radicals are "lower alkylthio" radicals having one to six carbon atoms. An example of "lower alkylthio" is methylthio (CH_3-S-). The "alkylthio" radicals may be further substituted with one or more halo atoms, such as fluoro, chloro or bromo, to provide "haloalkylthio" radicals. Examples of such radicals include fluoromethylthio, chloromethylthio, trifluoromethylthio, difluoromethylthio, trifluoroethylthio, fluoroethylthio, tetrafluoroethylthio, pentafluoroethylthio, and fluoropropylthio.

[0073] The term "alkyl aryl amino" embraces radicals containing a linear or branched alkyl radical, of one to ten carbon atoms, and one aryl radical both attached to an amino radical. Examples include N-methyl-4-methoxyaniline, N-ethyl-4-methoxyaniline, and N-methyl-4-trifluoromethoxyaniline.

[0074] The terms alkylamino denotes "monoalkylamino" and "dialkylamino" containing one or two alkyl radicals, respectively, attached to an amino radical.

[0075] The terms arylamino denotes "monoarylamino" and "diarylamino" containing one or two aryl radicals, respec-

tively, attached to an amino radical. Examples of such radicals include N-phenylamino and N-naphthylamino.

[0076] The term "aralkylamino", embraces aralkyl radicals attached to an amino radical, where aralkyl is defined as above. The term aralkylamino denotes "monoaralkylamino" and "diaralkylamino" containing one or two aralkyl radicals, respectively, attached to an amino radical. The term aralkylamino further denotes "monoaralkyl monoalkylamino" containing one aralkyl radical and one alkyl radical attached to an amino radical.

[0077] The term "arylsulfinyl" embraces radicals containing an aryl radical, as defined above, attached to a divalent S(=O) atom. The term "arylsulfinylalkyl" denotes arylsulfinyl radicals attached to a linear or branched alkyl radical, of one to ten carbon atoms.

[0078] The term "arylsulfonyl", embraces aryl radicals attached to a sulfonyl radical, where aryl is defined as above. "arylsulfonylalkyl", embraces arylsulfonyl radicals attached to an alkyl radical, where alkyl is defined as above. The term "heteroarylsulfinyl" embraces radicals containing an heteroaryl radical, as defined above, attached to a divalent S(=O) atom. The term "heteroarylsulfinylalkyl" denotes heteroarylsulfinyl radicals attached to a linear or branched alkyl radical, of one to ten carbon atoms. The term "Heteroarylsulfonyl", embraces heteroaryl radicals attached to a sulfonyl radical, where heteroaryl is defined as above. "Heteroarylsulfonylalkyl", embraces heteroarylsulfonyl radicals attached to an alkyl radical, where alkyl is defined as above.

[0079] The term "aryloxy" embraces aryl radicals, as defined above, attached to an oxygen atom. Examples of such radicals include phenoxy, 4-chloro-3-ethylphenoxy, 4-chloro-3-methylphenoxy, 3-chloro-4-ethylphenoxy, 3,4-dichlorophenoxy, 4-methylphenoxy, 3-trifluoromethoxyphenoxy, 3-trifluoromethylphenoxy, 4-fluorophenoxy, 3,4-dimethylphenoxy, 5-bromo-2-fluorophenoxy, 4-bromo-3-fluorophenoxy, 4-fluoro-3-methylphenoxy, 5,6,7,8-tetrahydronaphthyloxy, 3-isopropylphenoxy, 3-cyclopropylphenoxy, 3-ethylphenoxy, 4-*tert* -butylphenoxy, 3-pentafluoroethylphenoxy, and 3-(1,1,2,2-tetrafluoroethoxy)phenoxy.

[0080] The term "aroyl" embraces aryl radicals, as defined above, attached to an carbonyl radical as defined above. Examples of such radicals include benzoyl and toluoyl.

[0081] The term "aralkanoyl" embraces aralkyl radicals, as defined herein, attached to an carbonyl radical as defined above. Examples of such radicals include, for example, phenylacetyl.

[0082] The term "aralkoxy" embraces oxy-containing aralkyl radicals attached through an oxygen atom to other radicals. More preferred aralkoxy radicals are "lower aralkoxy" radicals having phenyl radicals attached to lower alkoxy radical as described above. Examples of such radicals include benzyloxy, 1-phenylethoxy, 3-trifluoromethoxybenzyloxy, 3-trifluoromethylbenzyloxy, 3,5-difluorobenyloxy, 3-bromobenzyloxy, 4-propylbenzyloxy, 2-fluoro-3-trifluoromethylbenzyloxy, and 2-phenylethoxy.

[0083] The term "aryloxyalkyl" embraces aryloxy radicals, as defined above, attached to an alkyl group. Examples of such radicals include phenoxymethyl.

[0084] The term "haloaryloxyalkyl" embraces aryloxyalkyl radicals, as defined above, wherein one to five halo radicals are attached to an aryloxy group.

[0085] The term "heteroaroyl" embraces heteroaryl radicals, as defined above, attached to an carbonyl radical as defined above. Examples of such radicals include furoyl and nicotinyl.

[0086] The term "heteroaralkanoyl" embraces heteroaralkyl radicals, as defined herein, attached to an carbonyl radical as defined above. Examples of such radicals include, for example, pyridylacetyl and furylbutyryl.

[0087] The term "heteroaralkoxy" embraces oxy-containing heteroaralkyl radicals attached through an oxygen atom to other radicals. More preferred heteroaralkoxy radicals are "lower heteroaralkoxy" radicals having heteroaryl radicals attached to lower alkoxy radical as described above.

[0088] The term "haloheteroaryloxyalkyl" embraces heteroaryloxyalkyl radicals, as defined above, wherein one to four halo radicals are attached to an heteroaryloxy group.

[0089] The term "heteroarylamino" embraces heterocyclyl radicals, as defined above, attached to an amino group. Examples of such radicals include pyridylamino.

[0090] The term "heteroarylaminoalkyl" embraces heteroarylamino radicals, as defined above, attached to an alkyl group. Examples of such radicals include pyridylmethylamino.

[0091] The term "heteroaryloxy" embraces heterocyclyl radicals, as defined above, attached to an oxy group. Examples of such radicals include 2-thiophenyloxy, 2-pyrimidyloxy, 2-pyridyloxy, 3-pyridyloxy, and 4-pyridyloxy.

[0092] The term "heteroaryloxyalkyl" embraces heteroaryloxy radicals, as defined above, attached to an alkyl group. Examples of such radicals include 2-pyridyloxymethyl, 3-pyridyloxyethyl, and 4-pyridyloxymethyl.

[0093] The term "arylthio" embraces aryl radicals, as defined above, attached to an sulfur atom. Examples of such radicals include phenylthio.

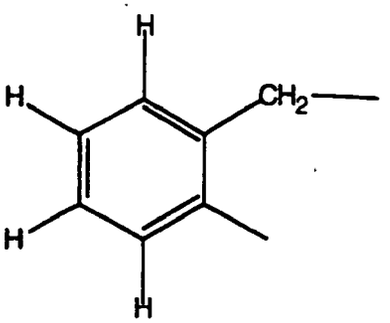
[0094] The term "arylthioalkyl" embraces arylthio radicals, as defined above, attached to an alkyl group. Examples of such radicals include phenylthiomethyl.

[0095] The term "alkylthioalkyl" embraces alkylthio radicals, as defined above, attached to an alkyl group. Examples of such radicals include methylthiomethyl. The term "alkoxyalkyl" embraces alkoxy radicals, as defined above, attached to an alkyl group. Examples of such radicals include methoxymethyl.

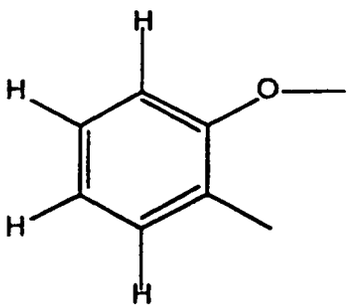
[0096] The term "carbonyl" denotes a carbon radical having two of the four covalent bonds shared with an oxygen atom. The term "carboxy" embraces a hydroxyl radical, as defined above, attached to one of two unshared bonds in a carbonyl group. The term "carboxamide" embraces amino, monoalkylamino, dialkylamino, monocycloalkylamino, alkylcycloalkylamino, and dicycloalkylamino radicals, attached to one of two unshared bonds in a carbonyl group. The term "carboxamidoalkyl" embraces carboxamide radicals, as defined above, attached to an alkyl group. The term "carboxyalkyl" embraces a carboxy radical, as defined above, attached to an alkyl group. The term "carboalkoxy" embraces alkoxy radicals, as defined above, attached to one of two unshared bonds in a carbonyl group. The term "carboaralkoxy" embraces aralkoxy radicals, as defined above, attached to one of two unshared bonds in a carbonyl group. The term "monocarboalkoxyalkyl" embraces one carboalkoxy radical, as defined above, attached to an alkyl group. The term "dicarboalkoxyalkyl" embraces two carboalkoxy radicals, as defined above, attached to an alkylene group. The term "monocyanoalkyl" embraces one cyano radical, as defined above, attached to an alkyl group. The term "dicyanoalkylene" embraces two cyano radicals, as defined above, attached to an alkyl group. The term "carboalkoxycyanoalkyl" embraces one cyano radical, as defined above, attached to an carboalkoxyalkyl group.

[0097] The term "acyl", alone or in combination, means a carbonyl or thionocarbonyl group bonded to a radical selected from, for example, hydrido, alkyl, alkenyl, alkynyl, haloalkyl, alkoxy, alkoxyalkyl, haloalkoxy, aryl, heterocyclyl, heteroaryl, alkylsulfinylalkyl, alkylsulfonylalkyl, aralkyl, cycloalkyl, cycloalkylalkyl, cycloalkenyl, alkylthio, arylthio, amino, alkylamino, dialkylamino, aralkoxy, arylthio, and alkylthioalkyl. Examples of "acyl" are formyl, acetyl, benzoyl, trifluoroacetyl, phthaloyl, malonyl, nicotinyl, and the like. The term "haloalkanoyl" embraces one or more halo radicals, as defined herein, attached to an alkanoyl radical as defined above. Examples of such radicals include, for example, chloroacetyl, trifluoroacetyl, bromopropanoyl, and heptafluorobutanoyl. The term "diacyl", alone or in combination, means having two or more carbonyl or thionocarbonyl groups bonded to a radical selected from, for example, alkylene, alkenylene, alkynylene, haloalkylene, alkoxyalkylene, aryl, heterocyclyl, heteroaryl, aralkyl, cycloalkyl, cycloalkylalkyl, and cycloalkenyl. Examples of "diacyl" are phthaloyl, malonyl, succinyl, adipoyl, and the like.

[0098] The term "benzylidenyl" radical denotes substituted and unsubstituted benzyl groups having attachment points for two covalent bonds. One attachment point is through the methylene of the benzyl group with the other attachment point through an ortho carbon of the phenyl ring. The methylene group is designated for attached to the lowest numbered position. Examples include the base compound benzylidene of structure:



[0099] The term "phenoxylidenyl" radical denotes substituted and unsubstituted phenoxy groups having attachment points for two covalent bonds. One attachment point is through the oxy of the phenoxy group with the other attachment point through an ortho carbon of the phenyl ring. The oxy group is designated for attached to the lowest numbered position. Examples include the base compound phenoxylidene of structure:



[0100] The term "phosphono" embraces a pentavalent phosphorus attached with two covalent bonds to an oxygen radical. The term "dialkoxyphosphono" denotes two alkoxy radicals, as defined above, attached to a phosphono radical with two covalent bonds. The term "diaralkoxyphosphono" denotes two aralkoxy radicals, as defined above, attached to a phosphono radical with two covalent bonds. The term "dialkoxyphosphonoalkyl" denotes dialkoxyphosphono radicals, as defined above, attached to an alkyl radical. The term "diaralkoxyphosphonoalkyl" denotes diaralkoxyphosphono radicals, as defined above, attached to an alkyl radical.

[0101] Said "alkyl", "alkenyl", "alkynyl", "alkanoyl", "alkylene", "alkenylene", "benzylidenyl", "phenoxylidenyl", "hydroxyalkyl", "haloalkyl", "haloalkylene", "haloalkenyl", "alkoxy", "alkenyloxy", "alkenyloxyalkyl", "alkoxyalkyl", "aryl", "perhaloaryl", "haloalkoxy", "haloalkoxyalkyl", "haloalkenyloxy", "haloalkenyloxyalkyl", "alkylenedioxy", "haloalkylenedioxy", "heterocyclyl", "heteroaryl", "hydroxyhaloalkyl", "alkylsulfonyl", "haloalkylsulfonyl", "alkylsulfonylalkyl", "haloalkylsulfonylalkyl", "alkylsulfinyl", "alkylsulfinylalkyl", "haloalkylsulfinylalkyl", "aralkyl", "heteroaralkyl", "perhaloaralkyl", "aralkylsulfonyl", "aralkylsulfonylalkyl", "aralkylsulfinyl", "aralkylsulfinylalkyl", "cycloalkyl", "cycloalkylalkanoyl", "cycloalkylalkyl", "cycloalkenyl", "halocycloalkyl", "halocycloalkenyl", "cycloalkylsulfinyl", "cycloalkylsulfinylalkyl", "cycloalkylsulfonyl", "cycloalkylsulfonylalkyl", "cycloalkoxy", "cycloalkoxyalkyl", "cycloalkylalkoxy", "cycloalkenyloxy", "cycloalkenyloxyalkyl", "cycloalkylenedioxy", "halocycloalkoxy", "halocycloalkoxyalkyl", "halocycloalkenyloxy", "halocycloalkenyloxyalkyl", "alkylthio", "haloalkylthio", "alkylsulfinyl", "amino", "oxy", "thio", "alkylamino", "arylamino", "aralkylamino", "arylsulfinyl", "arylsulfinylalkyl", "arylsulfonyl", "arylsulfonylalkyl", "heteroarylsulfinyl", "heteroarylsulfinylalkyl", "heteroarylsulfonyl", "heteroarylsulfonylalkyl", "heteroarylamino", "heteroarylaminoalkyl", "heteroaryloxy", "heteroaryloxylalkyl", "aryloxy", "aroyl", "aralkanoyl", "aralkoxy", "aryloxyalkyl", "haloaryloxyalkyl", "heteroaroyl", "heteroaralkanoyl", "heteroaralkoxy", "heteroaralkoxyalkyl", "arylthio", "arylthioalkyl", "alkoxyalkyl", "acyl" and "diacyl" groups defined above may optionally have 1 to 5 non-hydrido substituents such as perhaloaralkyl, aralkylsulfonyl, aralkylsulfonylalkyl, aralkylsulfinyl, aralkylsulfinylalkyl, halocycloalkyl, halocycloalkenyl, cycloalkylsulfinyl, cycloalkylsulfinylalkyl, cycloalkylsulfonyl, cycloalkylsulfonylalkyl, heteroarylamino. N-heteroarylamino-N-alkylamino, heteroarylaminoalkyl, heteroaryloxy, heteroaryloxylalkyl, haloalkylthio, alkanoyloxy, alkoxy, alkoxyalkyl, haloalkoxylalkyl, heteroaralkoxy, cycloalkoxy, cycloalkenyloxy, cycloalkoxyalkyl, cycloalkylalkoxy, cycloalkenyloxyalkyl, cycloalkylenedioxy, halocycloalkoxy, halocycloalkoxyalkyl, halocycloalkenyloxy, halocycloalkenyloxyalkyl, hydroxy, amino, thio, nitro, lower alkylamino, alkylthio, alkylthioalkyl, arylamino, aralkylamino, arylthio, arylthioalkyl, heteroaralkoxyalkyl, alkylsulfinyl, alkylsulfinylalkyl, arylsulfinylalkyl, arylsulfonylalkyl, heteroarylsulfinylalkyl, heteroarylsulfonylalkyl, alkylsulfonyl, alkylsulfonylalkyl, haloalkylsulfinylalkyl, haloalkylsulfonylalkyl, alkylsulfonamido, alkylaminosulfonyl, amidosulfonyl, monoalkyl amidosulfonyl, dialkyl amidosulfonyl, monoarylamidosulfonyl, arylsulfonamido, diarylamidosulfonyl, monoalkyl monoaryl amidosulfonyl, arylsulfinyl, arylsulfonyl, heteroarylthio, heteroarylsulfinyl, heteroarylsulfonyl, alkanoyl, alkenoyl, aroyl, heteroaroyl, aralkanoyl, heteroaralkanoyl, haloalkanoyl, alkyl, alkenyl, alkynyl, alkenyloxy, alkenyloxyalky, alkylenedioxy, haloalkylenedioxy, cycloalkyl, cycloalkylalkanoyl, cycloalkenyl, lower cycloalkylalkyl, lower cycloalkenylalkyl, halo, haloalkyl, haloalkenyl, haloalkoxy, hydroxyhaloalkyl, hydroxyaralkyl, hydroxyalkyl, hydoxyheteroaralkyl, haloalkoxyalkyl, aryl, aralkyl, aryloxy, aralkoxy, aryloxyalkyl, saturated heterocyclyl, partially saturated heterocyclyl, heteroaryl, heteroaryloxy, heteroaryloxyalkyl, arylalkyl, heteroarylalkyl, arylalkenyl, heteroarylalkenyl, carboxyalkyl, carboalkoxy, alkoxycarbonyl, carboaralkoxy, carboxamido, carboxamidoalkyl, cyano, carbohaloalkoxy, phosphono, phosphonoalkyl, diaralkoxyphosphono, and diaralkoxyphosphonoalkyl.

[0102] The term "spacer" can include a covalent bond and a linear moiety having a backbone of 1 to 7 continous atoms. The spacer may have 1 to 7 atoms of a univalent or multi-valent chain. Univalent chains may be constituted by a radical selected from =C(H)-, $=C(R_{17})$-, -O-, -S-, -S(O)-, $-S(O)_2$-, -NH-, $-N(R_{17})$-, -N=, -CH(OH)-, =C(OH)-, $-CH(OR_{17})$-, $=C(OR_{17})$-, and -C(O)- wherein R_{17} is selected from alkyl, alkenyl, alkynyl, aryl, heteroaryl, aralkyl, aryloxyalkyl, alkoxyalkyl, alkylthioalkyl, arylthioalkyl, cycloalkyl, cycloalkylalkyl, haloalkyl, haloalkenyl, haloalkoxyalkyl, perhaloaralkyl, heteroarylalkyl, heteroaryloxyalkyl, heteroarylthioalkyl, and heteroarylalkenyl. Multi-valent chains may consist of a straight chain of 1 or 2 or 3 or 4 or 5 or 6 or 7 atoms or a straight chain of 1 or 2 or 3 or 4 or 5 or 6 atoms with a side chain. The chain may be constituted of one or more radicals selected from: lower alkylene, lower alkenyl, -O-, $-O-CH_2$-, $-S-CH_2$-, $-CH_2CH_2$-, ethenyl, -CH=CH(OH)-, $-OCH_2O$-, $-O(CH_2)_2O$-, $-NHCH_2$-, $-OCH(R_{17})O$-, $-O(CH_2CHR_{17})O$-, $-OCF_2O$-, $-O(CF_2)_2O$-, -S-, -S(O)-, $-S(O)_2$-, -N(H)-, -N(H)O-, $-N(R_{17})O$-, $-N(R_{17})$-, -C(O)-, -C(O)NH-, $-C(O)NR_{17}$-, -N=, $-OCH_2$-, $-SCH_2$-, $S(O)CH_2$-, $-CH_2C(O)$-, -CH(OH)-, =C(OH)-, $-CH(OR_{17})$-, $=C(OR_{17})$-, $S(O)_2CH_2$-, and $-NR_{17}CH_2$- and many other radicals defined above or generally known or ascertained by one of skill-in-the art. Side chains may include substituents such as 1 to 5 non-hydrido substituents such as perhaloaralkyl, aralkylsulfonyl, aralkylsulfonylalkyl, aralkylsulfinyl, aralkylsulfinylalkyl, halocycloalkyl, halocycloalkenyl, cycloalkylsulfinyl, cycloalkylsulfinylalkyl, cycloalkylsulfonyl, cycloalkylsulfonylalkyl, heteroarylamino, N-heteroarylamino-N-alkylamino, heteroarylaminoalkyl, heteroaryloxy, heteroaryloxylalkyl, haloalkylthio, alkanoyloxy, alkoxy, alkoxyalkyl, haloalkoxylalkyl, heteroaralkoxy, cycloalkoxy, cycloalkenyloxy, cycloalkoxyalkyl, cycloalkylalkoxy, cycloalkenyloxyalkyl, cycloalkylenedioxy, halocycloalkoxy, halocycloalkoxyalkyl, halocycloalkenyloxy, halocycloalkenyloxyalkyl, hydroxy, amino, thio, nitro, lower alkylamino, alkylthio, alkylthioalkyl, arylamino, aralkylamino, arylthio, arylthioalkyl, heteroaralkoxyalkyl, alkylsulfinyl, alkylsulfinylalkyl, arylsulfinylalkyl, arylsulfonylalkyl, heteroarylsulfinylalkyl, heteroarylsulfonylalkyl, alkylsulfonyl, alkylsulfonylalkyl, haloalkylsulfinylalkyl, haloalkylsulfonylalkyl, alkylsulfonamido, alkylaminosulfonyl, amidosulfonyl, monoalkyl amidosulfonyl, dialkyl amidosul-

fonyl, monoarylamidosulfonyl, arylsulfonamido, diarylamidosulfonyl, monoalkyl monoaryl amidosulfonyl, arylsulfinyl, arylsulfonyl, heteroarylthio, heteroarylsulfinyl, heteroarylsulfonyl, alkanoyl, alkenoyl, aroyl, heteroaroyl, aralkanoyl, heteroaralkanoyl, haloalkanoyl, alkyl, alkenyl, alkynyl, alkenyloxy, alkenyloxyalky, alkylenedioxy, haloalkylenedioxy, cycloalkyl, cycloalkenyl, lower cycloalkylalkyl, lower cycloalkenylalkyl, halo, haloalkyl, haloalkenyl, haloalkoxy, hydroxyhaloalkyl, hydroxyaralkyl, hydroxyalkyl, hydoxyheteroaralkyl, haloalkoxyalkyl, aryl, aralkyl, aryloxy, aralkoxy, aryloxyalkyl, saturated heterocyclyl, partially saturated heterocyclyl, heteroaryl, heteroaryloxy, heteroaryloxyalkyl, arylalkyl, heteroarylalkyl, arylalkenyl, heteroarylalkenyl, carboxyalkyl, carboalkoxy, carboaralkoxy, carboxamido, carboxamidoalkyl, cyano, carbohaloalkoxy, phosphono, phosphonoalkyl, diaralkoxyphosphono, and diaralkoxyphosphonoalkyl.

[0103] Compounds of the present invention can exist in tautomeric, geometric or stereoisomeric forms. The present invention contemplates all such compounds, including cis- and trans-geometric isomers, E- and Z-geometric isomers, R- and S-enantiomers, diastereomers, d-isomers, 1-isomers, the racemic mixtures thereof and other mixtures thereof, as falling within the scope of the invention. Pharmaceutically acceptable sales of such tautomeric, geometric or stereoisomeric forms are also included within the invention.

[0104] The terms "cis" and "trans" denote a form of geometric isomerism in which two carbon atoms connected by a double bond will each have a hydrogen atom on the same side of the double bond ("cis") or on opposite sides of the double bond ("trans").

[0105] Some of the compounds described contain alkenyl groups, and are meant to include both cis and trans or "E" and "Z" geometric forms.

[0106] Some of the compounds described contain one or more stereocenters and are meant to include R, S, and mixtures of R and S forms for each stereocenter present.

[0107] Some of the compounds described herein may contain one or more ketonic or aldehydic carbonyl groups or combinations thereof alone or as part of a heterocyclic ring system. Such carbonyl groups may exist in part or principally in the "keto" form and in part or principally as one or more "enol" forms of each aldehyde and ketone group present. Compounds of the present invention having aldehydic or ketonic carbonyl groups are meant to include both "keto" and "enol" tautomeric forms.

[0108] Some of the compounds described herein may contain one or more amide carbonyl groups or combinations thereof alone or as part of a heterocyclic ring system. Such carbonyl groups may exist in part or principally in the "keto" form and in part or principally as one or more "enol" forms of each amide group present. Compounds of the present invention having amidic carbonyl groups are meant to include both "keto" and "enol" tautomeric forms. Said amide carbonyl groups may be both oxo (C=O) and thiono (C=S) in type.

[0109] Some of the compounds described herein may contain one or more imine or enamine groups or combinations thereof. Such groups may exist in part or principally in the "imine" form and in part or principally as one or more "enamine" forms of each group present. Compounds of the present invention having said imine or enamine groups are meant to include both "imine" and "enamine" tautomeric forms.

[0110] The following general synthetic sequences are useful in making the present invention. Abbreviations used in the schemes are as follows: "AA" represents amino acids, "BINAP" represents 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl, "Boc" represents tert-butyloxycarbonyl, "BOP" represents benzotriazol-1-yl-oxy-tris-(dimethylamino), "bu" represents butyl, "dba" represents dibenzylideneacetone, "DCC" represents 1,3-dicyclohexylcarbodiimide, "DIBAH" represents diisobutylaluminum hydride, "DIPEA" represents diisopropylethylamine, "DMF" represents dimethylformamide, "DMSO" represents dimethylsulfoxide, "Fmoc" represents 9-fluorenylmethoxycarbonyl, "LDA" represents lithium diisopropylamide, "PHTH" represents a phthaloyl group, "pnZ" represents 4-nitrobenzyloxycarbonyl, "PTC" represents a phase transfer catalyst, "p-TsOH" represents paratoluenesulfonic acid, "TBAF" represents tetrabutylammonium fluoride, "TBTU" represents 2-(1H-benZOtriozole-1-yl)-1,1,3,3-tetramethyl uronium tetrafluoroborate, "TEA" represents triethylamine, "TFA" represents trifluoroacetic acid, "THF" represents tetrahydrofuran. "TMS" represents trimethylsilyl, and "Z" represents benzyloxycarbonyl.

PHARMACEUTICAL UTILITY AND COMPOSITION

[0111] The present invention comprises a pharmaceutical composition comprising a therapeutically-effective amount of a compound of the invention in association with at least one pharmaceutically-acceptable carrier, adjuvant or diluent.

[0112] The present invention also comprises the use of the compounds of the invention for the manufacture of a medicament for the treatment and prophylaxis of coronary artery disease and other CETP-mediated disorders in a subject.

[0113] Compounds of the invention are capable of inhibiting activity of cholesteryl ester transfer protein (CETP), and thus could be used in the manufacture of a medicament, a method for the prophylactic or therapeutic treatment of diseases mediated by CETP, such as peripheral vascular disease, hyperlipidaemia, hypercholesterolemia, and other diseases attributable to either high LDL and low HDL or a combination of both, or a procedure to study the mechanism of action of the cholesteryl ester transfer protein (CETP) to enable the design of better inhibitors. The compounds of the invention would be also useful in prevention of cerebral vascular accident (CVA) or stroke.

[0114] Also included in the family of compounds of the invention are the pharmaceutically-acceptable salts thereof. The term "pharmaceutically-acceptable salts" embraces salts commonly used to form alkali metal salts and to form addition salts of free acids or free bases. The nature of the salt is not critical, provided that it is pharmaceutically acceptable. Suitable pharmaceutically-acceptable acid addition salts of compounds of the invention may be prepared from inorganic acid or from an organic acid. Examples of such inorganic acids are hydrochloric, hydrobromic, hydroiodic, nitric, carbonic, sulfuric and phosphoric acid. Appropriate organic acids may be selected from aliphatic, cycloaliphatic, aromatic, araliphatic, heterocyclic, carboxylic and sulfonic classes of organic acids, examples of which are formic, acetic, propionic, succinic, glycolic, gluconic, lactic, malic, tartaric, citric, ascorbic, glucoronic, maleic, fumaric, pyruvic, aspartic, glutamic, benzoic, anthranilic, mesylic, salicylic, p-hydroxybenzoic, phenylacetic, mandelic, embonic (parnoic), methanesulfonic, ethylsulfonic, benzenesulfonic, sulfanilic, stearic, cyclohexylaminosulfonic, algenic, galacturonic acid. Suitable pharmaceutically-acceptable base addition salts of compounds of the invention include metallic salts made from aluminum, calcium, lithium, magnesium, potassium, sodium and zinc or organic salts made from N,N'-dibenzylethyleneldiamine, choline, chloroprocaine, diethanolamine, ethylenediamine, meglumine (N-methylglucamine) and procain. All of these salts may be prepared by conventional means from the corresponding compounds of the invention by reacting, for example, the appropriate acid or base with the compounds of the invention.

[0115] Also embraced within this invention is a class of pharmaceutical compositions comprising the active compounds of the invention in association with one or more non-toxic, pharmaceutically-acceptable carriers and/or diluents and/or adjuvants (collectively referred to herein as "carrier" materials) and, if desired, other active ingredients. The active compounds of the present invention may be administered by any suitable route, preferably in the form of a pharmaceutical composition adapted to such a route, and in a dose effective for the treatment intended. The active compounds and composition may, for example, be administered orally, intravascularly, intraperitoneally, subcutaneously, intramuscularly or topically.

[0116] For oral administration, the pharmaceutical composition may be in the form of, for example, a tablet, capsule, suspension or liquid. The pharmaceutical composition is preferably made in the form of a dosage unit containing a particular amount of the active ingredient. Examples of such dosage units are tablets or capsules. The active ingredient may also be administered by injection as a composition wherein, for example, saline, dextrose or water may be used as a suitable carrier.

[0117] The amount of therapeutically active compounds which are administered and the dosage regimen for treating a disease condition with the compounds and/or compositions of this invention depends on a variety of factors, including the age, weight, sex and medical condition of the subject, the severity of the disease, the route and frequency of administration, and the particular compound employed, and thus may vary widely.

[0118] The pharmaceutical compositions may contain active ingredients in the range of about 0.1 to 2000 mg, and preferably in the range of about 0.5 to 500 mg. A daily dose of about 0.01 to 100 mg/kg body weight, and preferably between about 0.5 and about 20 mg/kg body weight, may be appropriate. The daily dose can be administered in one to four doses per day.

[0119] The compounds may be formulated in topical ointment or cream, or as a suppository, containing the active ingredients in a total amount of, for example, 0.075 to 30% wiw, preferably 0.2 to 20% w/w and most preferably 0.4 to 15% w/w. When formulated in an ointment, the active ingredients may be employed with either paraffinic or a water-miscible ointment base. Alternatively, the active ingredients may be formulated in a cream with an oil-in-water cream base. If desired, the aqueous phase of the cream base may include, for example at least 30% w/w of a polyhydric alcohol such as propylene glycol, butane-1,3-diol, mannitol, sorbitol, glycerol, polyethylene glycol and mixtures thereof. The topical formulation may desirably include a compound which enhances absorption or penetration of the active ingredient through the skin or other affected areas. Examples of such dermal penetration enhancers include dimethylsulfoxide and related analogs. The compounds of this invention can also be administered by a transdermal device. Preferably topical administration will be accomplished using a patch either of the reservoir and porous membrane type or of a solid matrix variety. In either case, the active agent is delivered continuously from the reservoir or microcapsules through a membrane into the active agent permeable adhesive, which is in contact with the skin or mucosa of the recipient. If the active agent is absorbed through the skin, a controlled and predetermined flow of the active agent is administered to the recipient. In the case of microcapsules, the encapsulating agent may also function as the membrane.

[0120] The oily phase of the emulsions of this invention may be constituted from known ingredients in a known manner. While the phase may comprise merely an emulsifier, it may comprise a mixture of at least one emulsifier with a fat or an oil or with both a fat and an oil. Preferably, a hydrophilic emulsifier is included together with a lipophilic emulsifier which acts as a stabilizer. It is also preferred to include both an oil and a fat. Together, the emulsifier(s) with or without stabilizer(s) make-up the so-called emulsifying wax, and the wax together with the oil and fat make up the so-called emulsifying ointment base which forms the oily dispersed phase of the cream formulations. Emulsifiers and emulsion stabilizers suitable for use in the formulation of the present invention include Tween 60, Span 80, cetostearyl alcohol, myristyl alcohol, glyceryl monostearate, and sodium lauryl sulfate, among others.

[0121] The choice of suitable oils or fats for the formulation is based on achieving the desired cosmetic properties,

since the solubility of the active compound in most oils likely to be used in pharmaceutical emulsion formulations is very low. Thus, the cream should preferably be a non-greasy, non-staining and washable product with suitable consistency to avoid leakage from tubes or other containers. Straight or branched chain, mono- or dibasic alkyl esters such as di-isoadipate, isocetyl stearate, propylene glycol diester of coconut fatty acids, isopropyl myristate, decyl oleate, isopropyl palmitate, butyl stearate, 2-ethylhexyl palmitate or a blend of branched chain esters may be used. These may be used alone or in combination depending on the properties required. Alternatively, high melting point lipids such as white soft paraffin and/or liquid paraffin or other mineral oils can be used.

[0122] For therapeutic purposes, the active compounds of this combination invention are ordinarily combined with one or more adjuvants appropriate to the indicated route of administration. If administered *per os,* the compounds may be admixed with lactose, sucrose, starch powder, cellulose esters of alkanoic acids, cellulose alkyl esters, talc, stearic acid, magnesium stearate, magnesium oxide, sodium and calcium salts of phosphoric and sulfuric acids, gelatin, acacia gum, sodium alginate, polyvinylpyrrolidone, and/or polyvinyl alcohol, and then tableted or encapsulated for convenient administration. Such capsules or tablets may contain a controlled-release formulation as may be provided in a dispersion of active compound in hydroxypropylmethyl cellulose. Formulations for parenteral administration may be in the form of aqueous or non-aqueous isotonic sterile injection solutions or suspensions. These solutions and suspensions may be prepared from sterile powders or granules having one or more of the carriers or diluents mentioned for use in the formulations for oral administration. The compounds may be dissolved in water, polyethylene glycol, propylene glycol, ethanol, corn oil, cottonseed oil, peanut oil, sesame oil, benzyl alcohol, sodium chloride, and/or various buffers. Other adjuvants and modes of administration are well and widely known in the pharmaceutical art.

[0123] All mentioned references are incorporated by reference as if here written.

[0124] Although this invention has been described with respect to specific embodiments, the details of these embodiments are not to be construed as limitations.

GENERAL SYNTHETIC PROCEDURES

[0125] The compounds of the present invention can be synthesized, for example, according to the following procedures of Schemes 1 through 15 below, wherein the substituents are as defined above except where further noted. It will be understood that the procedures of Schemes 1 through 15 may result in the synthesis of compounds other than those of claim 1.

[0126] Synthetic Scheme 1 shows the preparation of compounds of formula XIIIA-H ("Secondary Heteroaryl Amines") which are intermediates in the preparation of the compounds of the present invention

[0127] ("Generic Substituted Polycyclic Aryl tertiary-2-hydroxyalkylamines" and Generic Substituted Polycyclic Heteroaryl tertiary 2-Heteroalkylanunes or "Generic Substituted Polycyclic Heteroaryl tertiary-2-hydroxyalkylamines") wherein the heteroaryl amine (X-AH), Heteroaryl Bromide (XXI-AH), and Heteroaryl Carbonyl (XI-AH) can independently be both aryl and heteroaryl in type. Schemes 1 through 3, taken together, prepare tertiary heteroalkylamine compounds of the present invention by addition of a halogenated, heteroatom (for example, oxygen, sulfur, or nitrogen) containing precursor to a secondary amine to introduce a heteroatom containing alkyl group wherein the two groups making up the secondary amine both are made up of aromatic groups or both groups contain aromatic rings wherein said aromatic rings maybe 0 to 2 aryl rings and 0 to 2 heteroaryl rings.

[0128] The "Diheteroaryl Imine" corresponding to Formula XII-AH can be prepared through dehydration techniques generally known in or adaptable from the art by reacting "Heteroaryl Amine" of Formula X-AH with the "Heteroaryl Carbonyl" of Formula XI-AH in Scheme 1 and subsequent specific examples. For example, when Z is a covalent bond, methylene, methine substituted with another subsitutent, ethylene, or another subsituent, the two reactants (X-AH and XI-AH) react by refluxing them in an aprotic solvent, such as hexane, toluene, cyclohexane, benzene, and the like, using a Dean-Stark type trap to remove water. After about 2-8 hours or until the removal of water is complete, the aprotic solvent is removed *in vacuo* to yield the "Diheteroaryl Imine" of Formula XII-AH. Alternately, when Z is an oxygen, the "Diheteroaryl Imine" is an oxime derivative. Oxime type "Diheteroaryl Imine" compounds are readily prepared from the corresponding O-substituted hydroxylamine and the appropriate aldehyde or ketone type "Heteroaryl Carbonyl". Alternately, when Z is a nitrogen, the "Diheteroaryl Imine" is a hydrazone derivative. Hydrazone type "Diheteroaryl Imine" compounds are readily prepared from the corresponding hydrazine and the appropriate aldehyde or ketone type "Heteroaryl Carbonyl". Suitable procedures for forming oxime and hydrazone imines are also described by Shriner, Fuson, and Curtin in The Systematic Indentification of Organic Compounds, 5th Edition, John Wiley & Sons, and by Fieser and Fieser in Reagents for Organic Synthesis, Volume 1, John Wiley & Sons, which are incorporated herein by reference.

[0129] The "Secondary Heteroaryl Amines" of Formula XIIIA-H can be prepared from the corresponding "Diheteroaryl Imine" of Formula XII-AH in several ways. For example, in one synthetic scheme (Reduction Method-1), which is preferred when Z is a nitrogen, the "Generic Imine" hydrazone of Formula XII-AH is partially or completely dissolved in presence of a lower alcohol containing sufficient organic or mineral acid, as described in WO Patent Application No.9738973, Swiss Patent CH 441366 and U. S. Patent Nos. 3359316 and 3334017, which are incorporated herein by reference,

and then hydrogenated at 0-100˚C, more preferrably 20-50˚C, and most preferrably between 20-30˚C and pressures of 10-200 psi hydrogen or more preferrably between 50-70 psi hydrogen in the presence of a noble metal catalyst such as PtO_2.

[0130] In another synthetic scheme (Reduction Method-2), which is preferrred when Z is a single bond or carbon, the "Diheteroaryl Imine" of Formula XII-AH is slurried in a lower alcohol such as ethanol, methanol or like solvent at 0-10˚C and solid sodium borohydride is added in batches over 5-10 minutes at 0-10˚C with stirring. The reaction mixture is stirred below 10˚C for 30-90 minutes and then is warmed gradually to 15-30˚C. After about 1-10 hours, the mixture is cooled and acid is added until the aqueous layer was just acidic (pH 5-7).

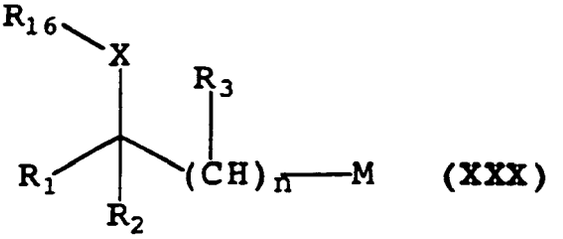
[0131] In yet another synthetic scheme (Reduction Method-3), which is preferrred when Z is an oxygen, the "Diheteroaryl Imine" oxime of Formula XII-AH is slurried in a lower alcohol solvent at 0-10˚C and acidified to a pH less than 4 and sodium cyanoborohydride is added in batches over 30-90 minutes at 0-20˚C with stirring and addition of a suitable organic or mineral acid to keep the pH at or below 4. The reaction mixture is stirred and warmed gradually to about 20-25˚C. After about 1-10 hours, the mixture is cooled and base added until the mixture was just slightly alkaline.

[0132] The "Secondary Heteroaryl Amines" of Formula XIII-AH can also be prepared, according to Scheme 1, by an alkylation procedure based on the nucleophilic substitution of bromides by amines. In one synthetic alkylation scheme (Alkylation Method-1), a "Heteroaryl Amine" of Formula X-AH is reacted with a "Heteroaryl Bromide-" of Formula XXIII-AH as described in Vogel's Textbook of Practical Organic Chemistry, Fifth Edition, 1989, pages 902 to 905 and references cited therein all of which are incorporated herein by reference. In an alternate synthetic alkylation scheme exemplified in Scheme 10, a "Heteroaryl Amine" of is reacted with a "Heteroaryl Bromide" in a method employing pallladium catalyzed carbon-nitrogen bond formation. Suitable procedures for this conversion are described in Wagaw and Buchwald. J. Org. Chem.(1996), 61, 7240-7241, Wolfe, Wagaw and Buchwald, J. Am. Chem. Soc. (1996), 118, 7215-7216, and Wolfe and Buchwald, Tetrahedron Letters (1997), 38(36), 6359-6362 and references cited therein all of which are incorporated herein by reference.

[0133] The "Secondary Heteroaryl Amine" amines, hydroxylamines, and hydrazines, the "Heteroaryl Carbonyl" aldehydes, ketones, hydrazones, and oximes, and "Heteroaryl Bromide" halides, tosylates, mesylates, triflates, and precursor alcohols required to prepare the "Secondary Heteroaryl Amine" compounds are available from commercial sources or can be prepared by one skilled in the art from published procedures. Commercial sources include but are not limited to Aldrich Chemical, TCI-America, Lancaster-Synthesis, Oakwood Products, Acros Organics, and Maybridge Chemical. Disclosed procedures for "Generic Amine" amines, hydroxylamines, and hydrazines include Sheradsky and Nov, J. Chem. Soc., Perkin Trans. 1 (1980), (12), 2781-6; Marcoux, Doye, and Buchwald, J. Am. Chem. Soc. (1997), 119, 1053-9; Sternbach and Jamison, Tetrahedron Lett. (1981), 22(35), 3331-4; U. S. Patent No. 5306718; EP No. 314435; WO No. 9001874; WO No. 9002113; JP No. 05320117; WO No. 9738973; Swiss Patent No. CH 441366; U. S. Patents Nos. 3359316 and 3334017; and references cited therein which are incorporated herein by reference.

[0134] Synthetic Scheme 2 shows the preparation of the class of compounds of the present invention corresponding to Formula VII ("Generic Substituted Polycyclic Aryl teraary-2-hydroxyalkylamines") and Formula VII-H (Generic Substituted Polycyclic Heteroaryl tertiary 2-Heteroalkylamines or "Generic Substituted Polycyclic Heteroaryl tertiary-2-hydroxyalkylamines").

[0135] Derivatives of "Generic Substituted Polycyclic Aryl tertiary-2-hydroxyalkylamines" or "Generic Substituted Polycyclic Heteroaryl tertiary-2-hydroxyalkylamines", in which the heteroatom (-O-) is attached to an alkyl group removed from the amine by two or more carbons are readily prepared by anion chemistry using the method of Scheme 2. The anion of "Secondary Heteroaryl Amine" amines, hydroxylamines, and hydrazines of Formula XIIIA-H are readily formed by dissolving the specific amine, hydroxylamine, or hydrazine in an aprotic solvent, such as tetrahydrofuran, toluene, ether, dimethylformamide, and dimethylformamide, under anhydrous conditions. The solution is cooled to a temperature between -78 and 0˚C, preferrably between - 78 and -60˚C and the anion formed by the addition of at least one equivalent of a strong, aprotic, non-nucleophillic base such as NaH or n-butyllithium under an inert atmosphere for each acidic group present. Maintaining the temperature between -78 and 0˚C, preferrably between -78 and -60˚C, with suitable cooling, an appropriate alkyl halide, alkyl benzenesulfonate such as a alkyl tosylate, alkyl mesylate, alkyl triflate or similar alkylating reagent of the general structure:

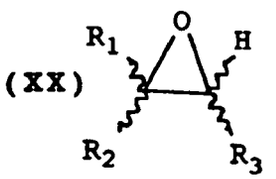


(XXX)

where m is zero, X can be RN, O, and S, and M is a readily displaceable group such as chloride, bromide, iodide, tosylate, triflate, and mesylate. After allowing the reaction mixture to warm to room temperature, the reaction product is added to water, neutralized if necessary, and extracted with a water-immiscible solvent such as diethyl ether or methylene chloride. The combined aprotic solvent extract is washed with saturated brine, dried over drying agent such as anhydrous MgSO4 and concentrated *in vacuo* to yield crude Formula VII ("Generic Substituted Polycyclic Aryl tertiary-2-hydroxyalkylamines" or Formula VII-H "Generic Substituted Polycyclic Heteroaryl tertiary-2-hydroxyalkylamines","). This material is purified, for example, by eluting through silica gel with a medium polar solvent such as ethyl acetate in a non-polar solvent such as hexanes to yield purified Formula VII-H and Formula VII. Products are structurally confirmed by low and high resolution mass spectrometry and NMR.

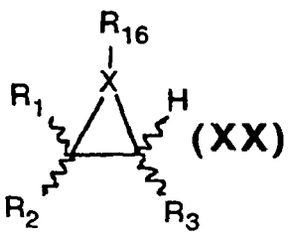
[0136] Compounds of Formula (XXX), which can be used to prepare the "Generic Substituted Polycyclic Heteroaryl and Aryl tertiary hydroxyalkylamines" compounds in Tables 3 and 4. are given in Table 2. Reagents 1a and 2a in Table 2 are prepared from the corresponding alcohols. The tosylates are readily obtained by reacting the corresponding alcohol with tosyl chloride using procedures found in House's Modem Synthetic Reactions. Chapter 7, W. A. Benjamin, Inc., Shriner, Fuson, and Curtin in The Systematic Indentification of Organic Compounds, 5th Edition, John Wiley & Sons, and Fieser and Fieser in Reagents for Organic Synthesis, Volume 1, John Wiley & Sons, which are incorporated herein by reference.

[0137] A preferred procedure for Formula VII ("Generic Substituted Polycyclic Aryl tertiary-2-hydroxyalkytamines") and Formula VII-H (Generic Substituted Polycyclic Heteroaryl tertiary 2-Heteroalkylamines or "Generic Substituted Polycyclic Heteroaryl tertiary-2-hydroxyalkylamines") compounds is Method A of Scheme 3. Oxirane reagents useful in Method A are exemplified, but not limited to those in Table 1. Formula VII ("Generic Substituted Polycyclic Aryl tertiary-2-hydroxyalkylamines") and Formula VII-H (Generic Substituted Polycyclic Heteroaryl tertiary 2-Heteroalkylamines or "Generic Substituted Polycyclic Heteroaryl terfiary-2-hydroxyalkylamines") compounds are prepared by using "Secondary Heteroaryl Amine" amines, hydroxylamines, and hydrazines of Formula XIIIA-H prepared above with oxiranes of the type listed in Table 1 and represented by the general structure:



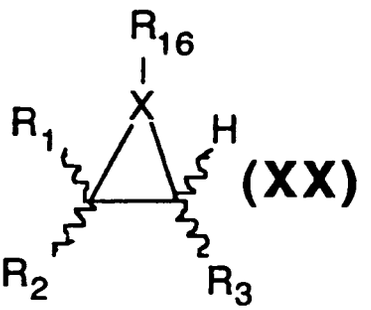
In some cases, the oxiranes are prepared by reaction of epoxidation reagents such as MCPBA and similar type reagents readily selectable by a person of skill-in-the-art with alkenes. Fieser and Fieser in Reagents for Organic Synthesis, John Wiley & Sons provides, along with cited references, numerous suitable epoxidation reagents and reaction conditions, which are incorporated herein by reference.

[0138] Formula VII ("Generic Substituted Polycyclic Aryl tertiary-2-heteroalkylamines") and Formula VII-H ("Generic Substituted Polycyclic Heteroaryl tertiary 2-Heteroalkylamines") compounds, wherein the 2-hetero group is an amino, substituted amino, or thiol, can be prepared by using appropriate aziridines and thirranes according to Method A of Scheme 3. Aziridine and thiirane reagents useful in Method A are exemplified, but not limited to those in Table 1. These Formula VII ("Generic Substituted Polycyclic Aryl tertiary 2-heteroalkylamine") and Formula VII-H ("Generic Substituted Polycyclic Heteroaryl tertiary-2-heteroalkylamines") compounds, wherein the 2-hetero group is an amino, substituted amino, or thiol, can be prepared by using "Secondary Heteroaryl Amine" amines, hydroxylamines, and hydrazines of Formula XIIIA-H prepared above with aziridines and thiiranes of the type listed in Table 1 and represented by the general structure:



wherein X is selected from N and S and R_{16} is hydrogen or another suitable group when X is N.

Table 1. Structure of Oxirane, Aziridine, and Thiirane Reagents.



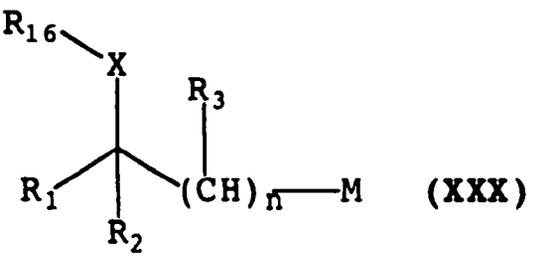
(XX)

Rgnt No.	R_{16}	X	R_1	R_2	R_3
1	-----	O	CF_3	H	H
2	-----	O	CCl_3	H	H
3	-----	O	CF_3	CH_3	H
4	-----	O	CF_3CF_2	H	H
5	-----	O	$CF_3CF_2CF_2$	H	H
6	-----	O	$CF_3OCF_2CF_2$	H	H
7	-----	O	CF_3CH_2	H	H
8	-----	O	CF_3	CHF_2	H
9	-----	O	CF_3	H	CF_3
10	-----	O	CF_3	CF_3	H
11	-----	O	CF_3	C_6H_5	H
12	-----	O	CCl_3	C_6H_5	H
13	-----	O	CCl_3	Cyclopropyl	H
14	----	O	CCl_3	CH_3	H
15	-----	O	CCl_3	$(CH_3)_2CH$	H
16	-----	O	$CHCl_2$	H	H
17	-----	O	$CHCl_2$	Cl	H
18	-----	O	CF_3	H	CH_3
19	H	N	CF_3	CF_3	H
20	H	N	CF_3	H	H
21	Benzyl	N	CF_3	H	H
22	CH_3O	N	CF_3	H	H
23	CH_3	N	CF_3	H	H
24	Benzyloxy	N	CF_3	H	H
25	-----	S	CF_3	H	H
26	-----	S	CF_3CF_2	H	H
27	-----	O	CCl_3CH_2	H	H
28	-----	O	CBr_3CH_2	H	H

(continued)

Rgnt No.	R_{16}	X	R_1	R_2	R_3
29	-----	O	$CHBr_2CH_2$	H	H
30	-----	O	$CBrCl_2$	H	H
31	-----	O	$CClF_2$	H	H
32	-----	O	CCl_2F	H	H
33	-----	O	CCl_3CCl_2	H	H
43	-----	O	FCH_2	H	H
46	-----	O	CF_3	$R_2+R_3 = (CH_2)_3$	
47	-----	O	CF_3	$R_2+R_3 = (CH_2)_4$	
48	-----	O	CHF_2	$R_2+R_3 = (CH_2)_4$	
56	-----	O	$CBrF_2CClFCH_2$	H	H
57	-----	O	$HCF_2CF_2OCH_2$	H	H

Table 2. Structure and Source of Alcohol and Glycol Reagents.

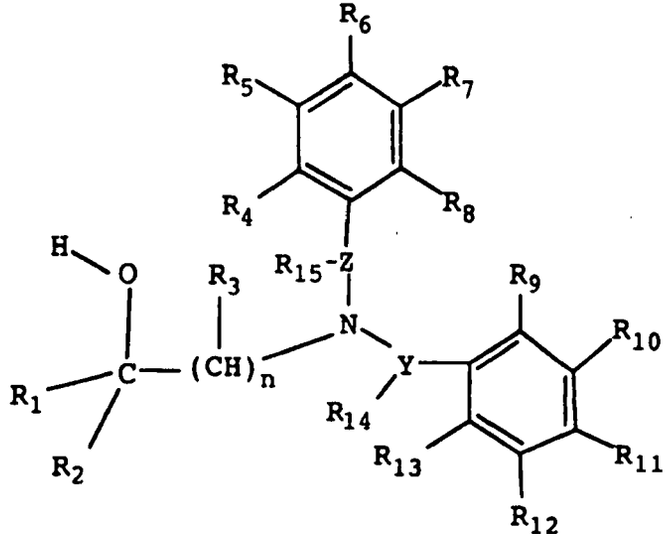


(XXX)

Reagent Number	R_1	n	M	R_2	R_3	X-R_{16}	Source of Reagent
1A	CF_3	3	OTs	H	H	OH	Chiral separation and then tosylation of alcohol from Justus Liebigs Ann. Chem. (1969), 720, 81-97.
2A	$CF_3CH_2CH_2$	3	OTs	H	H	OH	Chiral separation and then tosylation of alcohol from Z. Naturforsch., B: Chem. Sci. (1997), 52 (3). 413-418

Table 3. Structure of Substituted Phenyl *tertiary*- omega-Hydroxyalkylamines

(Y is CH; R_8, R_9, R_{12}, R_{13}, and R_{14} are each H; Z is covalent bond and R_{15} is absent).



Inhibitor Number Column1+Column 2		R_1	n	R_2	R_3	R_4	R_5	R_6	R_7	R_{10}	R_{11}
Reagent	Reagent										
1A	1N	CF_3	3	H	H	H	C_6H_5O	H	H	OCF_2CF_2H	H
1A	2N	CF_3	3	H	H	H	OCF_3	H	H	OCF_2CF_2H	H
1A	3N	CF_3	3	H	H	F	H	H	F	OCF_2CF_2H	H
1A	4N	CF_3	3	H	H	H	F	H	H	OCF_2CF_2H	H
1A	5N	CF_3	3	H	H	H	C_6H_5O	H	H	OCF_3	H
1A	6N	CF_3	3	H	H	H	OCF_3	H	H	OCF_3	H
1A	7N	CF_3	3	H	H	H	H	phenyl	H	OCF_3	H
1A	8N	CF_3	3	H	H	H	phenyl	H	H	OCF_3	H
1A	9N	CF_3	3	H	H	H	H	H	H	OCF_3	H

(continued)

Inhibitor Number Column1+Column 2		R_1	n	R_2	R_3	R_4	R_5	R_6	R_7	R_{10}	R_{11}
1A	10N	CF_3	3	H	H	H	Br	H	H	OCF_3	H
1A	11N	CF_3	3	H	H	H	CF_3	F	H	CF_3	H
1A	12N	CF_3	3	H	H	H	CH_3	H	H	CF_3	H
1A	13N	CF_3	3	H	H	H	CF_3	H	H	CF_3	H
1A	14N	CF_3	3	H	H	H	CH_3	H	H	OCF_3	H
1A	15N	CF_3	3	H	H	H	F	F	H	OCF_3	H
1A	16N	CF_3	3	H	H	H	Br	H	H	CF_3	H
1A	17N	CF_3	3	H	H	H	CF_3	F	H	OCF_3	H
1A	18N	CF_3	3	H	H	H	F	H	H	OCF_3	H
1A	19N	CF_3	3	H	H	H	Cl	H	H	OCF_3	H
1A	20N	CF_3	3	H	H	H	F	H	H	CF_3	H
1A	21N	CF_3	3	H	H	H	F	F	H	CF_3	H
1A	22N	CF_3	3	H	H	H	Cl	H	H	CF_3	H
1A	23N	CF_3	3	H	H	H	F	H	H	phenoxy	H
1A	24N	CF_3	3	H	H	H	CF_3	Cl	H	CH_3	H
1A	25N	CF_3	3	H	H	H	CF_3	F	H	CH_3	H
1A	26N	CF_3	3	H	H	H	H	H	H	CF_3	H
1A	27N	CF_3	3	H	H	F	F	H	H	CF_3	H
1A	28N	CF_3	3	H	H	H	H	OCH_3	H	CF_3	H
1A	29N	CF_3	3	H	H	H	F	F	H	CH_3	H
1A	30N	CF_3	3	H	H	H	OCH_3	H	H	CH_3	H
1A	31N	CF_3	3	H	H	H	H	CH_3	H	H	H
1A	32N	CF_3	3	H	H	H	Cl	H	H	H	H
1A	33N	CF_3	3	H	H	H	F	H	H	F	H
1A	34N	CF_3	3	H	H	H	H	OCH_3	H	CH_3	H

(continued)

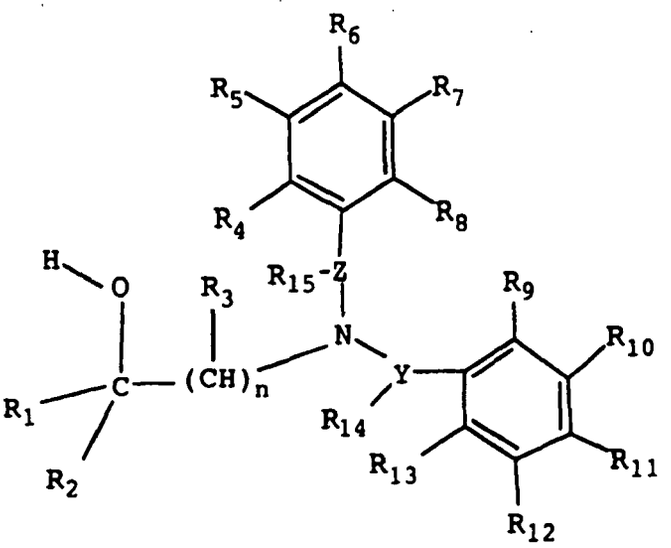
Inhibitor Number Column1+Column 2		R_1	n	R_2	R_3	R_4	R_5	R_6	R_7	R_{10}	R_{11}
1A	35N	CF_3	3	H	H	H	H	H	H	H	H
1A	36N	CF_3	3	H	H	H	H	CH_3	H	CH_3	H
1A	37N	CF_3	3	H	H	H	H	Cl	H	H	H
1A	38N	CF_3	3	H	H	H	F	H	H	3-CF_3-phenoxy	H
1A	39N	CF_3	3	H	H	H	F	H	H	4-CH_3O-phenoxy	H
1A	40N	CF_3	3	H	H	H	F	H	H	4-Cl-phenoxy	H
1A	41N	CF_3	3	H	H	H	F	H	H	H	H
1A	42N	CF_3	3	H	H	H	F	H	H	CH_3	H
1A	43N	CF_3	3	H	H	H	F	H	F	CH_3	H
1A	44N	CF_3	3	H	H	F	F	H	H	CH_3	H
1A	45N	CF_3	3	H	H	H	Cl	H	H	CH_3	H
1A	46N	CF_3	3	H	H	H	CH_3	H	H	CH_3	H
1A	48N	CF_3	3	H	H	H	H	CH_3	H	CF_3	H
1A	51N	CF_3	3	H	H	H	H	CH_3	H	F	H
1A	52N	CF_3	3	H	H	H	CF_3	H	H	F	H
1A	53N	CF_3	3	H	H	H	CF_3	H	H	CH_3	H
1A	54N	CF_3	3	H	H	H	OCH_3	H	H	CF_3	H
1A	56N	CF_3	3	H	H	H	H	CH_3	H	CF_3	H
1A	57N	CF_3	3	H	H	H	C_6H_5O	H	H	H	OCF_3
1A	58N	CF_3	3	H	H	H	H	H	H	H	OCF_3
1A	59N	CF_3	3	H	H	H	OCF_3	H	H	H	OCF_3
1A	60N	CF_3	3	H	H	H	CF_3	F	H	H	CF_3
1A	61N	CF_3	3	H	H	H	H	OCH_3	H	H	CF_3
1A	62N	CF_3	3	H	H	H	CH_3	H	H	H	CF_3
1A	63N	CF_3	3	H	H	H	Cl	H	H	H	CF_3

(continued)

Inhibitor Number	Column1+Column 2	R_1	n	R_2	R_3	R_4	R_5	R_6	R_7	R_{10}	R_{11}
1A	64N	CF_3	3	H	H	H	CF_3	H	H	H	OCF_3
1A	65N	CF_3	3	H	H	H	F	H	H	H	OCF_3
1A	66N	CF_3	3	H	H	H	F	H	F	H	OCF_3
1A	67N	CF_3	3	H	H	H	Br	H	H	H	OCF_3
1A	68N	CF_3	3	H	H	H	Cl	H	H	H	OCF_3
1A	69N	CF_3	3	H	H	H	F	F	H	H	OCF_3
1A	70N	CF_3	3	H	H	H	F	H	H	H	phenyl
1A	71N	CF_3	3	H	H	H	CH_3	H	H	H	OCF_3
1A	72N	CF_3	3	H	H	H	F	F	H	H	CF_3
1A	73N	CF_3	3	H	H	H	Cl	H	H	H	CH_3
1A	74N	CF_3	3	H	H	H	OCH_3	H	H	H	CH_3
1A	75N	CF_3	3	H	H	H	F	H	H	H	CH_3
1A	76N	CF_3	3	H	H	F	F	H	H	H	OCF_3
1A	78N	CF_3	3	H	H	H	H	OCH_3	H	H	CH_3
1A	79N	CF_3	3	H	H	H	H	CH_3	H	H	CH_3
1A	80N	CF_3	3	H	H	H	CH_3	H	H	H	CH_3
1A	82N	CF_3	3	H	H	H	F	F	H	H	CH_3
1A	83N	CF_3	3	H	H	H	F	H	F	H	CH_3
1A	84N	CF_3	3	H	H	F	F	H	H	H	CH_3
1A	85N	CF_3	3	H	H	F	CF_3	H	H	H	CH_3
1A	86N	CF_3	3	H	H	H	H	CH_3	H	H	CF_3
1A	88N	CF_3	3	H	H	H	CF_3	H	H	H	CH_3
1A	90N	CF_3	3	H	H	H	H	CF_3	H	H	CH_3
1A	92N	CF_3	3	H	H	H	CF_3	F	H	H	CH_3

Table 4. Structure of Substituted Phenyl *tertiary*- omega-Hydroxyatkylamines

(Y and Z are CH; R_8, R_9, R_{12}, R_{13}, R_{14}, and R_{15} are each H; Z is covalent R_{15} is absent).



Inhibitor Number Column 1+Column 2		R_1	n	R_2	R_3	R_4	R_5	R_6	R_9	R_{10}	R_{11}
Reagent	Reagent										
1A	1DB	CF_3	3	H	H	H	OCF_3	H	H	OCF_3	H
1A	2DB	CF_3	3	H	H	H	Cl	H	H	H	CF_3
1A	3DB	CF_3	3	H	H	H	Br	H	H	OCF_3	H
1A	4DB	CF_3	3	H	H	H	Cl	H	H	OCF_3	H
1A	5DB	CF_3	3	H	H	H	Cl	H	H	CF_3	H
1A	6DB	CF_3	3	H	H	H	H	Cl	H	CF_3	H
1A	7DB	CF_3	3	H	H	H	F	H	H	OCF_3	H
1A	8DB	CF_3	3	H	H	H	H	Cl	H	H	CF_3
1A	9DB	CF_3	3	H	H	H	F	H	H	H	CF_3
1A	10DB	CF_3	3	H	H	H	H	F	H	H	CF_3
1A	11DB	CF_3	3	H	H	F	H	H	H	H	CF_3
1A	12DB	CF_3	3	H	H	H	Cl	H	CF_3	H	H
1A	13DB	CF_3	3	H	H	H	H	Cl	CF_3	H	H
1A	14DB	CF_3	3	H	H	Cl	H	H	CF_3	H	H
1A	15DB	CF_3	3	H	H	H	F	H	CH_3	H	H
1A	16DB	CF_3	3	H	H	H	H	F	H	H	CH_3
1A	17DB	CF_3	3	H	H	H	F	H	H	CH_3	H
1A	18DB	CF_3	3	H	H	F	H	H	CH_3	H	H
1A	19DB	CF_3	3	H	H	H	H	F	H	CH_3	H
1A	20DB	CF_3	3	H	H	F	H	H	H	H	CH_3
1A	21DB	CF_3	3	H	H	F	H	H	H	CF_3	H

(continued)

Inhibitor Number Column 1+Column 2		R_1	n	R_2	R_3	R_4	R_5	R_6	R_9	R_{10}	R_{11}
1A	22DB	CF_3	3	H	H	Cl	H	H	H	CF_3	H
1A	23DB	CF_3	3	H	H	H	F	H	CF_3	H	H
1A	24DB	CF_3	3	H	H	H	H	F	CF_3	H	H
1A	25DB	CF_3	3	H	H	H	F	H	H	CF_3	H
1A	26DB	CF_3	3	H	H	H	H	F	H	CF_3	H
1A	27DB	CF_3	3	H	H	H	OCF_3	H	H	H	OCF_3

[0139] A mixture of a "Secondary Heteroaryl Amine" amine, hydroxylamine, or hydrazine of Formula XIIIA-H and an oxirane of Formula XX are stirred and heated to 40-90˚C for 5 to 48 hours in a tightly capped or contained reaction vessel. A Lewis acid such as ytterbium triflate in acetonitrile may be added to speed up reaction and improve yield. When a Lewis acid is used, the reaction should be carried out under inert, anhydrous conditions using a blanket of dry nitrogen or argon gas. After cooling to room temperature and testing the reaction mixture for complete reaction by thin layer chromatography or high pressure liquid chromatography (hplc), the reaction product is added to water and extracted with a water immiscible solvent such as diethyl ether or methylene chloride. (Note: If the above analysis indicates that reaction is incomplete, heating should be resumed until complete with the optional addition of more of the oxirane). The combined aprotic solvent extract is washed with saturated brine, dried over drying agent such as anhydrous $MgSO_4$ and concentrated *in vacuo* to yield crude Formula VII ("Generic Substituted Polycyclic Aryl *tertiary* 2-hydroxyalkylamine") and Formula VII-H ("Generic Substituted Polycyclic Heteroaryl tertiary-2-hydroxyalkylamine") compounds. This material is purified by eluting through silica gel with 5-40% of a medium polar solvent such as ethyl acetate in a non-polar solvent such as hexanes to yield the Formula VII ("Generic Substituted Polycyclic Aryl *tertiary* 2-hydroxyalkylamine") and Formula VII-H ("Generic Substituted Polycyclic Heteroaryl tertiary-2-hydroxyalkylamine"). Products are tested for purity by HPLC. If necessary, the Formula VII ("Generic Substituted Polycyclic Aryl *tertiary* 2-hydroxyalkylamine") and Formula VII-H ("Generic Substituted Polycyclic Heteroaryl terbary-2-hydroxyalkylamine") compounds are purified by additional chromatography or recrystallization. Products are structurally confirmed by low and high resolution mass spectrometry and NMR. Examples of specific Formula VII ("Generic Substituted Polycyclic Aryl *tertiary 2*-hydroxyalkylamine") compounds prepared are summarized in the Examples and Example Tables 1 through 54.

[0140] Specific Formula VII ("Generic Substituted Polycyclic Aryl *tertiary 2*-hydroxyalkytamine") and Formula VII-H ("Generic Substituted Polycyclic Heteroaryl tertiary-2-hydroxyalkylamine") analogs of the "Polycyclic Aryl tertiary -2-hydroxyalkylamine" compounds summarized in the Examples and Example Tables 1 through 54, wherein the hydroxyl or oxy group are replaced with an amino, substituted amino, aza, or thiol, can be prepared by using the appropriate aziridine reagents or thiirane reagents readily by adapting the procedures in the numerous specific **Examples** and **Schemes** disclosed in the present invention. Similarly, intermediates, in which the hydroxyl or oxy group of said intermediates are replaced with an amino, substituted amino, aza, or thiol, can be converted using the numerous specific **Examples** and **Schemes** disclosed in the present invention to other Formula VII ("Generic Substituted Polycyclic Aryl *tertiary* 2-hydroxyalkylamine") and Formula VII-H ("Generic Substituted Polycyclic Heteroaryl tertiary-2-hydroxyalkylamine") analogs of the "Polycyclic Aryl *tertiary* -2-hydroxyalkylamine" compounds.

[0141] Formula VII ("Generic Substituted Polycyclic Aryl tertiary-2-hydroxyalkylamines") and Formula VII-H ("Generic Substituted Polycyclic Heteroaryl tertiary-2-hydroxyalkylamines") can further be prepared in an alternate manner to procedures disclosed above and in Schemes 1, 2, and 3. Schemes 9 and 10 detail such procedures to prepare tertiary oxyalkylamine compounds of the present invention by initial formation of an halogenated, oxygen containing primary alkylamine XVL ("Generic Substituted Alkylamine"). Said halogenated, oxygen containing primary alkylamine XVL, formed in Scheme 9, is itself converted to secondary amine VLX-H ("Heteroaryl Alkyl Amine) using procedures disclosed above. Primary alkylamine XVL is first reacted with an aldehydic or ketonic carbonyl compound, XI-AH ("Heteroaryl Carbonyl") with azeotropic distillation to form imines, VL-H ("Heteroaryl Imine"). Said imine VL-H are then reduced with or without prior isolation by Reduction Methods 1, 2 or 3 as disclosed above and in Scheme 1 to yield secondary amines VLX-H ("Heteroaryl Alkyl Amine). Said secondary amine VLX-H can be converted according to Scheme 10 to VII-H ("Generic Substituted Polycyclic Heteroaryl Tertiary 2-hydroxyalkylamines"). Using similar schemes, VLX can be converted to VII ("Generic Substituted Polycyclic Phenyl Tertiary 2-hydroxyalkylamines"). Compounds of this invention in which one aromatic substituent is aryl and the other aromatic substitutent is heteroaryl can be readily prepared by reacting VLX-H with an aryl bromide or aralkyl bromide instead of using an heteroaryl bromide or heteroaralkyl bromide. Similarly, compounds of this invention in which one aromatic substituent is aryl and the other aromatic substitutent is

heteroaryl can be readily prepared by reacting the aryl analog of VLX-H with an heteroaryl bromide or heteroaralkyl bromide instead of using an aryl bromide or aralkyl bromide.

[0142] Formula VII ("Generic Substituted Polycyclic Aryl tertiary-2-hydroxyalkylamines") and Formula VII-H ("Generic Substituted Polycyclic Heteroaryl tertiary-2-hydroxyalkylamines") can further be prepared in an alternate manner to procedures disclosed above and in Schemes 1, 2, 3, 9, and 10. Schemes 13, 14, and 15 detail alternate procedures to prepare tertiary oxyalkylamine compounds of the present invention by initial formation of an halogenated, oxygen containing secondary alkylamines VLX and VLXX ("Phenyl Alkylamines") and VLXX-O ("Phenyl Oxy Alkylamines"). Said secondary alkylamines VLX and VLXX ("Phenyl Alkylamines") and VLXX-O ("Phenyl Oxy Alkylamines") can be converted according to Schemes 13, 14 and 15 to VII ("Generic Substituted Polycyclic Aryl Tertiary 2-hydroxyalkylamines") and VII-H ("Generic Substituted Polycyclic Heteroaryl Tertiary 2-hydroxyalkylamines") by reaction with appropriate aromatic halides such as aryl bromides and heteroaryl bromides as desired.

[0143] Formula VII ("Generic Substituted Polycyclic Aryl tertiary-2-hydroxyalkylamines") and Formula VII-H ("Generic Substituted Polycyclic Heteroaryl tertiary-2-hydroxyalkylamines") can further be prepared in an alternate manner to procedures disclosed above and in Schemes 1, 2, 3, 9, 10, 13, 14, and 15. Another alternate procedure to prepare tertiary oxyalkylamine compounds of the present invention by reacting secondary amine XIIIA-H ("Secondary Heteroaryl Amine") with a diazo ester. The intermediate glycinate tertiary amine can then be reduced, partially reoxidized to an aldehyde, and converted using a perfluoroalkyl trimethylsilyl compound (for example, trifluoromethyl-TMS) to the desired product, VII ("Generic Substituted Polycyclic Aryl Tertiary 2-hydroxyalkylamines") and VII-H ("Generic Substituted Polycyclic Heteroaryl Tertiary 2-hydroxyalkylamines").

[0144] A particularly useful procedure to prepare Formula VII ("Generic Substituted Polycyclic Aryl tertiary-2-hydroxyalkylamines") and Formula VII-H (Generic Substituted Polycyclic Heteroaryl tertiary 2-Heteroalkylamines or "Generic Substituted Polycyclic Heteroaryl tertiary-2-hydroxyalkylamines") compounds of the present invention in which the heteroaryl group is directly bonded is disclosed in Schemes 11 and 12. An halogenated, oxygen containing primary alkylamine XVL ("Generic Substituted Alkylamine") formed according to Scheme 9 is itself converted by reaction with LXXI-AH ("Heteroaryl Halide") to afford secondary amine VLXX-H ("Heteroaryl Secondary Amine) using procedures disclosed in Scheme 11 and above. VLXX-H is converted to VII-H ("Generic Substituted Polycyclic Phenyl Heteroaryl Tertiary 2-hydroxyalkylamine") by alkylation chemistry with an aralkyl bromide or aralkyloxyalkyl bromide using either of two procedures disclosed in Scheme 12. Isolation and purification is effected as disclosed previously.

[0145] Formula VII ("Generic Substituted Polycyclic Aryl tertiary-2-hydroxyalkytamines") and Formula VII-H (Generic Substituted Polycyclic Heteroaryl tertiary 2-Heteroalkylamines or "Generic Substituted Polycyclic Heteroaryl tertiary-2-hydroxyalkylamines") can themselves serve as intermediates for conversion to additional compounds of this invention. Compounds of Formula VII-H, Formula VII and the present invention useful as intermediates include those in which the R_7 position substituent in Formula VII ("Generic Substituted Polycyclic Aryl tertiary-2-hydroxyalkylamines") is a bromo group, hydroxyl group, sulfhydryl group, bromomethyl or other bromoalkyl groups, nitro group, amino group, methoxy carbonyl or other alkoxy carbonyl groups, cyano group, or acyl groups. Other preferred compounds of Formula VII-H, Formula VII and the present invention useful as intermediates include those in which the R_{10} position substituent in Formula VII is a bromo group, hydroxyl group, sulfhydryl group, bromomethyl or other bromoalkyl groups, nitro group, amino group, methoxy carbonyl or other alkoxy carbonyl groups, cyano group, or acyl groups. Other compounds of Formula VII-H, Formula VII and the present invention useful as intermediates include those in which one or more of R_6 , R_7 , R_{11} , and R_{12} substituents in Formula VII-H and Formula VII is a bromo group, hydroxyl group, sulfhydryl group, bromomethyl or other bromoalkyl groups, nitro group, amino group, methoxy carbonyl or other alkoxy carbonyl groups, cyano group, or acyl groups.

[0146] A 3-bromo substituent at the R_7 position in Formula VII ("Generic Substituted Polycyclic 3-Bromoaryl Tertiary 2-hydroxyalkylamine") can be reacted with a phenol to afford, as described in Examples, 3-phenoxy compounds of the present invention of Formula VII ("Generic Substituted Polycyclic 3-Phenoxyaryl Tertiary 2-Hydroxyalkylamine").

[0147] A 3-bromo substituent at the R_7 position in Formula VII-H ("Generic Substituted Polycyclic 3-Bromoheteroaryl Tertiary 2-hydroxyalkylamine") can, as shown in Scheme 4, be reacted with a phenol to afford, as described in Examples, additional compounds of the present invention of Formula VII-H ("Generic Substituted Polycyclic 3-Aryloxyaryl, 3-Heteroaryloxyaryl, 3-Heteroaryloxyheteroaryl, and 3-Aryioxyheteroaryl Tertiary 2-Hydroxyalkylamines").

[0148] A 3-bromo substituent at the R_7 position in Formula VII ("Generic Substituted Polycyclic 3-Bromoaryl Tertiary 2-hydroxyalkylamine") can, as shown in Scheme 7, be reacted with a phenol to afford, as described in Examples, additional compounds of the present invention of Formula VII ("Generic Substituted Polycyclic 3-Phenylaryl Tertiary 2-Hydroxyalkylamine').

[0149] Conversion of a 3-bromo substituent at the R_7 position in Formula VII ("Generic Substituted Polycyclic 3-Bromoaryl Tertiary 2-hydroxyalkylamine") by reaction with a primary or secondary amine can, as shown in Scheme 8, afford, as described in Examples, additional compounds of the present invention of Formula VII ("Generic Substituted Polycyclic 3- R_{22}aminoaryl Tertiary 2-Hydroxyalkylamine").

[0150] Conversion of a 3-bromo substituent at the R_{10} position in Formula VII ("Generic Substituted Polycyclic 3-

Bromoaryl Tertiary 2-hydroxyalkylamine") by reaction with an aryl borinate can afford, as described in Examples, additional compounds of the present invention of Formula VII ("Generic Substituted Polycyclic 3-Phenylaryl Tertiary 2-Hydroxyalkylamine").

[0151] Conversion of a 3-bromo substituent at the R_{10} position in Formula VII ("Generic Substituted Polycyclic 3-Bromoaryl Tertiary 2-hydroxyalkylamine") by reaction with a heteroaryl dibutyl tin compound can afford, as described in Examples, additional compounds of the present invention of Formula VII ("Generic Substituted Polycyclic 3-Heteroarylaryl Tertiary 2-Hydroxyalkylamine").

[0152] Conversion of a 3-bromomethyl substituent at the R_7 position in Formula VII ("Generic Substituted Polycyclic 3-Bromomethylaryl Tertiary 2-hydroxyalkylamine") by reaction with an aryl borinate can afford, as described in **Examples,** additional compounds of the present invention of Formula VII ("Generic Substituted Polycyclic 3-Arylmethylaryl Tertiary 2-Hydroxyalkylamine").

[0153] Conversion of a 3-hydroxyl substituent at the R_7 position in Formula VII-H ("Generic Substituted Polycyclic 3-Hydroxyheteroaryl Tertiary 2-hydroxyalkylamine") by reaction with an aryl bromide or heteroaryl bromide can afford, as described in **Examples**, additional compounds of the present invention of Formula VII-H ("Generic Substituted Polycyclic 3-Aryloxyaryl, 3-Heteroaryloxyaryl, 3-Heteroaryloxyheteroaryl, and 3-Aryloxyheteroaryl Tertiary 2-Hydroxyalkylamines").

[0154] Conversion of a 3-hydroxyl substituent at the R_7 position in Formula VII ("Generic Substituted Polycyclic 3-Hydroxyaryl Tertiary 2-hydroxyalkylamine") by reaction with an aryl bromide can afford, as described Scheme 5 and in **Examples**, additional compounds of the present invention of Formula VII ("Generic Substituted Polycyclic 3-Phenoxyaryl Tertiary 2-Hydroxyalkylamine").

[0155] Conversion of a 3-hydroxyl substituent at the R_7 position in Formula VII-H ("Generic Substituted Polycyclic 3-Hydroxyheteroaryl Tertiary 2-hydroxyalkylamine") by reaction with an aralkyl bromide or heteroaralkyl bromide can afford, as described in **Examples**, additional compounds of the present invention of Formula VII-H ("Generic Substituted Polycyclic 3-Aralkyloxyaryl, 3-Heteroaralkyloxyaryl, 3-Heteroaralkyloxyheteroaryl, and 3-Aralkyloxyheteroaryl Tertiary 2-Hydroxyalkylamines").

[0156] Conversion of a 3-hydroxyl substituent at the R_7 position in Formula VII ("Generic Substituted Polycyclic 3-Hydroxyaryl Tertiary 2-hydroxyalkylamine") by reaction with an aralkyl bromide can afford, as described in **Examples,** additional compounds of the present invention of Formula VII ("Generic Substituted Polycyclic 3-Aralkyloxyaryl Tertiary 2-Hydroxyalkylamine").

[0157] Conversion of a 3-hydroxyl substituent at the R_7 position in Formula VII ("Generic Substituted Polycyclic 3-Hydroxyaryl Tertiary 2-hydroxyalkylamine") by reaction with an R_{17}-bromide can afford, as described in **Examples,** additional compounds of the present invention of Formula VII ("Generic Substituted Polycyclic 3- R_{17}-oxyaryl Tertiary 2-Hydroxyalkylamine").

[0158] Conversion of a 3-thio substituent at the R_7 position in Formula VII ("Generic Substituted Polycyclic 3-thioaryl Tertiary 2-hydroxyalkylamine") by reaction with an R_{17}-bromide can afford, as described in **Examples,** additional compounds of the present invention of Formula VII ("Generic Substituted Polycyclic 3- R_{17}thiaaryl Tertiary 2-Hydroxyalkylamine"). "Generic Substituted Polycyclic 3- R_{17}thiaaryl Tertiary 2-Hydroxyalkylamines" can be oxidized to sulfonyl compounds of Formula VII ("Generic Substituted Polycyclic 3- R_7sulfonylaryl Tertiary 2-Hydroxyalkylamine").

[0159] Conversion of a 3-nitro substituent at the R_7 position in Formula VII ("Generic Substituted Polycyclic 3-Nitroaryl Tertiary 2-hydroxyalkylamine") by hydrogenation can afford, as described in **Examples**, additional compounds of the present invention of Formula VII ("Generic Substituted Polycyclic 3-Aminoaryl Tertiary 2-Hydroxyalkylamine"). "Generic Substituted Polycyclic 3-Aminoaryl Tertiary 2-Hydroxyalkylamines" can be acylated to acyl amide compounds of Formula VII ("Generic Substituted Polycyclic 3-Acylaminoaryl Tertiary 2-Hydroxyalkylamine").

[0160] Conversion of a 3-amino substituent at the R_7 position in Formula VII ("Generic Substituted Polycyclic 3-Aminoaryl Tertiary 2-hydroxyalkylamine") by reaction with carbonyl compounds can afford, as described in Examples, additional compounds of the present invention of Formula VII ("Generic Substituted Polycyclic 3-(Saturated Nitrogen Heterocycl-1yl)aryl Tertiary 2-Hydroxyalkylamine" and "Generic Substituted Polycyclic 3-(Unsaturated Nitrogen Heterocycl-1yl)aryl Tertiary 2-Hydroxyalkylamine").

[0161] Conversion of a 3-methoxycarbonyl substituent at the R_7 position in Formula VII ("Generic Substituted Polycyclic 3-Carbomethoxyaryl Tertiary 2-hydroxyalkylamine") by reaction with amination reagents can afford, as described in **Examples**, additional compounds of the present invention of Formula VII ("Generic Substituted Polycyclic 3-Carboxamidoaryl Tertiary 2-Hydroxyalkylamine").

[0162] Conversion of a 3-cyano substituent at the R_7 position in Formula VII ("Generic Substituted Polycyclic 3-Cyanoaryl Tertiary 2-hydroxyalkylamine") by reaction with organometallic reagents can afford, as described in **Examples**, additional compounds of the present invention of Formula VII ("Generic Substituted Polycyclic 3-Acylaryl Tertiary 2-Hydroxyalkylamine"). Said "Generic Substituted Polycyclic 3-Acylaryl Tertiary 2-Hydroxyalkylamines", can be reduced to hydroxyl compounds of Formula VII ("Generic Substituted Polycyclic 3-Hydroxysubstitutedmethylaryl Tertiary 2-Hydroxyalkylamine").

[0163] Conversion of a 3-methoxycarbonyl substituent at the R_{10} position in Formula VII ("Generic Substituted Polycyclic 3-Carbomethoxyaryl Tertiary 2-hydroxyalkylamine") by reaction with amination reagents can afford, as described in **Examples**, additional compounds of the present invention of Formula VII ("Generic Substituted Polycyclic 3-Carboxamidoaryl Tertiary 2-Hydroxyalkylamine").

[0164] Conversion of a 3-methoxycarbonyl substituent at the R_{10} position in Formula VII ("Generic Substituted Polycyclic 3-Carbomethoxyaryl Tertiary 2-hydroxyalkylamine") by reaction with an organometallic reagent can afford, as described in **Examples**, additional compounds of the present invention of Formula VII ("Generic Substituted Polycyclic 3-(bis-R_{20}-hydroxymethyl)aryl Tertiary 2-Hydroxyalkylamine").

[0165] Conversion of a 3-methoxycarbonyl substituent at the R_{10} position in Formula VII ("Generic Substituted Polycyclic 3-Carbomethoxyaryl Tertiary 2-hydroxyalkylamine") by reaction with lithium aluminum hydride can afford, as described in **Examples,** additional compounds of the present invention of Formula VII ("Generic Substituted Polycyclic 3-Hydroxymethylaryl Tertiary 2-Hydroxyalkylamine").

[0166] Conversion of a 3-methoxycarbonyl substituent at the R_{10} position in Formula VII ("Generic Substituted Polycyclic 3-Carbomethoxyaryl Tertiary 2-hydroxyalkylamine") by reaction with an alkylation reagent can afford, as described in **Examples,** additional compounds of the present invention of Formula VII ("Generic Substituted Polycyclic 3-(bis-R_{21}-hydroxymethyl)aryl Tertiary 2-Hydroxyalkylamine").

[0167] Conversion of a 3-methoxycarbonyl substituent at the R_{10} position in Formula VII ("Generic Substituted Polycyclic 3-Carbomethoxyaryl Tertiary 2-hydroxyalkylamine") by reaction intially with an amidation reagent and then an R_{20}-organometallic reagent can afford, as described in **Examples**, additional compounds of the present invention of Formula VII ("Generic Substituted Polycyclic 3-(R_{20}-carbonyl)aryl Tertiary 2-Hydroxyalkylamine").

[0168] Formula VII ("Generic Substituted Polycyclic Aryl tertiary-2-hydroxyalkylamines"), Formula VII-H ("Generic Substituted Polycyclic Heteroaryl tertiary-2-hydroxyalkylamines") and other compounds of this invention posssessing hydroxyl, thiol, and amine functional groups can be converted to a wide variety derivatives. The hydroxyl group X, wherein R_{16} is a hydrogen, of compounds of Formulas VII, VII-H, and other compounds of the present invention can be readily converted to esters of carboxylic, sulfonic, carbamic, phosphonic, and phosphoric acids. Acylation to form a carboxylic acid ester is readily effected using a suitable acylating reagent such as an aliphatic acid anhydride or acid chloride. The corresponding aryl and heteroaryl acid anhydrides and acid chlorides can also be used. Such reactions are generally carried out using an amine catalyst such as pyridine in an inert solvent. In like manner, compounds of Formulas VII, VII-H, and Cyclo-VII that have at least one hydroxyl group present in the form of an alcohol or phenol can be acylated to its corresponding esters. Similarly, carbamic acid esters (urethans) can be obtained by reacting any hydroxyl group with isocyanates and carbamoyl chlorides. Sulfonate, phosphonate, and phosphate esters can be prepared using the corresponding acid chloride and similar reagents. Compounds of Formulas VII, VII-H, and Cyclo-VII that have at least one thiol group present can be converted to the corresponding thioesters derivatives analogous to those of alcohols and phenols using the same reagents and comparable reaction conditions. Compounds of Formulas VII, VII-H, and Cyclo-VII that have at least one primary or secondary amine group present can be converted to the corresponding amide derivatives. Amides of carboxylic acids can be prepared using the appropriate acid chloride or anhydrides with reaction conditions analogous to those used with alcohols and phenols. Ureas of the corresponding primary or secondary amine can be prepared using isocyanates directly and carbamoyl chlorides in the presence of an acid scavenger such as triethylamine or pyridine. Sulfonamides can be prepared from the corresponding sulfonyl chloride in the presence of aqueous sodium hydroxide. Suitable procedures and methods for preparing these derivatives can be found in House's Modem Synthetic Reactions, W. A. Benjamin, Inc., Shriner. Fuson, and Curtin in The Systematic Indentification of Organic Compounds, 5th Edition, John Wiley & Sons, and Fieser and Fieser in Reagents for Organic Synthesis, Volume 1, John Wiley & Sons. Reagents of a wide variety that can be used to derivatize hydroxyl, thiol, and amines of compounds of Formulas VII, VII-H, and Cyclo-VII are available from commerical sources or the references cited above, which are incorporated herein by reference.

