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Biller et al.

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[45] **Date of Patent: May 23, 2000**

[54] **INHIBITORS OF MICROSOMAL TRIGLYCERIDE TRANSFER PROTEIN AND METHOD**

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[73] Assignee: **Bristol-Myers Squibb Company**, Princeton, N.J.

[21] Appl. No.: **08/898,303**

[22] Filed: **Jul. 21, 1997**

Related U.S. Application Data

[63] Continuation of application No. 08/472,067, Jun. 6, 1995, Pat. No. 5,739,135, which is a continuation-in-part of application No. 08/391,901, Feb. 21, 1995, abandoned, which is a continuation-in-part of application No. 08/284,808, Aug. 5, 1994, abandoned, which is a continuation-in-part of application No. 08/117,362, Sep. 3, 1993, Pat. No. 5,595,872.

[51] **Int. Cl.**[7] **A61K 31/445**; A61K 31/47; A61K 31/52; A61K 31/495; C07D 211/00; C07D 217/00; C07D 215/38; C07D 401/00

[52] **U.S. Cl.** **514/315**; 514/248; 514/252; 514/266; 514/307; 514/314; 514/318; 514/320; 514/321; 514/322; 514/323; 514/324; 514/326; 514/329; 544/235; 544/238; 544/277; 544/407; 546/146; 546/169; 546/194; 546/196; 546/197; 546/198; 546/199; 546/201; 546/202; 546/208; 546/209; 546/211; 546/213; 546/214; 546/223; 546/224

[58] **Field of Search** 514/248, 252, 514/266, 307, 314, 315, 318, 320, 321, 323, 322, 324, 326, 329; 544/235, 238, 277, 407; 546/146, 169, 194, 196, 197, 198, 199, 201, 202, 208, 209, 211, 213, 214, 224, 223

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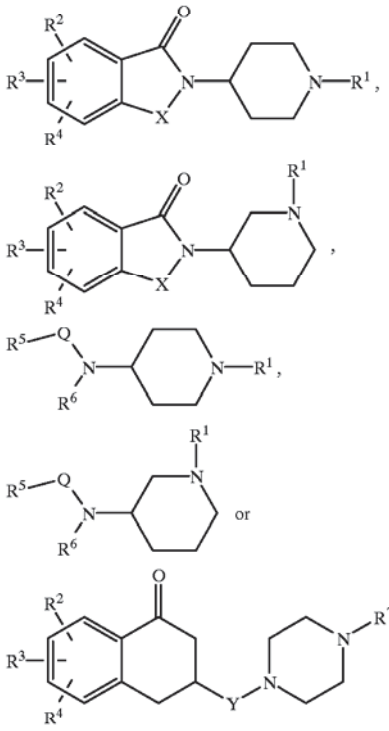
Primary Examiner—Richard L. Raymond
Assistant Examiner—Brenda Coleman
Attorney, Agent, or Firm—Burton Rodney

[57] **ABSTRACT**

Compounds are provided which inhibit microsomal triglyceride transfer protein and thus are useful for lowering serum lipids and treating atherosclerosis and related diseases. The compounds have the structure



wherein R^1 to R^7, Q, X and Y are as defined herein.

2 Claims, No Drawings

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INHIBITORS OF MICROSOMAL TRIGLYCERIDE TRANSFER PROTEIN AND METHOD

CROSS-REFERENCE TO RELATED APPLICATIONS

This is a continuation of application Ser. No. 08/472,067, filed Jun. 6, 1995 now U.S. Pat. No. 5,739,135, which is a continuation-in-part of application Ser. No. 08/391,901, filed Feb. 21, 1995, now abandoned, which is a continuation-in-part of application Ser. No. 08/284,808, filed Aug. 5, 1994, now abandoned, which is a continuation-in-part of application Ser. No. 08/117,362, filed Sep. 3, 1993, now U.S. Pat. No. 5,595,872.

FIELD OF THE INVENTION

This invention relates to novel compounds which inhibit microsomal triglyceride transfer protein, and to methods for decreasing serum lipids and treating atherosclerosis employing such compounds.

BACKGROUND OF THE INVENTION

The microsomal triglyceride transfer protein (MTP) catalyzes the transport of triglyceride (TG), cholesteryl ester (CE), and phosphatidylcholine (PC) between small unilamellar vesicles (SUV). Wetterau & Zilversmit, *Chem. Phys. Lipids* 38, 205–22 (1985). When transfer rates are expressed as the percent of the donor lipid transferred per time, MTP expresses a distinct preference for neutral lipid transport (TG and CE), relative to phospholipid transport. The protein from bovine liver has been isolated and characterized. Wetterau & Zilversmit, *Chem. Phys. Lipids* 38, 205–22 (1985). Polyacrylamide gel electrophoresis (PAGE) analysis of the purified protein suggests that the transfer protein is a complex of two subunits of apparent molecular weights 58,000 and 88,000, since a single band was present when purified MTP was electrophoresed under nondenaturing condition, while two bands of apparent molecular weights 58,000 and 88,000 were identified when electrophoresis was performed in the presence of sodium dodecyl sulfate (SDS). These two polypeptides are hereinafter referred to as 58 kDa and 88 kDa, respectively, or the 58 kDa and the 88 kDa component of MTP, respectively, or the low molecular weight subunit and the high molecular weight subunit of MTP, respectively.

Characterization of the 58,000 molecular weight component of bovine MTP indicates that it is the previously characterized multifunctional protein, protein disulfide isomerase (PDI). Wetterau et al., *J. Biol. Chem.* 265, 9800–7 (1990). The presence of PDI in the transfer protein is supported by evidence showing that (1) the amino terminal 25 amino acids of the bovine 58,000 kDa component of MTP is identical to that of bovine PDI, and (2) disulfide isomerase activity was expressed by bovine MTP following the dissociation of the 58 kDa–88 kDa protein complex. In addition, antibodies raised against bovine PDI, a protein which by itself has no TG transfer activity, were able to immunoprecipitate bovine TG transfer activity from a solution containing purified bovine MTP.

PDI normally plays a role in the folding and assembly of newly synthesized disulfide bonded proteins within the lumen of the endoplasmic reticulum. Bulleid & Freedman, *Nature* 353, 649–51 (1988). It catalyzes the proper pairing of cysteine residues into disulfide bonds, thus catalyzing the proper folding of disulfide bonded proteins. In addition, PDI has been reported to be identical to the beta subunit of human prolyl 4-hydroxylase. Koivu et al., *J. Biol. Chem.* 262, 6447–9 (1987). The role of PDI in the bovine transfer protein is not clear. It does appear to be an essential component of the transfer protein as dissociation of PDI from the 88 kDa component of bovine MTP by either low concentrations of a denaturant (guanidine HCl), a chaotropic agent (sodium perchlorate), or a nondenaturing detergent (octyl glucoside) results in a loss of transfer activity. Wetterau et al., *Biochemistry* 30, 9728–35 (1991). Isolated bovine PDI has no apparent lipid transfer activity, suggesting that either the 88 kDa polypeptide is the transfer protein or that it confers transfer activity to the protein complex.

The tissue and subcellular distribution of MTP activity in rats has been investigated. Wetterau & Zilversmit, *Biochem. Biophys. Acta* 875, 610–7 (1986). Lipid transfer activity was found in liver and intestine. Little or no transfer activity was found in plasma, brain, heart, or kidney. Within the liver, MTP was a soluble protein located within the lumen of the microsomal fraction. Approximately equal concentrations were found in the smooth and rough microsomes.

Abetalipoproteinemia is an autosomal recessive disease characterized by a virtual absence of plasma lipoproteins which contain apolipoprotein B (apoB). Kane & Havel in *The Metabolic Basis of Inherited Disease*, Sixth edition, 1139–64 (1989). Plasma TG levels may be as low as a few mg/dL, and they fail to rise after fat ingestion. Plasma cholesterol levels are often only 20–45 mg/dL. These abnormalities are the result of a genetic defect in the assembly and/or secretion of very low density lipoproteins (VLDL) in the liver and chylomicrons in the intestine. The molecular basis for this defect has not been previously determined. In subjects examined, triglyceride, phospholipid, and cholesterol synthesis appear normal. At autopsy, subjects are free of atherosclerosis. Schaefer et al., *Clin. Chem.* 34, B9–12 (1988). A link between the apoB gene and abetalipoproteinemia has been excluded in several families. Talmud et al., *J. Clin. Invest.* 82, 1803–6 (1988) and Huang et al., *Am. J. Hum. Genet.* 46, 1141–8 (1990).

Subjects with abetalipoproteinemia are afflicted with numerous maladies. Kane & Havel, supra. Subjects have fat malabsorption and TG accumulation in their enterocytes and hepatocytes. Due to the absence of TG-rich plasma lipoproteins, there is a defect in the transport of fat-soluble vitamins such as vitamin E. This results in acanthocytosis of erythrocytes, spinocerebellar ataxia with degeneration of the fasciculus cuneatus and gracilis, peripheral neuropathy, degenerative pigmentary retinopathy, and ceroid myopathy. Treatment of abetalipoproteinemic subjects includes dietary restriction of fat intake and dietary supplementation with vitamins A, E and K.

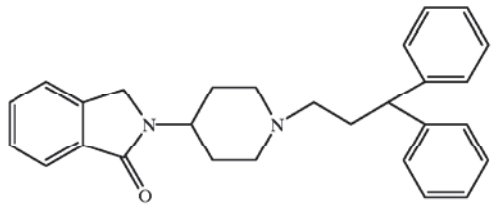
In vitro, MTP catalyzes the transport of lipid molecules between phospholipid membranes. Presumably, it plays a similar role in vivo, and thus plays some role in lipid metabolism. The subcellular (lumen of the microsomal fraction) and tissue distribution (liver and intestine) of MTP have led to speculation that it plays a role in the assembly of plasma lipoproteins, as these are the sites of plasma lipoprotein assembly. Wetterau & Zilversmit, *Biochem. Biophys. Acta* 875, 610–7 (1986). The ability of MTP to catalyze the transport of TG between membranes is consistent with this hypothesis, and suggests that MTP may catalyze the transport of TG from its site of synthesis in the endoplasmic reticulum (ER) membrane to nascent lipoprotein particles within the lumen of the ER.

Olofsson and colleagues have studied lipoprotein assembly in HepG2 cells. Bostrom et al., *J. Biol. Chem.* 263,

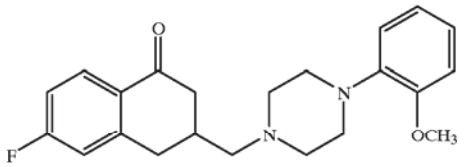
4434–42 (1988). Their results suggest small precursor lipoproteins become larger with time. This would be consistent with the addition or transfer of lipid molecules to nascent lipoproteins as they are assembled. MTP may play a role in this process. In support of this hypothesis, Howell and Palade, *J. Cell Biol.* 92, 833–45 (1982), isolated nascent lipoproteins from the hepatic Golgi fraction of rat liver. There was a spectrum of sizes of particles present with varying lipid and protein compositions. Particles of high density lipoprotein (HDL) density, yet containing apoB, were found. Higgins and Hutson, *J. Lipid Res.* 25, 1295–1305 (1984), reported lipoproteins isolated from Golgi were consistently larger than those from the endoplasmic reticulum, again suggesting the assembly of lipoproteins is a progressive event.

Recent reports (Science, Vol. 258, page 999, 1992; D. Sharp et. al., Nature, Vol. 365, page 65, 1993) demonstrate that the defect causing abetalipoproteinemia is in the MTP gene, and as a result, the MTP protein. Individuals with abetalipoproteinemia have no MTP activity, as a result of mutations in the MTP gene, some of which have been characterized. These results indicate that MTP is required for the synthesis of apoB containing lipoproteins, such as VLDL, the precursor to LDL. It therefore follows that inhibitors of MTP would inhibit the synthesis of VLDL and LDL, thereby lowering VLDL levels, LDL levels, cholesterol levels, and triglyceride levels in animals and man.

Canadian Patent Application No. 2,091,102 published Mar. 2, 1994 (corresponding to U.S. application Ser. No. 117,362, filed Sep. 3, 1993 (file DC21b)) reports MTP inhibitors which also block the production of apoB containing lipoproteins in a human hepatic cell line (HepG2 cells). This provides further support for the proposal that an MTP inhibitor would lower apoB containing lipoprotein and lipid levels in vivo. This Canadian patent application discloses a method for identifying the MTP inhibitors



which has the name 2-[1-(3,3-diphenylpropyl)-4-piperidinyl]-2,3-dihydro-3-oxo-1H-isoindole hydrochloride and

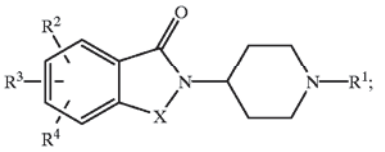


which has the name 1-[3-(6-fluoro-1-tetralanyl)methyl]-4-O-methoxyphenyl piperazine

SUMMARY OF THE INVENTION

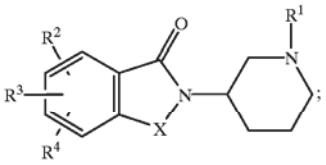
In accordance with the present invention, novel compounds are provided which are inhibitors of MTP and have the structure

I



or

Ii



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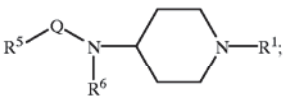
II



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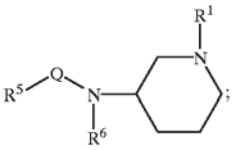
IIi



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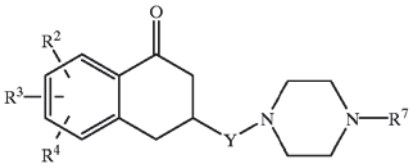
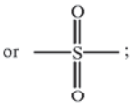
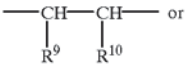
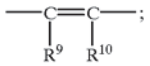
III

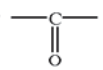


where Q is  ;

X is: CHR^8,  ;



R^8, R^9 and R^{10} are independently hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, cycloalkyl, or cycloalkylalkyl;

Y is  or

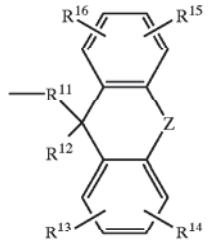
where m is 2 or 3;

R^1 is alkyl, alkenyl, alkynyl, aryl, heteroaryl, arylalkyl (wherein alkyl has at least 2 carbons, preferably at least

3 carbons), diarylalkyl, arylalkenyl, diarylalkenyl, arylalkynyl, diarylalkynyl, diarylalkylaryl, heteroarylalkyl (wherein alkyl has at least 2 carbons, preferably at least 3 carbons), cycloalkyl, or cycloalkylalkyl (wherein alkyl has at least 2 carbons, preferably at least 3 carbons); all of the aforementioned R^1 groups being optionally substituted through available carbon atoms with 1, 2, 3 or 4 groups selected from halo, haloalkyl, alkyl, alkenyl, alkoxy, aryloxy, aryl, arylalkyl, alkylmercapto, arylmercapto, cycloalkyl, cycloalkyl-alkyl, heteroaryl, fluorenyl, heteroarylalkyl, hydroxy or oxo; or

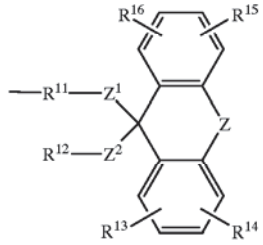
R^1 is a fluorenyl-type group of the structure

A



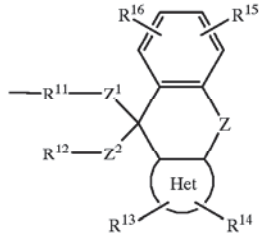
or

B



or

C



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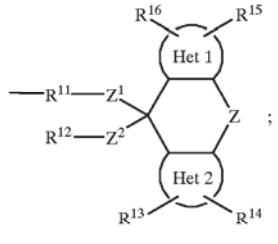
D

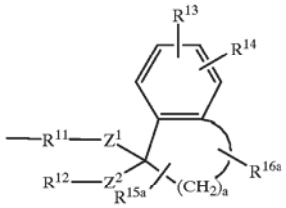


or

R^1 is an indenyl-type group of the structure

-continued

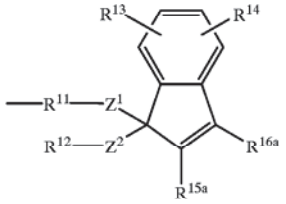
E



(a = 2, 3 or 4)