[0169] Formula VII ("Generic Substituted Polycyclic Aryl tertiary-2-hydroxyalkylamines"), Formula VII-H ("Generic Substituted Polycyclic Heteroaryl tertiary-2-hydroxyalkylamines") and other compounds of this invention posssessing hydroxyl, thiol, and amine functional groups can be alkylated to a wide variety derivatives. The hydroxyl group X. wherein R_{16} is a hydrogen, of compounds of Formulas VII, VII-H and other compounds of the present invention can be readily converted to ethers. Alkylation to form an ether is readily effected using a suitable alkylating reagent such as an alkyl bromide, alkyl iodide or alkyl sulfonate. The corresponding aralkyl, heteroaralkyl, alkoxyalkyl, aralkyloxyalkyl, and heteroaralkyloxyalkyl bromides, iodides, and sulfonates can also be used. Such reactions are generally carried out using an alkoxide forming reagent such as sodium hydride, potassium t-butoxide, sodium amide, lithium amide, and n-butyl lithium using an inert polar solvent such as DMF, DMSO, THF, and similar, comparable solvents, amine catalyst such as pyridine in an inert solvent. In like manner, compounds of Formulas VII, VII-H, and Cyclo-VII that have at least one hydroxyl group present in the form of an alcohol or phenol can be alkylated to their corresponding ethers. Compounds of Formulas VII, VII-H, and Cyclo-VII that have at least one thiol group present can be converted to the corresponding thioether derivatives analogous to those of alcohols and phenols using the same reagents and comparable reaction

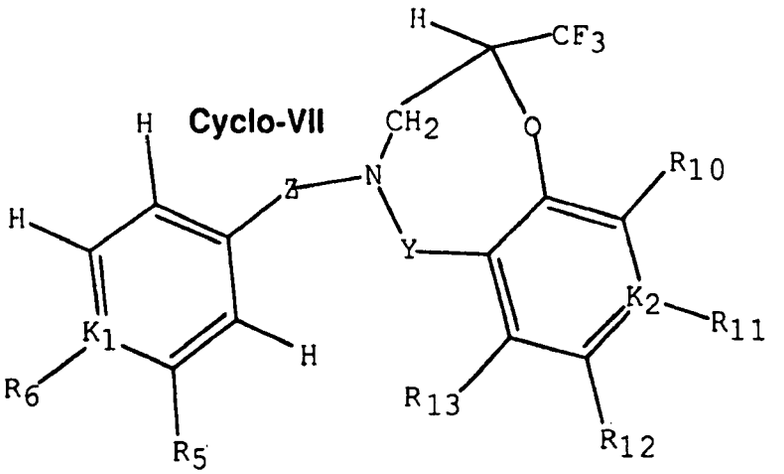
conditions. Compounds of Formulas VII, VII-H, and Cyclo-VII that have at least one primary, secondary or tertiary amine group present can be converted to the corresponding quaternary ammonium derivatives. Quaternary ammonium derivatives can be prepared using the appropriate bromides, iodides, and sulfonates analogous to those used with alcohols and phenols. Conditions involve reaction of the amine by warming it with the alkylating reagent with a stoichiometric amount of the amine (i.e., one equivalent with a tertiary amine, two with a secondary, and three with a primary). With primary and secondary amines, two and one equivalents, respectively, of an acid scavenger are used concurrently. Tertiary amines can be prepared from the corresponding primary or secondary amine by reductive alkylation with aldehydes and ketones using reduction methods 1, 2, or 3 as shown in Scheme 1. Suitable procedures and methods for preparing these derivatives can be found in House's Modem Synthetic Reactions, W. A. Benjamin, Inc., Shriner, Fuson, and Curtin in The Systematic Indentification of Organic Compounds. 5th Edition, John Wiley & Sons. and Fieser and Fieser in Reagents for Organic Synthesis, Volume 1, John Wiley & Sons. Perfluoroalkyl derivatives can be prepared as described by DesMarteau in J. Chem. Soc. Chem. Commun. 2241 (1998). Reagents of a wide variety that can be used to derivatize hydroxyl, thiol, and amines of compounds of Formulas VII, VII-H, and Cyclo-VII are available from commerical sources or the references cited above, which are incorporated herein by reference.

[0170] Formula VII ("Generic Substituted Polycyclic Aryl tertiary-2-hydroxyalkylamines"), Formula VII-H ("Generic Substituted Polycyclic Heteroaryl tertiary-2-hydroxyalkylamines") and certain other compounds of this invention can be converted, according to Scheme 6, to the corresponding cyclic derivatives represented by the general designation "Tricyclic *tertiary*-oxyalkylamines" exmplified by Formula Cyclo-VII ("Substituted Tricyclic Phenyl *tertiary*-2-oxyalkylamines"). The hydroxyl group X, wherein R_{16} is a hydrogen of compounds of Formulas VII and VII-H can be cyclized to corresponding cyclic ethers. Compounds suitable for cyclization will normally have at least one leaving group within 5 to 10 continuous atoms of the hydroxyl group X wherein R_{16} is a hydrogen. Most preferrably the leaving group will be within 5 to 7 atoms of the hydroxyl group X so as to form a 5 to 7 membered ring heteroatom containing ring. When the leaving group is part of an aromatic ring system, the leaving group will be preferrably in an ortho position. Suitable leaving groups generally include halides, sulfates, sulfonates, trisubsituted amino, disubstituted sulfonium, diazonium, and like, and, in the case of aromatic systems, also includes nitro, alkoxy, aryloxy, heteroaryloxy, and alkylthio. When X- R_{16} is a thiol, amino, or substituted amino, the corresponding analogous sulfur and nitrogen analogs, Cyclo-VII ("Substituted Tricyclic Phenyl *tertiary*-2-thioalkylamines and *tertiary*-2-azaalkylamines"), of Formula Cyclo-VII ("Substituted Tricyclic Phenyl *tertiary*-2-oxyalkylamines") can be obtained.

[0171] The cyclization reaction to form "Tricyclic *tertiary*-oxyalkylamines" can be accomplished by aromatic and aliphatic nucleophilic substitution reactions such as those disclosed in March's Advanced Organic Chemistry, 4th Edition, John Wiley & Sons, especially at pages 293-412 and 649-658 and the references cited therein, which are incorporated herein by reference. Hydroxyl containing suitably substituted compounds can be converted to a cyclic analog by heating a suitably substituted compound under anhydrous conditions in a suitable solvent, such as dimethylformamide, dimethylsulfoxide, N-methylpyrrolidone, tetraglyme, or hexamethylphosphoramide, in the presence of a suitable base such as potassium carbonate, cesium carbonate, sodium hydroxide, potassium *tertiary*-butoxide, or lithium diisopropylamide. Alternately, sodium amide in anhydrous ammonia solvent can be used. Temperatures in the range of -20 ˚C to 200 ˚C can be used for time periods of 30 minutes to more than 24 hours. The preferred temperature can be selected by standard synthetic chemical technique balancing maximum yield, maximum purity, cost, ease of isolation and operation, and time required. Isolation of the "Tricyclic *tertiary*-oxyalkylamines" can be effected as described above for other tertiary-oxyalkylamines. Representative "Tricyclic *tertiary*-oxyalkylamines" prepared using the methodology described above are included in Table 5.

[0172] The following examples are provided to illustrate the present invention and are not intended to limit the scope thereof. Those skilled in the art will readily understand that known variations of the conditions and processes of the following preparative procedures can be used to prepare these compounds.

Table 5. Structure of Substituted Tricyclic*tertiary*-2-oxyalkylamines

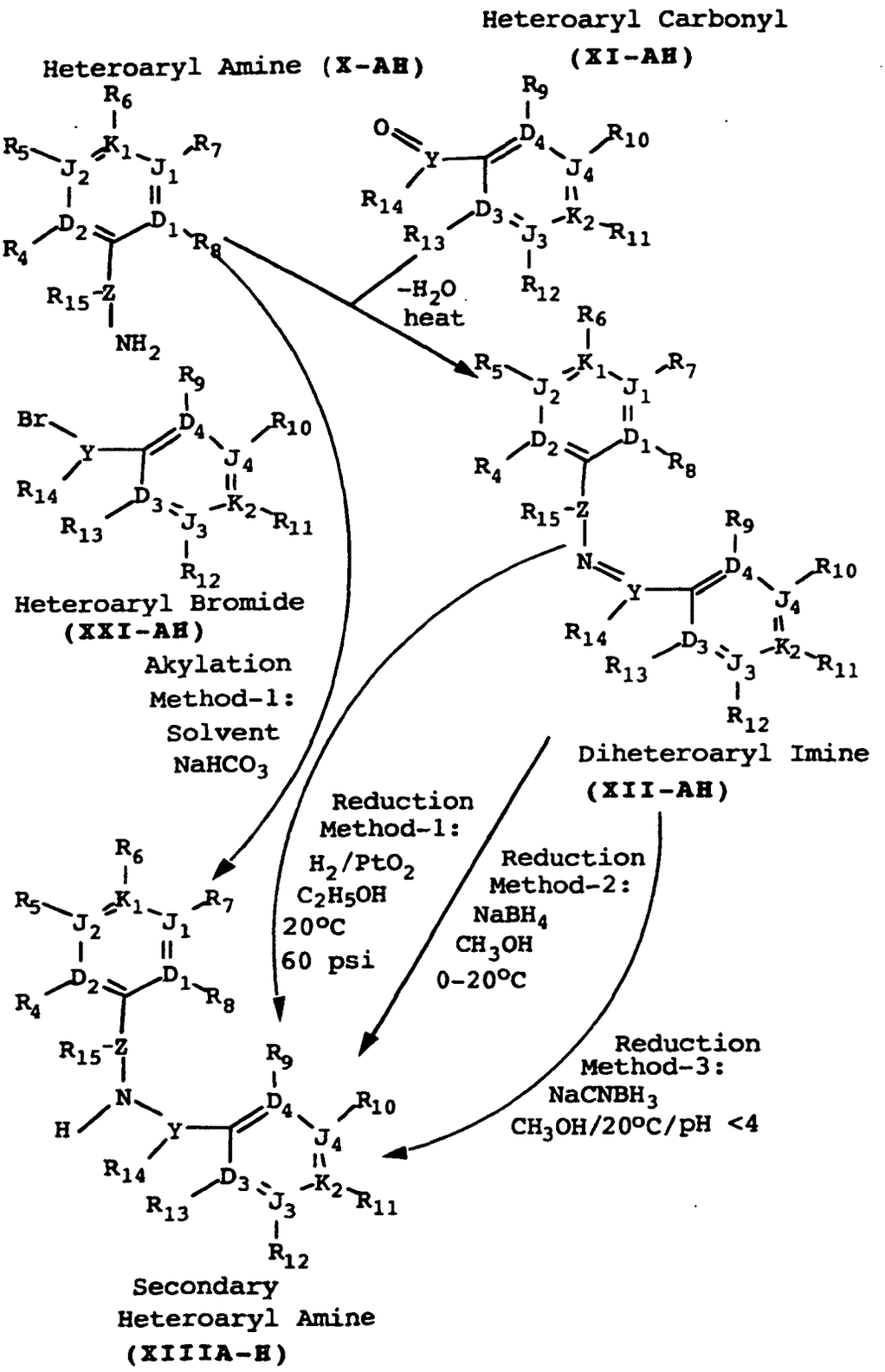


Y	Z	R_5	K_1-R_6	R_{10}	K_2-R_{11}	R_{12}	R_{13}
CH_2	-	4-chloro-3-ethylphenoxy	C-H	H	C- CF_3	H	H
CH_2	-	4-chloro-3-ethylphenoxy	N	H	C- CF_3	H	H
CH_2	-	4-chloro-3-ethylphenoxy	C-H	H	C- H	CF_3	H
CH_2	-	4-chloro-3-ethylphenoxy	N	H	C- H	CF_3	H
CH_2	-	4-chloro-3-ethylphenoxy	C-H	H	N	CF_3	H
-	-	4-chloro-3-ethylphenoxy	C-H	H	C-CF_3	H	H
-	-	4-chloro-3-ethylphenoxy	N	H	C-CF_3	H	H
-	-	4-chloro-3-ethylphenoxy	C-H	H	C- H	CF_3	H
-	-	4-chloro-3-ethylphenoxy	N	H	C- H	CF_3	H
-	-	4-chloro-3-ethylphenoxy	C-H	H	N	CF_3	H
CH_2	-	4-chloro-3-ethylphenoxy	C-H	OCF_2CF_2H	C- H	H	H
CH_2	-	4-chloro-3-ethylphenoxy	N	OCF_2CF_2H	C-H	H	H
CH_2	-	4-chloro-3-ethylphenoxy	C-H	OCF_2CF_2H	N	H	H
CH_2	-	phenoxy	C-H	OCF_2CF_2H	C-H	H	H
CH_2	-	phenoxy	N	OCF_2CF_2H	C-H	H	H
CH_2	-	phenoxy	C-H	OCF_2CF_2H	N	H	H

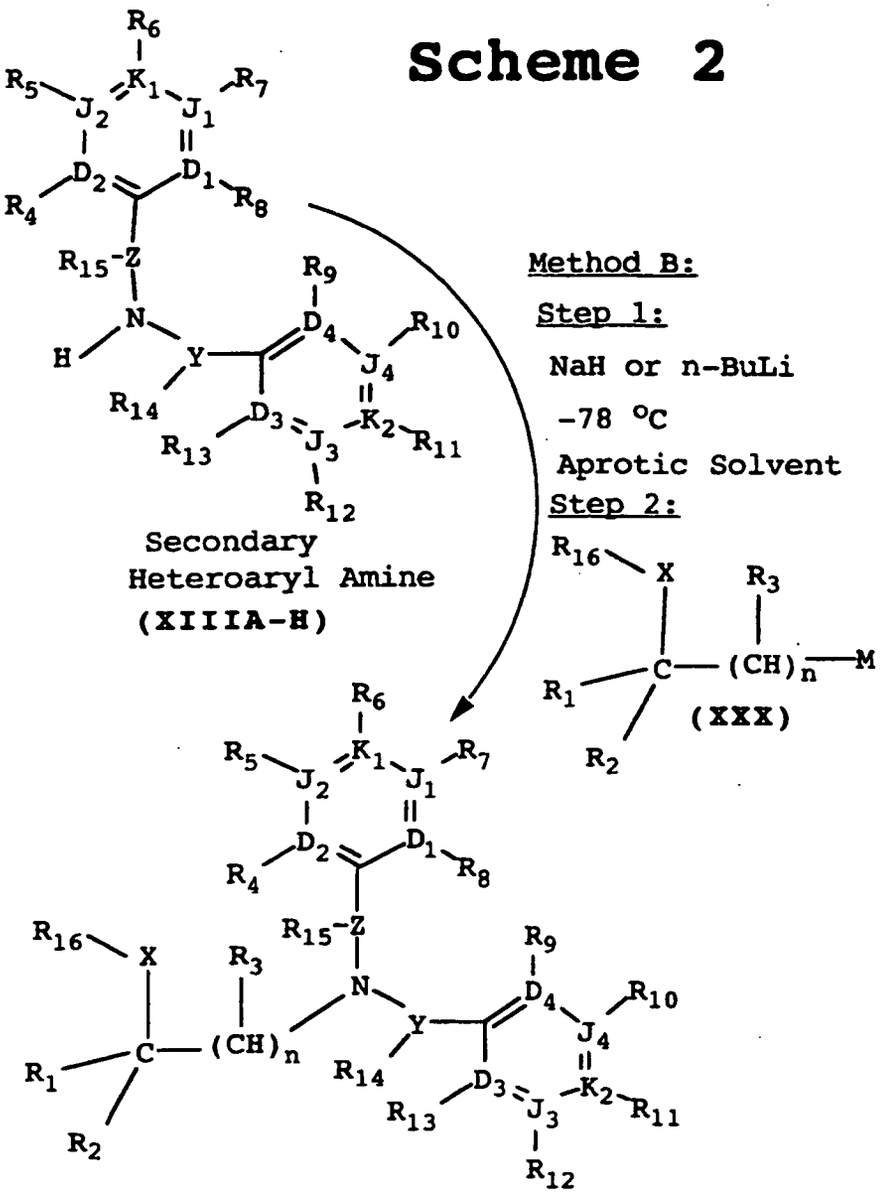
(continued)

Y	Z	R_5	K_1-R_6	R_{10}	K_2-R_{11}	R_{12}	R_{13}
CH_2	-	4-chloro-3-ethylphenoxy	C-H	CF_2CF_3	C- H	H	H
CH_2	-	4-chloro-3-ethylphenoxy	N	CF_2CF_3	C- H	H	H
CH_2	-	4-chloro-3-ethylphenoxy	C-H	CF_2CF_3	N	H	H
CH_2	-	phenoxy	C-H	CF_2CF_3	C-H	H	H
CH_2	-	phenoxy	N	CF_2CF_3	C- H	H	H
CH_2	-	phenoxy	C-H	CF_2CF_3	N	H	H
CH_2	-	4-chloro-3-ethylphenoxy	C-H	CF_3	C- H	H	H
CH_2	-	4-chloro-3-ethylphenoxy	N	CF_3	C-H	H	H
CH_2	-	4-chloro-3-ethylphenoxy	C-H	CF_3	N	H	H
CH_2	-	phenoxy	C-H	CF_3	C-H	H	H
CH_2	-	phenoxy	N	CF_3	C-H	H	H
CH_2	-	phenoxy	C-H	CF_3	N	H	H
CH_2	-	4-chloro-3-ethylphenoxy	C-H	OCF_2CF_2H	C-H	H	F
CH_2	-	4-chloro-3-ethylphenoxy	N	OCF_2CF_2H	C-H	H	F
CH_2	-	4-chloro-3-ethylphenoxy	C-H	OCF_2CF_2H	N	H	F
CH_2	-	4-chloro-3-ethylphenoxy	C-H	2-furyl	C-H	H	H
CH_2	-	4-chloro-3-ethylphenoxy	N	2-furyl	C-H	H	H
CH_2	-	4-chloro-3-ethylphenoxy	C-H	2-furyl	N	H	H
CH_2	-	4-chloro-3-ethylphenoxy	C-H	SCF_3	C-H	H	H
CH_2	-	4-chloro-3-ethylphenoxy	N	SCF_3	C-H	H	H

Scheme 1

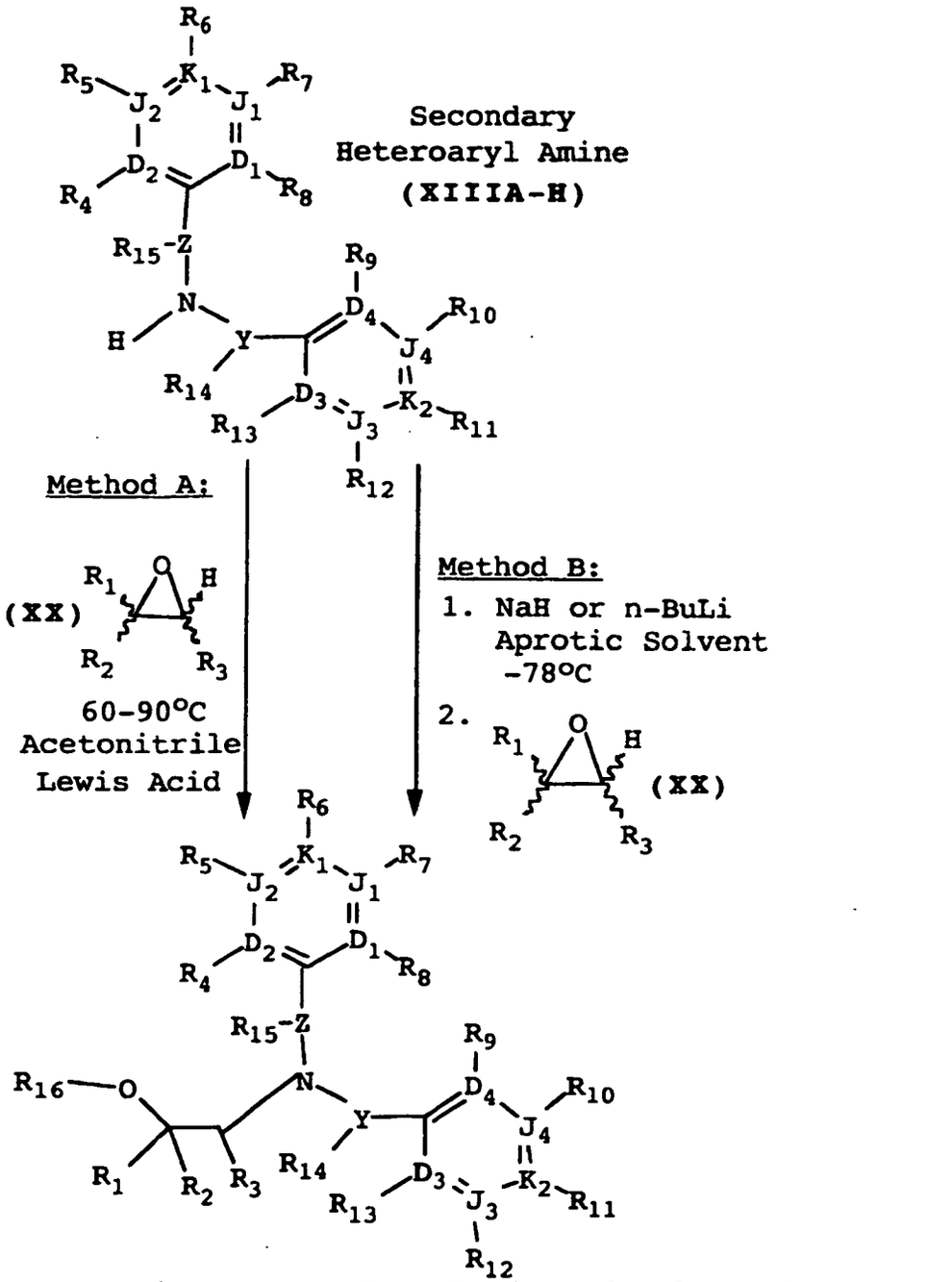

Heteroaryl Amine (X-AH)
Heteroaryl Carbonyl (XI-AH)
-H2O heat
Heteroaryl Bromide (XXI-AH)
Akylation Method-1: Solvent NaHCO3
Diheteroaryl Imine (XII-AH)
Reduction Method-1: H2/PtO2 C2H5OH 20°C 60 psi
Reduction Method-2: NaBH4 CH3OH 0-20°C
Reduction Method-3: NaCNBH3 CH3OH/20°C/pH <4
Secondary Heteroaryl Amine (XIIIA-H)

Scheme 2



VII-H/VII:(Generic Polycyclic Aryl and Heteroaryl Tertiary OmegaHydroxyalkylamines)

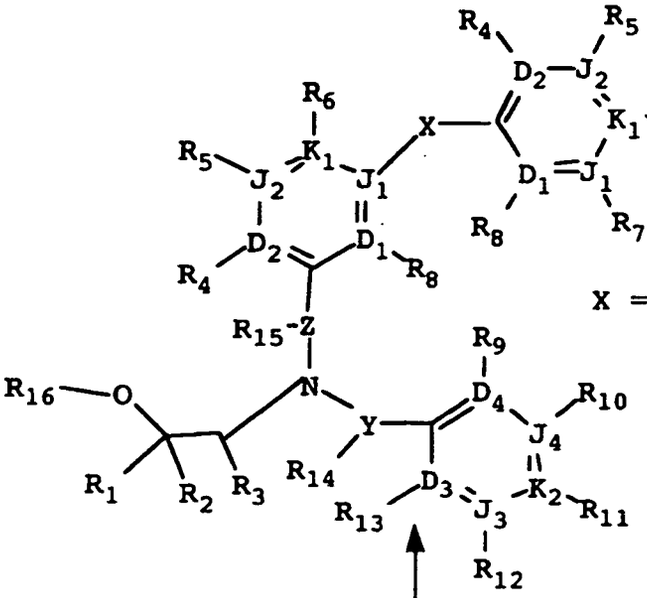
Scheme 3



VII-H/VII:(Generic Substituted Polycyclic Heteroaryl and Aryl Tertiary 2-Hydroxyalkylamine)

Scheme 4

VII-H/VII: (Generic Substituted Polycyclic 3-Aryloxyaryl, 3-Heteroaryloxyaryl, 3-Heteroaryloxyheteroaryl, 3-Aryloxyheteroaryl, 3-Arylthioaryl, 3-Heteroarylthioaryl, 3-Heteroarylthioheteroaryl, 3-Arylthioheteroaryl, Tertiary 2-Hydroxyalkylamine)



X = O and S

$Cu_2(triflate)_2 \cdot Benzene$

2 equivalents of Aryl-OH, Aryl-SH, Heteroaryl-OH, or Heteroaryl-SH

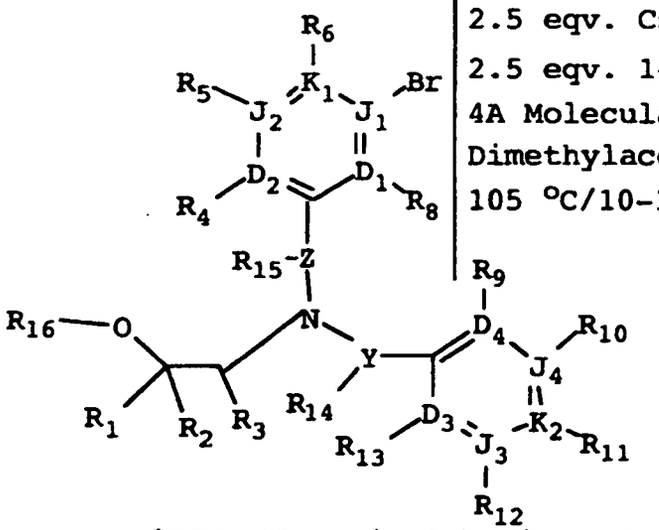
2.5 eqv. Cs_2CO_3

2.5 eqv. 1-Naphthoic Acid

4A Molecular Sieves

Dimethylacetamide/toluene

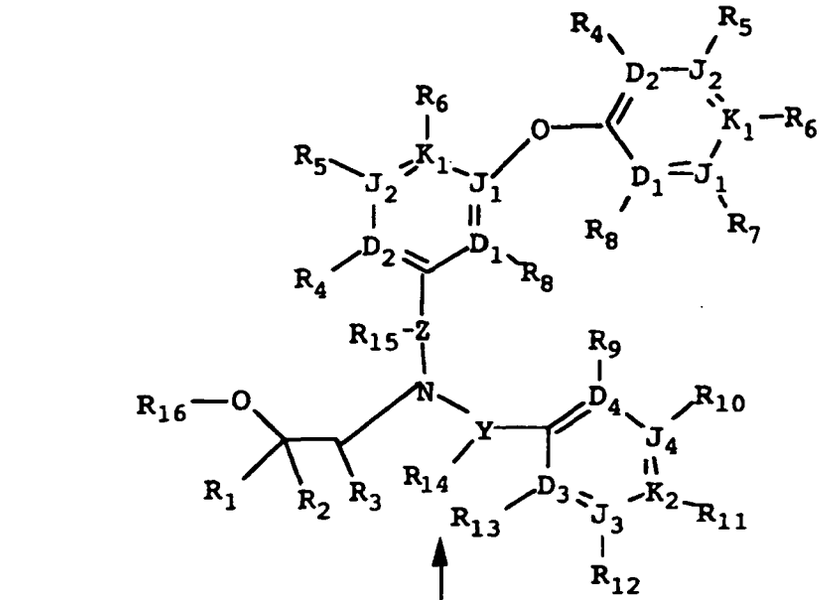
105 °C/10-14 Days



VII-H/VII: (Generic Substituted Polycyclic 3-Bromoheteroaryl and 3-Bromoaryl Tertiary 2-Hydroxyalkylamine)

Scheme 5

VII-H/VII: (Generic Substituted Polycyclic 3-Aryloxyaryl,3-Heteroaryloxyaryl 3-Aryloxyheteroaryl,or 3-Heteroaryloxyheteroaryl Tertiary 2-Hydroxyalkylamine)



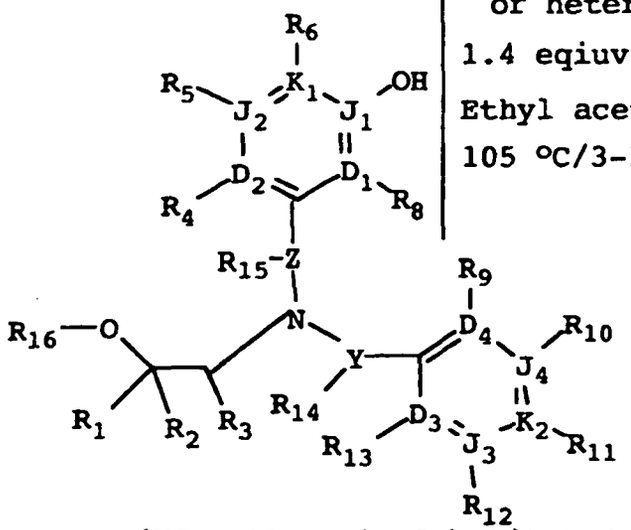
$Cu_2(triflate)_2 \cdot Benzene$

1 equiv. of aryl bromide or heteroaryl bromide

1.4 eqiuv. Cs_2CO_3

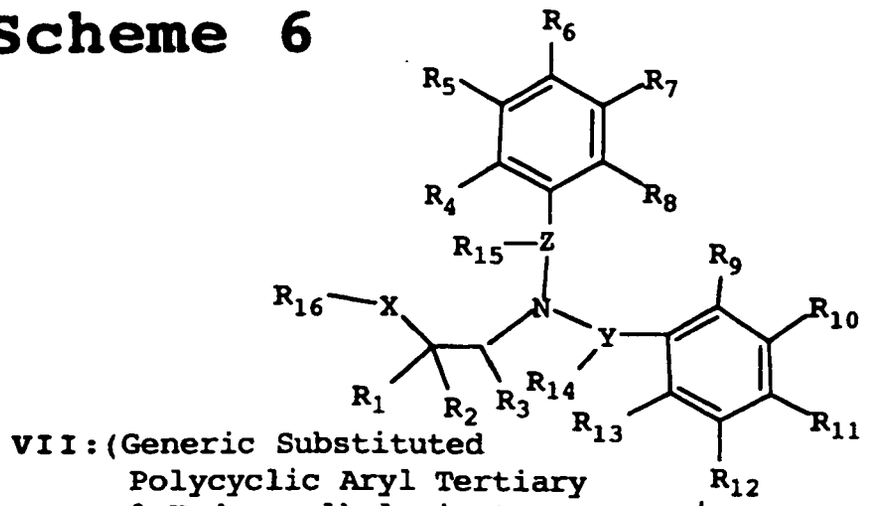
Ethyl acetate/toluene

105 °C/3-10 Days

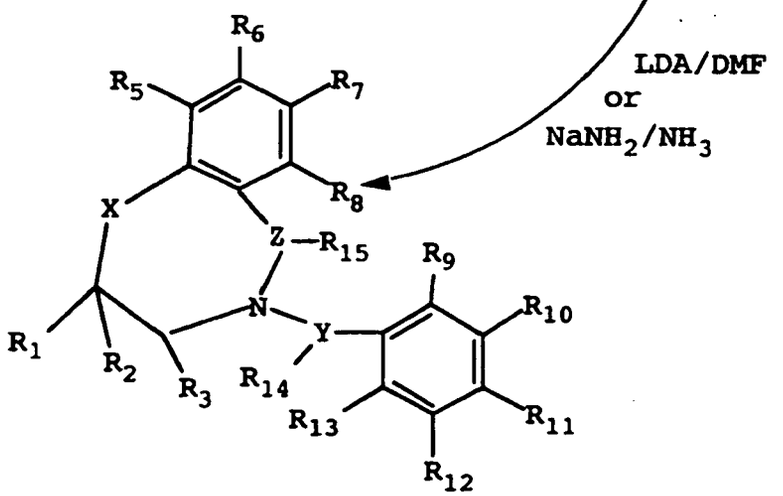


VII-H/VII: (Generic Substituted Polycyclic 3-Hydroxyheteroaryl and 3-Hydroxyaryl Tertiary 2-Hydroxyalkylamine)

Scheme 6



VII: (Generic Substituted Polycyclic Aryl Tertiary 2-Hydroxyalkylamine) (R_{16} = H)

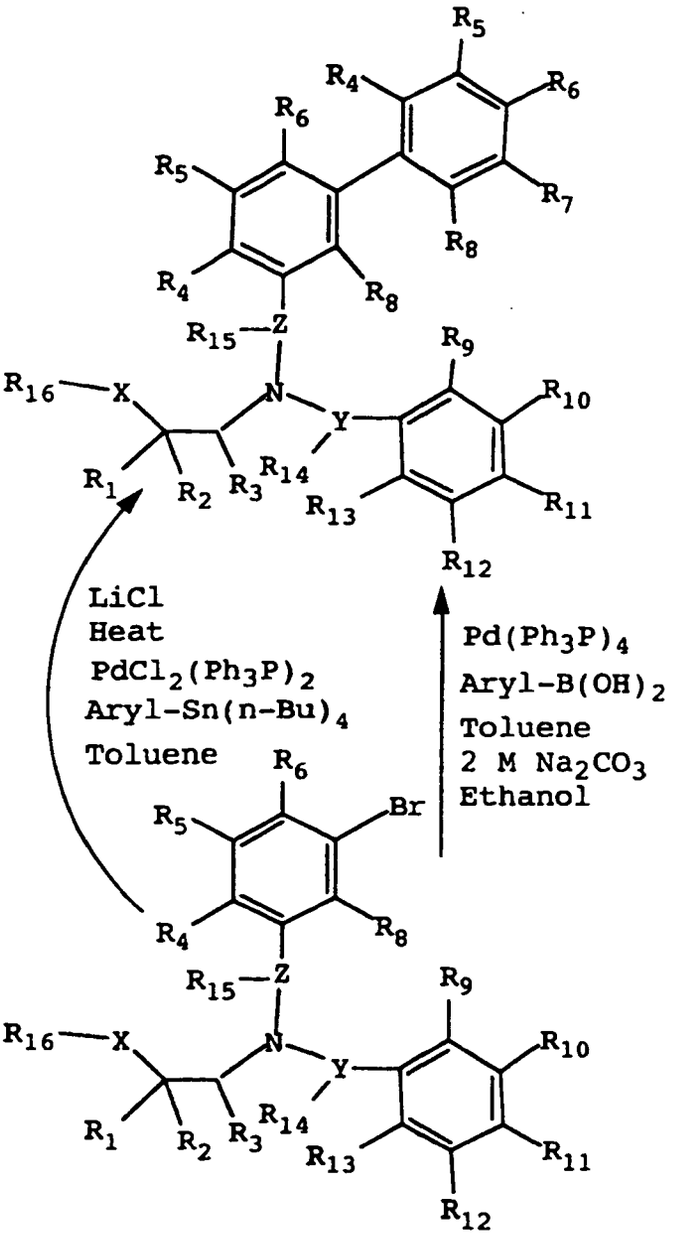


Phenyl **Cyclo-VII:** Substituted Tricyclic Phenyl tertiary-2-oxyalkylamines

NOTE: Use of VII-H will afford mono- and di-heteroaryl analogs of Cyclo-VII.

Scheme 7

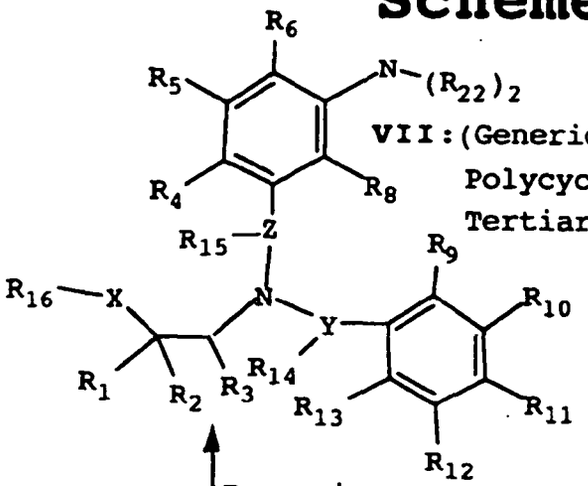
VII:(Generic Substituted Polycyclic 3-Arylaryl Tertiary 2-Hydroxyalkylamine)



VII:(Generic Substituted Polycyclic 3-Bromoaryl Tertiary 2-Hydroxyalkylamine)

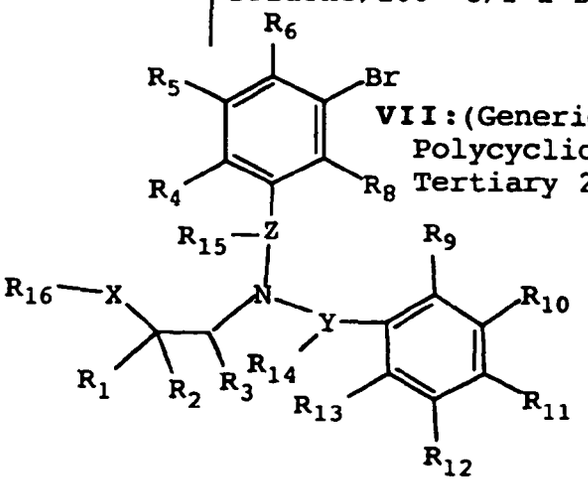
NOTE: Use of Heteroaryl-B(OH)$_2$ will give the heteroarylmethyl analog of **VII**.

Scheme 8



VII:(Generic Substituted Polycyclic 3- R_{22}-aminoaryl Tertiary 2-Hydroxyalkylamine)

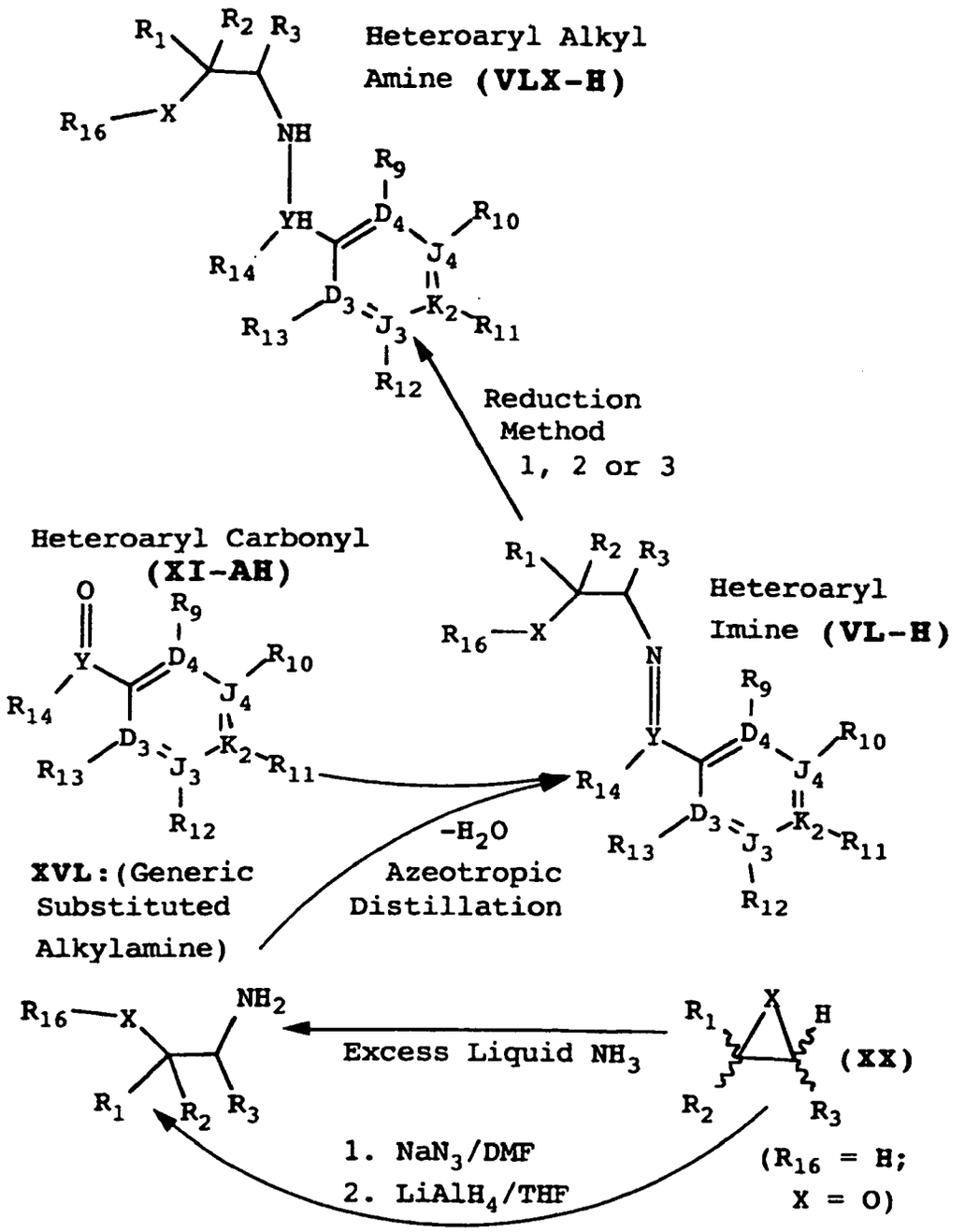
R_{22}-primary or secondary amine
$Pd(dba)_3$/R-(+)-BINAP
2.5 eqiuv. Cs_2CO_3
Toluene/100 °C/1-2 Days



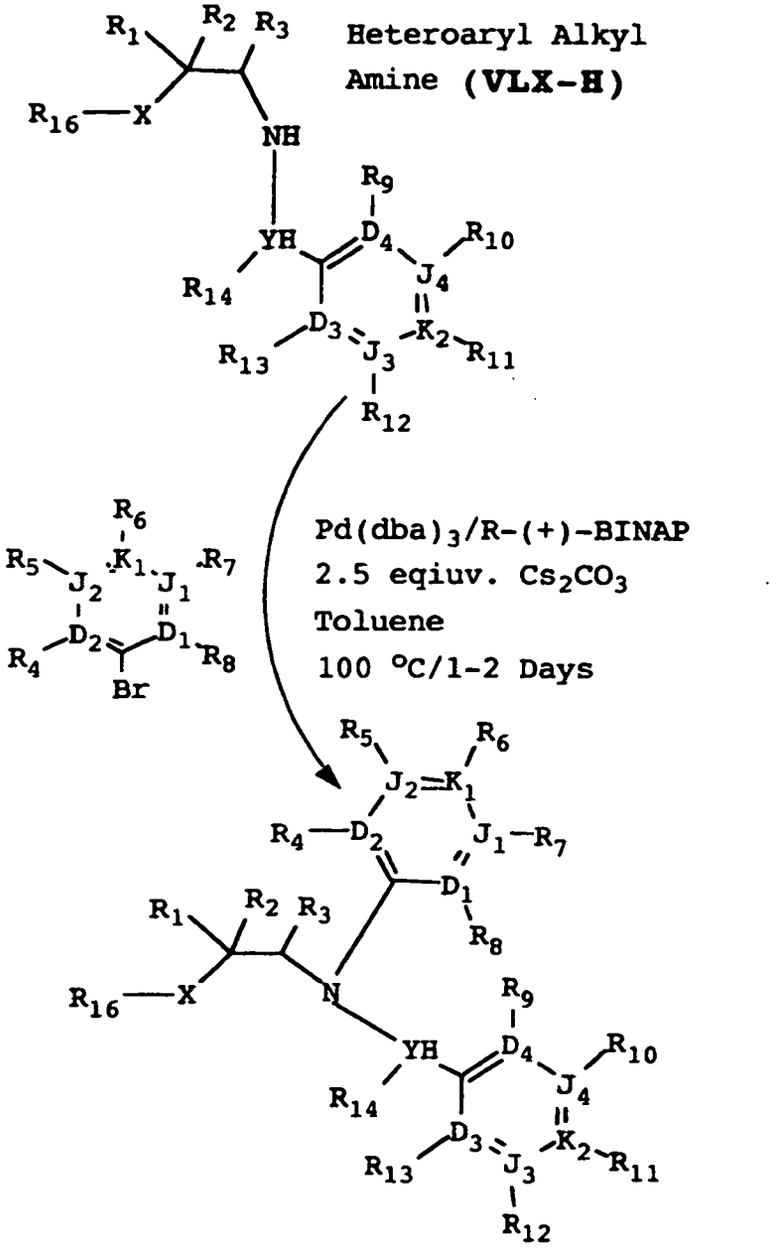
VII:(Generic Substituted Polycyclic 3-Bromoaryl Tertiary 2-Hydroxyalkylamine)

R_{22} is selected independently from any one or two of the following groups: hydrido, hydroxy, aryloxy, alkyl, alkenyl, alkynyl, aryl, aralkyl, aryloxyalkyl, alkoxyalkyl, aralkoxyalkyl, alkylsulfinylalkyl, haloalkyl, haloalkenyl, halocycloalkyl, halocycloalkoxy, halocycloalkoxyalkyl, arylsulfinylalkyl, arylsulfonylalkyl, alkylamino cycloalkylsulfinylalkyl, cycloalkylsufonylalkyl, heteroarylsulfonylalkyl,heteroarylsulfinylalkyl, aralkylsulfinylalkyl, aralkylsulfonylalkyl, hydroxyalkyl, amino, alkoxy, alkylsulfonylalkyl, aralkylthioalkyl, heteroaralkylthioalkyl, heteroaryloxyalkyl, alkenyloxyalkyl,haloalkoxy, haloalkoxyalkyl, haloalkenyloxyalkyl, heteroaryl, halocycloalkenyloxyalkyl, heteroarylalkyl, halocycloalkenyl, and heteroarylthioalkyl.

Scheme 9


Heteroaryl Alkyl Amine (VLX-H)
Reduction Method 1, 2 or 3
Heteroaryl Carbonyl (XI-AH)
Heteroaryl Imine (VL-H)
XVL: (Generic Substituted Alkylamine)
-H2O Azeotropic Distillation
Excess Liquid NH3
(XX)
1. NaN3/DMF
2. LiAlH4/THF
(R16 = H; X = O)

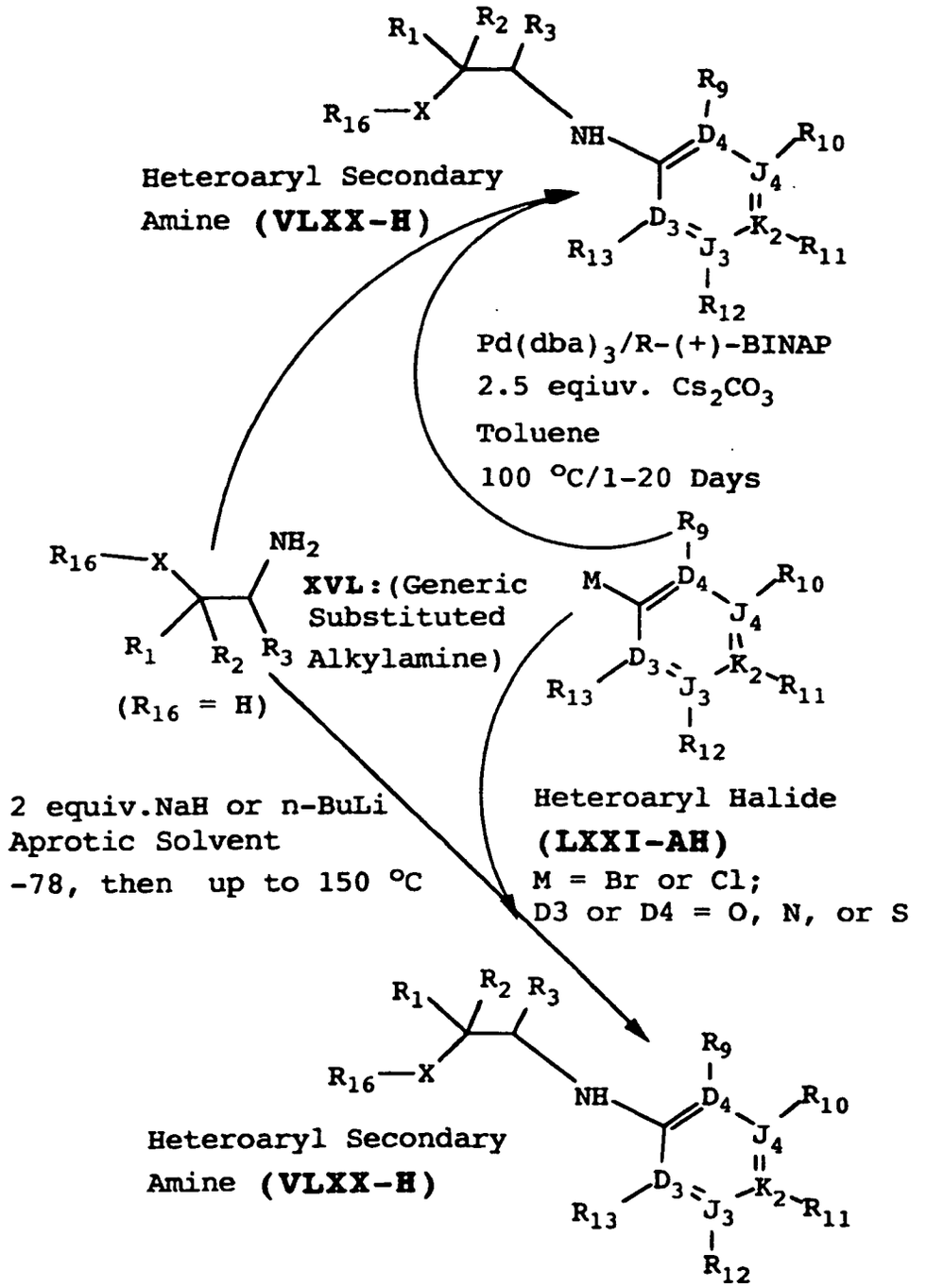
Scheme 10



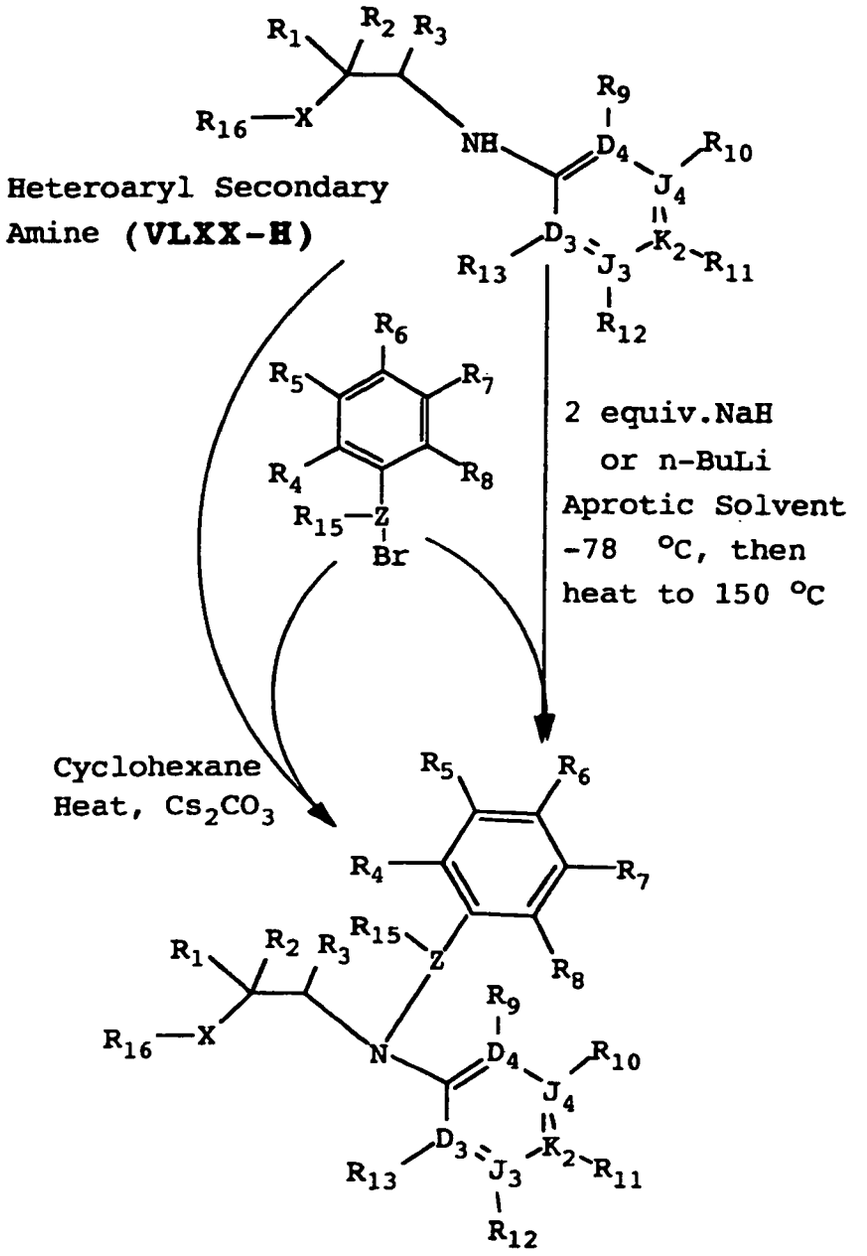
VII-H: (Generic Substituted Polycyclic Heteroaryl Tertiary 2-hydroxyalkylamine)

NOTE: Use of a heteroaryl alkyl amine with an aryl bromide or an aryl alkyl amine analog of VLX-H with an aryl bromide will afford mono or di aryl analogs of VII-H.

Scheme 11

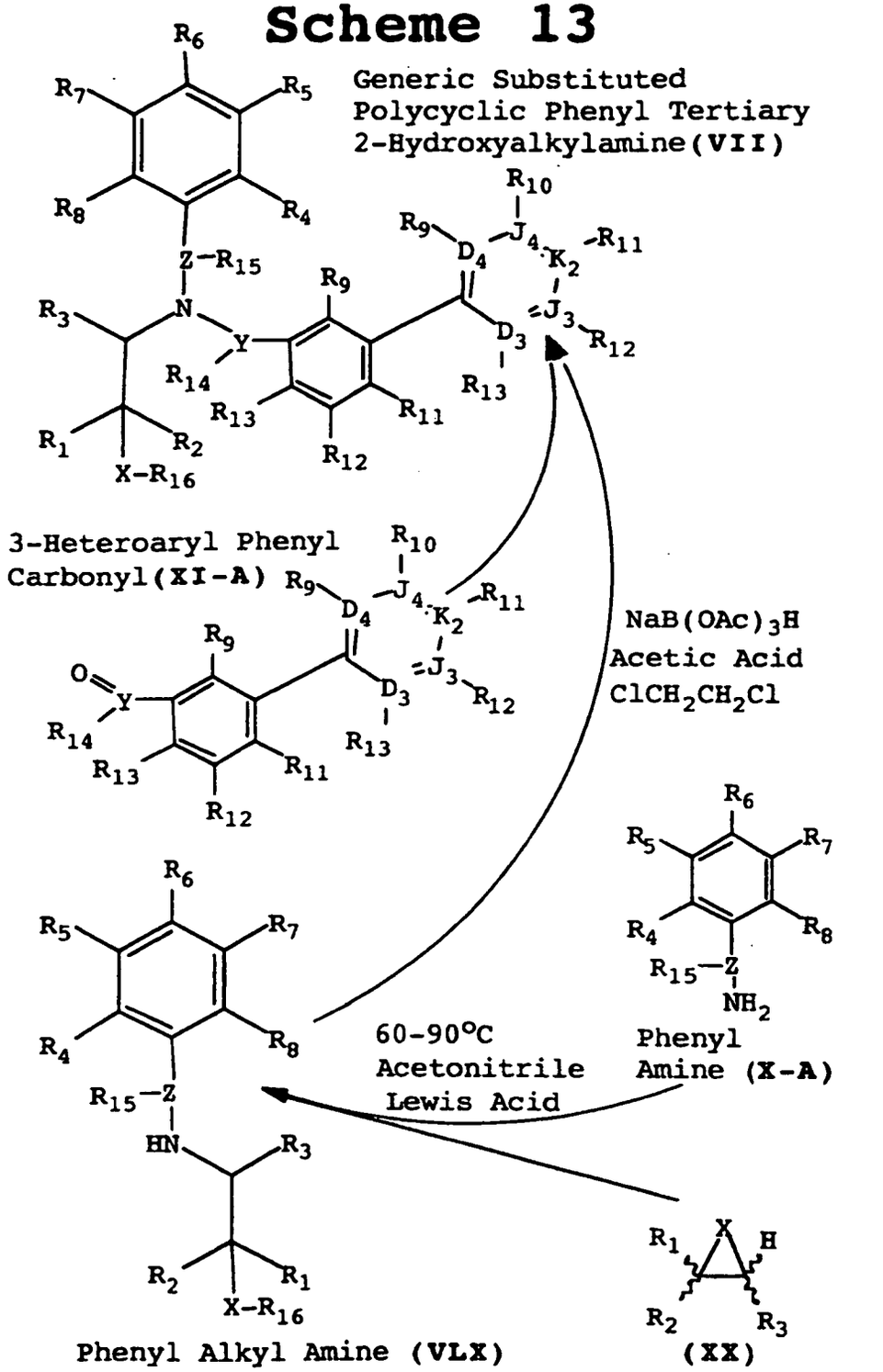

Heteroaryl Secondary Amine (VLXX-H)
Pd(dba)3/R-(+)-BINAP
2.5 eqiuv. Cs2CO3
Toluene
100 °C/1-20 Days
XVL:(Generic Substituted Alkylamine)
(R16 = H)
2 equiv.NaH or n-BuLi
Aprotic Solvent
-78, then up to 150 °C
Heteroaryl Halide (LXXI-AH)
M = Br or Cl;
D3 or D4 = O, N, or S
Heteroaryl Secondary Amine (VLXX-H)

Scheme 12



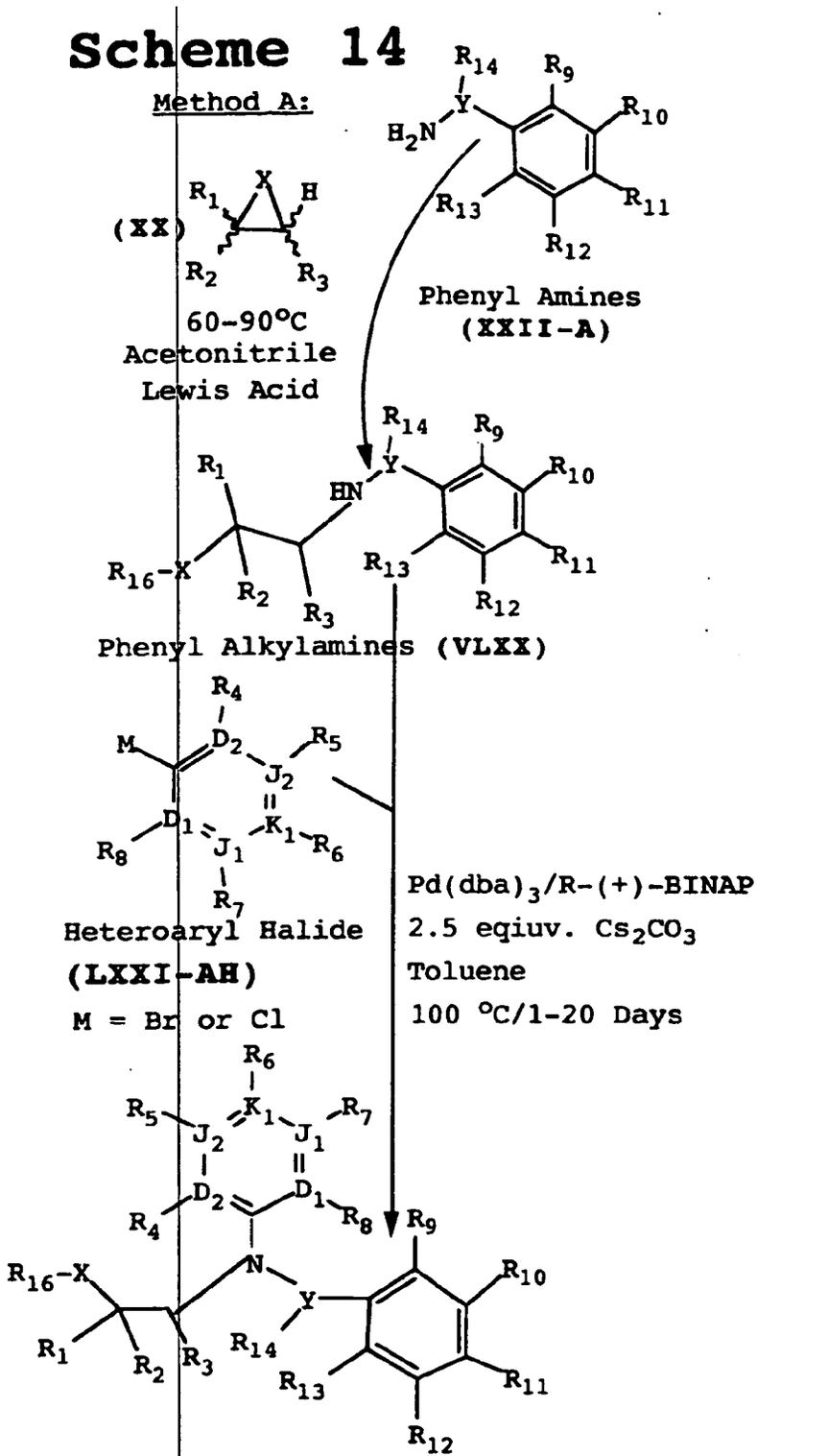
VII-H: (Generic Substituted Polycyclic Aryl Heteroaryl Tertiary 2-hydroxyalkylamine)

Scheme 13

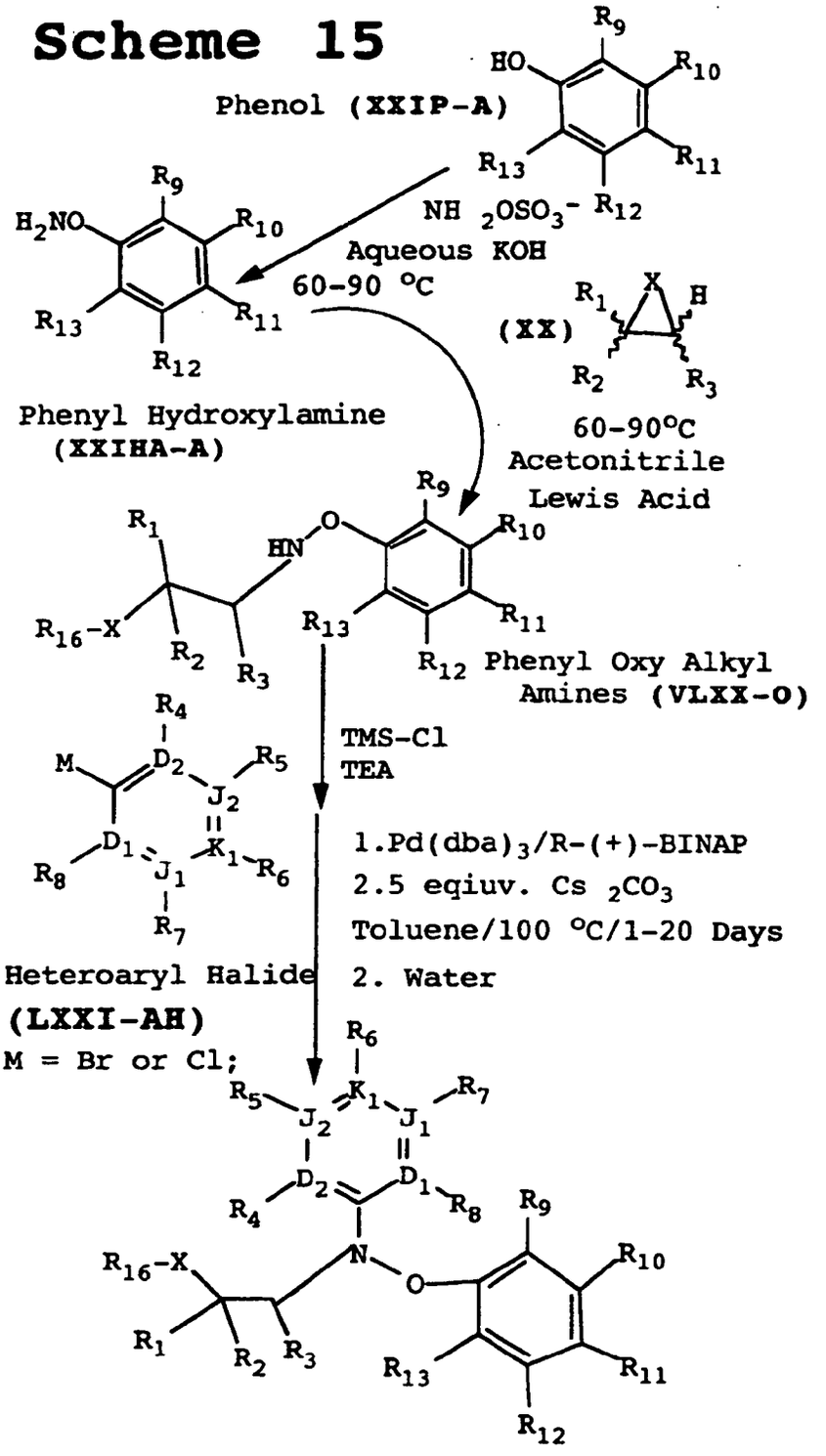


NOTE: Heteroaryl Analogs Can Be Prepared Using Heteroaryl Analogs of **X-A**, **VLX**, and **XI-A**.

Scheme 14



VII-H: (Generic Substituted Polycyclic Phenyl Heteroaryl Tertiary 2-Hydroxyalkyl-amine when R_{16}-X equals HO) NOTE: Aryl Analogs **(VII)** of **(VII-H)** Can Be Prepared by Starting With Aryl Bromide Analogs of **(LXXI-AH)**.



VII-H: (Generic Substituted Polycyclic Phenyl Heteroaryl Tertiary 2-Hydroxyalkylamine when R_{16}-X = HO and Y = O) NOTE: Diaryl and Diheteroaryl Analogs Can Be Prepared by Using Aryl Bromide and Heteroaryl-OH, respectively.

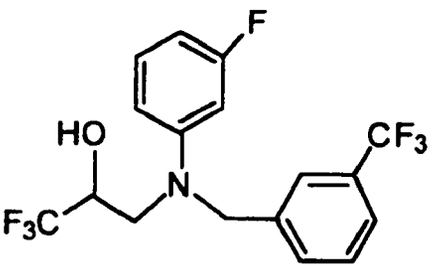
[0173] The following examples are provided to illustrate the present invention and are not intended to limit the scope thereof. (Compounds not within the scope of claim 1 are marked with an asterisk.) Without further elaboration, it is believed that one skilled in the art can, using the preceding descriptions, utilize the present invention to its fullest extent. Therefore the following preferred specific embodiments are to be construed as merely illustrative and not limitative of the remainder of the disclosure in any way whatsoever. Compounds containing multiple variations of the structural modifications illustrated in the preceding schemes or the following Examples are also contemplated. Those skilled in the art will readily understand that known variations of the conditions and processes of the following preparative procedures can be used to prepare these compounds.

[0174] One skilled in the art may use these generic methods to prepare the following specific examples, which have been or may be properly characterized by ^{1}H NMR and mass spectrometry. These compounds also may be formed in vivo.

[0175] The following examples contain detailed descriptions of the methods of preparation of compounds of the invention. These detailed descriptions fall within the scope and are presented for illustrative purposes only and are not intended as a restriction on the scope of the invention. All parts are by weight and temperatures are Degrees centigrade unless otherwise indicated.

EXAMPLE 1

[0176]



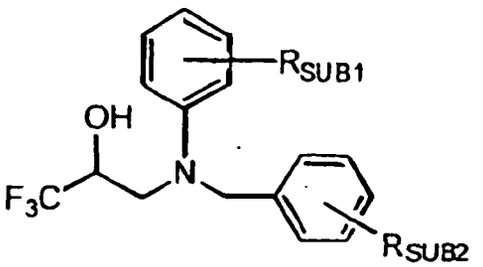
3-[(3-fluorophenyl)-[[3-(trifluoromethyl)phenyl] methyl]amino]-1,1,1-trifluoro-2-propanol

[0177] **EX-1A)** A solution of 3-fluoroaniline (1.92 mL, 0.02 mol) and trifluoro-*m*-tolualde-hyde (2.68 mL, 0.02 mol) in 30 mL of cyclohexane was refluxed using a Dean-Stark trap to remove water. After 4 hours, the cyclohexane was removed in *vacuo* to yield 5.4 g (100%) of the desired imine product as an amber oil. MS *m/z* = 267 [M^+]. ^{1}H NMR ($CDCl_3$) δ 8.50 (s, 1H), 8.22 (s, 1H), 8.09 (d, 1H), 7.78 (d, 1H), 7.63 (t, 1H), 7.39 (dq, 1H), 6.99 (m, 3H). This imine (5.34 g, 0.02 mol) was then slurried in 30 mL of methanol at 0 ˚C. Solid $NaBH_4$ (1.32 g, 0.0349 mol) was added in batches over 3 minutes at 0 ˚C. The reaction was stirred below 10 ˚C for 30 minutes and then warmed gradually to 15 ˚C. After 1 hour, the solution was cooled, and 3% aq. HCl solution was added until the aqueous layer was acidic. The aqueous solution was extracted twice with diethyl ether. The combined ether extracts were washed 3 times with brine, dried ($MgSO_4$), and concentrated in *vacuo* to yield 4.45 g (82%) of the desired *N*-(3-fluorophenyl)-[[3-(trifluoromethyl)phenyl] methyl]amine product as a light amber oil. MS *mlz* = 269 [M^+]. ^{1}H NMR ($CDCl_3$) δ 7.57 (m, 4H), 7.14 (dq, 1H), 6.45 (m, 2H), 6.33 (dt,1H), 4.41 (s, 2H), 4.27 (br, 1H).

[0178] The amine product **EX-1A** (2.69 g, 0.01 mol) was mixed with 3,3,3-trifluoro-1,2-epoxypropane (1.34 g, 0.012 mol), and the mixture was heated to 90 ˚C for 40 hours in a tightly capped vessel. After cooling to room temperature, the reaction product was purified by eluting through silica gel with 10% ethyl acetate in hexanes to yield 2.54 g (67%) of the desired aminopropanol as a light yellow oil, 100% pure product by GC and reverse phase HPLC. HRMS calcd. for $C_{17}H_{14}F_7NO$: 382.1042 [M+H]$^+$, found: 382.1032. ^{1}H NMR ($CDCl_3$) δ 7.47 (m, 4H), 7.19 (q, 1H), 6.50 (m, 3H), 4.50 (ABq, 2H), 4.39 (m.1H), 3.93 (dd, 1H), 3.60 (dd, 1H), 2.51 (d, 1H).

[0179] Additional substituted 3-[(*N*-aryl)-[[aryl]methyl]amino]-halo-2-propanols can be prepared by one skilled in the art using similar methods, as shown in Example Tables 1, 43, 46, and 47. Substituted 3-[(*N*-aralkyl)-[[aralkyl]amino]-halo-2-propanols can also be prepared by one skilled in the art using similar methods, as shown in Example Tables 2, 3, 44, and 45. Substituted 3-[(*N*-aryl)-[[aralkyl]amino]-halo-2-propanols can be prepared by one skilled in the art using similar methods, as shown in Example Table 4. Substituted 3-[(*N*-aryl or N-aralkyl)-[[aryl]methyl]amino]-haloalkoxy-2-propanols can be prepared by one skilled in the art using similar methods, as shown in Example Tables 5 and 48.

Example Table 1. 3-[*N*-(aryl)-[(aryl)methyl)amino]-1,1,1-trifluoro-2-propanols.



Ex. No.	R_{SUB1}	R_{SUB2}	Calc.* Mass [M^+]	Obs.* Mass [M^+]
2	H	H	295.1184	295.1180
3	3-OCH_3	3-CH_3	339.1446	339.1449
4	3-OCH_3	4-CH_3	339.1446	339.1444
5	4-CH_3	3-CH_3	323.1497	323.1491
6	4-OCH_3	4-CH_3	339.1446	339.1440
7	4-Cl	H	329.0794	329.0783
8	4-CH_3	4-CH_3	323.1497	323.1495
9	3-Cl	3-CH_3	343.0951	343.0950
10	3-F	H	313.1090	313.1086
11	3-CH_3	3-CH_3	323.1497	323.1509
12	3-CH_3	4-CH_3	323.1497	323.1504
13*	2-CH_3	4-CH_3	323.1497	323.1483
14	4-CH_3	H	309.1340	309.1331
15*	2-CH_3	H	309.1340	309.1337
16	3-Cl	H	329.0794	329.0794
17	3-F, 4-F	3-CH_3	345.1152	345.1143
18	3-F	3-F	331.0996	331.0984
19	3-F, 4-F	3-CF_3	399.0869	399.0827
20	4-CH_3	3-CF_3	377.1214	377.1180
21*	2-CH_3	3-CF_3	377.1214	377.1176
22	3-F, 4-F	4-CF_3	399.0869	399.0822
23	4-OCH_3	4-CF_3	393.1163	393.1159
24	3-F, 4-F	4-CH_3	345.1152	345.1136
25	3-CH_3	3-CF_3	377.1214	377.1231
26	3-OCH_3	4-CF_3	393.1163	393.1179
27*	2-CH_3	3-CH_3	323.1497	323.1486
28	4-OCH_3	3-CH_3	339.1446	339.1435
29	3-F, 5-F	4-CH_3	345.1152	345.1159
30	3-Br	3-CF_3	441.0163	441.0135
31	3-F	3-OCF_3	397.0913	397.0894

(continued)

Ex. No.	R_{SUB1}	R_{SUB2}	Calc.* Mass [M^+]	Obs.* Mass [M^+]
32	4-CH_3	3-F	327.1246	327.1291
33	3-F	4-CH_3	328.1324	328.1333
34	3-Cl	4-CH_3	344.1029	345.1045
35	H	3-CF_3	364.1136	364.1122
36	3-Br	3-OCF_3	458.0190	458.0145
37	4-CH_3	4-CF_3	378.1292	378.1259
38	3-Cl	3-CF_3	398.0746	398.0727
39	3-CH_3	4-CF_3	378.1292	378.1274
40*	2-CH_3	4-CF_3	378.1292	378.1259
41	3-Cl	3-OCF_3	414.0695	414.0699
42	3-CF_3	3-OCF_3	448.0959	448.0961
43	3-F	3-OCF_2CF_2H	430.1053	430.1042
44	3-J	3-OCF_2CF_2H	538.0114	538.0077
45	3-CF_3	4-CH_3	378.1292	378.1296
46	3-CF_3	3-F	382.1042	382.1073
47	3-CF_3	3-CF_3	432.1010	432.1026
48	3-OCH_3	3-CF_3	394.1241	394.1227
49	3-F	3-CH_3	328.1324	328.1300
50	3-Cl	4-CF_3	398.0746	398.0731
51	4-OCH_3	3-CF_3	394.1241	394.1237
52	3-CF_3, 4-F	3-CF_3	450.0915	450.0913
53	3-CF_3, 4-F	4-CH_3	396.1198	396.1179
54	3-CF_3	4-OCF_3	448.0959	448.0967
55	3-Cl	4-OCF_3	414.0695	414.0690
56	3-F, 4-F	4-OCF_3	416.0886	416.0904
57	3-F	4-OCF_3	398.0991	398.0975
58	3-CF_3, 4-F	3-CH_3	396.1197	396.1178
59	H	4-OCF_3	380.1085	380.1077
60	3-OCF_3	4-OCF_3	464.0908	464.0877
61	3-CH_3	4-OCF_3	394.1241	394.1248
62	3-Br	4-OCF_3	458.0189	458.0189
63	3-phenoxy	4-OCF_3	472.1347	472.1344
64	3-F	3-phenoxy	406.1430	406.1418
65	3-F	4-phenyl	390.1481	390.1468
66	3-phenyl	3-OCF_3	456.1397	456.1395
67	3-CF_3, 4-Cl	3-CH_3	412.0903	412.0892
68	3-F, 5-F	4-OCF_3	416.0896	416 .0895
69	2-F, 3-F	3-CF_3	400.0941	416.0956

(continued)

Ex. No.	R_{SUB1}	R_{SUB2}	Calc.* Mass [M^+]	Obs.* Mass [M^+]
70	2-F, 5-F	3-OCF_2CF_2H	448.0959	448.0940
71	3-OCF_3	3-OCF_2CF_2H	496.0971	496.0959
72	3-CH_3	3-OCF_3	394.1241	394.1244
73	H	3-OCF_3	380.1085	380.1075
74	3-OCF_3	3-OCF_3	464.0908	464.0898
75	3-CF_3, 4-F	4-CF_3	450.0915	450.0906
76	3,4-$(CH=CH)_2$-	3-OCF_3	430.1241	430.1253
77	3-phenoxy	3-OCF_3	472.1347	472.1342
78	3-F, 4-F	3-OCF_3	416.0896	416.0884
79	4-phenyl	3-OCF_3	456.1398	456.1368
80	2-F, 3-F	4-OCF_3	416.0897	416.0885
81	3-F, 5-F	3-CH_3	346.1230	346.1246
82	3-OCF_3	3-phenoxy	472.1347	472.1342
83	3-OCF_3	3-benzyloxy	486.1504	486.1503
84	3-phenoxy	3-phenoxy	480.1786	480.1772
85*	2-phenyl	3-phenoxy	464.1837	464.1821
86	4-phenyl	3-phenoxy	464.1837	464.1836
87	4-phenyl	3-OCF_2CF_2H	488.1460	488.1443
88	4-*n*-octyl	3-OCF_3	492.2337	492.2341
89	3,4-(OCF_2CF_2O)	3-OCF_3	510.0763	510.0747
90	4-F	3-OCF_3	398.0991	398.1023
91	3-phenoxy	3-ethoxy	432.1787	432.1770
92	3-phenoxy	3-(4-Cl-phenoxy)	514.1397	514.1426
93	3-OCF_3	3-(4-Cl-phenoxy)	506.0958	506.0971
94	3-phenoxy	3-(3,4-Cl_2-C_6H_3O)	548.1007	548.1002
95	3-OCF_3	3-(3,4-Cl_2-C_6H_3O)	540.0568	540.0555
96	3-OCF_3	3-(3,5-Cl_2-C_6H_3O)	540.0568	540.0568
97	3-OCF_3	4-OCH_3	502.1453	502.1466
98	3-OCF_3	3-CF_3	540.1221	540.1248
99	3-OCF_3	3-benzyloxy, 4-OCH_3	516.161	516.1626
100	3-OCF_3	3,4-dibenzyloxy	592.1922	592.1915
101	3-OCF_3	3-OCH_2CH_3	424.1347	424.1331
102	3-OCF_3	3-acetoxy	438.114	438.1142
103	3-OCF_3	3-(2-OH-ethoxy)	440.1297	440.1302
104	3-OCF_3	3-[(3-Cl, 2-OH)-*n*-propoxy]	488.1063	488.1050
105	3-OCF_3	3,4-(OCH_2CH_2O)	438.114	438.1142
106	3-OCF_3	4-benzyloxy, 3-OCH_3	516.1609	516.1608

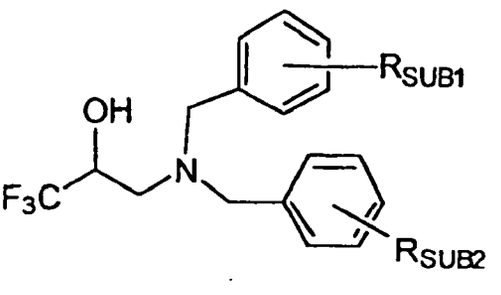
(continued)

Ex. No.	R_{SUB1}	R_{SUB2}	Calc.* Mass [M^+]	Obs.* Mass [M^+]
107	3-OCF_3	3,5-dibenzyloxy	592.1922	592.1903
108	3-CF_3	3-(3-CF_3-phenoxy)	524.1372	524.1281
109	3-CF_3	3-phenoxy	456.1398	456.1421
110	4-CF_3	3-(3-CF_3-phenoxy)	524.1272	524.1259
111	4-CF_3	3-phenoxy	456.1398	456.1415
112	4-CF_3	3-OCF_3	424.1347	424.1331
113	3-phenoxy	3-nitro	433.1375	433.1379
114	3-phenoxy	3-(3,5-Cl_2-C_6H_3O)	548.1007	548.1016
115	3-phenoxy	3-(3-CF_3-phenoxy)	548.166	548.1639
116	3-OCF_3	3,4-dimethoxy	440.1296	420.1294
117	3-OCF_3	3-OCH_2CH_3, 4-OCH_3	454.1453	454.1458
118	3-OCF_3	3,4-diacetoxy	496.1194	496.1183
119	3-OCF_3	4-acetoxy, 3-OCH_3	468.1245	468.1239
120	3-OCF_3	4-*n*-butoxy	452.1584	452.1614
121	3-OCF_3	3-OCH_3	410.1191	410.1179
122	3-OCF_3	4-OCH_3	410.1191	410.1177
123	3-OCH_3	3-OCH_3	356.1473	356.1469
124	3-OCH_3	3-OCF_3	410.1191	410.1158
125	3-OCF_3	4-*n*-propoxy	438.1503	438.1517
126	3-benzyloxy	3-OCF_3	486.1504	486.1524
127	3-benzyloxy	3-phenoxy	494.1947	494.1956
128	3-ethoxy	3-OCF_3	424.1347	424.1363
129	3,4-(OCH_2O)	3-OCF_3	424.0983	424.0990
130	3,4-(OCH_2O)	3-phenoxy	432.1424	432.1432
131	3,4-($O(CH_2)_2O$)	3-OCF_3	438.1140	438.1165
132	3,4-dimethoxy	3-OCF_3	440.1296	440.1319
133	4-phenoxy	3-OCF_3	472.1347	472.1334
134	4-OCF_3	3-OCF_3	464.0908	464.0923
135	4-*n*-butoxy	3-OCF_3	452.1660	452.1624
136	4-benzyl	3-OCF_3	470.1554	470.1148
137	3-phenoxy	3,4-(OCH_2CH_2O)	446.1579	446.1583
138	3-OCF_3	3,4-diethoxy	468.1609	468.1638
139	3,4-($O(CH_2)_3O$)	3-OCF_3	452.1297	452.1307
140	3-OCF_3	4-CF_3	448.0959	448.0985
141	4-phenyl	4-CF_3	440.1449	440.1451
142	3-cyano	4-CF_3	389.1089	389.1097
143	3-CF_3	4-phenyl	440.1449	440.1444
144	4-CF_3	4-phenyl	440.1449	440.1457

(continued)

Ex. No.	R_{SUB1}	R_{SUB2}	Calc.* Mass [M^+]	Obs.* Mass [M^+]
145	3-phenoxy	3-CF_3, 5-CF_3	524.1272	524.1285
146	3-phenoxy	4-cyano	413.1477	413.149
147	3-phenoxy	3-cyano	413.1477	413.1493
148	3-phenoxy	4-nitro	433.1375	433.1398
149	3-phenoxy	3-CF_3	456.1398	456.1414
150	3-phenoxy	4-CF_3	456.1398	456.1394
151	4-phenoxy	3-phenoxy	480.1786	480.1794
152	3-OCF_3	4-phenoxy	472.1347	472.1347
153	3-phenoxy	4-phenoxy	480.1786	480.1780
154	4-phenoxy	4-phenoxy	480.1786	480.1298
155	4-phenoxy	4-OCF_3	472.1347	472.1338
156	3-phenoxy	4-SO_2CH_3	466.1298	466.1253
157	3-phenoxy	4-CO_2CH_3	446.1579	446.1569
158	3-OCF_3	4-ethoxy	424.1347	424.1317
159	3-cyclopentoxy 4-methoxy	3-OCF_3	494.1766	494.1771
160	3,4,5-trimethoxy	3-OCF_3	470.1402	470.1408
161	3-phenoxy	3-(OC_6H_4-4-OCH_3)	510.1892	510.1881
162	3-cyano	3-OCF_3	405.1038	405.1021
163	4-cyano	3-OCF_3	405.1038	405.104
164	4-CO_2-*n*-C_4H_9	3-OCF_3	480.161	480.1594
165	4-(4-Cl-phenoxy)	3-phenoxy	514.1397	514.1407
166	3-(4-F-phenoxy)	3-OCF_3	490.1253	490.1211
167	4-(4-CN-C_6H_4)	3-OCF_3	481.135	481.1354
168	3-phenoxy	4-(OC_6H_4-4-OCH_3)	510.1892	510.1919
*Note: Calculated (Calc.) and Observed (Obs.) masses measured for Example Numbers 33 through 168 are $[M+H]^+$.				