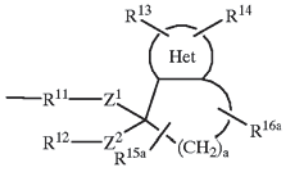
or

F



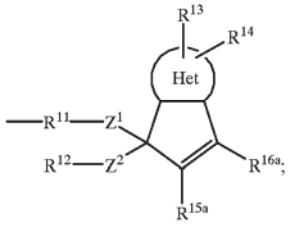
or

G

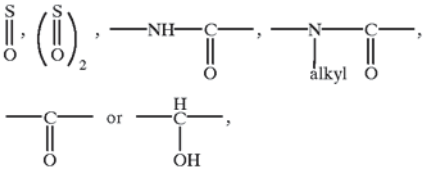


or

H



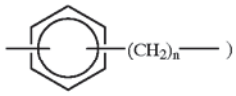
Z^1 and Z^2 are the same or different and are independently a bond, O, S,



with the proviso that with respect to B, at least one of Z^1 and Z^2 will be other than a bond;

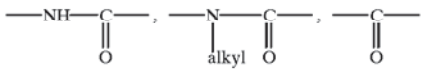
R^{11} is a bond, alkylene, alkenylene or alkynylene of up to 10 carbon atoms, arylene (for example

or mixed arylene-alkylene (for example



where n is 1 to 6;

R^{12} is hydrogen, alkyl, alkenyl, aryl, haloalkyl, trihaloalkyl, trihaloalkylalkyl, heteroaryl, heteroarylalkyl, arylalkyl, arylalkenyl, cycloalkyl, aryloxy, alkoxy, arylalkoxy or cycloalkylalkyl; with the provisos that (1) when R^{12} is H, aryloxy, alkoxy or arylalkoxy, then Z^2 is



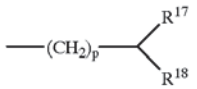
and (2) when Z^2 is a bond, R^{12} cannot be heteroaryl or heteroarylalkyl;

Z is a bond, O, S, N-alkyl, N-aryl, or alkylene or alkenylene of from 1 to 5 carbon atoms;

R^{13}, R^{14}, R^{15}, and R^{16} are independently hydrogen, alkyl, halo, haloalkyl, aryl, cycloalkyl, cycloheteroalkyl, alkenyl, alkynyl, hydroxy, alkoxy, nitro, amino, thio, alkylsulfonyl, arylsulfonyl, alkylthio, arylthio, aminocarbonyl, alkylcarbonyloxy, arylcarbonylamino, alkylcarbonylamino, arylalkyl, heteroaryl, heteroarylalkyl, or aryloxy;

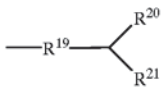
R^{15a} and R^{16a} are independently any of the R^{15} or R^{16} groups except hydroxy, nitro, amino or thio;

or R^1 is



wherein p is 1 to 8 and R^{17} and R^{18} are each independently H, alkyl, alkenyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, cycloalkyl or cycloalkylalkyl, at least one of R^{17} and R^{18} being other than H;

or R^1 is



wherein R^{19} is aryl or heteroaryl;

R^{20} is aryl or heteroaryl;

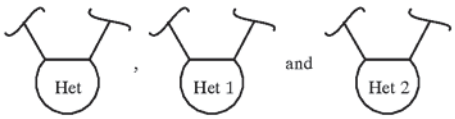
R^{21} is H, alkyl, aryl, alkylaryl, arylalkyl, aryloxy, arylalkoxy, heteroaryl, heteroarylalkyl, heteroarylalkoxy, cycloalkyl, cycloalkylalkyl or cycloalkylalkoxy;

R^2, R^3, R^4 are independently hydrogen, halo, alkyl, alkenyl, alkoxy, aryloxy, aryl, arylalkyl, alkylmercapto, arylmercapto, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroarylalkyl, hydroxy or haloalkyl;

R^5 is alkyl, alkenyl, alkynyl, aryl, alkoxy, aryloxy, arylalkoxy, heteroaryl, arylalkyl, heteroarylalkyl, cycloalkyl, cycloheteroalkyl, heteroaryloxy, cycloalkylalkyl, polycycloalkyl, polycycloalkylalkyl, cycloalkenyl, cycloalkenylalkyl, polycycloalkenyl, polycycloalkenylalkyl, heteroarylcarbonyl, amino, alkylamino, arylamino, heteroarylamino, cycloalkyloxy, cycloalkylamino, all of the R^5 substituents and R^6 substituents (set out hereinafter) being optionally substituted through available carbon atoms with 1, 2, 3 or 4 groups selected from hydrogen, halo, alkyl, haloalkyl, alkoxy, haloalkoxy, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, cycloheteroalkyl, cycloheteroalkylalkyl, aryl, heteroaryl, arylalkyl, arylcycloalkyl, arylalkenyl, arylalkynyl, aryloxy, aryloxyalkyl, arylalkoxy, arylazo, heteroaryloxo, heteroaryl-alkyl, heteroarylalkenyl, heteroaryloxy, hydroxy, nitro, cyano, amino, substituted amino (wherein the amino includes 1 or 2 substituents which are alkyl, aryl or heteroaryl, or any of the other aryl compounds mentioned in the definitions), thiol, alkylthio, arylthio, heteroarylthio, arylthioalkyl, alkylcarbonyl, arylcarbonyl, arylaminocarbonyl, alkoxycarbonyl, aminocarbonyl, alkynylaminocarbonyl, alkylaminocarbonyl, alkenylaminocarbonyl, alkylcarbonyloxy, arylcarbonyloxy, alkylcarbonylamino, arylcarbonylamino, arylsulfinyl, arylsulfinylalkyl, arylsulfonyl, alkylsulfonyl, arylsulfonylamino, heteroarylcarbonylamino, heteroarylsulfinyl, heteroarylthio, heteroarylsulfonyl, or alkylsulfinyl. Where R^5 is phenyl, aryl, heteroaryl or cycloalkyl; this group preferably includes an ortho hydrophobic substituent such as alkyl, haloalkyl (with up to 5 halo groups), alkoxy, haloalkoxy (with up to 5 halo groups), aryl, aryloxy or arylalkyl;

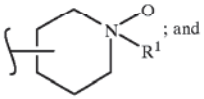
R^6 is hydrogen or C_1–C_4 alkyl or C_1–C_4 alkenyl;

R^7 is alkyl, aryl or arylalkyl wherein alkyl or the alkyl portion is optionally substituted with oxo; and



are the same or different and are independently selected from heteroaryl containing 5- or 6-ring members; and

including N-oxides of the formulae I, Ii, II and IIi compounds, that is



including pharmaceutically acceptable salts thereof such as alkali metal salts such as lithium sodium or potassium, alkaline earth metal salts such as calcium or magnesium, as well as zinc or aluminum and other cations such as ammonium, choline, diethanolamine, ethylenediamine, t-butylamine, t-octylamine, dehydroabietylamine, as well as pharmaceutically acceptable anions such as chloride, bromide, iodide, tartrate, acetate, methanesulfonate, maleate, succinate,

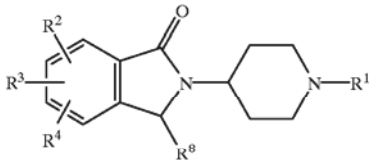
glutarate, and salts of naturally occurring amino acids such as arginine, lysine, alanine and the like, and prodrug esters thereof.

In the formula I compounds, where X is CH_2 and R^2, R^3 and R^4 are each H, R^1 will be other than 3,3-diphenylpropyl.

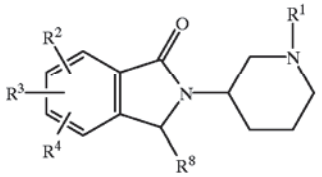
In the formula III compounds, where one of R^2, R^3 and R^4 is 6-fluoro, and the others are H, R^7 will be other than 4-(2-methoxy)phenyl.

Thus, the compounds of formulae I and II of the invention encompass compounds of the structure

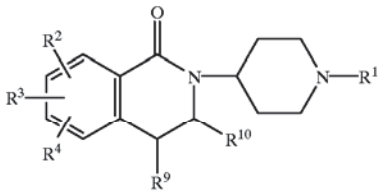
I^a



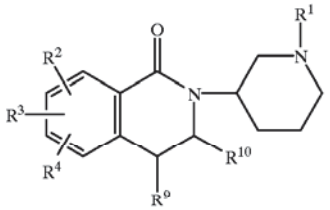
I_1^a



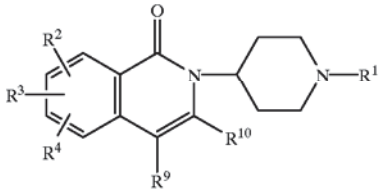
I^b



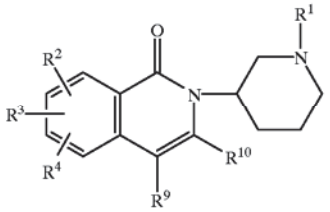
I_1^b



I^c



I_1^c



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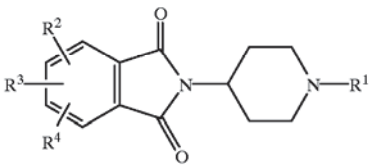
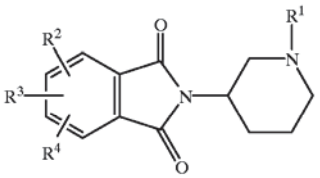
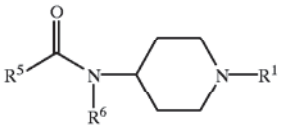
I^d



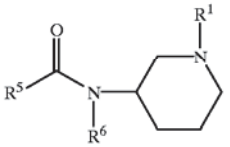
I_1^d



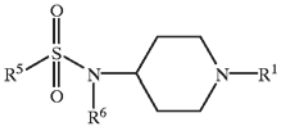
II^a



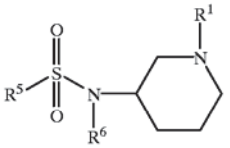
II_1^a



II^b

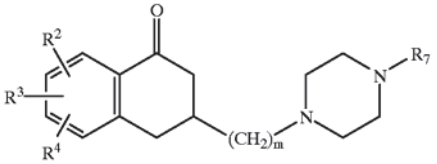


II_1^b

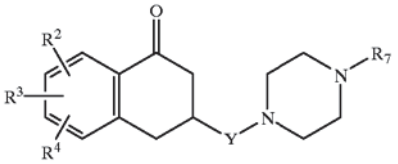


The compounds of formula III of the invention encompass compounds of the structure III^a

III^a



III^b



In addition, in accordance with the present invention, a method for preventing, inhibiting or treating atherosclerosis, pancreatitis or obesity is provided, wherein a compound of

formula I, Ii, II, IIi or III as defined hereinbefore wherein R^1 also includes arylmethyl, heteroarylmethyl and cycloalkylmethyl and Y also includes —CH_2—, is administered in an amount which decreases the activity of microsomal triglyceride transfer protein.

Furthermore, in accordance with the present invention, a method is provided for lowering serum lipid levels, cholesterol and/or triglycerides, or inhibiting and/or treating hyperlipemia, hyperlipidemia, hyperlipoproteinemia, hypercholesterolemia and/or hypertriglyceridemia, wherein a compound of formula I, Ii, II, IIi or III as defined hereinbefore wherein R^1 also includes arylmethyl, heteroarylmethyl, and cycloalkylmethyl, and Y also includes —CH_2—, is administered in an amount which decreases the activity of microsomal triglyceride transfer protein.

DETAILED DESCRIPTION OF THE INVENTION

The following definitions apply to the terms as used throughout this specification, unless otherwise limited in specific instances.

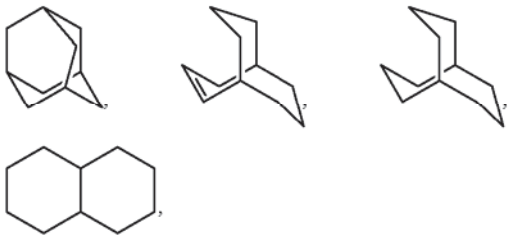
The term "MTP" refers to a polypeptide or protein complex that (1) if obtained from an organism (e.g., cows, humans, etc.), can be isolated from the microsomal fraction of homogenized tissue; and (2) stimulates the transport of triglycerides, cholesterol esters, or phospholipids from synthetic phospholipid vesicles, membranes or lipoproteins to synthetic vesicles, membranes, or lipoproteins and which is distinct from the cholesterol ester transfer protein [Drayna et al., *Nature* 327, 632–634 (1987)] which may have similar catalytic properties. However, the MTP molecules of the present invention do not necessarily need to be catalytically active. For example, catalytically inactive MTP or fragments thereof may be useful in raising antibodies to the protein.

The phrase "stabilizing" atherosclerosis as used in the present application refers to slowing down the development of and/or inhibiting the formation of new atherosclerotic lesions.

The phrase "causing the regression of" atherosclerosis as used in the present application refers to reducing and/or eliminating atherosclerotic lesions.

Unless otherwise indicated, the term "lower alkyl", "alkyl" or "alk" as employed herein alone or as part of another group includes both straight and branched chain hydrocarbons, containing 1 to 40 carbons, preferably 1 to 20 carbons, more preferably 1 to 12 carbons, in the normal chain,such as methyl, ethyl, propyl, isopropyl, butyl, t-butyl, isobutyl, pentyl, hexyl, isohexyl, heptyl, 4,4-dimethylpentyl, octyl, 2,2,4-trimethylpentyl, nonyl, decyl, undecyl, dodecyl, the various branched chain isomers thereof, and the like as well as such groups including 1 to 4 substituents such as halo, for example F, Br, Cl or I or CF_3, alkoxy, aryl, aryloxy, aryl(aryl) or diaryl, arylalkyl, arylalkyloxy, alkenyl, cycloalkyl, cycloalkylalkyl, cycloalkylalkyloxy, amino, hydroxy, acyl, heteroaryl, heteroaryloxy, heteroarylalkyl, heteroarylalkoxy, aryloxyalkyl, aryloxyaryl, alkylamido, alkanoylamino, arylcarbonylamino, nitro, cyano, thiol, haloalkyl, trihaloalkyl and/or alkylthio, as well as any of the other substituents as defined for R^5 and R^6.

Unless otherwise indicated, the term "cycloalkyl" as employed herein alone or as part of another group includes saturated or partially unsaturated (containing 1 or 2 double bonds) cyclic hydrocarbon groups containing 1 to 3 rings, including monocyclicalkyl, bicyclicalkyl and tricyclicalkyl, containing a total of 3 to 20 carbons forming the rings, preferably 4 to 12 carbons, forming the ring and which may be fused to 1 or 2 aromatic rings as described for aryl, which include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclodecyl and cyclododecyl, cyclohexenyl,



any of which groups may be optionally substituted with 1 to 4 substituents such as halogen, alkyl, alkoxy, hydroxy, aryl, aryloxy, arylalkyl, cycloalkyl, alkylamido, alkanoylamino, oxo, acyl, arylcarbonylamino, amino, nitro, cyano, thiol and/or alkylthio, as well as any of the other substituents as defined for R^5 or R^6.

The term "cycloalkenyl" as employed herein alone or as part of another group refers to cyclic hydrocarbons containing 5 to 20 carbons, preferably 6 to 12 carbons and 1 or 2 double bonds. Exemplary cycloalkenyl groups include cyclopentenyl, cyclohexenyl, cycloheptenyl, cyclooctenyl, cyclohexadienyl, and cycloheptadienyl, which may be optionally substituted as defined for cycloalkyl.

The term "polycycloalkyl" as employed herein alone or as part of another group refers to a bridged multicyclic group containing 5 to 20 carbons and containing 0 to 3 bridges, preferably 6 to 12 carbons and 1 or 2 bridges. Exemplary polycycloalkyl groups include [3.3.0]-bicyclooctanyl, adamantanyl, [2.2.1]-bicycloheptanyl, [2.2.2]-bicyclooctanyl and the like and may be optionally substituted as defined for cycloalkyl.

The term "polycycloalkenyl" as employed herein alone or as part of another group refers to bridged multicyclic group containing 5 to 20 carbons and containing 0 to 3 bridges and containing 1 or 2 double bonds, preferably 6 to 12 carbons and 1 or 2 bridges. Exemplary polycycloalkyl groups include [3.3.0]-bicyclooctenyl, [2.2.1]-bicycloheptenyl, [2.2.2]-bicyclooctenyl and the like and may be optionally substituted as defined for cycloalkyl.

The term "aryl" or "Ar" as employed herein alone or as part of another group refers to monocyclic and bicyclic aromatic groups containing 6 to 10 carbons in the ring portion (such as phenyl or naphthyl) and may optionally include one to three additional rings fused to Ar (such as aryl, cycloalkyl, heteroaryl or cycloheteroalkyl rings) and may be optionally substituted through available carbon atoms with 1, 2, 3 or 4 groups selected from hydrogen, halo, haloalkyl, alkyl, haloalkyl, alkoxy, haloalkoxy, alkenyl, trifluoromethyl, trifluoromethoxy, alkynyl, cycloalkylalkyl, cycloheteroalkyl, cycloheteroalkylalkyl, aryl, heteroaryl, arylalkyl, aryloxy, aryloxyalkyl, arylalkoxy, arylthio, arylazo, heteroarylalkyl, heteroarylalkenyl, heteroarylheteroaryl, heteroaryloxy, hydroxy, nitro, cyano, amino, substituted amino wherein the amino includes 1 or 2 substituents (which are alkyl, aryl or any of the other aryl compounds mentioned in the definitions), thiol, alkylthio, arylthio, heteroarylthio, arylthioalkyl, alkoxyarylthio, alkylcarbonyl, arylcarbonyl, alkylaminocarbonyl, arylaminocarbonyl, alkoxycarbonyl, aminocarbonyl, alkylcarbonyloxy, arylcarbonyloxy, alkylcarbonylamino, arylcarbonylamino, arylsulfinyl, arylsulfinylalkyl, arylsulfonylamino or arylsulfonaminocarbonyl, or any of the substituents as defined for the R^5 or R^6 groups set out above.

The term "aralkyl", "aryl-alkyl" or "aryllower alkyl" as used herein alone or as part of another group refers to alkyl groups as discussed above having an aryl substituent, such as benzyl or phenethyl, or naphthylpropyl, or an aryl as defined above.

The term "lower alkoxy", "alkoxy", "aryloxy" or "aralkoxy" as employed herein alone or as part of another group includes any of the above alkyl, aralkyl or aryl groups linked to an oxygen atom.

The term "amino" as employed herein alone or as part of another group may optionally be substituted with one or two substituents such as alkyl and/or aryl.

The term "lower alkylthio", alkylthio", "arylthio" or "aralkylthio" as employed herein alone or as part of another group includes any of the above alkyl, aralkyl or aryl groups linked to a sulfur atom.

The term "lower alkylamino", "alkylamino", "arylamino", or "arylalkylamino" as employed herein alone or as part of another group includes any of the above alkyl, aryl or arylalkyl groups linked to a nitrogen atom.

The term "acyl" as employed herein by itself or part of another group as defined herein, refers to an organic radical linked to a carbonyl

group, examples of acyl groups include alkanoyl, alkenoyl, aroyl, aralkanoyl, heteroaroyl, cycloalkanoyl and the like.

The term "alkanoyl" as used herein alone or as part of another group refers to alkyl linked to a carbonyl group.

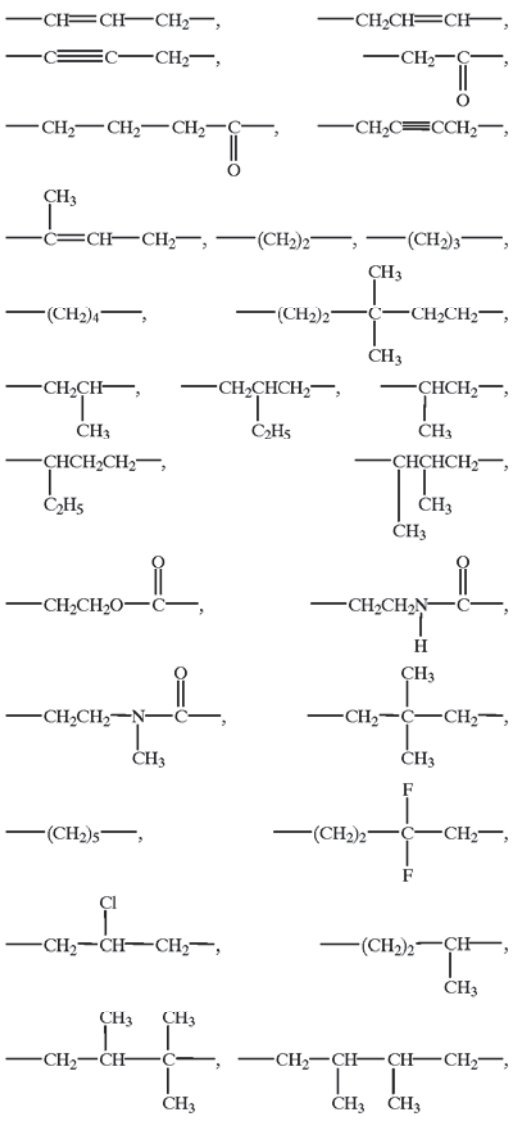
Unless otherwise indicated, the term "lower alkenyl" or "alkenyl" as used herein by itself or as part of another group refers to straight or branched chain radicals of 2 to 20 carbons, preferably 3 to 12 carbons, and more preferably 1 to 8 carbons in the normal chain, which include one to six double bonds in the normal chain, such as vinyl, 2-propenyl, 3-butenyl, 2-butenyl, 4-pentenyl, 3-pentenyl, 2-hexenyl, 3-hexenyl, 2-heptenyl, 3-heptenyl, 4-heptenyl, 3-octenyl, 3-nonenyl, 4-decenyl, 3-undecenyl, 4-dodecenyl, 4,8,12-tetradecatrienyl, and the like, and which may be optionally substituted with 1 to 4 substituents, namely, halogen, haloalkyl, alkyl, alkoxy, alkenyl, alkynyl, aryl, arylalkyl, cycloalkyl, amino, hydroxy, heteroaryl, cycloheteroalkyl, alkanoylamino, alkylamido, arylcarbonylamino, nitro, cyano, thiol and/or alkylthio, as well as any of the other substituents as defined for R^5 or R^6.

Unless otherwise indicated, the term "lower alkynyl" or "alkynyl" as used herein by itself or as part of another group refers to straight or branched chain radicals of 2 to 20 carbons, preferably 2 to 12 carbons and more preferably 2 to 8 carbons in the normal chain, which include one triple bond in the normal chain, such as 2-propynyl, 3-butynyl, 2-butynyl, 4-pentynyl, 3-pentynyl, 2-hexynyl, 3-hexynyl, 2-heptynyl, 3-heptynyl, 4-heptynyl, 3-octynyl, 3-nonynyl, 4-decynyl, 3-undecynyl, 4-dodecynyl and the like, and which may be optionally substituted with 1 to 4 substituents, namely, halogen, haloalkyl, alkyl, alkoxy, alkenyl, alkynyl, aryl, arylalkyl, cycloalkyl, amino, heteroaryl, cycloheteroalkyl, hydroxy, alkanoylamino, alkylamido, arylcarbonylamino, nitro, cyano, thiol, and/or alkylthio, as well as any of the other substituents as defined for R^5 or R^6.

The term "alkylene" as employed herein alone or as part of another group (which also encompasses "alkyl" as part of another group such as arylalkyl or heteroarylalkyl) refers to alkyl groups as defined above having single bonds for attachment to other groups at two different carbon atoms and may optionally be substituted as defined above for "alkyl". The definition of alkylene applies to an alkyl group which links one function to another, such as an arylalkyl substituent.

Ther terms "alkenylene" and "alkynylene" as employed herein alone or as part of another group (which also encompass "alkenyl" or "alkynyl" as part of another group such as arylalkenyl or arylalkynyl), refer to alkenyl groups as defined above and alkynyl groups as defined above, respectively, having single bonds for attachment at two different carbon atoms.

Suitable alkylene, alkenylene or alkynylene groups or $(CH_2)_m$, $(CH_2)_n$ or $(CH_2)_p$ (which may include alkylene, alkenylene or alkynylene groups) as defined herein, may optionally include 1,2, or 3 alkyl, alkoxy, aryl, heteroaryl, cycloheteroalkyl, alkenyl, alkynyl, oxo, aryloxy, hydroxy, halogen substituents as well as any of the substituents defined for R^5 or R^6, and in addition, may have one of the carbon atoms in the chain replaced with an oxygen atom, N—H, N-alkyl or N-aryl. Examples of alkylene, alkenylene, alkynylene, $(CH_2)_m$, $(CH_2)_n$ and $(CH_2)_p$ groups include



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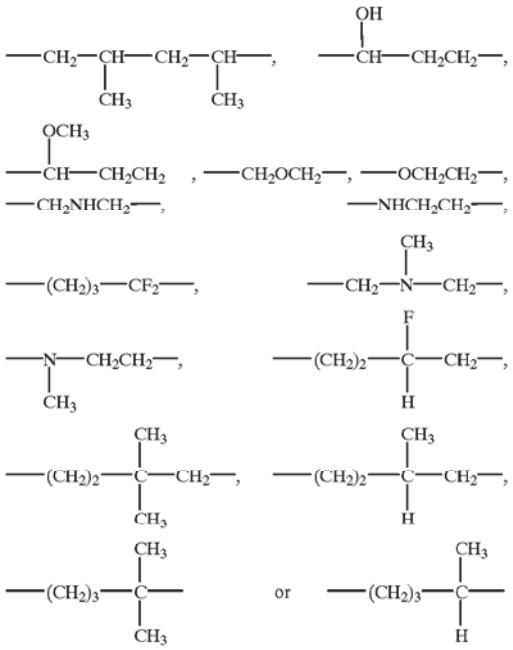
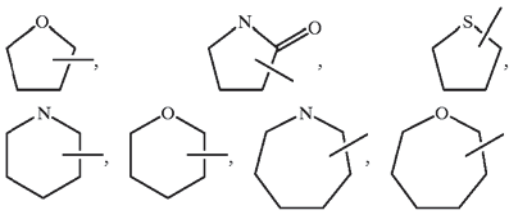


The term "halogen" or "halo" as used herein alone or as part of another group refers to chlorine, bromine, fluorine, and iodine as well as CF_3, with chlorine or fluorine being preferred.

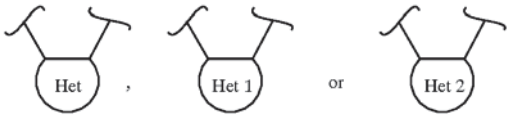
The term "metal ion" refers to alkali metal ions such as sodium, potassium or lithium and alkaline earth metal ions such as magnesium and calcium, as well as zinc and aluminum.

The term "cycloheteroalkyl" as used herein alone or as part of another group refers to a 5-, 6- or 7-membered saturated or partially unsaturated ring which includes 1 to 2 hetero atoms such as nitrogen, oxygen and/or sulfur, linked through a carbon atom or a heteroatom, where possible, optionally via the linker $(CH_2)_p$ (which is defined above), such as

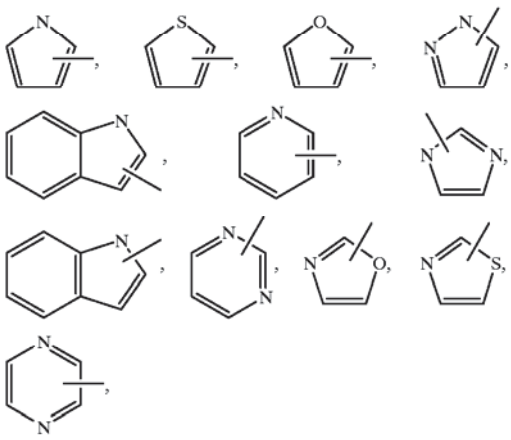


and the like. The above groups may include 1 to 3 substituents such as any of the R^1, R^5 or R^6 groups as defined above. In addition, any of the above rings can be fused to 1 or 2 cycloalkyl, aryl, heteroaryl or cycloheteroalkyl rings.

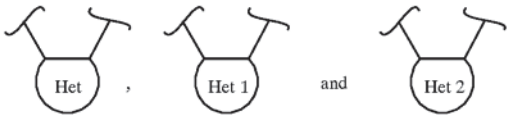
The term "heteroaryl" or



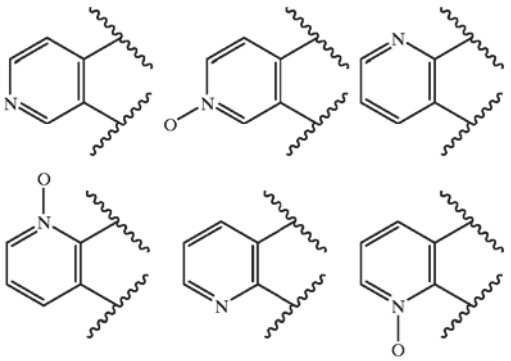
(also referred to as heteroaryl) as used herein alone or as part of another group refers to a 5- or 6-membered aromatic ring which includes 1, 2, 3 or 4 hetero atoms such as nitrogen, oxygen or sulfur, and such rings fused to an aryl, cycloalkyl, heteroaryl or cycloheteroalkyl ring (e.g. benzothiophenyl, indolyl), linked through a carbon atom or a heteroatom, where possible, optionally via the linker $(CH_2)_p$ (which is defined above), such as



and the like, and includes all possible N-oxide derivatives.



are the same or different as defined hereinbefore and are attached to the central ring of the indenyl or fluorenyl type group at adjacent positions (that is ortho or 1,2-positions). Examples of such groups include



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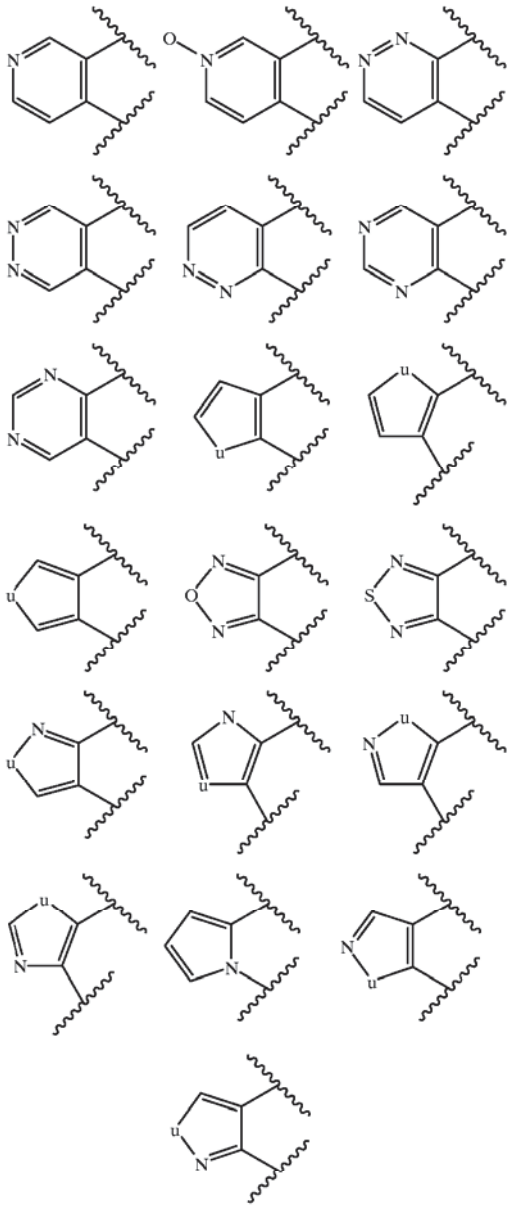


wherein u is selected from O, S, and NR^{7a};

R^{7a} is H, lower alkyl, aryl, —C(O)R^{7b}, —C(O)OR^{7b};

R^{7b} is alkyl or aryl, and includes all possible N-oxide derivatives.

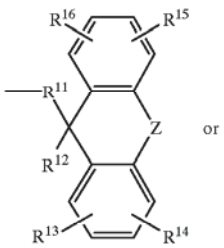
The heteroaryl groups including the above groups may optionally include 1 to 4 substituents such as any of the substituents listed for aryl, or those substituents indicated for R^5 or R^6 groups as defined above. In addition, any of the above rings can be fused to a cycloalkyl, aryl, heteroaryl or cycloheteroalkyl ring.

The term cycloheteroalkylalkyl" as used herein alone or as part of another group refers to cycloheteroalkyl groups as defined above linked through a C atom or heteroatom to a $(CH_2)_p$ chain.