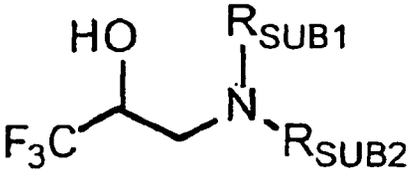
Example Table 2. 3-[*N*-[(aryl)methyl]-[(aryl)methyl]amino]-1,1,1-trifluoro-2-propanols. *



(continued)

Ex. No.	R_{SUB1}	R_{SUB2}	Calc.* Mass [M^+]	Obs.* Mass [M^+]
169	3-F	4-CF_3	395.1120	395.1107
170	4-F	4-CF_3	395.1120	395.1113
171	2-F	4-CF_3	395.1120	395.1102
172	3-Cl	4-CF_3	411.0825	411.0779
173	4-Cl	4-CF_3	411.0825	411.0756
174	2-Cl	4-CF_3	411.0825	411.0779
175	3-Cl	2-CF_3	411.0825	411.0753
176	4-Cl	2-CF_3	411.0825	411.0754
177	2-Cl	2-CF_3	411.0825	411.0760
178	3-F	4-CH_3	341.1403	341.1384
179	4-F	4-CH_3	341.1403	341.1369
180	3-F	3-CH_3	341.1403	341.1372
181	2-F	4-CH_3	341.1403	341.1391
182	4-F	3-CH_3	341.1403	341.1365
183	2-F	3-CH_3	341.1403	341.1359
184	2-F	3-CF_3	395.1120	395.1094
185	3-Cl	3-CF_3	411.0825	411.0767
186	4-Cl	3-CF_3	411.0825	411.0770
187	2-Cl	3-CF_3	411.0825	411.0759
188	3-F	2-CF_3	395.1120	395.1071
189	4-F	2-CF_3	395.1120	395.1119
190	3-F	3-CF_3	395.1120	395.1096
191	4-F	3-CF_3	395.1120	395.1124
192	3-OCF_3	3-OCF_3	478.1064	478.0157
193	3-Cl	3-OCF_3	428.0852	428.0878
194	3-Br	3-OCF_3	472.0346	472.0366
195	3-phenoxy	3-OCF_3	486.1503	486.1507
196	4-phenyl	3-OCF_3	470.1554	470.1566
197	3-nitro	3-OCF_3	439.1092	439.1051
*Note: Calculated (Calc.) and Observed (Obs.) masses measured for Example Numbers 192 through 197 are $[M+H]^+$.				

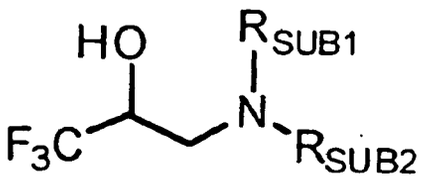
Example Table 3. 3-[*N*-(aralkyl)-*N*-(aralkyl)amino]-1,1,1-trifluoro-2-propanols.



(continued)

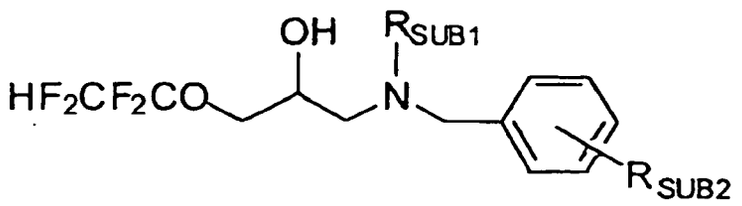
Ex. No.	R_{SUB1}	R_{SUB2}	Calculated Mass [M+H]	Observed Mass [M+H]
198*	2-(3-F-phenyl)-ethyl	3-(OCF_2CF_2H)-benzyl	458.1364	458.1384

Example Table 4. 3-[*N*-(aryl)-*N*-(aralkyl)amino]-1,1,1-trifluoro-2-propanols.



Ex. No.	R_{SUB1}	R_{SUB2}	Calculated Mass [M+H]	Observed Mass [M+H]
199*	3-F-phenyl	2-fluorenylmethyl	402.1481	402.1501
200*	3-F-phenyl	1-(4-OCH_3-naphthyl) methyl	390.1430	390.1415
201*	2-fluorenyl	3-OCF_3-benzy	468.1398	468.1375
202	3-phenoxyphenyl	1-(4-CN-phenyl)-ethyl	427.1633	427.1627
203	3-phenoxyphenyl	1-(3-F-phenyl)-ethyl	420.1587	420.1584
204*	2-(7-bromo-fluorenyl)	3-OCF_3-benzyl	546.0503	546.0531
205	3-phenoxyphenyl	1-(3-nitro-phenyl)ethyl	447.1531	447.1554
206	3-phenoxyphenyl	1-(3-OCF_3-phenyl) ethyl	486.1503	486.151
207*	3-dibenzofuryl	3-(OCF_2CF_2H) benzyl	502.1253	502.1241

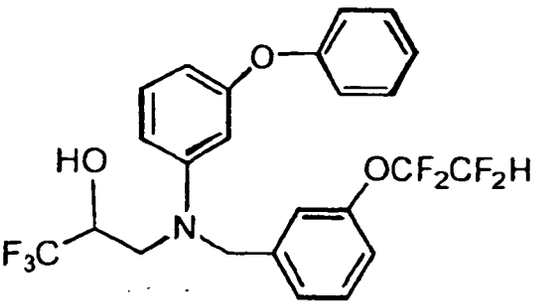
Example Table 5. 3-[*N*-(aryl or aralkyl)-*N*-(aralkyl)amino]-1-haloalkoxy-2-propanols.*



Ex. No.	R_{SUB1}	R_{SUB2}	Calculate d Mass [M+H]	Observed Mass [M+H]
208	3-OCF_3-benzyl	3-OCF_3	540.1232	540.1219
209	3-OCF_3-phenyl	3-OCF_3	526.1076	526.1049
210	3-phenoxy-phenyl	3-OCF_3	534.1473	534.1515
211	3-phenoxy-phenyl	isopropoxy	508.2111	508.2112
212	3-phenoxy-phenyl	3-OCF_2CF_2H	566.1577	566.1604
213	3-phenoxy-phenyl	3-ethoxy	494.1954	494.1982

EXAMPLE 214

[0180]



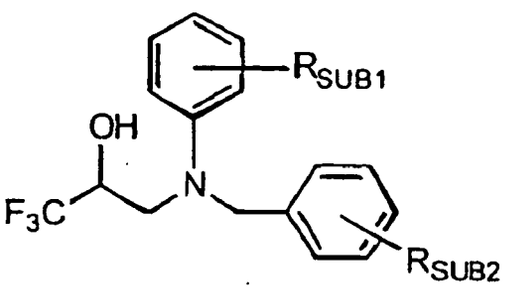
3-[(3-phenoxyphenyl)[[3-(1,1,2,2-tetrafluoroethoxy)phenyl] methyl]amino]-1,1,1-trifluoro-2-propanol

[0181] **EX.214A)** A solution of 3-(phenoxy)aniline (2.78 g, 15 mmol) and 3-(1, 1,2,2-tetrafluoroethoxy)benzaldehyde (3.33 g, 15 mmol) was prepared in 60 mL of dichloroethane. Acetic acid (0.92 mL, 16.05 mmol) and solid $NaBH(OAC)_3$ (4.13 g, 19.5 mmol) were added. The mixture was stirred at room temperature for 3 hours, then acidified with 1 N aqueous HCl. After neutralizing to pH 7.5 with 2.5 N sodium hydroxide, the mixture was extracted with methylene chloride. The organic layer was washed with brine and water, then dried over anhydrous $MgSO_4$, and evaporated to give 5.00 g (85%) of the desired *N*-(3-phenoxyphenyl)-[[3-(1,1,2,2-tetrafluoroethoxy)-phenyl]methyl] amine product as a brown oil, which was greater than 90% pure by reverse phase HPLC analysis. MS *m/z* = 391.

[0182] Amine product **EX-214A** (3.13 g, 8 mmol) and 3,3,3-trifluoromethyl-1,2-epoxypropane (1.34 g, 12 mmol) were dissolved in 1.5 mL of acetonitrile. Ytterbium (III) trifluoromethanesulfonate (0.25 g, 0.4 mmol) was added, and the stirred solution was warmed to 50 ˚C for 1 hour under an atmosphere of nitrogen, at which time HPLC analysis indicated that no secondary amine starting material remained. The reaction was quenched with water and extracted with ether. The ether layer was washed with water and brine, then dried over $MgSO_4$. The crude product was purified by flash column chromatography on silica gel eluting with ethyl acetate:hexane (1:16) to give 2.85 g (71%) of the desired aminopropanol product as a light amber oil, 99% pure by HPLC analysis. ^1H NMR ($CDCl_3$) δ 7.30 (m, 3H), 7.27 (t, 1H), 7.20 (m, 3H), 7.02 (s, 1H), 6.96 (m, 2H), 6.48 (dd, 1H), 6.41 (dd, 1H), 6.37 (m, 1H), 5.89 (tt, 1H), 4.64 (ABq, 2H), 4.34 (m, 1H), 3.87 (dd, 1H), 3.55(dd, 1H), 2.41 (bs, 1H). ^{19}F NMR ($CDCl_3$) δ -79.3 (d, 3F), -88.6 (m. 2F), -137.2 (dt, 2F). HRMS calcd. for $C_{24}H_{21}O_3NF_7$: 504.1410 $[M+H]^+$, found: 504.1425.

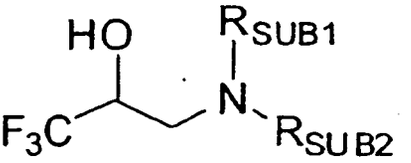
[0183] Additional examples of 3-[*N*-(aryl)-(aryl)methyl]amino]-1,1,1-trifluoro-2-propanols are prepared by one skilled in the art using similar methods, as shown in Example Tables 6 and 7.

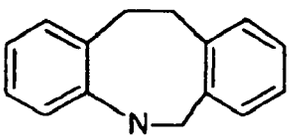
Example Table 6. 3-[*N*-(aryl)-[(aryl)methyl]amino]-1,1,1-trifluoro-2-propanols.



Ex. No.	R_{SUB1}	R_{SUB2}	Calculated Mass [M+H]	Observed Mass [M+H]
215	3-OCH_3, 5-CF_3	3-CF_3	462.1115	462.1115
216	3-phenoxy	3-SCF_3	488.1119	488.1116
217	3-phenoxy	H	388.1524	388.1558
218	3-SO_2-phenyl	3-OCF_2CF_2H	552.1080	552.1095

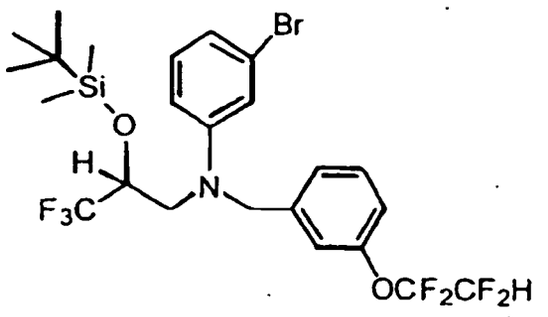
Example Table 7. 3-[*N*-(aryl)-[(aryl)methyl]amino]-1,1,1-thfluoro-2-propanols.



Ex. No.	R_{SUB1} -N-R_{SUB2}	Calculated Mass [M+H]	Observed Mass [M+H]
219*		322.1419	322.1426

EXAMPLE 220*

[0184]



***N*-(3-bromophenyl)-*N*-[2 [[(1,1-dimethylethyl)dimethylsilyl] oxy]-3,3,3-trifluoropropyl]- 3-(1,1,2,2-tetrafluoroethoxy)-benzenemethanamine**

[0185] EX-220A) To a 1,2-dichloroethane (30 mL) solution of 3-(1,1,2,2-tetrafluoroethoxy)-benzaldehyde (2.00 g, 9.0 mmol) was added 3-bromoaniline (0.98 mL, 9.0 mmol), $NaB(OAc)_3H$ (2.48 g, 11.7 mmol) and acetic acid (0.57 mL, 10 mmol). The cloudy mixture was stirred at room temperature for I hour. The reaction mixture was poured into water and extracted with dichloromethane. The organic layer was washed with saturated $NaHCO_3$ and brine, dried ($MgSO_4$) and evaporated to yield 3.27 g (96%) of the desired N-(3-bromophenyl)-[[3-(1,1,2,2-tetrafluoroethoxy)phenyl] methyl]amine product as a brown oil which was used without further purification. MS *m*/*z* = 377 [M^+].

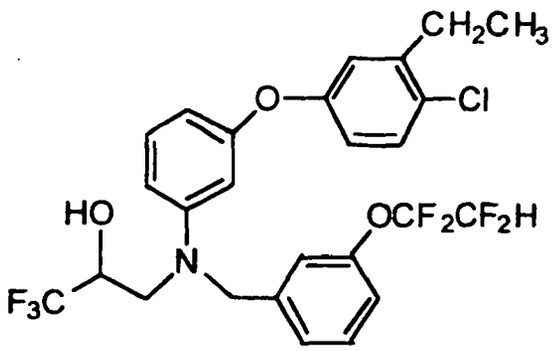
[0186] EX-220B) To a dichloromethane (9 mL) solution of the **EX-220A** amine (3.27 g, 8.65 mmol) was added 1,1,1-trifluoro-2,3-epoxypropane (0.968 mL, 11.3 mmol) and $Yb(OTf)_3$ (0.536 g, 0.86 mmol). The cloudy mixture was stirred at room temperature for 24 hours, then diluted with diethyl ether. The organic layer was washed with water and brine, dried ($MgSO_4$) and evaporated to yield 4.20 g (99%) of the desired 3-[(3-bromophenyl)-[[3-(1,1,2,2-tetrafluoroethoxy) phenyl]methyl]amino]-1,1,1-thnuoro-2-propanol product as a pale brown oil which can be used without further purification. The formation of the desired product was confirmed by the presence of the alcohol peak (δ 1.5, d) in the ^1H NMR spectrum (C_6D_6). An analytical sample was purified by silica gel chromatography eluting with 20% ethyl acetate in hexane to give the desired pure product as a yellow oil. FABMS *m*/*z* = 491 $[M+H]^+$. ^1H NMR ($CDCl_3$) δ 3.55-3.63 (m, 1H), 3.88 (dd, 1H), 4.36 (m, 1H), 4.69 (s, 2H), 5.914 (tt, 1H), 6.66 (dd, 1H), 6.92 (m, 2H), 7.06 (s, 1H), 7.09 (m, 3H), 7.36 (t, 1H).

[0187] To a dichloromethane (10 mL) solution of **EX-220B** aminopropanol (4.20 g, 8.57 mmol) was added *tert*-butyldimethylsilyl trifluoromethanesulfonate (3.0 mL, 13.1 mmol) and triethylamine (2.40 mL, 17.3 mmol). The resulting solution was stirred at room temperature for 4 hours. The reaction mixture was diluted with dichloromethane, and washed with saturated $NaHCO_3$ and brine.

[0188] The organic layer was dried ($MgSO_4$) and evaporated to an oil. Purification by flash chromatography on silica eluting with 2.5% EtOAc in hexane gave 3.0 g (58%) of the desired *N*-(3-bromophenyl)-*N*-[2-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-3,3,3-trifluoropropyl]-3-(1,1,2,2-tetrafluoroethoxy)benzenemethanamine product as a colorless oil. HRMS calcd for $C_{24}H_{29}BrF_7NO_2Si$: 606.1098 $[M+H]^+$, found 606.1118. ^1H NMR (C_6D_6) δ -0.19 (s, 3H), -0.06 (s, 3H), 0.88 (s, 9H), 3.38 (m, 2H), 4.11 (s, 2H), 4.12 (q, 1H), 5.10 (tt, 1H), 6.33 (dd, 1H), 6.61 (d, 1H), 6.68 (t, 1H), 6.81 (m, 2H), 6.89 (m, 2H), 6.97 (t, 1H).

EXAMPLE 221

[0189]

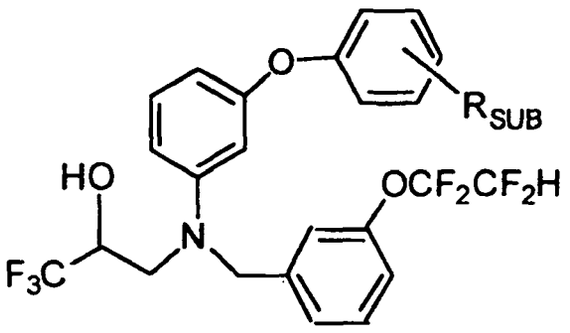


3-[[3-(4-chloro-3-ethylphenoxy)phenyl]-[[3-(1,1,2,2-tetrafluoroethoxy)phenyl]methyl]amino]-1,1,1-trifluoro-2-propanol

[0190] A solution of *N*-(3-bromophenyl)-*N*-[2-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-3,3,3-trifluoropropyl]-3-(1,1,2,2-tetrafluoroethoxy)benzenemethanamine (75 mg, 0.124 mmol), cesium carbonate (81 mg, 0.248mmol), 4-chloro-3-ethylphenol (44 mg, 0.358 mmol), copper triflate benzene complex (6.24 mg, 10 mol%), 1-naphthoic acid (43 mg, 0.248 mmol) in 2:1 toluene:dimethylacetamide (3.0 mL) was heated at 105 ˚C for 96 hours. The reaction mixture was filtered through celite, and the solvent was evaporated. The residue was purified by reverse phase chromatography eluting with 50-90% acetonitrile in water to afford 16.2 mg (23%) of the desired 3-[[3-(4-chloro-3-ethylphenoxy)phenyl]-[[3-(1,1,2,2-tetrafluoroethoxy)phenyl] methyl]amino]-1,1,1-trifluoro-2-propanol product as an orange oil. HRMS calcd. for $C_{26}H_{23}ClF_7NO_3$: 566.1332 $[M+H]^+$, found: 566.1332. ^1H NMR ($CDCl_3$) δ 1.18 (t, 3H), 2.69 (q, 2H), 3.50-3.61 (m, 1H), 3.87 (dd, 1H), 4.28-4.39 (m, 1H), 4.63 (s, 2H), 5.88 (tt, 1H), 6.32-6.40 (m, 2H), 6.48 (dd, 1H), 6.69 (dd, 1H), 6.87 (d, 1H), 7.0-7.34 (m, 5H).

[0191] Additional examples of 3-[(3-aryloxyphenyl and heteroaryloxyphenyl)[[3-(1,1,2,2-tetrafluoroethoxy)phenyl]methyl]amino]-1,1,1-trifluoro-2-propanols are prepared by one skilled in the art using similar methods, as shown in Example Tables 8 and 9. Additional examples of 3-[(3-arylthiophenyl)-[[3-(1,1,2,2-tetrafluoroethoxy)phenyl]-methyl]amino]-1,1,1-trifluoro-2-propanols are prepared by one skilled in the art using similar methods, as shown in Example Table 10.

Example Table 8. 3-[(3-Aryloxyphenyl)-[[3-(1,1,2,2-tetrafluoroethoxy) phenyl]methyl]amino]-1,1,1-trifluoro-2-propanols.



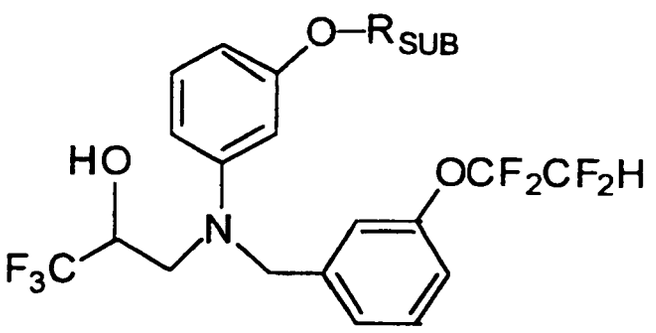
(continued)

Ex. No.	R_{SUB}	Calculated Mass $[M+H]^+$	Observed Mass $[M+H]^+$
222	2-chloro	538.1019	538.1021
223	2-fluoro	522.1315	522.1310
224	2-fluoro,4-CF_3	590.1189	590.1155
225	2,3,5-trifluoro	558.1127	558.1109
226	3-*N*,*N*-dimethylamino	547.1831	547.1844
227	2-fluoro, 3-CF_3	590.1189	590.1184
228	3-$NHCOCH_3$	561.1624	561.1590
229	2,3-dichloro	572.0630	572.0653
230	2-chloro, 4-fluoro	556.0925	556.0891
231	2-chloro, 4-chloro	572.0630	572.0667
232	3-methyl, 5-ethyl	546.1879	546.1899
233	3-ethyl	532.1722	532.1706
234	3,5-dimethyl	532.1722	532.1705
235	2,5-difluoro	540.1221	540.1255
236	4-(perfluorophenyl)-2,3,5,6-tetrafluoro-phenyl	741.0796	741.0799
237	2,3,4-trifluoro	558.1127	558.1161
238	2,3-difluoro	540.1221	540.1182
239	3-acetyl	546.1515	546.1549
240	3-fluoro	522.1315	522.1337
241	3,5-difluoro	540.1221	540.1217
242	4-fluoro, 3-methyl	536.1471	536.1480
243	4-propoxy	562.1828	562.1803
244	3-trifluoromethoxy	588.1232	588.1236
245	3-chloro, 4-fluoro	556.0925	556.0932
246	4-chloro, 3-fluoro	556.0925	556.0933
247	3,4,5-trimethyl	546.1879	546.1901
248	3-trifluoromethyl	572.1283	572.1265
249	3-isopropyl	546.1879	546.1878
250	4-isopropyl	546.1879	546.1899
251	4-butoxy	576.1958	576.1969
252	3-*tert*-butyl	560.2035	560.2055
253	4-isopropyl, 3-methyl	560.2035	560.2035
254	4-*sec*-butyl	560.2035	560.2051
255	4-(1,1-dimethyl-propyl)	574.2192	574.2208
256	3,4-dichloro	572.0630	572.0630
257	4-cyclopentyl	572.2035	572.2029
258	3,4-$(CH_2)_4$	558.1879	558.1881

(continued)

Ex. No.	R_{SUB}	Calculated Mass $[M+H]^+$	Observed Mass $[M+H]^+$
259	4-benzyl	594.1879	594.1906
260	4-phenyl	580.1722	580.1741
261	4-n-butyl	560.2036	560.2033
262	4-ethoxy	548.1672	548.1674
263	4-mercapto	536.1130	536.1163
264	3-phenyl	580.1723	580.1772
265	4-chloro, 2-fluoro	556.0926	556.0954
266	4-n-propyl	546.1879	546.1878
267	4-methylthio	550.1209	550.1251
268	3,5-dimethoxy	564.1623	564.1617
269	4-bromo	582.0716	582.0473
270	3-hydoxymethyl	564.1621	564.1617
271	3-methyl, 4-methylthio	564.1443	564.1476
272	4-chloro, 3,5-dimethyl	552.1176	552.1185
273	4-methoxy	533.1437	533.1458
274	3-methoxy	533.1437	533.1450
275	4-chloro	537.0942	537.0944
276	4-(imidazo-1-yl)	569.1549	569.1552
277	3,4-dimethyl	531.1644	531.1649
278	3-methyl	517.1488	517.1493
279	4-chloro, 3-methyl	551.1098	551.1101
280	4-ethoxy	547.1594	547.1594
281	4-methyl	517.1488	517.1495

Example Table 9. 3-[(3-Aryloxy and Heteroaryloxyphenyl)-[[3-(1,1,2,2-tetrafluoroethoxy) phenyl]methyl]amino]-1,1,1-trifluoro-2-propanols.

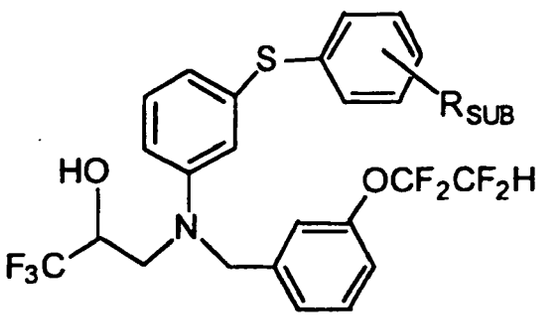


Ex. No.	R_{SUB}	Calculated Mass $[M+H]^+$	Observed Mass $[M+H]^+$
282	6-methyl-3-pyridyl	518.1440	518.1452

(continued)

Ex. No.	R_{SUB}	Calculated Mass $[M+H]^+$	Observed Mass $[M+H]^+$
283	2-pyridyl	504.1284	504.1284
284	3-isoquinolyl	555.1518	555.1513
285	2-naphthyl	554.1566	554.1578
286	3-pyridyl	505.1362	505.1369
287	5-chloro-3-pyridyl	539.0972	539.1002
288	5-indolyl	543.1519	543.1630
289	2-methyl-3-pyridyl	519.1518	519.15I7

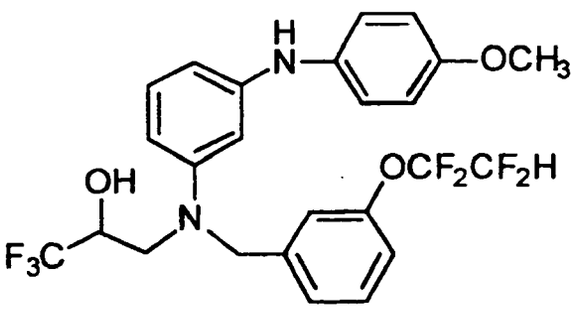
Example Table 10. 3-[(3-Arylthiophenyl)-[[3-(1.1,2.2-tetrafluoroethoxy) phenyl]-methyl]amino]-1,1,1-trifluoro-2-propanols.



Ex. No.	R_{SUB}	Calculated Mass $[M+H]^+$	Observed Mass $[M+H]^+$
290	H	519.1518	519.1119
291	4-methoxy	549.1209	549.1216

EXAMPLE 292

[0192]



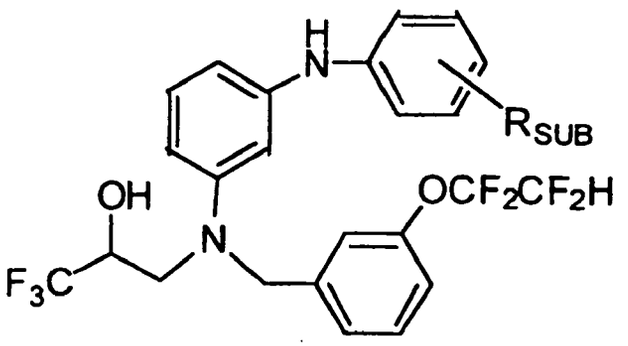
3-[[3-[(4-methoxyphenyl)amino]phenyl]-[[3-(1,1,2,2-tetrafluoroethoxy)phenyl]methyl]amino]-1,1,1-trifluoro-2-propanol

[0193] A mixture containing *N*-(3-bromophenyl)-*N*-[2-[[(1,1-dimethylethyl) dimethylsilyl]oxy]-3,3,3-trifluoropropyl]-3-(1,1,2,2-tetrafluoroethoxy) benzenemethanamine (75 mg, 0.124 mmol), cesium carbonate (57.5 mg, 0.176 mmol), 4-methoxyaniline (18.6 mg, 0.151 mmol) tris(dibenzylideneacetone) dipalladium(0) (4.6 mg, 0.005 mmol), *R*-(+)-2,2'-bis (diphenylphosphino)-1,1'-binaphthyl (4.7 mg, 0.0075 mmol) and toluene (2.5 mL) was heated to 95 ˚C in a sealed vial

for 48 h. Tetrabutylammonium fluoride (1 M, THF, 0.372 mL, 0.372 mmol) was added, and the reaction was stirred at 23 ˚C for 1.5 h. The reaction mixture was filtered through celite, and the solvent was evaporated. The residue was purified by silica gel chromatography eluting with 20% ethyl acetate in hexane to give 49 mg (73%) of the desired 3-[[3-[(4-methoxyphenyl)amino]phenyl]-[[3-(1,1,2,2-tetrafluoroethoxy)phenyl]methyl] amino]-1,1,1-trifluoro-2-propanol product as an orange oil. HRMS calcd for $C_{25}H_{23}F_7N_2O_3$: 532.1597, found: 532.1592 $[M]^+$. ^1H NMR ($CDCl_3$) δ 3.48-3.57 (m, 1H), 3.77 (s, 3H), 3.83 (dd, 1H), 4.33 (m, 1H), 4.59 (s. 2H), 5.87 (tt, 1H), 6.27 (m, 1H), 6.33 (bd, 1H), 6.86 (dd, 4H), 7.02-7.12 (m, 4H). 7.31 (t, 1H), 7.41 (m, 1H), 7.60 (m, 1H). 19 F NMR ($CDCl_3$) δ -137.201 (d, 2F), -88.515 (s, 2F), -79.120 (s, 3F).

[0194] Additional examples of 3-[[3-(*N*-arylamino and *N*-alkyl-*N*-arylamino)phenyl]-[[3-(1,1,2,2-tetrafluoroethoxy)phenyl]methyl]amino]-1,1,1-trifluoro-2-propanols are prepared by one skilled in the art using similar methods, as shown in Example Tables 11 and 12. Additional examples of 3-[[3-(piperidino)-phenyl]-[[3-(1,1,2,2-tetrafluoro-ethoxy)phenyl]methyl]amino]-1,1,1-trifluoro-2-propanols are prepared by one skilled in the art using similar methods, as shown in Example Table 13.

Example Table 11. 3-[[3-(Arylamino)phenyl]-[[3-(1,1,2,2-tetrafluoroethoxy) phenyl]-methyl]amino]-1,1,1-trifluoro-2-propanols.

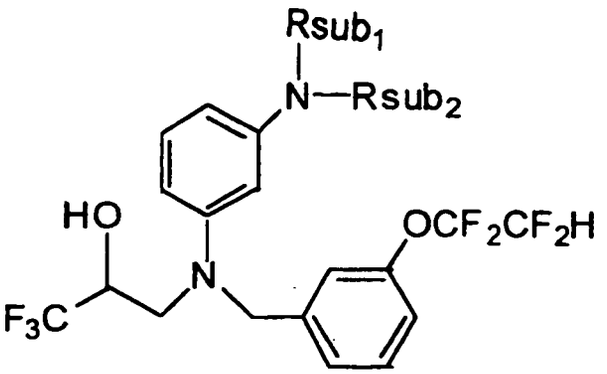


Ex. No.	R_{SUB}	Calculated Mass $[M]^+$	Observed Mass $[M]^+$
293	4-fluoro	520.1397	520.1389
294	H	502.1491	502.1473
295	4-trifluoromethyl	570.1365	570.1335
296	4-chloro	536.1102	536.1125
297	4-cyano	527.1444	527.1452
298	4-$CO_2CH_2CH_3$	574.1703	574.1703
299	4-*n*-propyl	544.1961	544.1959
300	4-[[3-(4-methyl-phenyl)]-1,2,4- oxadiazol-5-yl]	660.1971	660.1969
301	4-[COCH (CN)-$CO_2CH_2CH_3$]	641.1761	641.1755
302	3-cyano	527.1444	527.1448
303	3-$CO_2CH_2CH_3$	574.1703	574.1668
304	3-chloro	536.1102	536.1102
305	3-methoxy	532.1597	532.1593
306	3,4,5,-trimethoxy	592.1703	592.1703
307	3,5-difluoro	538.1303	538.1329
308	4-trifluoromethoxy	586.1314	586.1314

(continued)

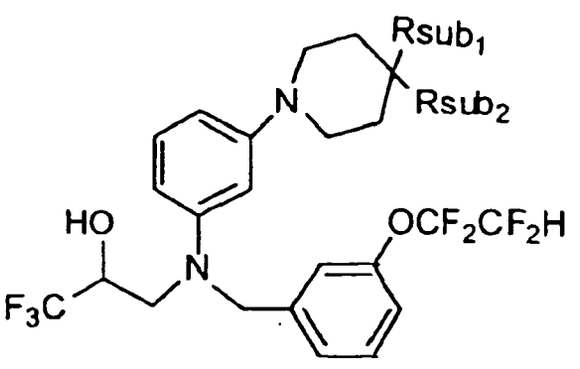
Ex. No.	R_{SUB}	Calculated Mass $[M]^+$	Observed Mass $[M]^+$
309	3,4-dimethoxy	562.1703	562.1713
310	3-trifluoromethyl	570.1365	570.1332

Example Table 12. 3-[[3-(*N*-alkyl-*N*-Arylamino)phenyl]-[[3-(1,1,2,2-tetrafluoroethoxy)phenyl]-methyl]amino]-1,1,1-trifluoro-2-propanols.



Ex. No.	$Rsub_1$	$Rsub_2$	Calculated Mass $[M]^+$	Observed Mass $[M]^+$
311	H	3-trifluoromethyl-benzyl	584.1522	584.1518
312	$-CH_2CH_3$	3-methyl-phenyl	544.1961	544.1959
313	*n*-C_4H_9	4-$CO_2CH_2CH_3$-phenyl	630.2329	630.2329
314	$-(CH_2)_2CN$	4-methyl-phenyl	569.1913	569.1920

Example Table 13. 3-[[3-(*N*-piperidino)phenyl]-[[3-(1,1,2,2-tetrafluoroethoxy) phenyl]-methyl]amino]-1,1,1-trifluoro-2-propanols.



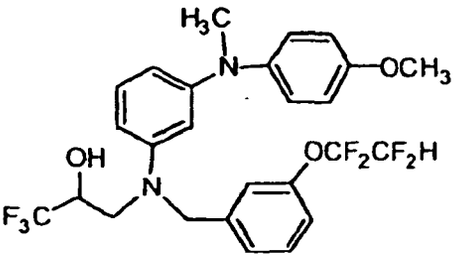
Ex. No.	$Rsub_1$	$Rsub_2$	Calculated Mass $[M]^+$	Observed Mass $[M]^+$
315	H	H	494.1804	494.1804

(continued)

Ex. No.	Rsub$_1$	Rsub$_2$	Calculated Mass $[M]^+$	Observed Mass $[M]^+$
316	H	benzyl	584.2274	584.2280
317	-OCH_2CH_2O-		552.1859	552.1863

EXAMPLE 318

[0195]

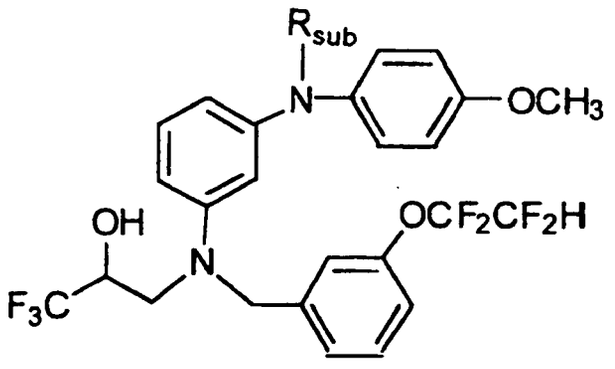


3-[[3-[(4-methoxyphenyl)methylamino]phenyl][[3-(1,1,2,2-tetrafluoroethoxy)phenyl]methyl]amino]-1,1,1-trifluoro-2-propanol

[0196] To a solution of 3-[[3-[(4-methoxyphenyl)amino]phenyl]-[[3-(1,1,2,2-tetrafluoro-ethoxy)phenyl]methyl]amino]-1,1,1-trifluoro-2-propanol (44.3 mg, 0.083 mmol) in tetrahydrofuran (1.0 mL), methyl iodide (6.21 μL, 0.099 mmol) and cesium carbonate (36.6 mg, 0.112 mmol) were added. The dark solution was stirred at 23 ˚C for 2 h, then heated to 55 ˚C for 12 h. The reaction mixture was filtered through celite, and the residue was purified by silica gel chromatography eluting with 20% ethyl acetate in hexane to give 25.2 mg (55%) of the desired 3-[[3-[(4-methoxyphenyl)methylarnino]-phenyl][[3-(1,1,2,2-tetrafluoroethoxy) phenyl]methyl]amino]-1,1,1-trifluoro-2-propanol product as an orange oil. HRMS calcd for $C_{26}H_{25}F_7N_2O_3$: 546.1753, found: 546.1750 $[M]^+$. ^1H NMR ($CDCl_3$), δ 3.54 (m, 1H), 3.38 (s, 3H), 3.65-3.80 (m. 4H), 4.59 (s, 2H), 5.90 (tt, 1H), 6.20 (d, 1H), 6.37 (d, 1H), 6.68 (s, 1H), 6.76 (d, 2H), 6.90-7.15 (m, 6H), 7.31 (t, 1H), ^{19}F NMR ($CDCl_3$), δ -137.21 (d, 2F), - 88.52 (s, 2F), -78.79 (s, 3F).

[0197] Additional examples of 3-[[3-[(4-methoxyphenyl)alkylamino and haloalkylamino)phenyl)-[[3-(1,1,2,2-tetrafluoroethoxy)phenyl]methyl]amino]-1,1,1-trifluoro-2-propanols are prepared by one skilled in the art using similar methods, as shown in Example Table 14.

Example Table 14. 3-[[3-[(4-methoxyphenyl)alkylamino and haloalkylamino)phenyl]-[[3 -(1,1, 2,2-tetrafluoroethoxy) phenyl]methyl]amino]-1,1,1-trifluoro-2-propanols.

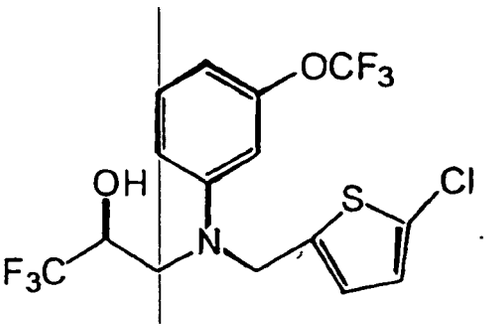


(continued)

Ex. No.	R_{sub}	Calculated Mass $[M]^+$	Observed Mass $[M]^+$
319	ethyl	560.1910	560.1910
320	$-(CH_2)_3CF_3$	642.1940	642.1920

EXAMPLE 321*

[0198]



3-[[(5-chloro-2-thienyl)methyl][(3-trifluoromethoxy)phenyl] amino]-1,1,1-trifluoro-2-propanol

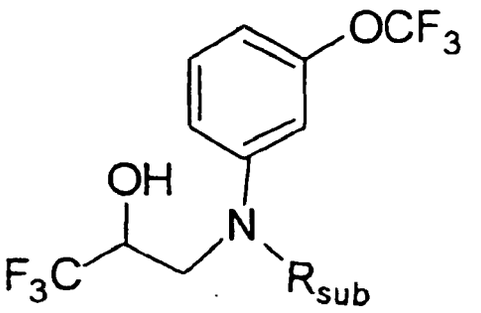
[0199] **EX-321A)** 3-Trifluoromethoxyamline (23.81 g, 134.4 mmol) and 3,3.3-trifluoro-1,2-epoxypropane (3.76 g, 33.6 mmol) were placed into a sealed tube and heated to 80 ˚C for 24 h. The excess aniline was removed by distillation (70 ˚C at 16.2 Torr) to give 8.6 g (88%) of the desired 3-[(3-trifluoromethoxyphenyl)aminol-1,1,1-txifluoro-2-propanol product as a light yellow oil. ^{1}H NMR ($CDCl_3$) δ 3.29-3.37 (m, 1H), 3.55 (dd, 1H), 4.20 (m, 1H), 6.48-6.63 (m, 3H), 7.12 (t, 1H). ^{19}F NMR ($CDCl_3$) δ -79.36 (s, 3F), - 58.44 (s, 3F).

[0200] **EX-321B)** The aminopropanol (18.68 g, 64.6 mmol) from **EX-321A** and imidazole (10.99 g, 0.162 mmol) were dissolved in dimethylformamide (40.0 mL) and *t*-butyl-dimethylsilyl chloride (11.69 g, 77.6 mmol) was added in 3.0 g portions over 15 min. The reaction was stirred at 23 ˚C for 18 h. The reaction solution was diluted with ethyl acetate and washed with water and brine. The organic layer was dried ($MgSO_4$) and concentrated *in vacuo.* The residue was purified by silica gel chromatography eluting with 25% ethyl acetate in hexane to afford 17.08 g (66%) of the desired silylated *N*-(3-trifluoromethoxyphenyl)-*N*-[2-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-3,3,3-trifluoro- propylamine product as a light golden oil. FABMS *m*/*z* = 404 $[M+H]^+$. ^{1}H NMR ($CDCl_3$) δ 0.042 (s, 3H), 0.085 (s, 3H), 0.91 (s, 9H), 3.25-3.35 (m, 1H), 3.50 (dd, 1H), 4.10 (m, 1H), 6.40 (bs, 1H), 6.50 (dd 1H), 6.59 (d, 1H), 7.17 (t, 1H).

[0201] **EX-321C)** The silylated aminopropanol (0.157 g. 0.40 mmol) from **EX-321B** was dissolved in tetrahydrofuran (150 μL) and cooled to O ˚C. Potassium *tert*-butoxide (1.0 M, THF, 0.60 mL, 0.60 mmol) was added in one portion via syringe. The dark solution was stirred at 0 ˚C for five minutes. 2-Chloro-5-bromomethyl-thiophene (73.5 mg, 0.44 mmol) was added in one portion to the cooled solution. The reaction mixture was stirred at 0 ˚C for 15 minutes then warmed to 23 ˚C for 16 h. Tetrabutyl-ammonium fluoride (1.0 M, THF. 1.2 mL, 1.2 mmol) was added to the dark reaction mixture and stirring followed for 2 h at 23 ˚C. The solution was diluted with ethyl acetate and washed with water and brine. The organic layer was dried ($MgSO_4$) and concentrated *in vacuo.* The residue was purified by silica gel chromatography eluting with 0-20% ethyl acetate in hexane to afford 63.4 mg (39%) of the desired 3-[[(5-chloro-2-thienyl)methyl][(3-trifluorornethoxy)phenyl]amino-1,1,1-trifluoro-2-propanol product as a light golden oil. HRMS calcd. for $C_{15}H_{12}ClF_6NO_2S$: 419.1518, found: 419.1527 $[M]^+$. ^{1}H NMR ($CDCl_3$) δ 3.50-3.56 (m, 1H), 3.77 (dd, 1H), 4.28 (m, 1H), 4.67 (s, 2H), 6.62-6.75 (m, 5H), 7.24 (t, 1H). 19 F NMR ($CDCl_3$) δ -79.24 (s, 3F), -58.04 (s, 3F).

[0202] Additional examples of 3-[[(aralkyl and heteroaralkyl)][(3-trifluoromethoxy)-phenyl]amino]-1,1,1-trifluoro-2-propanols are prepared by one skilled in the art using similar methods, as shown in Example Table 15.

Example Table 15. 3-[[(aralkyl and heteroaralkyl)][(3-trifluoromethoxy)-phenyl]amino]-1,1,1-trifluoro-2-propanols.



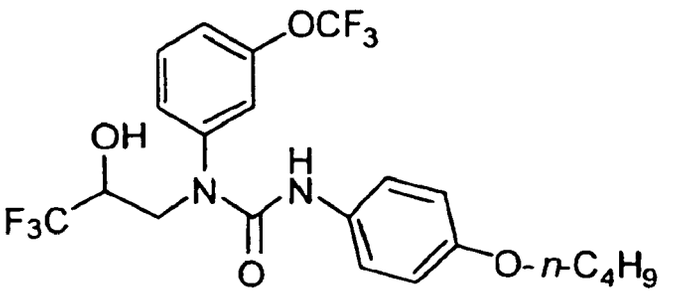
Ex. No.	R_{SUB}	Calc. Mol. Wt.	Obs. Mass $[M]^+$
322	3-iodo-benzyl	505	506
323	4-difluoromethoxy-benzyl	445	446
324	4-(2-cyanophenyl)-benzyl	480	481
325	3-CO_2CH_3-benzyl	437	438
326	2,3,5,6-tetrafluoro-4-methoxy-benzyl	481	482
327	3-cyano-benzyl	404	405
328	3,5-difluoro-benzyl	415	416
329	2,4-difluoro-benzyl	415	416
330	2,6-difluoro-benzyl	415	416
331	4-nitro-benzyl	424	425
332*	(1-napthyl)methyl	429	430
333	4-phenyl-benzyl	455	456
334	2-chloro-4,5-(OCH_2CH_2O)-benzyl	457	458
335	3-nitro-benzyl	424	425
336*	4-phenoxy-butyl	437	438
337*	3-pbenyl-propyl	407	408
338*	3-(4-methoxy)phenyl-propyl	437	438
339*	2-methoxyphenacetyl	437	438
340*	2-(2,5-dimethoxy-phenyl)-2-oxoethyl	467	468
341	4-CO_2CH_3-benzyl	437	438
342 *	2-(anthraquinonyl)-methyl	509	510
343 *	perfluorobenzoyl	483	484
344*	2-(3-indolyl)ethyl	432	433
345*	3-pyridinylmethyl	380	381
346*	(5-chloro-2-thienyl)-methyl	419	420
347	4-methoxy-benzyl	409	410
348	3-methoxy-benzyl	409	410
349*	4-pyridinylmethyl	380	381
350	3,5-dimethoxy-benzyl	439	440

(continued)

Ex. No.	R_{SUB}	Calc. Mol. Wt.	Obs. Mass $[M]^+$
351*	3-(phenyl)propenoyl	419	420
352*	3-phenyl-2,3-propenyl	405	406
353*	3,5-dimethoxy-benzoyl	453	454
354	2,4,5-trimethoxy-benzyl	469	470
355	2,5-dimethoxy-benzyl	439	440
356	3-CO_2H-benzyl	423	424
357	3-OH-benzyl	395	396
358	2,5-dihydroxy-benzyl	411	412
359	3,4,5-trihydroxy-benzyl	427	428
360	3,5.-dihydroxy-benzyl	411	412
361*	2-(phenoxy)phenacetyl	499	500
362*	2-quinolinylmethyl	430	431
363	2-pyridinylmethyl	380	381
364*	2-benzimidazofyl-methyl	419	420
365*	1-benzyl-2-imidazolyl-methyl	459	460
366*	(2,6-dichloro-4-pyridinyl)methyl	449	450

EXAMPLE 367 *

[0203]



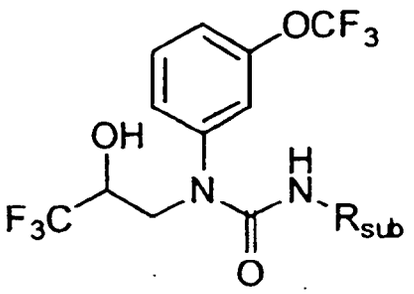
***N'*-(4-butoxyphenyl)-*N*-(3,3,3-trifluoro- 2-hydroxypropyl)-*N*-[3-(trifluoromethoxy)phenyl]urea**

[0204] The silylated aminopropanol (0.150 g, 0.372 mmol) from **EX-321B** was dissolved in chloroform (0.5 mL). Then 4-n-butoxyphenyl isocyanate (78.25 mg. 0.409 mmol) was added, and the resulting solution was stirred at 23 ˚C in a sealed vial for 16 h followed by heating to 65 ˚C for 24 h. The reaction was cooled to 23 ˚C, and a solution of tetrabutylammonium fluoride (1.0 M, THF, 0.5 mL, 0.50 mmol) was added to the reaction, which was then stirred at 23 ˚C for 2 h. The solution was diluted with ethyl acetate and washed with water and brine. The residue was purified by silica gel chromatography eluting with 0-50% ethyl acetate in hexane to afford 73.6 mg (38%) of the desired urea product as a pale yellow glass. FABMS *m/z* = 481 $[M+H]^+$. ^1H NMR ($CDCl_3$), δ 0.99 (t, 3H), 1.484 (m, 2H), 1.740 (m, 2H), 3.25-3.35 (m, 1H), 3.55 (dd, 1H), 3.94 (m, 2H), 4.207 (m, 1H), 6.17 (s, 1H), 6.48 (s, 1H), 6.50-6.65 (m, 2H), 6.83 (d, 2H), 7.15 (d, 2H), 7.58 (t, 1H), ^{19}F NMR ($CDCl_3$) δ -78.87 (s, 3F), -58.29 (s, 3F).

[0205] Additional examples of *N'*-(aryl and sulfonylaryl)-*N*-(3,3,3-trifluoro-2-hydroxy-propyl)-*N*-[3-(trifluoromethoxy) phenyl]ureas are prepared by one skilled in the art using similar methods, as shown in Example Table 16.

Example Table 16. *N*'-(aryl and sulfonylaryl)-*N*-(3,3,3-trifluoro-2-hydroxypropyl)-*N*-[3-(trifluoromethoxy)phenyl]ureas.

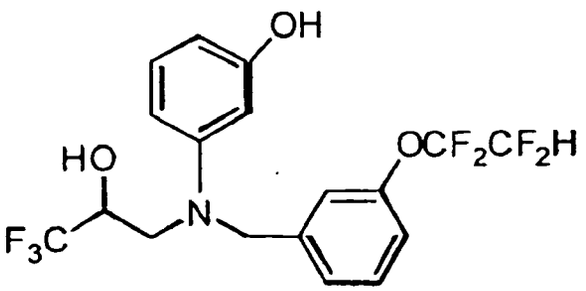
*



Ex. No.	R_{SUB}	Calculated Mol. Wt.	Observed Mass $[M]^+$
368	2-CH_3S-phenyl	454	455
369	4-biphenyl	484	485
370	4-CH_3-phenyl-SO_2-	486	487

EXAMPLE 371

[0206]



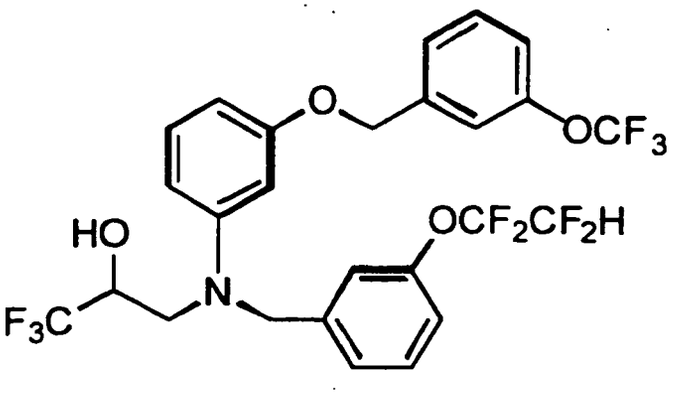
3-[[[3-(1,1,2,2-tetrafluoroethoxy)phenyl]methyl](3,3,3-trifluoro-2-hydroxypropyl)amino]phenol

[0207] **EX-371A)** To a solution of 3-aminophenol (4.91 g, 45.0 mmol) and 3-(1,1,2,2-tetrafluoroethoxy)benzaldehyde (10.0 g, 45.0 mmol) dissolved in 100 mL of 1,2-dichloroethane was added sodium triacetoxyborohydride (14.28 g 67.5 mmol) and glacial acetic acid (2.7 mL, 47.3 mmol). The reaction mixture was stirred for 6 h, water was added, and the mixture was extracted with dichloromethane. The organics were washed with saturated aqueous sodium bicarbonate then dried over $MgSO_4$. The dried organic layer was evaporated to give 11.00 g (78%) of the desired 3-[[[3-(1,1,2,2-tetrafluoroethoxy)phenyl]methyl]amino]phenol product as a dark orange oil. ^1H NMR ($CDCl_3$) δ 4.32 (s, 2H), 5.88 (tt, 1H), 6.08 (t, 1H), 6.17-6.22 (m, 2H), 7.00 (t, 1H), 7.11 (dd, 1H), 7.24-7.27 (m, 2H), 7.33 (t, 1H).

[0208] A solution of 3-[[[3-(1,1,2,2-tetrafluoroethoxy)phenyl]methyl]amino]phenol (11.0 g, 34.9 mmol), 3,3,3-trifluoro-1,2-epoxypropane (4.5 mL, 52.4 mmol) and ytterbium trifluoromethanesulfonate (2.2 g, 10 mol%) in 20 mL of acetonitrile was heated at 50 ˚C in a sealed glass tube for 16 h. The reaction mixture was cooled, water was added, and the reaction mixture was extracted with ether. The ether layer was washed with saturated aqueous sodium bicarbonate and brine and dried over $MgSO_4$. The dried organic layer was evaporated to give 8.07 g (89%) of the desired 3-[[[3-(1,1,2,2-tetrafluoroethoxy)phenyl]methyl](3,3,3-trifluoro-2hydroxypropyl)amino]phenol product as a yellow oil. HRMS calcd. for $C_{18}H_{17}F_7NO_3$: 428.1097 $[M+H]^+$, found: 428.1104. ^1H NMR ($CDCl_3$) δ 3.58 (dd, 1H), 3.88 (dd, 1H), 4.39 (m, 1H), 4.68 (s, 2H), 5.91 (tt, 1H), 6.25-6.37 (m, 3H), 7.07-7.14 (m, 4H), 7.35 (t, 1H).

EXAMPLE 372

[0209]

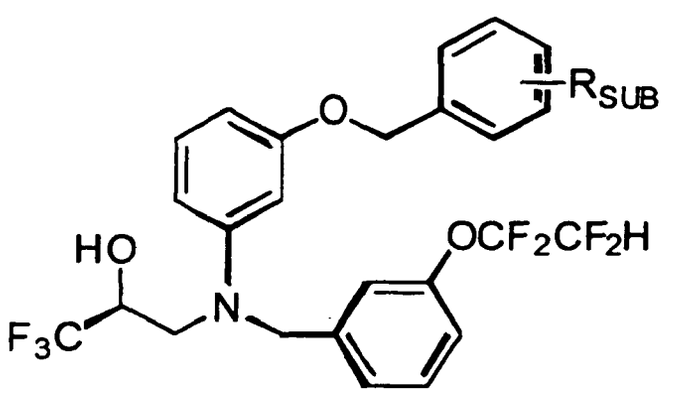


3-[[[3-(1,1,2,2-tetrafluoroethoxy)phenyl]methyl][3-[[3-(trifluoromethoxy)phenyl]-methoxy]phenyl]amino]-1,1,1-trifluoro-2-propanol

[0210] To a solution of 3-[[[3-(1,1,2,2-tetrafluoroethoxy)phenyl]methyl](3,3,3-trifluoro-2-hydroxypropyl)amino]phenol (100 mg, 0.23 mmol), 3-trifluoromethoxybenzyl bromide (70.0 mg, 0.27 mmol) in 2.5 mL of acetone and cesium carbonate (100 mg, 0.31 mmol) were added. The reaction mixture was heated to 60 ˚C for 18 h then cooled. The reaction mixture was filtered through celite, and the solvent was evaporated. The residue was purified by reverse phase HPLC eluting with 50% to 90% acetonitrile in water to afford 63.3 mg (45%) of the desired benzyl ether product as an orange oil. HRMS calcd. for $C_{26}H_{22}F_{10}NO_4$: 602.1389 $[M+H]^+$, found: 602.1380. ^1H NMR ($CDCl_3$) δ 3.61 (dd, 1H), 3.83 (dd, 1H), 4.32-4.39 (m, 1H), 4.62 (s, 2H), 4.98 (s, 2H), 5.84 (tt, 1H), 6.43-6.55 (m, 3H), 7.04-7.42 (m, 9H).

[0211] Additional examples of 3-[[[3-(1,1,2,2-tetrafluoroethoxy)-phenyl]methyl][3-[(substituted)methoxy]phenyl]amino]-1,1,1-trifluoro-2-propanols are prepared by one skilled in the art using similar methods as shown in Example Tables 17 and 18.

Example Table 17. 3-[[[3-(1,1,2,2-tetrafluoroethoxy)phenyl]methyl][3-[(substituted-phenyl)methoxy]phenyl]amino]-1,1,1-trifluoro-2-propanols.



Ex. No.	R_{SUB}	Calculated Mass $[M+H]^+$	Observed Mass $[M+H]^+$
373	H	518.1566	518.1578
374	4-trifluoromethoxy	602.1389	602.1383
375	4-nitro	563.1417	563.1457
376	2,3,4,5,6-pentafluoro	608.1095	608.1092

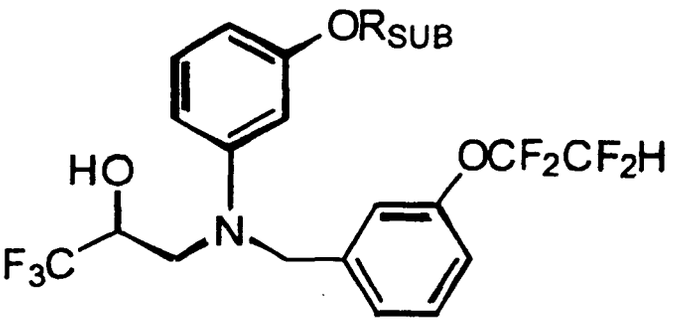
(continued)

Ex. No.	R_{SUB}	Calculated Mass $[M+H]^+$	Observed Mass $[M+H]^+$
377	3,5-di(trifluoromethyl)	654.1314	654.1308
378	3,5-difluoro	554.1378	554.1390
379	3-trifluoromethyl	586.1440	586.1419
380	2,3,5,6-tetrafluoro-4-trifluoromethyl	658.1063	658.1003
381	4-fluoro-2-trifluoromethyl	604.1346	604.1321
382	3-nitro	563.1417	563.1416
383	3-cyano	543.1519	543.1523
384	4-cyano	543.1519	543.1517
385	4-methyl	532.1723	532.1729
386	2.3,5.6-tetrafluoro -4-methoxy	620.1295	620.1261
387	3-methoxycarbonyl	576.1621	576.1613
388	4-methoxycarbonyl	576.1621	576.1614
389	4-difluoromethoxy	584.1483	584.1480
390	2-fluoro	536.1472	536.1465
391	4-fluoro	536.1472	536.1454
392	2,4,6-trifluoro	572.1284	572.1267
393	3-chloro-2-fluoro	570.1082	570.1069
394	2-6-difluoro	554.1378	554.1385
395	2,4-difluoro	554.1378	554.1346
396	2,4-di(trifluoromethyl)	654.1314	654.1321
397	2,5-difluoro	554.1378	554.1350
398	3,4-difluoro	554.1378	554.1381
399	2,3-difluoro	554.1378	554.1364
400	2-fluoro-3-trifluoromethyl	604.1346	604.1329
401	3-bromo	596.067	596.0641
402	3-methyl	532.1723	532.1692
403	2-bromo	596.0671	596.0666
404	2-chloro	552.1176	552.1175
405	3-iodo	644.0533	644.0517
406	3-fluoro	536.1472	536.1475
407	3-methoxy	548.1672	548.1676
408	2,3,5-trifluoro	572.1284	572.1276
409	4-trifluoromethylthio	618.1161	618.1165
410	3-trifluoromethylthio	618.1161	618.1151
411	3-fluoro-5-trifluoromethyl	604.1346	604.1309
412	4-fluoro-3-trifluoromethyl	604.1346	604.1336

(continued)

Ex. No.	R_{SUB}	Calculated Mass $[M+H]^+$	Observed Mass $[M+H]^+$
413	4-(phenylmethoxy)	624.1985	624.1956
414	4-phenyl	594.1879	594.1845
415	4-ethyl	546.1879	546.1862
416	4-trifluoromethyl	586.1440	586.1400
417	2-methyl-3-nitro	577.1573	577.1576
418	4-*tert*-butyl	574.2192	574.2163
419	3,4-dimethyl	546.1879	546.1881
420	3-chloro	552.1176	552.1157
421	4-bromo	596.0671	596.0669
422	3,5-dichloro	586.1787	586.1378
423	3,5-dimethyl	546.1879	546.1890
424	4-chloro	552.1176	552.1188
425	2-fluoro-3-methyl	550.1628	550.1625
426	3-phenoxy	610.1828	610.1819
427	4-isopropyl	560.2036	560.2020

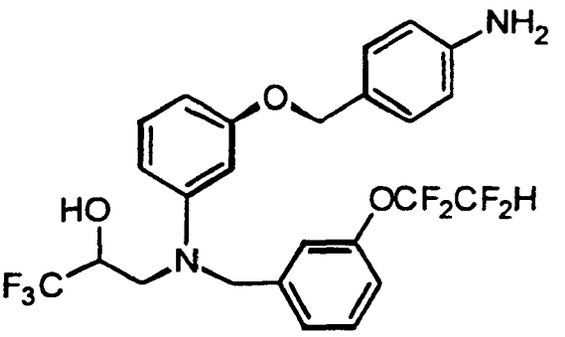
Example Table 18. 3-[[[3-(1,1,2,2-tetrafluoroethoxy)phenyl]methyl] [3-[(substituted)-methoxy]phenyl]amino]-1,1,1-trifluoro-2-propanols.



Ex. No.	R_{SUB}	Calculated Mass $[M+H]^+$	Observed Mass $[M+H]^+$
428	3-pyridylmethyl	519.1519	519.1483
429	1-phenylethyl	532.1723	532.1711
430	1-benzyli midazol-2-ylmethyl	598.1941	598.1946
431	5-chlorobenzo[b]thien-3-ylmethyl	608.0897	608.0884
432	2-pyridylmethyl	519.1519	519.1522
433	4-pyridylmethyl	519.1519	519.1515

EXAMPLE 434

[0212]



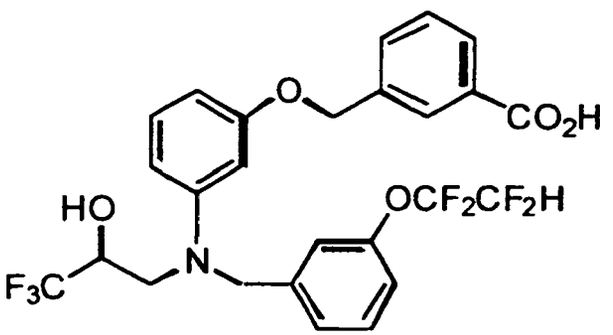
3-[[3-[(4-aminophenyl)methoxy]phenyl][[3-(1,1,2,2-tetrafluoroethoxy)phenyl]methyl]amino]-1,1,1-trifluoro-2-propanol

[0213] EX-434A) A solution of 3-[[[3-(1,1,2,2-tetrafluoroethoxy)phenyl]methyl][3-[(3-nitro-phenyl)methoxy]phenyl] amino]-1,1,1-trifluoro-2-propanol (42.0 mg, 0.07 mmol) and zinc dust (37 mg, 0.57 mmol) in acetic acid (0.5 mL) was stirred for 4 d. The reaction mixture was filtered, and the solvent was evaporated. The residue was purified by reverse phase HPLC eluting with 50% to 90% acetonitrile in water to afford 15.4 mg (39%) of the desired reduced amine product as a brown oil. HRMS calcd. for $C_{25}H_{24}F_7N_2O_3$: 533.1675 $[M+H]^+$, found: 533.1656. ^1H NMR (acetone-d_6) δ 3.60 (dd. 1H). 3.85 (m. 1H), 3.90 (s, 2H), 4.45 (m, 1H), 4.73 (s, 2H), 6.22-6.64 (m, 4H). 6.94 (dd, 1H), 7.12-7.45 (m, 9H).

[0214] EX-434B) 3-[[3-[(3-aminophenyl)methoxy]phenyl][[3-(1,1,2,2-tetrafluoroethoxy)-phenyl]methyl]amino]-1,1,1-trifluoro-2-propanol is prepared by one skilled in the art using similar methods. HRMS calcd. for $C_{25}H_{24}F_7N_2O_3$: 533.1675 $[M+H]^+$, found: 533.1654.

EXAMPLE 435

[0215]



3-[[3-[[[3-(1,1,2,2-tetrafluoroethoxy)phenyl]methyl](3,3,3-trifluoro-2-hydroxypropyt)amino]phenoxy]methyl] benzoic acid

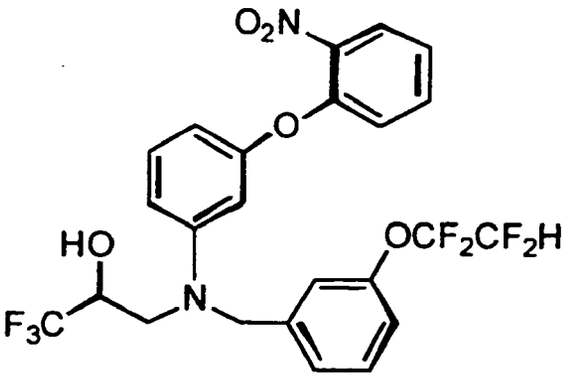
[0216] EX-435A) A solution of ethyl 3-[[3-[[[3-(1,1,2,2-tetrafluoroethoxy) phenyl]methyl]-(3,3,3-trifluoro-2-hydroxypropyl)amino]phenoxy]methyl] benzoate (22.1 mg, 0.04 mmol) and lithium hydroxide (5 mg, 0.12 mmol) in water (1 mL) and tetrahydrofuran (0.5 mL) was heated at 80 ˚C for 16 h. The reaction mixture was added to 6 N hydrochloric acid and extracted with ethyl acetate. The organic layer was dried over magnesium sulfate, and the solvent was evaporated. The residue was purified by reverse phase HPLC eluting with 10% to 90% acetonitrile in water to afford 5.6 mg (19%) of the desired benzoic acid product as a brown oil. HRMS calcd. for $C_{26}H_{23}F_7NO_5$: 562.1464 $[M+H]^+$, found: 562.1418. ^1H NMR (acetone-d_6) δ 3.64 (dd, 1H), 3.95 (m. 1H), 4.45-4.50 (m, 1H), 4.80 (s, 2H), 5.12 (s, 2H), 6.27-6.63 (m, 4H), 7.06-7.27 (m, 4H), 7.41 (t, 1H), 7.50 (t, 1H), 7.66 (d, 1H), 7.99 (d, 1H), 8.10 (s, 1H).

[0217] EX-435B) 4-[[3-[[[3-(1,1,2,2-tetrafluoroethoxy)phenyl]methyl](3,3,3-trifluoro-2-hydroxypropyl)amino]phenoxy] methyl]benzoic acid is prepared by one skilled in the art using similar methods. HRMS calcd. for $C_{26}H_{23}F_7NO_5$: 562.1464

$[M+H]^+$, found: 562.1445.

EXAMPLE 436

[0218]

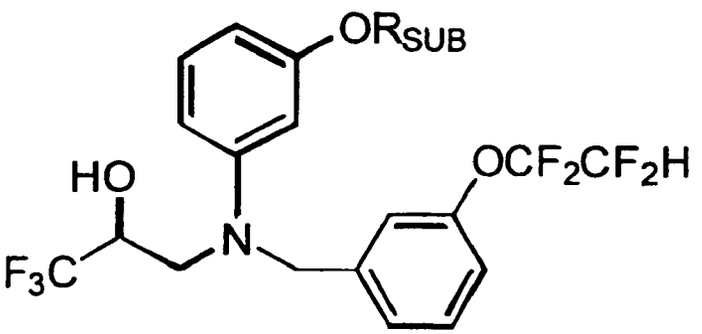


3-[[3-(2-nitrophenoxy)phenyl][[3-(1,1,2,2-tetrafluoroethoxy) phenyl]-methyl]amino]-1,1,1-trifluoro-2-propanol

[0219] A solution of 3-[[[3-(1,1,2,2-tetrafluoroethoxy)phenyl]methyl](3,3,3-trifluoro-2-hydroxypropyl)amino]phenol (100 mg, 0.23 mmol), 1-bromo-2-nitrobenzene (52.4 mg, 0.26 mmol), copper(I) trifluoromethanesulfonate benzene complex (3 mg, 2.5 mol%) and cesium carbonate (100 mg, 0.31 mmol) in toluene (1 mL) and ethyl acetate (1 mL) was heated at 95 ˚C in a sealed vial for 4 d. The reaction mixture was filtered through celite, and the solvent was evaporated. The residue was purified by reverse phase HPLC eluting with 50% to 90% acetonitrile in water to afford 14.1 mg (11%) of the desired 2-nitrophenyl ether product as an orange oil. HRMS calcd. for $C_{24}H_{20}F_7N_2O_5$: 549.1260 $[M+H]^+$, found: 549.1235. ^1H NMR ($CDCl_3$) δ 3.63 (dd, 1H). 3.84 (dd, 1H), 4.35-4.42 (m. 1H), 4.64 (s, 2H), 5.90 (tt, 1H), 6.47-6.67 (m. 3H), 6.98-7.50 (m. 8H). 7.97 (d, 1H).

[0220] Additional examples of 3-[[3-aryloxyphenyl][[3-(1,1,2,2-tetrafluoroethoxy)-phenyl]methyl]amino]-1,1,1-trifluoro-2-propanols are prepared by one skilled in the art using similar methods, as shown in Example Table 19.

Example Table 19. 3-[[3-aryloxyphenyl][[3-(1,1,2,2-tetrafluoroethoxy)-phenyl]methyl]amino]-1,1,1-trifluoro-2-propanols.



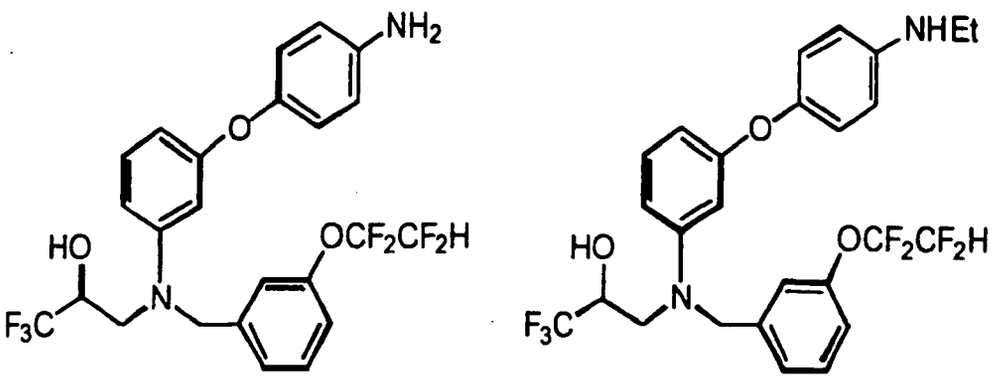
Ex. No.	R_{SUB}	Calculated Mass $[M+H]^+$	Observed Mass $[M+H]^+$
437	4-*tert*-butylphenyl	560.2036	560.2050
438	4-nitrophenyl	549.1260	549.1306
439	4-bromo-2-nitrophenyl	627.0366	627.0375
440	3-fluoro-2-nitrophenyl	567.1166	567.1135

(continued)

Ex. No.	R_{SUB}	Calculated Mass $[M+H]^+$	Observed Mass $[M+H]^+$
441	2-cyano-3-pyridyl	530.1315	530.1300
442	5-carboxy-3-pyridyl	549.1260	549.1269
443	4-fluoro-2-pyridyl	523.1268	523.1243
444	3-trifluoromethyl-2-pyridyl	573.1236	573.1205
445	5-trifluoromethyl-2-pyridyl	573.1236	573.1197
446	5-bromo-2-pyridyl	583.0667	583.0405
447	2-methyl-5-nitrophenyl	563.1417	563.1416
448	thiazol-2-yl	511.0926	511.0911
449	5-pyrimidinyl	506.1315	506.1315

EXAMPLE 450

[0221]

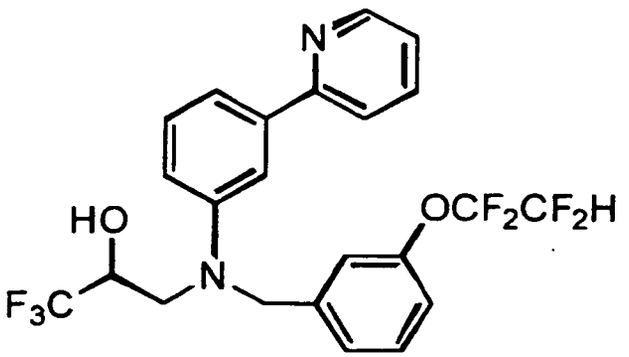


3-[[3-(4-aminophenoxy)phenyl][[3-(1,1,2,2-tetrafluoroethoxy) phenyl]-methyl]amino]-1,1,1-trifluoro-2-propanol and 3-[[3-[4-(ethylamino)phenoxy]phenyl][[3-(1,1,2,2-tetrafluoroethoxy)phenyl]-methyl]amino]-1,1,1-trifluoro-2-propanol

[0222] A solution of 3-[[3-(4-nitrophenoxy)phenyl][[3-(1,1,2,2-tetrafluoroethoxy) phenyl]-methyl]amino]-1,1,1-trifluoro-2-propanol (33.8 mg, 0.06 mmol) in ethanol and 5% palladium on carbon (4 mL) was placed under 40 psi hydrogen gas for 7 h. The mixture was filtered through celite, the solvent was evaporated, and the residue was purified by silica gel chromatography eluting with 25% ethyl acetate in hexane to give 13.4 mg (42%) of **(EX-450A)** as 3-[[3-(4-aminophenoxy) phenyl][[3-(1,1,2.2-tetrafluoroethoxy) phenyl]methyl]amino]-1,1,1-trifluoro-2-propanol and 13.9 mg (41%) of **(EX-450B)** as 3-[[3-[4-(ethylamino)phenoxy]phenyl][[3-(1,1,2,2-tetrafluoroethoxy)phenyl]methyl] amino]-1,1,1-trifluoro-2-propanol both as orange oils. 3-[[3-(4-aminophenoxy)phenyl][[3-(1,1,2,2-tetrafluoroethoxy)phenyl]methyl]-amino]-1,1,1-trifluoro-2-propanol: HRMS calcd. for $C_{24}H_{22}F_7N_2O_3$: 519.1519 $[M+H]^+$, found: 519.1529. ^1H NMR (acetone-d_6) δ 3.63 (dd, 1H), 3.96 (dd, 1H), 4.42-4.58 (m, 1H), 4.80 (s, 2H), 5.88 (m, 1H), 6.20 (m, 1H), 6.32-6.77 (m, 6H), 6.92 (d, 1H), 7.06-7.26 (m, 3H), 7.43 (m, 1H). 3-[[3-[4-(ethylamino)phenoxy]phenyl)[[3-(1,1,2,2-tetrafluoroethoxy) phenyl]-methyl] amino]-1,1,1-trifluoro-2-propanol: HRMS calcd. for $C_{26}H_{26}F_7N_2O_3$: 547.1832 $[M+H]^+$, found: 547.1819. ^1H NMR (acetone-d_6) δ 1.23 (t, 3H), 3.17 (q, 2H), 3.63 (dd, 1H), 3.96 (dd, 1H), 4.42-4.58 (m, 1H), 4.79 (s, 2H), 5.85 (d, 1H), 6.20 (m, 1H), 6.33 (m, 1H), 6.47 (m, 1H), 6.50 (tt, 1J), 6.61 (d, 2H), 6.78 (d, 2H), 7.09 (t, 1H), 7.20 (m, 1H), 7.23 (d, 1H), 7.42 (m, 1H).

EXAMPLE 451

[0223]

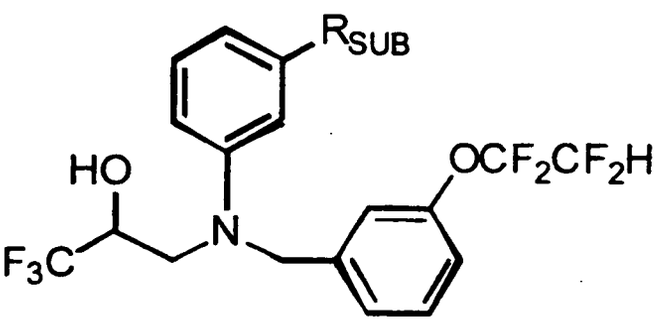


3-[[3-(2-pyridinyl)phenyl][[3-(1,1,2,2-tetrafluoroethoxy) phenyl]methyl]amino]-1,1,1-trifluoro-2-propanol

[0224] A solution of 3-[(3-bromophenyl)[[3-(1,1,2,2-tetrafluoroethoxy)phenyl]methyl] amino]-1,1,1-trifluoro-2-propanol (100 mg, 0.22 mmol), 2-tributylstannyl pyridine (96 mg, 0.26 mmol), dichlorobis(triphenylphospine)palladium(II) (6 mg, 6.7 mol%) and lithium chloride (46 mg, 1.09 mmol) in toluene (4 mL) was heated at 105 ˚C for 16 h. The reaction mixture was filtered through celite, and the solvent was evaporated. The residue was purified by silica gel column chromatography eluting with 25% ethyl acetate in hexane to afford 47.7 mg (45%) of the desired pyridyl product as an orange oil. HRMS calcd. for $C_{23}H_{20}F_7N_2O_2$: 489.1377 $[M+H]^+$, found: 489.1413. ^1H NMR (acetone-d_6) δ 3.78 (dd, 1H), 4.06 (dd, 1H), 4.52-4.61 (m, 1H), 4.94 (s, 2H), 5.89 (d, 1H), 6.43 (tt, 1H), 6.94 (m, 1H), 7.18 (m, 1H), 7.22-7.42 (m, 5H), 7.60 (s, 1H), 7.80 (m, 2H), 8.61 (m, 1H).

[0225] Additional examples of 3-[[3-(heteroaryl)phenyl][[3-(1,1,2,2-tetrafluoroethoxy)phenyl]methyl]amino]-1,1,1-trifluoro-2-propanols are prepared by one skilled in the art using similar methods, as shown in Example Table 20.

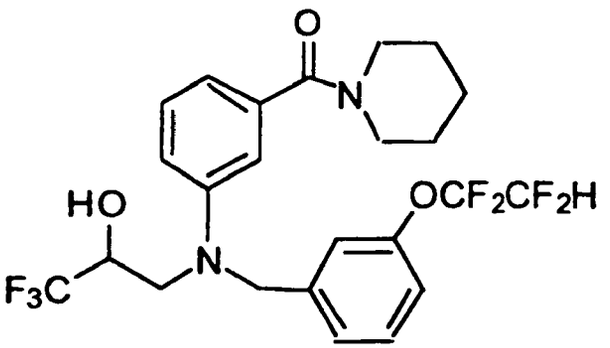
Example Table 20. 3-[[3-(heteroaryl)phenyl][[3-(1,1,2.2-tetrafluoroethoxy)-phenyl]methyl]amino]-1,1,1-trifluoro-2-propanols.



Ex. No.	R_{SUB}	Calculated Mass $[M+H]^+$	Observed Mass $[M+H]^+$
452	2-thienyl	494.1024	494.0987
453	2-furyl	478.1025	478.1025
454	3-pyridyl	489.1413	489.1391
455	3-methyl-2-pyridyl	503.1570	503.1531

EXAMPLE 456

[0226]



1-[3-[[[3-(1,1,2,2-tetrafluoroethoxy)phenyl]methyl](3,3,3-trifluoro-2-hydroxypropyl)benzoyl]piperidine

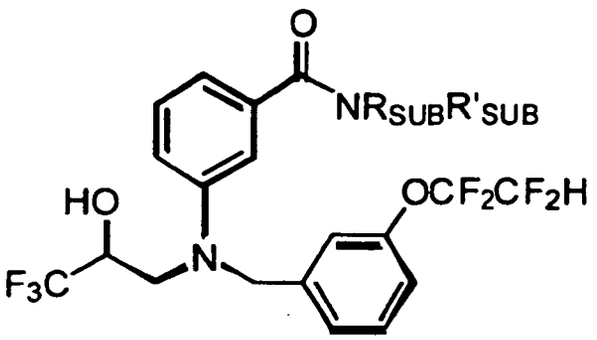
[0227] **EX-456A)** Ethyl 3-aminobenzoate (6.75 mL, 0.045 mol) and 3-(1,1,2,2-tetrafluoro-ethoxy)benzaldehyde (10 g, 45 mmol) were dissolved in 100 mL of dichloroethane and acetic acid (2.7 mL, 47 mmol), then solid $NaBH(OAc)_3$ (14.3 g, 67 mmol) was added. The mixture was stirred at room temperature for 3 hours, then quenched with aqueous sodium bicarbonate and extracted with dichloromethane. The organic layer was washed with brine, then dried over $MgSO_4$, and evaporated to give 16.7 g (98%) of the desired ethyl 3-[[[3-(1,1,2,2-tetrafluoroethoxy)phenyl]methyl]amino] benzoate product as a yellow oil. ^1H NMR ($CDCl_3$) δ 1.3 (t, 3H), 4.3 (q, 2H), 4.5 (s, 2H), 6.5 (tt, 1H), 6.9 (d, 1H), 7.1-7.4 (m, 7H).

[0228] **EX-456B)** A solution of **EX-456A** (16.7 g, 45 mmol) and 1,1,1-trifluoro-2,3-epoxypropane (4.26 mL, 49.5 mmol) were dissolved in 30 mL of acetonitrile. Ytterbium (III) trifluoromethanesulfonate (2.79 g, 4.5 mmol) was added, and the stirred solution was warmed to 50 ˚C for 18 hours. The reaction was quenched with water and extracted with ether. The ether layer was washed with brine, then dried over $MgSO_4$. The crude product was purified by flash column chromatography on silica gel eluting with dichloromethane to give 12 g (55%) of the desired ethyl 3-[[[3-(1,1,2,2-tetra-fluoroethoxy)phenyl] methyl](3,3,3-trifluoro-2-hydroxypropyl)amino]-benzoate product as a colorless oil, which was greater than 98% pure by reverse phase HPLC analysis. HRMS calcd. for $C_{21}H_{21}F_7NO_4$: 484.1359 $[M+H]^+$, found: 484.1342. ^1H NMR ($CDCl_3$) δ 1.4 (t, 3H), 3.6 (dd, 1H), 3.9 (dd, 1H), 4.3 (m, 3H), 4.7 (dd, 2H), 5.9 (tt, 1H), 6.9 (d, 1H), 7.1-7.2 (m. 3H), 7.2-7.4 (m, 2H), 7.5 (m, 1H).

[0229] To a solution of piperidine (102 μL, 1.03 mmol) in toluene (620 μL) was added 2 M trimethylaluminum in toluene (620 μL), and the solution was stirred for 2 h. To the reaction mixture was added a solution of ethyl 3-[(1,1,1-trifluoro-2-hydroxypropyl)[[3-(1,1,2,2-tetrafluoroethoxy)phenyl]methyl]amino]benzoate (100 mg, 0.21 mmol) in toluene (1 mL). The reaction mixture was heated at 40 ˚C for 20 h and 60 ˚C for 5 h, then cooled. To the reaction mixture was added water dropwise followed by 2 M hydrochloric acid and ethyl acetate. The solution was placed on a celite plug for 5 min, then eluted with dichloromethane, and the solvent was evaporated. The residue was purified by reverse phase HPLC eluting with 50% to 90% acetonitrile in water to afford 42.6 mg (38%) of the desired 1-[3-[[[3-(1,1,2,2-tetrafluoroethoxy) phenyl]-methyl]-(3,3,3-trifluoro-2-hydroxypropyl)benzoyl]piperidine product as an orange oil. HRMS calcd. for $C_{24}H_{26}F_7N_2O_3$: 523.1832 $[M+H]^+$, found: 523.1815. ^1H NMR (acetone-d_6) δ 1.22-1.63 (m, 6H), 3.16-3.62 (m, 4H), 3.74 (dd, 1H), 4.00 (dd, 1H), 4.44-4.55 (m, 1H), 4.83 (s, 2H), 6.46 (tt, 1H), 6.64-6.69 (m, 2H), 6.83 (dd, 1H), 7.14-7.28 (m, 4H), 7.41 (t, 1H).

[0230] Additional examples of *N,N*-disubstituted-3-[(3,3,3-trifluoro-2-hydroxypropyl)-[[3-(1,1,2,2-tetrafluoroethoxy) phenyl]methyl]amino]benzamide are prepared by one skilled in the art using similar methods, as shown in Example Table 21.

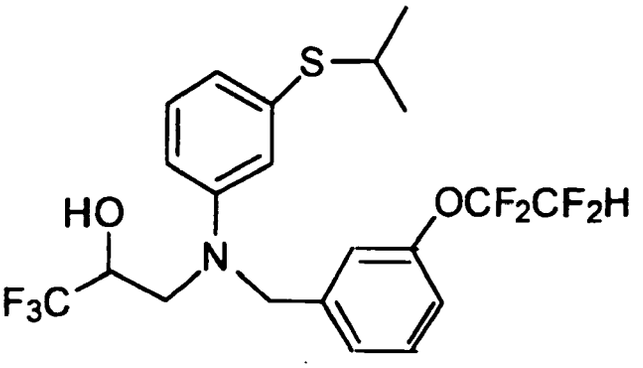
Example Table 21. *N,N*-disubstituted-3-[(3,3,3-trifluoro-2-hydroxypropyl)[[3-(1,1,2,2-tetrafluoroethoxy)phenyl] methyl]amino]benzamide



Ex. No.	R_{SUB}	R'_{SUB}	Calculated Mass $[M+H]^+$	Observed Mass $[M+H]^+$
457	H	isopropyl	497.1675	497.1697
458	H	n-butyl	511.1832	511.1809
459	H	cyclohexyl	537.1988	537.1969
460	H	*tert*-butyl	511.1832	511.1845
461	H	cyclopentyl	523.1832	523.1854
462	H	neo-pentyl	525.1988	525.2028
463	H	2,2,2-trifluoroethyl	537.1236	537.1250
464	H	2,2,3,3,4,4,4-heptafluorobutyl	637.1172	637.1177
465	H	phenylmethyl	545.1675	545.1705
466	H	(3-trifluoromethoxy)-phenylmethyl	629.1498	629.1510
467	H	4-(fluorophenyl)methyl	563.1581	563.1611
468	methyl	phenyl	545.1675	545.1631
469	methyl	phenylmethyl	559.1832	559.1853
470	$-CH_2CH_2N(CH_3)CH_2CH_2-$		538.1941	538.1969
471	$-CH_2CH_2OCH_2CH_2-$		525.1624	525.1615
472	$-CH_2CH_2CH_2CH_2-$		509.1675	509.1675

EXAMPLE 473

[0231]



3-[[3-[(1-methylethyl)thio]phenyl][[3-(1,1,2,2-tetrafluoroethoxy) phenyl]-methyl]amino]-1,1,1-trifluoro-2-propanol

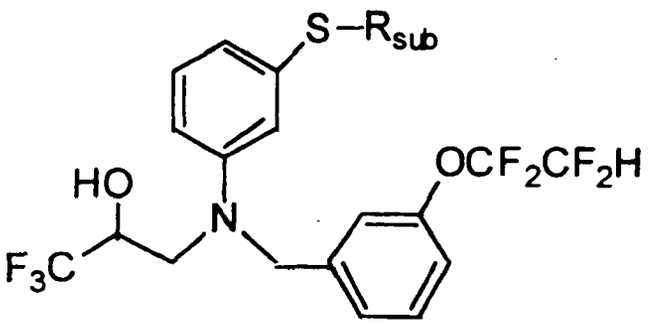
[0232] **EX-473A)** 3-Aminobenzenethiol (2.4 mL, 22.5 mmol) and 3-(1,1,2,2-tetrafluoro-ethoxy)benzaldehyde (5 g, 22.5 mmol) were dissolved in 40 mL of dichloroethane and acetic acid (1.35 mL, 23.7 mmol), then solid $NaBH(OAc)_3$ (6.2 g, 29.3 mmol) was added. The mixture was stirred at room temperature for 18 hours, then quenched with water and diluted with dichloromethane. The organic layer was washed with aqueous saturated sodium bicarbonate, then dried over $MgSO_4$, and concentrated *in vacuo.* The crude product was purified by flash column chromatography on silica gel eluting with ethyl acetate:hexane 1:10 to give 5.36 g (72%) of the desired 3-[[[3-(1,1,2,2-tetrafluoroethoxy) phenyl]methyl] amino]benzenethiol product as a brown oil. ^1H NMR ($CDCl_3$) δ 3.4 (s, 1H), 4.4 (s, 2H), 5.9 (tt, 1H), 6.4 (dd, 1H), 6.55 (m, 1H), 6.65 (d, 1H), 7.05 (t, 1H), 7.2-7.4 (m, 4H).

[0233] **EX-473B)** The **EX-473A** benzenethiol amine (5.36 g, 16.2 mmol) and 1,1,1-trifluoro-2,3-epoxypropane (1 g, 1.6 mmol) were dissolved in 20 mL of acetonitrile. Ytterbium (III) trifluoromethanesulfonate (1 g, 1.6 mmol) was added, and the stirred solution was warmed to 50 ˚C for 48 hours, at which time HPLC analysis indicated that no secondary amine starting material remained. The reaction was quenched with water and extracted with ether. The ether layer was washed with brine, then dried over $MgSO_4$, and concentrated *in vacuo.* The crude product was purified by flash column chromatography on silica gel eluting with ethyl acetate:hexane 1:10 to give 4.5 g (63%) of the desired 3-[[[3-(1,1,2,2-tetrafluoroethoxy)phenyl]methyl](3,3,3-trifluoro-2-hydroxypropyl)amino] benzenethiol product as a yellow oil. ^1H NMR ($CDCl_3$) δ 3.0 (s, 1H), 3.6 (dd, 1H), 3.9 (dd, 1H), 4.2 (m, 1H), 4.7 (m, 2H), 5.9 (tt, 1H), 6.5 (dd. 1H), 6.7 (m, 2H), 7.1 (m, 4H), 7.4 (t, 1H). HRMS calcd. for $C_{36}H_{31}F_{14}N_2O_4S_2$: 885.1502 $[2(M-1)+H]^+$, found: 885.1471.

[0234] The **EX-473B** thiol product (150 mg, 0.34 mmol) and 2-iodopropane (37 μL, 0.37 mmol) were dissolved in 2 mL of acetonitrile. Cesium carbonate (144 mg, 0.44 mmol) was added, and the stirred solution was warmed to 55 ˚C for 18 hours, at which time HPLC analysis indicated that no thiol/disulfide starting material remained. The reaction was quenched with water and filtered through pre-wetted celite eluting with ethyl acetate. The solvent was evaporated, and the residue was purified by reverse phase HPLC eluting with 10% to 90% acetonitrile in water to afford 69 mg (42%) of the desired 3-[[3-[(1-methylethyl)thiolphenyl][[3-(1,1,2,2-tetrafluoroethoxy)phenyl]-methyl]amino]-1,1,1-trifluoro-2-propanol product as a yellow oil, which was greater than 98% pure by reverse phase HPLC analysis. HRMS calcd. for $C_{21}H_{23}F_7NO_2S$: 486.1338 $[M+H]^+$, found: 486.1351. ^1H NMR ($CDCl_3$) δ 1.2 (t, 3H), 3.3 (q, 1H), 3.6 (dd, 1H), 3.9 (dd, 1H), 4.3 (m, 1H), 4.7 (m, 3H), 5.9 (tt, 1H), 6.7 (dd, 1H), 6.9 (m, 2H), 7.0-7.2 (m, 4H), 7.3 (t, 1H).

[0235] Additional examples of 3-[[3-(alkanoyl-, aryl-, heteroaryl-, and aralkylthio) phenyl][[3-(1,1,2,2-tetrafluoroethoxy) phenyl]methyl]amino]-1,1,1-trifluoro-2-propanols are prepared by one skilled in the art using similar methods, as shown in Example Table 22.

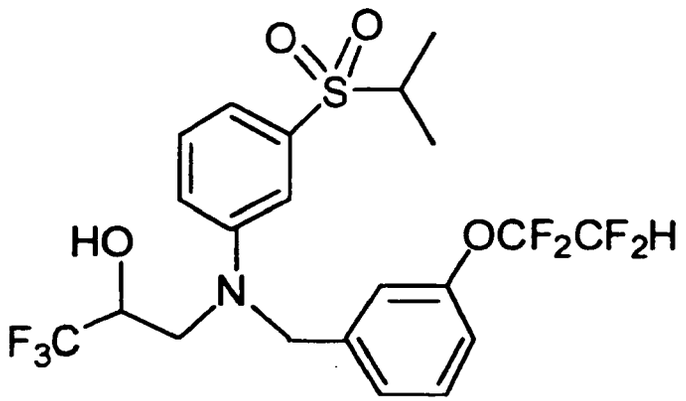
Example Table 22. 3-[[3-(alkanoyl-, aryl-, heteroaryl-, and aralkylthio)phenyl][[3-(1,1,2,2-tetrafluoro-ethoxy)phenyl] methyl]amino]-1,1,1-trifl uoro-2-propanols.



Ex. No.	R_{SUB}	Calculated Mass $[M+H]^+$	Observed Mass $[M+H]^+$
474	4-pyridyl	521.1134	521.1115
475	4-nitrophenyl	565.1032	565.1034
476	4-piperidyl	527.1603	527.1597
477	2-pyridylmethyl	535.1290	535.1291
478	4-acetylphenyl	562.1287	562.1261
479	4-(methylsulfonyl)phenyl	598.0957	598.0946
480	(4-chloro-thien-2-yl) methyl	574.0512	574.0523
481	acetyl	486.0974	486.0936

EXAMPLE 482

[0236]



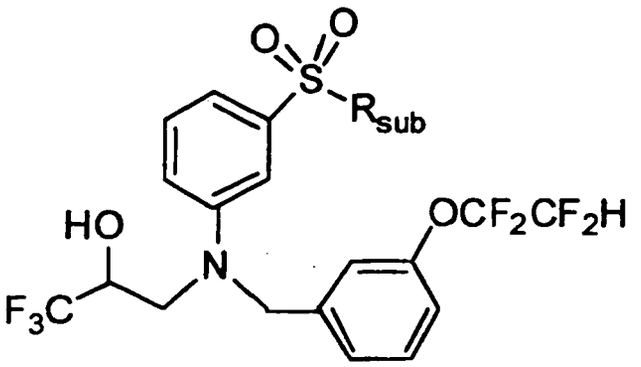
3-[[3-[(1-methylethyl)sulfonyl]phenyl][[3-(1,1,2,2-tetrafluoroethoxy)-phenyl]methyl] amino]-1,1,1-trifluoro-2-propanol

[0237] To a solution of 3-[[3-[(1-methylethyl)thio]phenyl][[3-(1,1,2,2-tetrafluoroethoxy)-phenyl]methyl]amino]-1,1,1-trifluoro-2-propanol (58 mg. 0.12 mmol) in 2 mL of trifluoroacetic acid, was added 30% aqueous H_2O_2 (28 μL, 0.25 mmol). The mixture was stirred at room temperature for 18 hours, then quenched with 5% aqueous sodium hydroxide and extracted with ether. The organic layer was concentrated *in vacuo.* The crude product was purified by reverse phase HPLC eluting with 10% to 90% acetonitrile in water to give 29.5 mg (48%) of the desired sulfone product as a brown oil, which was greater than 98% pure by reverse phase HPLC analysis. HRMS calcd. for $C_{21}H_{23}F_7NO_4S$: 518.1236 $[M+H]^+$,

found: 518.1226. ^{1}H NMR ($COCl_3$) δ 1.1 (d, 6H), 3 (q, 1H), 3.7 (dd, 1H), 3.9 (dd, 1H), 4.3 (m, 1H), 4.7 (s, 1H), 5.9 (tt, 1H), 7 (m, 2H), 7.1-7.2 (m, 4H), 7.3 (m, 2H).

[0238] Additional examples of 3-[(3-(aryl-, heteroaralkyl-, and heterocyclylsulfonyl) phenyl][[3-(1,1,2,2-tetra-fluoroethoxy)phenyl]methyl]amino]-1,1,1-trifluoro-2-propanols are prepared by one skilled in the art using similar methods, as shown in Example Table 23.

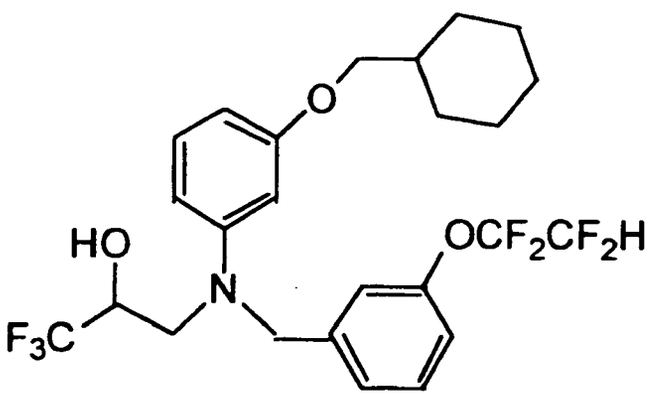
Example Table 23. 3-[(3-(aryl-, heteroaralkyl-, and heterocyclylsulfonyl)phenyl][[3-(1,1,2,2-tetrafluoroethoxy)phenyl] methyl]amino]-1,1,1-trifluoro-2-propanols.



Ex. No.	R_{SUB}	Calculated Mass $[M+H]^+$	Observed Mass $[M+H]^+$
483	4-nitrophenyl	597.0930	597.0925
484	4-piperidyl	559.1502	559.1526
485	3-(pyridyl-*N*-oxide)methyl	583.1138	583.1137
486	4-acetylphenyl	594.1185	594.1181
487	4-(methylsulfonyl)phenyl	630.0855	630.0826

EXAMPLE 488

[0239]



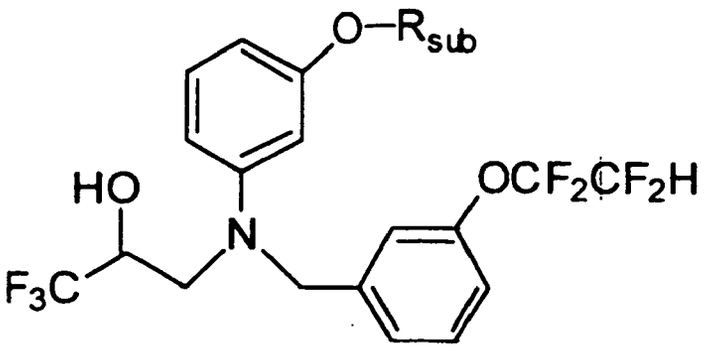
3-[[3-(cyclohexylmethoxy)phenyl][(3-(1,1,2,2-tetrafluoroethoxy) phenyl]-methyl] amino]-1,1,1-trifluoro-2-propanol

[0240] 3-[[[3-(1,1,2,2-tetrafluoroethoxy)phenyl]methyl](1,1,1-trifluoro-2-hydroxypropyl)-amino]phenol (100 mg, 0.23 mmol) and bromomethylcyclohexane (42μ L, 0.30 mmol) were dissolved in 2 mL of acetonitrile. Cesium carbonate (144 mg, 0.44 mmol) was added, and the stirred solution was warmed to 50˚C for 48 hours, at which time HPLC analysis

indicated that no phenolic starting material remained. The reaction was quenched with water and filtered through pre-wetted celite eluting with ethyl acetate. The solvent was evaporated and the residue was purified by reverse phase HPLC eluting with 10% to 90% acetonitrile in water to afford 55 mg (35%) of the desired ether product as a brown oil, which was greater than 99% pure by reverse phase HPLC analysis. HRMS calcd. for $C_{25}H_{29}F_7NO_3$: 524.2036 $[M+H]^+$, found: 524.2028. ^1H NMR ($CDCl_3$) δ 0.9-1.4 (m, 5H), 1.7-1.9 (m, 6H), 3.6 (m, 3H), 3.9 (dd, 1H), 4.3 (m, 1H), 4.7 (m, 2H), 5.1 (s, 1H), 5.9 (tt, 1H), 6.5 (m, 3H), 7.0-7.4 (m, 5H).

[0241] Additional examples of 3-[(3-alkoxy- and cycloalkoxy-phenyl)[[3-(1,1,2,2-tetrafluoroethoxy)phenyl]methyl] amino]-1,1,1-trifluoro-2-propanols are prepared by one skilled in the art using similar methods, as shown in Example Table 24.

Example Table 24. 3-[(3-alkoxy- and cycloalkoxy-phenyl)[[3-(1,1,2,2-tetrafluoroethoxy)phenyl]methyl]amino]-1,1,1-trifluoro-2-propanols.



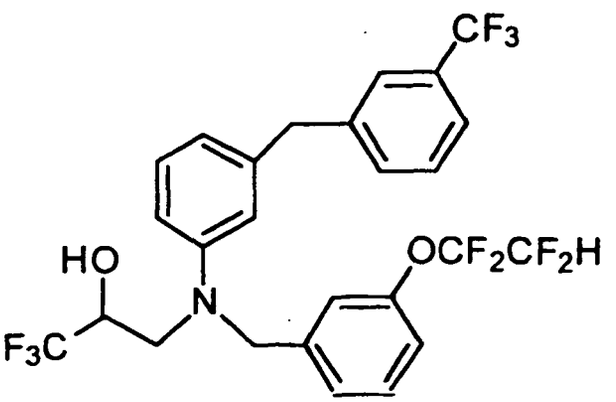
Ex. No.	R_{SUB}	Calculated Mass $[M+H]^+$	Observed Mass $[M+H]^+$
489	isopropyl	470.1488	470.1565
490	(methoxycarbonyl)methyl	500.1308	500.1297
491	cyanomethyl	467.1206	467.1228
492	2-methylpropyl	484.1723	484.1718
493	2-oxobutyl	498.1515	498.1529
494	cyclohexyl	510.1880	510.1910
495	5-oxohexyl	526.1828	526.1827
496	4-(methoxycarbonyl) butyl	542.1777	542.1827
497	2-(phenylsulphonyl)ethyl	596.1342	596.1349
498	2-pyrrolidinylethyl	525.1988	525.2008
499	3-(methoxycarbonyl)-2-propenyl	526.1464	526.1482
500	carbamoylmethyl	485.1311	485.1304
501	3-cyanopropyl	495.1519	495.1541
502	1-(*N*-phenylcarbamoyl) ethyl	575.1780	575.1778
503	2-oxo-2-phenylethyl	546.1515	546.1543
504	3-hydroxypropyl	486.1515	484.1481
505	2-methoxyethyl	486.1515	486.1537
506	neo-pentyl	498.1879	498.1845
507	4-tetrahydropyranyl	512.1672	512.1631
508	1-ethoxycarbonylbutyl	556.1934	556.1948

(continued)

Ex. No.	R_{SUB}	Calculated Mass $[M+H]^+$	Observed Mass $[M+H]^+$
509	cyclopentyl	496.1723	496.1719
510	3-methyl-2-butenyl	496.1722	496.1675
511	2-(*N,N*-dimethylamino) ethyl	499.1831	499.1826
512	3-hydroxy-2,2-dimethylpropyl	514.1828	514.1814
513	3,3-dimethyl-2-oxobutyl	526.1828	526.1806

EXAMPLE 514

[0242]



3-[[[3-(1,1,2,2-tetrafluoroethoxy)phenyl]methyl][3-[[(3-trifluoromethyl)-phenyl]methyl]phenyl]amino]-1,1,1-trifluoro-2-propanol

[0243] **EX-514A)** To a solution of (3-nitrobenzene)methanol (10 g, 65.3 mmol) in 50 mL of 5% aqueous sodium hydroxide, was added dimethylsulfate (20 g, 156 mmol). The mixture was stirred at 70 ˚C for 18 hours, then diluted with water and ethyl acetate. The organic layer was washed with water, then dried over $MgSO_4$, and concentrated *in vacuo.* The crude product was purified by flash column chromatography on silica gel eluting with ethyl acetate:hexane 1:5 to give 4.73 g (43%) of the desired 3-(methoxy-methyl)nitrobenzene product as a yellow oil. ^1H NMR ($CDCl_3$) δ 3.5 (s, 3H), 4.5 (s, 2H), 6.5 (t, 1H), 7.7 (d, 1H), 8.1 (d, 1H), 8.2 (s, 1H).

[0244] **EX-514B)** The 3-(methoxymethyl)nitrobenzene (4.18 g, 25 mmol) from **EX-514A** was dissolved in 160 mL of acetic acid. Zinc dust (5 g, 76.5 mmol) was added, and the solution was stirred at room temperature for 18 hours, at which time HPLC analysis indicated that no 3-(methoxymethyl)nitrobenzene starting material remained. The reaction mixture was filtered through celite and concentrated *in vacuo.* The residue was dissolved in ethyl acetate and washed with aqueous saturated sodium bicarbonate. The organic layer was washed with water, then dried over $MgSO_4$, and concentrated *in vacuo* to give 3.4 g (99%) of the desired 3-(methoxymethyl)aniline as a brown oil. The crude product was used without further purification. HRMS calcd. for $C_8H_{12}NO$: 138.0919 $[M+H]^+$, found: 138.0929. ^1H NMR ($COCl_3$) δ 3.4 (s, 3H), 3.7 (s, 2H), 4.4 (s, 2H), 6.6 (d, 1H), 6.7 (m, 2H), 7.2 (t, 1H).

[0245] **EX-514C)** The 3-(methoxymethyl)aniline (1.85 g, 13.51 mmol) product from **EX-514B** and 3-(1,1,2,2-tetrafluoroethoxy)benzaldehyde (3 g, 13.5 mmol) were dissolved in 25 mL of dichloroethane and acetic acid (0.85 mL, 14.8 mmol), then solid $NaBH(OAc)_3$ (3.73 g, 17.6 mmol) was added. The mixture was stirred at room temperature for 48 hours, then quenched with aqueous saturated sodium bicarbonate and diluted with ethyl acetate. The organic layer was washed with brine, then dried over $MgSO_4$, and concentrated *in vacuo* to give 4.27 g (12.4 mmol) of crude product. The crude product and 1,1,1-trifluoro-2,3-epoxypropane (1.2 mL, 13.7 mmol) were dissolved in 20 mL of acetonitrile. Ytterbium (III) trifluoromethanesulfonate (0.77 g, 1.24 mmol) was added, and the stirred solution was warmed to 50 ˚C for 18 hours. The reaction was quenched with water and extracted with ethyl acetate. The organic layer was washed with brine, then

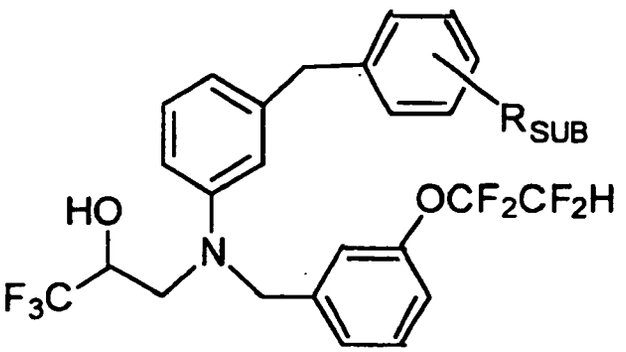
dried over $MgSO_4$, and concentrated *in vacuo* to give 5.96 g (97%) of the desired 3-[[3-(methoxymethyl)phenyl][[3-(1,1,2,2-tetrafluoroethoxy)-phenyl]methyl] amino]-1,1,1-trifluoro-2-propanol product as a brown oil. The crude product was greater than 95% pure by reverse phase HPLC analysis and was used without further purification. HRMS calcd. for $C_{20}H_{21}F_7NO_3$: 456.1410 $[M+H]^+$, found: 456.1409. ^1H NMR ($CDCl_3$) δ 3.3 (s, 3H), 3.6 (dd, 1H), 3.9 (dd, 1H), 4.3 (m, 1H), 4.4 (s, 2H), 4.7 (m, 2H), 5.9 (tt, 1H), 6.6-6.8 (m, 3H), 7.1-7.2 (m, 4H), 7.3 (t, 1H).

[0246] **EX-514D)** The 3-[[3-(methoxymethyl)phenyl][13-(1,1,2,2-tetrafluoroethoxy) phenyl]-methyl]amino]-1,1,1-trifluoro-2-propanol from **EX-514C** (1 g, 2.2 mmol) was dissolved in 10 mL of dichloromethane. The solution was cooled to -50 ˚C and a 1 M solution of BBr_3 in dichloromethane (2.3 mL, 2.3 mmol) was added. The solution was stirred at -50˚C for 1 hour and warmed to room temperature over 1 hour, at which time HPLC analysis indicated that no methyl ether starting material remained. The reaction mixture was quenched with aqueous saturated sodium bicarbonate and diluted in dichloromethane. The organic layer was washed with brine, then dried over $MgSO_4$, and concentrated *in vacuo.* The crude product was purified by flash column chromatography on silica gel eluting with ethyl acetate:hexane 1:7 to give 0.65 g (59%) of the desired 3-[[3-(bromomethyl)phenyl][[3-(1,1,2,2-tetrafluoroethoxy)-phenyl]methyl] amino]-1,1,1-trifluoro-2-propanol product as a brown oil. HRMS calcd. for $C_{19}H_{18}BrF_7NO_2$: 504.0409 $[M+H]^+$, found: 504.0361. ^1H NMR ($CDCl_3$) δ 3.3 (s, 1H), 3.6 (dd, 1H), 3.9 (dd, 1H), 4.3 (m, 1H), 4.4 (s, 2H), 4.8 (m, 2H), 5.9 (tt, 1H), 6.7 (d, 1H), 6.8-6.9 (m, 2H), 7.1-7.3 (m, 4H). 7.4 (t, 1H).

[0247] The 3-[[3-(bromomethyl)phenyl][[3-(1,1,2,2-tetrafluoroethoxy)phenyl]methyl] amino]-1,1,1-trifluoro-2-propanol from **EX-514D** (0.1 g, 0.19 mmol) and 3-trifluoromethyl-benzeneboronic acid (47.5 mg. 0.25 mmol) were dissolved in 2 mL of toluene and 0.2 mL of 2 M aqueous sodium carbonate. $Pd(PPh_3)_4$ was added, and the solution was stirred at 105˚C for 2.5 hours, at which time HPLC analysis indicated that no bromomethyl starting material remained. The reaction mixture was filtered through celite and concentrated *in vacuo.* The residue was quenched with water and filtered through pre-wetted celite eluting with ethyl acetate. The solvent was evaporated, and the residue was purified by reverse phase HPLC eluting with 10% to 90% acetonitrile in water to afford 16.7 mg (15%) of the desired 3-[[[3-(1,1,2,2-tetrafluoroethoxy) phenyl]methyl]-[3-[(3-trifluoromethyl)phenyl]methyl]phenyl]-amino]-1,1,1-trifluoro-2-propanol product as a brown oil. HRMS calcd. for $C_{26}H_{22}F_{10}NO_2$: 570.1413 $[M+H]^+$, found: 570.1480. ^1H NMR ($CDCl_3$) δ 3.8 (m, 2H), 4.0 (s, 2H), 4.3 (m, 1H), 4.5 (d, 1H), 4.8 (d, 1H), 5.9 (tt, 1H), 6.6-6.8 (m, 4H), 6.9-7.1 (m, 3H), 7.2-7.5 (m, 5H).

[0248] Additional examples of 3-[[[3-(1,1,2,2-tetrafluoroethoxy)phenyl]methyl] [3-(aryl)methyl]phenylamino]-1,1,1-trifluoro-2-propanols are prepared by one skilled in the art using similar methods, as shown in Example Table 25.

Example Table 25. 3-[[[3-(1,1,2,2-tetrafluoroethoxy)phenyl]methyl]-[3-(aryl)methyl]phenytamino]-1,1,1-trifluoro-2-propanols.



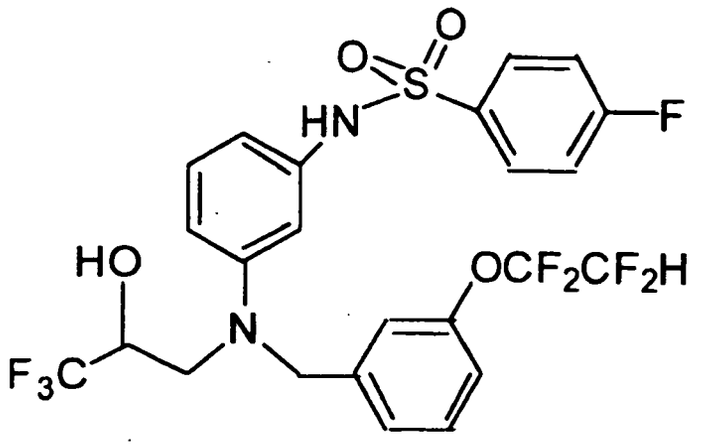
Example Number	R_{SUB}	Calculated Mass $[M+H]^+$	Observed Mass $[M+H]^+$
515	H	502.1617	502.1609
516	3-nitro	547.1468	547.1449
517	4-methyl	516.1774	516.1769
518	3,5-dichloro	570.0838	570.0801
519	4-fluoro	520.1523	520.1505
520	4-*tert*-butyl	558.2243	558.2236
521	3-methyl-4-fluoro	534.1679	534.1688

(continued)

Example Number	R_{SUB}	Calculated Mass $[M+H]^+$	Observed Mass $[M+H]^+$
522	3-methyl-4-chloro	550.1384	550.1380
523	3,4-dimethyl	530.1930	530.1887
524	3-chloro, 4-fluoro	554.1133	554.1108
525	3-chloro	536.1227	536.1218
526	4-methylthio	548.1494	548.1503
527	3-methoxy	532.1723	532.1705

EXAMPLE 528

[0249]



4-fluoro-*N*-[3-[[[3-(1,1,2,2-tetrafluoroethoxy)phenyl]methyl] (3,3,3-trifluoro-2-hydroxypropyl)amino]phenyl] benzenesulfonamide

[0250] **EX-528A)** 3-nitroaniline (1.87 g, 13.51 mmol) and 3-(1,1,2,2-tetrafluoroethoxy)-benzaldehyde (3 g, 13.5 mmol) were dissolved in 25 mL of dichloroethane and acetic acid (0.85 mL, 14.9 mmol), then solid $NaBH(OAc)_3$ (3.73 g, 17.6 mmol) was added. The mixture was stirred at room temperature for 48 hours, then quenched with aqueous saturated sodium bicarbonate and diluted with ethyl acetate. The organic layer was dried over $MgSO_4$, and concentrated *in vacuo.* The crude product was purified by flash column chromatography on silica gel eluting with ethyl acetate:hexane 1:7 to give 3.25 g (70%) of the desired *N*-(3-nitrophenyl)-3-(1,1,2,2-tetrafluoroethoxy) benzenemethan-amine product as a brown oil. HRMS calcd. for $C_{15}H_{13}F_4N_2O_3$: 345.0862 $[M+H]^+$, found: 345.0864. ^1H NMR ($CDCl_3$) δ 4.4 (s, 2H), 4.5 (s, 1H), 5.9 (tt, 1H), 6.9 (d, 1H), 7.1 (d, 1H), 7.2-7.3 (m, 3H), 7.4 (m, 2H), 7.5 (d, 1H).

[0251] **EX-528B)** *N*-(3-nitrophenyl)-3-(1,1,2,2-tetrafluoroethoxy) benzenemethanamine (3.25 g, 9.44 mmol) from **EX-528A** and 1,1,1-trifluoro-2,3-epoxypropane (0.895 mL, 10.4 mmol) were dissolved in 15 mL of acetonitrile. Ytterbium (III) trifluoromethane-sulfonate (0.77 g, 1.24 mmol) was added, and the stirred solution was warmed to 55 ˚C for 48 hours. The reaction was quenched with water and extracted with ethyl acetate. The organic layer was dried over $MgSO_4$, and concentrated *in vacuo.* The crude product was purified by flash column chromatography on silica gel eluting with ethyl acetate:hexane 1:10 to give 1.93 g (45%) of the desired 3-[(3-nitrophenyl)[[3-(1,1,2,2-tetrafluoroethoxy)phenyl] methyl]amino]-1,1,1-trifluoro-2-propanol product as a brown oil. HRMS calcd. for $C_{18}H_{16}F_7N_2O_4$: 457.0998 $[M+H]^+$, found: 457.1008. ^1H NMR($CDCl_3$) δ 3.7 (dd, 1H), 3.9 (dd, 1H), 4.4 (m, 1H), 4.8 (m, 2H), 5.9 (tt, 1H), 7.0-7.2 (m, 4H), 7.3-7.4 (m, 2H), 7.6 (m, 2H).

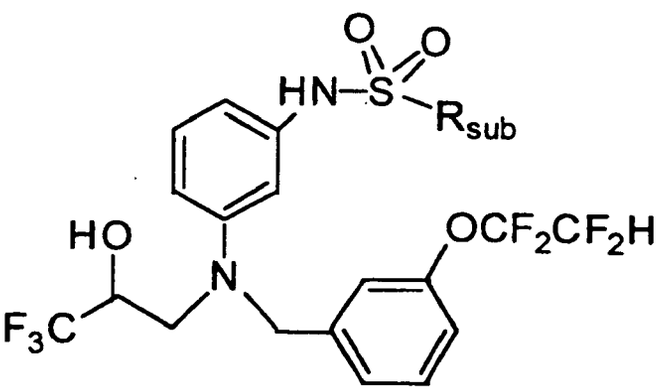
[0252] **EX-528C)** The 3-[(3-nitrophenyl)[[3-(1,1,2,2-tetrafluoroethoxy)phenyl] methyl]amino]-1,1,1-trifluoro-2-propanol (1.93 g, 4.2 mmol) from **EX-528B)** was dissolved in 60 mL of acetic acid. Zinc dust (2.1 g, 31.5 mmol) was added, and the solution was stirred at room temperature for 18 hours, at which time HPLC analysis indicated that no nitro starting material remained. The reaction mixture was filtered through celite and concentrated *in vacuo.* The residue was dissolved in ethyl acetate and washed with aqueous saturated sodium bicarbonate. The organic layer was washed with brine,

then dried over $MgSO_4$, and concentrated *in vacuo* to give 1.4 g (78%) of the desired 3-[(3-aminophenyl)[[3-(1,1,2,2-tetrafluoroethoxy)phenyl]methyl]amino]-1,1,1-trifluoro-2-propanol product as a red oil. The crude product was used without further purification. HRMS calcd. for $C_{18}H_{18}F_7N_2O_2$: 427.1256 $[M+H]^+$, found: 427.1251. ^1H NMR ($CDCl_3$) δ 3.4-3.7 (m, 4H), 3.8 (dd, 1H), 4.3 (m, 1H), 4.8 (m, 2H), 5.9 (tt, 1H), 6.1 (s, 1H), 6.2 (m, 2H), 7.0-7.2 (m, 4H), 7.3 (t, 1H).

[0253] The 3-[(3-aminophenyl)[[3-(1,1,2,2-tetrafluoroethoxy)phenyl]methyl]amino]-1,1,1-trifluoro-2-propanol from **EX-528C** (50 mg, 0.12 mmol) was dissolved in 1 mL of dichloromethane. Triethylamine (25 μL, 0.18 mmol) followed by 4-fluorobenzene-sulfonyl chloride were added. The solution was stirred at room temperature for 5 hours, at which time HPLC analysis indicated that no free amine starting material remained. The reaction was quenched with water and filtered through pre-wetted celite eluting with ethyl acetate. The solvent was evaporated, and the residue was purified by reverse phase HPLC eluting with 10% to 90% acetonitrile in water to afford 20.1 mg (29%) of the desired 4-fluoro-*N*-[3-[[[3-(1,1,2,2-tetrafluoroethoxy)phenyl]methyl]-(3,3,3-trifluoro-2-hydroxypropyl)amino]phenyl]benzenesulfonamide product as a yellow oil, which was greater than 98% pure by reverse phase HPLC analysis. HRMS calcd. for $C_{24}H_{21}F_8N_2O_4S$: 585.1094 $[M+H]^+$, found: 585.1083. ^1H NMR ($CDCl_3$) δ 3.6 (m, 2H), 3.8 (dd, 1H), 4.3 (m, 1H), 4.6 (s, 2H), 5.9 (tt, 1H), 6.4 (d, 1H), 6.5-6.6 (m, 3H), 6.9-7.4 (m, 7H), 7.6 (m, 1H).

[0254] Additional examples of *N*-[3-[[[3-(1,1,2,2-tetrafluoroethoxy)phenyl]methyl]-(3,3,-trifluoro-2-hydroxypropyl)amino]phenyl]aryl or alkylsulfonamide are prepared by one skilled in the art using similar methods, as shown in Example Table 26.

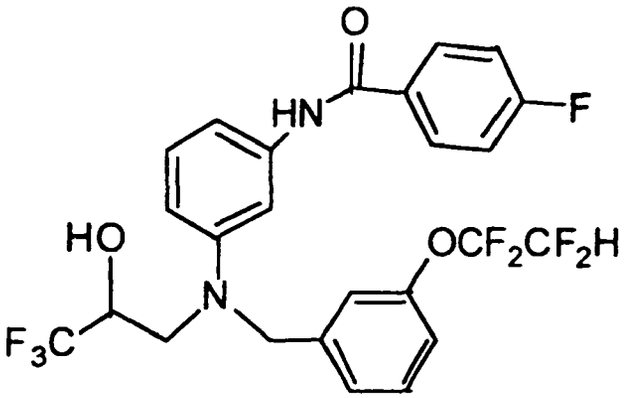
Example Table 26. *N*-(3-[[[3-(1,1,2,2-tetrafluoroethoxy)phenyl]methyl]-(3,3,3-trifluoro-2-hydroxypropyl)amino] phenyl]aryl or alkylsulfonamides.



Example Number	R_{SUB}	Calculated Mass $[M+H]^+$	Observed Mass $[M+H]^+$
529	phenyl	567.1189	567.1198
530	3-methylphenyl	581.1345	581.1327
531	3-trifluoromethylphenyl	635.1062	635.1066
532	3-nitrophenyl	612.1039	612.1011
533	3-chloro-4-fluorophenyl	619.0705	619.0711
534	isopropyl	533.1345	533.1359

EXAMPLE 535

[0255]

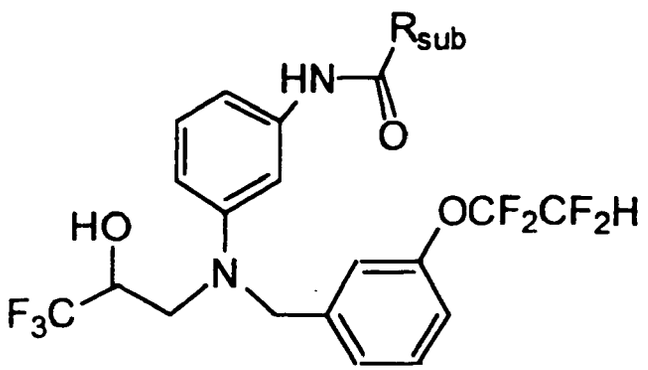


4-fluoro-*N*-[3-[[[3-(1,1,2,2-tetrafluoroethoxy)phenyl]methyl] (3,3,3-trifluoro-2-hydroxypropyl)amino]phenyl] benzamide

[0256] 3-[(3-aminophenyl)[[3-(1,1,2,2-tetrafluoroethoxy)phenyl]methyl]amino]-1,1,1-trifluoro -2-propanol (50 mg, 0.12 mmol) was dissolved in 1 mL of dichloromethane. Triethylamine (25 μL, 0.18 mmol) followed by 4-fluorobenzoyl chloride were added. The solution was stirred at room temperature for 5 hours, at which time HPLC analysis indicated that no starting material remained. The reaction was quenched with water and filtered through pre-wetted celite eluting with ethyl acetate. The solvent was evaporated, and the residue was purified by reverse phase HPLC eluting with 10% to 90% acetonitrile in water to afford 15 mg (23%) of the desired 4-fluoro-*N*-[3-[[[3-(1,1,2,2-tetrafluoroethoxy)phenyl]methyl] (3,3,3-trifluoro-2-hydroxypropyl)amino]-phenyl]benzamide product as a yellow oil, which was greater than 98% pure by reverse phase HPLC analysis. HRMS calcd. for $C_{25}H_{21}F_8N_2O_3$: 549.1424 $[M+H]^+$, found: 549.1436. ^1H NMR ($CDCl_3$) δ 3.6 (dd, 1H), 3.8 (dd, 1H), 4.4 (m, 1H), 4.6 (s, 2H), 5.9 (tt, 1H), 6.6 (d, 1H), 6.8 (d, 1H), 7.0-7.4 (m, 7H), 7.8 (m, 3H).

[0257] Additional examples of *N*-[3-[[[3-(1,1,2,2-tetrafluoroethoxy)phenyl] methyl]-(3,3,3-trifluoro-2-hydroxypropyl) amino]phenyl]carboxamides are prepared by one skilled in the art using similar methods, as shown in Example Table 27.

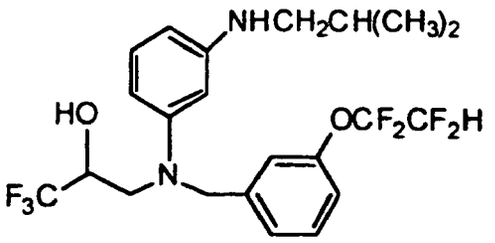
Example Table 27. *N*-[3-[[[3-(1,1,2,2-tetrafluoroethoxy)phenyl]methyl]-(3,3,3-trifluoro-2-hydroxypropyl)amino] phenyl]carboxamides.



Example Number	R_{SUB}	Calculated Mass $[M+H]^+$	Observed Mass $[M+H]^+$
536	phenyl	531.1589	531.1538
537	3-methoxylphenyl	561.1624	561.1625
538	isobutoxy	527.1781	527.1768
539	3-pyridyl	532.1471	532.1458
540	isopropyl	497.1675	497.1701

EXAMPLE 541

[0258]

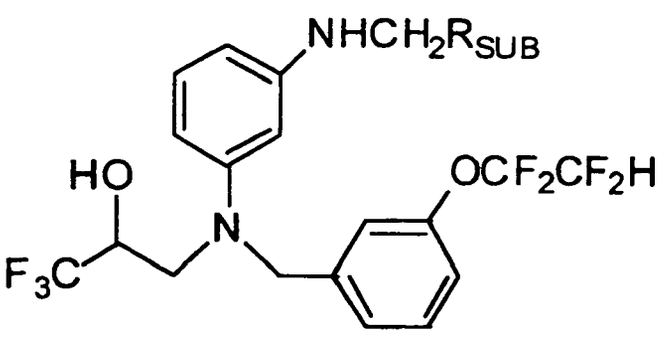


3-[[3-[(2-methylpropyl)amino]phenyl][[3-(1,1,2,2-tetrafluoroethoxy)-phenyl]-methyl]amino]-1,1,1-trifluoro-2-propanol

[0259] The 3-[(3-aminophenyl)[[3-(1,1,2,2-tetrafluoroethoxy)phenyl]methyl]amino]-1,1,1-trifluoro-2-propanol (50 mg, 0.12 mmol) was dissolved in 1 mL of dichloroethane. Acetic acid (8 μL, 0.14 mmol) followed by isobutyraldehyde (11.7 μL, 0.13 mmol) and solid $NaBH(OAc)_3$ (37.3 mg, 0.18 mmol) were added. The solution was stirred at room temperature for 18 hours. The reaction was filtered through pre-wetted celite.eluting with ethyl acetate. The solvent was evaporated, and the residue was purified by reverse phase HPLC eluting with 10% to 90% acetonitrile in water to afford 16.1 mg (29%) of the desired 3-[[3-[(2-methylpropyl)amino]phenyl][[3-(1,1,2,2-tetrafluoroethoxy) phenyl]methyl] amino]-1,1,1-trifluoro-2-propanol product as a yellow oil, which was greater than 98% pure by reverse phase HPLC analysis. HRMS calcd. for $C_{22}H_{26}F_7N_2O_2$: 483.1883 $[M+H]^+$, found: 483.1932. ^1H NMR ($CDCl_3$) δ 1.0 (m, 6H), 2.0 (m, 1H), 3.0 (m, 2H), 3.6 (dd, 1H), 3.8 (dd, 1H), 4.3 (m, 1H), 4.6 (m, 2H), 5.9 (tt, 1H), 6.6 (d, 1H), 6.7 (d, 1H), 6.9-7.4 (m, 6H).

[0260] Additional examples of 3-[[3-(aralkylamino)phenyl][[3-(1,1,2,2-tetrafluoro-ethoxy)phenyl]methyl]amino]-1,1,1-trifluoro-2-propanols are prepared by one skilled in the art using similar methods, as shown in Example Table 28.

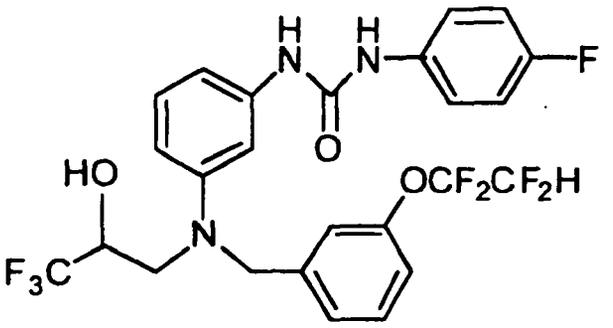
Example Table 28. 1,1,1-trifluoro-3-[[3-(aralkylamino)phenyl]-[(3-(1,1,2,2-tetrafluoroethoxy)phenyl)methyl]amino]-2-propanols.



Example Number	R_{SUB}	Calculated Mass $[M+H]^+$	Observed Mass $[M+H]^+$
542	phenyl	517.1726	517.1750
543	4-fluorophenyl	535.1632	535.1627
544	3-(OCF_2CF_2H)-phenyl	633.1611	633.1653

EXAMPLE 545

[0261]

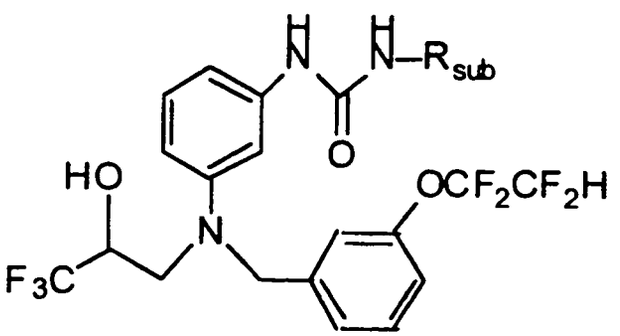


***N*-(4-fluorophenyl)-*N'*-(3-[[[3-(1,1,2,2-tetrafluoroethoxy)phenyl] methyl]-(3,3,3-trifluoro-2-hydroxypropyl)amino]phenyl)urea**

[0262] The 3-[(3-aminophenyl)[[3-(1,1,2,2-tetrafluoroethoxy)phenyl]methyl]amino]-1,1,1-trifluoro-2-propanol (50 mg, 0.12 mmol) was dissolved in 1 mL of dichloromethane. Triethylamine (20 μL, 0.14 mmol) followed by 4-fl uorophenyl isocyanate (14.6 μL, 0.13 mmol) were added. The solution was stirred at room temperature for 18 hours. The reaction was filtered through pre-wetted celite eluting with ethyl acetate. The solvent was evaporated, and the residue was purified by reverse phase HPLC eluting with 10% to 90% acetonitrile in water to afford 26 mg (40%) of the desired *N*-(4-fluorophenyl)-*N'*-[3-[[[3-(1,1,2,2-tetrafluoroethoxy)phenyl]methyl](3,3,3-trifluoro-2-hydroxypropyl)amino] phenyl]urea product as a yellow oil, which was greater than 95% pure by reverse phase HPLC analysis. HRMS calcd. for $C_{25}H_{22}F_8N_3O_3$: 564.1533 $[M+H]^+$, found: 564.1566. ^1H NMR ($CDCl_3$) δ 3.7 (m, 2H), 4.1 (m, 1H), 4.7 (m, 2H), 5.9 (tt, 1H), 6.6 (d, 1H), 6.9-7.4 (m, 11H), 7.5 (s, 1H), 7.8 (s, 1H).

[0263] Additional examples of *N*-substituted-*N'*-[3-[[[3-(1,1,2,2-tetrafluoroethoxy)-phenyl]methyl](3,3,3-trifluoro-2-hydroxypropyl)amino] phenyl]ureas are prepared by one skilled in the art using similar methods, as shown in Example Table 29.

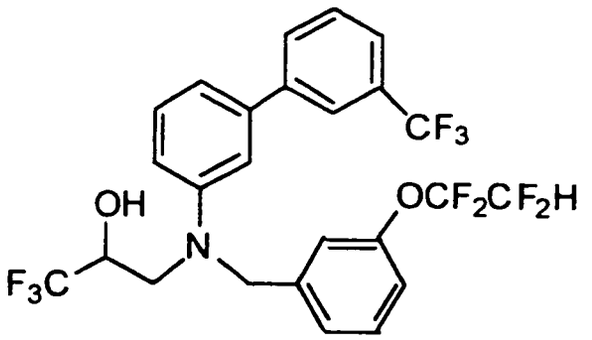
Example Table 29. *N*-substituted-*N'*-[3-[[[3-(1,1,2,2-tetrafluoroethoxy)phenyl]-methyl](3,3,3-trifluoro-2-hydroxypropyl)amino]phenyl]ureas.



Example Number	R_{SUB}	Calculated Mass $[M+H]^+$	Observed Mass $[M+H]^+$
546	phenyl	546.1628	546.1655
547	3-methoxyphenyl	576.1733	576.1773
548	3-trifluoromethylphenyl	614.1501	614.1518
549	isopropyl	512.1784	512.1801

EXAMPLE 550

[0264]

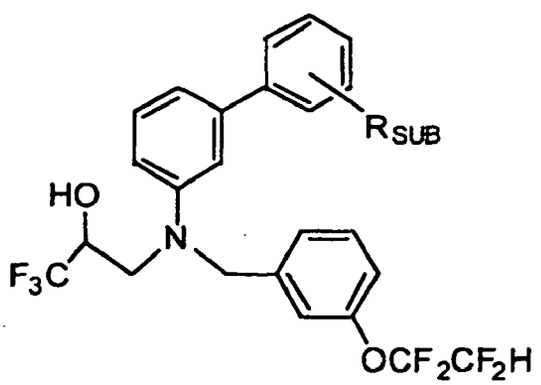


1,1,1-trifluoro-3-[[[3-(1,1,2,2-tetrafluoroethoxy)phenyl]methyl] [[3'-(trifluoromethyl)1,1'-biphenyl]-3-yl]amino]-2-propanol

[0265] 3-Trifluoromethylbenzene boronic acid (35.4 mg, 0.233 mmol) was dissolved in 640 mL of 2 M Na_2CO_3, and 630 mL of ethanol then 1.5 mL of a stock solution of 3-[(3-bromophenyl)[[3-(1,1,2,2-tetrafluoroethoxy)phenyl]methyl] amino]-1,1,1-trifluoro-2-propanol (0.105 M) and 10.9 mg/mL of $Pd(PPh_3)_4$ in toluene was added. After stirring at 105 ˚C for 5 hours, HPLC analysis indicated that the reaction had gone to completion. The reaction mixture was filtered through celite, evaporated, and the crude material purified by reverse phase HPLC eluting with 40% to 90% acetonitrile in water to afford 40.5 mg (44.7%) of the desired biphenyl aminopropanol product as an orange oil. HRMS calcd. for $C_{25}H_{19}F_{10}NO_2$: 556.1334 $[M+H]^+$, found: 556.1339. ^1H NMR ($CDCl_3$) δ 3.60-3.73 (m, 1H), 3.95 (dd, 1H), 4.36-4.44 (m, 1H), 4.76 (s, 2H), 5.87 (tt, 1H), 6.81 (dd, 1H), 6.95 (s, 1H), 7.03 (d, 1H), 7.05-7.20 (m, 3H), 7.26-7.40 (m, 2H), 7.46-7.73 (m, 4H).

[0266] Additional examples of 3-[[[3-(1,1,2,2-tetrafluoroethoxy)phenyl] methyl][[3-aryl]phenyl]amino]-1,1,1-trifluoro-2-propanols are prepared by one skilled in the art using similar methods, as shown in Example Table 30.

Example Table 30. 3-[[[3-(1,1,2,2-tetrafluoroethoxy)phenyl]methyl][[3-aryl]phenyl]amino]-1,1,1-trifluoro-2-propanols.



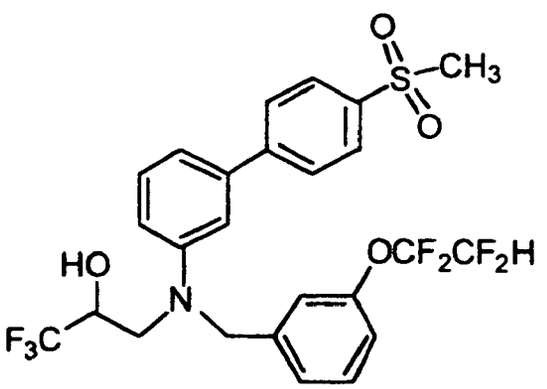
Example Number	R_{SUB}	Calculated Mass $[M+H]^+$	Observed Mass $[M+H]^+$
551	3,5-di(trifluoromethyl)	624.1208	624.1216
552	4-trifluoromethyl	556.1334	556.1355
553	4-methylthio	534.1337	534.1366
554	3-chloro-4-fluoro	540.0976	540.0957
555	3,5-dichloro-4-methoxy	586.0786	586.0818
556	3-nitro	533.131	533.1262
557	3,5-dichloro	556.0681	556.0612

(continued)

Example Number	R_{SUB}	Calculated Mass $[M+H]^+$	Observed Mass $[M+H]^+$
558	4-methoxy	518.1566	518.1533
559	3,4-difluoro	524.1272	524.1249
560	2,3,4-trifluoro	542.1177	542.1152
561	3,4-dichloro	556.0681	556.0698
562	3-methyl-4-methoxy	532.1722	532.1676
563	3,5-dimethyl-4-(*N,N*-dimethylamino)	559.2195	559.2182
564	H	488.1460	488.1457
565	4-chloro	522.1071	522.1049
566	4-methyl	502.1617	502.1613
567	2,4-dichloro	556.0681	556.0651
568	4-fluoro	506.1366	506.1336
569	4-fluoro-3-methyl	520.1523	520.1494
570	2-trifluoromethyl	556.1334	556.1286
571	3-methoxy	518.1566	518.1544
572	3-amino	503.1569	503.1593
573	4-carboxy	532.1358	532.1329
574	4-*tert*-butyl	544.2087	544.2090

EXAMPLE 575

[0267]



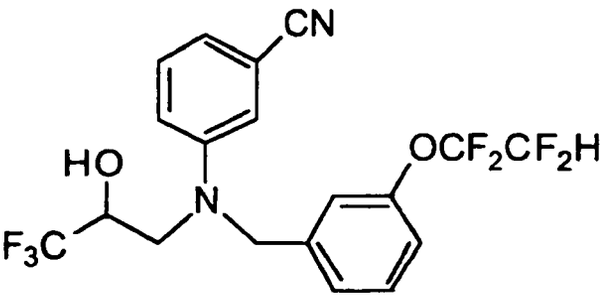
3-[[[4'-(methylsulfonyl)1,1'-biphenyl]-3-yl][[3-(1,1,2,2-tetrafluoroethoxy)phenyl]-methyl]amino]-1,1,1-trifluoro-2-propanol

[0268] To a solution of 3-[[[3-(1,1,2,2-tetrafluoroethoxy)phenyl]methyl][[4-(methylthio)-phenyl]phenyl]amino]-1,1,1-trifluoro-2-propanol in 2 mL of trifluoroacetic acid was added 11 mL of 30% H_2O_2 (0.097 mmol). After stirring at room temperature overnight, an additional 11 mL of 30% H_2O_2 (0.097 mmol) was added. After 5 hours, TLC analysis indicated that the reaction had gone to completion. The solvent was removed, and the residue was filtered through silica gel eluting with 30% ethyl acetate in hexane. The material was evaporated to give 36.6 mg (100%) of the desired sulfone product as an oil which was 100% pure by reverse phase HPLC analysis. HRMS calcd. for $C_{25}H_{22}F_7NO_4S$: 566.1236

$[M+H]^+$, found: 566.1193. ^1H NMR ($CDCl_3$) δ 3.04 (s, 3H), 3.66-3.79 (m, 1H), 3.97 (d, 1H), 4.35-4.43 (m, 1H), 4.69-4.81 (m, 2H), 5.86 (dt, 1H), 6.90 (d, 1H), 7.01(s, 1H), 7.05-7.18 (m, 4H), 7.31-7.40 (m, 2H), 7.60 (d, 2H), 7.93 (d, 2H).

EXAMPLE 576

[0269]



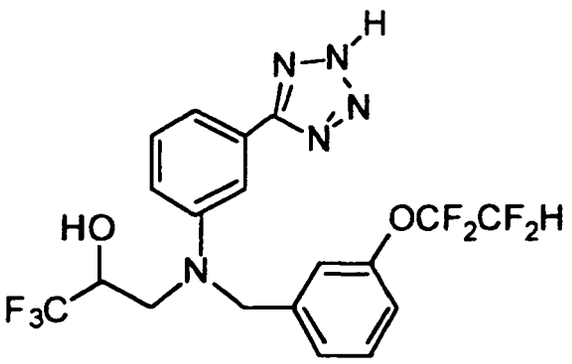
3-[[[3-(1,1,2,2-tetrafluoroethoxy)phenyl]methyl] (3,3,3-trifluoro-2-hydroxypropyl) amino]benzonitrile

[0270] **EX-576A)** A solution of 3-aminobenzonitrile (1.06 g, 9.1 mmol) and 3-(1,1,2,2-tetrafluoroethoxy)benzaldehyde (2.00g, 9.01 mmol) was dissolved in 25 mL of dichloroethane and acetic acid (536 mL, 9.37 mmol), then solid $NaBH(OAC)_3$ (2.48 g, 11.7 mmol) was added. The mixture was stirred at room temperature for 3 hours, then quenched with water and extracted with dichloromethane. The organic layer was washed with saturated $NaHCO_3$, then dried over $MgSO_4$, and evaporated. The crude product was purified by MPLC on silica gel eluting with 20% to 30% ethyl acetate in hexane to give 1.58 g (54%) of the desired 3-[[[3-(1,1,2,2-tetrafluoroethoxy)-phenyl]methyl]amino] benzonitrile product as a clear oil. ^1H NMR ($CDCl_3$) δ 4.38 (s, 3H), 5.89 (dt, 1H), 6.79 (t, 1H), 6.98 (d, 2H), 7.12-7.28 (m, 4H), 7.40 (t, 1H).

[0271] The benzonitrile (1.58 g, 4.88 mmol) from **EX-576A** and 1,1,1-trifluoro-2,3-epoxy-propane (546 mL, 6.34 mmol) were dissolved in 4 mL of acetonitrile. Ytterbium (III) trifluoromethanesulfonate (304 mg, 0.49 mmol) was added, and the stirred solution was warmed to 50 ˚C overnight. The reaction was quenched with water and extracted with ether. The ether layer was washed with brine, dried over $MgSO_4$ and evaporated. The crude product was purified by MPLC on silica gel eluting with dichloromethane to give 1.61 g (76%) of the desired 3-[[[3-(1,1,2,2-tetrafluoroethoxy)phenyl] methyl]-(3,3,3-trifluoro-2-hydroxypropyl)amino] benzonitrile product as a clear oil, greater than 98% by reverse phase HPLC. HRMS calcd. for $C_{19}H_{15}F_7N_2O_2$: 437.1100 $[M+H]^+$, found: 437.1097. ^1H NMR ($CDCl_3$) δ 3.60-3.69 (m, 1H), 3.86 (d, 1H), 4.32 (bs, 1H), 4.69 (q, 2H), 5.86 (dt, 1H), 6.85-6.95 (m, 2H), 6.97-7.01 (m, 2H), 7.04-7.12 (m, 2H), 7.23-7.37 (m, 2H).

EXAMPLE 577

[0272]

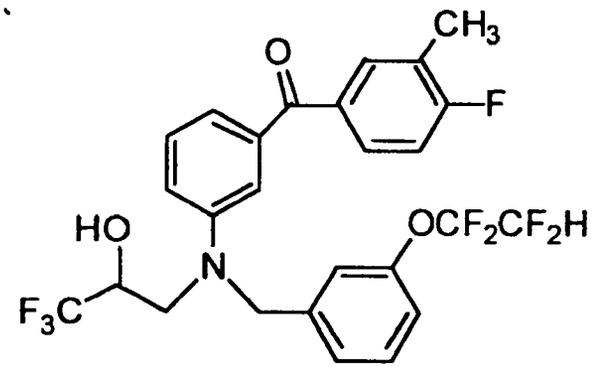


3-[[[3-(1,1,2,2-tetrafluoroethoxy)phenyl]methyl][3-(1H-tetrazol-5-yl)phenyl]amino]-1,1,1-trifluoro-2-propanol

[0273] To a solution of 3-[[[3-(1,1,2,2-tetrafluoroethoxy)phenyl]methyl](3,3,3-trifluoro-2-hydroxypropyl)amino]benzonitrile (76 mg, 0.17 mmol) in 2 mL of toluene was added trimethyltin azide (41 mg, 0.20 mmol). The reaction mixture was heated to 105 ˚C and stirred overnight. TLC showed starting material to still be present so additional trimethyltin azide (41 mg. 0.20 mmol) was added. The reaction mixture was stirred overnight at 105 ˚C. cooled to room temperature, then THF (800 μL) and concentrated HCl (500 μL) were added. HPLC analysis showed 2 peaks after 5 hours, so additional concentrated HCl (200 μL) was added. After stirring overnight, HPLC analysis showed the reaction to be complete. The mixture was filtered through a celite plug and evaporated *in vacuo.* The residue was purified by reverse phase HPLC eluting with 10% to 90% acetonitrile in water to give 27.2 mg (33%) of the desired tetrazole product as an oil. HRMS calcd. for $C_{19}H_{16}F_7N_5O_2$: 480.1270 $[M+H]^+$, found: 480.1252. ^1H NMR ($COCl_3$) δ 3.66-3.99 (m, 2H), 4.45-4.75 (m, 3H), 5.80 (dt, 1H), 6.49-6.70 (m, 1H), 6.95 (s, 1H), 6.97-7.06 (m, 3H), 7.18-7.28 (m, 3H), 7.34 (s, 1H).

EXAMPLE 578

[0274]

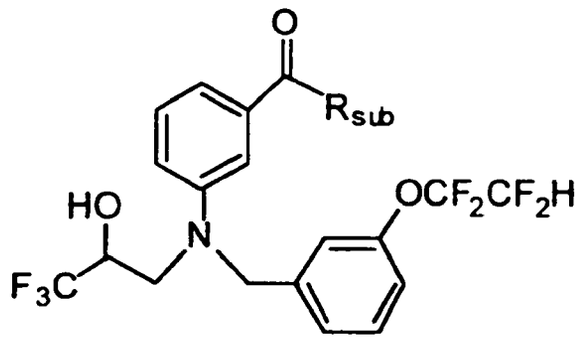


(4-Fluoro-3-methylphenyl)[3-[[[(1,1,2,2-tetrafluoroethoxy) phenyl]methyl](3,3,3-trifluoro-2-hydroxypropyl)amino] phenyl]methanone

[0275] To a solution of 3-[[[3-(1,1,2,2-tetrafluoroethoxy)phenyl]methyl](3,3,3-trifluoro-2-hydroxypropyl)amino]benzonitrile (100 mg, 0.23 mmol) in I mL of anhydrous THF under nitrogen was added 4-fluoro-3-methylphenylmagnesium bromide (0.81 mL of 1.0 M solution, 0.81 mmol), and the mixture was stirred at room temperature overnight. HPLC analysis of the reaction mixture showed the presence of starting material so additional 4-fluoro-3-methylphenylmagnesium bromide (0.46 mL, 0.41 mmol) was added. HPLC analysis 24 hours later showed the reaction to be complete. The reaction was quenched and acidified with 1 N HCl. After hydrolysis of imine was complete by HPLC analysis, the mixture was filtered through celite and evaporated. The crude product was purified by reverse phase HPLC eluting with 10% to 90% acetonitrile in water to give 28.0 mg (22%) of the desired ketone product as an oil. HRMS calcd. for $C_{26}H_{21}F_8NO_3$: 548.1410 $[M+H]^+$, found: 548.1441. ^1H NMR ($CDCl_3$) δ 2.26 (s, 3H), 3.60-3.70 (m, 1H), 3.92 (d, 1H), 4.26-4.40 (m, 1H), 4.68 (t, 2H), 5.87 (dt, 1H), 6.91-7.03 (m, 3H), 7.05-7.12 (m, 4H), 7.26-7.35 (m, 2H), 7.43-7.52 (m, 1H), 7.63 (d, 1H).

[0276] Additional examples of (aryl-, alkyl- or cycloalkyl-)[3-[[[(1,1,2,2-tetrafluoroethoxy)phenyl]methyl](3,3,3-trifluoro-2-hydroxypropyl)amino]phenyl] methanones are prepared by one skilled in the are using similar methods, as shown in Example Table 31.

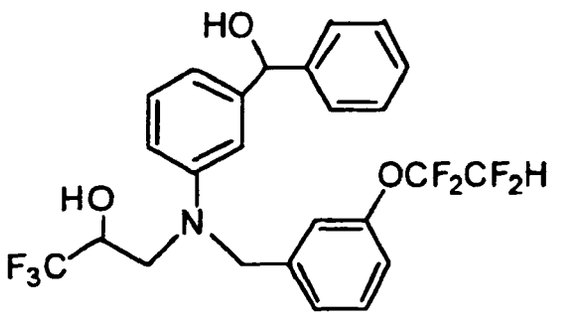
Example Table 31. (Aryl-, alkyl- or cycloalkyl-)[3-[[[(1,1,2,2-tetrafluoroethoxy)-phenyl]methyl](3,3,3-trifluoro-2-hydroxypropyl)amino]phenyl]methanones.



Example Number	R_{SUB}	Calculated Mass $[M+H]^+$	Observed Mass $[M+H]^+$
579	phenyl	516.1410	516.1383
580	4-fluorophenyl	534.1315	534.1273
581	cyclopentyl	508.1723	508.1675
582	isopropyl	482.1566	482.1576

EXAMPLE 583

[0277]

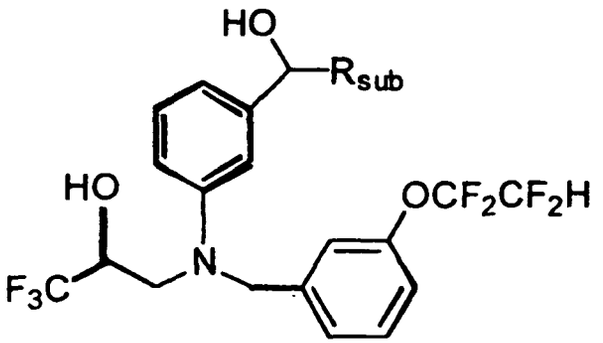


α-Phenyl-3-[[[3-(1,1,2,2-tetrafluoroethoxy)phenyl]methyl]] (3,3,3-trifluoro-2-hydroxypropyl)benzenemethanol

[0278] To a solution of phenyl[3-[[[(1,1,2,2-tetrafluoroethoxy)phenyl]methyl](3,3,3-trifluoro-2-hydroxypropyl)amino] phenyl]methanone (155.8 mg, 0.302 mmol) in 2.3 mL of methanol cooled to 5 ˚C was added solid $NaBH_4$ (34.5 mg, 0.912 mmol). HPLC analysis after 1 hour showed no ketone starting material. The reaction was evaporated to dryness and purified by reverse phase HPLC eluting with 50% to 90% acetonitrile in water to give 35.6 mg (24%) of the desired alcohol product as an oil. HRMS calcd. for $C_{25}H_{22}F_7NO_3$: 518.1566 $[M+H]^+$, found: 518.1563. ^1H NMR (acetone-d_6) δ 3.56-3.73 (m, 1H), 3.92-4.06 (m, 1H), 4.40-4.55 (m, 1H). 4.82 (s, 2H), 5.71 (s, 1H), 6.28-6.69 (m, 2H), 6.71-6.82 (m, 1H), 6.93 (s, 1H), 7.07-7.51 (m, 10H).

[0279] Additional examples of α-alkyl-3-[[[3-(1,1,2,2-tetrafluoroethoxy) phenyl]methyl][(3,3,3-trifluoro-2-hydroxypropyl)benzenemethanols are prepared by one skilled in the art using similar methods, as shown in Example Table 32.

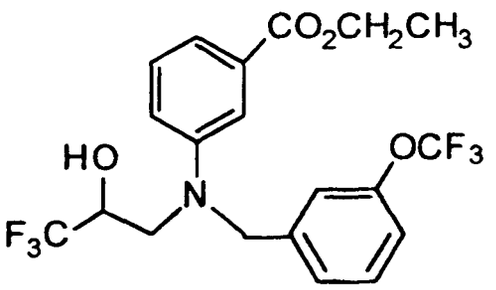
Example Table 32. α-alkyl-3-[[[3-(1,1,2,2-tetrafluoroethoxy)phenyl]methyl]-[(3,3,3-trifluoro-2-hydroxypropyl) benzenemethanols



Example Number	R_{SUB}	Calculated Mass $[M+H]^+$	Observed Mass $[M+H]^+$
584	isopropyl	484.1723	484.1725

EXAMPLE 585

[0280]



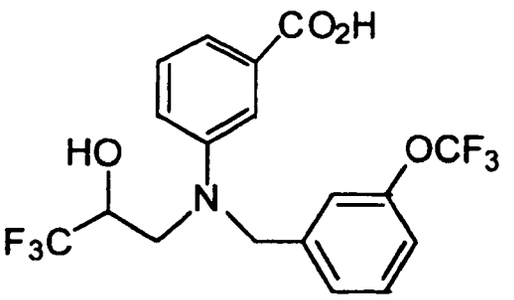
Ethyl 3-[(3,3,3-trifluoro-2-hydroxypropyl)[[(3-trifluoromethoxy) phenyl]methyl]amino]benzoate

[0281] **EX-585A)** Ethyl 3-aminobenzoate (3.9 mL, 26 mmol) and 3-trifluoromethoxybenzaldehyde (4.91 g, 25.8 mmol) were dissolved in 65 mL of dichloroethane and acetic acid (1.6 mL, 28 mmol), then solid $NaBH(OAc)_3$ (7.5 g, 34.2 mmol) was added. The mixture was stirred at room temperature overnight, then quenched with water and extracted with dichloromethane. The organic layer was washed with brine, then dried over $MgSO_4$, and evaporated to give 9.76 g (>100%) of the desired ethyl 3-[[[(3-trifluoromethyl)phenyl]methyl] amino]benzoate product as a yellow oil, which was greater than 95% pure by reverse phase HPLC analysis. ^1H NMR ($CDCl_3$) δ 1.35 (t, 3H), 4.26-4.41 (m, 5H), 6.73 (d. 1H), 7.12 (d, 1H), 7.15-7.25 (m, 2H), 7.25-7.43 (m, 4H).

[0282] The ethyl 3-[[[(3-trifluoromethyl)phenyl]methyl]amino]benzoate (9.76 g, 25.8 mmol) product from **EX-585A** and 1,1,1-trifluoro-2,3-epoxypropane (2.9 mL, 33.5 mmol) were dissolved in 25 mL of acetonitrile. Ytterbium (III) trifluoromethanesulfonate (1.6 g, 2.6 mmol) was added, and the stirred solution was warmed to 50 °C for 20 hours. The reaction was quenched with water and extracted with dichloromethane. The organic layer was washed with water and brine, then dried over $MgSO_4$. The crude product was purified by column chromatography on silica gel eluting with dichloromethane to give 10.7 g (92%) of the desired ethyl 3-[(3,3,3-trifluoro-2-hydroxypropyl)[[(3-trifluoromethyl) phenyl]methyl]amino] benzoate product as a yellow oil. HRMS calcd. for $C_{20}H_{19}NO_4F_6$. 452.1297 $[M+H]^+$, found: 452.1256. ^1H NMR ($COCl_3$) δ 1.32 (t, 3H), 2.94-3.02 (m, 1H), 3.54-3.64 (m, 1H), 3.91 (d, 1H), 4.24-4.40 (m, 3H), 4.69 (t, 2H), 6.86 (d, 1H), 7.05 (s, 1H), 7.07-7.14 (m, 2H), 7.20-7.34 (m, 2H), 7.39-7.47 (m, 2H).

EXAMPLE 586

[0283]

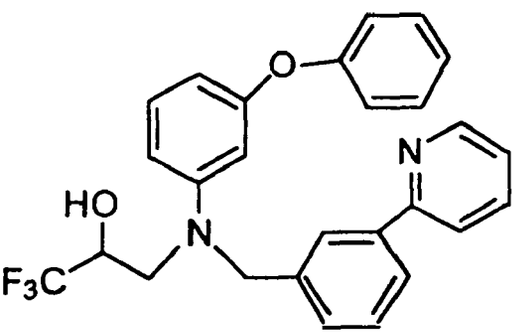


3-[(3,3,3-trifluoro-2-hydroxypropyl)[[(3-trifluoromethyl) phenyl]methyl]amino]benzoic Acid

[0284] Ethyl 3-[(3,3,3-trifluoro-2-hydroxypropyl)[[(3-trifluoromethyl)phenyl]methyl] amino]-benzoate was dissolved in 70 mL of THF and 35 mL of water. Lithium hydroxide monohydrate (2.93 g, 69.8 mmol) was added, and the mixture was heated to 45 ˚C under nitrogen overnight, at which time HPLC analysis indicated that the reaction had gone to completion. The mixture was acidified with I N HCl to a pH of 3-4, then extracted with ethyl acetate several times, and the combined organic layers were dried over $MgSO_4$. The dried organic layer was evaporated to give 11.2 g (100%) of the desired benzoic acid product as a pale orange oil, which was greater than 98% pure by reverse phase HPLC analysis. HRMS calcd. for $C_{18}H_{15}NO_4F_6$. 424.0984 $[M+H]^+$, found: 424.0991. ^1H NMR (acetone-d_6) δ 3.68-3.81 (m, 1H), 3.99-4.09 (m, 1H), 4.43-4.58 (m, 1H), 4.87 (s, 2H), 7.02 (d, 1H), 7.19 (d, 1H), 7.22-7.40 (m, 4H), 7.40-7.49 (m, 2H).

EXAMPLE 587

[0285]



3-[(3-phenoxyphenyl)[[3-(2-pyridinyl)phenyl]methyl]amino]-1,1,1-trifluoro-2-propanol

[0286] **EX-587A)** To a THF solution (8 mL) of 2-bromopyridine (1.30 g, 8.23 mmol) at -78 ˚C was added 1.6 M *n*-BuLi in hexanes (5.3 mL, 8.48 mmol). The resulting dark red solution was stirred at -78 ˚C for 10 min, and a solution of 0.5 M $ZnCl_2$ in THF (18 mL, 9.0 mmol) was added giving a light brown slurry. After warming to room temperature, 3-bromobenzaldehyde (0.816 mL, 7.0 mmol) and $Pd(PPh_3)_4$ (0.242 g, 0.21 mmol) were added, and the mixture was stirred for 18 h at room temperature under argon. The reaction mixture was poured into 1 N HCl (30 mL) and washed with diethyl ether. The aqueous layer was neutralized with $NaHCO_3$ and extracted with diethyl ether. The solvent was removed *in vacuo* to give the crude product as an oil. Purification by flash chromatography on silica gel eluting with 20% ethyl acetate in hexane gave 0.49 g (38%) of the desired 3-(2-pyridinyl)benzaldehyde product as a colorless oil. GCMS: *m*/*z* = 183 $[M^+]$.

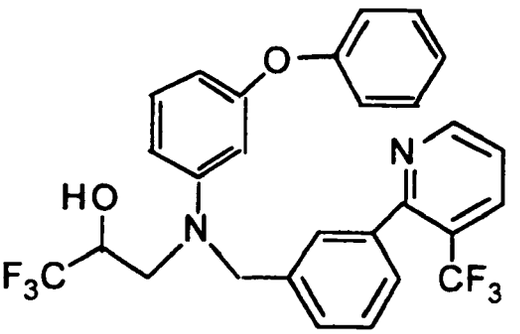
[0287] **EX-587B)** To a 1,2-dichloroethane (5 mL) solution of aldehyde (0.37 g, 2.0 mmol) from **EX-587A** was added 3-phenoxyaniline (0.37 g, 2.0 mmol), $NaB(OAc)_3H$ (0.55 g, 2.6 mmol) and acetic acid (0.12 mL, 2.0 mmol). The cloudy solution was stirred at room temperature for 2 h. The reaction mixture was poured into water and extracted with dichloromethane. The organic layer was washed with saturated $NaHCO_3$ and brine, dried ($MgSO_4$) and evaporated to yield 0.70 g (100%) of the desired *N*-3-(phenoxyphenyl)-[[3-(2-pyridinyl)phenyl]methyl]amine product as a yellow oil. HRMS:

calcd. for $C_{24}H_{21}N_2O$: 353.1654 $[M+H]^+$, found: 353.1660.

[0288] A THF (1 mL) solution of amine (0.47 g, 1.3 mmol) from **EX-587B** and 1,1,1-trifluoro -2,3-epoxypropane (0.35 mL, 4.1 mmol) was placed in a sealed vial and heated to 90 ˚C for 18 h with stirring. The solvent was removed *in vacuo* to give the crude product as an oil. Purification by flash chromatography on silica gel eluting with 20% ethyl acetate in hexane gave 0.026 g (4.2%) of the desired 3-[(3-phenoxyphenyl) [(3-(2-pyridinyl)phenyl)methyl]amino]-1,1,1-trifluoro-2-propanol product as a yellow oil. HRMS calcd. for $C_{27}H_{24}N_2O_2F_3$: 465.1790 $[M+H]^+$, found: 465.1798. ^1H NMR ($CDCl_3$) δ 3.63 (dd, 1H), 3.73 (br s, 1H), 3.82 (dd, 1H), 4.30 (m, 1H), 4.67 (d, 2H), 6.34 (dd, 1H), 6.44 (t, 1H), 6.52 (dd, 1H), 6.92 (d, 2H), 7.02 (t, 1H), 7.12 (t, 1H), 7.2 (m, 4H), 7.38 (t, 1H), 7.65 (d, 1H), 7.72 (d, 1H), 7.74 (d 1H), 7.84 (s, 1H), 8.62 (d, 1H).

EXAMPLE 588

[0289]



3-[(3-phenoxyphenyl)[[3-[(3-trifluoromethyl)-2-pyridinyl] phenyl] methyl]amino]-1,1,1-trifluoro-2-propanol

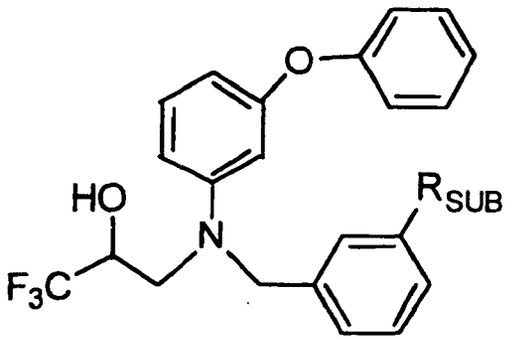
[0290] **EX-588A)** To a toluene (10 mL) solution of 2-bromo-3-trifluoromethylpyridine (1.10 g, 4.87 mmol) was added 3-formylphenylboronic acid (0.90 g, 6.0 mmol) and DMF (4 mL). To the resulting solution was added K_2CO_3 (1.67 g, 12.1 mmol) and $Pd(PPh_3)_4$ (0.35 g, 0.30 mmol). The slurry was heated to reflux under argon for 18 h. The cooled mixture was poured into water and extracted with ethyl acetate. The organic layer was washed with brine, dried ($MgSO_4$) and evaporated to an oil. Purification by flash chromatography on silica gel eluting with 20% ethyl acetate in hexane gave 0.55 g (45 %) of the desired 3-[(3-trifluoromethyl)-2-pyridinyl]benzaidehyde product as a color-less oil which solidified upon standing. HRMS: calcd. for $C_{13}H_9NOF_3$: 252.0636 $[M+H]^+$, found: 252.0639.

[0291] **EX-588B)** A mixture of solid 3-phenoxyaniline (2.96 g, 16 mmol) and 1,1,1-trifluoro-2,3-epoxypropane (1.30 mL, 15.0 mmol) was placed in a sealed tube and heated to 100 ˚C giving a dark solution. The stirred solution was heated 18 h and cooled to give a dark oil. Purification by flash chromatography on silica gel eluting with dichloromethane gave 3.15 g (71%) of the desired 3-[(*N*-3-phenoxy-phenyl)amino]-1,1,1-trifluoro-2-propanol product as a colorless oil. Anal. calcd. for $C_{15}H_{14}NO_2F_3 \cdot 0.05\ CH_2Cl_2$: C, 59.92; H, 4.71; N, 4.64. Found: C. 59.92; H, 4.53; N, 4.73. HRMS calcd. 298.1055 $[M+H]^+$, found: 298.1056.

[0292] To a 1.2-dichloroethane (8 mL) solution of aldehyde (0.55 g, 2.2 mmol) from **EX-588A** was added the amine (0.66 g, 2.2 mmol) from **EX-588B.** $NaB(OAc)_3H$ (0.61 g, 2.9 mmol) and acetic acid (0.15 mL, 2.6 mmol). The cloudy solution was stirred at room temperature for 4 h. The reaction mixture was poured into water and extracted with dichloromethane. The organic layer was washed with saturated $NaHCO_3$ and brine, dried ($MgSO_4$) and evaporated to give an oil. Purification by flash chromatography on silica gel eluting with 20% ethyl acetate in hexane gave 0.33 g (29%) of the desired 3-[(3-phenoxyphenyl)[[3-[(3-trifluoromethyl)-2-pyridinyl]phenyl] methyl]amino]-1,1,1-trifluoro-2-propanol product as a white foam, >97% pure by HPLC analysis. Anal. calcd. for $C_{28}H_{22}N_2O_2F_6$: C, 63.16; H, 4.16; N, 5.26. Found: C, 62.87; H, 4.02; N, 5.33. HRMS: calcd. 533.1664 $[M+H]^+$, found: 533.1658. ^1H NMR (C_6D_6) δ 2.97 (d, 1H), 3.26 (dd, 1H), 3.46 (dd, 1H), 3.77 (m, 1H). 4.22 (dd, 2H), 6.31 (dd, 1H), 6.35 (dd, 1H), 6.40 (dd, 1H), 6.54 (t, 1H). 6.80 (t, 1H), 6.9-7.0 (m, 7H), 7.26 (d, 1H), 7.33 (d, 1H), 7.40 (s, 1H), 8.17 (d, 1H).

[0293] Additional examples of 3-[(3-phenoxyphenyl)[[3-(heteroaryl)phenyl] methyl]-amino]-1,1,1-trifluoro-2-propanols are prepared by one skilled in the art using similar methods, as shown in Example Table 33.

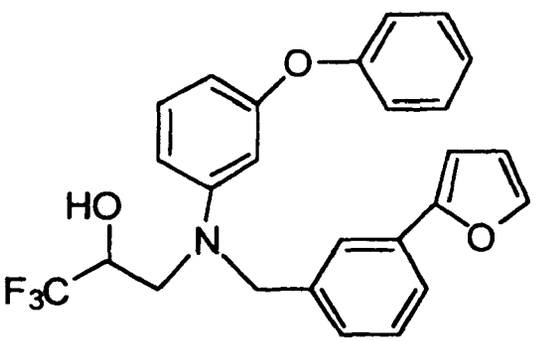
Example Table 33. 3-[(3-phenoxyphenyl)([3-(heteroaryl)phenyl]methyl]amino]-1,1,1-trifluoro-2-propanols.



Ex. No.	R_{SUB}	Calculated Mass $[M+H]^+$	Observed Mass $[M+H]^+$
589	3-methyl-pyridin-2-yl	479.1949	479.1946
590	pyridin-3-yl	465.1790	465.1778
591	pyridin4-yl	465.1790	465.1821

EXAMPLE 592

[0294]



3-[(3-phenoxyphenyl)[[3-(2-furanyl)phenyl]methyl]amino]-1,1,1-trifluoro-2-propanol

[0295] **EX-592A)** To a dioxane (20 mL) solution of 3-bromobenzaldehyde (0.63 mL, 5.4 mmol) was added 2-(tributylstannyl)furan (1.89 mL, 6.00 mL) and $Pd(PPh_3)_2Cl_2$ (0.21 g, 0.30 mmol). The mixture was heated to reflux under argon for 1.5 h. The cooled mixture was poured into a mixture of saturated KF and ethyl acetate and stirred 18 h. The slurry was filtered through celite. The organic layer was separated, washed with brine, dried ($MgSO_4$) and evaporated to an oil. Purification by flash chromatography on silica gel eluting with 5% ethyl acetate in hexane gave 0.80 g (86%) of the desired 3-(2-furanyl)benzaldehyde product as an yellow oil which solidified upon standing. MS: *m/z* = 173.1 $[M+H]^+$.

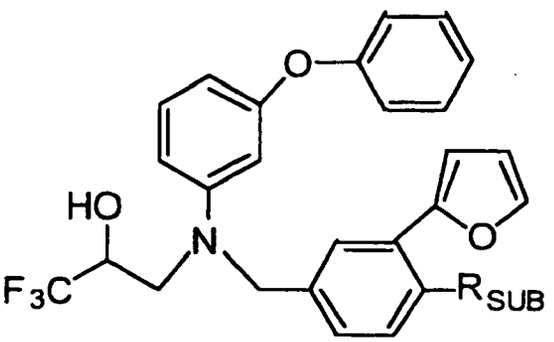
[0296] **EX-592B)** To a 1,2-dichloroethane (7 mL) solution of aldehyde (0.40 g, 2.3 mmol) from **EX-592A** was added 3-phenoxyaniline (0.43 g, 2.3 mmol), $NaB(OAc)_3H$ (0.64 g, 3.0 mmol) and acetic acid (0.15 mL, 2.6 mmol). The cloudy solution was stirred at room temperature for 2 h. The reaction mixture was poured into water and extracted with dichloromethane. The organic layer was washed with saturated $NaHCO_3$ and brine, dried ($MgSO_4$) and evaporated to yield 0.74 g (94%) of the desired *N*-(3-phenoxyphenyl)[[3-(2-furanyl)phenyl]methyl]amine product as an yellow oil which was used without further purification. MS: *m/z* = 342.3 $[M+H]^+$.

[0297] To a dichloromethane (3 mL) solution of amine (0.74 g, 2.2 mmol) from **EX-592B** was added 1,1,1-trifluoro-2,3-epoxypropane (0.28 mL, 3.3 mmol) and $Yb(OTf)_3$ (0.136 g, 0.20 mmol). The cloudy solution was stirred at room temperature for 4 days, then diluted with diethyl ether, and washed with water and brine. The organic layer was dried ($MgSO_4$) and evaporated to an oil. Purification by flash chromatography on silica gel eluting with 10% ethyl acetate in

hexane gave an oil which was dissolved in EtOH, stripped and dried *in vacuo* to give 0.49 g (49%) of the desired 3-[(3-phenoxyphenyl)[[3-(2-furanyl)phenyl]methyl]amino]-1,1,1-trifluoro-2-propanol product as a colorless oil, > 98% pure by HPLC analysis. Anal. calcd. for $C_{26}H_{22}NO_3F_3 \cdot 0.5$ EtOH$\cdot 0.3$ H_2O: C, 67.30; H, 5.35; N, 2.91. Found: C, 67.12; H, 5.12; N, 2.89. HRMS calcd. 454.1630 $[M+H]^+$, found: 454.1635. ^{1}H NMR (C_6D_6) δ 2.15 (d, 1H), 3.21 (dd, 1H), 3.50 (dd, 1H), 3.81 (m, 1H), 4.24 (s, 2H), 6.09 (dd, 1H), 6.33 (d, 1H), 6.35 (d, 1H), 6.44 (dd, 1H), 6.52 (t, 1H), 6.79 (m, 1H), 6.81 (s, 1H), 6.9-7.0 (m, 7H), 7.44 (d, 1H), 7.47 (s, 1H).

[0298] Additional examples of 3-[(3-phenoxyphenyl) [[4-substituted-3-(2-furanyl)-phenyl]methyl]amino]-1,1,1-trifluoro-2-propanols are prepared by one skilled in the art using similar methods, as shown in Example Table 34.

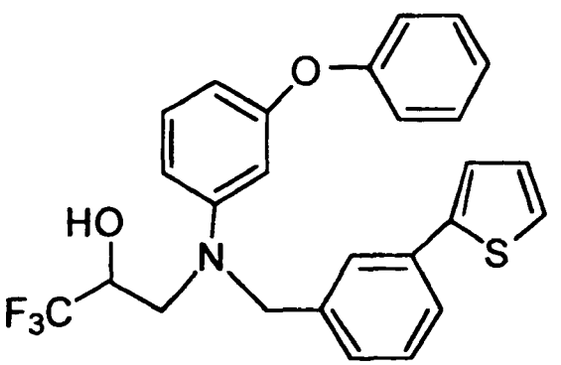
Example Table 34. 3-[(3-phenoxyphenyl) [[4-substituted-3-(2-furanyl)-phenyl]methyl]amino]-1,1,1-trifluoro-2-propanols.