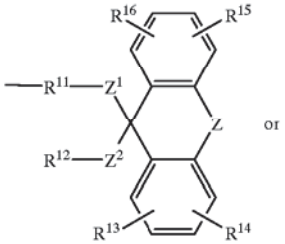
The term "heteroarylalkyl" or "heteroarylalkenyl" as used herein alone or as part of another group refers to a heteroaryl group as defined above linked through a C atom or heteroatom to a —$(CH_2)_p$— chain, alkylene or alkenylene as defined above.

The term "fluorenyl" or "fluorenyl analog" or "fluorenyl-type group" as employed herein refers to a group of the structure:

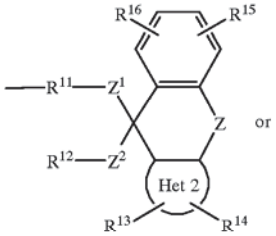
A



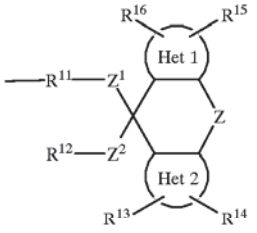
B



C

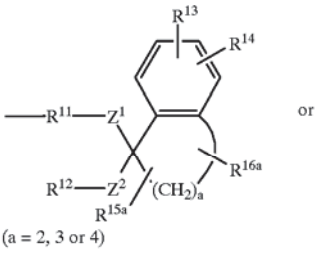


D



The term "indenyl-type group" as employed herein refers to a group of the structure

E



(a = 2, 3 or 4)

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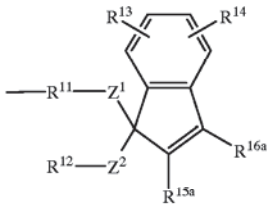
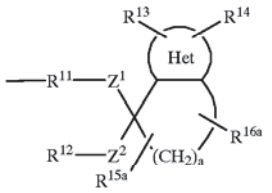
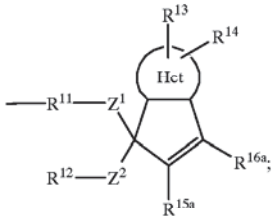


or



or

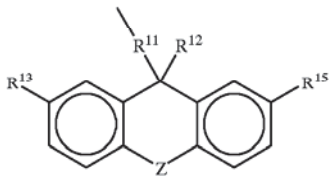


Z, Z^1, Z^2, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, R^{15a} and R^{16a} as used in the above groups A through H are as defined hereinbefore.

Preferred are compounds of formulae I and II wherein

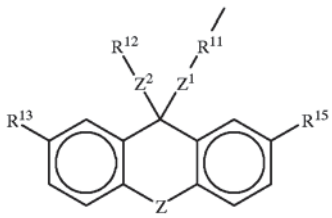
R^1 is arylalkyl, arylalkenyl, heteroarylalkyl, heteroarylalkenyl,

A'



or

B'

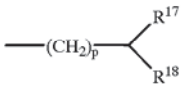


(including where Z^1 is a bond and R^{11} is alkylene or alkenylene and Z^2 is

F

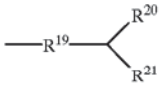
and R^{12} is C_1–C_3 alkyl or 1,1,1-trifluoroethyl, R^{13} is H or F and R^{15} is H or F, and Z is a bond or O; and where R^{11} is alkylene or alkenylene or alkylene substituted with oxo, R^{12} is alkyl, alkenyl, aralkyl, aralkenyl, Z is O, S or a bond); or

G



(wherein R^{17} and R^{18} are each independently alkyl, alkenyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, cycloalkyl or cycloalkylalkyl); or

H



wherein

R^{19} is aryl or heteroaryl;

R^{20} is aryl or heteroaryl;

R^{21} is alkyl, aryl, alkylaryl, arylalkyl aryloxy, arylalkoxy, heteroaryl, heteroarylalkyl, heteroarylalkoxy, cycloalkyl, cycloalkylalkyl or cycloalkylalkoxy.

In structure I, it is preferred that R^2, R^3 and R^4 are each H and X is CH_2, CH_2CH_2, or CH═CH.

In structure II, it is preferred that R^6 is H or CH_3 and R^5 is cycloalkyl, phenyl, aryl or heteroaryl, or cycloalkyl, phenyl, aryl heteroaryl having an ortho hydrophobic substituent which is alkyl, alkoxy, haloalkyl (containing up to five halo groups), trifluoromethyl, aryl, aryloxy, arylalkyl, arylalkoxy, haloalkoxy (containing up to five halo groups).

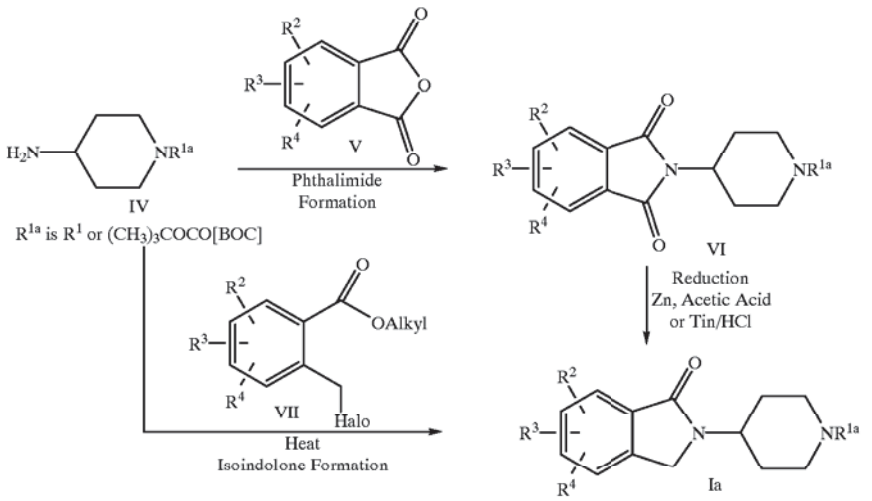
In structure II, it is also preferred that R^1 is arylalkyl or heteroarylalkyl wherein alkyl of each has at least 2 carbons (preferably at least 3 carbons) and R^5 and R^6 may be as defined hereinbefore and may or may not be the preferred groups set out above.

In structure III, it is preferred that R^2, R^3 and R^4 are each H or halo and R^7 is aryl.

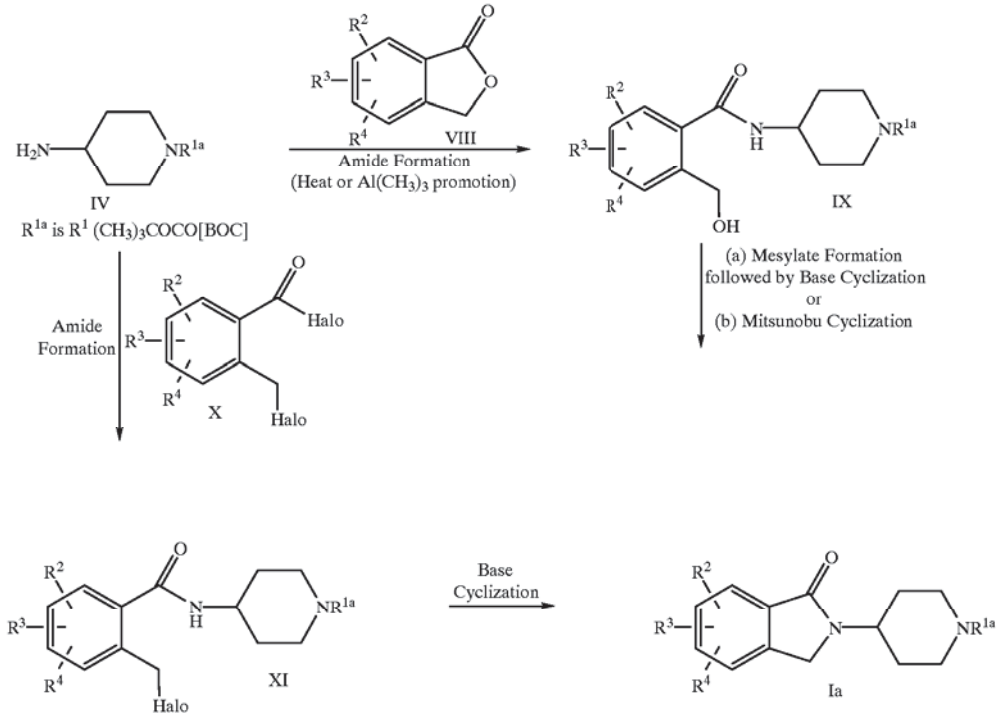
It is to be understood that combinations of substituents which lead to chemically unstable molecules are not included within the scope of the present invention; for example, compounds of the invention will not include —O—O—, —O—C—OH, N—C—OH and —S—C—OH linkages.

The compounds of formulae I, Ii, II, IIi and III may be prepared by the exemplary processes described in the following reaction schemes. Exemplary reagents and procedures for these reactions appear hereinafter and in the working Examples.

Scheme I
Routes to Isoindolinone Piperidines I

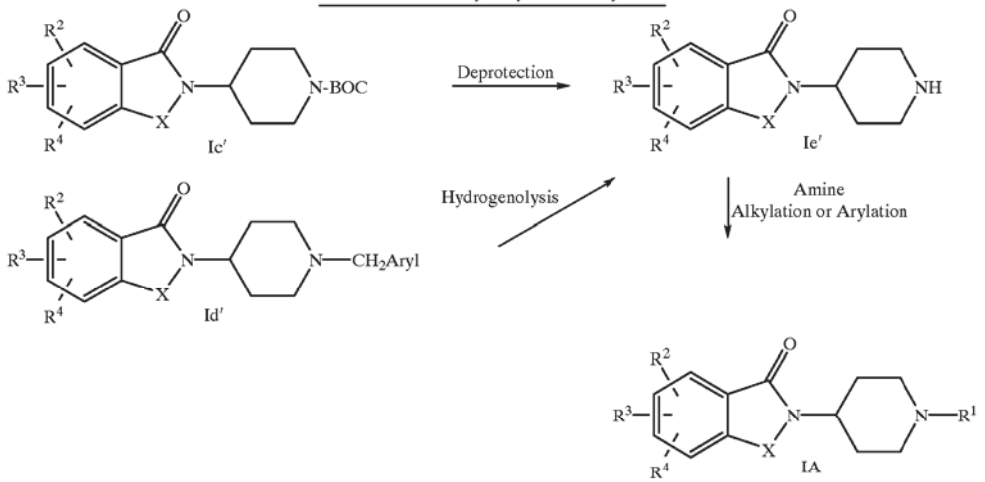


Scheme II
Additional Routes to Isoindolinone Piperidines I



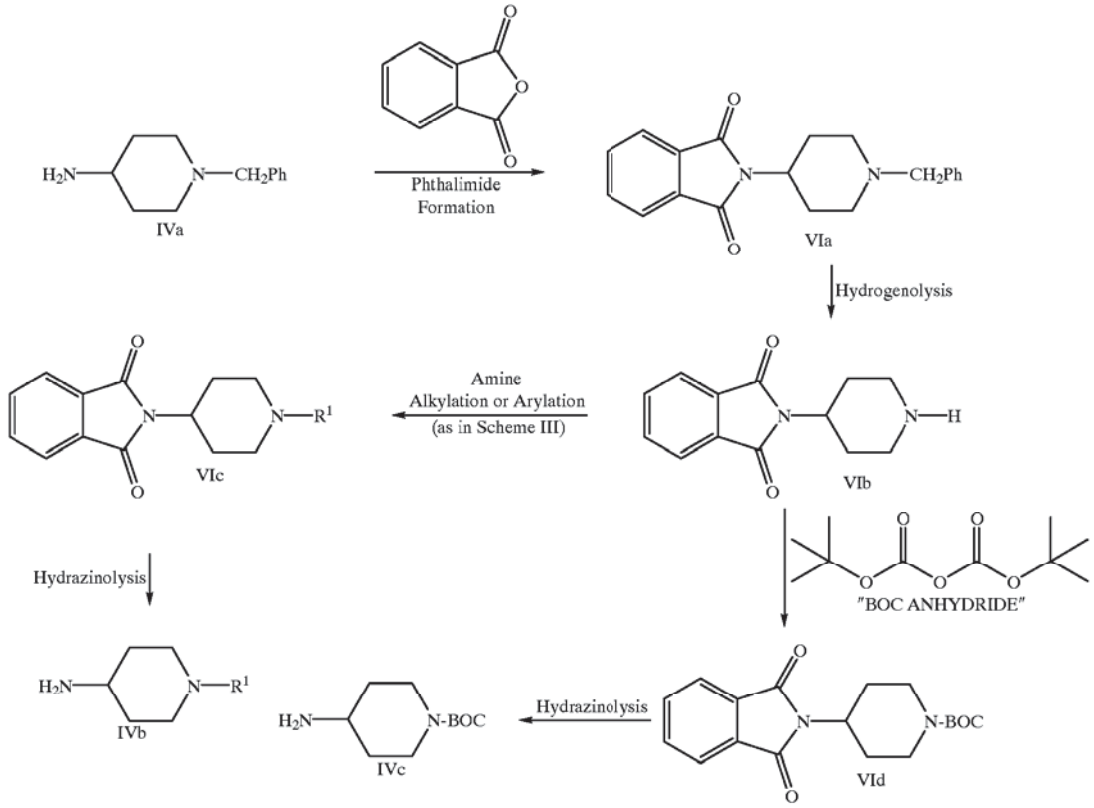
Scheme III

Introduction of R^1 by Alkylation or Arylation

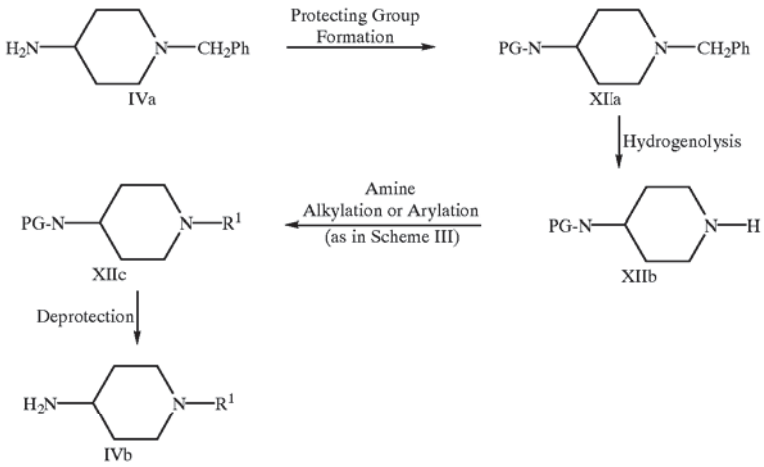


Scheme IV

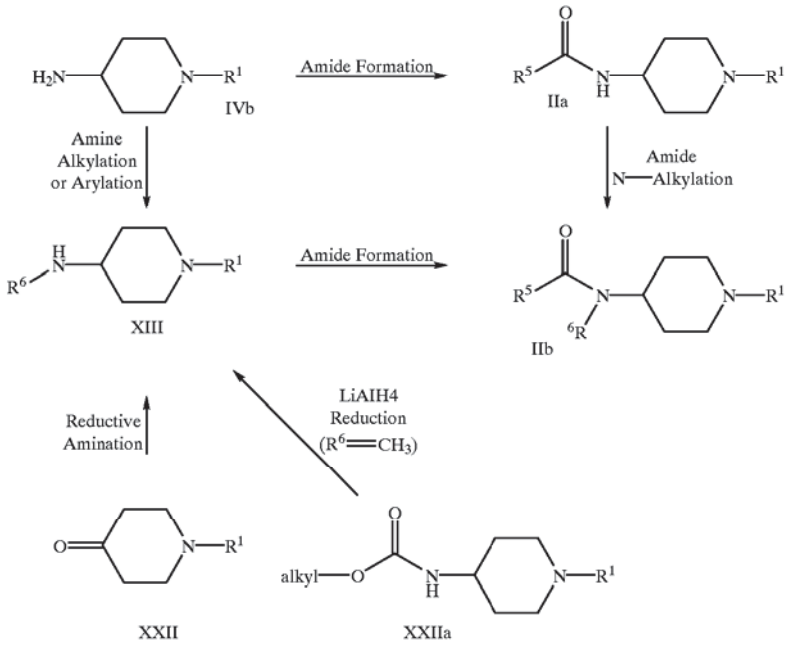
Routes to Starting Materials IVb and IVc