Ex. No.	R_{SUB}	Calculated Mass $[M+H]^+$	Observed Mass $[M+H]^+$
593	F	472.1536	472.1530
594	Me	468.1787	468.1783

EXAMPLE 595

[0299]



3-[(3-phenoxyphenyl)[[3-(2-thienyl)phenyl]methyl]amino]-1,1,1-trifluoro-2-propanol

[0300] EX-595A) To a 1,2-dichloroethane (90 mL) solution of 3-bromobenzaldehyde (5.60 g, 30.3 mmol) was added 3-phenoxyaniline (5.60 g, 30.2 mmol), $NaB(OAc)_3H$ (8.26 g, 39.0 mmol) and acetic acid (1.8 mL, 31. mmol). The cloudy solution was stirred at room temperature for 1.5 h. The reaction mixture was poured into water and extracted with dichloromethane. The organic layer was washed with saturated $NaHCO_3$ and brine, dried ($MgSO_4$) and evaporated to yield 10.49 g (98%) of the desired *N*-(3-phenoxyphenyl)[(3-bromophenyl)methyl]amine product as a light brown oil. ^{1}H NMR ($CDCl_3$) δ 4.26 (s, 2H), 6.27 (s, 1H), 6.38 (d, 2H), 7.00 (d, 2H), 7.13 (m, 2H), 7.19 (t, 1H), 7.26 (d, 1H), 7.30 (m,

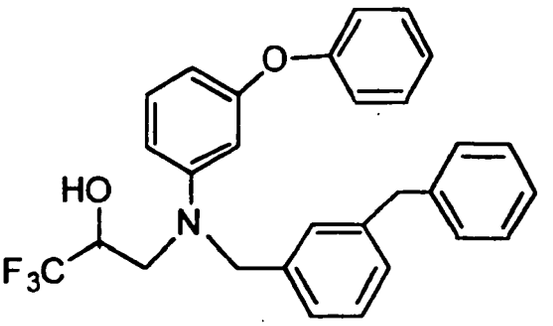
2H), 7.38 (d, 1H), 7.96 (s, 1H). The formation of the desired product was monitored by the disappearance of the aldehyde peak (δ ~ 10) and the formation of the benzyl peak (δ 4.26) in the ^{1}H NMR spectrum.

[0301] **EX-595B)** To a dichloromethane (15 mL) solution of amine from **EX-595A** (6.01 g, 17.0 mmol) was added 1,1,1-trifluoro-2,3-epoxypropane (1.75 mL, 20.3 mmol) and $Yb(OTf)_3$ (1.05 g, 1.69 mmol). The cloudy solution was stirred at room temperature for 24 h, diluted with diethyl ether, and washed with water and brine. The organic layer was dried ($MgSO_4$) and evaporated to an oil. Purification by flash chromatography on silica gel eluting with 3-8% ethyl acetate in hexane gave an oil which was dissolved in EtOH, stripped and dried *in vacuo* to give 4.71 g (60%) of the desired 3-[(3-phenoxyphenyl)[[3-bromophenyl]methyl]amino]-1,1,1-trifluoro-2-propanol product as a colorless oil. Anal. calcd. for $C_{22}H_{19}NO_2F_3Br$·0.41 EtOH: C, 56.49; H, 4.46; N, 2.89. Found: C, 56.15; H, 4.22; N, 2.92. HRMS calcd. 466.0629 $[M+H]^+$, found: 466.0598.

[0302] To a dioxane (5 mL) solution of aminopropanol from **EX-595B** (0.38 g, 0.82 mmol) was added 2-(tributylstannyl) thiophene (0.29 mL, 0.90 mmol) and $Pd(PPh_3)_2Cl_2$ (0.040 g, 0.057 mmol). The mixture was heated to reflux under argon for 18 h. The cooled mixture was poured into a mixture of 10 % aq. KF and ethyl acetate and stirred 1 h. The slurry was filtered through celite. The organic layer was separated, washed with brine, dried ($MgSO_4$) and evaporated to an oil. Purification by flash chromatography on silica gel eluting with 5-15% ethyl acetate in hexane gave an oil which was dissolved in EtOH, stripped and dried *in vacuo* to give 0.17 g (45%) of the desired 3-[(3-phenoxy-phenyl)[[3-(2-thienyl) phenyl]methyl]amino]-1,1,1-trifluoro-2-propanol product as a colorless oil. Anal. calcd. for $C_{26}H_{22}NO_2F_3S$·0.62 EtOH: C, 65.69; H, 5.20; N, 2.81. Found: C, 65.36; H, 4.84; N, 2.81. HRMS calcd. 470.1402 $[M+H]^+$, found: 470.1392. ^{1}H NMR ($CDCl_3$) δ 2.60 (br s, 1H), 3.64 (dd, 1H), 3.89 (dd, 1H), 4.37 (m, 1H), 4.68 (s, 2H), 6.42 (dd, 1H), 6.45 (t, 1H), 6.55 (dd, 1H), 6.98 (dd, 2H), 7.1 (m, 3H), 7.20 (t, 1H), 7.2-7.3 (m, 5H), 7.43 (s, 1H), 7.52 (d, 1H).

EXAMPLE 596

[0303]

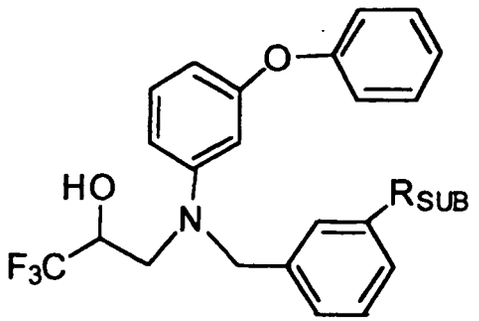


3-[(3-phenoxyphenyl)[[3-(phenylmethyl)phenyl]methyl]amino]-1,1,1-trifluoro-2-propanol

[0304] To a THF (4 mL) solution of 3-[(3-phenoxyphenyl)[[3-bromophenyl]methyl] amino]-1,1,1-trifluoro-2-propanol (0.60 g, 1.3 mmol) from **EX-595B** was added benzyl-magnesium bromide in THF (2.0 mL, 2.0 M, 4.0 mmol) and Pd $(PPh_3)_4$. The resulting yellow solution was refluxed under N_2 for 18 h. The cooled solution was poured into saturated aq. NH_4Cl, extracted with ethyl acetate, dried ($MgSO_4$) and evaporated to an oil. Purification by flash chromatography on silica gel eluting with 15% ethyl acetate in hexane gave an oil which was dissolved in EtOH, stripped and dried *in vacuo* to give 0.39 g (62%) of the desired 3-[(3-phenoxyphenyl) [[3-(phenylmethyl)phenyl] methyl]amino]-1,1,1-trifluoro-2-propanol product as a colorless oil. Anal. calcd. for $C_{29}H_{26}NO_2F_3$-0.4 EtOH: C, 72.17; H, 5.77; N, 2.82. Found: C, 72.17; H, 5.42; N, 2.83. HRMS calcd. 478.1994 ([M+H]$^+$, found: 478.1984. ^{1}H NMR (C_6D_6) δ 1.58 (d, 1H), 3.22 (dd, 1H), 3.46 (dd, 1H), 3.69 (s, 2H), 3.73 (m, 1H), 4.18 (s, 2H), 6.34 (dd, 1H), 6.47 (dd, 1H), 6.53 (t, 1H), 6.8-7.1 (m 15H).

[0305] Additional examples of 3-[(3-phenoxyphenyl)[[3-(alkyl- or cycloalkyl)phenyl] methyl]amino]-1,1,1-trifluoro-2-propanols are prepared by one skilled in the art using similar methods, as shown in Example Table 35.

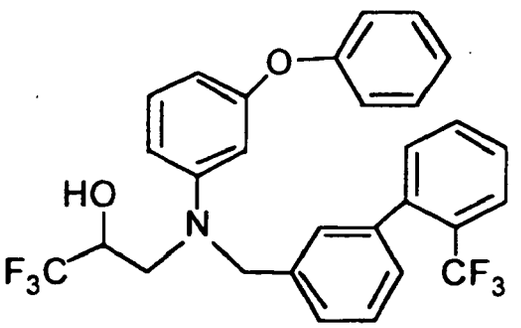
Example Table 35. 3-[(3-phenoxyphenyl)[[3-(alkyl- or cycloalkyl-)phenyl] methyl]amino]-1,1,1-trifluoro-2-propanols.



Ex. No.	R_{SUB}	Calculated Mass $[M+H]^+$	Observed Mass $[M+H]^+$
597	3-methylbutyl	458.2307	458.2295
598	2-methylpropyl	444.2150	444.2157
599	cyclopropyl	428.1837	428.1806

EXAMPLE 600

[0306]

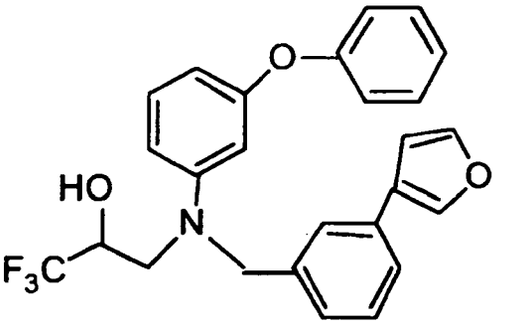


3-[(3-phenoxyphenyl)[[2'-(trifluoromethyl)[1,1'-biphenyl]-3-yl]methyl]amino]-1,1,1-trifluoro-2-propanol

[0307] To a toluene (8 mL) solution of 3-[(3-phenoxyphenyl)[[3-bromophenyl] methyl)-amino]-1,1,1-trifluoro-2-propanol (0.51 g, 1.1 mmol) from **EX-595B** was added 2-(tri-fluoromethyl)phenylboronic acid (0.33 g, 1.7 mmol) and DMF (3 mL). To the resulting solution was added K_2CO_3 (0.31 g, 2.2 mmol) and $Pd(PPh_3)_4$ (0.060 g, 0.05 mmol). The slurry was heated to reflux under argon for 18 h. The cooled mixture was poured into water and extracted with ethyl acetate. The organic layer was washed with brine, dried ($MgSO_4$) and evaporated to an oil. Purification by flash chromatography on silica gel eluting with 20% ethyl acetate in hexane gave an oil which was dissolved in EtOH, stripped and dried *in vacuo* to give 0.32 g (55%) of the desired 3-[(3-phenoxyphenyl) [[(2'-(trifluoromethyl)[1,1'-biphenyl)-3-yl]methyl]amino]-1,1,1-tri-fluoro-2-propanol product as a colorless oil. Anal. calcd. for $C_{29}H_{23}NO_2F_6$-0.8 EtOH: C, 64.67; H, 4.93; N, 2.46. Found: C, 64.53; H. 4.69; N, 2.49. HRMS calcd. 532.171 $[M+H]^+$, found: 532.1708. ^1H NMR (C_6D_6) δ 1.72 (d, 1H), 3.17 (dd, 1H), 3.46 (dd, 1H), 3.72 (m, 1H). 4.23 (s, 2H), 6.33 (dd, 1H), 6.43 (dd, 1H), 6.52 (t, 1H), 6.82 (m, 2H), 6.9-7.1 (m, 11H), 7.43 (d, 1H).

EXAMPLE 601

[0308]



3-[(3-phenoxyphenyl)[[3-(3-furanyl)phenyl]methyl]amino]-1,1,1-trifluoro-2-propanol

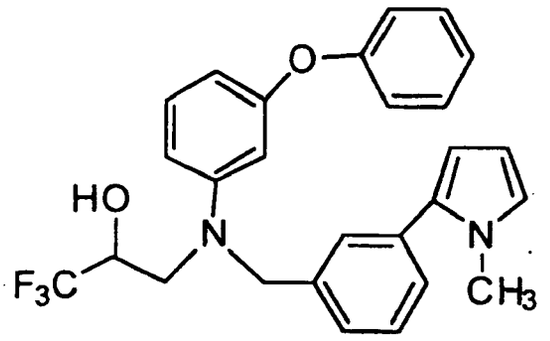
[0309] **EX-601A)** To a toluene (10 mL) solution of 3-bromofuran (0.54 mL, 6.0 mmol) was added 3-formylphenylboronic acid (1.00 g, 6.7 mmol) and DMF (4 mL). To the resulting solution was added K_2CO_3 (1.85 g, 13.4 mmol) and $Pd(PPh_3)_4$ (0.40 g, 0.35 mmol). The slurry was heated to reflux under argon for 2 h. The cooled mixture was poured into water and extracted with ethyl acetate. The organic layer was washed with brine, dried ($MgSO_4$) and evaporated to an oil. Purification by flash chromatography on silica gel eluting with 5 % ethyl acetate in hexane gave 0.10 g (10%) of the desired 3-(3-furanyl)benzaldehyde product as a yellow oil. MS: *m*/*z* = 173.0 $[M+H]^+$.

[0310] **EX-601B)** To a 1.2-dichloroethane (3 mL) solution of the aldehyde (0.10 g, 0.58 mmol) from **EX-601A** was added 3-phenoxyaniline (0.11 g, 0.59 mmol), $NaB(OAc)_3H$ (0.16 g, 0.75 mmol) and acetic acid (0.040 mL, 0.70 mmol). The cloudy solution was stirred at room temperature for 2 h. The reaction mixture was poured into water and extracted with dichloromethane. The organic layer was washed with saturated $NaHCO_3$ and brine, dried ($MgSO_4$) and evaporated to yield 0.20 g (100%) of the desired *N*-3-phenoxyphenyl)-[[3-(3-furanyl)phenyl]methyl]amine product as a yellow oil which was used without further purification. ^1H NMR ($CDCl_3$) δ 4.1 (br s, 1H), 4.30 (s, 2H), 6.29 (d, 1H), 6.32 (dd, 1H), 6.39 (dd, 1H), 6.66 (s, 1H), 6.95-7.05 (m, 4H), 7.2-7.5 (m, 7H), 7.70 (s, 1H). The formation of the desired product was monitored by the disappearance of the aldehyde peak (δ ~ 10) and the formation of the benzyl peak (δ 4.30) in the ^1H NMR spectrum.

[0311] To a CH_3CN (2 mL) solution of amine (0.20 g, 0.58 mmol) from **EX-601B** was added 1,1,1-trifluoro-2,3-epoxypropane (0.10 mL, 1.2 mmol) and $Yb(OTf)_3$ (0.035 g, 0.056 mmol). The cloudy solution was stirred in a sealed flask at 40 ˚C. After 18 h, additional 1,1,1-trifluoro-2,3-epoxypropane (0.20 mL, 2.4 mmol) and $Yb(OTf)_3$ (0.035 g, 0.056 mmol) were added, and the mixture was heated an additional 4 h, diluted with diethyl ether and washed with water and brine. The organic layer was dried ($MgSO_4$) and evaporated to an oil. Purification by flash chromatography on silica gel eluting with 10% ethyl acetate in hexane gave an oil which was dissolved in EtOH, stripped and dried *in vacuo* to give 0.14 g (53%) of the desired 3-[(3-phenoxyphenyl) [[3-(3-furanyl)phenyl]methyl]amino]-1,1,1-trifluoro-2-propanol product as a colorless oil, > 99% pure by HPLC analysis. Anal. calcd. for $C_{26}H_{22}NO_3F_3 \cdot 0.3$ EtOH: C, 68.37; H, 5.13; N, 3.00. Found: C, 68.29; H, 5.09; N, 2.99. HRMS calcd. 454.1630 $[M+H]^+$, found: 454.1635. ^1H NMR (C_6D_6) δ 1.62 (d, 1H), 3.18 (dd, 1H), 3.48 (dd, 1H), 3.74 (m, 1H), 4.22 (s, 2H), 6.32 (dd, 1H), 6.35 (m, 1H), 6.44 (dd, 1H), 6.52 (t, 1H), 6.78 (m, 1H), 6.82 (d, 1H), 6.9-7.1 (m, 9H), 7.37 (s, 1 H).

EXAMPLE 602

[0312]



3-[(3-phenoxyphenyl)[[3-(1-methyl-1*H*-pyrrol-2-yl)phenyl] methyl]amino]-1,1,1-trifluoro-2-propanol

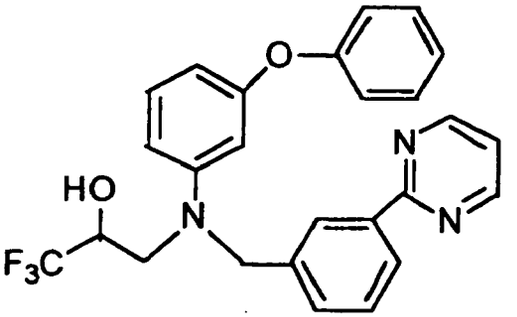
[0313] **EX-602A)** To solution of N-methylpyrrole (0.97 mL, 11 mmol) in Et_2O (20 mL) was added neat TMEDA (1.5 mL, 10 mmol) and 1.6 M n-BuLi in hexanes (6.3 mL, 10 mmol). The solution was heated to reflux under N_2 for 1 h and then cooled to -78 ˚C. A 1.0 M solution of Me_3SnCl in THF was added over 15 min, and the resulting solution stirred for 30 min at -78 ˚C. After warming to room temperature, 3-bromo-benzaldehyde (0.70 mL, 6.0 mmol), $Pd(PPh_3)_2Cl_2$ (0.25 g, 0.35 mmol) and dioxane (10 mL) were added. The slurry was heated to reflux for 18 h. The cooled mixture was poured into a mixture of saturated KF and ethyl acetate and stirred 15 min. The slurry was filtered through celite. The organic layer was separated, washed with brine, dried ($MgSO_4$) and evaporated to an oil. Purification by flash chromatography on silica gel eluting with 5% ethyl acetate in hexane gave 0.45 g (24%) of the desired 3-(1-methyl-1*H*-pyrrol-2-yl) benzaldehyde product as a yellow oil. MS: *m*/*z* =186.2 $[M+H]^+$.

[0314] **EX-602B)** To a 1,2-dichloroethane (10 mL) solution of aldehyde (0.45 g, 2.4 mmol) from **EX-602A** was added 3-phenoxyaniline (0.45 g, 2.4 mmol), $NaB(OAc)_3H$ (0.67 g, 3.2 mmol) and acetic acid (0.15 mL, 2.4 mmol). The cloudy solution was stirred at room temperature for 2 h. The reaction mixture was poured into water and extracted with dichloromethane. The organic layer was washed with saturated $NaHCO_3$ and brine, dried ($MgSO_4$) and evaporated to yield 0.67 g (79%) of the desired *N*-(3-phenoxyphenyl)[[3-(1-methyl-1*H*-pyrrol-2-yl)phenyl]methyl] amine product as a yellow oil which was used without further purification. ^1H NMR ($CDCl_3$) δ 3.60 (s, 3H), 4.15 (br s, 1H), 4.35 (s, 2H), 6.2- 6.4 (m, 5H), 6.67 (s, 1H), 7.00-7.05 (m, 4H), 7.1-7.2 (m, 6H). The formation of the desired product was monitored by the disappearance of the aldehyde peak (δ ~ 10) and the formation of the benzyl peak (δ 4.35) in the ^1H NMR spectrum.

[0315] To a CH_3CN (2 mL) solution of amine (0.67 g, 1.9 mmol) from **EX-602B** was added 1,1,1-trifluoro-2,3-epoxypropane (0.33 mL, 3.8 mmol) and $Yb(OTf)_3$ (0.120 g, 0.19 mmol). The cloudy solution as stirred in a sealed flask at 40 ˚C for 18 h. The cooled reaction mixture was diluted with diethyl ether and washed with water and brine. The organic layer was dried ($MgSO_4$) and evaporated to an oil. Purification by flash chromatography on silica gel eluting with 10% ethyl acetate in hexane gave an oil which was dissolved in EtOH, stripped and dried *in vacuo* to give 0.57 g (66 %) of the desired 3-[(3-phenoxyphenyl)[[3-(1-methyl-1*H*-pyrrol-2-yl)phenyl]methyl]amino]-1,1,1-trifluoro-2-propanol product as a colorless oil, > 99% pure by HPLC analysis. Anal. calcd. for $C_{27}H_{25}N_2O_2F_3 \cdot 0.9$ EtOH: C, 68.10; H, 6.03; N, 5.51. Found: C, 68.36; H, 5.94; N, 5.65. HRMS calcd. 467.1946 $[M+H]^+$, found: 467.1950. ^1H NMR (C_6D_6) δ 2.01(d, 1H), 2.97 (s, 3H), 3.21 (dd, 1H), 3.49 (dd, 1H), 3.78 (m, 1H), 4.28 (s, 2H), 6.3-6.4 (m, 4H), 6.45 (dd, 1H), 6.53 (t, 1H), 6.8-7.1 (m, 10H).

EXAMPLE 603

[0316]



3-[(3-phenoxyphenyl)[[3-(2-pyrimidinyl)phenyl]methyl]amino] 1,1,1-trifluoro-2-propanol

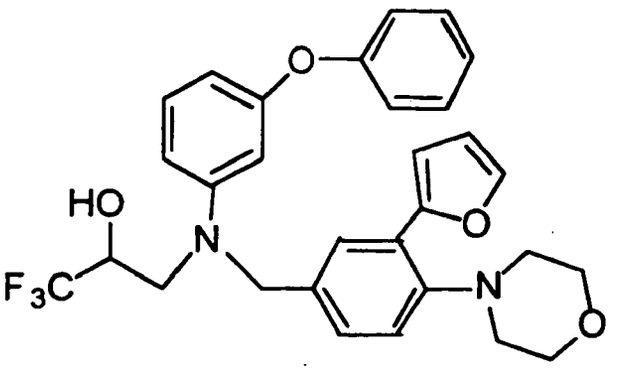
[0317] **EX-603A)** To a toluene (15 mL) solution of 2-chloropyrimidine (1.00 g, 8.7 mmol) was added 3-formylphenylboronic acid (1.42 g, 9.5 mmol) and DMF (8 mL). To the resulting solution was added K_2CO_3 (2.63 g, 19.0 mmol) and $Pd(PPh_3)_4$ (0.52 g, 0.45 mmol). The slurry was heated to reflux under argon for 18 h. The cooled mixture was poured into water and extracted with ethyl acetate. The organic layer was washed with brine, dried ($MgSO_4$) and evaporated to an oil. Purification by flash chromatography on silica gel eluting with 20% ethyl acetate in hexane gave 0.63 g (39%) of the desired 3-(2-pyrimidinyl)benzaldehyde product as a brown oil which solidified upon standing. MS: *m*/*z* = 185.1 $[M+H]^+$.

[0318] **EX-603B)** To a 1,2-dichloroethane (10 mL) solution of aldehyde (0.62 g, 3.4 mmol) from **EX-603A** was added 3-phenoxyaniline (0.62 g, 3.4 mmol), $NaB(OAc)_3H$ (0.93 g, 4.4 mmol) and acetic acid (0.20 mL, 3.4 mmol). The cloudy solution was stirred at room temperature for 2 h. The reaction mixture was poured into water and extracted with dichloromethane. The organic layer was washed with saturated $NaHCO_3$ and brine, dried ($MgSO_4$) and evaporated to yield 1.19 g (99%) of the desired *N*-(3-phenoxyphenyl)-[[3-(2-pyrimidinyl)phenyl]methyl]amine product as a brown oil which was used without further purification. MS: *m*/*z* = 354.2 $[M+H]^+$.

[0319] To a CH_3CN (4 mL) solution of amine (1.19 g, 3.4 mmol) from **EX-603B** was added 1.1,1-trifluoro-2,3-epoxypropane (0.585 mL, 6.8 mmol) and $Yb(OTf)_3$ (0.112 g, 0.18 mmol). The cloudy solution was stirred in a sealed flask at 40 ˚C. After 18 h, more 1,1,1-trifluoro-2,3-epoxypropane (0.585 mL. 6.8 mmol) and $Yb(OTf)_3$ (0.112 g, 0.18 mmol) were added, and the slurry was heated an additional 4 h. The cooled reaction mixture was diluted with diethyl ether and washed with water and brine. The organic layer was dried ($MgSO_4$) and evaporated to an oil. Purification by silica gel flash chromatography eluting with 25% ethyl acetate in hexane gave an oil which was dissolved in EtOH. concentrated and dried *in vacuo* to give 0.33 g (21 %) of the desired 3-[(3-phenoxyphenyl)[[3-(2-pyrimidinyl)phenyl]methyl]amino]-1,1,1-trifluoro-2-propanol product as a pale yellow oil, > 99% pure by HPLC analysis. Anal. calcd. for $C_{26}H_{22}N_3O_2F_3 \cdot 0.5$ EtOH: C, 66.39; H, 5.16; N, 8.60. Found: C, 66.26; H, 4.85; N, 8.60. HRMS calcd. 466.1742 $[M+H]^+$, found: 466.1724. ^1H NMR (C_6D_6) δ 2.28 (br s, 1H), 3.27 (dd. 1H), 3.50 (dd, 1H), 3.78 (m, 1H), 4.26 (m, 2H), 6.08 (t, 1H), 6.39 (dd, 1H), 6.52 (t, 1H), 6.75 (m, 1H), 6.9-7.0 (m, 6H), 7.18 (t, 1H), 8.12 (d, 2H), 8.58 (s, 1H), 8.66 (d, 1H).

EXAMPLE 604

[0320]



3-[(3-phenoxyphenyl)[[3-(2-furanyl)-4-(4-morpholinyl)phenyl] methyl]amino]-1,1,1-trifluoro-2-propanol

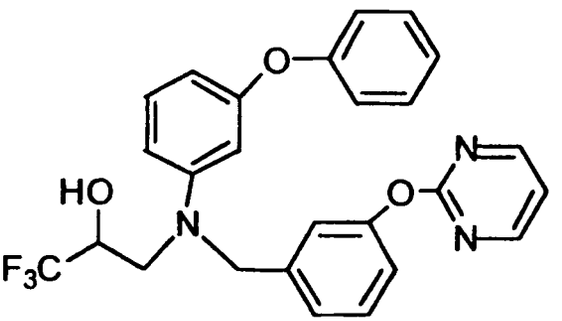
[0321] **EX-604A)** To a pyridine (15 mL) solution of 3-bromo-4-fluorobenzaldehyde (1.0 g, 4.9 mmol) was added morpholine (0.5 mL, 5.7 mmol) and K_2CO_3 (0.69 g, 5.0 mmol), and the slurry was refluxed for 18 h. The solvent was removed, and the residue was partitioned between ethyl acetate and water. The organic layer was separated, dried ($MgSO_4$) and evaporated to a yellow oil. Purification by flash chromatography on silica gel eluting with 15 % ethyl acetate in hexane gave 0.77 g (58 %) of the desired 3-bromo-4-(4-morpholinyl)benzaldehyde product as an white solid. ^{1}H NMR ($CDCl_3$) δ 3.18 (m, 4H), 3.90 (m, 4H), 7.10 (d, 1H), 7.78 (d, 1H), 8.07 (s, 1H), 9.83 (s, 1H).

[0322] **EX-604B)** To a dioxane (8 mL) solution of the aldehyde from **EX-604A** (0.77 g, 2.8 mmol) was added 2-(tributylstannyl)furan (1.07 mL, 3.42 mmol) and $Pd(PPh_3)_2Cl_2$ (0.12 g, 0.17 mmol). The mixture was heated to reflux under argon for 18 h. The cooled mixture was poured into a mixture of saturated aq. KF and ethyl acetate and stirred 3 h. The slurry was filtered through celite. The organic layer was separated, washed with brine, dried ($MgSO_4$) and evaporated to a yellow oil. Purification by silica gel flash chromatography eluting with 20 % ethyl acetate in hexane gave 0.61 g (84%) of the desired 3-(2-furanyl)-4-(4-morpholinyl)benzaldehyde product as a yellow oil. MS: *m*/*z* = 258.1 $[M+H]^+$.

[0323] To a 1,2-dichloroethane (6 mL) solution of aldehyde (0.59 g, 2.0 mmol) from **EX-604B** was added *N*-(3-phenoxyphenyl)-3-amino-1,1,1-trifluoro-2-propanol (0.50 g, 1.9 mmol), $NaB(OAC)_3H$ (0.52 g, 2.5 mmol) and acetic acid (0.12 mL, 2.1 mmol). The cloudy solution was stirred at room temperature for 18 h. The reaction mixture was poured into water and extracted with dichloromethane. The organic layer was washed with saturated $NaHCO_3$ and brine, dried ($MgSO_4$) and evaporated to give an oil. Purification by flash chromatography on silica gel eluting with 15 % ethyl acetate in hexane gave 0.25 g (25 %) of the desired 3-[(3-phenoxyphenyl)[[3-(2-furanyl)-4-(4-morpholinyl)phenyl]methyl]amino]-1,1,1-trifluoro-2-propanol product as a white foam, > 99% pure by HPLC analysis. Anal. calcd. for $C_{30}H_{29}N_2O_4F_3$: C, 66.91; H, 5.43; N, 5.20. Found: C, 66.54; H, 5.67; N, 5.02. HRMS: calcd. 539.2187 $[M+H]^+$, found: 539.2158. ^{1}H NMR (C_6D_6) δ 1.73 (d, 1H), 2.55 (m, 4H), 3.23 (dd, 1H), 3.50 (dd, 1H), 3.52 (m, 4H), 3.75 (m, 1H), 4.25 (s, 2H), 6.21 (dd, 1H), 6.36 (dd, 1H), 6.34 (dd, 1H), 6.56 (t, 1H), 6.69 (d, 1H), 6.8 (m, 2H), 6.9-7.0 (m, 5H), 7.09 (t, 1H), 7.22 (d, 1H), 7.34 (d, 1H).

EXAMPLE 605

[0324]



3-[(3-phenoxyphenyl)[[3-(2-pyrimidinyloxy)phenyl]methyl] amino]-1,1,1-trifluoro-2-propanol

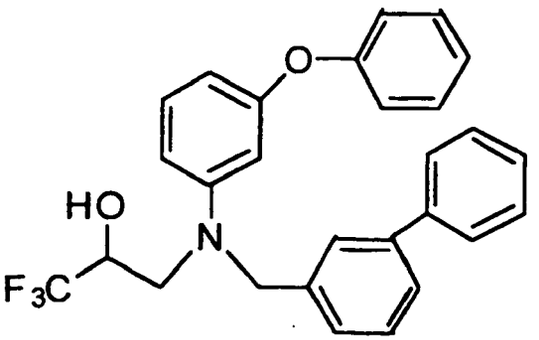
[0325] **EX-605A)** A slurry of 3-hydroxybenzaldehyde (1.22 g, 10 mmol), 2-chloropyrimidine (1.14 g, 10 mmol) and K_2CO_3 (1.65 g, 12 mmol) in DMSO (20 mL) was heated to 100˚C for 1 h. The cooled mixture was poured into water and extracted with Et_2O. The organic layer was washed with 2.5 N NaOH, 1 N HCl, saturated $NaHCO_3$ and brine, dried ($MgSO_4$) and evaporated to yield 1.42 g (71 %) of the desired 3-(2-pyrimidinyl-oxy)benzaldehyde product as a white solid which was used without further purification. ^{1}H NMR (C_6D_6) δ 7.12 (t, 1H), 7.54 (m, 1H), 7.66 (t, 1H), 7.78 (m, 1H), 7.83 (m, 1H), 8.64 (d, 2H), 10.05 (s, 1H).

[0326] To a 1,2-dichloroethane (10 mL) solution of aldehyde (0.56 g, 2.8 mmol) from **EX-605A** was added *N*-(3-phenoxyphenyl)-3-amino-1,1,1-trifluoro-2-propanol (0.83 g, 2.8 mmol), $NaB(OAc)_3H$ (0.77 g, 3.6 mmol) and acetic acid (0.84 mL, 15 mmol). The cloudy solution was stirred at room temperature for 18 h. The reaction mixture was poured into water and extracted with dichloromethane. The organic layer was washed with saturated $NaHCO_3$ and brine, dried ($MgSO_4$) and evaporated to give an oil. Purification by flash chromatography on silica gel eluting with 2 % methanol in CH_2Cl_2 gave an oil which was dissolved in EtOH, stripped and dried *in vacuo* to give 0.28 g (21 %) of the desired 3-[(3-phenoxyphenyl)[[3-(2-pyrimidinyloxy)phenyl]-methyl]amino]-1,1,1-trifluoro-2-propanol product as a colorless oil, > 99% pure by HPLC analysis. Anal. calcd. for $C_{26}H_{22}N_3O_3F_3 \cdot 0.4$ EtOH: C, 64.39; H, 4.92; N, 8.41. Found: C, 64.22; H, 4.87;

N, 8.53. HRMS calcd. 482.1692 $[M+H]^+$, found: 482.1698. ^1H NMR (C_6D_6) δ 3.12 (d, 1H), 3.16 (dd, 1H), 3.49 (d, 1H), 3.79 (m, 1H), 4.12 (dd, 1H), 5.88 (t, 1H), 6.31 (dd, 1H), 6.41 (dd, 1H), 6.51 (t, 1H), 6.65 (t, 1H), 6.80 (t, 1H), 6.85-7.05 (m, 8H), 7.82 (d, 2H).

EXAMPLE 606

[0327]



3-[(3-phenoxyphenyl)[([1,1'-biphenyl]-3-ylmethyl)amino]-1,1,1-trifluoro-2-propanol

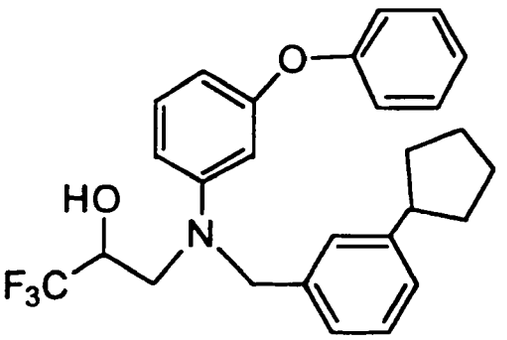
[0328] **EX-606A)** To an ethylene glycol dimethyl ether (10 mL) solution of 3-bromobenzaldehyde (0.63 mL, 5.4 mmol) was added phenylboronic acid (0.73 g, 6.0 mmol), 2 M Na_2CO_3 (10 mL) and $Pd(PPh_3)_4$ (0.35 g, 0.30 mmol). The slurry was heated to reflux under argon for 18 h. The cooled mixture was poured into water and extracted with ethyl acetate. The organic layer was washed with brine, dried ($MgSO_4$) and evaporated to an oil. Purification by flash chromatography on silica gel eluting with 15 % ethyl acetate in hexane gave 0.77 g (98%) of the desired [(1,1'-biphenyl)-3-yl]-carboxaldehyde product as a colorless oil which solidified upon standing. ^1H NMR (C_6D_6) δ 7.45 (m, 3H), 7.65 (m, 3H), 7.70 (dd, 2H), 8.15 (m, 1H), 10.13 (s, 1H).

[0329] **EX-606B)** To a 1.2-dichloroethane (12 mL) solution of aldehyde (0.77 g, 4.2 mmol) from **EX-606A** was added 3-phenoxyaniline (0.78 g, 4.2 mmol), $NaB(OAc)_3H$ (1.16 g, 5.5 mmol) and acetic acid (0.25 mL, 4.2 mmol). The cloudy solution was stirred at room temperature for 2 h. The reaction mixture was poured into water and extracted with dichloromethane. The organic layer was washed with saturated $NaHCO_3$ and brine, dried ($MgSO_4$) and evaporated to yield 1.49 g (100%) of the desired *N*-(3-phenoxyphenyl)([1,1'-biphenyl]-3-ylmethyl)amine product as a colorless oil which was used without further purification. ^1H NMR ($CDCl_3$) δ 4.35 (s, 2H), 6.35 (m, 2H), 6.44 (d, 1H), 6.97 (d, 2H), 7.05 (t, 1H), 7.12 (t, 1H), 7.3-7.4 (m, 7H), 7.49 (d, 1H), 7.56 (m, 3H). The formation of the desired product was monitored by the disappearance of the aldehyde peak (δ ~ 10) and the formation of the benzyl peak (δ 4.35) in the ^1H NMR spectrum.

[0330] To a CH_3CN (4 mL) solution of amine (1.48 g, 4.2 mmol) from **EX-606B** was added 1,1,1-trifluoro-2,3-epoxypropane (0.475 mL, 5.5 mmol) and $Yb(OTf)_3$ (0.26 g, 0.42 mmol). The cloudy solution was stirred in a sealed flask at 40 ˚C for 18 h. The cooled reaction mixture was diluted with diethyl ether and washed with water and brine. The organic layer was dried ($MgSO_4$) and evaporated to an oil. Purification by flash chromatography on silica gel eluting with 10% ethyl acetate in hexane gave an oil which was dissolved in EtOH, stripped and dried *in vacuo* to give 0.65 g (34%) of the desired 3-[(3-phenoxyphenyl)[([1,1'-biphenyl]-3-ylmethyl)amino]-1,1,1-trifluoro-2-propanol product as a colorless oil which solidified upon standing, > 99% pure by HPLC analysis. Anal. calcd. for $C_{28}H_{24}NO_2F_3 \cdot 0.05\ CH_2O_2$: C, 72.03; H, 5.19; N, 2.99. Found: C, 71.67; H, 5.10; N, 2.94. HRMS calcd. 464.1837 $[M+H]^+$, found: 464.1834. ^1H NMR (C_6D_6) δ 1.43 (d, 1H), 3.17 (dd, 1H), 3.46 (dd, 1H) 3.70 (m, 1H), 4.26 (s, 2H), 6.32 (dd, 1H), 6.44 (dd, 1H), 6.52 (t, 1H), 6.77 (m, 1H), 6.85-6.95 (m, 5H), 7.1 (m, 3H), 7.16 (t, 2H), 7.26 (s, 1H), 7.27 (d, 1H), 7.40 (dd, 2H).

EXAMPLE 607

[0331]

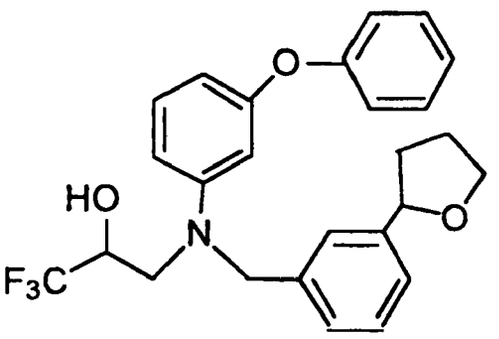


3-[(3-phenoxyphenyl)[[3-cyclopentylphenyl]methyl]amino]-1,1,1-trifluoro-2-propanol

[0332] **EX-607A)** To a 1,2-dichloroethane (12 mL) solution of 3-cyclopentylbenzaldehyde (0.69 g, 4.0 mmol; P. L. Ornstein et al., J. Med. Chem. 1998, 41, 358-378) was added 3-phenoxyaniline (0.73 g, 4.0 mmol). $NaB(OAc)_3H$ (1.08 g, 5.1 mmol) and acetic acid (0.24 mL, 4.2 mmol). The cloudy solution was stirred at room temperature for 2 h. The reaction mixture was poured into water and extracted with dichloromethane. The organic layer was washed with saturated $NaHCO_3$ and brine, dried ($MgSO_4$) and evaporated to an oil. Purification by flash chromatography on silica gel eluting with 10% ethyl acetate in hexane gave 0.30 g (22 %) of the desired *N*-(3-phenoxyphenyl)-[[3-cyclopentylphenyl]methyl] amine product as a colorless oil. ^1H NMR ($CDCl_3$) δ 1.55 (m, 2H), 1.63 (m, 2H), 1.78 (m, 2H), 2.02 (m, 2H), 2.94 (m, 1H), 4.10 (m, 1H), 4.22 (m, 2H), 6.35 (m, 3H), 7.0-7.2 (m, 10H). The formation of the desired product was monitored by the disappearance of the aldehyde peak (δ~10) and the formation of the benzyl peak (δ 4.22) in the ^1H NMR spectrum.
[0333] To a CH_3CN (0.9 mL) solution of amine (0.30 g, 0.87 mmol) from **EX-607A** was added 1,1,1-trifluoro-2,3-epoxypropane (0.15 mL, 1.7 mmol) and $Yb(OTf)_3$ (0.080 g, 0.13 mmol). The cloudy solution was stirred in a sealed flask at 50 ˚C for 18 h. The cooled reaction mixture was diluted with diethyl ether and washed with water and brine. The organic layer was dried ($MgSO_4$) and evaporated to an oil. Purification by flash chromatography on silica gel eluting with 10% ethyl acetate in hexane gave an oil which was dissolved in EtOH, stripped and dried *in vacuo* to give 0.19 g (48 %) of the desired 3-[(3-phenoxyphenyl)[[3-cyclopentylphenyl]methyl]amino]-1,1,1-trifluoro-2-propanol product as a colorless oil which solidified upon standing, > 99% pure by HPLC analysis. Anal. calcd. for $C_{27}H_{28}NO_2F_3 \cdot 0.4$ EtOH: C, 70.45; H, 6.47; N. 2.96. Found: C, 70.21; H, 6.39; N, 2.94. HRMS calcd. 456.2150 $[M+H]^+$, found: 456.2143. ^1H NMR (C_6D_6) δ 1.43 (m, 4H), 1.58 (m, 2H), 1.62 (d, 2H), 1.85 (m, 2H), 2.71 (m, 1H), 3.22 (dd, 1H), 3.49 (dd, 1H), 3.73 (m. 1H), 4.26 (s, 2H), 6.35 (dd, 1H), 6.43 (dd, 1H), 6.55 (t, 1H), 6.8 (m, 2H), 6.95-7.05 (m, 8H).

EXAMPLE 608

[0334]



3-[(3-phenoxyphenyl)[[3-(tetrahydro-2-furanyl)phenyl] methyl]amino]-1,1,1-trifluoro-2-propanol

[0335] **EX-608A)** Trifluoromethanesulfonic anhydride (2.0 mL, 11.9 mmol) was added dropwise over 5 minutes to a slurry of 3-hydroxybenzaldehyde (1.11 g, 9.09 mmol) in dichloromethane (40 mL) at -78 ˚C. To this slurry was added

neat N,N-di-isopropyl-ethylamine (2.4 mL, 13.8 mmol) dropwise over 5 min, and the resulting yellow solution was allowed to warm to room temperature. After 30 min at room temperature, the dark solution was diluted with dichloromethane and washed with 2.5 N NaOH. 1 N HCl, saturated $NaHCO_3$ and brine. The organic layer was dried ($MgSO_4$) and evaporated to give a red oil. Purification by flash chromatography on silica gel eluting with 10 % ethyl acetate in hexane gave 1.70 g (74%) of the desired triflate ester product as a pale yellow oil. MS: *m*/*z* = 254 $[M+H]^+$.

[0336] **EX-608B)** To a mixture of $Pd_2(dba)_3$ (120 mg, 0.13 mmol) and P(*o*-tolyl)$_3$ (150 mg, 0.50 mmol) in toluene (15 mL) was added the triflate ester from **EX-608A** (1.70 g, 6.7 mmol), *N,N*-di-isopropylethylamine (3.50 mL, 20.1 mmol) and 2,3-dihydrofuran (2.53 mL, 33.5 mmol). The solution was heated to 70 ˚C in a sealed flask under argon for 18 h. The cooled solution was then diluted with ethyl acetate and washed with water, 1 N HCl, saturated $NaHCO_3$ and brine.

[0337] The organic layer was dried ($MgSO_4$) and evaporated to give a red oil. The major product was isolated by flash chromatography on silica gel eluting with 10% ethyl acetate in hexane and gave 0.72 g (62 %) of the desired 3-(dihydro-2-furanyl)benzaldehyde product as a cloudy yellow oil. MS: *m*/*z* = 175.1 $[M+H]^+$.

[0338] **EX-608C)** A THF (15 mL) solution of the aldehyde from **EX-608B** (0.70 g, 4.0 mmol) and 2,6-lutidine (0.46 mL, 4.0 mmol) was stirred in a hydrogen atmosphere (50 psi) in the presence of 10% Pd/C (0.29 g) for 18 h at room temperature. The slurry was filtered through celite, and the solvent was removed. The residue was taken up in ethyl acetate and washed with 1 N HCl and brine. The organic layer was dried ($MgSO_4$) and evaporated to give 0.50 g (70 %) of the desired 3-(tetrahydro-2-furanyl)phenylmethanol product as a yellow oil. The formation of the desired product was monitored by the disappearance of the aldehyde (δ ~ 10) and olefin peaks in the ^1H NMR spectrum.

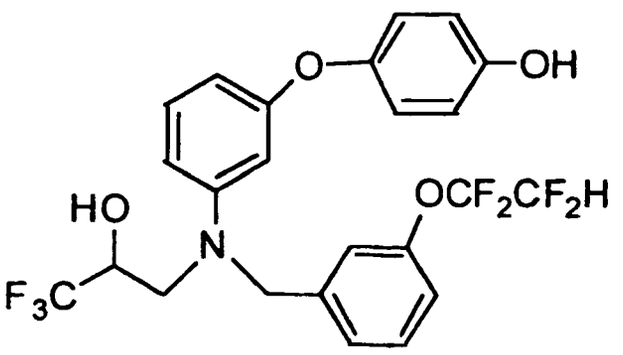
[0339] **EX-608D)** A slurry of the phenylmethanol product from **EX-608C** (0.50 g, 2.8 mmol) and MnO_2 (2.10 g, 24.3 mmol) in dichloromethane (15 mL) was refluxed for 3 h. The slurry was filtered through celite, and the filtrate was evaporated to a yellow oil. Purification by flash chromatography on silica gel eluting with 10% ethyl acetate in hexane gave 0.19 g (45%) of the desired aldehyde product as a pale yellow oil. GCMS: *m*/*z* = 177 $[M+H]^+$.

[0340] **EX-608E)** To a 1,2-dichloroethane (4 mL) solution of the aldehyde (0.19 g, 1.1 mmol) from **EX-608D** was added 3-phenoxyaniline (0.20 g, 1.1 mmol), $NaB(OAc)_3H$ (0.30 g, 1.4 mmol) and acetic acid (0.065 mL, 1.1 mmol). The cloudy solution was stirred at room temperature for 3 h. The reaction mixture was poured into water and extracted with dichloromethane. The organic layer was washed with saturated $NaHCO_3$ and brine, dried ($MgSO_4$) and evaporated to yield 0.32 g (84%) of the desired *N*-(3-phenoxyphenyl)-[[3-(tetrahydro-2-furanyl)phenyl]methyl]amine product as a yellow oil which was used without further purification. The formation of the desired product was monitored by TLC.

[0341] To a CH_3CN (1 mL) solution of the amine (0.32 g, 0.93 mmol) from EX-608E was added 1,1,1-trifluoro-2,3-epoxypropane (0.24 mL, 2.8 mmol) and $Yb(OTf)_3$ (0.115 g, 0.18 mmol). The cloudy solution was stirred in a sealed flask at 40 ˚C for 18 h. The cooled reaction mixture was diluted with diethyl ether and washed with water and brine. The organic layer was dried ($MgSO_4$) and evaporated to an oil. Purification by flash chromatography on silica gel eluting with 15% ethyl acetate in hexane gave an oil which was dissolved in EtOH, stripped and dried *in vacuo* to give 0.13 g (30%) of the desired 3-[(3-phenoxyphenyl)[[3-(tetrahydro-2-furanyl)phenyl]methyl]aminol-1,1,1-trifluoro-2-propanol product as a colorless oil. Anal. calcd. for $C_{26}H_{26}NO_3F_3 \cdot 0.5$ EtOH: C, 67.33; H, 6.04; N, 2.94. Found: C, 67.49; H, 6.08; N, 2.91. HRMS calcd. 458.1943 $[M+H]^+$, found: 458.1937. ^1H NMR (C_6D_6) δ 0.45 (d, 1H), 1.43 (m, 3H), 1.79 (m, 1H), 1.99 (m, 1H), 3.24 (m, 1H), 3.43 (m, 1H), 3.76 (m, 2H), 4.24 (s, 2H), 4.60 (t, 1H), 6.35 (m, 1H), 6.43 (dd, 1H), 6.54 (dd, 1H), 6.8 (m, 2H), 6.9-7.0 (m, 7H), 7.15 (d, 1H).

EXAMPLE 609

[0342]



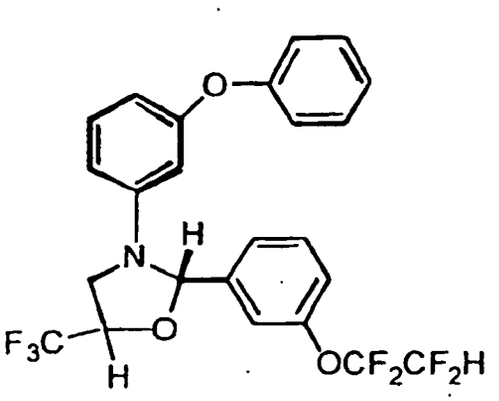
4-[3-[[[3-(1,1,2,2-tetrafluoroethoxy)phenyl]methyl](3,3,3-trifluoro-2-hydroxypropyl)amino]phenoxy]phenol

[0343] A 1,2-dichloroethane (4 mL) solution of *N*-[(4-methoxyphenoxy)phenyl]-3-[[3-(1,1,2,2-tetrafluoroethoxy)phenyl] methyl]amino]-1,1,1-trifluoro-2-propanol (0.33g, 0.62 mmol) and boron tribromide-methyl sulfide complex (2.5 mL, 1.0 M in CH_2Cl_2, 2.5 mmol) was refluxed for 8 h under argon. The reaction was diluted with Et_2O and washed with water, 1 N NaOH and saturated aq. NH_4Cl.

[0344] The organic layer was dried ($MgSO_4$) and evaporated to give a red oil. Purification by flash chromatography on silica gel eluting with 30% ethyl acetate in hexane gave an oil which was dissolved in EtOH, stripped and dried *in vacuo* to give 0.082 g (25%) of the desired 4-[3-[[[3-(1,1,2,2-tetrafluoroethoxy)phenyl]methyl](3,3,3-trifluoro-2-hydroxy-propyl)amino] phenoxy]phenol product as a light red oil. Anal. calcd. for $C_{24}H_{20}NO_4F_7 \cdot 0.35$ EtOH$\cdot 0.65$ H_2O: C, 54.21; H, 4.31; N, 2.56. Found: C, 54.20; H, 4.30; N , 2.55. HRMS calcd. 520.1359 $[M+H]^+$, found: 520.1325. ^1H NMR (C_6D_6) δ 1.96 (d, 1H), 3.09 (dd, 1H), 3.43 (dd, 1H), 3.74 (m, 1H), 4.10 (s, 2H), 4.52 (s, 1H), 5.09 (tt, 1H), 6.17 (dd, 1H), 6.4 (m, 4H), 6.66 (d, 1H), 6.8-6.9 (m, 6H).

EXAMPLE 610 *

[0345]

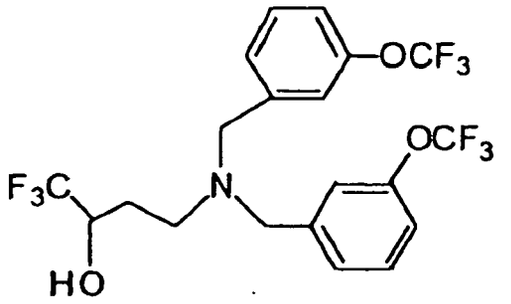


3-(3-phenoxyphenyl)-2-[3-(1,1,2,2-tetrafluoroethoxy)phenyl]-5-(trifluoromethyl)oxazolidine

[0346] A toluene solution (5 mL) of 3-(1,1,2,2-tetrafluoroethoxy)benzaldehyde (0.45 g, 2.0 mol) and *N*-(3-phenoxy-phenyl)-3-amino-1,1,1-trifluoro-2-propanol (0.60 g, 2.0 mmol) was refluxed in the presence of molecular sieves and ZnI_2 (-5 mg) for 18 h under N_2. The reaction mixture was filtered to remove the sieves, and the filtrate was diluted with ethyl acetate. The organic layer.was washed with brine, dried ($MgSO_4$) and evaporated to give 0.92 g (92%) of the desired 3-(3-phenoxyphenyl)-2-[3-(1,1,2,2-tetrafluoro-ethoxy)phenyl]-5-(trifluoromethyl) oxazolidine product as a colorless oil. The formation of the desired product was monitored by the disappearance of the aldehyde peak (δ ~ 10) in the ^1H NMR spectrum. HRMS calcd. 502.1253 $[M+H]^+$, found: 502.1220.

EXAMPLE 611 *

[0347]



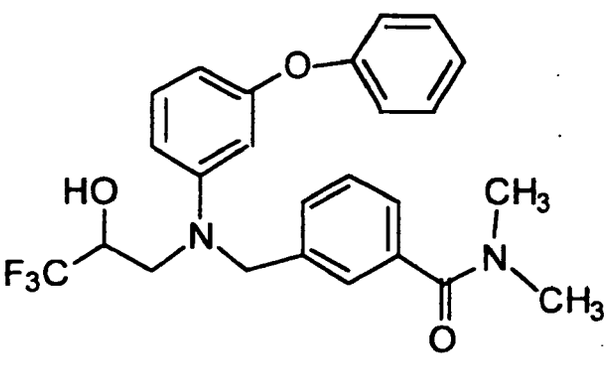
4-[bis-[[3-(trifluoromethoxy)phenyl]metbyl]amino]-1,1,1-trifluoro-2-butanol

[0348] **EX-611A)** The 2-hydroxy-1,1,1-trifluorobutyronitrile (5.0 g, 36 mmol; H. C. Brown et al. J. Org. Chem. 60, 41-46, 1995) was added slowly to a stirred suspension of $LiAlH_4$ (1.7 g, 43.7 mmol) in 8 mL of dry diethyl ether at 0-5 ˚C. The mixture was stirred at this temperature for 30 min, heated for 45 min, then stirred at room temperature for 2 h. The reaction mixture was quenched with 5.5 mL of aq. sat. Na_2SO_4 and stirred for 1 h. The mixture was filtered through a celite pad, and the pad was washed with ether. The filtrate and ether washings were collected and evaporated to give 4.2 g (82%) of crude 4-amino-2-hydroxy-1,1,1-trifluorobutane product as a brownish solid. HRMS calcd. for $C_4H_8NOF_3$: 144.0636 $[M+H]^+$, found 144.0622.

[0349] The 4-amino-2-hydroxy-1,1,1-trifluorobutane (0.57 g, 4 mmol) from **EX-611A** and 3-(trifluoromethoxy)benzyl bromide (2.04 g, 8.0 mmol) were dissolved in 10 mL of anhydrous ethanol. Potassium carbonate (1.10 g, 8 mmol) was added, and the mixture was heated to reflux for 3 days, at which time HPLC analysis indicated the formation of product, as confirmed by MS. The reaction mixture was quenched with water and extracted with ether. The ether layer was washed with water and brine, then dried over $MgSO_4$, and evaporated to give crude product, which was purified by flash column chromatography on silica gel eluting with 1:10:0.01 to 1:7:0.01 of ethyl acetate:hexane:ammonium hydroxide to give 0.53 (27%) of the desired 4-[bis-[[3-(tri-fluoromethoxy)phenyl]methyl]amino]-1,1,1-trifluoro-2-butanol product as a yellow oil. ^1H NMR ($CDCl_3$) δ 7.37 (t, 2H), 7.23 (d, 2H), 7.14 (d, 4H), 5.68 (bs, 1H), 3.98 (m, 1H), 3.76 (d, 2H), 3.45 (d, 2H), 2.78 (dd, 2H), 1.90 (m, 1H), 1.83 (m, 1H). 19 F NMR ($CDCl_3$) δ -58.27 (s, 6F), -80.54 (d, 3F). HRMS calcd. for $C_{20}H_{18}NO_3F_9$: 492.1221 $[M+H]^+$, found: 492.1184.

EXAMPLE 612

[0350]



***N,N*-dimethyl-3-[[(3-phenoxyphenyl)(3,3,3-trifluoro-2-hydroxypropyl)amino]methyl]benzamide**

[0351] **EX-612A)** Methyl 3-(bromomethyl)benzoate (7.2 g, 0.031 mol) was added dropwise to a solution of 3-phenoxy-aniline (20.5 g, 0.11 mol) in 160 mL of cyclohexane. The reaction mixture was refluxed overnight then cooled to room temperature and diluted with water and methylene chloride. The layers were separated, and the aqueous layer was

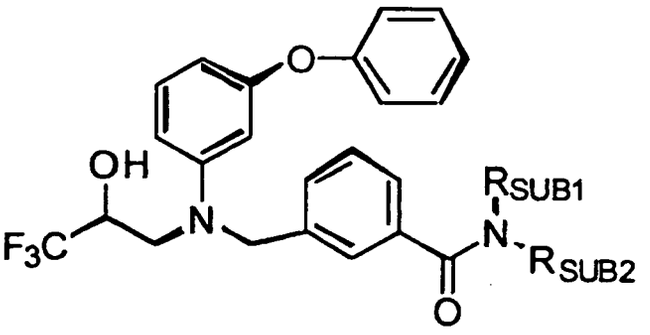
extracted with methylene chloride. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated *in vacuo* to give a dark oil. The crude product was purified by reverse phase HPLC eluting with 20% to 90% acetonitrile in water to afford 6.2 g (59%) of the desired methyl 3-[[(3-phenoxyphenyl)amino]methyl] benzoate product as a yellow oil. ESMS *m/z* = 334 $[M+H]^+$.

[0352] **EX-612B)** To a mixture of methyl 3-[[(3-phenoxyphenyl)amino]methyl]benzoate (6.2 g, 0.019 mol) from **EX-612A** and 1,1,1-trifluoro-2,3-epoxypropane (8.58 g, 0.077 mol) in 12 mL of acetonitrile was added ytterbium (III) trifluoromethanesulfonate (1.2 g. 0.0019 mol). The resulting mixture was heated at 50˚C in a sealed glass tube for 18 h. The reaction mixture was cooled to room temperature, then diluted with water and methylene chloride. The aqueous layer was extracted with methylene chloride. The organic layers were combined, dried over $MgSO_4$, and concentrated *in vacuo.* The crude product was purified by column chromatography on silica gel eluting with 1:9 ethyl acetate in hexane to afford 8.0 g (96%) of the desired methyl 3-[[(3-phenoxy-phenyl)(3,3,3-trifluoro-2-hydroxypropyl)amino]methyl] benzoate product as a yellow oil. Anal. calcd. for $C_{24}H_{22}F_3NO_4 \cdot 1.4\ H_2O$: C, 61.25; H, 5.31; N, 2.98. found: C, 61.52; H, 5.06; N, 2.89. HRMS calcd.: 446.1579 $[M+H]^+$, found: 446.1596. ^{1}H NMR($CDCl_3$) δ 7.28 (m, 4H), 7.14 (t, 1H), 7.07, (m, 3H), 7.00 (s, 1H), 6.94 (d, 2H), 6.46 (dd, 1H), 6.38 (dd, 1H), 6.35 (t, 1H), 5.84 (t, 1H), 4.60 (t, 2H), 4.36 (m, 1H), 3.82 (d, 1H), 3.48 (m, 1H), 2.51 (s, 1H). ^{19}F NMR ($CDCl_3$) δ -79.0 (d, 3 F).

[0353] To a solution of *N,N*-dimethylamine hydrochloride (525 mg, 0.0064 mol) in 3.0 mL of toluene at -40 ˚C was added dropwise a 2.0 M solution of trimethylaluminum in toluene (3.2 mL, 0.0064 mol) over 15 min. The reaction mixture was warmed to room temperature and stirred for 2 h. To a solution of methyl 3-[[(3-phenoxyphenyl)(3,3,3-trifluoro-2-hydroxypropyl)amino] methyl] benzoate (209 mg, 0.00047 mol) from **EX-612B** in 2.5 mL of toluene at -10 ˚C was slowly added the (*N,N*-dimethylamino)-chloromethylaluminum reagent (850 μL, 0.00085 mol). The reaction mixture was warmed to room temperature then heated at 40 ˚C overnight. The reaction mixture was cooled to room temperature, then diluted with ethyl acetate and quenched with 10% aqueous potassium hydrogen phosphate. The organic layer was dried over $MgSO_4$ and concentrated *in vacuo.* The crude product was purified by column chromatography on silica gel eluting with 2:3 ethyl acetate in hexane to afford 195 mg (91%) of the desired *N,N*-dimethyl-3-[[(3-phenoxyphenyl)(3,3,3-trifluoro-2-hydroxypropyl) amino]methyl]-benzamide product as a pale yellow solid. Anal. calcd. for $C_{25}H_{25}F_3N_2O_3 \cdot 0.5\ H_2O$: C, 64:23; H, 5.61; N, 5.99. Found: C, 64.49; H, 5.77; N, 5.85. HRMS calcd. 459.1896 $[M+H]^+$, found: 458.1887. ^{1}H NMR (C_6D_6) δ 7.01-6.95 (m, 3H), 6.92-6.87 (m, 5H), 6.79 (t. 1H). 6.46 (s, 1H), 6.37 (t, 2H), 4.91 (bs, 1H), 4.26 (s, 2H), 4.10 (bq, 1H), 3.84 (dd, 1H), 3.38 (dd, 1H), 2.53 (bs, 3H), 2.14 (bs, 3H). ^{19}F NMR (C_6D_6) δ -78.69 (d, 3F).

[0354] Additional examples of *N,N*-dialkyl- and *N,N*-cycloalkyl-3-[[(3-phenoxy-phenyl)-(3,3,3-trifluoro-2-hydroxypropyl)amino]methyl]benzamides can be prepared by one skilled in the art using similar methods, as shown in Example Table 36.

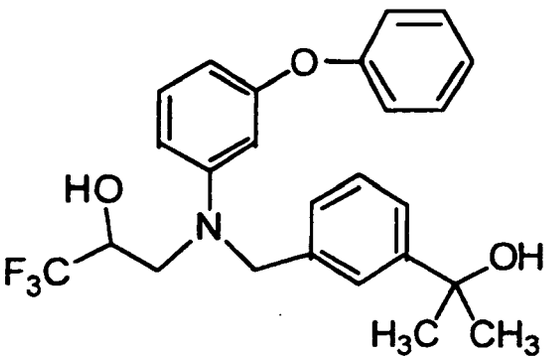
Example Table 36. *N,N*-dialkyl- and *N,N*-cycloalkyl-3-[[(3-phenoxyphenyl)-(3,3,3-trifluoro-2-hydroxypropyl)amino] methyl]benzamides.



Ex. No.	R_{SUB1}	R_{SUB2}	Calculated Mass $[M+H]^+$	Observed Mass $[M+H]^+$
613	methyl	ethyl	473.2052	473.2055
614	methyl	propyl	487.2209	487.2193
615	methyl	butyl	501.2365	501.2357
616	-($CH_2CH_2CH_2CH_2$)-		485.2052	485.2057

EXAMPLE 617

[0355]

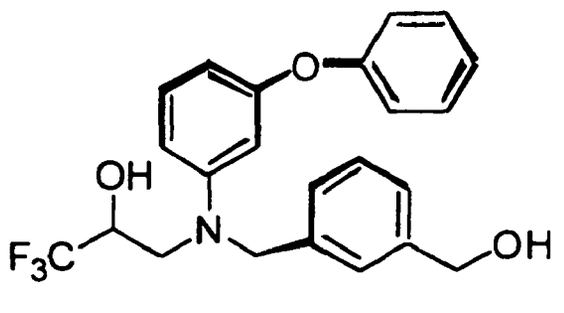


α, α-dimethyl-3-[[(3-phenoxyphenyl)(3,3,3-trifluoro-2-hydroxypropyl)amino]methyl]benzenemethanol

[0356] To a solution of methyl 3-[[(3-phenoxyphenyl)(3,3,3-trifluoro-2-hydroxypropyl)amino]methyl]benzoate (218 mg, 0.00049 mol) in 0.7 mL of tetrahydrofuran at 0 ˚C was slowly added a 3.0 M solution of methylmagnesium chloride in THF (650 μL, 0.0020 mol). The reaction mixture was warmed to room temperature, stirred for 2 h, then diluted with diethyl ether and quenched with saturated aqueous ammonium chloride. The aqueous layer was extracted with dichloromethane, and the combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo.* The crude product was purified by column chromatography on silica gel eluting with 1:4 ethyl acetate:hexane to afford 174 mg (80%) of the desired α,α-dimethyl-3-[[(3-phenoxy-phenyl)(3,3,3-trifluoro-2-hydroxypropyl) amino]methyl]benzenemethanol product as a slightly yellow oil. Anal. calcd. for $C_{25}H_{26}F_3NO_3 \cdot 0.5\ H_2O$: C, 66.07; H, 5.99; N, 3.08. found: C, 66.12; H, 6.34; N, 2.92. HRMS calcd. 466.1943 $[M+H]^+$, found: 446.1938. ^1H NMR ($CDCl_3$) δ 7.34 (s, 1H), 7.32-7.21 (m, 4H), 7.13 (t, 1H), 7.09-7.01 (m, 2H), 6.94 (d, 2H), 6.50 (d, 1H), 6.41 (s, 1H), 6.37 (d, 1H), 4.61 (s, 2H), 4.27 (bt, 1H), 3.81 (appd, 1H), 3.53 (dd, 1H), 3.33 (bs, 1H), 1.96 (bs, 1H), 1.51 (s, 6H). ^{19}F NMR ($CDCl_3$) δ -78.88 (d, 3F).

EXAMPLE 618

[0357]



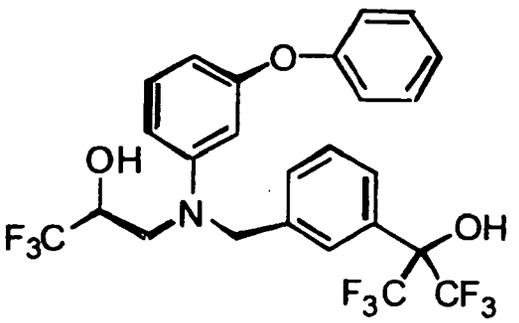
3-[[(3-phenoxyphenyl)(3,3,3-trifluoro-2-hydroxypropyl) amino]methyl]benzenemethanol

[0358] To a solution of methyl 3-[[(3-phenoxyphenyl)(3,3,3-trifluoro-2-hydroxypropyl)amino]methyl]benzoate (197 mg, 0.00044 mol) in 2.0 mL of dichloromethane at -40 ˚C was slowly added a 1.0 M solution of lithium aluminum hydride in THF (1.1 mL, 0.0011 mol). The reaction mixture was stirred at -40 ˚C for 1 h, then diluted with ethyl acetate and quenched with water. The organic layer was dried over $MgSO_4$ and concentrated *in vacuo.* The crude material was determined to contain a significant amount of unreacted starting material by HPLC at this stage. The crude material was resubjected to the reaction conditions using 2 mL of anhydrous tetrahydrofuran and 1.0 M lithium aluminum hydride (1.3 mL, 0.0013

mol) at -40 ˚C for 1 h, then diluted with ethyl acetate and quenched with water. The aqueous layer was extracted with ethyl acetate, and the combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo.* The crude product was purified by column chromatography on silica gel eluting with 2:3 ethyl acetate:hexane to afford 99 mg (54%) of the desired 3-[[(3-phenoxyphenyl)-(3,3,3-trifluoro-2-hydroxypropyl)amino]methyl]benzenemethanol product as a white solid. Anal. calcd. for $C_{23}H_{22}F_3NO_3$: C, 66.18; H, 5.31; N, 3.36. Found: C, 65.98; H, 5.39; N, 3.22. HRMS calcd. 418.1630 $[M+H]^+$, found: 418.1636. ^1H NMR (C_6D_6) δ 7.08-6.92 (m, 8H), 6.89-6.80 (m, 2H), 6.56 (s, 1H), 6.46 (d, 1H), 6.38 (d, 1H), 4.26 (s, 2H), 4.21 (d, 2H), 3.77 (appq, 1H), 3.52 (d, 1H), 1.92 (bs, 1H), 0.96 (bs, 1H). ^{19}F NMR (C_6D_6) δ -78.91 (d, 3F).

EXAMPLE 619

[0359]

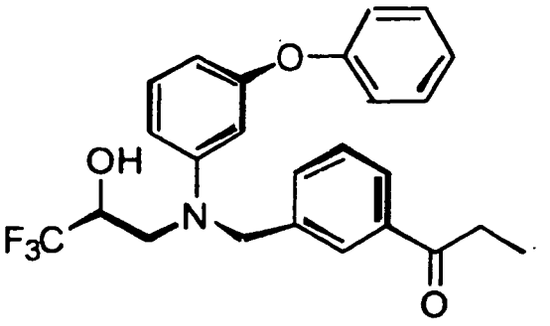


α,α-bis(trifluoromethyl)-3-[[(3-phenoxyphenyl)(3,3,3-trifluoro-2-hydroxypropyl)amino]methyl]benzenemethanol

[0360] To a solution of methyl 3-[[(3-phenoxyphenyl)(3,3,3-trifluoro-2-hydroxypropyl)-amino]methyl]benzoate (331 mg, 0.00074 mol) and trimethyl(trifluoromethyl)silane (423 mg, 0.0030 mol) in 3.0 mL of toluene at room temperature was added a 1.0 M solution of tetrabutylammonium fluoride in THF (150 μL, 0.00015 mol) which had been dried over molecular sieves. The reaction mixture was heated at 40 ˚C for 18 h. HPLC analysis indicated incomplete reaction therefore additional trimethyl(trifluoro-methyl)silane (440 μL, 0.0030 mol) and tetrabutylammonium fluoride (150 μL, 0.00015 mol) were added, and the reaction mixture was heated to 50 ˚C in a sealed glass vial. After 2 h, HPLC analysis indicated no ester starting material remained. The reaction mixture was quenched with water and extracted with dichloromethane. The organic layer was dried over $MgSO_4$ and concentrated *in vacuo.* The crude product was purified by column chromatography on silica gel eluting with 1:9 ethyl acetate:hexane to afford 26 mg (6%) of the desired a,a-bis (trifluoromethyl)-3-[[(3-phenoxyphenyl)(3,3,3-trifluoro-2-hydroxypropyl) amino]methyl]benzenemethanol product as a yellow-brown oil. HRMS calcd. for $C_{25}H_{20}F_9NO_3$: 554.1378 $[M+H]^+$, found: 554.1385. ^1H NMR ($CDCl_3$) δ 7.69 (dd. 1H), 7.57 (apps, 1H), 7.52 (dd, 1H), 7.37 (t, 1H), 7.29-7.23 (m, 2H), 7.14 (t, 1H), 7.05 (t. 1H), 6.92 (d. 2H), 6.47 (d. 1H), 6.38 (d. 1H). 6.37 (s, 1H), 4.66 (s, 2H), 4.29 (m, 1H), 3.82 (d, 1H), 3.54 (dd, 1H), ^{19}F NMR ($CDCl_3$) δ -75.81 (dq, 6F), -79.18 (d, 3F).

EXAMPLE 620

[0361]



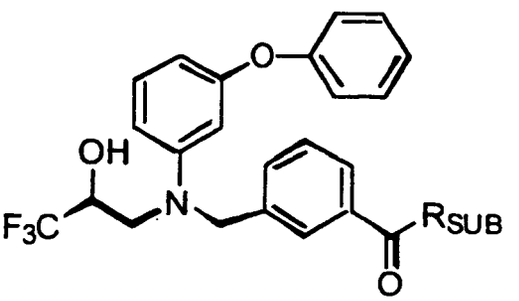
1-[3-[[(3-phenoxyphenyl)(3,3,3-trifluoro-2-hydroxypropyl)-amino]methyl]phenyl]-1-propanone

[0362] **EX-620A)** To a slurry of methyl 3-[[(3-phenoxyphenyl)(3,3,3-trifluouo-2-hydroxypropyl)amino]methyl]benzoate (1.03 g, 0.0023 mol) and N, O-dimethylhydroxylamine hydrochloride (386 mg, 0.0040 mol) in 4.6 mL of tetrahydrofuran at -15 ˚C was added a 2.0 M solution of isopropylmagnesium chloride in THF (4.6 mL, 0.0092 mol) over 15 min. The reaction was stirred for 1 h at -15 ˚C, then quenched with 20% aqueous ammonium chloride and extracted with ethyl acetate. The organic layers were dried over Na_2SO_4 and concentrated *in vacuo.* The crude product was purified by column chromatography on silica gel eluting with 1:1 ethyl acetate:hexane to afford 0.72 g (66%) of the desired *N*-methoxy-*N*-methyl-3-[[(3-phenoxyphenyl)-(3,3,3-trifluoro-2-hydroxypropyl)amino.imethyl]benzamide product as an off-white solid. HRMS calcd. for $C_{25}H_{25}N_2O_4F_3$: 475.1845 $[M+H]^+$, found: 475.1840.

[0363] To a solution of *N*-methoxy-*N*-methylbenzamide (208 mg, 0.00044 mol) from **EX-620A** in 2.2 mL of tetrahydrofuran at -15 ˚C was added a 1.0 M solution of ethyl-magnesium bromide in THF (950 μL, 0.0095 mol). The reaction mixture was slowly warmed to room temperature then left stirring overnight. HPLC analysis indicated unreacted starting material was still present so additional ethylmagnesium bromide (440 μL, 0.0044 mol) was added. After 3 h at room temperature, the reaction mixture was diluted with diethyl ether and quenched with 1 N HCl. The aqueous layer was extracted with diethyl ether and the combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo.* The crude product was purified by column chromatography on silica gel eluting with 1:4 ethyl acetate in hexane to afford 121 mg (62%) of the desired 1-[3-[[(3-phenoxyphenyl)(3,3,3-trifluoro-2-hydroxypropyl)-amino]methyl]phenyl]-1-propanone product as a pale yellow oil. HRMS calcd. for $C_{25}H_{24}F_3NO_3$: 444.1787 $[M+H]^+$, found: 444.1786. ^1H NMR ($CDCl_3$) δ 7.83 (d, 1H), 7.78 (s, 1H), 7.38 (appq, 2H), 7.27 (appq, 2H), 7.15 (t, 1H), 7.06 (t, 1H). 6.94 (d, 2H), 6.48 (d, 1H), 6.39 (d, 1H), 6.37 (s, 1H), 4.68 (s, 2H), 4.35 (m, 1H), 3.88 (dd, 1H), 3.56 (dd, 1H), 2.95 (q, 2H), 1.20 (t, 3H). ^{19}F NMR ($CDCl_3$) δ -79.17 (d, 3F).

[0364] Additional examples of 1-[3-[[(3-phenoxyphenyl)(3,3.3-trifluoro-2-hydroxypropyl)amino]methyl]-phenyl]-1-alkanones can be prepared by one skilled in the art using similar methods, as shown in Example Table 37.

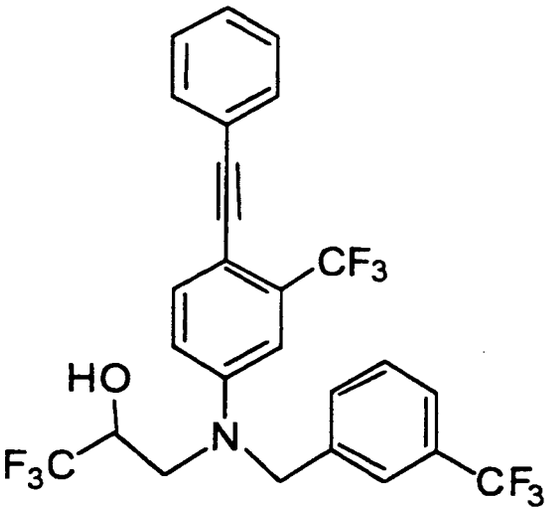
Example Table 37. 1-[3-[[(3-phenoxyphenyl)(3,3,3-trifluoro-2-hydroxypropyl)amino]methyl]-phenyl]-1-alkanones.



Ex. No.	R_{SUB}	Calculated Mass $[M+H]^+$	Observed Mass $[M+H]^+$
621	isobutyl	472.2130	472.2100

EXAMPLE 622

[0365]

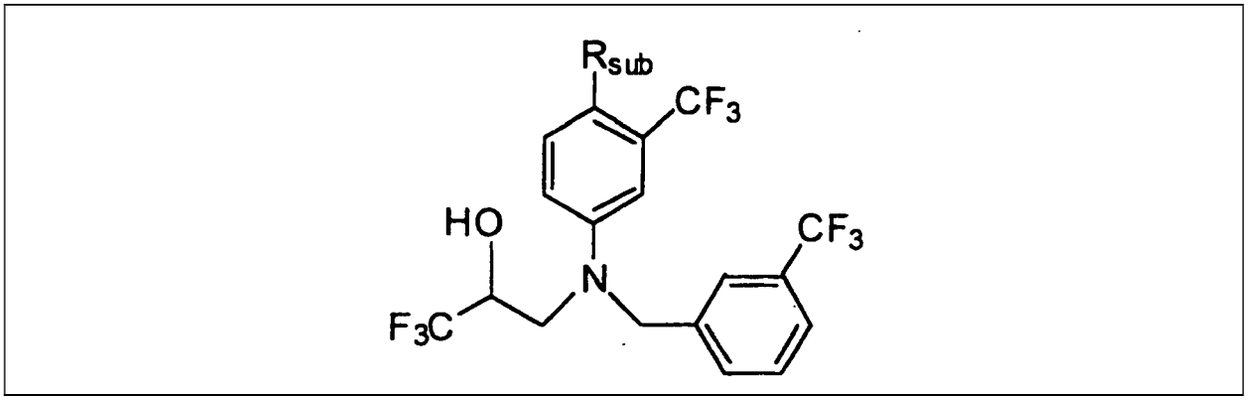


3-[[4-(phenylethynyl)-(3-(trifluoromethyl)phenyl][[3-(trifluoromethyl)phenyl]methyl]amino]-1,1,1-trifluoro-2-propanol

[0366] The 3-[(3-(trifluoromethyl)-4-bromophenyl)[[3-(1,1,1-trifluoromethyl)phenyl] methyl]-amino]-1,1,1-trifluoro-2-propanol (0.33 g, 0.648 mmol) and tributylstannylphenyl- acetylene (0.278 g, 0.712 mmol) were added to degassed 1,2-dichloroethane. The resulting mixture was stirred at room temperature for 10 min, then $Pd(PPh_3)_2Cl_2$ (0.032 g. 0.045 mmol) was added. The mixture was stirred 18 h at room temperature. More tributyl-stannylphenylacetylene (0.278 g, 0.712 mmol) and $Pd(PPh_3)_2Cl_2$ (0.032 g, 0.045 mmol) were added. The solution was refluxed for 72 h. The reaction mixture was diluted with diethyl ether and stirred in 10% aq. KF for 18 h. The organic layer was collected, dried over $MgSO_4$ and concentrated. The crude product was purified by flash column chromatography on silica gel eluting with 1: 4 ethyl acetate in hexane to give 0.102 g (30%) of the desired 3-[[4-(phenylethynyl)-(3-(trifluoromethyl)phenyl]-[[3-(trifluoromethyl)phenyl]methyl]amino]-1,1,1-trifluoro-2-propanol product as a pure yellow oil. Anal calcd. For $C_{26}H_{18}NOF_9$: C, 58.76; H, 3.41; N, 2.64. Found: C. 58.72; H, 3.67; N, 2.47. HRMS calcd. 532.1322 $[M+H]^+$, found: 532.1304. ^1H NMR ($COCl_3$) δ 7.52 (m, 4H), 7.38 (dd, 2H), 7.32 (dd, 2H), 7.24 (dd, 1H). 7.00 (s, 1H), 6.78 (dd, 1H), 4.80 (s, 2H), 4.36 (m, 1H), 3.92 (d, 1H), 3.65 (m, 1H), 2.60 (d, 1H). ^{19}F NMR ($CDCl_3$) δ -63.5 (s, 6F), - 79.38 (d, 3F).

[0367] Additional examples of 3-[[4-(heteroaryl)-(3-(trifluoromethyl)phenyl][[3-(tri-fluoromethyl)phenyl]methyl]amino]-1,1,1-trifluoro-2-propanols can be prepared by one skilled in the art using similar methods, as shown in Example Table 38.

Example Table 38. 3-[[4-(heteroaryl)-(3-(trifluoromethyl)phenyl]-[[3-(trifluoromethyl)phenyl]methyl]amino]-1,1,1-trifluoro-2-propanols.

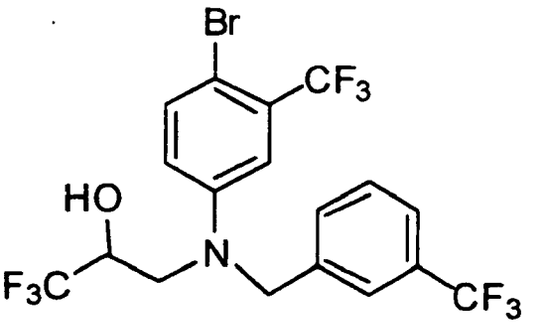


(continued)

Ex. No.	R_{SUB}	Calculated Mass $[M+H]^+$	Observed Mass $[M+H]^+$
623	2-thienyl	514.0887	514.0912
624	2-furanyl	498.1037	498.1116

EXAMPLE 625

[0368]



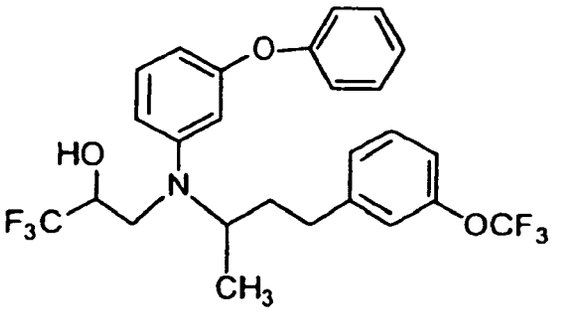
3-[4-bromo-3-(trifluoromethyl)phenyl[[3-(trifluoromethyl)-phenyl]methyl]amino]-1,1,1-trifluoro-2-propanol

[0369] **EX-625A)** The α,α,α-trifluoro-*m*-tolualdehyde (3.63 g, 0.021 mol) was added neat to 4-bromo-3-trifluoromethylaniline (5.0 g, 0.021 mol). Dichloroethane (50 mL) was added followed by sodium triacetoxyborohydride (4.85 g, 0.023 mol) and acetic acid (1.42 g, 0.024 mol). The resulting mixture was stirred at room temperature for 18 h, then diluted with methylene chloride, quenched with sodium bicarbonate and extracted with methylene chloride. The organic layers were combined and dried over $MgSO_4$ and concentrated to give 6.97 g of the desired 3-[4-bromo-3-(trifluoromethyl)-phenyl[[3-(trifluoromethyl) phenyl]methyl]amine product as a yellow oil, which was carried forward without purification. ESMS *m*/*z* = 397 $[M+H]^+$.

[0370] The amine product (6.97 g, 0.018 mol) from **EX-625A** was mixed with 1,1,1-trifluoro-2,3-epoxypropane (3.92 g, 0.035 mol) in a pressurized vial. A suspension of ytterbium triflate (1.08 g, 0.002 mol) in 2.0 mL of acetonitrile was added. The resulting mixture was stirred at room temperature for 18 h, then quenched with water and extracted with ethyl acetate. The crude product was purified by flash column chromatography on silica gel eluting with 1:4 ethyl acetate in hexane to give 1.04 g (11%) of the desired 3-[4-bromo-3-(trifluoromethyl)phenyl[[3-(trifluoromethyl)-phenyl]methyl] amino]-1,1,1-trifluoro-2-propanol product as a pure yellow oil. Anal calcd. for $C_{18}H_{13}NOF_9Br$: C, 42.38; H, 2.57; N, 2.75. Found: C, 42.16: H, 2.71; N, 2.71. HRMS calcd. 510.0115 $[M+H]^+$, found: 510.0139. ^1H NMR (C_6D_6) δ 7.40 (d, 2H), 7.20 (d, 1H), 7.10 (m, 2H), 6.98 (d, 1H), 6.18 (dd, 1H), 4.00 (s, 2H), 3.63 (m, 1H), 3.40 (d, 1H), 3.02 (m, 1H), 1.80 (d, 1H). ^{19}F NMR (C_6D_6) δ -62.35 (s, 3F), -65.00 (s, 3F), -78.58 (d,3F).

EXAMPLE 626 *

[0371]



3-[[1-metbyl-3-[3-(trifluoromethoxy)phenyl]propyl](3-phenoxyphenyl)amino]- 1,1,1-trifluoro-2-propanol

[0372] **EX-626A)** Tetrabutylammonium iodide (0.4 g, 0.05 mol) was added to a well-stirred biphasic mixture of 12 mL of 50% NaOH and 20 mL of methylene chloride under a nitrogen atmosphere. A solution of 3-trifluoromethoxybenzatdebyde (4.0 g, 0.021 mol) and diethyl (2-oxopropyl)phosphonate (4.08 g, 0.021 mol) in 4.0 mL of methylene chloride was added dropwise to the stirred solution. The resulting mixture was stirred at room temperature for 15 min, then quenched with water and extracted with hexane. The hexane layer was dried over $MgSO_4$. The crude product was purified by flash column chromatography on silica gel eluting with 1:10 ethyl acetate in hexane to give 2.6 g (54%) of the desired 4-[3-(trifluoromethoxy)phenyl]-3-buten-2-one product as a yellow oil. ^1H NMR ($CDCl_3$) δ 7.43 (m, 4H), 7.20 (d, 1H), 6.65 (d, 2H), 2.29 (s, 3H). ^{19}F NMR ($CDCl_3$) δ -62.05 (s, 3F).

[0373] **EX-626B)** The product (1.0 g, 0.0004 mol)from **EX-626A** was dissolved in 25 mL of ethanol and the reaction vessel was charged with nitrogen. Palladium (10% on carbon) (0.30 g, 30%) was added to the solution. The mixture was hydrogenated for 3 h at room temperature. The palladium was filtered off through a celite pad. The filtrate was concentrated to give 0.79 g (85%) of the desired 4-[3-(trifluoromethoxy)phenyl]- butan-2-one as a yellow oil. ESMS *m/z* = 232 $[M+H]^+$.

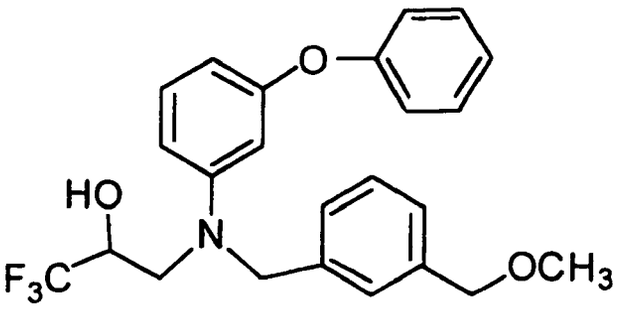
[0374] **EX-626C)** In a flask equipped with a stir bar and molecular sieves, a solution of 3-phenoxyaniline (1.1 g, 0.0059 mol) in 15 mL of cyclohexane was prepared under nitrogen. A solution of the ketone (1.3 g, 0.006 mol) product from **EX-626B** dissolved in 5 mL of cyclohexane was added. The mixture was refluxed for 18 h, filtered and concentrated to give the desired imine product as a dark yellow oil. ESMS *m/z* = 400 $[M+H]^+$.