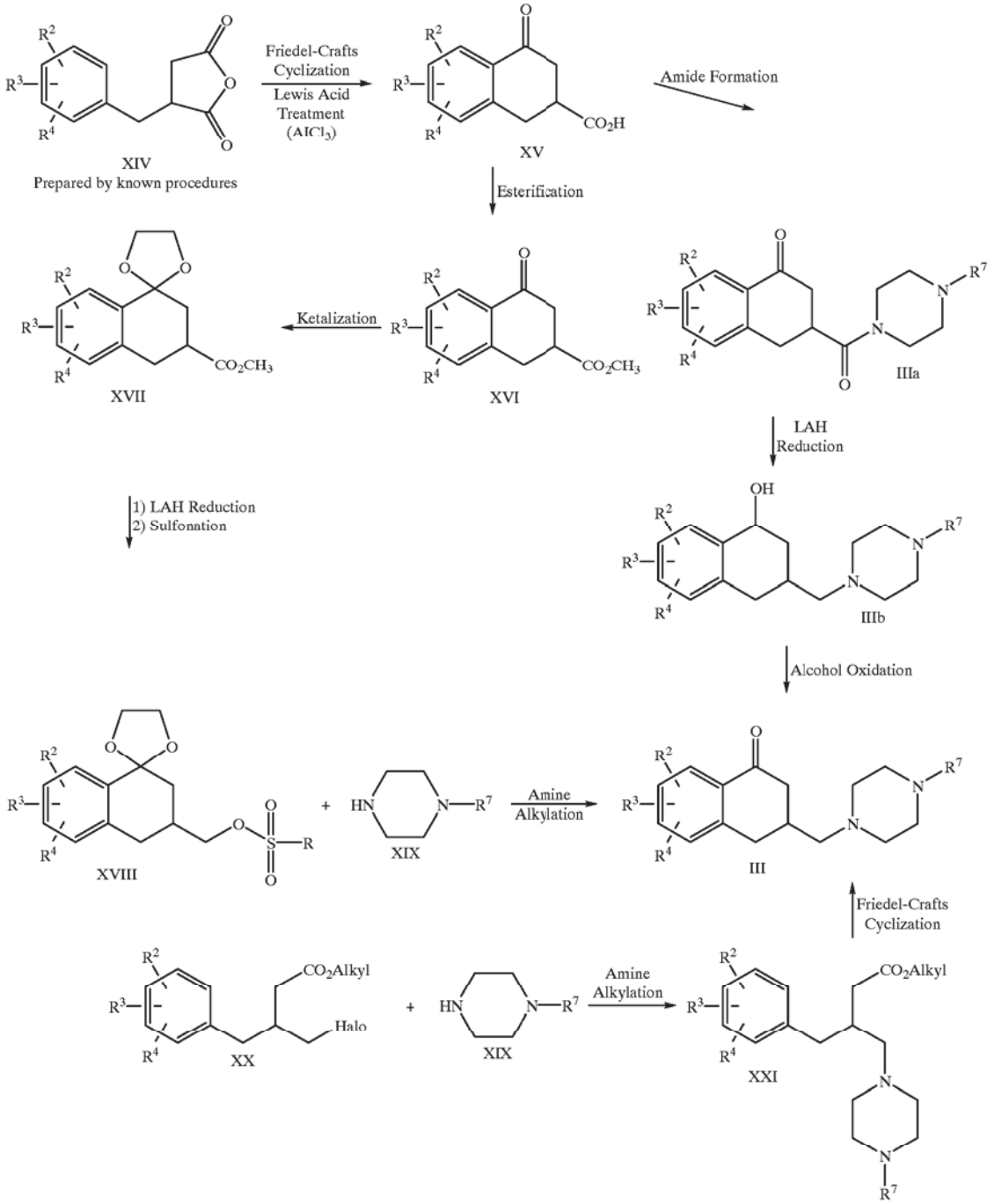
Scheme V
General Routes to Starting Material IVb



Scheme VI
General Routes to II

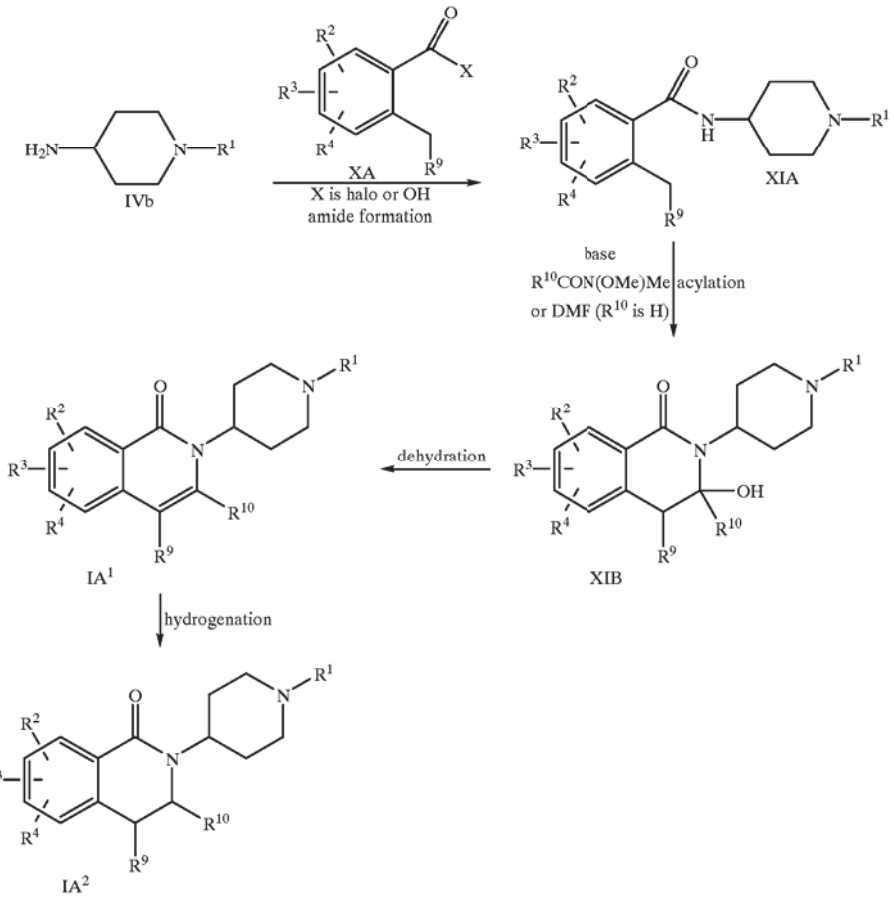


Scheme VII
General Route to III



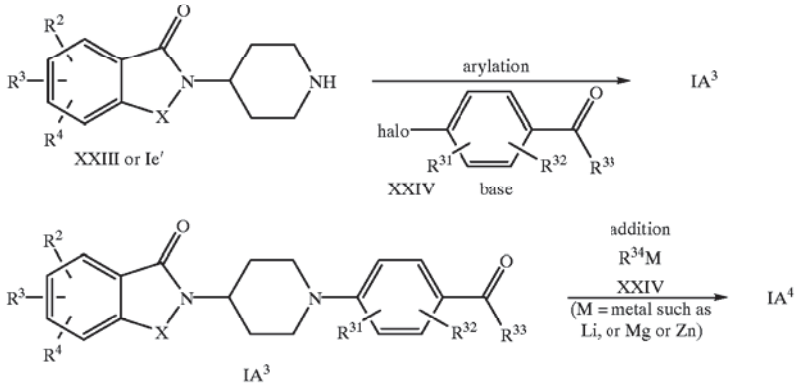
Scheme VIII

Preparation of Compounds IA^1, IA^2



Scheme IX

Preparation of Compounds IA^3–IA^6



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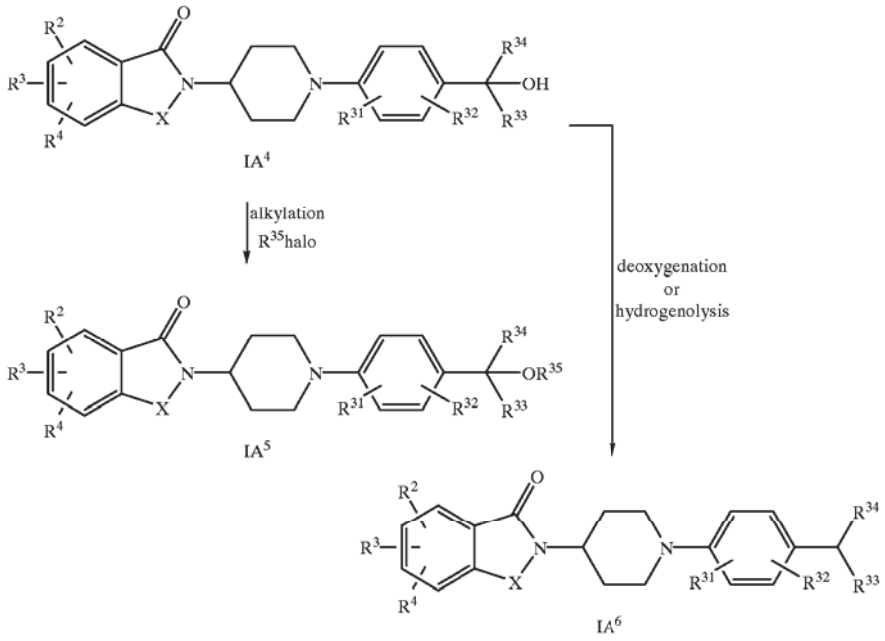


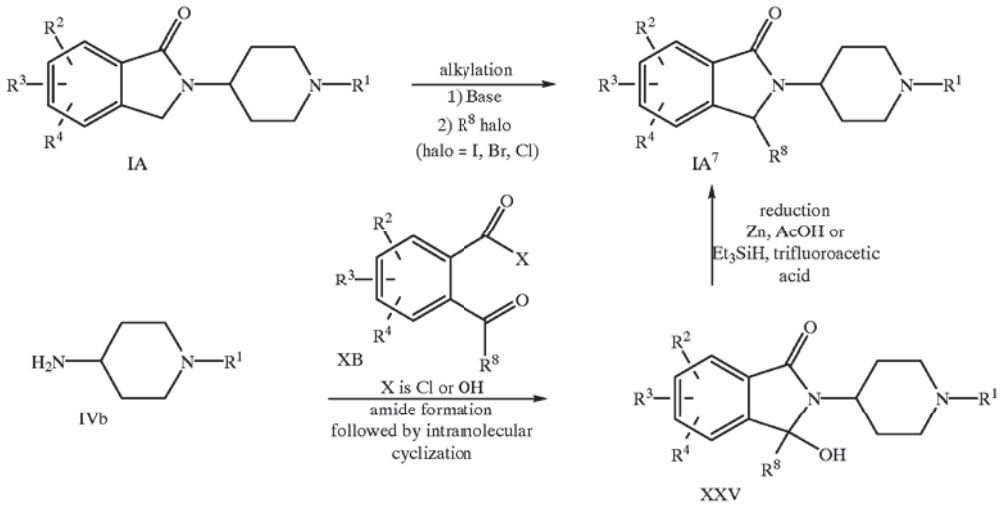
R^{31} and R^{32} are independently selected from any of the R^2, R^3, or R^4 radicals;

R^{33} and R^{34} are independently selected from any of the R^1 radicals as well as aryloxy, alkoxy, arylalkoxy, heteroaryloxy and heteroaryloxy;

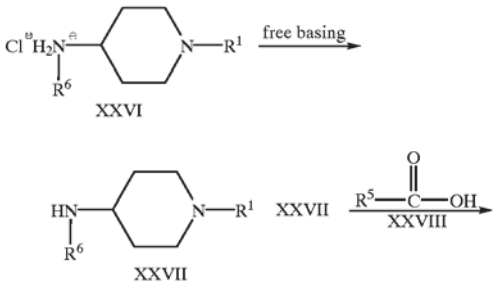
R^{35} can be any of the R^1 radicals.

Scheme X

Preparation of Compound IA^7



Scheme XI
Preparation of Compound II (Robotic Amide Coupling)



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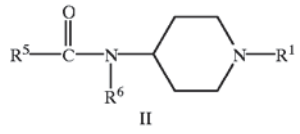
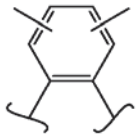
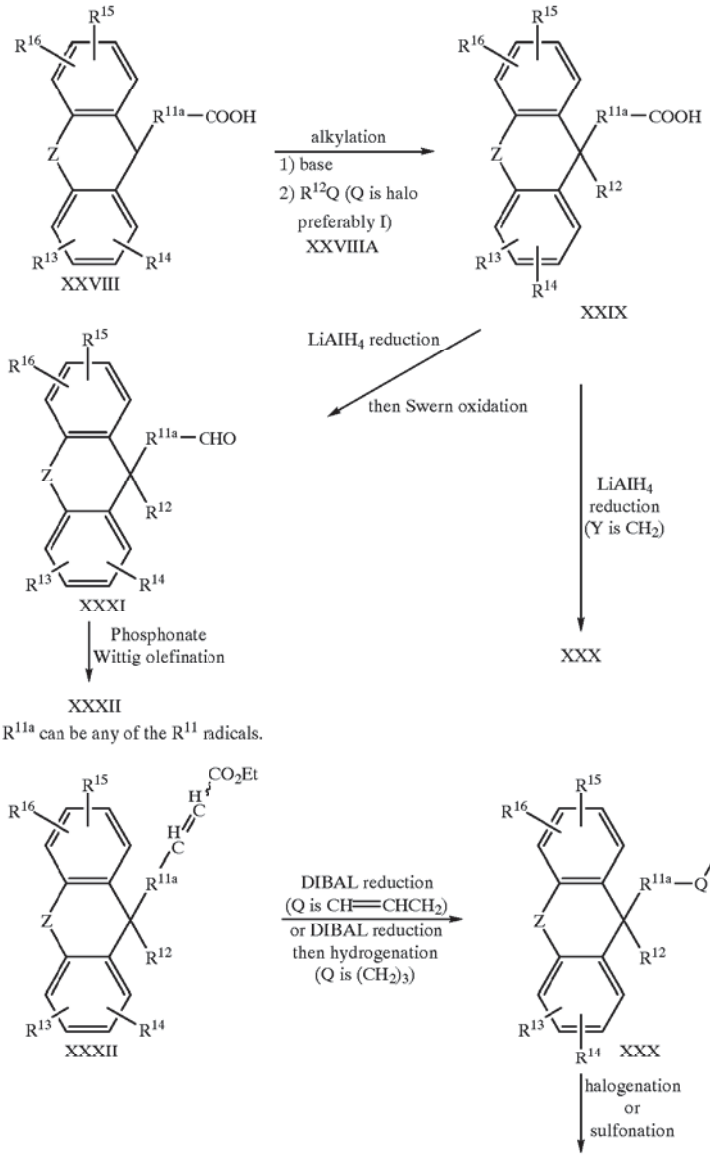


In the following Schemes XII et al, in the fluorenyl rings or fluorenyl analogs, the fused aryl groups:



may each optionally be replaced by a 5- or 6-membered heteroaryl ring as defined herein.

Scheme XII



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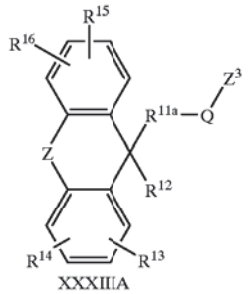

XXXIIIA

Z^3 is halo or Osulfonate

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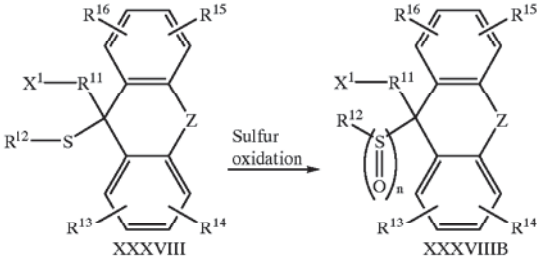


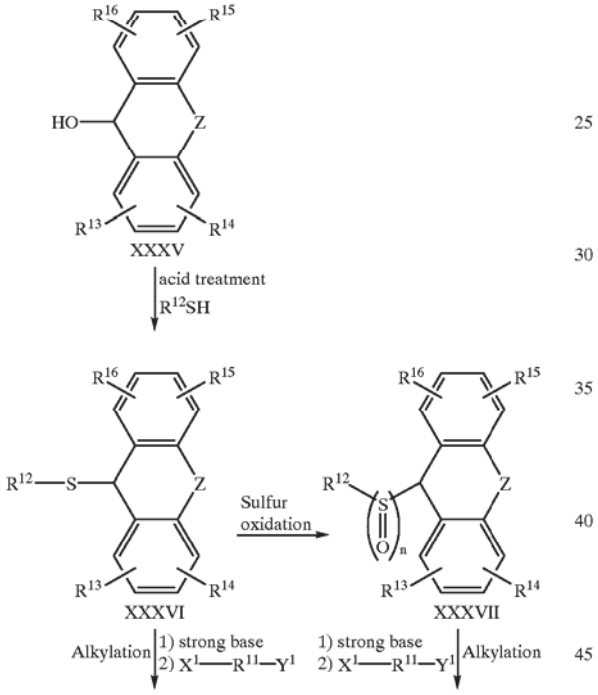
XXXVIII XXXVIIIB

Sulfur oxidation

X^1, Y^1 are the same or different halo or Osulfonate

n = 1 or 2

Scheme XIII-Preparation of Intermediates where Z^2 is S, SO, or SO_2



XXXV

acid treatment

$R^{12}SH$

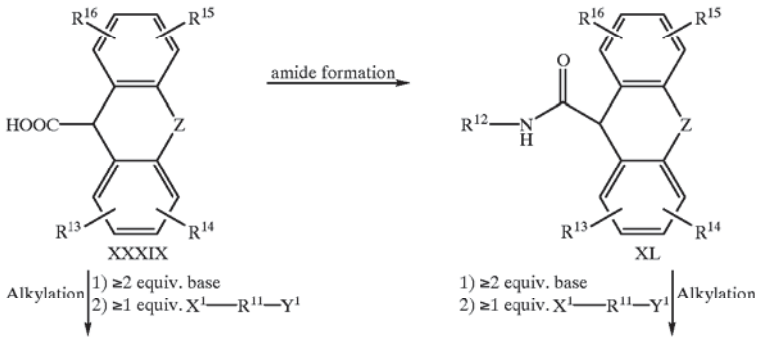
XXXVI XXXVII

Sulfur oxidation

Alkylation 1) strong base 2) $X^1—R^{11}—Y^1$

1) strong base 2) $X^1—R^{11}—Y^1$ Alkylation

Scheme XIVA-Preparation of A (Intermediates where Z^2 is NHCO)



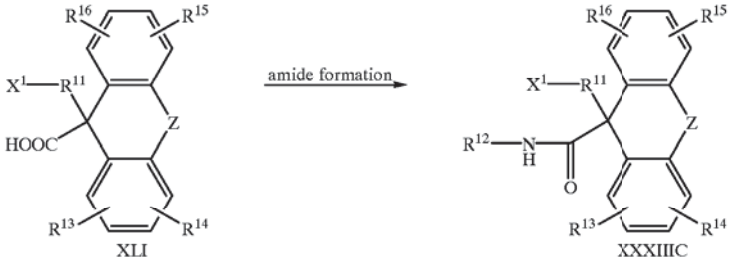
XXXIX XL

amide formation

Alkylation 1) ≥2 equiv. base 2) ≥1 equiv. $X^1—R^{11}—Y^1$

1) ≥2 equiv. base 2) ≥1 equiv. $X^1—R^{11}—Y^1$ Alkylation

-continued

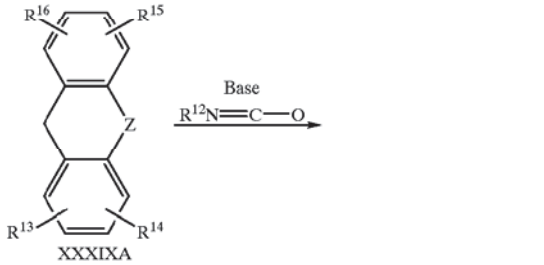


XLI

XXXIIIC

X^1, Y^1 are same or different halo or Osulfonate

Scheme XIVB
Alternative Procedure for Preparing Intermediate XL
(Shown in Scheme XIVA)



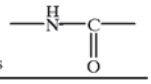
XXXIXA

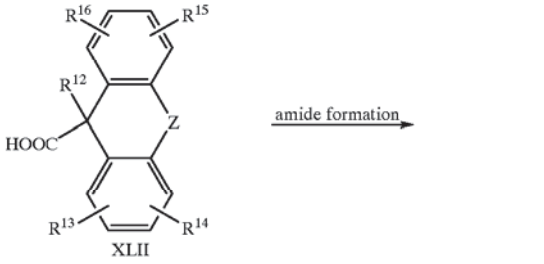
XL

In carring out the above reaction, bases such as n-butylithiun, lithium bis(trimethylsilyl) amide and sodium bis(trimethylsilyl) amide may be employed in an aprotic solvent such as THF, at between -78° C. and 35° C.

It is preferable to have the starting material and isocyanate ($R^{12}N{=}C{=}O$) together in solvent, and then add the base, and optionally add further excess isocyanate subsequently.

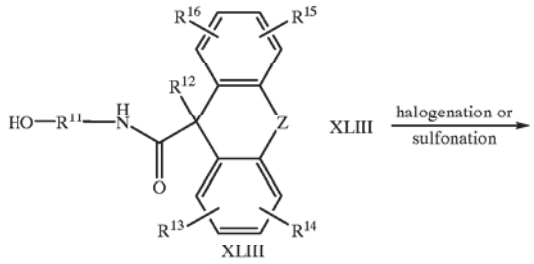
Scheme XV-Preparation of Intermediate where Z^1 is





XLII

-continued

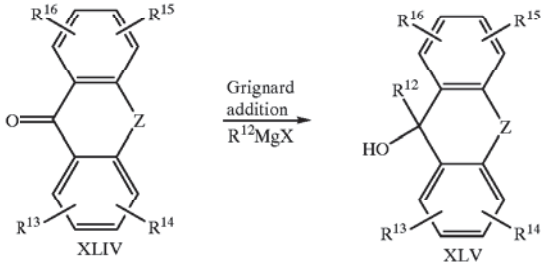


XLIII

XXXIIID

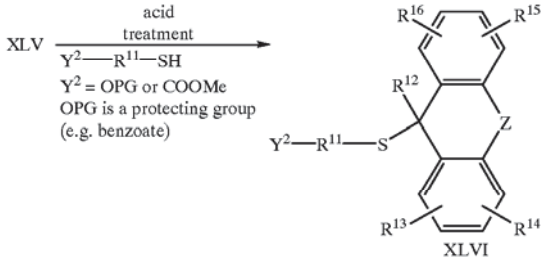
X^1 is halo or Osulfonate

Scheme XVI



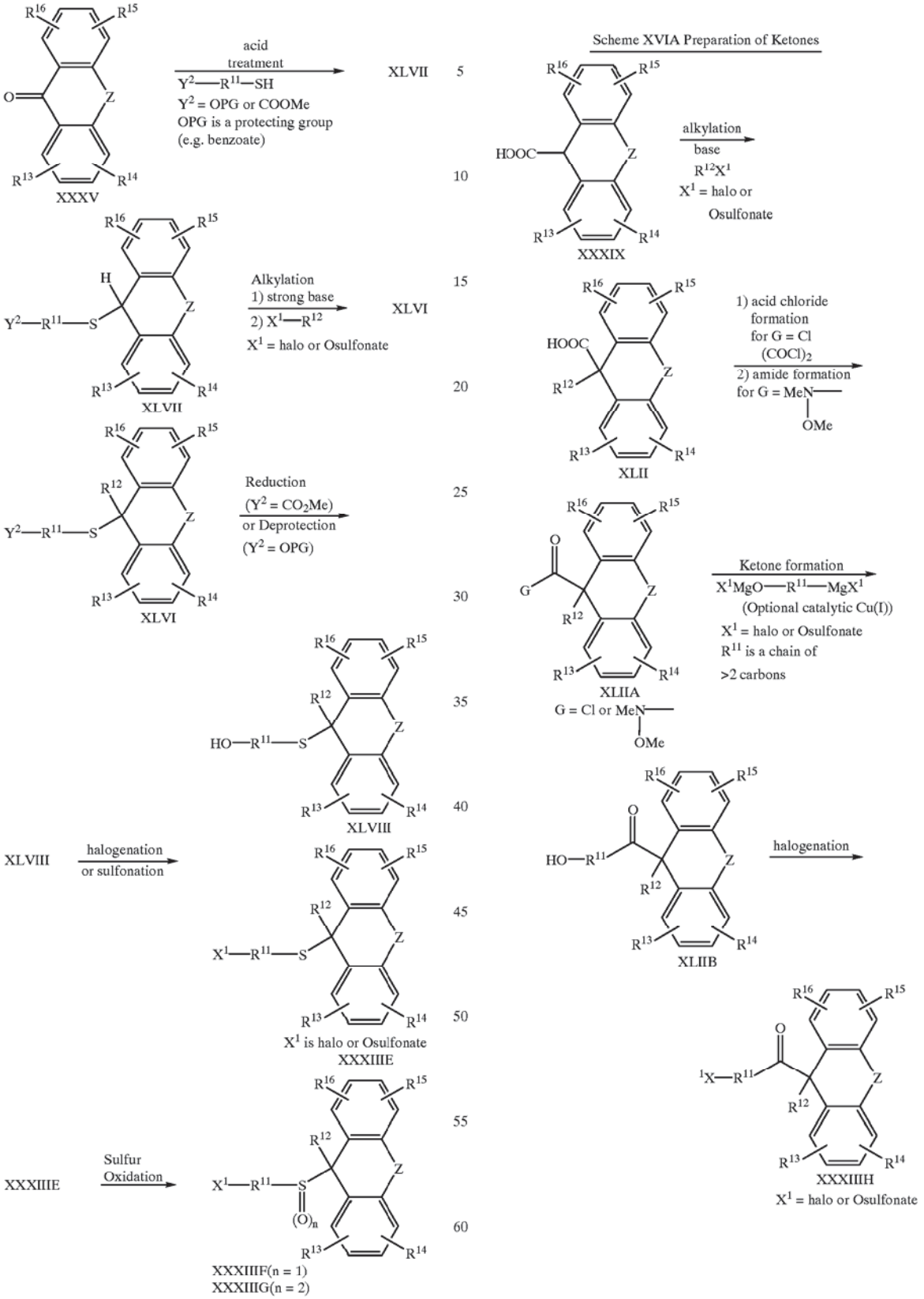
XLIV

XLV

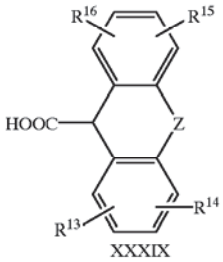


XLVI

-continued

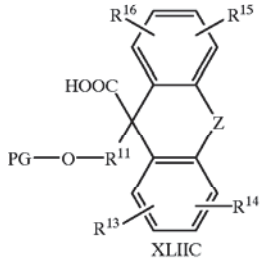


Scheme XVIB-Preparation of Ketones(Preferred Route)



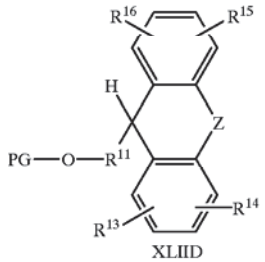
XXXIX

Alkylation
1) Pase
2) PG—OR^{11}X^{1}
X^{1} = halo or O-sulfonate



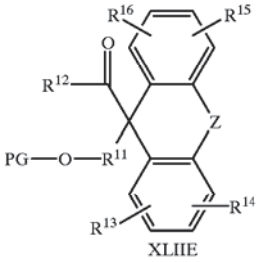
XLIIC

Decarboxylation
DMSO, RT



XLIID

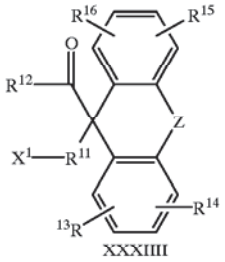
Ketone Formation
(Acylation)
1) base
2) R^{12}COCl



XLIIE

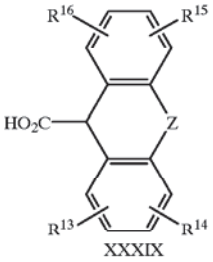
1) Deprotection
2) Hallde Formation

PG is an appropiate protecting group: such as t-butyl(dimethyl)silyl or t-butyl(diphenyl)silyl, which can be deprotected with aqueous acid or n-Bu$_4$NF.



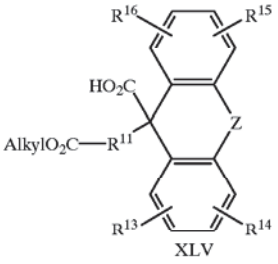
XXXIIII

Scheme XVIIA-Preparation of Amide Linked Compounds



XXXIX

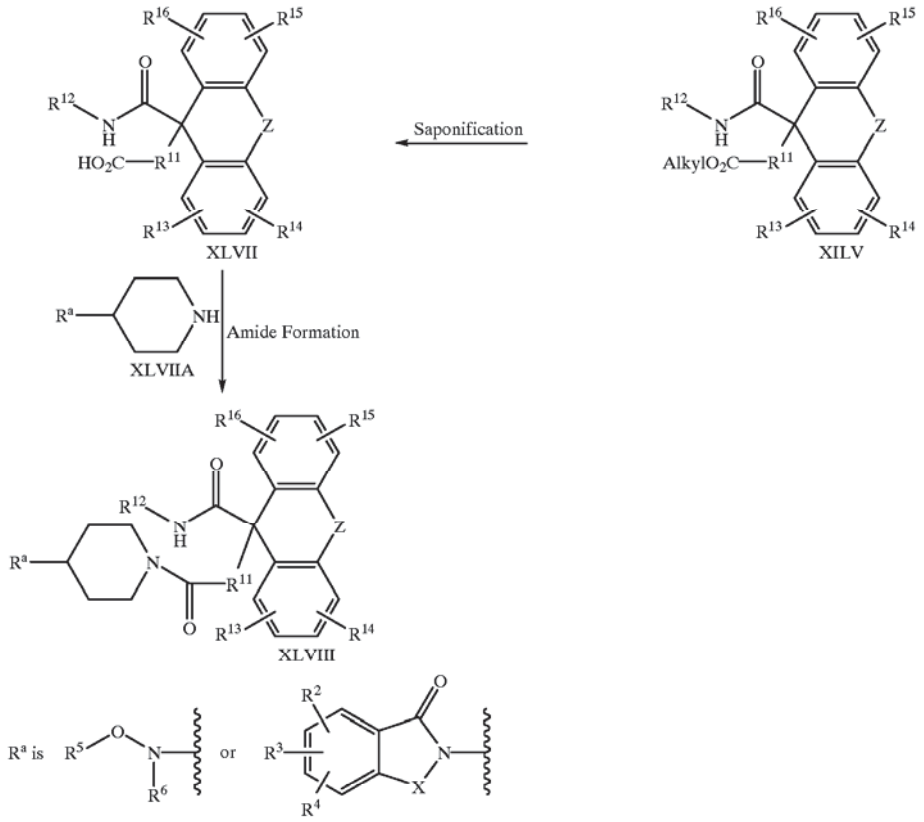
1) base
2) X^{1}—R^{11}—CO$_2$Alkyl
where X^{1} is halo or O-sulfonate