[0375] **EX-626D)** The imine product (1.3 g, 0.003 mol) from **EX-626C** was stirred with 5 mL of methanol at 0 ˚C. Sodium borohydride (0.23 g, 0.005 mol) was added to the mixture, and the mixture was stirred at room temperature for 18 h. The mixture was acidified with 4 mL of 3% HCl and extracted with diethyl ether. The ether layers were combined, dried over $MgSO_4$ and concentrated to give 1.07 g (81%) of the desired 3-[1-methyl-3-[3-(trifluoromethoxy)phenyl] propyl] (3-phenoxyphenyl)amine product as an orange oil. ESMS *m/z* = 402 $[M+H]^+$.

[0376] The 3-[1-methyl-3-[3-(trifluoromethoxy)phenyl]propyl](3-phenoxyphenyl)amine (1.0 g, 0.002 mol) product from **EX-626D** and 1,1,1-trifluoro-2,3-epoxypropane (0.56 g, 0.005 mol) were heated at 90 ˚C for 18 h. Excess epoxide was evaporated. The crude product was purified by flash column chromatography on silica gel eluting with 1:13 ethyl acetate in hexane to give 0.16 g (13%) of the desired 3-[[1-methyl-3-[3-(trifluoro-methoxy)phenyl] propyl](3-phenoxyphenyl) amino]-1,1,1-trifluoro-2-propanol product as a yellow oil. Anal calcd. for $C_{26}H_{25}NO_3F_6$: C, 60.82; H, 4.91; N, 2.72. Found: C, 60.63; H, 4.89; N, 2.70. HRMS calcd. 514.1816 $[M+H]^+$, found: 514.1789. ^1H NMR (C_6D_6) δ 7.28 (m, 4H), 7.14 (t, 1H), 7.07, (m, 3H), 7.00 (s, 1H), 6.94 (d, 2H), 6.46(dd, 1H), 6.38 (dd, 1H), 6.35 (t, H), 4.18 (m, 1H), 3.78 (m, 1H), 3.52 (dd, 1H), 3.28 (m, 1H), 2.76 (s, 1H), 2.53 (m, 2H), 1.92 (m, 1H), 1.63 (m, 1H), 1.24 (m, 3H). ^{19}F NMR ($CDCl_3$) δ -56.84 (s, 3F), -79.0 (s, 3F).

EXAMPLE 627

[0377]



3-[[(3-phenoxyphenyl)(3,3,3-trifluoro-2-hydroxypropyl) amino]methyl)methoxymethylbenzene

[0378] **EX-627A)** A suspension of *N*-bromosuccinimide (17.6 g, 0.099 mol) in carbon tetra-chloride was added to a stirring solution of *m*-xylene in carbon tetrachloride. Then 2,2-azobisisobutyronitrile catalyst (0.71 g, 0.004 mol) was added. The resulting mixture was refluxed for 2 h, then quenched with 50 mL of water. The organic layer was collected, washed with water followed by brine, dried over $MgSO_4$ and concentrated to give 2.0 g (16%) of the desired crude 1,3-dibromoxylene product. ESMS *m*/*z* = 264 $[M+H]^+$.

[0379] **EX-627B)** The 1,3-dibromoxylene (2.0 g, 0.0076 mol) from **EX-627A** and sodium methoxide (2.45 g, 0.045 mol) were mixed in 25 mL of MeOH. The resulting mixture was stirred at room temperature for 18 h, concentrated, dissolved in methylene chloride and washed with water. The organic layer was further washed with brine and dried over $MgSO_4$ and concentrated to give 0.912 g (72%) of the desired 1,3-di-(methoxy-methyl)benzene product as a yellow oil. ESMS *m*/*z* = 166 $[M+H]^+$.

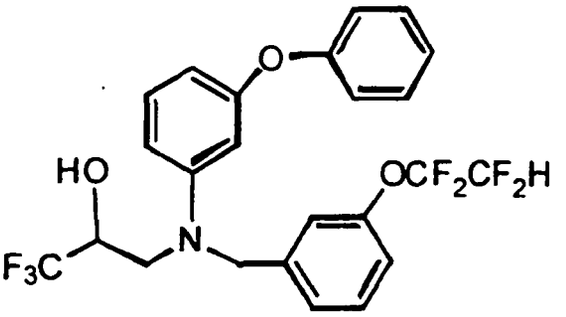
[0380] **EX-627C)** The diether product (0.90 g, 0.0054 mol) from **EX-627B** was stirred in a mixture of 10:1 methylene chloride:water. To this was added 2,3-dichloro-5,6-dicyano-benzoquinone (1.84 g, 0.0081 mol). The resulting biphasic mixture was stirred at room temperature for 72 h. The mixture was then washed with saturated sodium bicarbonate followed by brine, dried over $MgSO_4$ and concentrated. The crude product was purified by flash column chromatography on silica eluting with 1:4 ethyl acetate:hexane to give 0.430 g (53%) of the desired 3-(methoxymethyl)benzaldehyde product as a pink oil. ^1H NMR ($CDCl_3$) δ 10.00 (s, 1H), 7.89 (s, 1H), 7.83 (d, 1H), 7.63 (d, 1 H), 7.51 (t, 1H), 4.58 (s, 2H), 3.40 (s, 3H).

[0381] **EX-627D)** The 3-(methoxymethyl)benzaldehyde (0.430 g, 2.87 mmol) from **EX-627C** was added to a stirring solution of 3-phenoxyaniline (0.530 g, 2.87 mmol) in 5 mL of dichloromethane. Then sodium triacetoxyborohydride (0.670 g, 3.16 mmol) was added followed by acetic acid (0.196 g, 3.27 mmol). The resulting mixture was stirred at room temperature 18 h, then diluted in methylene chloride and quenched with sodium bicarbonate. The organic layer was washed with brine, dried over $MgSO_4$ and concentrated to give 0.870 g (95%) of the desired *N*-3-(phenoxyphenyl)-[[3-(methoxy-methyl)phenyl]methyl]amine product as a pink oil. ESMS *m*/*z* = 320 $[M+H]^+$.

[0382] The *N*-3-(phenoxyphenyl)-[[3-(methoxymethyl)phenyl]methyl)amine product (0.87 g, 0.003 mol) from **EX-627D** was mixed with 1,1,1-trifluoro-2,3-epoxypropane (0.61 g, 0.005 mol) in a pressurized vial. A suspension of ytterbium triflate (0.16 g, 0.272 mmol) in 0.5 mL of acetonitrile was added. The resulting mixture was stirred at room temperature for 18 h, then quenched with water and extracted with ethyl acetate. The crude product was purified by flash column chromatography on silica gel eluting with 1:4 ethyl acetate:hexane to give 0.35 g (30%) of the desired 3-[[(3-phenoxy-phenyl)-(3,3,3-trifluoro-2-hydroxypropyl)amino]methyl]methoxymethylbenzene product as a pure yellow oil. Anal calcd. for $C_{24}H_{24}NO_3F_3 \cdot 0.5\ H_2O$: C, 65.18; H, 5.61; N, 3.17. Found: C, 65.19; H, 5.36; N, 3.13. HRMS calcd. 432.1786 $[M+H]^+$, found: 432.1803. ^1H NMR (C_6D_6) δ 6.82 (m, 7H), 6.60 (dd, 1H), 6.42 (dd, 1H), 6.38 (s, 1H), 6.18 (dd, 1H), 4.00 (s, 2H), 3.63 (m, 1H), 3.40 (d, 1H), 3.02 (m, 1H), 1.80 (d, 1H). ^{19}F NMR (C_6D_6) δ -78.55 (s, 3F).

EXAMPLE 628

[0383]



3-[(3-phenoxyphenyl) [[3-(1,1,2,2-tetrafluoroethoxy)phenyl] methyl]amino]-1,1,1-trifluoro-2-propanol

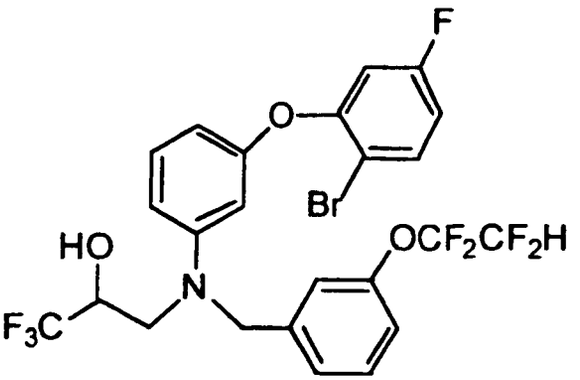
[0384] EX-628A) To a solution of 3-(1,1,2,2-tetrafluoroethoxy)toluene (50 g, 0.24 mol) and *N*-bromosuccinimide (42.75 g, 0.24 mol) in 100 mL of carbon tetrachloride under nitrogen was added 2.2'-azobisisobutyronitrile (0.71 g, 0.004 mol). The resultant mixture was refluxed for 2 h then cooled to room temperature and quenched with 300 mL of water. The organic layer was collected, washed with water and brine, dried over $MgSO_4$, and concentrated in *vacuo* to give 66.0 g (96%) of the desired crude 3-(1,1,2,2-tetrafluoroethoxy)bromomethylbenzene product as a yellow oil. ^1H NMR indicates that this oil is a mixture of products: 7% dibrominated, 67% monobrominated, and 20% starting material. The crude product was used without further purification. ESMS *m*/*z* = 287 $[M+H]^+$.

[0385] EX-628B) The crude product (56 g, 0.14 mol) from **EX-628A** in 200 mL of cyclohexane was added dropwise under nitrogen to a solution of 3-phenoxyaniline (89 g, 0.480 mol) in 500 mL of cyclohexane. The reaction mixture was refluxed overnight, then cooled to room temperature and diluted with water and diethyl ether. The layers were separated, and the aqueous layer was extracted with diethyl ether. The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo* to give a dark oil. The crude product was purified by column chromatography on silica gel eluting with 1:4 ethyl acetate in hexane to afford 44.96 g (83%) of the desired *N*-3-(phenoxyphenyl)-[[3-(1,1,2,2-tetrafluoroethoxy) phenyl]methyl]amine product as a yellow oil. ESMS *m*/*z* = 392 $[M+H]^+$.

[0386] To a mixture of the amine product (15.0 g, 0.038 mol) from **EX-628B** and 1,1,1-tri-fluoro-2,3-epoxypropane (8.58 g, 0.077 mol) was added a suspension of ytterbium (III) trifluoromethanesulfonate (2.37 g, 0.0031 mol) in 15 mL of acetonitrile. The resulting mixture was heated at 50°C in a sealed glass vial for 1.5 h. The reaction mixture was cooled to room temperature then diluted with water and ethyl acetate and extracted. The organic layers were combined, dried over $MgSO_4$. and concentrated *in vacuo.* The crude product was purified by column chromatography on silica gel eluting with 1:4 ethyl acetate in hexane to afford 12.03 g (62%) of the desired 3-[(3-phenoxyphenyl)-[[3-(1,1,2,2-tetrafluoroethoxy) phenyl]methyl]amino]-1,1,1-trifluoro-2-propanol product as a yellow oil. Anal. calcd. for $C_{24}H_{20}F_7NO_3$: C, 57.26; H, 4.00; N, 2.78. Found: C, 56.96; H, 4.35; N, 2.69. HRMS calcd. 504.1410 $[M+H]^+$, found: 504.1431. ^1H NMR ($CDCl_3$) δ 7.28 (m, 4H), 7.14 (t, 1H). 7.07, (m, 3H), 7.00 (s, 1H), 6.94 (d, 2H), 6.46 (dd, 1H), 6.38 (dd, 1H), 6.35 (t, 1H), 5.84 (t, 1H), 4.60 (t, 2H), 4.36 (m, 1H), 3.82 (d, 1H), 3.48 (m, 1H), 2.51 (s, 1H). ^{19}F NMR ($CDCl_3$) δ -79.0 (s, 3F), -88.21 (d, 2F), -137.05 (dd. 2F).

EXAMPLE 629

[0387]



3-[[3-(2-bromo-5-fluorophenoxy)phenyl][[3-(1,1,2,2-tetrafluoroethoxy)phenyl]methyl]amino]-1,1,1-trifluoro-2-propanol

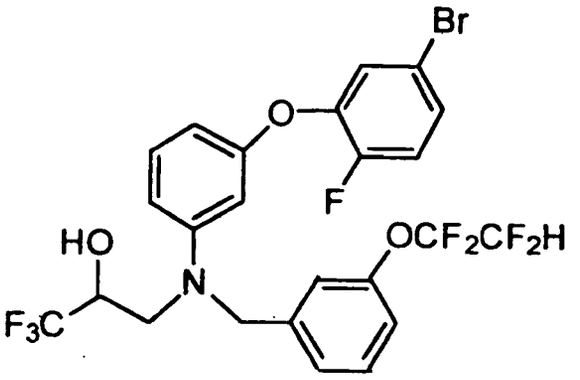
[0388] **EX-629A)** 3-Aminophenol (5 g, 46 mmol), 1-bromo-2,4-difluorobenzene (10 g, 50 mmol) and Cs_2CO_3 (16 g, 50 mmol) were mixed in 25 mL of dimethylformamide. Solid $(CuOTf)_2C_6H_6$ (100 mg) was added, and the mixture was stirred under nitrogen at 85 ˚C for 22 h, at which time HPLC analysis indicated that the reaction had gone to completion and formed two products. The DMF was removed under reduced pressure. The residue was diluted with ether and filtered through a celite pad. The pad was washed with ether and a small amount of water. The mixture was extracted with ether several times. The combined ether layers were washed with water and brine, then dried over $MgSO_4$. The dried organic layer was evaporated to give 10.2 g (80%) of the desired product, which consisted of a 11:1 ratio of 3-(2-bromo-5-fluorophenoxy)-aniline and 3-(4-bromo-3-fluorophenoxy)aniline. The crude product was purified by flash column chromatography on silica gel eluting with 1:7:0.01 of ethyl acetate:hexane:ammonium hydroxide to give 8.8 g (68%) of the desired product as a yellow oil, which was a 25:1 ratio of 3-(2-bromo-5-fluorophenoxy)aniline and 3-(4-bromo-3-fluorophenoxy)aniline. HRMS calcd. for $C_{12}H_9NOFBr$: 281.9930 $[M+H]^+$, found: 281.9950.

[0389] **EX-629B**) The crude 3-(2-bromo-5-fluorophenoxy)aniline (1.39 g, 4.95 mmol) product from **EX-629A** and 3-(1,1,2,2-tetrafluoroethoxy)benzaldehyde (1.0 g, 4.5 mmol) were dissolved in 15 mL of dichloroethane and acetic acid (0.30 mL. 5.4 mmol), then solid $NaBH(OAc)_3$ (1.26 g, 5.9 mmol) was added. The mixture was stirred at room temperature for 1 h, then quenched with water and extracted with ether. The ether layer was washed with water and brine, then dried over $MgSO_4$, and evaporated to give 2.1 g (97%) of crude product. which was purified by flash column chromatography on silica gel eluting with 1:7:0.01 of ethyl acetate:hexane:ammonium hydroxide to give 2.0 g (91 %) of the desired 3-[3-(2-bromo-5-fluorophenoxy)phenyl][[3-(1,1,2,2-tetrafluoro-ethoxy)phenyl] methyl]amine product, as a light yellow oil, > 90% pure by HPLC analysis. HRMS calcd. for $C_{21}H_{15}NO_2BrF_5$: 488.0285 $(M+H)^+$, found: 488.0269.

[0390] The 3-[3-(2-bromo-5-fluorophenoxy)phenyl][[3-(1,1,2,2-tetraftuoroethoxy) phenyl]-methyllamine (0.97 g, 2.0 mmol) product from **EX-629B** and 1,1,1-trifluoro-2,3-epoxypropane (0.45 g, 4.0 mmol) were dissolved in 1.0 mL of acetonitrile. Ytterbium (III) trifluoromethanesulfonate (0.12 g, 0.2 mmol) was added, and the stirred solution was warmed to 40 ˚C for 1 h, at which time HPLC analysis indicated that no secondary amine starting material remained. The reaction was quenched with water and extracted with ether. The ether layer was washed with water and brine, then dried over $MgSO_4$. The crude product was purified by flash column chromatography on silica gel eluting with 1:7:0.01 of ethyl acetate:hexane:ammonium hydroxide to give 0.83 g (69%) of the desired 3-[[3-(2-bromo-5-fluorophenoxy)phenyl][[3-(1,1,2,2-tetrafluoroethoxy) phenyl] -methyl]amino]-1,1,1-trifluoro-2-propanol product as a clear colorless oil, > 95% pure by HPLC analysis. ^1H NMR ($CDCl_3$) δ 7.50 (dd, 1H), 7.30 (t, 1H), 7.18 (t, 1H), 7.07 (t, 2H), 6.99 (s, 1H), 6.70 (dt, 1H), 6.56 (dd, 1H), 6.52 (dd, 1H), 6.38 (dd, 1H), 6.32 (m, 1H), 5.87 (tt, 1H), 4.65 (d, 2H), 4.33 (m, 1H), 3.85 (dd, 1H), 3.56 (dd, 1H), 2.48 (bs, 1H). NOE difference spectra confirmed that the isolated material was the indicated *N*-[3-(2-bromo-5-fluorophenoxy)phenyl]-3-aminopropanol product. ^{19}F NMR ($CDCl_3$) δ -79.24 (d, 3F), -88.57 (m, 2F), -112.04 (q, 1H), -137.16 (dt, 2F). Anal. calcd. for $C_{24}H_{18}NO_3BrF_8$: C, 48.02; H, 3.02; N, 2.33. Found: C. 48.48; H, 3.18; N, 2.33. HRMS calcd. 600.0420 $[M+H]^+$, found: 600.0415.

EXAMPLE 630

[0391]



3-[[3-(-5-bromo-2-fluorophenoxy)phenyl][[3-(1,1,2,2-tetrafluoroethoxy)phenyl]methyl]amino]-1,1,1-tritluoro-2-propanol

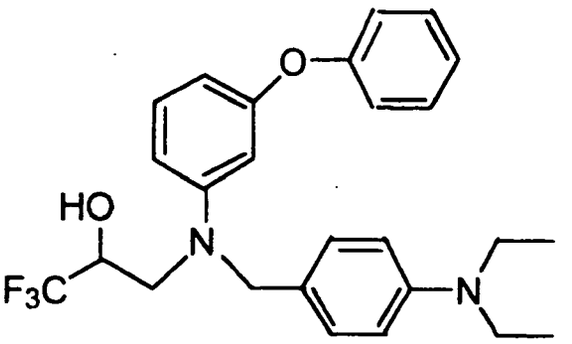
[0392] **EX-630A)** 3-Aminophenol (5 g, 46 mmol), 1-bromo-3,4-difluorobenzene (10 g, 50 mmol) and Cs_2CO_3 (16 g, 50 mmol were mixed in 25 mL of DMF. Solid $(CuOTf)_2C_6H_6$ (100 mg) was added, and the mixture was stirred under nitrogen at 85 ˚C for 22 h, at which time HPLC analysis indicated that the reaction had gone to completion and formed two products. The DMF was removed under reduced pressure. The residue was diluted with ether and filtered through a celite pad. The pad was washed with ether and a small amount of water. The mixture was extracted with ether several times. The combined ether layers were washed with water and brine, then dried over $MgSO_4$. The dried organic layer was evaporated to give 7.5 g (58%) of the desired products, which comprised a 10:1 ratio of 3-(5-bromo-2-fluorophenoxy) aniline and 3-(4-bromo-2-fluorophenoxy) aniline. The crude product was purified by flash column chromatography on silica gel eluting with 1:7:0.01 of ethyl acetate:hexane:ammonium hydroxide to give 4.5 g (35%) of the desired products as a yellow oil, which were a 20:1 ratio of 3-(5-bromo-2-fluorophenoxy)aniline and 3-(4-bromo-2-fluorophenoxy)-aniline. HRMS calcd. for $C_{12}H_9NOFBr$: 281.9930 $[M+H]^+$, found 281.9951.

[0393] **EX-630B)** The crude 3-(5-bromo-2-fluorophenoxy)aniline (1.39 g, 4.95 mmol) product from **EX-630A** and 3-(1,1,2,2-tetrafluoroethoxy)benzaldehyde (1.0 g, 4.5 mmol) were dissolved in 15 mL of dichloroethane and acetic acid (0.30 mL, 5.4 mmol), then solid $NaBH(OAC)_3$ (1.26 g, 5.9 mmol) was added. The mixture was stirred at room temperature for 1 h, then quenched with water and extracted with ether. The ether layer was washed with water and brine, then dried over $MgSO_4$, and evaporated to give 2.1 g (97%) of crude product, which was purified by flash column chromatography on silica gel eluting with 1:7 ethyl acetate:hexane to give 2.0 g (91%) of the desired 3-[3-(5-bromo-2-fluorophenoxy) phenyl][[3-(1,1,2,2-tetrafluoroethoxy)phenyl]methyl]amine product, as a yellow oil, > 95% pure by HPLC analysis. Anal. calcd. for $C_{21}H_{15}NO_2BrF_2$: C, 51.66; H, 3.10; N, 2.87. Found: C, 51.90; H, 3.08; N, 2.86. HRMS calcd. 488.0284 $[M+H]^+$, found 488.0281.

[0394] The amine (1.1 g, 2.26 mmol) product from **EX-630B** and 1,1,1-trifluoro-2,3-epoxypropane (0.38 g, 3.39 mmol) were dissolved in I mL of acetonitrile. Ytterbium (III) trifluoromethanesulfonate (0.14 g, 0.23 mmol) was added, and the stirred solution was warmed to 40 ˚C for 1 h, at which time HPLC analysis indicated that no secondary amine starting material remained. The reaction was quenched with water and extracted with ether. The ether layer was washed with water and brine, then dried over $MgSO_4$. The crude product was purified by flash column chromatography on silica gel eluting with 1:7 ethyl acetate:hexane to give 0.5 g (37%) of the desired 3-[[3-(5-bromo-2-fluorophenoxy)phenyl][[3-(1,1,2,2-tetrafluoroethoxy)phenyl]methyl]amino]-1,1,1-tri-fluoro-2-propanol product as a yellow oil, > 95% pure by HPLC analysis. ^1H NMR ($CDCl_3$) δ 7.50 (t, 1H), 7.20 (dd, 1H), 7.17 (dd, 1H), 7.17 (dd, 1H), 7.09 (t, 2H), 7.00 (dd, 2H), 6.52 (dd, 1H), 6.38 (dd, 1H), 6.37 (s, 1H), 5.87 (tt, 1H), 4.64 (s, 2H), 4.33 (m, 1H), 3.85 (dd, 1H), 3.56 (dd, 1H). ^{19}F NMR ($CDCl_3$) δ - 79.20 (d, 3F), -88.55 (m, 2F), -113.04 (m, 1H), -137.05 (dt, 2F). NOE difference and pcosy spectra confirmed that the isolated material was the indicated *N*-[3-(5-bromo-2-fluorophenoxy)phenyl]-3-aminopropanol product. Anal. calcd. for $C_{24}H_{18}NO_3BrF_8$: C, 48.02; H, 3.02; N, 2.33. Found: C, 48.07; H, 3.14; N, 2.31. HRMS calcd. 600.0420 $[M+H]^+$, found: 600.0404.

EXAMPLE 631

[0395]



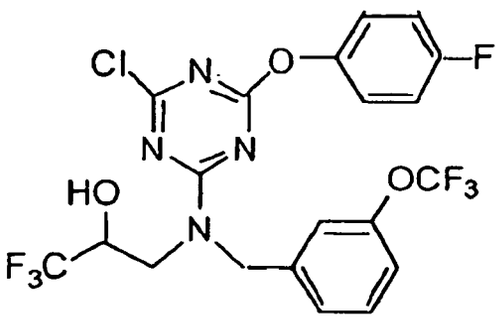
3-[(3-phenoxyphenyl)[[4-(*N,N*-diethylamino)phenyl]methyl] amino]-1,1,1-trifluoro-2-propanol

[0396] **EX-631A)** The 3-phenoxyaniline aniline (0.74 g, 4.0 mmol) and 4-(*N,N*-diethylamino) benzaldehyde (0.59 g, 3.3 mmol) were dissolved in 10 mL of dichloroethane and acetic acid (0.22 mL, 4.0 mmol). Then solid $NaBH(OAc)_3$ (0.94 g, 4.4 mmol) was added. The mixture was stirred at room temperature for 1 h, then quenched with water and extracted with ether. The ether layer was washed with water and brine, then dried over $MgSO_4$, and evaporated to give 1.3 g of crude product, which was purified by flash column chromatography on silica gel eluting with 1:7 ethyl acetate: hexane to give 1.0 g (87%) of the desired 3-[(3-phenoxyphenyl)[4-(*N,N*-diethylamino)phenyl]methyl]-amine product. HRMS calcd. for $C_{23}H_{26}N_2O$: 347.2123 $[M+H]^+$, found 347.2124.

[0397] The 3-[(3-phenoxyphenyl)[4-(*N,N*-diethylamino)phenyl]methyl]amine (0.69 g, 2.0 mmol) product from **EX-631A** and 1,1,1-trifluoro-2,3-epoxypropane (0.45 g, 4 mmol) were dissolved in 1 mL of acetonitrile. Ytterbium (III) trifluoromethanesulfonate (0.12 g, 0.1 mmol) was added, and the stirred solution was warmed to 40 ˚C for 4 h, at which time HPLC analysis indicated that no secondary amine starting material remained. The reaction was quenched with water and extracted with ether. The ether layer was washed with water and brine, then dried over $MgSO_4$. The crude product was purified by flash column chromatography on silica gel eluting with 1:7:0.01 ethyl acetate: hexane:ammonium hydroxide followed by reverse phase preparative HPLC eluting with 10% to 90% acetonitrile in water to give 160 mg (17%) of the desired 3-[(3-phenoxyphenyl)-[[4-(*N,N*-diethylamino)phenyl]methyl]amino]-1,1,1-trifluoro-2-propanol product as a yellow oil, > 95% pure by HPLC analysis. ^1H NMR (CD_3OD) δ 7.39 (d. 2H). 7.31 (d, 2H), 7.22 (m. 3H), 7.13 (d, 1H), 6.98 (t, 1H), 6.75 (dd, 2H), 6.47 (dd, 1H), 6.20 (d, 1H), 4.03 (m, 1H), 3.90 (s, 2H), 3.58 (m, 4H), 3.36 (dd, 1H), 3.12 (dd. 1H), 1.05 (t, 6H). ^{19}F NMR (CD_3OD) δ -80.51 (d, 3F). HRMS calcd. 459.2259 $[M+H]^+$, found: 459.2250.

EXAMPLE 632 *

[0398]



***N*-[2-chloro-6-(p-fluorophenoxy)-1,3,5-triazin-4-yl]-3-[[[3-(trifluoromethoxy)phenyl]methyl]amino]-1,1,1-trifluoro-2-propanol**

[0399] **EX-632A)** 3-Trifluoromethoxybenzenemethanamine (1.15g, 6 mmol) and 1,1,1-trifluoro-2,3-epoxypropane (0.67 g, 6 mmol) were combined and stirred at 80 ˚C for 1.5 h. The mixture was cooled to room temperature, and the resulting solid was recrystallized from hot hexanes. The white solid was isolated by vacuum filtration and washed with cold hexanes

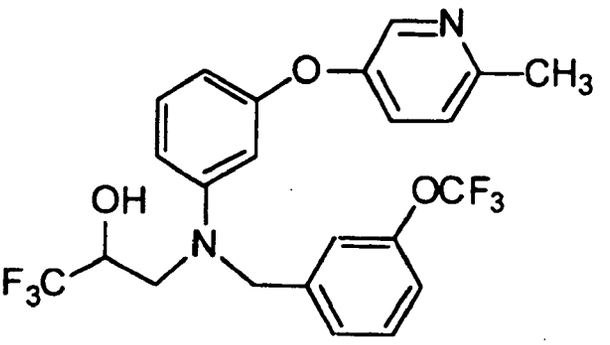
to give 0.67 g (37%) of pure 3-[[[3-(trifluoromethoxy)-phenyl]methyl]amino]-1,1,1-trifluoro-2-propanol. ^{1}H NMR ($CDCl_3$) δ 7.37 (t, 1H), 7.24 (d, 1H), 7.15 (m, 2H), 3.99 (m, 1H), 3.85 (d, 2H), 2.98 (dd, 1H), 2.88 (dd, 1H), 2.79 (s, 1H). ^{19}F NMR ($CDCl_3$) δ -58.19 (s, 3F), -78.88 (s, 3F). HRMS calcd. for $C_{11}H_{11}F_6NO_2$: 304.0772 [M+H]$^+$, found: 304.0794.

[0400] EX-632B) To a solution of 4-fluorophenol 1.00 g (8.92 mmol) in 30 mL of tetrahydrofuran at 0 ˚C was added a 60% dispersion of sodium hydride in mineral oil (0.36 g, 8.92 mmol). After 30 min, cyanuric chloride (1.64 g, 8.92 mmol) was added as a heterogeneous mixture in tetrahydrofuran at 0 ˚C. The reaction mixture was allowed to slowly warm to room temperature. After 14 h, the mixture was cooled to 0 ˚C, and a saturated aq. NH_4Cl solution was added. The aqueous solution was extracted with diethyl ether (3 x 50 mL). The combined ether extracts were washed with brine, dried ($MgSO_4$), and concentrated *in vacuo* to afford 1.34 g (58%) of the desired 2,4-dichloro-6-(4-fluorophenoxy)-1,3,5-triazine product as an off white solid which was taken on to the next step without purification. MS *m*/*z* = 260 [M+H]$^+$.

[0401] To a stirred solution of aminopropanol from **EX-632A** (0.100 g, 0.330 mmol) in *N,N*-dimethylformamide at 0 ˚C was added the 2,4-dichloro-(4-fluorophenoxy)-1,3,5-triazine ether product from **EX-632B** (0.086 g, 0.330 mmol) as a solution in *N,N*-di-methylformamide. The reaction mixture was allowed to slowly warm to room temperature. After 14 h, the reaction mixture was cooled to 0 ˚C, and a saturated aq. $NaHCO_3$ solution was added. After stirring the reaction mixture for 30 min at room temperature, the aqueous layer was extracted with ether (3 x 30 mL). The combined ether extracts were washed with brine, dried ($MgSO_4$), and concentrated *in vacuo* to give a yellow oil. The crude residue was purified by column chromatography on silica gel eluting with 20 % ethyl acetate in hexanes to give 0.075 g (43%) of the desired *N*-[2-chloro-6-(p-fluorophenoxy)-1,3,5-triazin-4-yl]-3-[[[3-(trifluoromethoxy)phenyl]-methyl]amino]-1,1,1-trifluoro-2-propanol product as a pale yellow oil. HRMS calcd. for $C_{20}H_{14}ClF_7N_4O_3$: 526.0643 [M$^+$], found: 526.0632. ^{1}H NMR (C_6D_6) δ 6.95 (s, 1H), 6.63 (m, 14H), 4.74 (d, 1H), 4.37 (d, 1H), 4.16 (d, 1H), 4.00 (d, 2H), 3.73 (m, 1H), 3.48 (m, 2H), 3.26 (m, 2H), 3.12 (m, 2H).

EXAMPLE 633

[0402]



3-[[3-(2-methyl-5-pyridyloxy)phenyl][[3-(trifluoromethoxy) phenyl] methyl]-amino]-1,1,1-trifluoro-2-propanol

[0403] EX-633A) 3-Bromoaniline (2.15 g, 12.5 mmol) and 1,1,1-trifluoro-2,3-epoxypropane (1.0 g, 8.9 mmol) were placed in a sealed vial, heated to 70 ˚C and stirred for 1 h under an atmosphere of nitrogen. The crude product was purified by flash column chromatography on silica gel eluting with CH_2CH_2:hexane (2:1) to give 2.11 g (84%) of the desired 3-[(3-bromophenyl)amino]-1,1,1-trifluoro-2-propanol product as a light amber oil, 98% pure by HPLC analysis. MS *m*/*z* = 284/286 [M+H]$^+$.

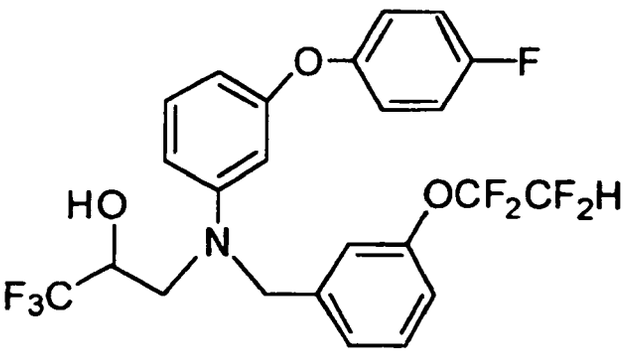
[0404] EX-633B) The 3-[(3-bromophenyl)amino]-1,1,1-trifluoro-2-propanol (1.14 g, 4 mmol) from **EX-633A** and 3-(trifluoromethoxy)benzaldehyde (0.78 g, 4.1 mmol) were dissolved in dichloroethane (18 mL). Acetic acid (0.253 mL, 4.2 mmol) and solid $NaBH(OAc)_3$ (1.07 g, 5.05 mmol) were added. The mixture was stirred at room temperature for 3 h, then acidified with 1 N HCl solution. After neutralizing to pH 7.5 with 2.5 N sodium hydroxide, the mixture was extracted with methylene chloride. The organic layer was washed with brine and water, then dried over anhydrous $MgSO_4$, and evaporated to give 1.12 g (62%) of the desired *N*-3-bromophenyl-[[3-(trifluoromethoxy)phenyl]methyl]amino]-1,1,1-trifluoro-2-propanol product as a brown oil, which was greater than 80% pure by reverse phase HPLC analysis. HRMS calcd. for $C_{17}H_{14}NO_2F_6Br$: 458.0190 [M+H]$^+$, found: 458.0199.

[0405] The 3-[(3-bromophenyl)[[3-(trifluoromethoxy)phenyl]methyl]amino]-1,1,1-trifluoro-2-propanol (500 mg, 1.1 mmol) product from **EX-633B** and 5-hydroxy-2-methylpyridine (262 mg, 2.4 mmol) were dissolved in dimethylacetamide (6 mL). Cs_2CO_3 (1.0 g, 3.1 mmol) and $(CuCF_3SO_3)_2C_6H_6$ (150 mg) were added, and the mixture was heated to 105 ˚C for 96 h under an atmosphere of nitrogen, at which time HPLC analysis indicated that most of the starting materials had

been consumed. After adding water, the reaction mixture was extracted with ether, and the ether extracts were washed with brine and dried over anhydrous $MgSO_4$. The crude product was purified by flash column chromatography on silica gel eluting with ethyl acetate:hexane (1:12) to give 326 mg (61%) of the desired 3-[[3-(2-methyl-5-pyridyloxy)phenyl][[3-(trifluoro-methoxy)phenyl]methyl]amino]-1,1,1-trifluoro-2-propanol product as a light amber oil, 99% pure by HPLC analysis. ^1H NMR ($CDCl_3$) δ 8.00 (s, 1H), 7.29 (t 1H), 6.99 (s, 1H), 7.02-7.15 (m, 5H), 6.46 (dd, 1H), 6.29 (t, 1H), 6.25 (dd, 1H), 4.88 (br s, 1H), 4.67 (ABq, 2H), 4.36 (m, 1H), 3.88 (dd, 1H), 3.56(dd, 1H), 2.49 (s, 3H). ^{19}F NMR ($CDCl_3$) δ -58.2, (s, 3F), -79.1 (d, 3F). HRMS calcd. for $C_{23}H_{20}N_2O_3F_6$: 487.1456 $[M+H]^+$, found: 487.1425.

EXAMPLE 634

[0406]



3-[[3-(4-fluorophenoxy)phenyl][[3-(1,1,2,2-tetrafluoroethoxy)-phenyl]methyl]amino]-1,1,1-trifluoro-2-propanol

[0407] **EX-634A)** Dinitrobenzene (1.68 g, 10 mmol) and 4-fluorophenol (1.13 g, 10 mmol) were dissolved in anhydrous dimethylsulfoxide (25 mL), and powdered cesium carbonate (8 g, 24.8 mmol) was added. The mixture was stirred and heated to 100 ˚C using a reflux condenser under a nitrogen atmosphere. After 16 h, the mixture was diluted with water (120 mL), and the aqueous layer was extracted with diethyl ether (4 x 60 mL). The combined ether layers were washed with 3 % HCl, 5% sodium hydroxide, and water, then dried over anhydrous $MgSO_4$. The ether was removed *in vacuo,* and the recovered oil was purified by flash column chromatography on silica gel eluting with ethyl acetate in hexane (1:25) to give 1.68 g (69%) of the desired 3-(4-fluorophenoxy)nitrobenzene product as orange crystals, 97% pure by HPLC analysis. MS *m/z* = 234 $[M+H]^+$.

[0408] **EX-634B)** 3-(4-Fluorophenoxy)nitrobenzene (1.15 g, 4.93 mmol) from **EX-634A** was dissolved in ethanol (45 mL), and the solution was hydrogenated for 4 h in the presence of 5% palladium on charcoal. After the mixture was filtered through celite, the ethanol was removed *in vacuo.* The product was purified by flash column chromatography on silica gel eluting with ethyl acetate in hexane (1:10) to give 0.92 g (90%) of 3-(4-fluorophenoxy)aniline as a yellow oil, 99% pure by HPLC analysis. HRMS calcd. for $C_{12}H_{11}$ FNO: 204.0824 $[M+H]^+$, found: 204.0837.

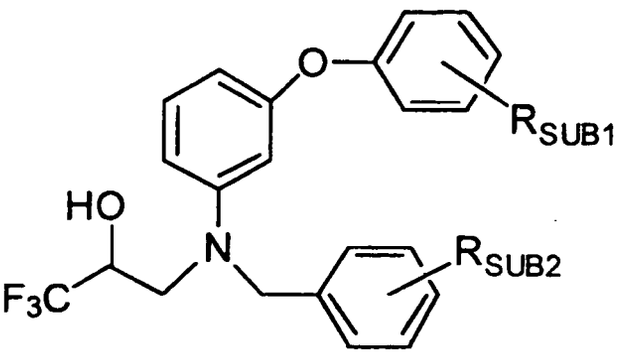
[0409] **EX-634C)** The 3-(4-fluorophenoxy)aniline (812 mg. 4 mmol) from **EX-634B** and 3-(1,1,2,2-tetrafluoroethoxy) benzaldehyde (888 mg, 2 mmol) were dissolved in dichloroethane (15 mL) and acetic acid (0.25 mL. 4.2 mmol), then solid $NaBH(OAc)_3$ (1.01 g, 5 mmol) was added. The mixture was stirred at room temperature for 3 h, then acidified with 1 N HCl. After neutralizing to pH 7.5 with 2.5 N sodium hydroxide, the mixture was extracted with methylene chloride. The organic layer was washed with brine and water, then dried over anhydrous $MgSO_4$, and evaporated to give 1.32 g (78%) of the desired of *N*-[3-(4-fluorophenoxy)phenyl][[3-(1,1,2,2-tetrafluoroethoxy)phenyl]methyl]amine product as a brown oil, which was greater than 90% pure by reverse phase HPLC analysis. MS *mlz* = 410 $[M+H]^+$.

[0410] The *N*-[3-(4-fluorophenoxy)phenyl][[3-(1,1,2,2-tetrafluoroethoxy)phenyl] methyl]amine (612 mg, 1.5 mmol) product from **EX-634C** and 1,1,1-trifluoro-2,3-epoxypropane (268 mg, 2.4 mmol) were dissolved in 1.0 mL of acetonitrile. Ytterbium (III) trifluoromethanesulfonate (43 mg, 0.07 mmol) was added, and the stirred solution was warmed to 40 ˚C for 2.5 h under an atmosphere of nitrogen, at which time HPLC analysis indicated that no secondary amine starting material remained. The reaction was quenched with water and extracted with ether. The ether layer was washed with brine and water, then dried over anhydrous $MgSO_4$. The ether was removed *in vacuo,* and the crude product was purified by flash column chromatography on silica gel eluting with ethyl acetate in hexane (1:11) to give 633 mg (81%) of the desired 3-[[3-(4-fluorophenoxy)phenyl][[3-(1,1,2,2-tetrafluoro-ethoxy)phenyl]methyl] amino]-1,1,1-trifluoro-2-propanol product as a yellow oil, 99% pure by HPLC analysis. ^1H NMR ($CDCl_3$) δ 7.35 (t, 1H), 7.15 (m, 3H), 6.98 (m, 5H), 6.49

(dd, 1H), 6.38 (dd, 1H), 6.33 (m, 1H), 5.92 (tt, 1H), 4.67 (ABq, 2H), 4.37 (m, 1H), 3.91 (dd, 1H), 3.59 (dd, 1H), 2.48 (d, 1H). ^{19}F NMR ($CDCl_3$) δ -79.2 (d, 3F), -88.5 (m, 2F), -120.33 (m, 1F), -137.2 (dt, 2F). HRMS calcd. for $C_{24}H_{19}F_8NO_3$: 522.1315 $[M+H]^+$, found: 522.1297.

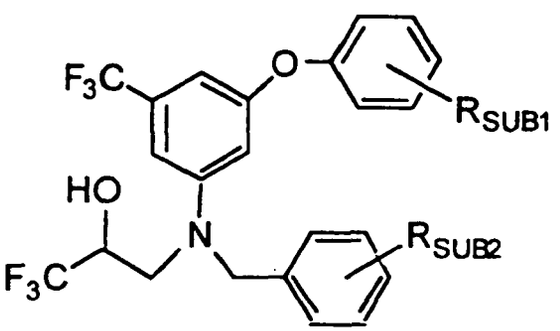
[0411] Additional examples 3-[(aryloxyphenyl)[[phenyl]methyl]amino]-1,1,1-trifluoro-2-propanols are prepared by one skilled in the art using similar methods, as shown in Example Tables 39 and 40.

Example Table 39. 3-[(aryloxyphenyl)[[phenyl]methyl]amino]-1,1,1-trifluoro-2-propanols.



Ex. No.	R_{SUB1}	R_{SUB2}	Calculated Mass $[M+H]^+$	Observed Mass $[M+H]^+$
635	4-F	3-OH	422.1379	422.1396
636	4-F	3-SCF_3	505.0946	505.0927
637	4-CH_3	3-SCF_3	502.1275	502.1261
638	3,4-F_2	3-OCF_2CF_2H	540.1221	540.1248
639	2,4-F_2	3-OCF_2CF_2H	540.1221	540.1194
640	4-F	4-CF_3	474.1304	474.1300

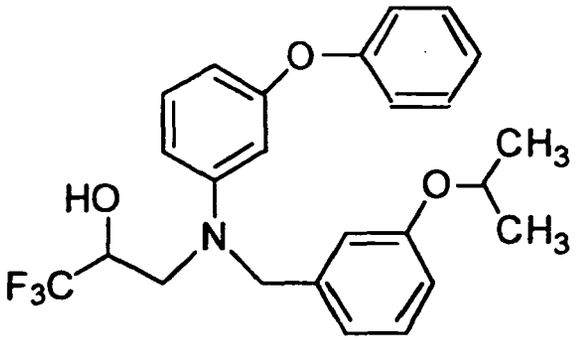
Example Table 40. 3-[[(3-aryloxy)-5-(trifluoromethyl)phenyl][[phenyl methyl]amino]-1,1,1-trifluoro-2-propanols.



Ex. No.	R_{SUB1}	R_{SUB2}	Calculated Mass $[M+H]^+$	Observed Mass $[M+H]^+$
641	4-F	3-CF_3	542.1178	542.1205
642	4-F	3-SCF_3	574.0898	574.0899
643	4-F	3-OCF_3	558.1127	558.1137
644	4-F	3-OCF_2CF_2H	590.1189	590.1212

EXAMPLE 645

[0412]



3-[(3-phenoxyphenyl)[[3-(isopropoxy)phenyl]methyl]amino]-1,1,1-trifluoro-2-propanol

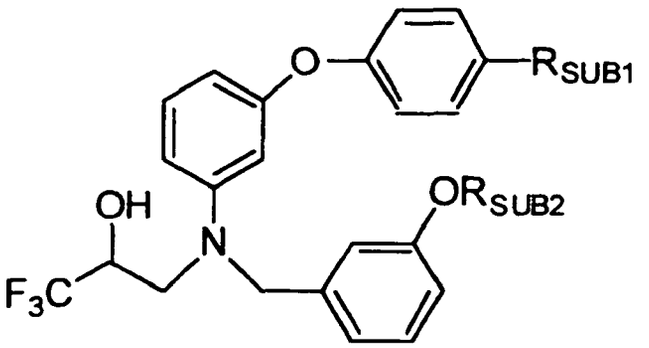
[0413] **EX-645A)** 3-Hydroxybenzaldehyde (5.60 g, 45.9 mmol) and 2-iodopropane (7.86 g, 46.2 mmol) were dissolved in 50 mL of isopropanol. Potassium carbonate (20 g, 145 mmol) was added, and the mixture was heated to reflux for 8 h, at which time TLC analysis indicated that the reaction had gone to completion. Water was added to dissolve all solids, and the mixture was extracted with ether (3x). The combined ether layer was washed with water, 2 M NaOH, again with water until clear (4x), and finally with brine. The solution was dried over $MgSO_4$, filtered, and evaporated to give 5.03 g (67%) of the desired 3-isopropoxybenzaldehyde product as a pale oil. ^{1}H NMR (C_6D_6) δ 9.62 (s, 1H), 7.29 (s, 1H), 7.03 (m, 1H), 6.91 (t, 1H), 6.84 (m, 1H), 4.03 (septet, 1H), 0.96 (d, 6H).

[0414] **EX-645B)** The 3-isoproxybenzaldehyde (0.780 g, 4.75 mmol) product from **EX-645A** and 3-phenoxyaniline (0.881 g, 4.76 mmol) were combined in 20 mL of methanol, then solid $NaCNBH_3$ (0.238 g, 3.79 mmol) was added, and the mixture was stirred until uniform. Acetic acid (2 ml) was added, and the mixture was stirred at room temperature overnight, then quenched with water, made basic with potassium carbonate, and extracted with ether (3x). The combined ether layers were washed with water and brine, dried over $MgSO_4$, filtered, and evaporated to give 1.32 g (84%) of the desired N-(3-phenoxyphenyl)-[[3-isopropoxyphenyl]methyl]amine product as an amber oil. ^{1}H NMR (C_6D_6) δ 6.6-7.1 (m, 10H), 6.44 (m, 1H), 6.25-6.00 (dd, 1H), 6.15 (m, 1H), 4.25 (s, 1H), 4.19 (m, 1H), 3.80 (s, 1H), 2.65 (s, 1H), 1.07 (m, 6H). MS *m*/*z* = 333 [M^+].

[0415] The *N*-(3-phenoxyphenyl)-[[3-isopropoxyphenyl]methyl]amine (0.528 g, 1.59 mmol) product from **EX-645B** and 1,1,1-trifluoro-2,3-epoxypropane (0.506 g, 4.51 mmol) were heated to 90 °C in a sealed container for 2 d under an argon atmosphere. The resulting mixture was eluted from silica gel with an ethyl acetate in hexane gradient (0-10% ethyl acetate) and fractions were pooled after TLC analysis to give 197 mg (28%) of the desired 3-[(3-phenoxyphenyl)[[3-(isopro-poxy)phenyl]methyl]amino]-1,1,1-trifluoro-2-propanol product as clear, colorless oil. HRMS calcd. for $C_{25}H_{26}F_3NO_3$: 446.1943 [M+H]$^+$, found: 446.1936. ^{1}H NMR (C_6D_6) δ 6.9-7.1 (m, 6H), 6.84 (tt, 1H), 6.74 (s, 1H), 6.66 (dd, 1H), 6.61 (d, 1H), 6.56 (t, 1H), 6.41 (td, 2H), 4.33 (s, 2H), 4.17 (septet, 1H), 3.91 (br s, 1H), 3.56 (dd, 1H), 3.31 (m, 1H,), 2.8 (br s. 1H). 1.06 (s, 6H). ^{19}F NMR (C_6D_6) δ -78.85 (d, 3F).

[0416] Additional examples of 3-[aryloxyphenyl[[3-aryl]methyl]amino]-1,1,1-trifluoro-2-propanols are prepared by one skilled in the art using similar methods, as shown in Example Table 41.

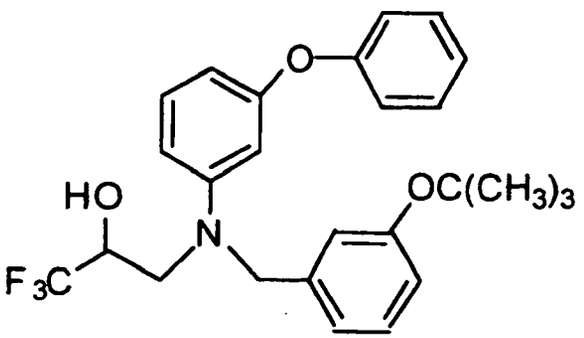
Example Table 41. 3-[aryloxyphenyl[[3-aryl]methyl]amino]-1,1,1-trifluoro-2-propanols.



Ex. No.	R_{SUB1}	R_{SUB2}	Calculated Mass $[M+H]^+$	Observed Mass $[M+H]^+$
646	F	ethyl	450.1692	450.1682
647	F	isopropyl	464.1849	464.1867
648	F	n-propyl	464.1849	464.1820
649	F	*n*-butyl	478.2005	478.2015
650	F	*sec*-butyl	478.2005	478.1880
651	F	-CH_2-cyclopropyl	476.1849	476.1857
652	F	isobutyl	478.2005	478.1970
653	F	cyclopentyl	490.2005	490.1998

EXAMPLE 654

[0417]



3-[(3-phenoxyphenyl)[[3-(1,1-dimethylethoxy)phenyl]methyl] amino]-1,1,1-trifluoro-2-propanol

[0418] **EX-654A)** 3-Hydroxybenzaldehyde (4.08 g, 33.4 mmol) was slurried in 50 mL of anhydrous CH_2Cl_2 and added to *t*-butyl-2,2,2-trichloroacetimidate (25.0 g, 114 mmol) in 200 mL of anhydrous cyclohexane with an additional 50 mL of CH_2Cl_2 used in transfer. The mixture was stirred under nitrogen until uniform, then boron trifluoride diethyl etherate (0.50 mL. 4 mmol) was added via syringe and stirring was continued for 1 h. Powdered sodium bicarbonate (50 g, 0.6 mol) was added, and the solution was filtered through a silica gel plug, washing the plug with hexane. The solvent was evaporated to give crude product 3.54 g (59%) as an amber oil (85% pure by GC analysis). Chromatography on silica gel eluting with 0-10% ethyl acetate in hexane gave 1.88 g (32%) of pure 3-*t*-butoxybenzaldehyde product as a colorless oil. ^1H NMR (C_6D_6) δ 9.59 (s, 1H), 7.44 (br s, 1H), 7.20 (d t, 1H), 6.92 (m, 2H), 1.07 (s, 9H).

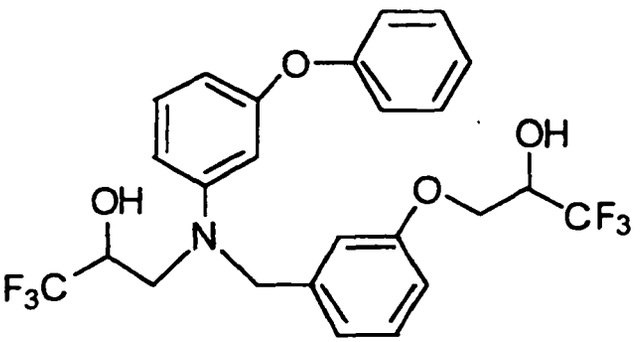
[0419] **EX-654B)** The 3-*t*-butoxybenzaldehyde (0.585 g, 3.27 mmol) product from **EX-654A** and 3-phenoxyaniline

(0.595 g, 3.21 mmol) were combined in 50 mL of THF, then solid $NaBH(OAc)_3$ (0.860 g, 4.06 mmol) was added, and the mixture was stirred until uniform. Acetic acid (0.2 g, 3.33 mmol) was added, and the mixture was stirred at room temperature for 4 h, then quenched with 5% aq. $NaHCO_3$. The aqueous layer was separated and extracted twice with ether. The combined ether layers were washed with water and brine, dried over $MgSO_4$, filtered, and evaporated to give 1.29 g (115%) of crude product as a brown oil. Chromatography on silica gel eluting with 0-10% ethyl acetate in hexane gave 464 mg (40%) of the desired *N*-(3-phenoxyphenyl)[[3-(1,1-dimethyl-ethoxy)phenyl]methyl]amine product as a colorless oil, pure by TLC. MS *m/z* = 347 [M^+].

[0420] The *N*-(3-phenoxyphenyl)[[3-(1,1-dimethylethoxy)phenyl]methyl]amine (0.270 g, 0.78 mmol) product from **EX-654B** was dissolved in 2 mL of acetonitrile. Ytterbium triflate (16 mg, 0.026 mmol) was added in 0.5 mL of acetonitrile, and the mixture was stirred under nitrogen. 1,1,1-Trifluoro-2.3-epoxypropane (0.105 g, 0.94 mmol) was added, the vial was sealed and heated to 45 ˚C. After 24 h, TLC analysis showed 50% conversion, so additional 1,1,1-trifluoro-2,3-epoxypropane (88.6 mg, 0.79 mmol) was added and heating continued for an additional 24 h. The resulting mixture was eluted from silica gel with an ethyl acetate in hexane gradient (1.5-7% ethyl acetate). Fractions were pooled based on TLC analysis to give 150 mg (42%) of the desired 3-[(3-phenoxy-phenyl)[[3-(1,1-dimethylethoxy)phenyl]methyl]amino]-1,1,1-trifluoro-2-propanol product as a clear, colorless oil, and an additional 60 mg (17%) was obtained as an amber oil. HRMS calcd. for $C_{26}H_{28}F_3NO_3$: 460.2100 [M+H]$^+$, found: 460.2103. ^{1}H NMR (C_6D_6) δ 6.78-7.08 (m, 9H), 6.68 (d, 1H), 6.55 (t, 1H), 6.43 (dd, 1H), 6.34 (dd, 1H), 4.23 (s, 2H), 3.81 (m, 1H), 3.48 (dd, 1H), 3.24 (m, 1H), 2.25 (br s, 1H), 1.07 (s, 9H). 19 F NMR (C_6D_6) δ -78.92 (d, 3F).

EXAMPLE 655

[0421]



3-[(3-phenoxyphenyl)[[3-(2-hydroxy-3,3,3-trifluoro-*n*-propoxy)phenyl]methyl]amino]-1,1,1-trifluoro-2-propanol

[0422] **EX-655A)** The 3-(phenoxy)aniline (555 mg, 3 mmol) and 3-hydroxybenzaldehyde (366 mg, 3 mmol) were dissolved in 7 mL of 1,2-dichloroethane. Acetic acid (0.189 mL, 3.15 mmol) and solid $NaBH(OAc)_3$ (1.01 g, 5 mmol) were added. The mixture was stirred at room temperature for 3 h, then acidified with 1 N HCl solution. After neutralizing to pH 7.5 with 2.5 N sodium hydroxide, the mixture was extracted with methylene chloride. The organic layer was washed with brine and water, then dried over anhydrous $MgSO_4$, and evaporated to give 609 mg (69%) of the desired N-(3-phenoxyphenyl)[[3-hydroxyphenyl]methyl]amine product as a brown oil, which was greater than 90% pure by reverse phase HPLC analysis. MS *m/z* = 291.

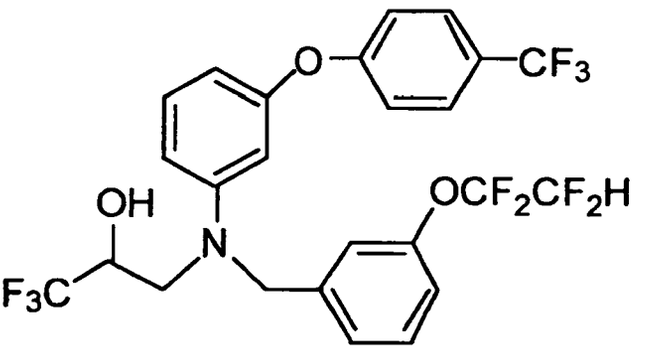
[0423] The *N*-(3-phenoxyphenyl)[[3-hydroxyphenyl]methyl]amine (400 mg, 1.35 mmol) product from **EX-655A** and 1,1,1-trifluoro-2,3-epoxypropane (348 mg, 3 mmol) were placed in a sealed vial, then stirred and heated to 95 ˚C for 15 h under an atmosphere of nitrogen. The vial was cooled, and more 1,1,1-trifluoro-2,3-epoxypropane (112 mg, 1 mmol) was added. The vial was sealed, then stirred and heated to 95 ˚C for a further 20 h under an atmosphere of nitrogen. The crude product was purified by flash column chromatography on silica gel eluting with ethyl acetate in hexane (1:6) to give 518 mg (77%) of the desired 3-[(3-phenoxyphenyl)[[3-(2-hydroxy-3,3,3-trifluoro-*n*-propoxy)-phenyl]methyl] amino]-1,1,1-trifluoro-2-propanol product as a light amber oil, 98% pure by HPLC analysis. ^{1}H NMR ($CDCl_3$) δ 7.20-7.32 (m, 3H), 7.14 (t, 1H), 7.07 (t, 1H), 6.95 (d, 2H), 6.80 (m, 2H), 6.74 (s, 1H), 6.48 (dd, 1H), 6.38 (m, 2H), 4.59 (ABq, 2H), 4.31 (m, 1H), 4.18 (dd, 1H), 4.10 (dd, 1H), 3.83 (dd, 1H), 3.54 (dd, 1H), 2.92 (d, 1H), 2.61 (d, 1H), ^{19}F NMR ($CDCl_3$) δ -78.0 (d, 3F), -79.2 (d, 3F). HRMS calcd. for $C_{25}H_{23}F_6NO_4$: 516.1611 [M+H]$^+$, found: 516.1618.

[0424] **EX-655B)** Another example, 3-[3-(4-fluorophenoxy)phenyl[[3-(2-hydroxy-3,3,3-trifluoro-*n*-propoxy)phenyl]me-

thyl]amino]-1,1,1-trifluoro-2-propanol, was prepared by a similar method using 3-(4-fluorophenoxy)aniline as the staring material. HRMS calcd. for $C_{25}H_{22}F_7NO_4$: 534.1515 $[M+H]^+$, found: 534.1505.

EXAMPLE 656

[0425]



3-[[3-(4-trifluoromethylphenoxy)phenyl][[3-(1,1,2,2-tetrafluoroethoxy)-phenyl]methyl]amino]-1,1,1-trifluoro-2-propanol

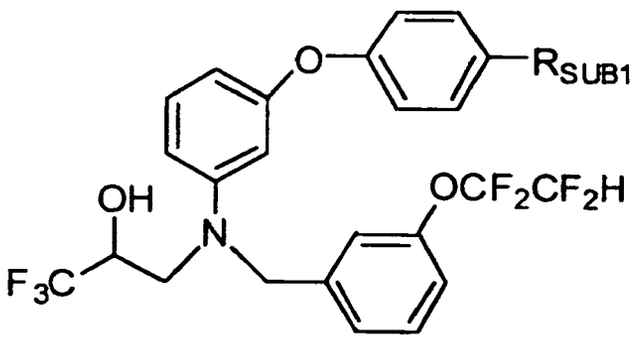
[0426] **EX-656A)** 3-Aminophenol (5.0 g, 45.8 mmol) and 4-bromo-α,α,α-trifluorotoluene (14.0 g, 62.2 mmol) were dissolved in anhydrous dimethylacetamide (20 mL), then anhydrous cesium carbonate (30 g, 92.3 mmol) and copper triflate benzene complex (200 mg) were added. The mixture was stirred and heated to 85 ˚C using a reflux condenser under an argon atmosphere. After 16 h, the mixture was diluted with water (120 mL), and the aqueous layer was extracted with diethyl ether (4 x 60 mL). The combined ether layers were washed with 3 % HCl, 5% NaOH and water, then dried over anhydrous $MgSO_4$. The ether was removed *in vacuo,* and the recovered oil purified by flash column chromatography on silica gel eluting with ethyl acetate in hexane (1:8) to give 6.8 g (59 %) of the desired 3-(4-trifluoromethylphenoxy) aniline product as a yellow oil, which solidified to a yellow powder, 98% pure by HPLC analysis. HRMS calcd. for $C_{13}H_{10}F_3NO$: 254.0792 $[M+H]^+$, found: 254.0798.

[0427] **EX-656B)** The 3-(4-trifluoromethylphenoxy)aniline (632 mg, 2.5 mmol) from **EX-656A** and 3-(1,1,2,2-tetrafluoroethoxy)benzaldehyde (555 mg, 2.5 mmol) were dissolved in 6 mL of dichloroethane and glacial acetic acid (0.15 mL, 2.8 mmol), and solid $NaBH(OAc)_3$ (1.01 g, 5 mmol) was added. The mixture was stirred at room temperature for 3 h, then acidified with 1 N HCl. After neutralizing to pH 7.5 with 2.5 N sodium hydroxide, the mixture was extracted with CH_2Cl_2 (3 x 20 mL). The organic layer was washed with brine and water, then dried over anhydrous $MgSO_4$, and evaporated to give 861 mg (75%) of the desired *N*-3-(4-trifluoromethylphenoxy)-phenyl[[3-(1,1,2,2-tetrafluoroethoxy) phenyl]methyl]amine product as a brown oil, which was greater than 90% pure by reverse phase HPLC analysis. MS *m*/*z* = 460 $[M+H]^+$.

[0428] The *N*-3-(4-trifluoromethylphenoxy)-phenyl[[3-(1,1,2,2-tetrafluoroethoxy) phenyl]-methyl]amine (689 mg, 1.5 mmol) product from **EX-656B** and 1,1,1-trifluoro-2,3-epoxypropane (252 mg, 2.25 mmol) were dissolved in 1.0 mL of acetonitrile. Ytterbium (III) trifluoromethanesulfonate (43 mg, 0.07 mmol) was added, and the stirred solution was warmed to 50 ˚C for 2.5 h under an atmosphere of nitrogen, at which time HPLC analysis indicated that no secondary amine starting material remained. The reaction was quenched with water and extracted with ether. The ether layer was washed with brine and water, then dried over anhydrous $MgSO_4$. The crude product was purified by flash column chromatography on silica gel eluting with ethyl acetate in hexane (1:12) to give 520 mg (61%) of the desired 3-[[3-(4-trifluoromethylphenoxy) phenyl][[3-(1,1,2,2-tetrafluoroethoxy)phenyl]methyl]amino]-1,1,1-trifluoro-2-propanol product as a yellow oil, 99% pure by HPLC analysis. H NMR ($CDCl_3$) δ 7.49 (d, 2H), 7.30 (t, 1H), 7.20 (t, 1H), 7.07 (m, 2H), 7.00 (s, 1H), 6.95 (d, 2H), 6.55 (dd, 1H), 6.43 (dd, 1H), 6.34 (t, 1H), 5.87 (tt, 1H), 4.64 (ABq, 2H), 4.33 (m, 1H), 3.88 (dd, 1H), 3.58 (dd, 1H), 2.43 (bs, 1H). ^{19}F NMR ($CDCl_3$) δ -62.2 (s, 3F), -79.2 (d, 3F), -88.6 (m, 2F), -137.2 (dt, 2F). HRMS calcd. for $C_{25}H_{19}F_{10}NO_3$: 572.1282 $[M+H]^+$, found: 572.1268.

[0429] Additional examples of 3-[aryloxyphenyl[[phenyl]methyl]amino]-1,1,1-tri-fluoro-2-propanols are prepared by one skilled in the art using similar methods, as shown in Example Table 42.

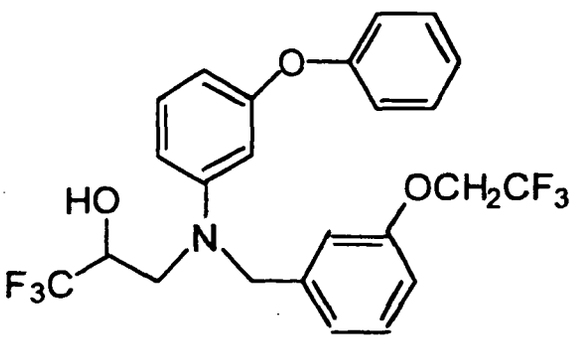
Example Table 42. 3-[Aryloxyphenyl[[phenyl]methyl]amino]-1,1,1-trifluoro-2-propanols



Ex. No.	R_{SUB1}	Calculated Mass $[M+H]^+$	Observed Mass $[M+H]^+$
657	CN	529.1362	529.1364
658	OCF_3	588.1233	588.1241

EXAMPLE 659

[0430]



3-[(3-phenoxyphenyl)[[3-(2,2,2-trifluoroethoxy)phenyl]methyl] amino]-1,1,1-trifluoro-2-propanol

[0431] **EX-659A)** 3-Hydroxybenzaldehyde (12.22 g, 0.10 mol) and 100 mL of anhydrous methanol were combined in a 250 mL round-bottom flask. Sodium methoxide was slowly added as a 25 wt. % solution in methanol (21.61 g, 0.10 mol), and the methanol was removed under vacuum. Then 2,2,2-trifluoroethyl-p-toluenesulfonate (25.42 g, 0.10 mol) was added, the flask was purged with nitrogen, and 100 mL of *N*-methyl pyrrolidine was added. The solution was stirred for 24 h at 90 ˚C, quenched with water, and extracted with ether (3x). The combined ether layers were washed with 1 M NaOH (2x), water, and brine, dried over $MgSO_4$, filtered, and evaporated to give 11.72 g of crude product. Chromatography over silica gel eluting with 0-10% ethyl acetate in hexane followed by a second chromatography with toluene gave 5.24 g (26%) of the desired 3-(2,2,2-trifluoroethoxy)benzaidehyde product as a pale oil. ^1H NMR (C_6D_6) δ 9.61 (s, 1H), 7.14 (d, 1H), 7.06 (s, 1H), 6.97 (t, 1H), 6.75 (m, I H), 3.75 (m, 2H). ^{19}F NMR (C_6D_6) δ -74.45 (t, 3F).

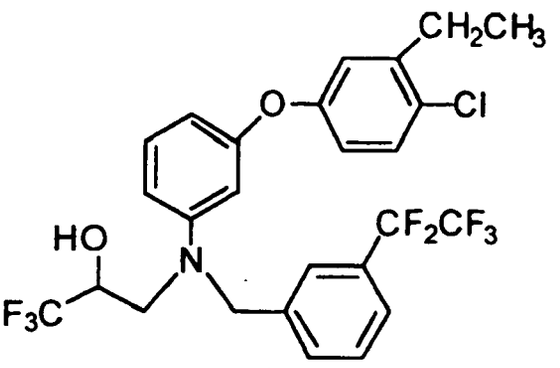
[0432] **EX-659B)** The 3-(2,2,2-trifluoroethoxy)benzaldehyde (0.360 g, 1.76 mmol) product from **EX-659A** and 3-phenoxyaniline (0.326 g, 1.76 mmol) were combined in 50 mL of cyclohexane with 3A molecular sieves (1 g) and stirred overnight at 80 ˚C. The mixture was cooled, filtered, and evaporated, then dissolved in 50 mL of methanol and cooled to 0 ˚C. Solid sodium borohydride (0.030 g, 0.79 mmol) was added in portions, and the mixture was stirred overnight. The reaction was quenched with 5% aq. $NaHCO_3$ and extracted with ether (3x). The combined ether layers were washed with water and brine, dried over $MgSO_4$, filtered, and evaporated to give 0.50 g (76%) of the desired N-(3-phenoxyphenyl) [[3-(2,2,2-tnfluoroethoxy)phenyltmethyl]amine product as an amber oil, >95% pure by normal phase HPLC analysis. MS

m/*z* = 373 [M^+].

[0433] The *N*-(3-phenoxyphenyl)[[3-(2,2,2-trifluoroethoxy)phenyl]methyl]amine (0.50 g, 1.35 mmol) product from **EX-659B** and 1,1,1-trifluoro-2,3-epoxypropane (1.0 ml, 11 mmol) were heated to 90 ˚C in a sealed container under argon for 2 d. The resulting mixture was eluted from silica gel with 4% ethyl acetate in hexane, and fractions were pooled based on TLC analysis to give 134 mg (21 %) of the desired 3-[(3-phenoxyphenyl)[[3-(2,2,2-trifluoroethoxy)phenyl] methyl] amino]-1,1,1-trifluoro-2-propanol product as a clear, colorless oil. ^{1}H NMR (C_6D_6) δ 6.80-7.08 (m, 7H), 6.64 (d, 1H), 6.53 (bt, 1H), 6.49 (t, 1H), 6.44 (dd, 1H), 6.34 (dt, 2H), 4.23 (s, 2H), 3.84 (m, 1H), 3.61 (m, 2H), 3.53 (dd, 1H), 3.20 (m, 1H), 2.03 (d, 1H). ^{19}F NMR (C_6D_6) δ -74.20 (t, 3F), -78.95 (d, 3F). HRMS calcd. for $C_{24}H_{21}F_6NO_3$: 486.1504 [M+H]$^+$, found: 486.1498.

EXAMPLE 660

[0434]



3-[(4-chloro-3-ethylphenoxy)phenyl[[3-(pentafluoroethyl)phenyl] methyl]-amino]-1,1,1-trifluoro-2-propanol.

[0435] **EX-660A)** Sodium pentafluoroethyl propionate (8.4 g, 50 mmol) and 3-iodotoluene (5.5 g, 25 mmol) were dissolved in anhydrous DMF (300 mL). CuI (9.5 g, 50 mmol) was added, and the mixture was heated to 160 ˚C under nitrogen for 4 h, at which time a 15 mL fraction of a mixture of DMF and 3-pentafluoroethyl toluene was collected. The distillate was diluted with Et_2O and was washed with brine. The ether layer was dried over $MgSO_4$, filtered and concentrated *in vacuo* to give 5.25 g (55%) of the desired 3-pentafluoroethyl-toluene product as a colorless oil. ^{1}H NMR ($CDCl_3$) δ 7.36 (m, 4H), 2.40 (s, 3H). 19 F NMR ($CDCl_3$) δ -85.2 (s, 3F), -115.2 (s, 2F).

[0436] **EX-660B)** The 3-pentafluoroethyl-toluene (2.9 g, 13.8 mmol) product from **EX-660A** and *N*-bromosuccinimide (2.5 g. 13.8 mmol) were dissolved in CCl_4 (25 mL). AIBN (50 mg) was added, and the mixture was refluxed for 3.5 h under N_2. The reaction mixture was cooled to room temperature and diluted with water. The layers were separated, and the organic layer was washed with brine, dried with anhydrous $MgSO_4$, filtered, and concentrated *in vacuo* to give 3.4 g (87%) of a colorless oil. The ^{1}H NMR spectrum indicated that the crude product contained 3-pentafluoroethyl-benzyl-bromide (70%), the benzyl dibromide (10%) and 3-pentafluoroethyl toluene (20%). ^{1}H NMR ($CDCl_3$) δ 7.60 (m, 2H), 7.50 (m, 2H), 4.50 (s, 2H). ^{19}F NMR ($CDCl_3$) δ -85.1 (s. 3F), -115.4 (s, 2F).

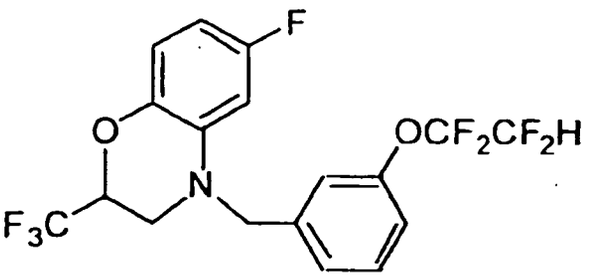
[0437] **EX-660C)** A solution of 3-(4-chloro-3-ethylphenoxy)aniline (1.7g, 6.9 mmol) was prepared in cyclohexane (13 mL). A solution of crude 3-pentafluoroethyl benzylbromide (1 g, 3.5 mmol) product from **EX-660B** in cyclohexane (10 mL) was added dropwise over 3 min. The reaction mixture was refluxed under N_2 for 24 h and then was cooled to room temperature. The mixture was diluted with Et_2O and saturated aqueous $NaHCO_3$. The layers were separated, and the aqueous layer was extracted with Et_2O. The organic layer was washed with brine, dried with anhydrous $MgSO_4$, filtered and concentrated *in vacuo.* The residue was purified by chromatography on silica gel eluting with hexanes in ethyl acetate (95:5) which gave 0.56 g (35%) of the desired N-[3-(4-chloro-3-ethylphenoxy)phenyl][[3-(pentafluoro-ethyl)phenyl] methyl]amine product as an amber oil. ^{1}H NMR ($CDCl_3$) δ 7.53 (m, 4H), 7.27 (d, 1H), 7.15 (t, 1H), 6.93 (d, 1H), 6.77 (dd, 1H), 6.41 (tt, 2H), 6.30 (t, 1H), 4.41 (s, 2H), 2.73 (q, 2H), 1.23 (t, 3H). ^{13}C NMR ($CDCl_3$) δ 158.6, 156.1, 143.4, 141.3, 140.2, 131.3, 130.7, 130.4, 129.4, 128.1, 120.4, 117.8, 108.8. 103.9, 48.5, 27.5, 14.1. ^{19}F NMR ($CDCl_3$) δ -85.1 (s, 3F), -115.2 (s, 2F). HRMS calcd. for $C_{23}H_{19}ClF_5NO$: 456.1154 [M+H]$^+$, found: 456.1164.

[0438] The *N*-[3-(4-chloro-3-ethylphenoxy)phenyl][[3-(pentafluoroethyl)phenyl] methyl]-amine (0.05 g, O.llmmol) product of **EX-660C** was dissolved in anhydrous acetonitrile (0.2 mL). 1,1,1-trifluoro-2,3-epoxypropane (0.1 g, 0.89 mmol) and $Yb(OTf)_3$ (7 mg, 0.001 mmol) were added, and the reaction mixture was stirred under N_2 at 45 ˚C. After 3 h, the

reaction mixture was cooled to room temperature and diluted with Et_2O and saturated aqueous $NaHCO_3$. The layers were separated and the aqueous layer was extracted with Et_2O. The ether layers were combined, washed with brine, dried with anhydrous Na_2SO_4. filtered, and concentrated *in vacuo.* The viscous oil was adsorbed onto silica gel and eluted with hexanes in ethyl acetate (95:5) which gave 20 mg (32%) of the desired 3-[(4-chloro-3-ethylphenoxy)phenyl[[3-(pentafluoroethyl)phenyl]-methyl]amino]-1,1,1-trifluoro-2-propanol product as a viscous, colorless oil. ^1H NMR ($CDCl_3$) δ 7.47 (m, 4H), 7.23 (m, 3H), 6.90 (d, 1H), 6.72 (dd, 1H). 6.52 (d, 1H), 6.42 (m, 2H), 4.73 (s, 2H), 4.39 (m, 1H), 3.91 (dd, 1H), 3.58 (m, 2H), 2.73 (q, 2H), 2.57 (s, 1H), 1.22 (t, 3H). ^{19}F NMR ($CDCl_3$) δ -79.2 (s, 3F), -84.9(s, 3F), -115.2 (s, 2F). HRMS calcd. for $C_{26}H_{22}ClF_8NO_2$: 568.1290 $[M+H]^+$, found: 568.1314.

EXAMPLE 661*

[0439]



6-fluoro-3,4-dihydro-4-[[3-(1,1,2,2-tetrafluoroethoxy)phenyl] methyl]-2-(trifluoromethyl)-2H-1,4-benzoxazine

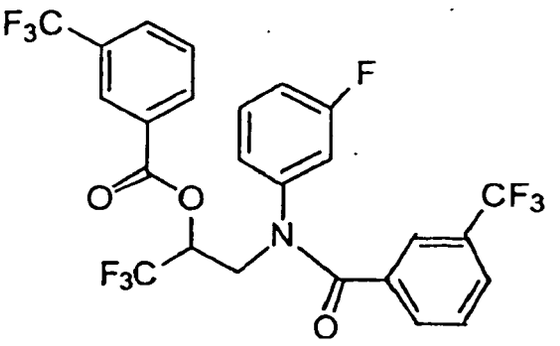
[0440] EX-661A) A mixture of 2,5-difluoroaniline (2.58 g, 20 mmol) and 3-(1,1,2,2-tetrafluoroethoxy)benzaldehyde (4.44 g, 20 mmol) in cyclohexane (50 mL) was heated under reflux for 5 h using a Dean-Stark trap to remove water. The solvent was removed *in vacuo,* and the residue was dissolved in methanol (30 mL). The solution was stirred and cooled to 0 ˚C, then sodium borohydride was added (1.32 g, 35 mmol). The mixture was allowed to warm to room temperature and stirred for 2 h, then acidified with 1 N HCl. After neutralizing to pH 7.5 with 2.5 N sodium hydroxide, the mixture was extracted with diethyl ether (3 x 20 mL). The organic layer was washed with brine and water, then dried over anhydrous $MgSO_4$, and evaporated to give 5.7 g (86%) of the desired *N*-(2,5-difluorophenyl)[[3-(1,1,2,2-tetrafluoroethoxy)phenyl]-methyl]amine product as a brown oil, which was greater than 90% pure by reverse phase HPLC analysis. MS *m*/*z* = 336 $[M^+]$.

[0441] EX-661B) The *N*-(2,5-difluorophenyl)[[3-(1,1,2,2-tetrafluoroethoxy)phenyl] methyl]-amine (2.22 g, 6.67 mmol) product from **EX-661A** and 1,1,1-trifluoro-2,3-epoxypropane (1.12 g, 10 mmol) were dissolved in 1.5 mL of acetonitrile. Ytterbium (III) trifluoromethanesulfonate (0.21 g, 0.33 mmol) was added, and the stirred solution was warmed to 50 ˚C for 2 h under an atmosphere of nitrogen, at which time HPLC analysis indicated that no secondary amine starting material remained. The reaction was quenched with water and extracted with ether. The ether layer was washed with water and brine, then dried over anhydrous $MgSO_4$. The crude product was purified by flash column chromatography on silica gel eluting with ethyl acetate in hexane (1:10) to give 2.49 g (84%) of the desired 3-[(2,5-difluorophenyl)[[3-(1,1,2,2-tetrafluoro-ethoxy)phenyl]methyl]amino]-1,1,1-thfluoro-2-propanol product as a yellow oil, 99% pure by HPLC analysis. HRMS calcd. for $C_{18}H_{14}F_9NO_2$: 448.0959 $[M+H]^+$, found: 448.0940.

[0442] The 3-[(2,5-difluorophenyl)[[3-(1,1,2,2-tetrafluoroethoxy)phenyl]methyl] amino]-1,1,1-trifluoro-2-propanol (200 mg, 0.45 mmol) product from **EX-661B** was dissolved in anhydrous dimethylformamide (20 mL), and powdered K_2CO_3 (180 mg) was added. The mixture was stirred and heated to 145˚C for 15 h. The mixture was diluted with water (60 mL) and extracted into ether (2 x 40 mL), which was washed with brine and water. The ether solution was dried over anhydrous $MgSO_4$, and the ether was removed *in vacuo.* The crude product was purified by flash column chromatography on silica gel eluting with ethyl acetate in hexane (1:15) to give 86.9 mg (48%) of the desired 6-fluoro-3,4-dihydro-4-[[3-(1,1,2,2-tetrafluoroethoxy)phenyl]methyl]-2-(tri-fluoromethyl)-2H-1,4-benzoxazine product as a yellow oil, 98% pure by HPLC analysis. ^1H NMR ($CDCl_3$) δ 7.39 (t. 1H), 7.17 (m. 3H), 6.88 (m, 1H), 6.41 (m, 2H), 5.92 (tt, 1H), 4.54 (m, 1H), 4.45 (s, 2H), 3.44 (m. 2H). ^{19}F NMR ($CDCl_3$) δ - 77.7 (d, 3F), -88.6 (m, 2F), -120.28 (m, 1F), -137.2 (dt, 2F). HRMS calcd. for $C_{18}N_{13}F_8NO_2$: 428.0899 $[M+H]^+$, found: 428.0910.

EXAMPLE 662 *

[0443]



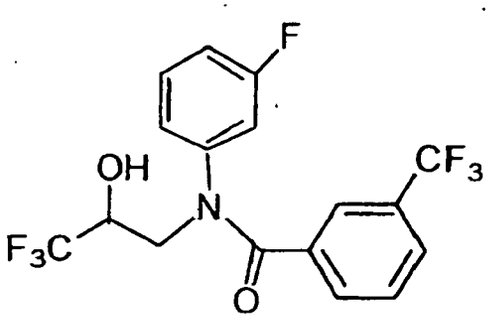
2,2,2-trifluoro-1-[[(3-fluorophenyl)[3-(trifluoromethyl) benzoyl]amino]-methyl]ethyl 3-trifluoromethylbenzoate

[0444] **EX-662A)** 3-[(3-fluorophenyl)[phenylmethyl]amino]-1,1,1-thfluoro-2-propanol (2.56 g, 8.2 mmol) was dissolved in methanol (30 mL) and hydrogenated over 5% palladium on charcoal for 3 h. The mixture was filtered through celite, and the solvent was removed in *vacuo* to give 1.8 g (98%) of the desired 3-[(3-fluorophenyl)amino]-1,1,1-trifluoro-2-propanol product as an oil, 99% pure by HPLC analysis. MS *m*/*z* = 224 $[M+H]^+$.

[0445] The 3-[(3-fluorophenyl)amino]-1,1,1-trifluoro-2-propanol (446 mg, 2.0 mmol) from **EX-662A** and triethylamine (544 mg) were dissolved in anhydrous $CHCl_3$ (30 mL) and cooled to 0 ˚C. Then a solution of 3-trifluoromethylbenzoyl chloride (1.04 g, 5.0 mmol) in anhydrous $CHCl_3$ (6 mL) was added over a period of 15 min. The solution was stirred at room temperature. After 14 h, the solution was washed with 5% $NaHCO_3$ (2 x 20 mL) and brine (2 x 10 mL), and then dried over anhydrous $MgSO_4$. Removal of the solvent *in vacuo* gave 832 mg (73%) of the desired 2,2,2-trifluoro-1-[[(3-fluoro-phenyl)[3-(trifluoromethyl)benzoyl]amino]methyl]ethyl 3-trifluoromethyl-benzoate product as an amber oil, which was greater than 95% pure by reverse phase HPLC analysis. ^1H NMR ($CDCl_3$) δ 7.25-8.39 (m, 9H), 7.02 (q, 1H), 6.71 (m, 2H), 6.11 (m, 1H), 4.58 (dd, 1H), 4.35 (dd, 1H). ^{19}F NMR ($CDCl_3$) δ -64.4 (m, 6F), -77.4 (s, 3F), -111.3 (m, 1F). HRMS calcd. for $C_{25}H_{15}F_{10}NO_3$: 568.0970 $[M+H)^+$, found: 568.0968.

EXAMPLE 663 *

[0446]



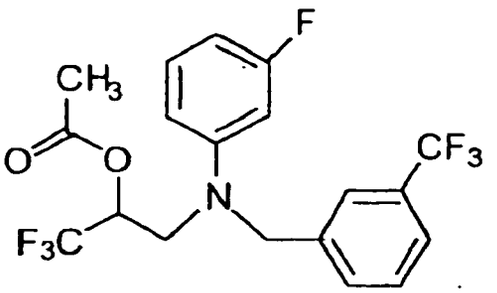
***N*-(3-fluorophenyl)-*N*-(3,3,3-trifluoro-2-hydroxypropyl)-3-(trifluoromethyl)benzamide**

[0447] A solution of 2,2,2-thfluoro-1-[[(3-fluorophenyl)[3-(trifluoromethyl)benzoyl] amino]-methyl]ethyl 3-trifluoromethyl-benzoate (600 mg, 1.06 mmol) from **EX-662** in methanol was treated with 28% ammonia solution (122 μL). The solution was stirred at room temperature for 10 h. The reaction was quenched with water and extracted with ether. The ether layer was washed with brine and water, then dried over anhydrous $MgSO_4$. The crude product was purified by flash column chromatography on silica gel eluting with ethyl acetate in hexane (1:8) to give 255 mg (61%) of the desired

N-(3-fluorophenyl)-*N*-(3,3,3-trifluoro-2-hydroxypropyl)-3-(trifluoromethyl)benzamide product as a white powder, 97% pure by HPLC analysis. ^{1}H NMR ($CDCl_3$) δ 7.56 (m, 3H), 7.32 (m 2H), 6.98 (m, 1H), 6.90 (m. 2H), 4.49 (dd, 1H), 4.34 (d, 1H), 4.26 (m. 1H), 4.01 (dd, 1H). ^{19}F NMR ($CDCl_3$) δ -64.7 (s, 3F), -80.3 (s, 3F), -111.0 (m, 1F). HRMS calcd. for $C_{17}H_{12}F_7NO_2$: 396.0854 $[M+H]^+$, found: 396.0821.

EXAMPLE 664 *

[0448]

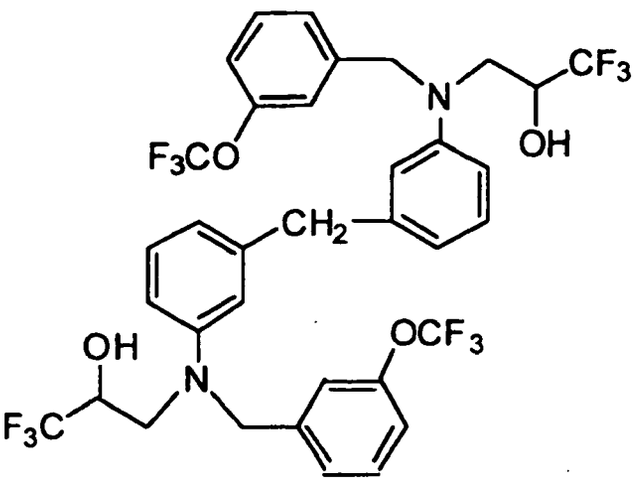


2,2,2-trifluoro-1-[[[(3-fluorophenyl)[3-(trifluoromethyl) phenyl]-methyl]amino]methyl]ethyl acetate

[0449] A solution of 3-[(3-fluorophenyl)[[3-(3-trifluoromethyl)phenyl]methyl]amino]-1,1,1-tri-fluoro-2-propanol (200 mg, 0.52 mmol) from **EX-1** in triethylan-ine (0.6 mL) and acetic anhydride (0.5 mL) was stirred and heated to 80 ˚C for 1 h. The mixture was cooled and diluted with water (20 mL) and extracted into ether (2 x 40 mL), which was washed with 0.1 N NaOH and water. The ether solution was dried over anhydrous $MgSO_4$. The ether was removed in *vacuo* giving the desired 2,2,2-trifluoro-1-[[[(3-fluorophenyl) [3-(trifluoromethyl) phenyl]methyl]amino] methyl]ethyl acetate product as an amber oil, 98% pure by HPLC analysis. ^{1}H NMR ($CDCl_3$) δ 7.42-7.59 (m, 3H), 7.38 (d 1H), 7.18 (q, 1H), 6.42-6.56 (m, 3H), 5.69 (m, 1H), 4.64 (ABq, 2H), 3.89 (d, 1H), 3.87(s, 1H), 1.98 (s, 3H). ^{19}F NMR ($CDCl_3$) δ 64.0 (s, 3F), -77.2 (s, 3F), -112.9 (s, 1F). HRMS calcd. for $C_{19}H_{16}F_7NO_2$:424.1148 $[M+H]^+$, found: 424.1159.