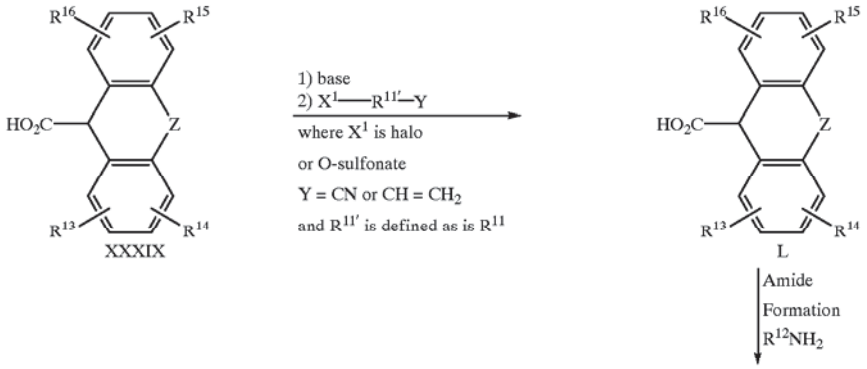
XLV

Amide Formation
R^{12}NH$_2$

-continued



Scheme XVIIB-Preparation of Carbamate and Urea Linked Compounds



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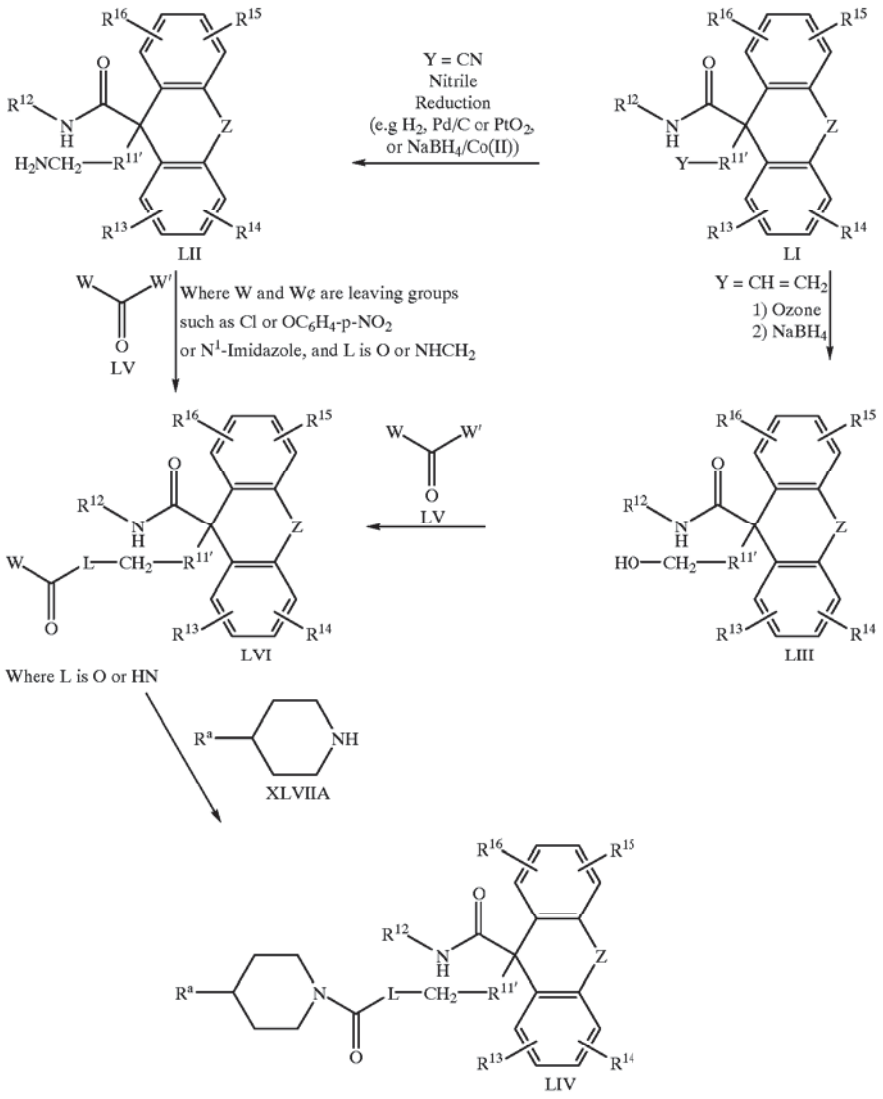

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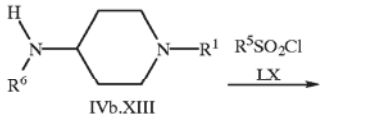
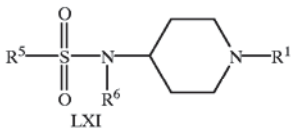
-continued

Scheme XVIIIA
Formation of Sulfonamides

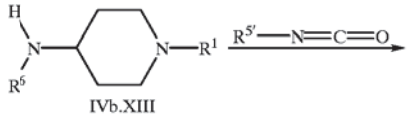


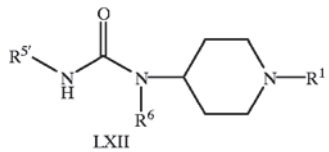


(Reaction in a variety of solvents (CH_2Cl_2, THF, pyridine) opitionally in the presence of a tertiary amine base, such as pyridine or triethyl amine).

-continued

Scheme XVIIIB
Formation of Ureas (R^5 is Amino)



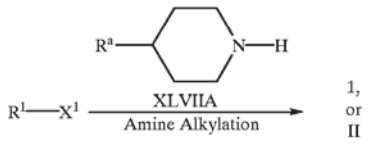


(1 to 10 equiv. of R—C=N=O, in aprotic solvent such toluene, from 0° C. to 150° C.) ($R^{5'}$ is alkyl, aryl, heteroaryl or arylalkyl).

-continued

Scheme XIXA

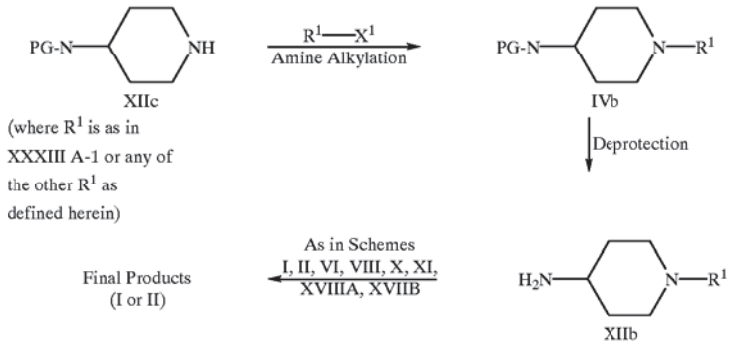
General Route to Final Product



(where R^1 is as in XXXIII A-K or any other R^1 as defined herein)

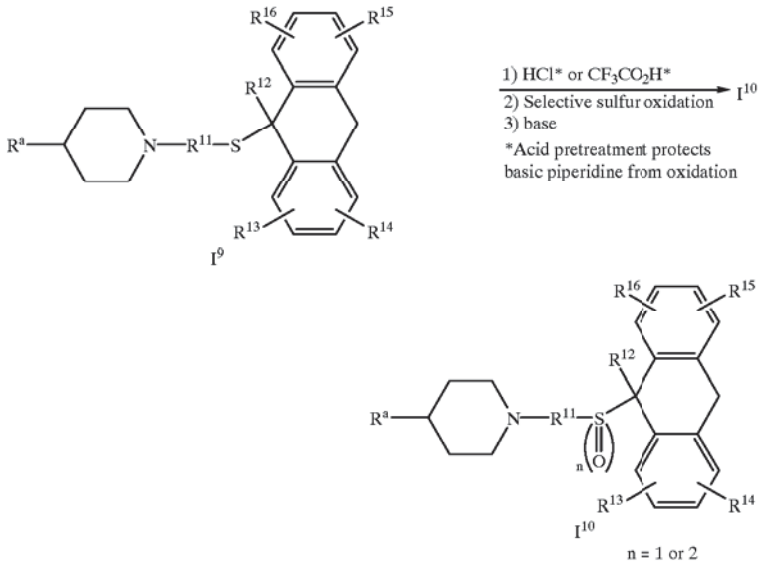
Scheme XIXB

General Route to Final Products (I or II)



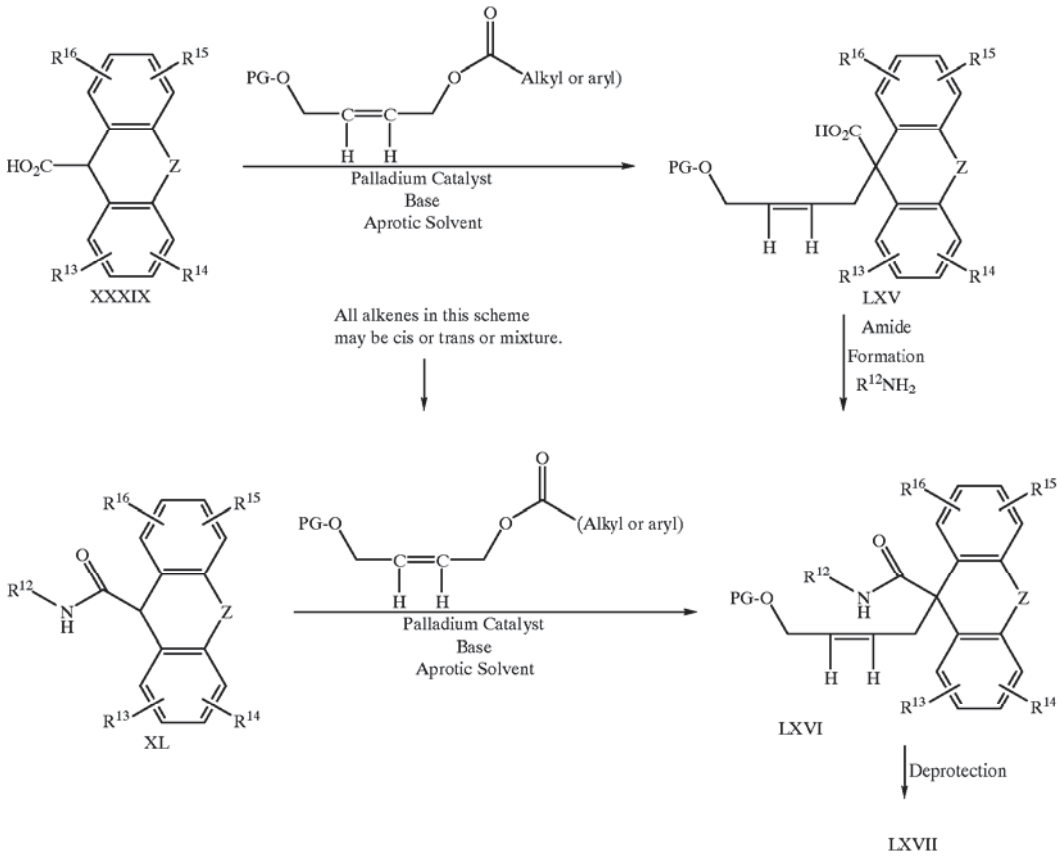
(Example of a protected nitrogen (PG-N) is the t-BuOC = ONH (BOC amino) group, which can be deprotected under mild conditions, such as anhydrous HCl in dioxane or neat trifluoroacetic acid).

Scheme XX-Oxidation of sulfur at the end of the reaction sequence

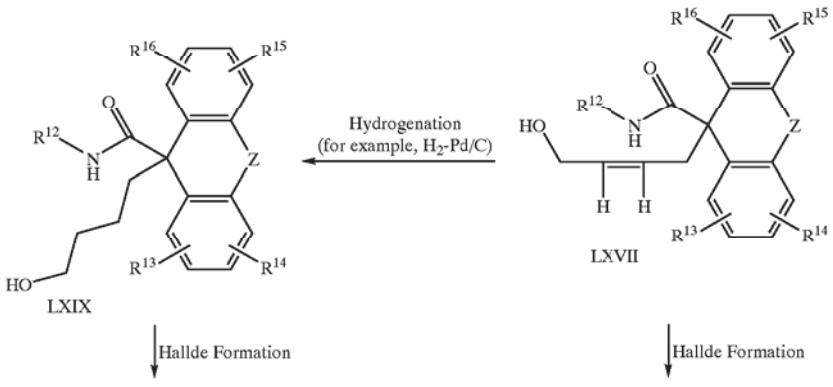


(R^a is defined as in Scheme XVIIA)

Scheme XXI
Preparation of Halide Intermediates



For example: Palladium catalyst can be $Pd(Ph_3P)_4$,
base can be NaH or bis(trimethylsilyl)acetamide,
aprotic solvent can be THF or DMF or mixtures.
PG- can be organosilyl, such as t-$Bu(Ph)_2Sl$-,
and deprotection conditions can be n-Bu_4NF, THF.



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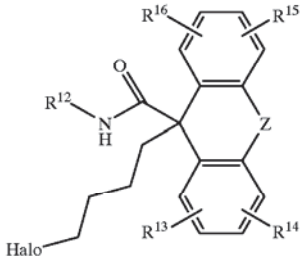
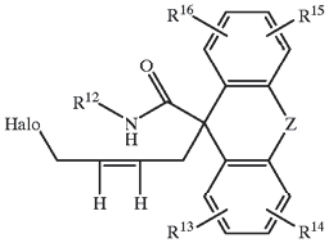


XXXIIIJ

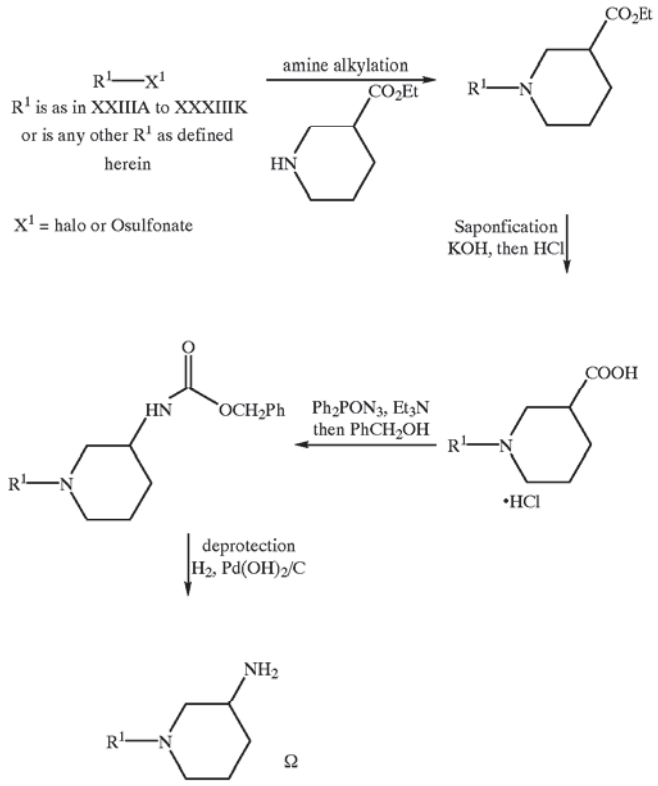
Halo is Cl, Br, I



XXXIIIK

Scheme XXII

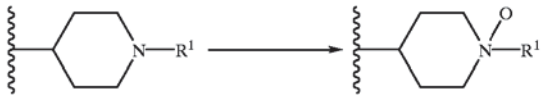
Preparation of 3-Substituted Piperidine Starting Materials



Intermediate Ω can be utilized as a starting material to prepare 3-substituted isomers Ii and IIi via the same methodology as outlined in the Schemes herein, specifically Schemes I, II, IV, V, VI, VIII, X, XI, XVIIIA, XVIIIB, XIXB, XX, XXIII.

Scheme XXIII

Preparation of N-Oxides of Formulae I and II compounds



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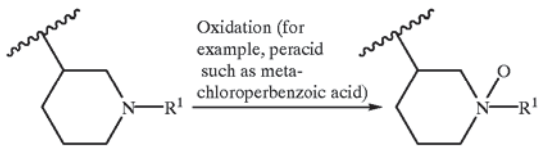


It is to be understood that in Schemes I to VI, VIII to XI, XVIIA, XVIIB, XVIIIA, XVIIIB, XIXA, XIXB, XX and XXI (which relate to preparation of compounds of the invention of formula I or II), the starting materials which are depicted as the 4-substituted piperidine isomers may be substituted with the corresponding 3-substituted piperidine

isomers to afford the corresponding compounds of the invention Ii or IIi which include the 3-substituted piperidine isomer.

In the above Reaction Schemes XII through XXI, the starting fluorenyl-type acid XXVIII, alcohol XXXV, acids XXXIX and XLII, ketone XLIV, hydride XXXIXA, and amide XL groups may be substituted with corresponding acid, alcohol, ketone, hydride and amide containing fluorenyl type groups as set out in A, B, C and D or indenyl-type groups as set out in E, F, G and/or H to provide an intermediate compound for use in preparing a compound of formula I, I', II or II' of the invention as per Reaction Schemes I to XXIII.

Phthalimide formation (Reaction Schemes I, IV) may be carried out by heating to about 80 to 150° C. in an oil bath optionally in an inert solvent or by various other procedures known in the art. See, e.g., Example 13 hereinafter.

Reduction (Reaction Scheme I) may be carried out by treatment with such reducing agents as zinc in the presence of acetic acid or tin in the presence of hydrochloric acid under an inert atmoshphere (e.g., argon).

Isoindolone formation (Reaction Scheme I) may be carried out by heating in the range of about 50 to 150° C. in an organic solvent (e.g., toluene, ethanol, dimethylformamide) optionally in the presence of a salt (e.g., potassium carbonate) or a tertiary amine base (e.g., 2,6-di-t-butylpyridine or triethylamine).