EXAMPLE 665

[0450]



1,1'-[methylenebis[3,1-phenylene[[[3- (trifluoromethoxy)phenyl] methyl]imino]]]bis[3,3,3-trifluoro-2-propanol]

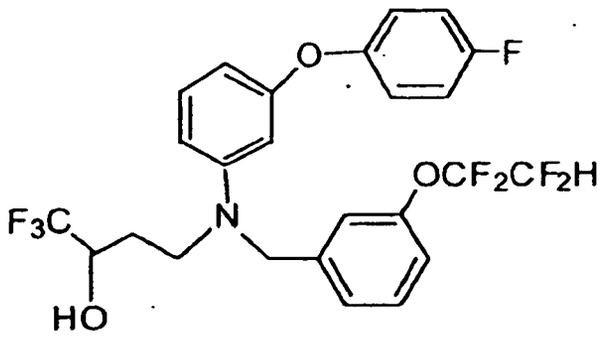
[0451] EX-665A) A solution of 3,3'-diaminophenylmethane (1.48 g, 7.5 mmol) and 3-trifluoromethoxy-benzaldehyde (2.85 g, 15 mmol) in cyclohexane (50 mL) was heated under reflux for 5 h using a Dean-Stark trap to remove water.

The solvent was removed *in vacuo,* and the residue was dissolved in methanol (30 mL). The solution was stirred and cooled to 0 ˚C, and solid sodium borohydride was added (0.87 g, 23 mmol). The mixture was allowed to warm to room temperature and stirred for 2 h, then acidified with 1 N HCl. After neutralizing to pH 7.5 with 2.5 N sodium hydroxide, the mixture was extracted with diethyl ether (3 x 30 mL). The organic layer was washed with brine and water, then dried over anhydrous $MgSO_4$, and evaporated to give 3.19 g (78%) of the desired 3,3'-*N,N'*-bis(trifluoromethoxyphenyl)diamino-phenylmethane product as a brown oil, which was greater than 90% pure by reverse phase HPLC analysis. MS *m/z* = 546 [M^+].

[0452] The amine (2.18 g, 4 mmol) product from **EX-665A** and 1,1,1-trifluoro-2,3-epoxy-propane (0.67 g, 6 mmol) were combined in a sealed vial and heated to 95 ˚C for 2 days, at which time HPLC analysis indicated that little secondary amine starting material remained. The excess oxirane was removed under nitrogen, and the crude product was purified by flash column chromatography on silica gel eluting with ethyl acetate in hexane (1:12) to give 2.0 g (67%) of the desired 1,1'-[methylenebis[3,1-phenylene[[[3-(trifluoromethoxy)phenyl)methyl)imino]]] bis-[3,3,3-trifluoro-2-propanol] product as a light amber oil. 99% pure by HPLC analysis. ^1H NMR ($CDCl_3$) δ 7.30 (t, 2H), 7.10 (m. 6H), 7.02 (s, 2H), 6.58 (m, 4H), 6.52 (s, 2H), 4.60 (s, 4H), 4.22 (m, 2H), 3.80 (s, 2H), 3.79 (dd, 2H), 3.48 (dd, 2H), 2.60 (br s, 2H). ^{19}F NMR ($CDCl_3$) δ -66.2 (s, 6F), -79.2 (d, 6F). HRMS calcd. for $C_{35}H_{30}F_{12}N_2O_4$: 771.2092 $[M+H]^+$, found: 771.2072.

EXAMPLE EX-666 *

[0453]



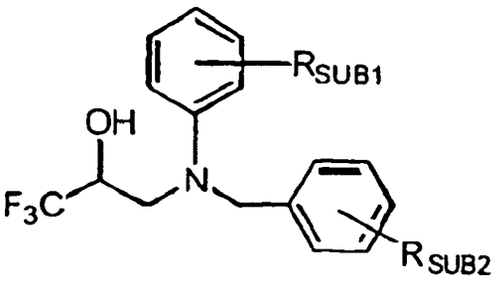
4-[[(4-fluorophenoxy)phenyl][[3-(1,1,2,2-tetrafluoroethoxy) phenyl]-methyl]amino]-1,1,1-trifluoro-2-butanol

[0454] **EX-666A)** The 4-amino-2-hydroxy-1,1,1-trifluorobutane (1.0 g, 7.0 mmol) from **EX-611A** and 3-(1,1,2,2-tetrafluoroethoxy)benzaidehyde (1.5 g, 7.0 mmol) were dissolved in 20 mL of dichloroethane and acetic acid (0.40 mL, 7.7 mmol), then solid $NaBH(OAc)_3$ (1.8 g, 8.4 mmol) was added. The mixture was stirred at room temperature for 3 d, then quenched with water and extracted with ether. The ether layer was washed with water and brine, then dried over $MgSO_4$, and evaporated to give 1.6 g of crude product, which was purified by reverse phase HPLC to give 0.90 g (37 %) of the desired 4-[[[3-(1,1,2,2-tetrafluoroethoxy)phenyl]methyl]amino]-1,1,1-trifluoro-2-butanol product as a yellow oil. HRMS calcd. for $C_{13}H_{14}F_7NO_2$: 350.0991 $[M+H]^+$, found: 350.0971.

[0455] The 1,1,1-trifluoro[[3-(1,1,2,2-tetrafluoroethoxy)phenyl]methyl]amino]-2-butanol (0.35 g, 1 mmol) from **EX-666A,** 3-(4-fluorophenoxy)bromobenzene (0.32 g, 1.2 mmol), $Pd_2(dba)_2$ (18 mg, 0.02 mmol), (R,+) BINAP (49 mg, 0.08 mmol), and Cs_2CO_3 (0.46 g, 1.4 mmol) were mixed in 9 mL of toluene and heated to 100 ˚C for over 2 weeks, at which time FABMS (*m/z* = 536.3 $[M+H]^+$) indicated that the desired 4-[[(4-fluorophenoxy)phenyl]-[[3-(1,1,2,2-tetrafluoroethoxy) phenyl] methyl]amino]-1,1,1-tri-fluoro-2-butanol product had formed.

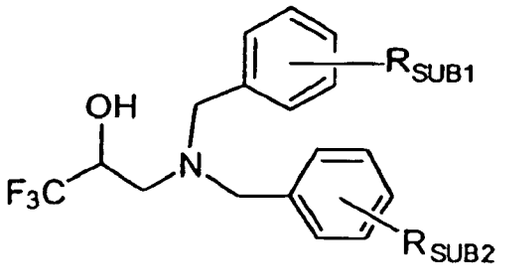
[0456] Based on the preceding procedures, other substituted 3-[(*N*-aryl)-[[aryl]methyl]aminol-halo-2-propanols can be prepared by one skilled in the art using similar methods, as shown in Example Tables 43, 46, and 47. Substituted 3-[(*N*-aralkyl)-[[aralkyl]amino]-halo-2-propanols can also be prepared by one skilled in the art using similar methods, as shown in Example Tables 44 and 45. Substituted 3-[(*N*-aryl)-[[aryl]methyl]amino]-haloalkoxy-2-propanols can be prepared by one skilled in the art using similar methods, as shown in Example Table 48.

Example Table 43. 3-[(*N*-aryl)-[(aryl)methyl]amino]-1,1,1-trifluoro-2-propanols.



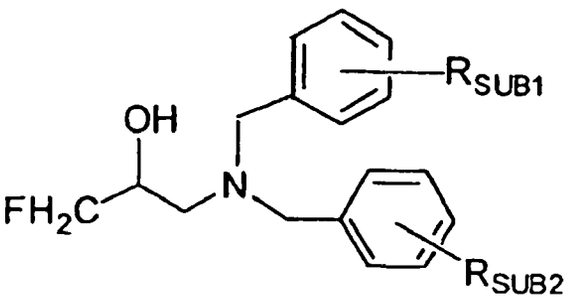
Ex. No.	R_{SUB1}	R_{SUB2}	Calculated Mass $[M+H]^+$	Observed Mass $[M+H]^+$
667*	2-OCH_3	4-CH_3	340.1524	340.1492
668*	2-OCH_3	3-CH_3	340.1524	340.1527
669*	2-OCH_3	3-CF_3	394.1242	394.1239
670*	3-F	2-CF_3	382.1042	382.1029
671*	3-F	2-CH_3	328.1325	328.1319
672	4-CF_3	4-CH_3	378.1293	378.1273
673*	2-CF_3	4-CH_3	378.1293	378.1284
674	3-F	3-(3-CF_3-phenoxy)	474.1304	474.1276
675	3-F	3-(4-OCH_3-phenoxy)	436.1536	436.1532
676	3-F	3-(4-Cl-phenoxy)	440.1040	440.1048
677	3-F	3,5-$(CF_3)_2$	450.0916	450.0923
678	2,3-difluoro	3-CH_3	346.1230	346.1209
679	2-F, 3-CF_3	4-CH_3	396.1198	396.1200
680	2-F, 3-CF_3	3-CH_3	396.1198	396.1180
681	2,3-difluoro	4-CH_3	346.1230	346.1228
682*	2-OCH_3	4-CF_3	394.1242	394.1246
683	3-OCF_3	4-benzyloxy	486.1504	486.1538
684*	3-phenoxy	2-NO_2, 4-Cl	467.9	467.9
685	3-phenoxy	4-(3,4-Cl_2-phenoxy)	548	548
686	3-phenoxy	4-OCH_3	418	418
687	3-phenoxy	3,4-(OCF_2CF_2O)	518.1202	518.1286
688	3-OCF_3	3-CF_3	448	448
689	4-phenyl	3-CF_3	440.1449	440.1430
690	3,5-$(CF_3)_2$	3-phenoxy	524	524
691*	2,5-$(CF_3)_2$	3-CF_3	500	500
692	3-OH	3-OCF_3	396.1034	396.1053
693	3-[4-(propanoyl) phenoxy]	3-OCF_2CF_2H	560.1672	560.1694

Example Table 44. 3-[*N*-[(aryl)methyl]-[(aryl)methyl]amino]-1,1,1-trifluoro-2-propanols.



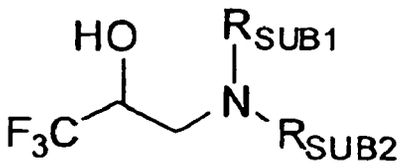
Ex. No.	R_{SUB1}	R_{SUB2}	Calculated Mass [M+H]	Observed Mass [M+H]
694	3-Cl	3-OCF_3	428.0852	428.0817
695	3-Br	3-OCH_3	472.0347	472.0312
696*	2-F	2-CF_3	396.1198	396.1193

Example Table 45. 3-[*N*-[(aryl)methyl]-[(aryl)methyl]amino]-1,1,1-trifluoro-2-propanols.



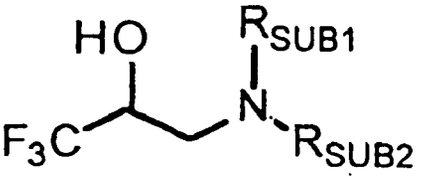
Ex. No.	R_{SUB1}	R_{SUB2}	Calculated Mass [M+H]	Observed Mass [M+H]
697*	3-OCF_3	3-OCF_3	442.1253	442.1232

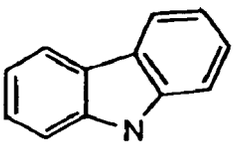
Example Table 46. 3-[*N*-(aryl)-*N*-(aralkyl)amino]-1,1,1-trifluoro-2-propanols.



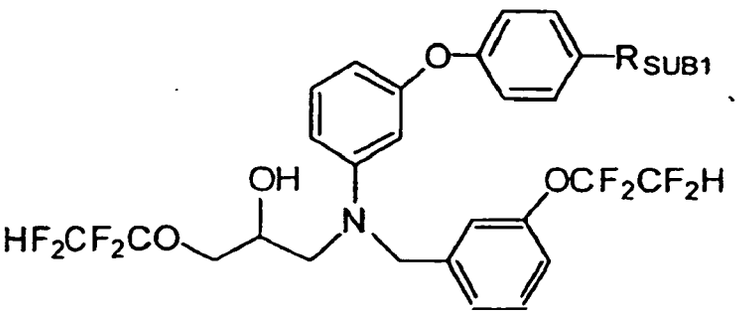
Ex. No.	R_{SUB1}	R_{SUB2}	Calculated Mass [M+H]	Observed Mass [M+H]
698*	3-OCF_3-benzyl	2-methoxy-dibenzofuran-3-yl	500.1297	500.1295
699*	3-OCF_3-benzyl	2-fluorenyl	468.1398	468.1374

Example Table 47. 3-[*N*-(aryl)-[(aryl)methyl]amino]-1,1,1-trifluoro-2-propanols.



Ex. No.	R_{SUB1} - N- R_{SUB2}	Calculated Mass [M+H]	Observed Mass [M+H]
700*		280.0949	280.0938

Example Table 48. 3-[*N*-(aryl)-*N*-(aralkyl)amino]-1-haloalkoxy-2-propanols.*



Ex. No.	R_{SUB1}	Calculated Mass [M+H]	Observed Mass [M+H]
701	F	584.1483	594.1473
702	CF_3	634.1451	634.1432

[0457] Based on the preceding procedures, additional substituted 3-[(*N*-aryl)-[[aryl]methyl]amino]-halo-2-propanols are prepared by one skilled in the art using similar methods, as shown in the multiple sections of Example Table 49. Substituted 4-[*N*-(aryl)-[(aryl)methyl]amino]-1,1,1,2,2-pentafluoro-3-butanols are prepared by one skilled in the art using similar methods, as shown in Example Table 50. Substituted 3-[*N*-(aryl)-[(aryl)oxy]amino]-1,1,1-trifluoro-2-propanols are prepared by one skilled in the art using similar methods, as shown in Example Table 51. Substituted 3-[*N*-(aryl)-[(aryl) methyl]amino]-1,1,1-trifluoro-2-butanols are prepared by one skilled in the art using similar methods, as shown in Example Table 52.

[0458] Substituted 3-[*N,N*'-(diaryl)amino]-1,1,1-trifluoro-2-propanols are prepared by one skilled in the art using similar methods, as shown in Example Table 53. Substituted 2-[*N*-(aryl)-[(aryl)methyl]amino]-1-trifluoromethylcyclopentanols are prepared by one skilled in the art using similar methods, as shown in Example Table 54.

Example Table 49. Substituted 3-[*N*-(aryl)-[(aryl)methyl]amino]-1,1,1-trifluoro-2-propanols.

Ex. No.	R_{SUB1}	Ex. No.	R_{SUB2}
703	3-isopropyl	1048	3-CF_3O-benzyloxy
704	2-Cl, 3-Cl	1049	3-CF_3-benzyioxy
705	3-CF_3O	1050	3-F, 5-F-benzyloxy
706	4-F	1051	cyclohexylmethyleneoxy
707	4-CH_3	1052	benzyloxy
708	2-F, 5-Br	1053	3-CF_3, 5-CF_3-benzyloxy
709	3-CHF_2O	1054	4-CF_3O-benzyloxy
710	3-CH_3CH_2	1055	4-CH_3CH_2-benzyloxy
711	3-CH_3, 5-CH_3	1056	isopropoxy
712	3-$(CH_3)_3C$	1057	3-CF_3-benzyl
713	4-F, 3-CH_3	1058	isopropylthio
714	3-Cl, 4-Cl	1059	cyclopentoxy
715	3,4-$(CH_2)_4$	1060	3-Cl-5-pyridinyloxy
716	3-HCF_2CF_2O	1061	3-CF_3S-benzyloxy
717	H	1062	3-CH_3, 4-CH_3-benzyloxy
718	3-$(CH_3)_2N$	1063	2-F, 3-CF_3-benzyloxy

(continued)

Ex. No.	R_{SUB1}	Ex. No.	R_{SUB2}
719	3-cyclopropyl	1064	3-F, 5-CF_3-benzyloxy
720	3-(2-furyl)	1065	4-$(CH_3)_2CH$-benzyloxy
721	3-CF_3CF_2	1066	1-phenylethoxy
722	4-NH_2	1067	4-F, 3-CH_3-benzoyl
723	3-CH_3, 4-CH_3, 5-CH3	1068	3-CF_3-phenyl-
724	4-$CH_3CH_2CH_2O$	1069	4-CH_3O-phenylamino-
725	2-NO_2	1070	4-NO_2-phenylthio-

Ex. No.	R_{SUB1}	Ex. No.	R_{SUB2}
726	3-isopropyl	1071	3-CF_3O-benzyloxy
727	2-Cl, 3-Cl	1072	3-CF_3-benzyloxy
728	3-CF_3O	1073	3-F, 5-F-benzyloxy
729	4-F	1074	cyclohexylmethyleneoxy
730	4-CH_3	1075	benzyloxy
731	2-F, 5-Br	1076	3-CF_3, 5-CF_3-benzyloxy
732	2-Br, 5-F	1077	4-CF_3O-benzyloxy
733	3-CH_3CH_2	1078	4-CH_3CH_2-benzyloxy
734	3-CH_3, 5-CH_3	1079	isopropoxy

(continued)

Ex. No.	R_{SUB1}	Ex. No.	R_{SUB2}
735	3-$(CH_3)_3C$	1080	$_3$-CF_3-benzyl
736	4-F, 3-CH_3	1081	isopropylthio
737	3-Cl, 4-Cl	1082	cyclopentoxy
738	3,4-$(CH_2)_4$	1083	3-Cl-5-pyridinyloxy
739	3-HCF_2CF_2O	1084	3-CF_3S-benzyloxy
740	3-CHF_2O	1085	3-CH_3, 4-CH_3-benzyloxy
741	3-$(CH_3)_2N$	1086	2-F, 3-CF_3-benzyloxy
742	3-cyclopropyl	1087	3-F, 5-CF_3-benzyloxy
743	3-(2-furyl)	1088	4-$(CH_3)_2CH$-benzyloxy
744	3-CF_3CF_2	1089	1-phenylethoxy
745	4-NH_2	1090	4-F, 3-CH_3-benzoyl
746	3-CH_3, 4-CH_3, 5-CH_3	1091	3-CF_3-phenyl-
747	4-$CH_3CH_2CH_2O$	1092	4-CH_3O-phenylamino-
748	2-NO_2	1093	4-NO_2-phenylthio-

Ex. No.	R_{SUB1}	Ex. No.	R_{SUB2}
749	3-isopropyl	1094	3-CF_3O-benzyloxy

(continued)

Ex. No.	R_{SUB1}	Ex. No.	R_{SUB2}
750	2-Cl, 3-Cl	1095	3-CF_3-benzyloxy
751	3-CF_3O	1096	3-F, 5-F-benzyloxy
752	4-F	1097	cyclohexylmethyleneoxy
753	4-CH_3	1098	benzyloxy
754	2-F, 5-Br	1099	3-CF_3, 5-CF_3-benzyloxy
755	4-Cl, 3-CH_3CH_2	1100	4-CF_3O-benzyloxy
756	3-CH_3CH_2	1101	4-CH_3CH_2-benzyloxy
757	3-CH_3, 5-CH_3	1102	isopropoxy
758	3-$(CH_3)_3C$	1103	3-CF_3-benzyl
759	4-F, 3-CH_3	1104	isopropylthio
760	3-Cl, 4-Cl	1105	cyclopentoxy
761	3,4-$(CH_2)_4$	1106	3-Cl-5-pyridinyloxy
762	3-HCF_2CF_2O	1107	3-CF_3S-benzyloxy
763	3-CHF_2O	1108	3-CH_3, 4-CH_3-benzyloxy -
764	3-$(CH_3)_2N$	1109	2-F, 3-CF_3-benzyloxy
765	3-cyclopropyl	1110	3-F, 5-CF_3-benzyloxy
766	3-(2-furyl)	1111	4-$(CH_3)_2CH$-benzyloxy
767	3-CF_3CF_2	1112	1-phenylethoxy
768	4-NH_2	1113	4-F. 3-CH_3-benzoyl
769	3-CH_3, 4-CH_3, 5-CH_3	1114	3-CF_3-phenyl-
770	4-$CH_3CH_2CH_2O$	1115	4-CH_3O-phenylamino-
771	2-NO_2	1116	4-NO_2-phenylthio-

(continued)

Ex. No.	R_{SUB1}	Ex. No.	R_{SUB2}
772	3-isopropyl	1117	3-CF_3O-benzyloxy
773	2-Cl, 3-Cl	1118	3-CF_3-benzyloxy
774	3-CF_3O	1119	3-F,5-F-benzyloxy
775	4-F	1120	cyclohexylmethyleneoxy
776	4-CH_3	1121	benzyloxy
777	2-F, 5-Br	1122	3-CF_3, 5-CF_3-benzyloxy
778	4-Cl, 3-CH_3CH_2	1123	4-CF_3O-benzyloxy
779	3-CH_3CH_2	1124	4-CH_3CH_2-benzyloxy
780	3-CH_3, 5-CH_3	1125	isopropoxy
781	3-$(CH_3)_3C$	1126	3-CF_3-benzyl
782	4-F, 3-CH_3	1127	isopropylthio
783	3-Cl, 4-Cl	1128	cyclopentoxy
784	3,4-$(CH_2)_4$	1129	3-Cl-5-pyridinyloxy
785	3-HCF_2CF_2O	1130	3-CF_3S-benzyloxy
786	3-CHF_2O	1131	3-CH_3, 4-CH_3-benzyloxy

(continued)

Ex. No.	R_{SUB1}	Ex. No.	R_{SUB2}
787	3-$(CH_3)_2N$	1132	2-F, 3-CF_3-benzyloxy
788	3-cyclopropyl	1133	3-F, 5-CF_3-benzyloxy
789	3-(2-furyl)	1134	4-$(CH_3)_2CH$-benzyloxy
790	3-CF_3CF_2	1135	1-phenylethoxy
791	4-NH_2	1136	4-F, 3-CH_3-benzoyl
792	3-CH_3, 4-CH_3, 5-CH_3	1137	3-CF_3-phenyl-
793	4-$CH_3CH_2CH_2O$	1138	4-CH_3O-phenylamino-
794	2-NO_2	1139	4-NO_2-phenylthio-

Ex. No.	R_{SUB1}	Ex. No.	R_{SUB2}
795	3-isopropyl	1140	3-CF_3O-benzyloxy
796	2-Cl, 3-Cl	1141	3-CF_3-benzyloxy
797	3-CF_3O	1142	3-F, 5-F-benzyloxy
798	4-F	1143	cyclohexylmethyleneoxy
799	4-CH_3	1144	benzyloxy
800	2-F, 5-Br	1145	3-CF_3, 5-CF_3-benzyloxy
801	4-Cl, 3-CH_3CH_2	1146	4-CF_3O-benzyloxy
802	3-CH_3CH_2	1147	4-CH_3CH_2-benzyloxy

(continued)

Ex. No.	R_{SUB1}	Ex. No.	R_{SUB2}
803	3-CH_3, 5-CH_3	1148	isopropoxy
804	3-$(CH_3)_3C$	1149	3-CF_3-benzyl
805	4-F, 3-CH_3	1150	isopropylthio
806	3-Cl, 4-Cl	1151	cyclopentoxy
807	3,4-$(CH_2)_4$	1152	3-Cl-5-pyridinyloxy
808	3-HCF_2CF_2O	1153	3-CF_3S-benzyloxy
809	3-CHF_2O	1154	3-CH_3, 4-CH_3-benzyloxy
810	3-$(CH_3)_2N$	1155	2-F, 3-CF_3-benzyloxy
811	3-cyclopropyl	1156	3-F, 5-CF_3-benzyloxy
812	3-(2-furyl)	1157	4-$(CH_3)_2CH$-benzyloxy
813	3-CF_3CF_2	1158	1-pherylethoxy
814	4-NH_2	1159	4-F, 3-CH_3-benzoyl
815	3-CH_3, 4-CH_3, 5-CH_3	1160	3-CF_3-phenyl-
816	4-$CH_3CH_2CH_2O$	1161	4-CH_3O-phenylamino-
817	2-NO_2	1162	4-NO_2-phenylthio-

Ex. No.	R_{SUB1}	Ex. No.	R_{SUB2}
818	3-isopropyl	1163	3-CF_3O-benzyloxy

(continued)

Ex. No.	R_{SUB1}	Ex. No.	R_{SUB2}
819	2-Cl, 3-Cl	1164	3-CF_3-benzyloxy
820	3-CF_3O	1165	3-F, 5-F-benzyloxy
821	4-F	1166	cyclohexylmethyleneoxy
822	4-CH_3	1167	benzyloxy
823	2-F, 5-Br	1168	3-CF_3, 5-CF_3-benzyloxy
824	4-Cl, 3-CH_3CH_2	1169	4-CF_3O-benzyloxy
825	3-CH_3CH_2	1170	4-CH_3CH_2-benzyloxy
826	3-CH_3, 5-CH_3	1171	isopropoxy
827	3-$(CH_3)_3C$	1172	3-CF_3-benzyl
828	4-F, 3-CH_3	1173	isopropylthio
829	3-Cl, 4-Cl	1174	cyclopentoxy
830	3,4-$(CH_2)_4$	1175	3-Cl-5-pyridinyloxy
831	3-HCF_2CF_2O	1176	3-CF_3S-benzyloxy
832	3-CHF_2O	1177	3-CH_3, 4-CH_3-benzyloxy
833	3-$(CH_3)_2N$	1178	2-F, 3-CF_3-benzyloxy
834	3-cyclopropyl	1179	3-F, 5-CF_3-benzyloxy
835	3-(2-furyl)	1180	4-$(CH_3)_2CH$-benzyloxy
836	3-CF_3CF_2	1181	1-phenylethoxy
837	4-NH_2	1182	4-F, 3-CH_3-benzoyl
838	3-CH_3, 4-CH_3, 5-CH_3	1183	3-CF_3-phenyl-
839	4-$CH_3CH_2CH_2O$	1184	4-CH_3O-phenylamino-
840	2-NO_2	1185	4-NO_2-phenylthio-

(continued)

Ex. No.	R_{SUB1}	Ex. No.	R_{SUB2}
841	3-isopropyl	1186	3-CF_3O-benzyloxy
842	2-Cl, 3-Cl	1187	3-CF_3-benzyloxy
843	3-CF_3O	1188	3-F, 5-F-benzyloxy
844	4-F	1189	cyclohexylmethyleneoxy
845	4-CH_3	1190	benzyloxy
846	2-F, 5-Br	1191	3-CF_3, 5-CF_3-benzyloxy
847	4-Cl, 3-CH_3CH_2	1192	4-CF_3O-benzyloxy
848	3-CH_3CH_2	1193	4-CH_3CH_2-benzyloxy
849	3-CH_3, 5-CH_3	1194	isopropoxy
850	3-$(CH_3)_3C$	1195	3-CF_3-benzyl
851	4-F, 3-CH_3	1196	isopropylthio
852	3-Cl, 4-Cl	1197	cyclopentoxy
853	3,4-$(CH_2)_4$	1198	3-Cl-5-pyridinyloxy
854	3-HCF_2CF_2O	1199	3-CF_3S-benzyloxy
855	3-CHF_2O	1200	3-CH_3, 4-CH_3-benzyloxy
856	3-$(CH_3)_2N$	1201	2-F, 3-CF_3-benzyloxy

(continued)

Ex. No.	R_{SUB1}		Ex. No.	R_{SUB2}
857	3-cyclopropyl		1202	3-F, 5-CF_3-benzyloxy
858	3-(2-furyl)		1203	4-$(CH_3)_2$CH-benzyloxy
859	3-CF_3CF_2		1204	1-phenylethoxy
860	4-NH_2		1205	4-F, 3-CH_3-benzoyl
861	3-CH_3, 4-CH_3, 5-CH3		1206	3-CF_3-phenyl-
862	4-$CH_3CH_2CH_2O$		1207	4-CH_3O-phenylamino-
863	2-NO_2		1208	4-NO_2-phenylthio-

Ex. No.	R_{SUB1}	Ex. No.	R_{SUB2}
864	3-isopropyl	1209	3-CF_3O-benzyloxy
865	2-Cl, 3-Cl	1210	3-CF_3-benzyloxy
866	3-CF_3O	1211	3-F, 5-F-benzyloxy
867	4-F	1212	cyclohexylmethyleneoxy
868	4-CH_3	1213	benzyloxy
869	2-F, 5-Br	1214	3-CF_3, 5-CF_3-benzyloxy
870	4-Cl, 3-CH_3CH_2	1215	4-CF_3O-benzyloxy
871	3-CH_3CH_2	1216	4-CH_3CH_2-benzyloxy
872	3-CH_3, 5-CH_3	1217	isopropoxy

(continued)

Ex. No.	R_{SUB1}	Ex. No.	R_{SUB2}
873	3-$(CH_3)_3C$	1218	3-CF_3-benzyl
874	4-F, 3-CH_3	1219	isopropylthio
875	3-Cl, 4-Cl	1220	cyclopentoxy
876	3,4-$(CH_2)_4$	1221	3-Cl-5-pyridinyloxy
877	3-HCF_2CF_2O	1222	3-CF_3S-benzyloxy
878	3-CHF_2O	1223	3-CH_3, 4-CH_3-benzyloxy
879	3-$(CH_3)_2N$	1224	2-F, 3-CF_3-benzyloxy
880	3-cyclopropyl	1225	3-F, 5-CF_3-benzyloxy
881	3-(2-furyl)	1226	4-$(CH_3)_2CH$-benzyloxy
882	3-CF_3CF_2	1227	1-phenylethoxy
883	4-NH_2	1228	4-F, 3-CH_3-benzoyl
884	3-CH_3, 4-CH_3, 5-CH_3	1229	3-CF_3-phenyl-
885	4-$CH_3CH_2CH_2O$	1230	4-CH_3O-phenylamino-
886	2-NO_2	1231	4-NO_2-phenylthio-

Ex. No.	R_{SUB1} No.	Ex.	R_{SUB2}
887	3-isopropyl	1232	3-CF_3O-benzyloxy
888	2-Cl, 3-Cl	1233	3-CF_3-benzyloxy

(continued)

Ex. No.	R_{SUB1} No.	Ex.	R_{SUB2}
889	3-CF_3O	1234	3-F, 5-F-benzyloxy
890	4-F	1235	cyclohexylmethyleneoxy
891	4-CH_3	1236	benzyloxy
892	2-F, 5-Br	1237	3-CF_3, 5-CF_3-benzyloxy
893	4-Cl, 3-CH_3CH_2	1238	4-CF_3O-benzyloxy
894	3-CH_3CH_2	1239	4-CH_3CH_2-benzyloxy
895	3-CH_3, 5-CH_3	1240	isopropoxy
896	3-$(CH_3)_3C$	1241	3-CF_3-benzyl
897	4-F, 3-CH_3	1242	isopropylthio
898	3-Cl, 4-Cl	1243	cyclopentoxy
899	3,4-$(CH_2)_4$	1244	3-Cl-5-pyridinyloxy
900	3-HCF_2CF_2O	1245	3-CF_3S-benzyloxy
901	3-CHF_2O	1246	3-CH_3, 4-CH_3-benzyloxy
902	3-$(CH_3)_2N$	1247	2-F, 3-CF_3-benzyloxy
903	3-cyclopropyl	1248	3-F, 5-CF_3-benzyloxy
904	3-(2-furyl)	1249	4-$(CH_3)_2CH$-benzyloxy
905	3-CF_3CF_2	1250	1-phenylethoxy
906	4-NH_2	1251	4-F, 3-CH_3-benzoyl
907	3-CH_3, 4-CH_3, 5-CH_3	1252	3-CF_3-phenyl-
908	4-$CH_3CH_2CH_2O$	1253	4-CH_3O-phenylamino-
909	2-NO_2	1254	4-NO_2-phenylthio-

(continued)

Ex. No.	R_{SUB1} No.	Ex.	R_{SUB2}

Ex. No.	R_{SUB1}
910	3-isopropyl
911	2-Cl, 3-Cl
912	3-CF_3O
913	4-F
914	4-CH_3
915	2-F, 5-Br
916	4-Cl, 3-CH_3CH_2
917	3-CH_3CH_2
918	3-CH_3, 5-CH_3
919	3-$(CH_3)_3C$
920	4-F, 3-CH_3
921	3-Cl, 4-Cl
922	3,4-$(CH_2)_4$
923	3-HCF_2CF_2O
924	3-CHF_2O
925	3-$(CH_3)_2N$

Ex. No.	R_{SUB2}
1255	3-CF_3O-benzyloxy
1256	3-CF_3-benzyloxy
1257	3-F, 5-F-benzyloxy
1258	cyclohexylmethyleneoxy
1259	benzyloxy
1260	3-CF_3, 5-CF_3-benzyloxy
1261	4-CF_3O-benzyloxy
1262	4-CH_3CH_2-benzyloxy
1263	isopropoxy
1264	3-CF_3-benzyl
1265	isopropylthio
1266	cyclopentoxy
1267	3-Cl-5-pyridinyloxy
1268	3-CF_3S-benzyloxy
1269	3-CH_3, 4-CH_3-benzyloxy
1270	2-F, 3-CF_3-benzyloxy

(continued)

Ex. No.	R_{SUB1}	Ex. No.	R_{SUB2}
926	3-cyclopropyl	1271	3-F, 5-CF_3-benzyloxy
927	3-(2-furyl)	1272	4-$(CH_3)_2CH$-benzyloxy
928	3-CF_3CF_2	1273	1-phenylethoxy
929	4-NH_2	1274	4-F, 3-CH_3-benzoyl
930	3-CH_3, 4-CH_3, 5-CH_3	1275	3-CF_3-phenyl-
931	4-$CH_3CH_2CH_2O$	1276	4-CH_3O-phenylamino-
932	2-NO_2	1277	4-NO_2-phenylthio-

Ex. No.	R_{SUB1}	Ex. No.	R_{SUB2}
933	3-isopropyl	1278	3-CF_3O-benzyloxy
934	2-Cl, 3-Cl	1279	3-CF_3-benzyloxy
935	3-CF_3O	1280	3-F, 5-F-benzyloxy
936	4-F	1281	cyclohexylmethyleneoxy
937	4-CH_3	1282	benzyloxy
938	2-F, 5-Br	1283	3-CF_3, 5-CF_3-benzyloxy
939	4-Cl, 3-CH_3CH_2	1284	4-CF_3O-benzyloxy
940	3-CH_3CH_2	1285	4-CH_3CH_2-benzyloxy
941	3-CH_3, 5-CH_3	1286	isopropoxy

(continued)

Ex. No.	R_{SUB1}	Ex. No.	R_{SUB2}
942	3-$(CH_3)_3C$	1287	3-CF_3-benzyl
943	4-F, 3-CH_3	1288	isopropylthio
944	3-Cl, 4-Cl	1289	cyclopentoxy
945	3,4-$(CH_2)_4$	1290	3-Cl-5-pyridinyloxy
946	3-HCF_2CF_2O	1291	3-CF_3S-benzyloxy
947	3-CHF_2O	1292	3-CH_3, 4-CH_3-benzyloxy
948	3-$(CH_3)_2N$	1293	2-F, 3-CF_3-benzyloxy
949	3-cyclopropyl	1294	3-F, 5-CF_3-benzyloxy
950	3-(2-furyl)	1295	4-$(CH_3)_2CH$-benzyloxy
951	3-CF_3CF_2	1296	1-phenylethoxy
952	4-NH_2	1297	4-F, 3-CH_3-benzoyl
953	3-CH_3, 4-CH_3, 5-CH_3	1298	3-CF_3-phenyl-
954	4-$CH_3CH_2CH_2O$	1299	4-CH_3O-phenylamino-
955	2-NO_2	1300	4-NO_2-phenylthio-

Ex. No.	R_{SUB1}	Ex. No.	R_{SUB2}
956	3-isopropyl	1301	3-CF_3O-benzyloxy

(continued)

Ex. No.	R_{SUB1}	Ex. No.	R_{SUB2}
957	2-Cl, 3-Cl	1302	3-CF_3-benzyloxy
958	3-CF_3O	1303	3-F, 5-F-benzyloxy
959	4-F	1304	cyclohexylmethyleneoxy
960	4-CH_3	1305	benzyloxy
961	2-F, 5-Br	1306	3-CF_3, 5-CF_3-benzyloxy
962	2-Br, 5-F	1307	4-CF_3O-benzyloxy
963	3-CH_3CH_2	1308	4-CH_3CH_2-benzyloxy
964	3-CH_3, 5-CH_3	1309	isopropoxy
965	3-$(CH_3)_3C$	1310	3-CF_3-benzyl
966	4-F, 3-CH_3	1311	isopropylthio
967	3-Cl, 4-Cl	1312	cyclopentoxy
968	3,4-$(CH_2)_4$	1313	3-Cl-5-pyridinyloxy
969	3-HCF_2CF_2O	1314	3-CF_3S-benzyloxy
970	3-CHF_2O	1315	3-CH_3, 4-CH_3-benzyloxy
971	3-$(CH_3)_2N$	1316	2-F, 3-CF_3-benzyloxy
972	3-cyclopropyl	1317	3-F, 5-CF_3-benzyloxy
973	3-(2-furyl)	1318	4-$(CH_3)_2CH$-benzyloxy
974	3-CF_3CF_2	1319	1-phenylethoxy
975	4-NH_2	1320	4-F, 3-CH_3-benzoyl
976	3-CH_3, 4-CH_3, 5-CH_3	1321	3-CF_3-phenyl-
977	4-$CH_3CH_2CH_2O$	1322	4-CH_3O-phenylamino-
978	2-NO_2	1323	4-NO_2-phenylthio-

(continued)

Ex. No.	R_{SUB1}	Ex. No.	R_{SUB2}
979	3-isopropyl	1324	3-CF_3O-benzyloxy
980	2-Cl, 3-Cl	1325	3-CF_3-benzyloxy
981	3-CF_3O	1326	3-F, 5-F-benzyloxy
982	4-F	1327	cyclohexylmethyleneoxy
983	4-CH_3	1328	benzyloxy
984	2-F, 5-Br	1329	3-CF_3, 5-CF_3-benzyloxy
985	4-Cl, 3-CH_3CH_2	1330	4-CF_3O-benzyloxy
986	3-CH_3CH_2	1331	4-CH_3CH_2-benzyloxy
987	3-CH_3, 5-CH_3	1332	isopropoxy
988	3-$(CH_3)_3C$	1333	3-CF_3-benzyl
989	4-F, 3-CH_3	1334	isopropylthio
990	3-Cl, 4-Cl	1335	cyclopentoxy
991	3,4-$(CH_2)_4$	1336	3-Cl-5-pyridinyloxy
992	3-HCF_2CF_2O	1337	3-CF_3S-benzyloxy

(continued)

Ex. No.	R_{SUB1}	Ex. No.	R_{SUB2}
993	3-CHF_2O	1338	3-CH_3, 4-CH_3-benzyloxy
994	3-$(CH_3)_2N$	1339	2-F, 3-CF_3-benzyloxy
995	3-cyclopropyl	1340	3-F, 5-CF_3-benzyloxy
996	3-(2-furyl)	1341	4-$(CH_3)_2CH$-benzyloxy
997	3-CF_3CF_2	1342	1-phenylethoxy
998	4-NH_2	1343	4-F, 3-CH_3-benzoyl
999	3-CH_3, 4-CH_3, 5-CH_3	1344	3-CF_3-phenyl-
1000	4-$CH_3CH_2CH_2O$	1345	4-CH_3O-phenylamino-
1001	2-NO_2	1346	4-NO_2-phenylthio-

Ex. No.	R_{SUB1}	Ex. No.	R_{SUB2}
1002	3-isopropyl	1347	3-CF_3O-benzyloxy
1003	2-Cl, 3-Cl	1348	3-CF_3-benzyloxy
1004	3-CF_3O	1349	3-F, 5-F-benzyloxy
1005	4-F	1350	cyclohexylmethyleneoxy
1006	4-CH_3	1351	benzyloxy

(continued)

Ex. No.	R_{SUB1}	Ex. No.	R_{SUB2}
1007	2-F, 5-Br	1352	3-CF_3, 5-CF_3-benzyloxy
1008	4-Cl, 3-CH_3CH_2	1353	4-CF_3O-benzyloxy
1009	3-CH_3CH_2	1354	4-CH_3CH_2-benzyloxy
1010	3-CH_3, 5-CH_3	1355	isopropoxy
1011	3-$(CH_3)_3C$	1356	3-CF_3-benzyl
1012	4-F, 3-CH_3	1357	isopropylthio
1013	3-Cl, 4-Cl	1358	cyclopentoxy
1014	3,4-$(CH_2)_4$	1359	3-Cl-5-pyridinyloxy
1015	3-HCF_2CF_2O	1360	3-CF_3S-benzyloxy
1016	3-CHF_2O	1361	3-CH_3, 4-CH_3-benzyloxy
1017	3-$(CH_3)_2N$	1362	2-F, 3-CF_3-benzyloxy
1018	3-cyclopropyl	1363	3-F, 5-CF_3-benzyloxy
1019	3-(2-furyl)	1364	4-$(CH_3)_2CH$-benzyloxy
1020	3-CF_3CF_2	1365	1-phenylethoxy
1021	4-NH_2	1366	4-F, 3-CH_3-benzoyl
1022	3-CH_3, 4-CH_3, 5-CH3	1367	3-CF_3-phenyl-
1023	4-$CH_3CH_2CH_2O$	1368	4-CH_3O-phenylamino-
1024	2-NO_2	1369	4-NO_2-phenylthio-

(continued)

Ex. No.	R_{SUB1}	Ex. No.	R_{SUB2}
1025	3-isopropyl	1370	3-CF_3O-benzyioxy
1026	2-Cl, 3-Cl	1371	3-CF_3-benzyloxy
1027	3-CF_3O	1372	3-F, 5-F-benzyloxy
1028	4-F	1373	cyclohexylmethyleneoxy
1029	4-CH_3	1374	benzyloxy
1030	2-F, 5-Br	1375	3-CF_3, 5-CF_3-benzyloxy
1031	4-Cl, 3-CH_3CH_2	1376	4-CF_3O-benzyloxy
1032	3-CH_3CH_2	1377	4-CH_3CH_2-benzyloxy
1033	3-CH_3, 5-CH_3	1378	isopropoxy
1034	3-$(CH_3)_3C$	1379	3-CF_3-benzyl
1035	4-F, 3-CH_3	1380	isopropylthio
1036	3-Cl, 4-Cl	1381	cyclopentoxy
1037	3,4-$(CH_2)_4$	1382	3-Cl-5-pyridinyloxy
1038	3-HCF_2CF_2O	1383	3-CF_3S-benzyloxy
1039	3-CHF_2O	1384	3-CH_3, 4-CH_3-benzyloxy

(continued)

Ex. No.	R_{SUB1}	Ex. No.	R_{SUB2}
1040	3-$(CH_3)_2N$	1385	2-F, 3-CF_3-benzyloxy
1041	3-cyclopropyl	1386	3-F, 5-CF_3-benzyloxy
1042	3-(2-furyl)	1387	4-$(CH_3)_2CH$-benzyloxy
1043	3-CF_3CF_2	1388	1-phenylethoxy
1044	4-NH_2	1389	4-F, 3-CH_3-benzoyl
1045	3-CH_3, 4-CH_3, 5-CH_3	1390	3-CF_3-phenyl-
1046	4-$CH_3CH_2CH_2O$	1391	4-CH_3O-phenylamino-
1047	2-NO_2	1392	4-NO_2-phenylthio-

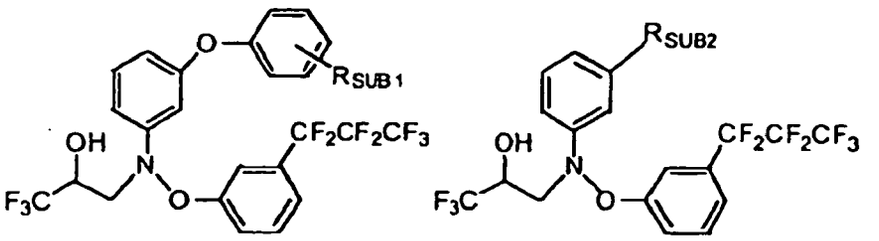
Example Table 50. Substituted 4-[*N*-(aryl)-[(aryl)methyl]amino]-1,1,1,2,2-pentafl uoro-3-butanol s.

Ex. No.	R_{SUB1}	Ex. No.	R_{SUB2}
1393	3-isopropyl	1416	3-CF_3O-benzyloxy
1394	2-Cl, 3-Cl	1417	3-CF_3-benzyloxy
1395	3-CF_3O	1418	3-F, 5-F-benzyloxy
1396	4-F	1419	cyclohexylmethyleneoxy
1397	4-CH_3	1420	benzyloxy
1398	2-F, 5-Br	1421	3-CF_3, 5-CF_3-benzyloxy
1399	4-Cl, 3-CH_3CH_2	1422	4-CF_3O-benzyloxy
1400	3-CH_3CH_2	1423	4-CH_3CH_2-benzyloxy
1401	3-CH_3, 5-CH_3	1424	isopropoxy
1402	3-$(CH_3)_3C$	1425	3-CF_3-benzyl
1403	4-F, 3-CH_3	1426	isopropylthio
1404	3-Cl, 4-Cl	1427	cyclopentoxy
1405	3,4-$(CH_2)_4$	1428	3-Cl-5-pyridinyloxy
1406	3-HCF_2CF_2O	1429	3-CF_3S-benzyloxy
1407	3-CHF_2O	1430	3-CH_3, 4-CH_3-benzyloxy
1408	3-$(CH_3)_2N$	1431	2-F, 3-CF_3-benzyloxy
1409	3-cyclopropyl	1432	3-F, 5-CF_3-benzyloxy

(continued)

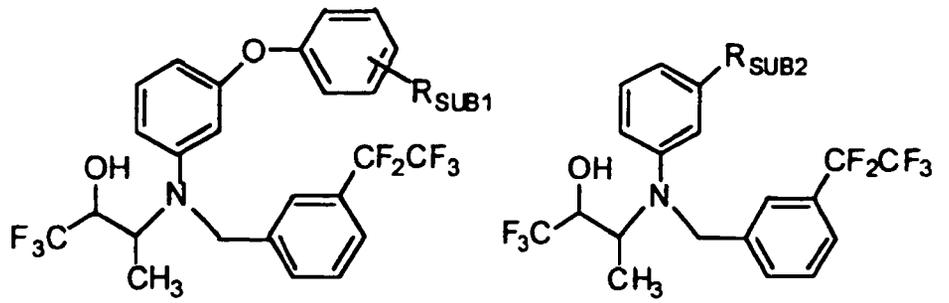
Ex. No.	R_{SUB1}	Ex. No.	R_{SUB2}
1410	3-(2-furyl)	1433	4-$(CH_3)_2$CH-benzyloxy
1411	3-CF_3CF_2	1434	1-phenylethoxy
1412	4-NH_2	1435	4-F, 3-CH_3-benzoyl
1413	3-CH_3, 4-CH_3, 5-CH_3	1436	3-CF_3-phenyl-
1414	4-$CH_3CH_2CH_2O$	1437	4-CH_3O-phenylamino-
1415	2-NO_2	1438	4-NO_2-phenylthio-

Example Table 51. Substituted 3-[*N*-(aryl)-[(aryl)oxy]amino]-1,1,1-trifluoro-2-propanols. *



Ex. No.	R_{SUB1}		Ex. No.	R_{SUB2}
1439	3-isopropyl		1462	3-CF_3O-benzyloxy
1440	2-Cl, 3-Cl		1463	3-CF_3-benzyloxy
1441	3-CF_3O		1464	3-F, 5-F-benzyloxy
1442	4-F		1465	cyclohexylmethyleneoxy
1443	4-CH_3		1466	benzyloxy
1444	2-F, 5-Br		1467	3-CF_3, 5-CF_3-benzyloxy
1445	4-Cl, 3-CH_3CH_2		1468	4-CF_3O-benzyloxy
1446	3-CH_3CH_2		1469	4-CH_3CH_2-benzyloxy
1447	3-CH_3, 5-CH_3		1470	isopropoxy
1448	3-$(CH_3)_3C$		1471	3-CF_3-benzyl
1449	4-F, 3-CH_3		1472	isopropylthio
1450	3-Cl, 4-Cl		1473	cyclopentoxy
1451	3,4-$(CH_2)_4$		1474	3-Cl-5-pyridinyloxy
1452	3-HCF_2CF_2O		1475	3-CF_3S-benzyloxy
1453	3-CHF_2O		1476	3-CH_3, 4-CH_3-benzyloxy
1454	3-$(CH_3)_2N$		1477	2-F, 3-CF_3-benzyloxy
1455	3-cyclopropyl		1478	3-F, 5-CF_3-benzyloxy
1456	3-(2-furyl)		1479	4-$(CH_3)_2CH$-benzyloxy
1457	3-CF_3CF_2		1480	1-phenylethoxy
1458	4-NH_2		1481	4-F, 3-CH_3-benzoyl
1459	3-CH_3, 4-CH_3, 5-CH_3		1482	3-CF_3-phenyl-
1460	4-$CH_3CH_2CH_2O$		1483	4-CH_3O-phenylamino-
1461	2-NO_2		1484	4-NO_2-phenylthio-

Example Table 52. Substituted 3-[*N*-(aryl)-[(aryl)methyl]amino]-1,1,1-trifluoro-2-butanols.

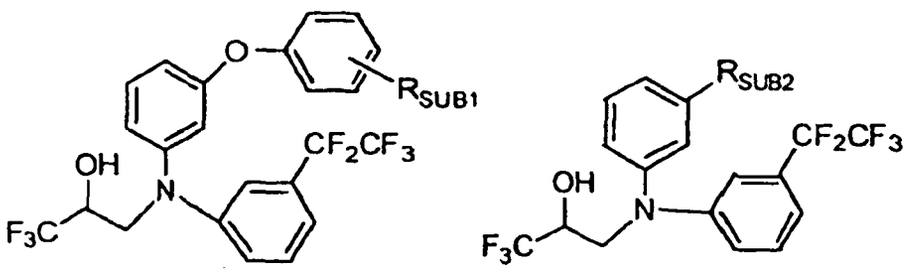


Ex. No.	R_{SUB1}		Ex. No.	R_{SUB2}
1485	3-isopropyl		1531	3-CF_3O-benzyloxy
1486	2-Cl, 3-Cl		1532	3-CF_3-benzyloxy
1487	3-CF_3O		1533	3-F, 5-F-benzyloxy
1488	4-F		1534	cyclohexylmethyleneoxy
1489	4-CH_3		1535	benzyloxy
1490	2-F, 5-Br		1536	3-CF_3, 5-CF_3-benzyloxy
1491	4-Cl, 3-CH_3CH_2		1537	4-CF_3O-benzyloxy
1492	3-CH_3CH_2		1538	4-CH_3CH_2-benzyloxy
1493	3-CH_3, 5-CH_3		1539	isopropoxy
1494	3-$(CH_3)_3C$		1540	3-CF_3-benzyl
1495	4-F, 3-CH_3		1541	isopropylthio
1496	3-Cl, 4-Cl		1542	cyclopentoxy
1497	3,4-$(CH_2)_4$		1543	3-Cl-5-pyridinyloxy
1498	3-HCF_2CF_2O		1544	3-CF_3S-benzyloxy
1499	3-CHF_2O		1545	3-CH_3, 4-CH_3-benzyloxy
1500	3-$(CH_3)_2N$		1546	2-F, 3-CF_3-benzyloxy
1501	3-cyclopropyl		1547	3-F, 5-CF_3-benzyloxy
1502	3-(2-furyl)		1548	4-$(CH_3)_2CH$-benzyloxy
1503	3-CF_3CF_2		1549	1-phenylethoxy
1504	4-NH_2		1550	4-F, 3-CH_3-benzoyl
1505	3-CH_3, 4-CH_3, 5-CH_3		1551	3-CF_3-phenyl-
1506	4-$CH_3CH_2CH_2O$		1552	4-CH_3O-phenylamino-
1507	2-NO_2		1553	4-NO_2-phenylthio-
1508	3-isopropyl		1554	3-CF_3O-benzyloxy
1509	2-Cl, 3-Cl		1555	3-CF_3-benzyloxy
1510	3-CF_3O		1556	3-F, 5-F-benzyloxy
1511	4-F		1557	cyclohexylmethyleneoxy
1512	4-CH_3		1558	benzyloxy
1513	2-F, 5-Br		1559	3-CF_3, 5-CF_3-benzyloxy
1514	4-Cl, 3-CH_3CH_2		1560	4-CF_3O-benzyloxy

(continued)

Ex. No.	R_{SUB1}		Ex. No.	R_{SUB2}
1515	3-CH_3CH_2		1561	4-CH_3CH_2-benzyloxy
1516	3-CH_3, 5-CH_3		1562	isopropoxy
1517	3-$(CH_3)_3C$		1563	3-CF_3-benzyl
1518	4-F, 3-CH_3		1564	isopropylthio
1519	3-Cl, 4-Cl		1565	cyclopentoxy
1520	3,4-$(CH_2)_4$		1566	3-Cl-5-pyridinyloxy
1521	3-HCF_2CF_2O		1567	3-CF_3S-benzyloxy
1522	3-CHF_2O		1568	3-CH_3, 4-CH_3-benzyloxy
1523	3-$(CH_3)_2N$		1569	2-F, 3-CF_3-benzyloxy
1524	3-cyclopropyl		1570	3-F, 5-CF_3-benzyloxy
1525	3-(2-furyl)		1571	4-$(CH_3)_2CH$-benzyloxy
1526	3-CF_3CF_2		1572	1-phenylethoxy
1527	4-NH_2		1573	4-F, 3-CH_3-benzoyl
1528	3-CH_3, 4-CH_3, 5-CH_3		1574	3-CF_3-phenyl-
1529	4-$CH_3CH_2CH_2O$		1575	4-CH_3O-phenylamino-
1530	2-NO_2		1576	4-NO_2-phenylthio-

Example Table 53. Substituted 3-[*N,N'*-(diaryl)amino]-1,1,1.2,2-pentafluoro-2-propanols. *

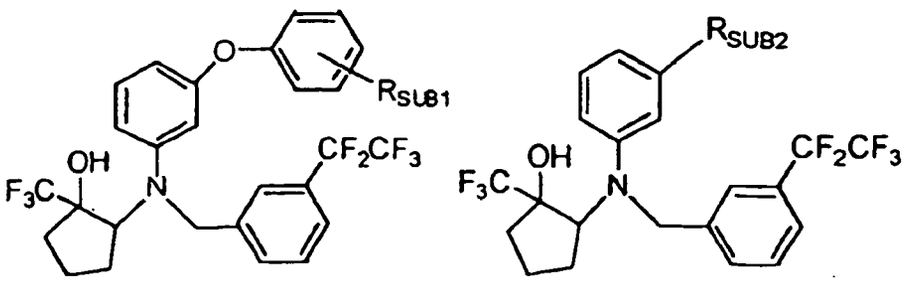


Ex. No.	R_{SUB1}		Ex. No.	R_{SUB2}
1577	3-isopropyl		1600	3-CF_3O-benzyloxy
1578	2-Cl, 3-Cl		1601	3-CF_3-benzyloxy
1579	3-CF_3O		1602	3-F, 5-F-benzyloxy
1580	4-F		1603	cyclohexylmethyleneoxy
1581	4-CH_3 3		1604	benzyloxy
1582	2-F, 5-Br		1605	3-CF_3, 5-CF_3-benzyloxy
1583	4-Cl, 3-CH_3CH_2		1606	4-CF_3O-benzyloxy
1584	3-CH_3CH_2		1607	4-CH_3CH_2-benzyloxy
1585	3-CH_3, 5-CH_3		1608	isopropoxy
1586	3-$(CH_3)_3C$		1609	3-CF_3-benzyl
1587	4-F, 3-CH_3		1610	isopropylthio

(continued)

Ex. No.	R_{SUB1}		Ex. No.	R_{SUB2}
1588	3-Cl, 4-Cl		1611	cyclopentoxy
1589	3,4-$(CH_2)_4$		1612	3-Cl-5-pyridinyloxy
1590	3-HCF_2CF_2O		1613	3-CF_3S-benzyloxy
1591	3-CHF_2O		1614	3-CH_3, 4-CH_3-benzyloxy
1592	3-$(CH_3)_2N$		1615	2-F, 3-CF_3-benzyloxy
1593	3-cyclopropyl		1616	3-F, 5-CF_3-benzyloxy
1594	3-(2-furyl)		1617	4-$(CH_3)_2CH$-benzyloxy
1595	3-CF_3CF_2		1618	1-phenylethoxy
1596	4-NH_2		1619	4-F, 3-CH_3-benzoyl
1597	3-CH_3, 4-CH_3, 5-CH_3		1620	3-CF_3-phenyl
1598	4-$CH_3CH_2CH_2O$		1621	4-CH_3O-phenylamino
1599	2-NO_2		1622	4-NO_2-phenylthio

Example Table 54. Substituted 2-[*N*-(aryl)-[(aryl)methyl]amino]-1-trifluoromethylcyclopentanols. *



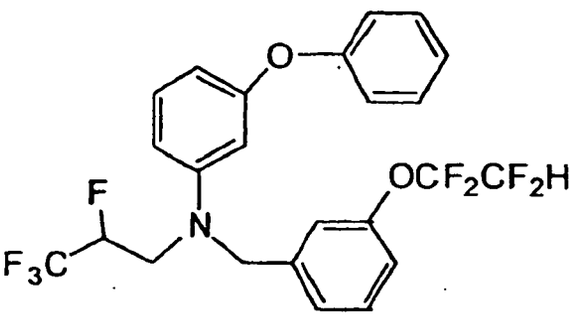
Ex. No.	R_{SUB1}		Ex. No.	R_{SUB2}
1623	3-isopropyl		1646	3-CF_3O-benzyloxy
1624	2-Cl, 3-Cl		1647	3-CF_3-benzyloxy
1625	3-CF_3O		1648	3-F,5-F-benzyloxy
1626	4-F		1649	cyclohexylmethyleneoxy
1627	4-CH_3		1650	benzyloxy
1628	2-F, 5-Br		1651	3-CF_3, 5-CF_3-benzyloxy
1629	4-Cl, 3-CH_3CH_2		1652	4-CF_3O-benzyloxy
1630	3-CH_3CH_2		1653	4-CH_3CH_2-benzyloxy
1631	3-CH_3, 5-CH_3		1654	isopropoxy
1632	3-$(CH_3)_3C$		1655	3-CF_3-benzyl
1633	4-F, 3-CH_3		1656	isopropylthio
1634	3-Cl, 4-Cl		1657	cyclopentoxy
1635	3,4-$(CH_2)_4$		1658	3-Cl-5-pyridinyloxy
1636	3-HCF_2CF_2O		1659	3-CF_3S-benzyloxy

(continued)

Ex. No.	R_{SUB1}		Ex. No.	R_{SUB2}
1637	3-CHF_2O		1660	3-CH_3, 4-CH_3-benzyloxy
1638	3-$(CH_3)_2N$		1661	2-F, 3-CF_3-benzyloxy
1639	3-cyclopropyl		1662	3-F, 5-CF_3-benzyloxy
1640	3-(2-furyl)		1663	4-$(CH_3)_2CH$-benzyloxy
1641	3-CF_3CF_2		1664	1-phenylethoxy
1642	4-NH_2		1665	4-F, 3-CH_3-benzoyl
1643	3-CH_3, 4-CH_3, 5-CH_3		1666	3-CF_3-phenyl-
1644	4-$CH_3CH_2CH_2O$		1667	4-CH_3O-phenylamino-
1645	2-NO_2		1668	4-NO_2-phenylthio-

EXAMPLE 1669 *

[0459]

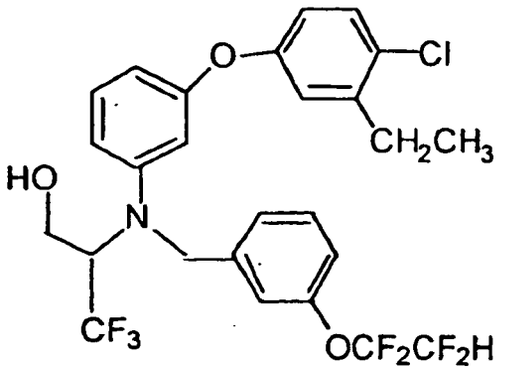


N-(3-phenoxyphenyl)-N-(3,3,3,2-tetrafluoropropyl)-3-(1,1,2,2-tetrafluoroethoxy)benzenemethanamine

[0460] To a solution of 3-[(3-phenoxyphenyl)[[3-(1,1,2,2-tetrafluoroethoxy) phenyl]-methyl]amino]-1,1,1-trifluoro-2-propanol (474 mg, 0.00094 mol) in 4.5 mL of dichloromethane at 0 ˚C was added (diethylamino)sulfur trifluoride (378 mg, 0.0023 mol). The reaction mixture was warmed to room temperature and stirred for 2 h, then quenched with water and extracted with dichloromethane. The organic layers were combined, dried over $MgSO_4$, and concentrated *in vacuo.* The crude product was purified by column chromatography on silica gel eluting with 1:9 ethyl acetate in hexane to afford 240 mg (50%) of the desired N-(3-phenoxyphenyl)-N-(3,3,3,2-tetra-fluoropropyl)-3-(1,1,2,2-tetrafluoroethoxy)benzenemethanamine product as a yellow oil. HRMS calcd. for $C_{24}H_{19}F_8NO_2$: 506.1366 $[M+H]^+$, found: 506.1368. ^1H NMR ($CDCl_3$) δ 7.26 (m, 3H), 7.20 (m, 5H), 6.87 (d, 2H), 6.62 (d, 1H), 6.50 (s, 1H), 6.49 (d, 1H), 5.87 (t, 1H), 4.89 (d, 1H), 4.77-4.52 (m, 1H), 4.73 (d, 1H), 4.60 (s, 2H). ^{19}F NMR ($CDCl_3$) δ -69.83 (t, 3F), -88.63 (s, 2F), -137.19 (dt, 2F), -228.82 (1F).

EXAMPLE 1670 *

[0461]

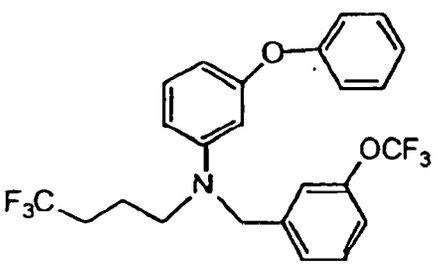


2-[[3-(4-chloro-3-ethylphenoxy)phenyl][[3-(1,1,2,2-tetrafluoroethoxy)phenyl]methyl]amino]-3,3,3-tritluoropropanol

[0462] To a dichloromethane (2 mL) solution of *N*-[(4-chloro-3-ethylphenoxy)phenyl][[3-(1,1,2,2-tetrafluoroethoxy)phenyl]methyl]amine (0.25g, 0.55 mmol) and 2-diazo-3,3,3-triftuoropropionic acid *p*-nitrophenyl ester (0.14 g, 0.51 mmol) was added solid $Rh_2(OAc)_4$ (0.015 g, 0.034 mmol). The resulting green slurry was stirred at room temperature under nitrogen for 24 h. The solvent was removed to give a green oil, and the crude intermediate was dissolved in THF (4 mL). This green solution was cooled to 0 ˚C, and a 1.0 M solution of $LiAlH_4$ in THF (0.6 mL, 0.6 mmol) was added dropwise. The resulting dark solution was stirred for 30 min at 0 ˚C and quenched by the slow addition of water. The reaction mixture was extracted with Et_2O, dried ($MgSO_4$) and evaporated to give a brown oil. Purification by flash column chromatography on silica gel eluting with 20% ethyl acetate in hexane gave 0.032 g (11%) of the desired 2-[[3-(4-chloro-3-ethylphenoxy)phenyl][[3-(1,1,2,2-tetrafluoro-ethoxy)phenyl]methyl]amino]-3,3,3-trifluoropropanol product as a light brown oil HRMS calcd. for $C_{26}H_{23}NO_3ClF_7$: 566.1333 $[M+H]^+$, found: 566.1335. ^1H NMR (C_6D_6) δ 0.53 (t, 1H, exchangeable with D_2O), 0.93 (t, 3H), 2.43 (t, 2H), 3.33 (m, 2H), 4.11 (s, 2H), 4.13 (m, 1H), 5.04 (tt, 1H), 6.4 (m, 3H), 6.5 (t, 1H), 6.7-6.8 (m, 5H), 6.97 (d, 1H), 7.04 (s, 1H).

EXAMPLE 1671 *

[0463]



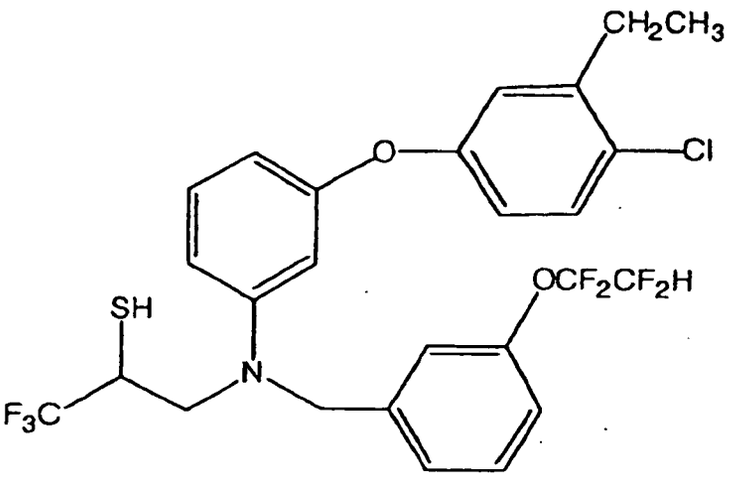
N-(3-phenoxyphenyl)-N-(4,4,4-tritluorobutyl)-3-(trifluoromethoxy) benzenemethanamine

[0464] **EX-1671A)** To a solution of 3-phenoxyaniline (10.9 g, 58.8 mmol) in 100 mL of cyclohexane was added solid NaH (60% in mineral oil, 1.96 g, 49 mmol). Then 3-trifluoromethoxybenayl bromide (10.0 g, 39.2 mmol) was added dropwise under a nitrogen atmosphere, and the mixture was heated to reflux for 18 h, at which time TLC analysis indicated that no 3-trifluoromethoxybenzyl bromide remained. The reaction mixture was cooled to room temperature and quenched with water, then extracted with ether: The ether layer was washed with water and brine, then dried over $MgSO_4$, and evaporated to give crude product. The crude product was purified by flash column chromatography on silica gel eluting with 1:7:0.01 of ethyl acetate:hexane:ammonium hydroxide to give the desired N-benrylaniline product, which contained a small portion of dibenzylated amine. This product was further purified by conversion to the corresponding HCl salt to give 11.0 g (73%) of the desired *N*-(3-phenoxyphenyl)-*N*-[(3-trifluoromethoxy)phenyl]methyl]amine hydrochloride product. HRMS calcd. for $C_{20}H_{16}NO_2F_3$: 360.1211 $[M+H]^+$, found 360.1208.

[0465] The *N*-(3-phenoxyphenyl)-*N*-[(3-trifluoromethoxy)phenyl]methyl]amine hydrochloride (1.0 g, 2.5 mmol) product from **EX-1671A** was dissolved in 20 mL of THF under nitrogen. Solid $NaNH_2$ (50% in xylene, 0.2 g, 2.6 mmol) was added, and the mixture was stirred at room temperature. Then 1-iodo-4,4,4-trifluorobutone (1.0 g, 4.2 mmol) and additional $NaNH_2$ (50% in xylene, 0.2 g, 2.6 mmol) was added. The mixture was heated at reflux for 24 h, at which time HPLC analysis indicated that no secondary amine starting material remained. The reaction was quenched with water and extracted with ether. The ether layer was washed with water and brine, then dried over $MgSO_4$. The crude product was purified by flash column chromatography on silica gel eluting with 1:4:0.01 of ethyl acetate:hexane:ammonium hydroxide to give 1.0 g (85%) of the desired N-(3-phenoxyphenyl)-N-(4,4,4-trifluorobutyl)-3-(trifluoromethoxy) benzenemethanamine product as an off-white oil. ^1H NMR ($CDCl_3$) δ 7.29 (m, 3H), 7.09 (m, 4H), 7.01 (s, 1H), 6.95 (d, 2H), 6.43 (d, 1H), 6.36 (d, 1H), 6.31 (s, 1H), 4.49 (s, 2H), 3.41 (t, 2H), 2.08 (m, 2H), 1.89 (q, 2H). ^{19}F NMR ($CDCl_3$) δ -58.18 (s, 3F), -66.44 (t, 3F). Anal. calcd. for $C_{24}H_{21}NO_2F_6$: C, 61.41; H, 4.51; N, 2.98. Found: C, 61.16; H, 4.53; N, 2.92. HRMS calcd. 470.1555 $[M+H]^+$, found: 470.1565.

EXAMPLE 1672 *

[0466]



3-[[3-(4-chloro-3-ethylphenoxy)phenyl]-[[3-(1,1,2,2-tetrafluoroethoxy)phenyl]methyl]amino]-1,1,1-trifluoro-2-propanthiol

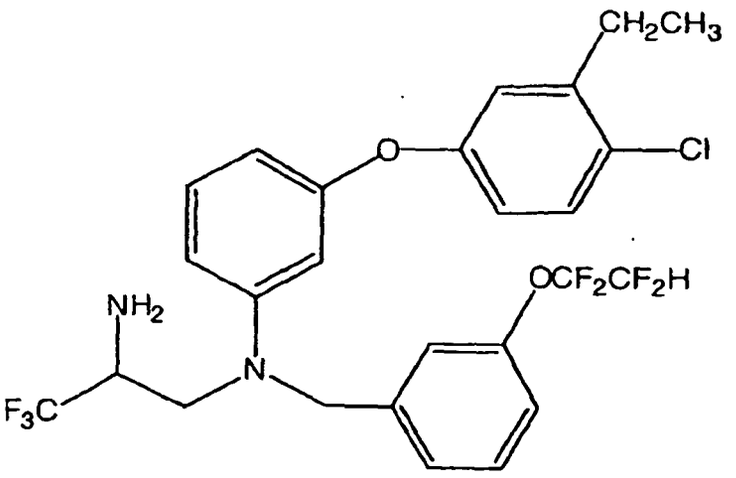
[0467] **EX-1672A)** A solution of 3-(4-chloro-3-ethylphenoxy)aniline (3.72 g, 15 mmol) and 3-(1,1,2,2-tetrafluorocthoxy) benzaldehyde (3.33 g, 15 mmol) is prepared in 60 mL of dichloroethane. Acetic acid (0.92 mL, 16.05 mmol) and solid $NaBH(OAc)_3$ (4.13 g, 19.5 mmol) are added. The mixture is stirred at room temperature for 3 hours, then is acidified with 1 N aqueous HCl. After neutralizing to pH 7.5 with 2.5 N sodium hydroxide, the mixture is extracted with methylene chloride. The organic layer is washed with brine and water, then dried over anhydrous $MgSO_4$, and evaporated to give 5.00 g (85%) of the desired *N*-(3-(4-chioro-3-ethylphenoxy)phenyl)-[[3-(1,1,2,2-tetranuoroethoxy)-phenyl]methyl]amine product.

[0468] Amine product **EX-1672A** (8 mmol) and 3,3,3-trifluoromethylthijrane (1.54 g, 12 mmol) are dissolved in 1.5 mL of acetonitrile. Ytterbium (III) trifluoromethanesulfonate (0.25 g, 0.4 mmol) is added, and the stirred solution is warmed to 50 ˚C under an atmosphere of nitrogen until completion of reaction as is indicated by HPLC analysis showing that no secondary amine starting material remains. The reaction is quenched with water and extracted with ether.

[0469] The ether layer is washed with water and brine, then is dried over $MgSO_4$. The crude product is purified by flash column chromatography on silica gel with a solvent mixture to give the desired aminopropanethiol product.

EXAMPLE 1673 *

[0470]



3-[[3-(4-chloro-3-ethylphenoxy)phenyl]-[[3-(1,1,2,2-tetrafluoroethoxy)phenyl] methyl]amino]-1,1,1-trifluoro-2-propanamine

[0471] Amine product **EX-1672A** (8 mmol) and 3,3,3-trifluoromethylaziridine (1.33 g, 12 mmol) are dissolved in 1.5 mL of acetonitrile. Ytterbium (III) trifluoromethanesulfonate (0.25 g, 0.4 mmol) is added, and the stirred solution is warmed to 50 ˚C under an atmosphere of nitrogen until completion of reaction as is indicated by HPLC analysis showing that no secondary amine starting material remains. The reaction is quenched with water, the pH is adjusted to 9.5 with 2.5 N sodium hydroxide, and it is extracted with ether. The ether layer is washed with water and brine, then is dried over Na_2CO_3. The crude product is purified by flash column chromatography on silica gel with a solvent mixture to give the desired propanediamine product.

BIOASSAYS

CETP Activity *In Vitro*

ASSAY OF CETP INHIBITION USING PURIFIED COMPONENTS (RECONSTITUTED BUFFER ASSAY)

[0472] The ability of compounds to inhibit CETP activity was assessed using an *in vitro* assay that measured the rate of transfer of radiolabeled cholesteryl ester ([^{3}H]CE) from HDL donor particles to LDL acceptor particles. Details of the assay are provided by Glenn, K. C. et al. (Glenn and Melton, "Quantification of Cholesteryl Ester Transfer Protein (CETP): A) CETP Activity and B) Immunochemical Assay of CETP Protein," Meth. Enzymol., 263, 339-351 (1996)). Human recombinant CETP can be obtained from the serum-free conditioned medium of CHO cells transfected with a cDNA for CETP and purified as described by Wang, S. et al. (J. Biol. Chem. 267, 17487-17490 (1992)). To measure CETP activity, [^{3}H]CE-labeled-HDL, LDL, CETP and assay buffer (50 mM tris(hydroxymethyl)aminomethane, pH 7.4; 150 mM sodium chloride; 2 mM ethylenediamine-tetraacetic acid (EDTA); 1% bovine serum albumin) were incubated in a final volume of 200 μL, for 2 hours at 37˚C in 96 well plates. Inhibitors were included in the assay by diluting from a 10 mM DMSO stock solution into 16% (v/v) aqueous DMSO so that the final concentration of inhibitor was 800 μM. The inhibitors were then diluted 1:1 with CETP in assay buffer, and then 25 μL of that solution was mixed with 175 μL of lipoprotein pool for assay. Following incubation, LDL was differentially precipitated by the addition of 50 μL of 1% (w/v) dextran sulfate/ 0.5 M magnesium chloride, mixed by vortex, and incubated at room temperature for 10 minutes. A potion of the solution (200 μL) was transferred to a filter plate (Millipore). After filtration, the radioactivity present in the precipitated LDL was measured by liquid scintillation counting. Correction for non-specific transfer or precipitation was made by including samples that do not contain CETP. The rate of [^{3}H]CE transfer using this assay was linear with respect to time and CETP concentration, up to 25-30% of [^{3}H]CE transferred.

[0473] The potency of test compounds was determined by performing the above described assay in the presence of varying concentrations of the test compounds and determining the concentration required for 50% inhibition of transfer of [^{3}H]CE from HDL to LDL. This value was defined as the IC_{50}. The IC_{50} values determined from this assay are accurate when the IC_{50} is greater than 10 nM. In the case where compounds have greater inhibitory potency, accurate measurements of IC_{50} may be determined using longer incubation times (up to 18 hours) and lower final concentrations of CETP (< 50 nM).

[0474] Examples of IC_{50} values determined by these methods are specified in Table 6.

ASSAY OF CETP INHIBITION IN HUMAN PLASMA

[0475] Blood was obtained from healthy volunteers, recruited from the personnel of Monsanto Company, Saint Louis, MO. Blood was collected in tubes containing EDTA (EDTA plasma pool). The EDTA human plasma pool, previously stored at -20 ˚C, was thawed at room temperature and centrifuged for 5 minutes to remove any particulate matter. Tritiated HDL, radiolabeled in the cholesteryl ester moiety ([^{3}H]CE-HDL) as described by Morton and Zilversmit (J. Biol. Chem., 256, 11992-95 (1981)), was added to the plasma to a final concentration of 25 μg/mL cholesterol. Equal volumes (396 μL) of the plasma containing the [^{3}H]CE-HDL were added by pipette into micro tubes (Titertube®, Bio-Rad laboratories, Hercules, CA). Inhibitor compounds, dissolved as 20-50 mM stock solutions in DMSO, were serially diluted in DMSO (or an alternative solvent in some cases, such as dimethylformamide or ethanol). Four μL of each of the serial dilutions of inhibitor compounds or DMSO alone were then added to each of the tubes containing plasma (396 μL). After mixing, triplicate aliquots (100 μL) from each plasma tube were then transferred to wells of 96-well roundbottomed polystyrene microtiter plates (Corning, Corning, NY). Plates were sealed with plastic film and incubated at 37 ˚C for 4 hours. "Test" samples contained plasma with dilutions of inhibitor compounds. "Control" samples contained plasma with DMSO diluted to the same concentration as the test samples, but without inhibitor. "Blank" samples were prepared as "control" samples, but were left in the micro tubes at 4 ˚C for the 4 hour incubation and were then added to the microtiter wells at the end of the incubation period. VLDL and LDL were precipitated by the addition of 10 μL of precipitating reagent (1% (w/v) dextran sulfate (Dextralip50)/0.5 M magnesium chloride, pH 7.4) to all wells. The wells were mixed on a plate mixer and then incubated at ambient temperature for 10 min. The plates were then centrifuged at 1000 x g for 30 min at 10 ˚C. The supernatants (50 μL) from each well were then transferred to Picoplate™ 96 plate wells (Packard, Meriden. CT) containing Microscint™-40 (Packard, Meriden, CT). The plates were heat-sealed (TopSeal™-P, Packard, Meriden, CT) according to the manufacturer's directions and mixed for 30 min. Radioactivity was measured on a microplate scintillation counter (TopCount. Packard, Meriden, CT). The maximum percentage transfer in the control wells (% transfer) was determined using the following equation:

$$\% \text{ Transfer} = \frac{[dpm_{blank} - dpm_{control}] \times 100}{dpm_{blank}}$$

[0476] The percentage of transfer relative to the control (% control) was determined in the wells containing inhibitor compounds was determined as follows:

$$\% \text{ Control} = \frac{[dpm_{blank} - dpm_{test}] \times 100}{dpm_{blank} - dpm_{control}}$$

[0477] IC_{50} values were then calculated from plots of % control versus concentration of inhibitor compound. IC_{50} values were determined as the concentration of inhibitor compound inhibiting transfer of [^{3}H]CE from the supernatant [^{3}H]CE-HDL to the precipitated VLDL and LDL by 50% compared to the transfer obtained in the control wells.

[0478] Examples of IC_{50} values determined by this method are specified in Table 7.

Table 6. Inhibition of CETP Activity by Examples in Reconstituted Buffer Assay.

Ex. No.	IC_{50} (μM)		Ex. No.	IC_{50} (μM)		Ex. No.	IC_{50} (μM)
249	0.020		419	0.19		425	0.34
244	0.029		230	0.20		514	0.34
634	0.032		248	0.20		237	0.35
221	0.034		266	0.20		399	0.35
229	0.034		378	0.20		645	0.35

(continued)

Ex. No.	IC_{50} (μM)	Ex. No.	IC_{50} (μM)	Ex. No.	IC_{50} (μM)
660	0.040	488	0.20	225	0.37
630	0.050	241	0.21	247	0.37
629	0.054	245	0.21	473	0.37
372	0.062	400	0.21	216	0.39
233	0.063	639	0.21	243	0.39
234	0.069	226	0.22	636	0.39
252	0.075	373	0.22	650	0.41
242	0.076	377	0.23	385	0.42
277	0.076	253	0.24	427	0.42
256	0.079	411	0.25	436	0.42
232	0.080	638	0.26	509	0.42
278	0.098	222	0.27	619	0.42
379	0.098	240	0.27	521	0.43
258	0.099	374	0.27	250	0.44
238	0.12	420	0.27	429	0.44
227	0.13	223	0.29	658	0.44
423	0.13	415	0.29	637	0.47
656	0.13	235	0.31	592	0.48
214	0.14	607	0.31	251	0.49
628	0.14	265	0.33	421	0.49
281	0.14	402	0.33	271	0.50
224	0.16	489	0.33	287	0.50
279	0.16	231	0.34	550	0.50
401	0.18	275	0.34	416	0.51
410	0.19	390	0.34	438	0.52
647	0.52	518	0.79	442	1.1
598	0.54	397	0.81	595	1.1
567	0.55	393	0.82	642	1.1
391	0.56	499	0.83	450B	1.1
559	0.56	648	0.83	71	1.2
246	0.57	282	0.84	305	1.2
268	0.58	396	0.86	381	1.2
527	0.58	581	0.87	441	1.2
269	0.59	294	0.88	446	1.2
292	0.59	557	0.88	492	1.2
405	0.60	218	0.91	496	1.2
409	0.61	601	0.91	524	1.2
475	0.64	653	0.91	569	1.2

(continued)

Ex. No.	IC_{50} (μM)	Ex. No.	IC_{50} (μM)	Ex. No.	IC_{50} (μM)
254	0.65	422	0.92	693	1.2
450A	0.66	556	0.92	286	1.3
654	0.67	506	0.97	296	1.3
558	0.69	541	0.97	655B	1.3
389	0.70	274	0.99	264	1.4
412	0.71	651	0.99	392	1.4
408	0.75	77	1.0	406	1.4
554	0.75	267	1.0	522	1.4
280	0.76	293	1.0	526	1.4
525	0.76	439	1.0	568	1.4
578	0.76	560	1.0	582	1.4
440	0.77	657	1.0	74	1.5
523	0.77	659	1.0	79	1.5
646	0.77	599	1.0	403	1.5
166	0.78	285	1.1	407	1.5
424	0.78	395	1.1	444	1.5
593	0.78	398	1.1	495	1.5
456B	1.5	167	2.0	302	2.5
565	1.5	307	2.0	426	2.5
652	1.5	597	2.0	519	2.5
699	1.5	315	2.1	555	2.5
91	1.6	404	2.1	564	2.5
140	1.6	418	2.1	688	2.5
149	1.6	503	2.1	690	2.5
255	1.6	508	2.1	309	2.6
384	1.6	513	2.1	311	2.6
517	1.6	562	2.1	494	2.6
571	1.6	643	2.1	44	2.7
644	1.6	257	2.2	452	2.7
150	1.7	387	2.2	543	2.7
261	1.7	437	2.2	566	2.7
432	1.7	483	2.2	445	2.8
505	1.7	490	2.2	73	3.0
584	1.7	89	2.3	104	3.0
1670	1.8	299	2.3	115	3.0
212	1.8	318	2.3	220B	3.0
289	1.8	382	2.3	322	3.0
312	1.8	383	2.3	388	3.0

(continued)

Ex. No.	IC_{50} (μM)	Ex. No.	IC_{50} (μM)	Ex. No.	IC_{50} (μM)
478	1.8	507	2.3	460	3.0
493	1.8	544	2.3	464	3.0
515	1.8	580	2.3	516	3.0
561	1.8	608	2.3	691	3.0
570	1.8	128	2.4	316	3.1
579	1.8	542	2.4	394	3.1
304	1.9	168	2.5	633	3.1
480	1.9	259	2.5	386	3.2
70	2.0	260	2.5	376	3.3
459	3.3	595B	4.5	310	6.6
317	3.4	701	4.5	514C	6.6
63	3.5	414	4.6	603	6.7
159	3.5	454	4.6	428	6.8
204	3.5	319	4.7	602	6.8
609	3.5	482	4.8	632	6.8
622	3.5	553	4.8	42	7.0
210	3.6	273	4.9	52	7.0
501	3.6	649	4.9	59	7.0
655	3.6	84	5.0	75	7.0
262	3.7	141	5.0	127	7.0
371	3.9	321	5.0	162	7.0
449	3.9	620	5.0	172	7.0
36	4.0	689	5.0	194	7.0
43	4.0	60	5.5	346	7.7
66	4.0	433	5.6	617	7.9
87	4.0	502	5.7	26	8.0
126	4.0	585	5.8	82	8.0
153	4.0	76	6.0	122	8.0
201	4.0	101	6.0	124	8.0
588	4.1	134	6.0	139	8.0
627	4.1	208	6.0	147	8.0
594	4.2	474	6.0	152	8.0
606	4.2	239	6.1	453	8.0
448	4.3	512	6.1	290	8.1
640	4.3	591	6.2	625	8.3
297	4.4	576	6.4	291	8.4
491	4.4	583	6.4	90	9.0
209	4.5	434B	6.4	112	9.0

(continued)

Ex. No.	IC_{50} (μM)	Ex. No.	IC_{50} (μM)	Ex. No.	IC_{50} (μM)
375	4.5	270	6.5	129	9.0
323	9.0	136	12	67	15
215	9.2	158	12	68	15
456	9.2	288	12	98	15
621	9.3	431	12	145	15
447	9.8	462	12	148	15
25	10	466	12	185	15
47	10	605	12	186	15
72	10	611	12	198	15
78	10	687	12	200	15
131	10	38	13	308	15
146	10	451	13	347	15
163	10	457	13	589	15
193	10	458	13	661	15
199	10	461	13	686	15
236	10	463	13	694	15
486	10	596	13	695	15
551	10	211	14	514D	15
572	10	314	14	35	16
613	10	504	14	692	16
213	11	590	14	612A	16
301	11	19	15	276	17
380	11	23	15	295	17
472	11	39	15	413	17
477	11	50	15	417	17
641	11	53	15	1669	17
528B	11	54	15	62	18
1671	11	57	15	197	18
31	12	58	15	220	18
41	12	64	15	574	18
92	12	33	15	616	18
51	20	106	30	17	45
55	20	138	30	118	45
56	20	195	30	345	45
65	20	520	30	362	45
69	20	626	30	604	46
80	20	300	31	529	49
83	20	217	32	22	50

(continued)

Ex. No.	IC_{50} (μM)	Ex. No.	IC_{50} (μM)	Ex. No.	IC_{50} (μM)
86	20	320	32	34	50
113	20	303	33	93	50
135	20	103	35	96	50
137	20	105	35	120	50
160	20	348	35	350	50
173	20	352	35	351	50
313	20	468	35	471	50
324	20	612	35	662	50
610	20	702	35	697	55
683	20	1	38	3	60
30	22	94	40	4	60
455	22	114	40	14	60
61	23	116	40	16	60
192	23	142	40	18	60
587	23	156	40	95	60
298	24	196	40	102	60
620A	24.6	335	40	108	60
109	25	357	40	110	60
117	25	363	40	203	60
125	25	497	42	685	60
132	25	473B	42	111	65
133	25	528C	42	119	70
306	25	528	43	342	70
353	70	435	>50	263	>50
664	70	435B	>50	284	>50
28	75	443	>50	430	>50
88	75	465	>50	434	>50
107	75	467	>50	563	>50
355	75	469	>50	573	>50
85	80	470	>50	575	>50
130	80	476	>50	577	>50
143	80	479	>50	586	>50
332	80	484	>50	632A	>50
366	80	487	>50	5	>100
635	80	498	>50	6	>100
665	80	500	>50	7	>100
97	90	511	>50	8	>100
100	90	530	>50	9	>100

(continued)

Ex. No.	IC_{50} (μM)	Ex. No.	IC_{50} (μM)	Ex. No.	IC_{50} (μM)
123	90	531	>50	10	>100
165	90	532	>50	11	>100
207	90	533	>50	12	>100
2	100	534	>50	13	>100
45	100	535	>50	15	>100
144	100	536	>50	20	>100
333	100	537	>50	21	>100
334	100	538	>50	24	>100
340	100	539	>50	27	>100
343	100	540	>50	29	>100
618	100	545	>50	32	>100
663	100	546	>50	37	>100
672	100	547	>50	40	>100
696	100	548	>50	46	>100
698	100	549	>50	48	>100
49	>100	325	>100	588B	>100
81	>100	326	>100	614	>100
99	>100	327	>100	615	>100
121	>100	328	>100	631	>100
161	>100	329	>100	634C	>100
164	>100	330	>100	667	>100
169	>100	331	>100	668	>100
170	>100	336	>100	669	>100
171	>100	337	>100	670	>100
174	>100	338	>100	671	>100
175	>100	339	>100	673	>100
176	>100	341	>100	674	>100
177	>100	344	>100	675	>100
178	>100	349	>100	676	>100
179	>100	354	>100	677	>100
180	>100	356	>100	678	>100
181	>100	358	>100	679	>100
182	>100	359	>100	680	>100
183	>100	360	>100	681	>100
184	>100	361	>100	682	>100
187	>100	364	>100	684	>100
188	>100	365	>100		
189	>100	367	>100		

(continued)

Ex. No.	IC_{50} (μM)	Ex. No.	IC_{50} (μM)	Ex. No.	IC_{50} (μM)
190	>100	368	>100		
191	>100	369	>100		
202	>100	370	>100		
205	>100	151	>100		
206	>100	154	>100		
219	>100	155	>100		
283	>100	157	>100		

Table 7. Inhibition of CETP Activity by Examples in Human Plasma Assay.

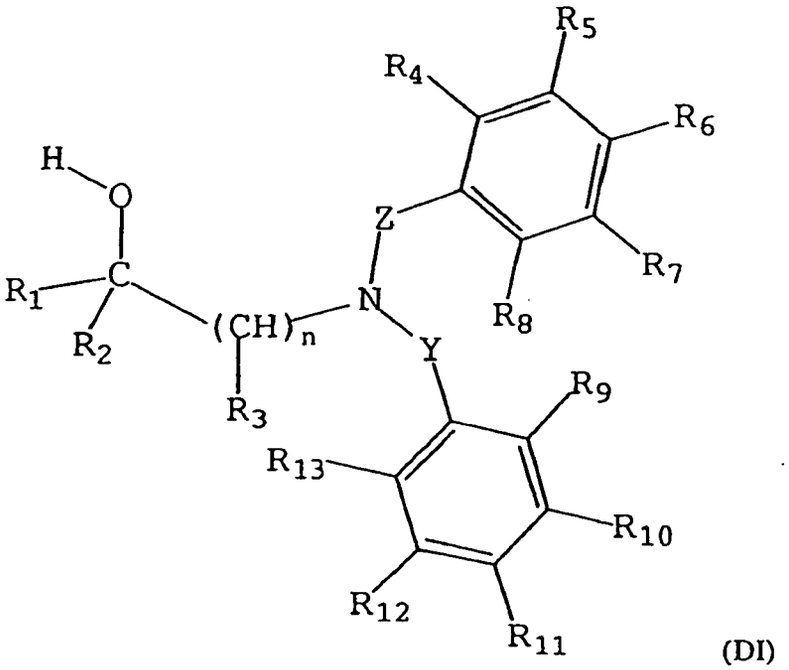
Ex. No.	IC_{50} (μM)	Ex. No.	IC_{50} (μM)	Ex. No.	IC_{50} (μM)
229	0.56	256	7.8	554	18
221	0.88	559	8.0	266	21
233	1.0	637	8.0	645	21
234	1.0	245	8.4	269	22
660	1.1	489	8.8	287	22
630	1.8	450A	9.0	280	23
249	2.3	265	9.6	216	24
402	2.9	240	9.7	377	24
242	3.1	248	10	390	24
399	3.4	275	10	440	24
232	3.4	395	10	657	24
629	3.4	396	10	391	25
244	3.8	397	10	251	26
252	3.9	281	11	253	27
634	4.1	560	11	267	27
401	4.2	638	11	385	29
488	4.3	241	12	438	29
429	4.4	282	12	166	30
619	4.9	373	12	294	30
393	5.0	378	12	550	30
639	5.0	654	12	650	30
258	5.2	246	13	658	30
214	5.7	278	13	218	31
628	5.7	439	13	250	31
372	5.7	647	13	243	34
405	6.2	436	14	271	34
400	6.3	279	15	499	34
277	6.5	274	16	557	34

(continued)

Ex. No.	IC_{50} (μM)	Ex. No.	IC_{50} (μM)	Ex. No.	IC_{50} (μM)
656	6.9	473	16	128	35
379	7.7	247	17	71	36
268	37	42	80	299	>100
475	37	140	80	302	>100
292	38	150	80	309	>100
558	38	307	81	311	>100
653	38	601	83	315	>100
374	39	296	86	316	>100
77	40	59	100	317	>100
293	42	73	100	321	>100
595	42	43	110	322	>100
126	45	201	110	346	>100
74	48	60	120	600	>100
655	48	63	120	649	>100
556	49	66	120	686	>100
593	49	75	200	688	>100
642	50	389	>50	691	>100
592	52	447	>50	220B	>100
699	55	104	>100	595B	>100
79	60	115	>100	35	>200
87	60	127	>100	36	>200
89	60	131	>100	76	>200
655B	63	141	>100	661	>200
70	65	149	>100	664	>200
312	65	168	>100	33	500
659	65	204	>100		
84	70	208	>100		
91	70	209	>100		
690	75	210	>100		
304	76	219	>100		
305	76	273	>100		
254	77	297	>100		

Claims

1. A compound of Formula DI:

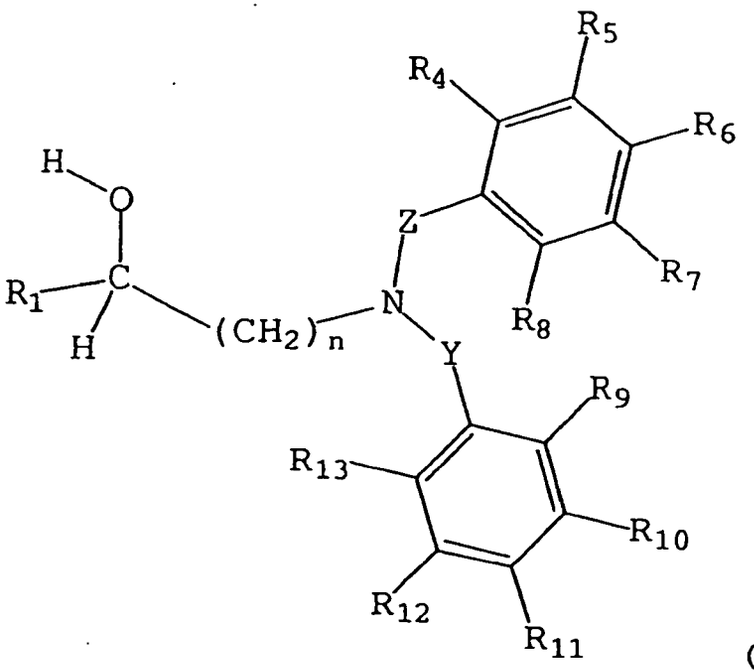


(DI)

or a pharmaceutically acceptable salt thereof, wherein;

n is 1;
R_1 is haloalkyl;
R_2 is selected from the group consisting of hydrogen, alkyl, haloalkyl, aryl, and haloalkoxy;
R_3 is selected from the group consisting of hydrogen, alkyl, and haloalkyl;
Y is C1-C2 alkylene;
Z is covalent single bond;
R_4, R_8, R_9, and R_{13} are hydrogen or halo;
R_5, R_6, R_7, R_{10}, R_{11}, and R_{12} are independently selected from the group consisting of hydrogen, perhaloaryloxy, N-aryl-N-alkylamino, heterocyclylalkoxy, heterocyclylthio, hydroxyalkoxy, aralkanoylalkoxy, aralkenoyl, cycloalkylcarbonyl, cyanoalkoxy, heterocyclylcarbonyl, alkyl, halo, haloalkyl, haloalkoxy, aryl, alkylthio, arylamino, arylthio, aroyl, arylsulfonyl, aryloxy, aralkoxy, heteroaryloxy, alkoxy, aralkyl, cycloalkoxy, cycloalkylalkoxy, cycloalkylalkanoyl, heteroaryl, cycloalkyl, haloalkylthio, hydroxyhaloalkyl, heteroaralkoxy, and heteroaryloxyalkyl.

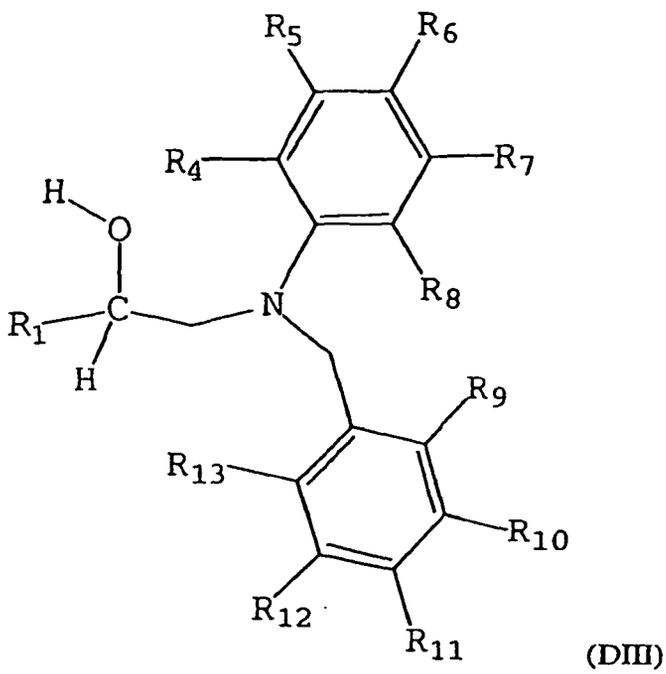
2. A compound of Claim 1 of Formula DII:



(DII)

or a pharmaceutically acceptable salt thereof.

3. Compound of Claim 2 of Formula DIII:



(DIII)

or a pharmaceutically acceptable salt, wherein;

R_1 is haloalkyl;
R_5, R_6, R_7, R_{10}, R_{11}, and R_{12} are independently selected from the group consisting of hydrogen, perhaloaryloxy, N-aryl-N-alkylamino, heterocyclylalkoxy, heterocyclylthio, hydroxyalkoxy, aralkanoylalkoxy, aralkenoyl, cy-

cloalkylcarbonyl, cyanoalkoxy, heterocyclylcarbonyl, alkyl, halo, haloalkyl, haloalkoxy, aryl, alkylthio, arylamino, arylthio, aroyl, arylsulfonyl, aryloxy, aralkoxy, heteroaryloxy, alkoxy, aralkyl, cycloalkoxy, cycloalkylalkoxy, cycloalkylalkanoyl, heteroaryl, cycloalkyl, haloalkylthio, hydroxyhaloalkyl, heteroaralkoxy, and heteroaryloxyalkyl.

4. Compound of Claim 3, or a pharmaceutically acceptable salt thereof, wherein:

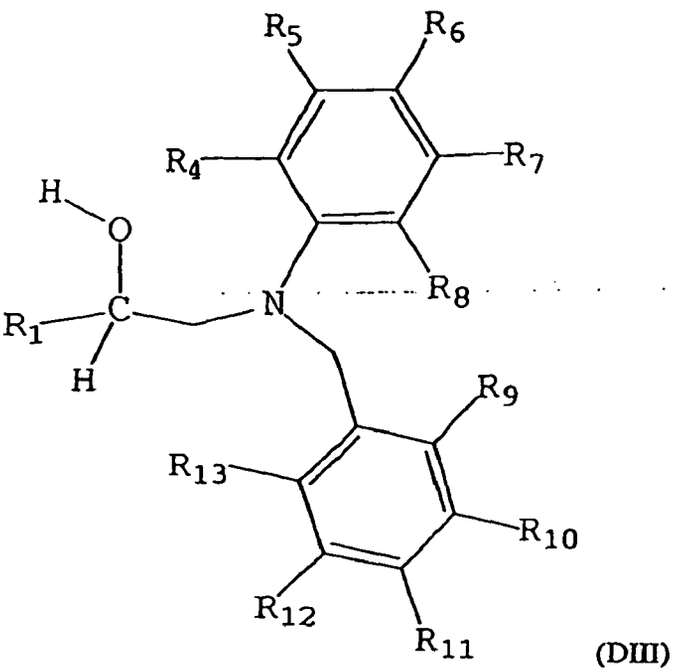
R_1 is trifluoromethyl;
R_4, R_6, R_7, R_8, R_9, R_{11}, R_{12}, and R_{13} are hydrogen or fluoro;
R_5 is selected from the group consisting of 5-bromo-2-fluorophenoxy, 4-chloro-3-ethylphenoxy, 2,3-dichlorophenoxy, 3,4-dichlorophenoxy, 3-difluoromethoxyphenoxy, 3,5-dimethylphenoxy, 3,4-dimethylphenoxy, 3-ethylphenoxy, 3-ethyl-5-methylphenoxy, 4-fluoro-3-methylphenoxy, 4-fluorophenoxy, 3-isopropylphenoxy, 3-methylphenoxy, 3-pentafluoroethylphenoxy, 3-tert-butylphenoxy, 3-(1,1,2,2-tetrafluoroethoxy)phenoxy, 2-(5,6,7,8-tetrahydronaphthyloxy), 3-trifluoromethoxybenzyloxy, 3-trifluoromethoxyphenoxy, 3-trifluoromethylbenryloxy, and 3-trifluoromethylthiophenoxy;
R_{10} is selected from the group consisting of cyclopentyl, 1,1,2,2-tetrafluoroethoxy, 2-furyl, 1,1-bis-trifluoromethyl-1-hydroxymethyl, pentafluoroethyl, trifluoromethoxy, trifluoromethyl, and trifluoromethylthio.

5. Compound of Claim 4, or a pharmaceutically acceptable salt thereof, wherein,

R_{10} is selected from the group consisting of 1,1,2,2-tetrafluoroethoxy, pentafluoroethyl, and trifluoromethyl.

6. Compound of Claim 1, or a pharmaceutically acceptable salt thereof, wherein said compound is 3-[[3-(4-chloro-3-ethylphenoxy)phenyl][[3-(1,1,2,2-tetrafluoroethoxy)phenyl]-methyl]amino]-1,1,1-trifluoro-2-propanol;

7. Compound of Claim 1 of Formula DIII:



(DIII)

or a pharmaceutically acceptable salt, wherein;

R_1 is selected from the group consisting of trifluoromethyl, difluoromethyl, chlorodifluoromethyl, and pentafluoroethyl;
R_4, R_8, R_9, and R_{13} are hydrogen or fluoro;
R_5 and R_{10} are independently selected from the group consisting of benzyloxy, 5-bromo-2-fluorophenoxy, 4-

bromo-3-fluorophenoxy, 3-bromobenzyloxy, 4-bromophenoxy,4-butoxyphenoxy, 3-chlorobenzyloxy, 2-chlorophenoxy, 4-chloro-3-ethylphenoxy, 4-chioro-3-methylphenoxy, 2-chloro-4-fluorophenoxy, 4-chloro-2-fluorophenoxy, 4-chlorophenoxy, 3-chloro-4-ethylphenoxy, 3-chloro-4-ruethylphenoxy, 3-chloro-4-fluorophenoxy, 4-chloro-3-fluorophenoxy, 4-chlorophenylamino, 5-chloropyrid-3-yloxy, cyclobutoxy, cyclobutyl, cyclohexylmethoxy, cyclopentoxy, cyclopentyl, cyclopentylcarbonyl, cyclopropylmethoxy, 2,3-dichlorophenoxy, 2,4dichlorophenoxy, 2,4-dichlorophenyl, 3,5-dichlorophenyl, 3,5-dichlorobenzyl, 3,4-dichlorophenoxy, 3,4-difluorophenoxy, 2,3-difluorobenzyloxy, 3,5-difluorobenzyloxy, difluoromethoxy, 3,5-difluorophenoxy, 3,4-difluorophenyl, 2,3-difluorophenoxy, 2,4-difluorophenoxy, 2,5-difluorophenoxy, 3,5-dimethoxyphenoxy, 3-dimethylaminophenoxy. 3,4-dimethylbenzyloxy, 3,5-dimethylbenryloxy, 3,5-dimethylphenoxy, 3,4-dimethylphenoxy, 1,3-dioxolan-2-yl, 3-ethylbenzyloxy, 3-ethylphenoxy, 4-ethylaminophenoxy, 3-ethyl-5-methylphenoxy, 4-fluoro-3-methylbenzyl, 4-fluorobenzyloxy, 2-fluoro-3-methylphenoxy, 3-fluoro-4-methylphenoxy, 3-fluorophenoxy, 3-fluoro-2-nitrophenoxy, 2-fluoro-3-trifluommethylbenzyloxy, 3-fluoro-5-trifluoromethylbenzyloxy, 2-fluorophenoxy, 4-fluorophenoxy, 2-fluoro-3-trifluoromethylphenoxy, 2-fluorobenzyloxy, 4-fluorophenylamino, 2-fluoro-4-trifluoromethylphenoxy, 2-furyl, 3-furyl, heptafluoropropyl, 1,1,1,3,3,3-hexafluoropropyl, 2-hydroxy-3,3,3-trifluoropropoxy, isobutoxy, isobutyl, 3-isoxazolyl, 4-isoxazolyl, 5-isoxazolyl, isopropoxy, 3-isopropylbenzyloxy, 3-isopropylphenoxy, isopropylthio, 4-isopropyl-3-methylphenoxy, 3-isothiazolyl, 4-isothiazolyl, 5-isothiazolyl, 3-methoxybenzyl, 4-methoxyphenylamino, 3-methylbenzyloxy, 4-methylbenxyloxy, 3-methylphenoxy, 3-methyl-4-methylthiophenoxy, 4-methylphenoxy, 1-methylpropoxy, 2-methylpyrid-5-yloxy, 4-methylthiophenoxy, 2-naphthyloxy, 2-nitrophenoxy, 4-nitrophenoxy, 3-nitrophenyl, 2-oxazolyl, 4-oxazolyl, 5-oxazolyl, pentafluoroethyl, pentafluoroethylthio, 2,2,3,3,3-pentafluoropropyl, 1,1,3,3,3-pentafluoropropyl, 1,1,2,2,3-pentafluoropropyl, phenoxy, phenylamino, 1-phenylethoxy, 4-propylphenoxy, 4-propoxyphenoxy, thiophen-3-yl,tert -butoxy, 3-tert -butylphenoxy, 4-tert -butylphenoxy, 1,1,2,2-tetrafluoroethoxy, tetrahydrofuran-2-yl, 2-(5,6,7,8-tetrahydronaphthyloxy), thiazol-2-yl, thiazol-4-yl, thiazol-5-yl, thiophen-2-yl, 2,2,2-trifluoroethoxy, 2,2,2-trifluoroethyl, 3,3,3-trifluoro-2-hydroxypropyl, trifluoromethoxy, 3-trifluoromethoxybenzyloxy, 4-trifluoromethoxybenzyloxy, 4-trifluoromethoxyphenoxy, 3-trifluoromethoxyphenoxy, trifluoromethyl, 3-trifluoromethylbenzyloxy, 1,1-bis-trifluoromethyl-1-hydroxymethyl, 3-trifluoromethylbenzyl, 3,5-bis-trifluoromethylbenzyloxy, 4-trifluoromethylphenoxy, 3-trifluoromethylphenoxy, 3-trifluoromethylphenyl, 2,3,4-trifluorophenoxy, 2,3,5-trifluorophenoxy, 3,4,5-trimethylphenoxy, 3-difluoromethoxyphenoxy, 3-pentafluoroethylphenoxy, 3-(1,1,2,2-tetrafluoroethoxy)phenoxy, 3-trifluoromethylthiophenoxy, 3-trifluoromethylthiobenzyloxy, and trifluoromethylthio;

R_6 and R_{11} are independently selected from the group consisting of chloro, fluoro, hydrogen, pentafluoroethyl, 1,1,2,2-tetrafluoroethoxy, and trifluoromethyl;

R_7 and R_{12} are independently selected from the group consisting of hydrogen, fluoro, and trifluoromethyl.

8. Compound of Claim 1, or a pharmaceutically acceptable salt thereof, wherein the aralkyl of one or more of the substituents R_5, R_6, R_7, R_{10}, R_{11}, and R_{12} are substituted with one to five substituents selected from the substituent group consisting of perhaloaralkyl, aralkylsulfonyl, aralkylsulfonylalkyl, aralkylsulfinyl, aralkylsulfinylalkyl, halocycloalkyl, halocycloalkenyl, cycloalkylsulfinyl, cycloalkylsulfinylalkyl, cycloalkylsulfonyl, cycloalkylsulfonylalkyl, heteroarylamino, N-heteroarylamino-N-alkylamino, heteroarylaminoalkyl, heteroaryloxy, heteroaryloxylalkyl, haloalkylthio, alkanoyloxy, alkoxy, alkoxyalkyl, haloalkoxylalkyl, heteroaralkoxy, cycloalkoxy, cycloalkenyloxy, cycloalkoxyalkyl, cycloalkylalkoxy, cycloalkenyloxyalkyl, cycloalkylenedioxy, halocycloalkoxy, halocycloalkoxyalkyl, halocycloalkenyloxy, halocycloalkenyloxyalkyl, hydroxy, amino, thio, nitro, lower alkylamino, alkylthio, alkylthioalkyl, arylamino, aralkylamino, arylthio, arylthioalkyl, heteroaralkoxyalkyl, alkylsulfinyl, alkylsulfinylalkyl, arylsulfinylalkyl, arylsulfonylalkyl, heteroarylsulfinylalkyl, heteroarylsulfonylalkyl, alkylsulfonyl, alkylsulfonylalkyl, haloalkylsulfinylalkyl, haloalkylsulfonylalkyl, alkylsulfonamido, alkylaminosulfonyl, amidosulfonyl, monoalkyl amidosulfonyl, dialkyl amidosulfonyl, monoarylamidosulfonyl, arylsulfonamido, diarylamidosulfonyl, monoalkyl monoaryl amidosulfonyl, arylsulfinyl, arylsulfonyl, heteroarylthio, heteroarylsulfinyl, heteroarylsulfonyl, alkanoyl, alkenoyl, aroyl, heteroaroyl, aralkanoyl, heteroaralkanoyl, haloalkanoyl, alkyl, alkenyl, alkynyl, alkenyloxy, alkenyloxyalky, alkylenedioxy, haloalkylenedioxy, cycloalkyl, cycloalkylalkanoyl, cycloalkenyl, lower cycloalkylalkyl, lower cycloalkenylalkyl, halo, haloalkyl, haloalkenyl, haloalkoxy, hydroxyhaloalkyl, hydroxyaralkyl, hydroxyalkyl, hydoxyheteroaralkyl, haloalkoxyalkyl, aryl, aralkyl, aryloxy, aralkoxy, aryloxyalkyl, saturated heterocyclyl, partially saturated heterocyclyl, heteroaryl, heteroaryloxy, heteroaryloxyalkyl, arylalkyl, heteroarylalkyl, arylalkenyl, heteroarylalkenyl, carboxyalkyl, carboalkoxy, alkoxycarbonyl, carboaralkoxy, carboxamido, carboxamidoalkyl, cyano, carbohaloalkoxy, phosphono, phosphonoalkyl, diaralkoxyphosphono, and diaralkoxyphosphonoalkyl.

9. Compound of Claim 1, or a pharmaceutically acceptable salt thereof, wherein the arylamino of one or more of the substituents R_5, R_6, R_7, R_{10}, R_{11}, and R_{12} are substituted with one to five substituents selected from the substituent group of Claim 8.

10. Compound of Claim 1, or a pharmaceutically acceptable salt thereof, wherein the arylthio of one or more of the substituents R_5, R_6, R_7, R_{10}, R_{11}, and R_{12} are substituted with one to five substituents selected from the substituent group of Claim 8.

11. Compound of Claim 1, or a pharmaceutically acceptable salt thereof, wherein the aroyl of one or more of the substituents R_5, R_6, R_7, R_{10}, R_{11}, and R_{12} are substituted with one to five substituents selected from the substituent group of Claim 8.

12. Compound of Claim 1, or a pharmaceutically acceptable salt thereof, wherein the alkyl of one or more of the substituents R_5, R_6, R_7, R_{10}, R_{11}, and R_{12} are substituted with one to five substituents selected from the substituent group of Claim 8.

13. Compound of Claim 1, or a pharmaceutically acceptable salt thereof, wherein the haloalkoxy of one or more of the substituents R_5, R_6, R_7, R_{10}, R_{11}, and R_{12} are substituted with one to five substituents selected from the substituent group of Claim 8.

14. Compound of Claim 1, or a pharmaceutically acceptable salt thereof, wherein the aryl of one or more of the substituents R_5, R_6, R_7, R_{10}, R_{11}, and R_{12} are substituted with one to five substituents selected from the substituent group of Claim 8.

15. Compound of Claim 1, or a pharmaceutically acceptable salt thereof, wherein the aryloxy of one or more of the substituents R_5, R_6, R_7, R_{10}, R_{11}, and R_{12} are substituted with one to five substituents selected from the substituent group of Claim 8.

16. Compound of Claim 15, or a pharmaceutically acceptable salt thereof, wherein the substituted aryloxy is selected from the group consisting of
4-chloro-3-ethylphenoxy, 4-chloro-3-methylphenoxy,
3-chloro-4-ethylphenoxy, 3,4-dichlorophenoxy, 4-methylphenoxy,
3-trifluoromethoxyphenoxy, 3-trifluoromethylphenoxy, 4-fluorophenoxy,
3,4-dimethylphenoxy, 5-bromo-2-fluorophenoxy, 4-bromo-3-fluorophenoxy,
4-fluoro-3-methylphenoxy, 5,6,7,8-tetrahydronaphthyloxy,
3-isopropylphenoxy, 3-cyclopropylphenoxy, 3-ethylphenoxy,
4-*tert*-butylphenoxy, 3-pentafluoroethylphenoxy, and
3-(1,1,2,2-tetrafluoroethoxy)phenoxy.

17. Compound of Claim 1, or a pharmaceutically acceptable salt thereof, wherein the aralkoxy of one or more of the substituents R_5, R_6, R_7, R_{10}, R_{11}, and R_{12} are substituted with one to five substituents selected from the substituent group of Claim 8.

18. Compound of Claim 1, or a pharmaceutically acceptable salt thereof, wherein the heterocyclyl of one or more of the substituents R_5, R_6, R_7, R_{10}, R_{11}, and R_{12} are substituted with one to five substituents selected from the substituent group of Claim 8.

19. Compound of Claim 1, or a pharmaceutically acceptable salt thereof, wherein the hetetaryl of one or more of the substituents R_5, R_6, R_7, R_{10}, R_{11}, and R_{12} are substituted with one to five substituents selected from the substituent group of Claim 8.

20. Compound of Claim 1, or a pharmaceutically acceptable salt thereof, wherein the heteraryloxy of one or more of the substituents R_5, R_6, R_7, R_{10}, R_{11}, and R_{12} are substituted with one to five substituents selected from the substituent group of Claim 8.

21. Compound of Claim 1, or a pharmaceutically acceptable salt thereof, wherein the haloalkylthio of one or more of the substituents R_5, R_6, R_7, R_{10}, R_{11}, and R_{12} are substituted with one to five substituents selected from the substituent group of Claim 8.

22. Compound of Claim 1, or a pharmaceutically acceptable salt thereof, wherein the alkoxy of one or more of the substituents R_5, R_6, R_7, R_{10}, R_{11}, and R_{12} are substituted with one to five substituents selected from the substituent group of Claim. 8.

23. Compound of Claim 1, or a pharmaceutically acceptable salt thereof, wherein the cycloalkyl of one or more of the substituents R_5, R_6, R_7, R_{10}, R_{11}, and R_{12} are substituted with one to five substituents selected from the substituent group of Claim 8.

24. Compound of Claim 1, or a pharmaceutically acceptable salt thereof, wherein the haloalkyl of one or more of the substituents R_5, R_6, R_7, R_{10}, R_{11}, and R_{12} are substituted with one to five substituents selected from the substituent group of Claim 8.

25. A pharmaceutical composition comprising a therapeutically effective amount of a compound of Claim 1 or a pharmaceutically acceptable salt thereof, together with a pharmaceutically acceptable carrier.

26. The use of a compound of Claim 1 or a pharmaceutically acceptable salt thereof for the manufacture of a medicament for treating or preventing a CETP (cholesteryl Esther Transfer Protein)-mediated disorder in a subject.

27. The use of Claim 26 wherein the treating of a CETP-mediated disorder is treating of coronary artery disease.

28. The use of Claim 26 wherein the preventing of a CETP-mediated disorder is preventing of coronary artery disease.

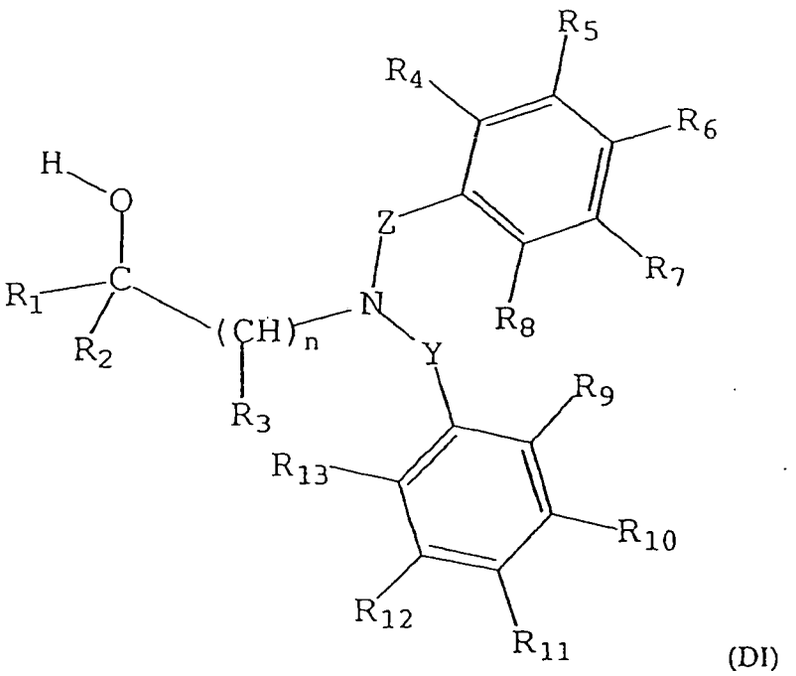
29. The use of Claim 26 wherein the preventing of a CETP-mediated disorder is preventing of cerebral vascular accident (CVA).

30. The use of Claim 26 wherein the treating of a CETP-mediated disorder is treating of dyslipidemia.

31. The use of Claim 26 wherein the preventing of a CETP-mediated disorder is preventing of dyslipidemia.

Patentansprüche

1. Verbindung der Formel DI:

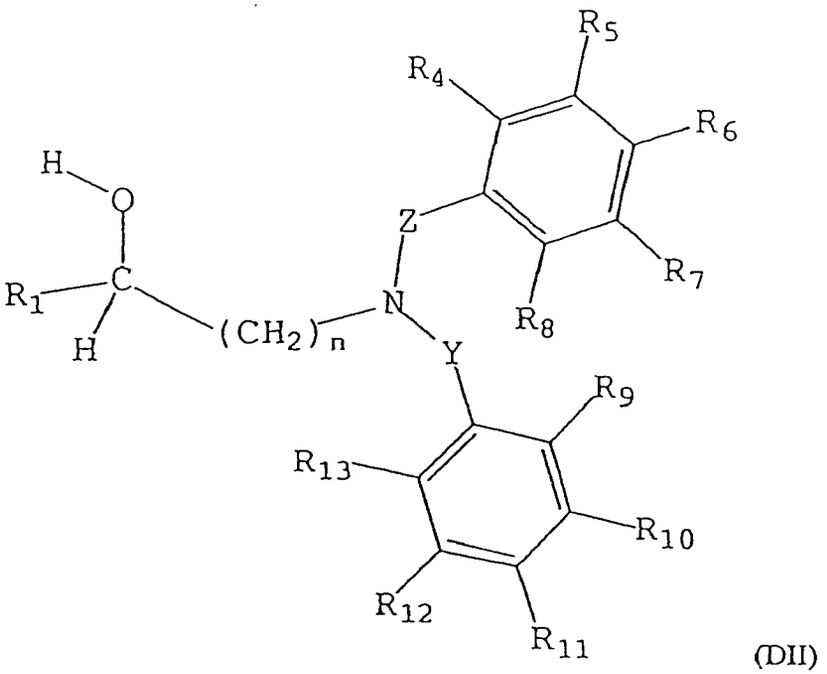


(DI)

oder ein pharmazeutisch annehmbares Salz davon, worin
n 1 ist;
R_1 Halogenalkyl ist;
R_2 ausgewählt ist aus der Gruppe, bestehend aus Wasserstoff, Alkyl, Halogenalkyl, Aryl und Halogenalkoxy;

R_3 ausgewählt ist aus der Gruppe, bestehend aus Wasserstoff, Alkyl und Halogenalkyl;
Y C_1-C_2-Alkylen ist;
Z eine kovalente Einfachbindung ist;
R_4, R_8, R_9 und R_{13} Wasserstoff oder Halogen sind;
R_5, R_6, R_7, R_{10}, R_{11} und R_{12} unabhängig ausgewählt sind aus der Gruppe, bestehend aus Wasserstoff, Perhalogenaryloxy, N-Aryl-N-alkylamino, Heterocyclylalkoxy, Heterocyclylthio, Hydroxyalkoxy, Aralkanoylalkoxy, Aralkenoyl, Cycloalkylcarbonyl, Cyanoalkoxy, Heterocyclylcarbonyl, Alkyl, Halogen, Halogenalkyl, Halogenalkoxy, Aryl, Alkylthio, Arylamino, Arylthio, Aroyl, Arylsulfonyl, Aryloxy, Aralkoxy, Heteroaryloxy, Alkoxy, Aralkyl, Cycloalkoxy, Cycloalkylalkoxy, Cycloalkylalkanoyl, Heteroaryl, Cycloalkyl, Halogenalkylthio, Hydroxyhalogenalkyl, Heteroaralkoxy und Heteroaryloxyalkyl.

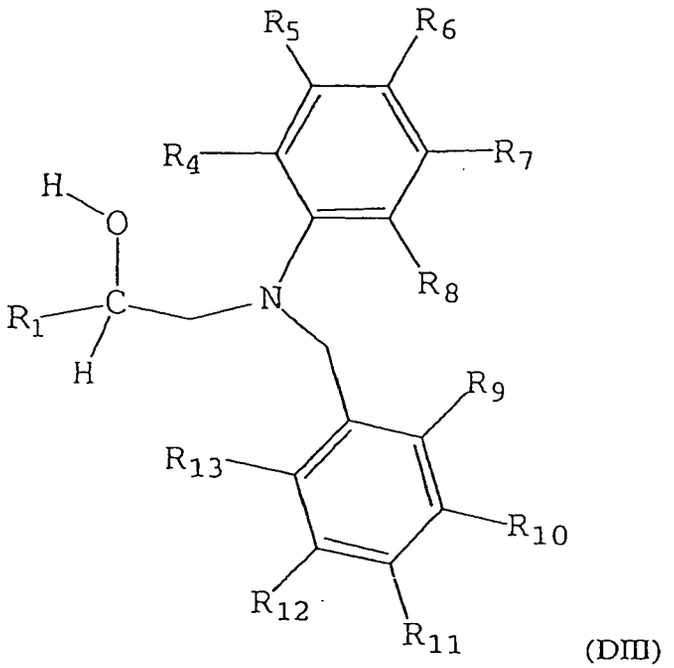
2. Verbindung nach Anspruch 1 der Formel DII:



(DII)

oder ein pharmazeutisch annehmbares Salz davon.

3. Verbindung nach Anspruch 2 der Formel DIII:



(DIII)

oder ein pharmazeutisch annehmbares Salz, worin:

R_1 Halogenalkyl ist;
R_5, R_6, R_7, R_{10}, R_{11} und R_{12} unabhängig ausgewählt sind aus der Gruppe, bestehend aus Wasserstoff, Perhalogenaryloxy, N-Aryl-N-alkylamino, Heterocyclylalkoxy, Heterocyclylthio, Hydroxyalkoxy, Aralkanoylalkoxy, Aralkenoyl, Cycloalkylcarbonyl, Cyanoalkoxy, Heterocyclylcarbonyl, Alkyl, Halogen, Halogenalkyl, Halogenalkoxy, Aryl, Alkylthio, Arylamino, Arylthio, Aroyl, Arylsulfonyl, Aryloxy, Aralkoxy, Heteroaryloxy, Alkoxy, Aralkyl, Cycloalkoxy, Cycloalkylalkoxy, Cycloalkylalkanoyl, Heteroaryl, Cycloalkyl, Halogenalkylthio, Hydroxyhalogenalkyl, Heteroaralkoxy und Heteroaryloxyalkyl.

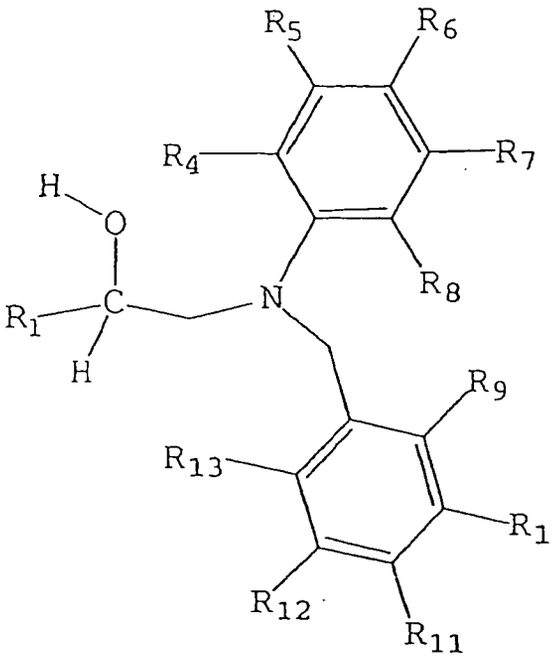
4. Verbindung nach Anspruch 3 oder ein pharmazeutisch annehmbares Salz davon, worin:

R_1 Trifluormethyl ist;
R_4, R_6, R_7, R_8, R_9, R_{11}, R_{12} und R_{13} Wasserstoff oder Fluor sind;
R_5 ausgewählt ist aus der Gruppe, bestehend aus 5-Brom-2-fluorphenoxy, 4-Chlor-3-ethylphenoxy, 2,3-Dichlorphenoxy, 3,4-Dichlorphenoxy, 3-Difluormethoxyphenoxy, 3,5-Dimethylphenoxy, 3,4-Dimethylphenoxy, 3-Ethylphenoxy, 3-Ethyl-5-methylphenoxy, 4-Fluor-3-methylphenoxy, 4-Fluorphenoxy, 3-Isopropylphenoxy, 3-Methylphenoxy, 3-Pentafluorethylphenoxy, 3-tert.-Butylphenoxy, 3-(1,1,2,2-tetrafluorethoxy)phenoxy, 2-(5,6,7,8-tetrahydronaphthyloxy), 3-Trifluormethoxybenzyloxy, 3-Trifluormethoxyphenoxy, 3-Trifluormethylbenzyloxy und 3-Trifluormethylthiophenoxy;
R_{10} ausgewählt ist aus der Gruppe, bestehend aus Cyclopentyl, 1,1,2,2-Tetrafluorethoxy, 2-Furyl, 1,1-Bistrifluormethyl-1-hydroxymethyl, Pentafluorethyl, Trifluormethoxy, Trifluormethyl und Trifluormethylthio.

5. Verbindung nach Anspruch 4 oder ein pharmazeutisch annehmbares Salz davon, worin
R_{10} ausgewählt ist aus der Gruppe, bestehend aus 1,1,2,2-Tetrafluorethoxy, Pentafluorethyl und Trifluormethyl.

6. Verbindung nach Anspruch 1 oder ein pharmazeutisch annehmbares Salz davon, wobei die Verbindung 3-[[3-(4-Chlor-3-ethylphenoxy)phenyl][[3-(1,1,2,2-tetrafluorethoxy)phenyl]-methyl]amino]-1,1,1-trifluor-2-propanol ist.

7. Verbindung nach Anspruch 1 der Formel DIII:



(DIII)

oder ein pharmazeutisch annehmbares Salz, worin

R_1 ausgewählt ist aus der Gruppe, bestehend aus Trifluormethyl, Difluormethyl, Chlordifluormethyl und Pentafluorethyl;
R_4, R_8, R_9 und R_{13} Wasserstoff oder Fluor sind;
R_5 und R_{10} unabhängig ausgewählt sind aus der Gruppe, bestehend aus Benzyloxy, 5-Brom-2-fluorphenoxy, 4-Brom-3-fluorphenoxy, 3-Brombenzyloxy, 4-Bromphenoxy, 4-Butoxyphenoxy, 3-Chlorbenzyloxy, 2-Chlorphenoxy, 4-Chlor-3-ethylphenoxy, 4-Chlor-3-methylphenoxy, 2-Chlor-4-fluorphenoxy, 4-Chlor-2-fluorphenoxy, 4-Chlorphenoxy, 3-Chlor-4-ethylphenoxy, 3-Chlor-4-methylphenoxy, 3-Chlor-4-fluorphenoxy, 4-Chlor-3-fluorphenoxy, 4-Chlorphenylamino, 5-Chlorpyrid-3-yloxy, Cyclobutoxy, Cyclobutyl, Cyclohexylmethoxy, Cyclopentoxy, Cyclopentyl, Cyclopentylcarbonyl, Cyclopropylmethoxy, 2,3-Dichlorphenoxy, 2,4-Dichlorphenoxy, 2,4-Dichlorphenyl, 3,5-Dichlorphenyl, 3,5-Dichlorbenzyl, 3,4-Dichlorphenoxy, 3,4-Difluorphenoxy, 2,3-Difluorbenzyloxy, 3,5-Difluorbenzyloxy, Difluormethoxy, 3,5-Difluorphenoxy, 3,4-Difluorphenyl, 2,3-Difluorphenoxy, 2,4-Difluorphenoxy, 2,5-Difluorphenoxy, 3,5-Dimethoxyphenoxy, 3-Dimethylaminophenoxy, 3,4-Dimethylbenzyloxy, 3,5-Dimethylbenzyloxy, 3,5-Dimethylphenoxy, 3,4-Dimethylphenoxy, 1,3-Dioxolan-2-yl, 3-Ethylbenzyloxy, 3-Ethylphenoxy, 4-Ethylaminophenoxy, 3-Ethyl-5-methylphenoxy, 4-Fluor-3-methylbenzyl, 4-Fluorbenzyloxy, 2-Fluor-3-methylphenoxy, 3-Fluor-4-methylphenoxy, 3-Fluorphenoxy, 3-Fluor-2-nitrophenoxy, 2-Fluor-3-trifluormethylbenzyloxy, 3-Fluor-5-trifluormethylbenzyloxy, 2-Fluorphenoxy, 4-Fluorphenoxy, 2-Fluor-3-trifluormethylphenoxy, 2-Fluorbenzyloxy, 4-Fluorphenylamino, 2-Fluor-4-trifluormethylphenoxy, 2-Furyl, 3-Furyl, Heptafluorpropyl, 1,1,1,3,3,3-Hexafluorpropyl, 2-Hydroxy-3,3,3-trifluorpropoxy, Isobutoxy, Isobutyl, 3-Isoxazolyl, 4-Isoxazolyl, 5-Isoxazolyl, Isopropoxy, 3-Isopropylbenzyloxy, 3-Isopropylphenoxy, Isopropylthio, 4-Isopropyl-3-methylphenoxy, 3-Isothiazolyl, 4-Isothiazolyl, 5-Isothiazolyl, 3-Methoxybenzyl, 4-Methoxyphenylamino, 3-Methylbenzyloxy, 4-Methylbenzyloxy, 3-Methylphenoxy, 3-Methyl-4-methylthiophenoxy, 4-Methylphenoxy, 1-Methylpropoxy, 2-Methylpyrid-5-yloxy, 4-Methylthiophenoxy, 2-Naphthyloxy, 2-Nitrophenoxy, 4-Nitrophenoxy, 3-Nitrophenyl, 2-Oxazolyl, 4-Oxazolyl, 5-Oxazolyl, Pentafluorethyl, Pentafluorethylthio, 2,2,3,3,3-Pentafluorpropyl, 1,1,3,3,3-Pentafluorpropyl, 1,1,2,2,3-Pentafluorpropyl, Phenoxy, Phenylamino, 1-Phenylethoxy, 4-Propylphenoxy, 4-Propoxyphenoxy, Thiophen-3-yl, tert.-Butoxy, 3-tert-Butylphenoxy, 4-tert.-Butylphenoxy, 1,1,2,2-Tetrafluorethoxy, Tetrahydrofuran-2-yl, 2-(5,6,7,8-Tetrahydronaphthyloxy), Thiazol-2-yl, Thiazol-4-yl, Thiazol-5-yl, Thiophen-2-yl, 2,2,2-Trifluorethoxy, 2,2,2-Trifluorethyl, 3,3,3-Trifluor-2-hydroxypropyl, Trifluormethoxy, 3-Trifluormethoxybenzyloxy, 4-Trifluormethoxybenzyloxy, 4-Trifluormethoxyphenoxy, 3-Trifluormethoxyphenoxy, Trifluormethyl, 3-Trifluormethylbenzyloxy, 1,1-Bis-trifluormethyl-1-hydroxymethyl, 3-Trifluormethylbenzyl, 3,5-Bis-trifluormethylbenzyloxy, 4-Trifluormethylphenoxy, 3-Trifluormethylphenoxy, 3-Trifluormethylphenyl, 2,3,4-Trifluorphenoxy, 2,3,5-Trifluorphenoxy, 3,4,5-Trimethylphenoxy, 3-Difluormethoxyphenoxy, 3-Pentafluorethylphenoxy, 3-(1,1,2,2-Tetrafluorethoxy)phenoxy, 3-Trifluormethylthiophenoxy, 3-Trifluormethylthiobenzylo-

xy und Trifluormethylthio;
R_6 und R_{11} unabhängig ausgewählt sind aus der Gruppe, bestehend aus Chlor, Fluor, Wasserstoff, Pentafluorethyl, 1,1,2,2-Tetrafluorethoxy und Trifluormethyl;
R_7 und R_{12} unabhängig ausgewählt sind aus der Gruppe, bestehend aus Wasserstoff, Fluor und Trifluormethyl.

8. Verbindung nach Anspruch 1 oder ein pharmazeutisch annehmbares Salz davon, wobei das Aralkyl von einem oder mehreren der Substituenten R_5, R_6, R_7, R_{10}, R_{11} und R_{12} mit 1 bis 5 Substituenten substituiert ist, die ausgewählt sind aus der Gruppe, bestehend aus Perhalogenaralkyl, Aralkylsulfonyl, Aralkylsulfonylalkyl, Aralkylsulfinyl, Aralkylsulfinylalkyl, Halogencycloalkyl, Halogencycloalkenyl, Cycloalkylsulfinyl, Cycloalkylsulfinylalkyl, Cycloalkylsulfonyl, Cycloalkylsulfonylalkyl, Heteroarylamino, N-Heteroarylamino-N-alkylamino, Heteroarylaminoalkyl, Heteroaryloxy, Heteroaryloxylalkyl, Halogenalkylthio, Alkanoyloxy, Alkoxy, Alkoxyalkyl, Halogenalkoxylalkyl, Heteroaralkoxy, Cycloalkoxy, Cycloalkenyloxy, Cycloalkoxyalkyl, Cycloalkylalkoxy, Cycloalkenyloxyalkyl, Cycloalkylendioxy, Halogencycloalkoxy, Halogencycloalkoxyalkyl, Halogencycloalkenyloxy, Halogencycloalkenyloxyalkyl, Hydroxy, Amino, Thio, Nitro, Niederalkylamino, Alkylthio, Alkylthioalkyl, Arylamino, Aralkylamino, Arylthio, Arylthioalkyl, Heteroaralkoxyalkyl, Alkylsulinyl, Alkylsulfinylalkyl, Arylsulfinylalkyl, Arylsulfonylalkyl, Heteroarylsulfinylalkyl, Heteroarylsulfonylalkyl, Alkylsulfonyl, Alkylsulfonylalkyl, Halogenalkylsulfinylalkyl, Halogenalkylsulfonylalkyl, Alkylsulfonamido, Alkylaminosulfonyl, Amidosulfonyl, Monoalkylamidosulfonyl, Dialkylamidosulfonyl, Monoarylamidosulfonyl, Arylsulfonamido, Diarylamidosulfonyl, Monoalkylmonoarylamidosulfonyl, Arylsulfinyl, Arylsulfonyl, Heteroarylthio, Heteroarylsulfinyl, Heteroarylsulfonyl, Alkanoyl, Alkenoyl, Aroyl, Heteroaroyl, Aralkanoyl, Heteroaralkanoyl, Halogenalkanoyl, Alkyl, Alkenyl, Alkinyl, Alkenyloxy, Alkenyloxyalkyl, Alkylendioxy, Halogenalkylendioxy, Cycloalkyl, Cycloalkylalkanoyl, Cycloalkenyl, Niedercycloalkylalkyl, Niedercycloalkenylalkyl, Halogen, Halogenalkyl, Halogenalkenyl, Halogenalkoxy, Hydroxyhalogenalkyl, Hydroxyaralkyl, Hydroxyalkyl, Hydoxyheteroaralkyl, Halogenalkoxyalkyl, Aryl, Aralkyl, Aryloxy, Aralkoxy, Aryloxyalkyl, gesättigtes Heterocyclyl, teilweise gesättigtes Heterocyclyl, Heteroaryl, Heteroaryloxy, Heteroaryloxyalkyl, Arylalkyl, Heteroarylalkyl, Arylalkenyl, Heteroarylalkenyl, Carboxyalkyl, Carboalkoxy, Alkoxycarbonyl, Carboaralkoxy, Carboxamido, Carboxamidoalkyl, Cyano, Carbohalogenalkoxy, Phosphono, Phosphonoalkyl, Diaralkoxyphosphono und Diaralkoxyphosphonoalkyl.

9. Verbindung nach Anspruch 1 oder ein pharmazeutisch annehmbares Salz davon, wobei das Arylamino von einem oder mehreren der Substituenten R_5, R_6, R_7, R_{10}, R_{11} und R_{12} mit ein bis fünf Substituenten substituiert ist, die aus der Substituentengruppe von Anspruch 8 ausgewählt sind.

10. Verbindung nach Anspruch 1 oder ein pharmazeutisch annehmbares Salz davon, wobei das Arylthio von einem oder mehreren der Substituenten R_5, R_6, R_7, R_{10}, R_{11} und R_{12} mit ein bis fünf Substituenten substituiert ist, die aus der Substituentengruppe von Anspruch 8 ausgewählt sind.

11. Verbindung nach Anspruch 1 oder ein pharmazeutisch annehmbares Salz davon, wobei das Aroyl von einem oder mehreren der Substituenten R_5, R_6, R_7, R_{10}, R_{11} und R_{12} mit ein bis fünf Substituenten substituiert ist, die aus der Substituentengruppe von Anspruch 8 ausgewählt sind.

12. Verbindung nach Anspruch 1 oder ein pharmazeutisch annehmbares Salz davon, wobei das Alkyl von einem oder mehreren der Substituenten R_5, R_6, R_7, R_{10}, R_{11} und R_{12} mit ein bis fünf Substituenten substituiert ist, die aus der Substituentengruppe von Anspruch 8 ausgewählt sind.

13. Verbindung nach Anspruch 1 oder ein pharmazeutisch annehmbares Salz davon, wobei das Halogenalkoxy von einem oder mehreren der Substituenten R_5, R_6, R_7, R_{10}, R_{11} und R_{12} mit ein bis fünf Substituenten substituiert ist, die aus der Substituentengruppe von Anspruch 8 ausgewählt sind.

14. Verbindung nach Anspruch 1 oder ein pharmazeutisch annehmbares Salz davon, wobei das Aryl von einem oder mehreren der Substituenten R_5, R_6, R_7, R_{10}, R_{11} und R_{12} mit ein bis fünf Substituenten substituiert ist, die aus der Substituentengruppe von Anspruch 8 ausgewählt sind.

15. Verbindung nach Anspruch 1 oder ein pharmazeutisch annehmbares Salz davon, wobei das Aryloxy von einem oder mehreren der Substituenten R_5, R_6, R_7, R_{10}, R_{11} und R_{12} mit ein bis fünf Substituenten substituiert ist, die aus der Substituentengruppe von Anspruch 8 ausgewählt sind.

16. Verbindung nach Anspruch 15 oder ein pharmazeutisch annehmbares Salz davon, wobei das substituierte Aryloxy ausgewählt ist aus der Gruppe, bestehend aus 4-Chlor-3-ethylphenoxy, 4-Chlor-3-methylphenoxy, 3-Chlor-4-ethylphenoxy, 3,4-Dichlorphenoxy, 4-Methylphenoxy, 3-Trifluormethoxyphenoxy, 3-Trifluormethylphenoxy, 4-Fluor-

phenoxy, 3,4-Dimethylphenoxy, 5-Brom-2-fluorphenoxy, 4-Brom-3-fluorphenoxy, 4-Fluor-3-methylphenoxy, 5,6,7,8-Tetrahydronaphthyloxy, 3-Isopropylphenoxy, 3-Cyclopropylphenoxy, 3-Ethylphenoxy, 4-tert.-Butylphenoxy, 3-Pentafluorethylphenoxy und 3-(1,1,2,2-Tetrafluorethoxy)phenoxy.

17. Verbindung nach Anspruch 1 oder ein pharmazeutisch annehmbares Salz davon, wobei das Araloxy von einem oder mehreren der Substituenten R_5, R_6, R_7, R_{10}, R_{11} und R_{12} mit ein bis fünf Substituenten substituiert ist, die aus der Substituentengruppe von Anspruch 8 ausgewählt sind.

18. Verbindung nach Anspruch 1 oder ein pharmazeutisch annehmbares Salz davon, wobei das Heterocyclyl von einem oder mehreren der Substituenten R_5, R_6, R_7, R_{10}, R_{11} und R_{12} mit ein bis fünf Substituenten substituiert ist, die aus der Substituentengruppe von Anspruch 8 ausgewählt sind.

19. Verbindung nach Anspruch 1 oder ein pharmazeutisch annehmbares Salz davon, wobei das Heteroaryl von einem oder mehreren der Substituenten R_5, R_6, R_7, R_{10}, R_{11} und R_{12} mit ein bis fünf Substituenten substituiert ist, die aus der Substituentengruppe von Anspruch 8 ausgewählt sind.

20. Verbindung nach Anspruch 1 oder ein pharmazeutisch annehmbares Salz davon, wobei das Heteroaryloxy von einem oder mehreren der Substituenten R_5, R_6, R_7, R_{10}, R_{11} und R_{12} mit ein bis fünf Substituenten substituiert ist, die aus der Substituentengruppe von Anspruch 8 ausgewählt sind.

21. Verbindung nach Anspruch 1 oder ein pharmazeutisch annehmbares Salz davon, wobei das Halogenalkylthio von einem oder mehreren der Substituenten R_5, R_6, R_7, R_{10}, R_{11} und R_{12} mit ein bis fünf Substituenten substituiert ist, die aus der Substituentengruppe von Anspruch 8 ausgewählt sind.

22. Verbindung nach Anspruch 1 oder ein pharmazeutisch annehmbares Salz davon, wobei das Alkoxy von einem oder mehreren der Substituenten R_5, R_6, R_7, R_{10}, R_{11} und R_{12} mit ein bis fünf Substituenten substituiert ist, die aus der Substituentengruppe von Anspruch 8 ausgewählt sind.

23. Verbindung nach Anspruch 1 oder ein pharmazeutisch annehmbares Salz davon, wobei das Cycloalkyl von einem oder mehreren der Substituenten R_5, R_6, R_7, R_{10}, R_{11} und R_{12} mit ein bis fünf Substituenten substituiert ist, die aus der Substituentengruppe von Anspruch 8 ausgewählt sind.

24. Verbindung nach Anspruch 1 oder ein pharmazeutisch annehmbares Salz davon, wobei das Halogenalkyl von einem oder mehreren der Substituenten R_5, R_6, R_7, R_{10}, R_{11} und R_{12} mit ein bis fünf Substituenten substituiert ist, die aus der Substituentengruppe von Anspruch 8 ausgewählt sind.

25. Pharmazeutische Zusammensetzung, die eine therapeutisch wirksame Menge einer Verbindung nach Anspruch 1 oder eines pharmazeutisch annehmbaren Salzes davon zusammen mit einem pharmazeutisch annehmbaren Träger umfasst.

26. Verwendung einer Verbindung nach Anspruch 1 oder eines pharmazeutisch annehmbaren Salzes davon für die Herstellung eines Medikaments zur Behandlung oder Prävention einer CETP(Cholesteryl Ester Transfer Protein)-vermittelten Störung beim einem Subjekt.

27. Verwendung nach Anspruch 26, wobei die Behandlung einer CETP-vermittelten Störung die Behandlung einer Erkrankung der Koronararterie ist.

28. Verwendung nach Anspruch 26, wobei die Prävention einer CETP-vermittelten Störung die Prävention einer Erkrankung der Koronararterie ist.

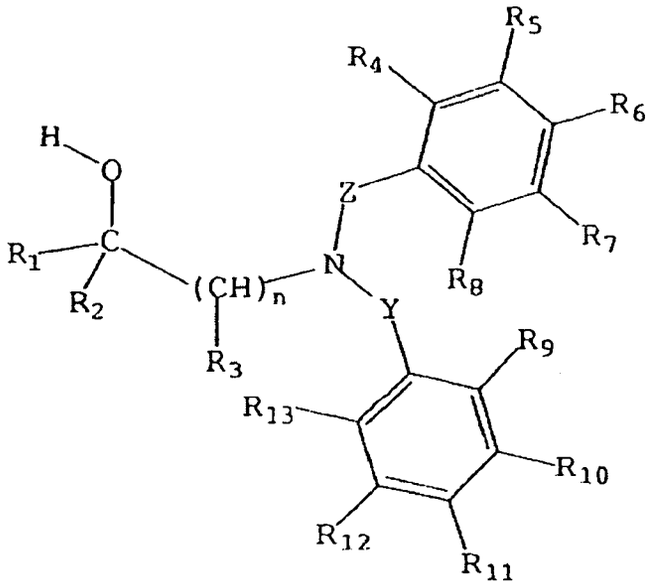
29. Verwendung nach Anspruch 26, wobei die Prävention einer CETP-vermittelten Störung die Prävention eines cerebrovaskulären Insults (cerebral vascular accident (CVA)) ist.

30. Verwendung nach Anspruch 26, wobei die Behandlung einer CETP-vermittelten Störung die Behandlung von Dyslipidämie ist.

31. Verwendung nach Anspruch 26, wobei die Prävention einer CETP-vermittelten Störung die Prävention von Dyslipidämie ist.

Revendications

1. Composé de formule DI :

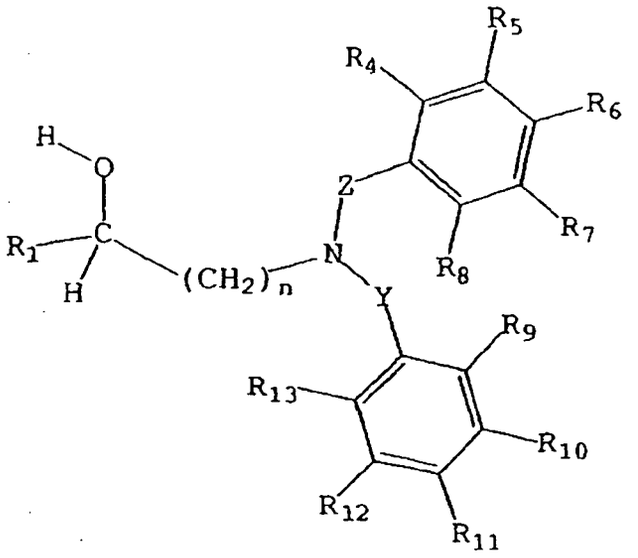


(DI)

ou un sel pharmaceutiquement acceptable de celui-ci, dans lequel :

n est 1 ;
R_1 est un halogénoalkyle ;
R_2 est choisi dans le groupe constitué de l'hydrogène, un alkyle, un halogénoalkyle, un aryle et un halogénoalcoxy ;
R_3 est choisi dans le groupe constitué de l'hydrogène, un alkyle, et un halogénoalkyle ;
Y est un alkylène en C1-C2 ;
Z est une simple liaison covalente ;
R_4, R_8, R_9 et R_{13} sont l'hydrogène ou un halogène ;
R_5, R_6, R_7, R_{10}, R_{11} et R_{12} sont indépendamment choisis dans le groupe constitué de l'hydrogène, un perhalogénoaryloxy, un N-aryl-N-alkylamino, un hétérocyclylalcoxy, un hétérocyclylthio, un hydroxyalcoxy, un aralcanoylalcoxy, un aralcénoyle, un cycloalkylcarbonyle, un cyanoalcoxy, un hétérocyclylcarbonyle, un alkyle, un halogène, un halogénoalkyle, un halogénoalcoxy, un aryle, un alkylthio, un arylamino, un arylthio, un aroyle, un arylsulfonyle, un aryloxy, un aralcoxy, un hétéroaryloxy, un alcoxy, un aralkyle, un cycloalcoxy, un cycloalkylalcoxy, un cycloalkylalcanoyle, un hétéroaryle, un cycloalkyle, un halogénoalkylthio, un hydroxyhalogénoalkyle, un hétéroaralcoxy, et un hétéroaryloxyalkyle.

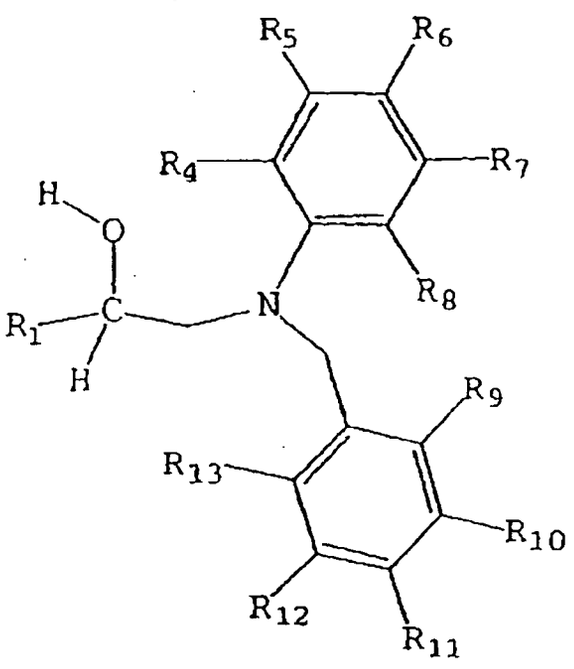
2. Composé selon la revendication 1 de formule DII :



(DII)

ou un sel pharmaceutiquement acceptable de celui-ci.

3. Composé selon la revendication 2 de formule DIII :



(DIII)

ou un sel pharmaceutiquement acceptable, dans lequel ;

R_1 est un halogénoalkyle ;
R_5, R_6, R_7, R_{10}, R_{11}, et R_{12} sont indépendamment choisis dans le groupe constitué de l'hydrogène, un perhalogénoaryloxy, un N-aryl-N-alkylamino, un hétérocyclylalcoxy, un hétérocyclylthio, un hydroxyalcoxy, un aralcanoylalcoxy, un aralcénoyle, un cycloalkylcarbonyle, un cyanoalcoxy, un hétérocyclylcarbonyle, un alkyle, un halogène, un halogénoalkyle, un halogénoalcoxy, un aryle, un alkylthio, un arylamino, un arylthio, un aroyle, un arylsulfonyle, un aryloxy, un aralcoxy, un hétéroaryloxy, un alcoxy, un aralkyle, un cycloalcoxy, un cycloalk-

ylalcoxy, un cycloalkylalcanoyle, un hétéroaryle, un cycloalkyle, un halogénoalkylthio, un hydroxyhalogénoalkyle, un hétéroaralcoxy, et un hétéroaryloxyalkyle.

4. Composé selon la revendication 3, ou un sel pharmaceutiquement acceptable de celui-ci, dans lequel :

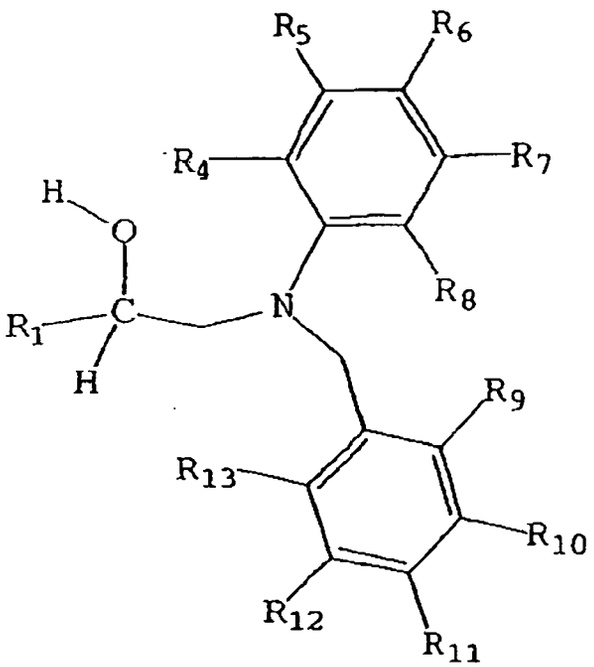
R_1 est le trifluorométhyle ;
R_4, R_6, R_7, R_8, R_9, R_{11}, R_{12}, et R_{13} sont l'hydrogène ou un fluoro ;
R_5 est choisi dans le groupe constitué du 5-bromo-2-fluorophénoxy, du 4-chloro-3-éthylphénoxy, du 2,3-dichlorophénoxy, du 3,4-dichlorophénoxy, du 3-difluorométhoxyphénoxy, du 3,5-diméthylphénoxy, du 3,4-diméthylphénoxy, du 3-éthylphénoxy, du 3-éthyl-5-méthylphénoxy, du 4-fluoro-3-méthylphénoxy, du 4-fluorophénoxy, du 3-isopropylphénoxy, du 3-méthylphénoxy, du 3-pentafluoroéthylphénoxy, du 3-tert-butylphénoxy, du 3-(1,1,2,2-tétrafluoroéthoxy)phénoxy, du 2-(5,6,7,8-tétrahydronaphtyloxy), du 3-trifluorométhoxybenzyloxy, du 3-trifluorométhoxyphénoxy, du 3-trifluorométhylbenzyloxy, et du 3-trifluorométhylthiophénoxy ;
R_{10} est choisi dans le groupe constitué du cyclopentyle, du 1,1,2,2-tétrafluoroéthoxy, du 2-furyle, du 1,1-bis-trifluorométhyl-1-hydroxyméthyle, du pentafluoroéthyle, du trifluorométhoxy, du trifluorométhyle, et du trifluorométhylthio.

5. Composé selon la revendication 4, ou un sel pharmaceutiquement acceptable de celui-ci, dans lequel:

R_{10} est choisi dans le groupe constitué du 1,1,2,2-tétrafluoroéthoxy, du pentafluoroéthyle, et du trifluorométhyle.

6. Composé selon la revendication 1, ou un sel pharmaceutiquement acceptable de celui-ci, dans lequel ledit composé est le 3-[[3-(4-chloro-3-éthylphénoxy)phényl][[3-(1,1,2,2-tétrafluoroéthoxy)phényl]-méthyl]amino]-1,1,1-trifluoro-2-propanol.

7. Composé selon la revendication 1 de formule DIII :



(DIII)

ou un sel pharmaceutiquement acceptable, dans lequel :

R_1 est choisi dans le groupe constitué du trifluorométhyle, du difluorométhyle, du chlorodifluorométhyle, et du pentafluoroéthyle ;
R_4, R_8, R_9, et R_{13} sont l'hydrogène ou un fluoro ;

R_5 et R_{10} sont indépendamment choisis dans le groupe constitué du benzyloxy, du 5-bromo-2-fluorophénoxy, du 4-bromo-3-fluorophénoxy, du 3-bromobenzyloxy, du 4-bromophénoxy, du 4-butoxyphénoxy, du 3-chlorobenzyloxy, du 2-chlorophénoxy, du 4-chloro-3-éthylphénoxy, du 4-chloro-3-méthylphénoxy, du 2-chloro-4-fluorophénoxy, du 4-chloro-2-fluorophénoxy, du 4-chlorophénoxy, du 3-chloro-4-éthylphénoxy, du 3-chloro-4-méthylphénoxy, du 3-chloro-4-fluorophénoxy, du 4-chloro-3-fluorophénoxy, du 4-chlorophénylamino, du 5-chloropyrid-3-yloxy, du cyclobutoxy, du cyclobutyle, du cyclohexylméthoxy, du cyclopentoxy, du cyclopentyle, du cyclopentylcarbonyle, du cyclopropylméthoxy, du 2,3-dichlorophénoxy, du 2,4-dichlorophénoxy, du 2,4-dichlorophényle, du 3,5-dichlorophényle, du 3,5-dichlorobenzyle, du 3,4-dichlorophénoxy, du 3,4-difluorophénoxy, du 2,3-difluorobenzyloxy, du 3,5-difluorobenzyloxy, du difluorométhoxy, du 3,5-difluorophénoxy, du 3,4-difluorophényle, du 2,3-difluorophénoxy, du 2,4-difluorophénoxy, du 2,5-difluorophénoxy, du 3,5-diméthoxyphénoxy, du 3-diméthylaminophénoxy, du 3,4-diméthylbenzyloxy, du 3,5-diméthylbenzyloxy, du 3,5-diméthylphénoxy, du 3,4-diméthylphénoxy, du 1,3-dioxolan-2-yle, du 3-éthylbenzyloxy, du 3-éthylphénoxy, du 4-éthylaminophénoxy, du 3-éthyl-5-méthylphénoxy, du 4-fluoro-3-méthylbenzyle, du 4-fluorobenzyloxy, du 2-fluoro-3-méthylphénoxy, du 3-fluoro-4-méthylphénoxy, du 3-fluorophénoxy, du 3-fluoro-2-nitrophénoxy, du 2-fluoro-3-trifluorométhylbenzyloxy, du 3-fluoro-5-trifluorométhylbenzyloxy, du 2-fluorophénoxy, du 4-fluorophénoxy, du 2-fluoro-3-trifluorométhylphénoxy, du 2-fluorobenzyloxy, du 4-fluorophénylamino, du 2-fluoro-4-trifluorométhylphénoxy, du 2-furyle, du 3-furyle, du heptafluoropropyle, du 1,1,1,3,3,3-hexafluoropropyle, du 2-hydroxy-3,3,3-trifluoropropoxy, de l'isobutoxy, de l'isobutyle, du 3-isoxazolyle, du 4-isoxazolyle, du 5-isoxazolyle, de l'isopropoxy, du 3-isopropylbenzyloxy, du 3-isopropylphénoxy, de l'isopropylthio, du 4-isopropyl-3-méthylphénoxy, du 3-isothiazolyle, du 4-isothiazolyle, du 5-isothiazolyle, du 3-méthoxybenzyle, du 4-méthoxyphénylamino, du 3-méthylbenzyloxy, du 4-méthylbenxyloxy, du 3-méthylphénoxy, du 3-méthyl-4-méthylthiophénoxy, du 4-méthylphénoxy, du 1-méthylpropoxy, du 2-méthylpyrid-5-yloxy, du 4-méthylthiophénoxy, du 2-naphtyloxy, du 2-nitrophénoxy, du 4-nitrophénoxy, du 3-nitrophényle, du 2-oxazolyle, du 4-oxazolyle, du 5-oxazolyle, du pentafluoroéthyle, du pentafluoroéthylthio, du 2,2,3,3,3-pentafluoropropyle, du 1,1,3,3,3-pentafluoropropyle, du 1,1,2,2,3-pentafluoropropyle, du phénoxy, du phénylamino, du 1-phényléthoxy, du 4-propylphénoxy, du 4-propoxyphénoxy, du thiophén-3-yle, du tert-butoxy, du 3-tert-butylphénoxy, du 4-tert-butylphénoxy, du 1,1,2,2-tétrafluoroéthoxy, du tétrahydrofuran-2-yle, du 2-(5,6,7,8-tétrahydronaphtyloxy), du thiazol-2-yle, du thiazol-4-yle, du thiazol-5-yle, du thiophén-2-yle, du 2,2,2-trifluoroéthoxy, du 2,2,2-trifluoroéthyle, du 3,3,3-trifluoro-2-hydroxypropyle, du trifluorométhoxy, du 3-trifluorométhoxybenzyloxy, du 4-trifluorométhoxybenzyloxy, du 4-trifluorométhoxyphénoxy, du 3-trifluorométhoxyphénoxy, du trifluorométhyle, du 3-trifluorométhylbenzyloxy, du 1,1-bis-trifluorométhyl-1-hydroxyméthyle, du 3-trifluorométhylbenzyle, du 3,5-bis-trifluorométhylbenzyloxy, du 4-trifluorométhylphénoxy, du 3-trifluorométhylphénoxy, du 3-trifluorométhylphényle, du 2,3,4-trifluorophénoxy, du 2,3,5-trifluorophénoxy, du 3,4,5-trirnéthylphénoxy, du 3-difluorométhoxyphénoxy, du 3-pentafluoroéthylphénoxy, du 3-(1,1,2,2-tétrafluoroéthoxy)phénoxy, du 3-trifluorométhylthiophénoxy, du 3-trifluorométhylthiobenzyloxy, et du trifluorométhylthio ;

R_6 et R_{11} sont indépendamment choisis dans le groupe constitué du chloro, du fluoro, de l'hydrogène, du pentafluoroéthyle, du 1,1,2,2-tétrafluoroéthoxy, et du trifluorométhyle ;

R_7 et R_{12} sont indépendamment choisis dans le groupe constitué de l'hydrogène, du fluoro et du trifluorométhyle.

8. Composé selon la revendication 1, ou un sel pharmaceutiquement acceptable de celui-ci, dans lequel l'aralkyle d'un ou plusieurs des substituants R_5, R_6, R_7, R_{10}, R_{11}, et R_{12} est substitué avec un à cinq substituants choisis dans le groupe de substituants constitué d'un perhalogénoaralkyle, un aralkylsulfonyle, un aralkylsulfonylalkyle, un aralkylsulfinyle, un aralkylsulfinylalkyle, un halogénocycloalkyle, un halogénocycloalcényle, un cycloalkylsulfinyle, un cycloalkylsulfinylalkyle, un cycloalkylsulfonyle, un cycloalkylsulfonylalkyle, un hétéroarylamino, un N-hétéroarylamino-N-alkylamino, un hétéroarylaminoalkyle, un hétéroaryloxy, un hétéroaryloxylalkyle, un halogénoalkylthio, un alcanoyloxy, un alcoxy, un alcoxyalkyle, un halogénoalcoxylalkyle, un hétéroaralcoxy, un cycloalcoxy, un cycloalcényloxy, un cycloalcoxyalkyle, un cycloalkylalcoxy, un cycloalcényloxyalkyle, un cycloalkylènedioxy, un halogénocycloalcoxy, un halogénocycloalcoxyalkyle, un halogénocycloalcényloxy, un halogénocycloalcényloxyalkyle, un hydroxy, un amino, un thio, un nitro, un alkylamino inférieur, un alkylthio, un alkylthioalkyle, un arylamino, un aralkylamino, un arylthio, un arylthioalkyle, un hétéroaralcoxyalkyle, un alkylsulfinyle, un alkylsulfinylalkyle, un arylsulfinylalkyle, un arylsulfonylalkyle, un hétéroarylsulfinylalkyle, un hétéroarylsulfonylalkyle, un alkylsulfonyle, un alkylsulfonylalkyle, un halogénoalkylsulfinylalkyle, un halogénoalkylsulfonylalkyle, un alkylsulfonamido, un alkylaminosulfonyle, un amidosulfonyle, un monoalkylamidosulfonyle, un dialkylamidosulfonyle, un monoarylamidosulfonyle, un arylsulfonamido, un diarylamidosulfonyle, un monoalkylmonoarylamidosulfonyle, un arylsulfinyle, un arylsulfonyle, un hétéroarylthio, un hétéroarylsulfinyle, un hétéroarylsulfonyle, un alcanoyle, un alcénoyle, un aroyle, un hétéroaroyle, un aralcanoyle, un hétéroaralcanoyle, un halogénoalcanoyle, un alkyle, un alcényle, un alcynyle, un alcényloxy, un alcényloxyalky, un alkylènedioxy, un halogénoalkylènedioxy, un cycloalkyle, un cycloalkylalcanoyle, un cycloalcényle, un cycloalkylalkyle inférieur, un cycloalcénylalkyle inférieur, un halogène, un halogénoalkyle,

un halogénoalcényle, un halogénoalcoxy, un hydroxyhalogénoalkyle, un hydroxyaralkyle, un hydroxyalkyle, un hydroxyhétéroaralkyle, un halogénoalcoxyalkyle, un aryle, un aralkyle, un aryloxy, un aralcoxy, un aryloxyalkyle, un hétérocyclyle saturé, un hétérocyclyle partiellement saturé, un hétéroaryle, un hétéroaryloxy, un hétéroaryloxyalkyle, un arylalkyle, un hétéroarylalkyle, un arylalcényle, un hétéroarylalcényle, un carboxyalkyle, un carboalcoxy, un alcoxycarbonyle, un carboaralcoxy, un carboxamido, un carboxamidoalkyle, un cyano, un carbohalogénoalcoxy, un phosphono, un phosphonoalkyle, un diaralcoxyphosphono, et un diaralcoxyphosphonoalkyle.

9. Composé selon la revendication 1, ou un sel pharmaceutiquement acceptable de celui-ci, dans lequel l'arylamino d'un ou plusieurs des substituants R_5, R_6, R_7, R_{10}, R_{11}, et R_{12} est substitué avec un à cinq substituants choisis dans le groupe de substituants de la revendication 8.

10. Composé selon la revendication 1, ou un sel pharmaceutiquement acceptable de celui-ci, dans lequel l'arylthio d'un ou plusieurs des substituants R_5, R_6, R_7, R_{10}, R_{11} et R_{12} est substitué avec un à cinq substituants choisis dans le groupe de substituants de la revendication 8.

11. Composé selon la revendication 1, ou un sel pharmaceutiquement acceptable de celui-ci, dans lequel l'aroyle d'un ou plusieurs des substituants R_5, R_6, R_7, R_{10}, R_{11}, et R_{12} est substitué avec un à cinq substituants choisis dans le groupe de substituants de la revendication 8.

12. Composé selon la revendication 1, ou un sel pharmaceutiquement acceptable de celui-ci, dans lequel l'alkyle d'un ou plusieurs des substituants R_5, R_6, R_7, R_{10}, R_{11}, et R_{12} est substitué avec un à cinq substituants choisis dans le groupe de substituants de la revendication 8.

13. Composé selon la revendication 1, ou un sel pharmaceutiquement acceptable de celui-ci, dans lequel l'halogénoalcoxy d'un ou plusieurs des substituants R_5, R_6, R_7, R_{10}, R_{11}, et R_{12} est substitué avec un à cinq substituants choisis dans le groupe de substituants de la revendication 8.

14. Composé selon la revendication 1, ou un sel pharmaceutiquement acceptable de celui-ci, dans lequel l'aryle d'un ou plusieurs des substituants R_5, R_6, R_7, R_{10}, R_{11}, et R_{12} est substitué avec un à cinq substituants choisis dans le groupe de substituants de la revendication 8.

15. Composé selon la revendication 1, ou un sel pharmaceutiquement acceptable de celui-ci, dans lequel l'aryloxy d'un ou plusieurs des substituants R_5, R_6, R_7, R_{10}, R_{11}, et R_{12} est substitué avec un à cinq substituants choisis dans le groupe de substituants de la revendication 8.

16. Composé selon la revendication 1, ou un sel pharmaceutiquement acceptable de celui-ci, dans lequel l'aryloxy substitué est choisi dans le groupe constitué du 4-chloro-3-éthylphénoxy, du 4-chloro-3-méthylphénoxy, du 3-chloro-4-éthylphénoxy, du 3,4-dichlorophénoxy, du 4-méthylphénoxy, du 3-trifluorométhoxyphénoxy, du 3-trifluorométhylphénoxy, du 4-fluorophénoxy, du 3,4-diméthylphénoxy, du 5-bromo-2-fluorophénoxy, du 4-bromo-3-fluorophénoxy, du 4-fluoro-3-méthylphénoxy, du 5,6,7,8-tétrahydronaphtyloxy, du 3-isopropylphénoxy, du 3-cyclopropylphénoxy, du 3-éthylphénoxy, du 4-tert-butylphénoxy, du 3-pentafluoroéthylphénoxy, et du 3-(1,1,2,2-tétrafluoroéthoxy)phénoxy.

17. Composé selon la revendication 1, ou un sel pharmaceutiquement acceptable de celui-ci, dans lequel l'aryloxy d'un ou plusieurs des substituants R_5, R_6, R_7, R_{10}, R_{11}, et R_{12} est substitué avec un à cinq substituants choisis dans le groupe de substituants de la revendication 8.

18. Composé selon la revendication 1, ou un sel pharmaceutiquement acceptable de celui-ci, dans lequel l'hétérocyclyle d'un ou plusieurs des substituants R_5, R_6, R_7, R_{10}, R_{11}, et R_{12} est substitué avec un à cinq substituants choisis dans le groupe de substituants de la revendication 8.

19. Composé selon la revendication 1, ou un sel pharmaceutiquement acceptable de celui-ci, dans lequel l'hétéroaryle d'un ou plusieurs des substituants R_5, R_6, R_7, R_{10}, R_{11}, et R_{12} est substitué avec un à cinq substituants choisis dans le groupe de substituants de la revendication 8.

20. Composé selon la revendication 1, ou un sel pharmaceutiquement acceptable de celui-ci, dans lequel l'hétéroaryloxy d'un ou plusieurs des substituants R_5, R_6, R_7, R_{10}, R_{11}, et R_{12} est substitué avec un à cinq substituants choisis dans le groupe de substituants de la revendication 8.

21. Composé selon la revendication 1, ou un sel pharmaceutiquement acceptable de celui-ci, dans lequel l'halogénoalkylthio d'un ou plusieurs des substituants R_5, R_6, R_7, R_{10}, R_{11}, et R_{12} est substitué avec un à cinq substituants choisis dans le groupe de substituants de la revendication 8.

22. Composé selon la revendication 1, ou un sel pharmaceutiquement acceptable de celui-ci, dans lequel l'alcoxy d'un ou plusieurs des substituants R_5, R_6, R_7, R_{10}, R_{11}, et R_{12} est substitué avec un à cinq substituants choisis dans le groupe de substituants de la revendication 8.

23. Composé selon la revendication 1, ou un sel pharmaceutiquement acceptable de celui-ci, dans lequel le cycloalkyle d'un ou plusieurs des substituants R_5, R_6, R_7, R_{10}, R_{11}, et R_{12} est substitué avec un à cinq substituants choisis dans le groupe de substituants de la revendication 8.

24. Composé selon la revendication 1, ou un sel pharmaceutiquement acceptable de celui-ci, dans lequel l'halogénoalkyle d'un ou plusieurs des substituants R_5, R_6, R_7, R_{10}, R_{11}, et R_{12} est substitué avec un à cinq substituants choisis dans le groupe de substituants de la revendication 8.

25. Composition pharmaceutique comprenant une quantité thérapeutiquement efficace d'un composé selon la revendication 1 ou un sel pharmaceutiquement acceptable de celui-ci, conjointement avec un véhicule pharmaceutiquement acceptable.

26. Utilisation d'un composé selon la revendication 1 ou un sel pharmaceutiquement acceptable de celui-ci pour la fabrication d'un médicament pour traiter ou prévenir un trouble véhiculé par CETP (protéine de transfert d'ester de cholestéryle) chez un sujet.

27. Utilisation selon la revendication 26, dans laquelle le traitement d'un trouble véhiculé par CETP est le traitement d'une maladie artérielle coronarienne.

28. Utilisation selon la revendication 26, dans laquelle la prévention d'un trouble véhiculé par CETP est la prévention d'une maladie artérielle coronarienne.

29. Utilisation selon la revendication 26, dans laquelle la prévention d'un trouble véhiculé par CETP est la prévention d'un accident cérébrovasculaire (CVA).

30. Utilisation selon la revendication 26, dans laquelle le traitement d'un trouble véhiculé par CETP est le traitement d'une dyslipidémie.

31. Utilisation selon la revendication 26, dans laquelle la prévention d'un trouble véhiculé par CETP est la prévention d'une dyslipidémie.

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