Amide formation (Reaction Schemes II, VI, VII, VIII, X, XI, XIVA, XV, XVI, XVIA, XVIB, XVIIA, XVIIB), XXI may be carried out by a number of methods known in the art. For example, an amine substrate may be treated with (1) an acid halide $R^5C(O)$halo or compound X or XA in an aprotic solvent, optionally in the presence of a tertiary amine base (e.g., triethylamine); (2) the acid halide in the presence of an aqueous base under Schotten-Baumann conditions; (3) a free carboxylic acid (R^5CO_2H) in the presence of a coupling agent such as dicyclohexylcarbodiimide (DCC), diisopropyl carbodiimide (DIC) or 1-(3-dimethylamino-propyl)-3-ethylcarbodiimide hydrochloride (WSC), optionally in the presence of 1-hydroxybenzotriazole (HOBT); (4) the free acid in the presence of N, N-carbonyldiimidazole in an aprotic organic solvent followed by the amine substrate; (5) trialkylaluminum (e.g., $Al(CH_3)_3$) in an aprotic solvent, followed by an ester (e.g., R^5CO_2alkyl or compound VIII) or (6) mixed anhydride formation, by reacting the acid with an acid chloride (e.g., isobutyl chloroformate or bis-(2-oxo-3-oxazolidinyl)-phosphinic chloride (Bop-Cl)) in the presence of a tertiary amine base (e.g., triethylamine) followed by treatment with the amine substrate.

Mesylate formation (Reaction Scheme II) may be carried out by treatment of the amine-alcohol substrate with methanesulfonyl chloride and triethylamine or pyridine or in an aprotic solvent, such as dichloromethane.

Base cyclization (Reaction Schemes II, VIII) may be carried out by treatment with a base (e.g., potassium t-butoxide or sodium hydride) in an inert solvent (e.g., dimethylformamide, tetrahydrofuran, dimethoxymethane, or toluene). Mitsunobu cyclization (Reaction Scheme II) may be carried out by procedures generally known in the art. See, e.g., R. K. Olsen, *J. Org. Chem.,* 49, 3527 (1984); Genin, M. J., et al., *J. Org. Chem.,* 58, 2334–7 (1993).

Alternatively, a mixture of compounds IV and VIII can be converted to compound Ia in a single pot by heating the mixture in a protic solvent (e.g., water, methanol, ethenyl or isopropanol or mixtures thereof) at 100 to 200° C. See, e.g., European patent application 81/26,749, FR 2, 548,666 (1983).

Protection and deprotection (Reaction Schemes III, IV, V, XVI, XVIB, XIXB, XXI) may be carried out by procedures generally known in the art. See, for example, T. W. Greene, *Protecting Groups in Organic Synthesis*, Second edition, 1991. PG in Scheme V denotes a nitrogen-protecting group. One particularly useful group is tert-butoxycarbonyl (BOC) which can be derived from the associated anhydride as shown in Scheme IV. BOC-protected amines may typically be deprotected by treatment with acid (e.g., trifluoroacetic acid or hydrochloric acid) in procedures well understood by those having ordinary skill in the art.

Hydrogenolysis (Reaction Schemes III, IV, V) may be carried out with H_2 using a balloon apparatus or a Parr Shaker in the presence of a catalyst (e.g., pallladium on activated carbon).

Amine alkylation and arylation (Reaction Schemes III, IV, V, VII, IX, XII, XIXA, XIXB) may be carried out by methods known in the art. Suitable procedures are described in Cortizo, L., *J. Med. Chem.* 34, 2242–2247 (1991). For example, the alkylation or arylation may be carried out by treating the amine substrate with a halide (e.g., R^1-halo) or an oxytosylate (e.g., R^1-O-tosylate) in an aprotic solvent (e.g., dimethylformamide), optionally in the presence of a tertiary amine (e.g., triethylamine) or an inorganic base (e.g., potassium carbonate).

Reductive amination may be employed as an alternative to the foregoing amine alkylation and arylation procedures when R^1, R^6 or R^7 is $R^9R^{10}CH$— and R^9 and R^{10} are each independently hydrogen, alkyl, alkenyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl, cycloalkyl, or cycloalkylalkyl, or R^9 and R^{10} together are alkylene (i.e., $R^9R^{10}CH$— forms a cycloalkyl group). Such reductive amination may be carried out by treating the amine with (a) a ketone or aldehyde (R^9—C(O)—R^{10}), (b) $NaBH_4$, $NaBH_3CN$ or $NaB(acetoxy)_3H$, (c) a protic solvent (e.g., methanol) or a dipolar aprotic solvent (e.g., acetonitrile), and, optionally, (d) an acid (e.g., acetic acid, trifluoroacetic acid, hydrochloric acid, or titanium isopropoxide). When R^1 is aryl or heteroaryl, transition metals (e. g., palladium or copper salts or complexes) may be used to promote the arylation reaction.

Alkylation of the isoindolone (Reaction Scheme X) may be carried out by treatment of the isoindolone with a strong base (i.e. sodium bis(trimethylsilyl)amide or lithium diisopropylamide) followed by an alkyl halide (e.g. R^8-halo) or alkyl sulfonate (e.g. R^8-tosylate) in an inert solvent (e.g. tetrahydrofuran or dimethoxy-ethane). Alternatively, as seen in Scheme X, amine IVb can be treated under amide formation conditions with a ketone with the structure XB to provide a hydroxylactam XXV, which could be subjected to reduction conditions with such reducing agents as zinc in acetic acid or triethylsilane in trifluoroacetic acid to give IA^7.

Hydrazinolysis of phthalimides may be carried out by standard means known in the art. See, e.g., T. W. Greene, *Protecting Groups in Organic Synthesis*, Second edition, 1991.

Amide N-alkylation (Reaction Scheme VI) may be carried out by base treatment (e.g., NaH, KH, $KN[Si(CH_3)_3]_2$, K_2CO_3, P4-phosphazene base, or butyl lithium) in an aprotic organic solvent, followed by treatment with R^6-halo or R^6-O-tosylate. Use of P-phosphazene base is described in T. Pietzonka, D. Seebach, *Angew. Chem. Int. Ed. Engl.* 31, 1481, 1992.

In Scheme VII, the Friedel-Crafts cyclization may be carried out with, for example, aluminum chloride, boron trifluoride or polyphosphoric acid and aprotic solvents such as nitrobenzene, nitromethane or carbon disulfide at about

−20° C. to 80° C. The esterification may be carried out with a common esterifying agent (e.g., sulfuric acid in methanol) with heating to reflux. Ketalization may be carried out by treatment with such reagents as ethylene glycol in an organic solvent (e.g., benzene) in the presence of an acid catalyst (e.g., p-toluenesulfonic acid). Reduction with lithium aluminum hydride (LAH) may be carried out in an organic solvent (e.g., tetrahydrofuran) from 0° C. to 70° C. Oxidation of alcohols may be carried out by Oppenauer oxidation, such as treatment with potassium t-butoxide and benzophenone, or by other procedures known in the art. The sulfonation may be carried out with RSO_2Cl wherein R is alkyl, haloalkyl or aryl in an organic solvent (e.g., pyridine, dichloromethine) in an inert atmosphere (e.g., nitrogen) optionally in the presence of a tertiary amine base (e.g., triethylamine).

Compound III can also be prepared from compound XX as described by Cortizo, L., *J. Med. Chem.* 34, 2242–2247 (1991).

Dehydration (Scheme VIII) may be carried out employing a strong acid such as hydrochloric acid, sulfuric acid or trifluoroacetic acid.

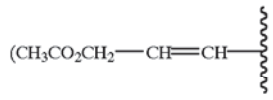
Hydrogenation (Scheme VIII) may be carried out in the presence of a conventional catalyst such as Pd/C or Pt or Rh under a H_2 atmosphere.

The addition reaction shown in Scheme IX may be carried out by treating IA^3 with an organometallic reagent XXIV, such as an organolithium or organic magnesium compound where organo is alkyl or aryl.

The deoxygenation or hydrogenation reaction (Scheme IX) is carried out in the presence of a strong acid such as trifluoroacetic acid or boron trifluoride etherate, in the presence of a hydride source such as triethyl silane or tris(trimethylsilyl)silane.

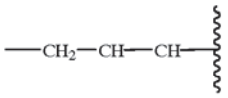
The alkylation in Schemes XII, XIII, XIV, XVI, XVIA, XVIB is carried out in the presence of base such as butyllithium or sodium bis(trimethylsilyl)amide. It will be appreciated that R^{12} in $R^{12}Q$ may be any of the R^{12} groups as defined hereinbefore.

Alternatively, the alkylation in the above Schemes can be performed where either or both Z^1 or Z^2 is a bond, using a palladium catalyzed allylic alkylation procedure. In this reaction, the fluorenyl-type or indenyl-type precursors (compounds XXVIII, XXXVI, XXXVII, XXXIX, XL, XLVII) are reacted with a base (sodium hydride, sodium bis(trimethylsilyl)amide or bis(trimethylsilyl)acetamide), a palladium catalyst (for example $Pd(Ph_3)_4$) and an allylic acetate



or

in an inert solvent (for example THF). This reaction is to introduce either $—R^{12}$ (Scheme XII) or $—R^{11}—X^1$ (Schemes XIII, XIV, XVI, XVIA) or $—R^{11}—$OPG (Scheme XVIB, Scheme XXI). The product of this reaction contains either an $—R^{12}$ group or an $—R^{11}—X^1$ group (or an $—R^{11}—$OPG group) which begins with



Saturation of the alkene in R^{11} or R^{12} can be accomplished by standard catalytic hydrogenation conditions.

With respect to Scheme XII, the $LiAlH_4$ reduction, Swern oxidation, Wittig olefination and halogenation/sulfonation reactions are conventional reactions well known to those skilled in the art.

The sulfur oxidation in Schemes XIII, XVI and XVIII is carried out as follows.

Sulfides of structures XXXVI, XXXVIII, XXXIIIE and I^9 can be selectively oxidized to sulfoxides by 1 molar equivalent of reagents known in the art, such as 30% H_2O_2, $NaIO_4$, and peracids (e.g., meta-chloroperbenzoic acid). The resulting sulfoxides can be further transformed to corresponding sulfones by another molar equivalent or excess of 30% H_2O_2, $KMnO_4$, $KHSO_5$, or peracids (e.g., meta-chloroperbenzoic acid). Alternatively, the sulfones can be directly prepared from sulfides with 2 molar equivalents or more of oxidizing agents, such as 30% H_2O_2 and peracids (e.g., meta-chloroperbenzoic acid). In cases where an amine (such as a piperidine in I^9) is present during the oxidation, the basic nitrogen may be protected by pretreatment with an acid such as HCl or CF_3CO_2H (see Scheme XIX).

To prepare examples where Z^1 or Z^2 is —CHOH, the compounds I, Ii, II and IIi where Z^1 or Z^2 is C═O can be reduced with a hydride reagent, for example $NaBH_4$.

The compounds of the invention may be employed in preventing, stabilizing or causing regression of atherosclerosis in a mammalian species by administering a therapeutically effective amount of a compound to decrease the activity of MTP.

The compounds of the invention can be tested for MTP inhibitory activity employing the procedures set out in U.S. application Ser. No. 117,362 filed Sep. 3, 1993, employing MTP isolated from one of the following sources:

(1) bovine liver microsomes,

(2) $HepG_2$ cells (human hepatoma cells) or

(3) recombinant human MTP expressed in baculovirus.

The compounds of the invention may also be employed in lowering serum lipid levels, such as cholesterol or triglyceride (TG) levels, in a mammalian species, by administering a therapeutically effective amount of a compound to decrease the activity of MTP.

The compounds of the invention may be employed in the treatment of various other conditions or diseases using agents which decrease activity of MTP. For example, compounds of the invention decrease the amount or activity of MTP and therefore decrease serum cholesterol and TG levels, and TG, fatty acid and cholesterol absorption and thus are useful in treating hypercholesterolemia, hypertriglyceridemia, hyperlipidemia, pancreatitis, hyperglycemia and obesity.

The compounds of the present invention are agents that decrease the activity of MTP and can be administered to various mammalian species, such as monkeys, dogs, cats, rats, humans, etc., in need of such treatment. These agents can be administered systemically, such as orally or parenterally.

The agents that decrease the activity or amount of MTP can be incorporated in a conventional systemic dosage form, such as a tablet, capsule, elixir or injectable formulation. The above dosage forms will also include the necessary physi-

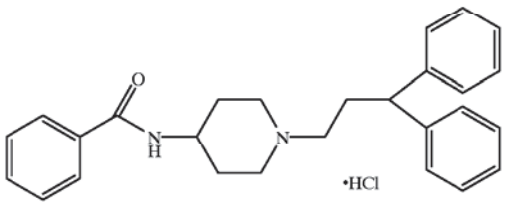
ologically acceptable carrier material, excipient, lubricant, buffer, antibacterial, bulking agent (such as mannitol), antioxidants (ascorbic acid or sodium bisulfite) or the like. Oral dosage forms are preferred, although parenteral forms are quite satisfactory as well.

The dose administered must be carefully adjusted according to the age, weight, and condition of the patient, as well as the route of administration, dosage form and regimen, and the desired result. In general, the dosage forms described above may be administered in amounts of from about 5 to about 500 mg per day in single or divided doses of one to four times daily.

The following Examples represent preferred embodiments of the invention. All temperatures are in ° C. unless indicated otherwise.

EXAMPLE 1

N-[1-(3,3-Diphenylpropyl)-4-piperidinyl]benzamide monohydrochloride



A. [1-(Phenylmethyl)-4-piperidinyl]carbamic acid, 1,1-dimethylethyl ester

To a solution of 4-amino-1-benzylpiperidine (20.0 g, 105 mmol) in dichloromethane (150 mL) was added dropwise a solution of di-tert-butyldicarbonate (25.2 g, 116 mmol) in dichloromethane (50 mL) at 0° C. After addition, the reaction was warmed to room temperature. The reaction was maintained at this temperature for 2 hours. The reaction was evaporated to dryness. The resulting residue was recrystallized from ethyl ether to give compound A (23.5 g, 76%) as a white solid (melting point 119–121° C.).

B. 4-Piperidinylcarbamic acid, 1,1-dimethylethyl ester

A suspension of 64.94 g (0.224 mol) of compound A and 25.6 mL (0.447 mol) of acetic acid in 500 mL of absolute ethanol was warmed to dissolve all solids. After cooling, 6.5 g (1 wt %) of 10% palladium on charcoal was added and the mixture was shaken on a Parr apparatus under initial hydrogen pressure of 40 psi for 23 hours. The catalyst was removed by filtration and the solution was concentrated to a clear oil which was dissolved in 1.5 L of chloroform. The organics were washed with a 3 N KOH solution saturated with NaCl (2×75 mL). The aqueous layer was back extracted with chloroform (5×200 mL). The combined organics were dried (sodium sulfate) and concentrated to provide 65 g of a white solid which was redissolved in 1.5 L of chloroform and washed with brine (2×200) mL to remove residual acetate. The combined aqueous layers were back extracted and the combined organics were dried (sodium sulfate) and concentrated to provide 40.15 g (90%) of compound B as a white solid (melting point 156–159° C.).

C. g-Phenylbenzenepropanol, 4-methylbenzenesulfonate ester

To a solution of tosyl chloride (4.94 g, 25.9 mmol) in dichloromethane (10 mL) was added 3,3-diphenyl-1-propanol (5.00 g, 23.6 mmol) and pyridine (2.86 mL, 35.4 mmol) at room temperature. The reaction was stirred overnight at room temperature. Ethyl ether (200 mL) was added to dilute the reaction, and the organic layer was washed with 1 N HCl (50 mL×2), saturated sodium carbonate (50 mL×2), brine (50 mL×2) and dried over $MgSO_4$. Purification was performed by flash chromatography, loaded and eluted with 25% ethyl acetate in hexane. Pure fractions were combined and evaporated to give compound C (5.2 g, 60%) as a colorless oil.

D. [1-(3,3-Diphenylpropyl)-4-piperidinyl]carbamic acid, 1,1-dimethylethyl ester

To a solution of compound C (1.83 g, 5.00 mmol) and compound B (1.00 g, 5.00 mmol) in isopropanol (25 mL) was added potassium carbonate (1.1 g, 8.00 mmol). The reaction was refluxed overnight. The reaction was cooled to room temperature and filtered, and the filtrate was evaporated to dryness. Purification was performed by flash chromatography, loaded and eluted with 2.5% methanol in dichloromethane. Pure fractions were combined and evaporated to give compound D (1.5 g, 76%) as a colorless oil.

E. 1-(3,3-Diphenylpropyl)-4-piperidinamine, hydrochloride

To a stirred solution of 9.21 g (23.34 mmol) of compound D in 60 mL of dioxane was added 58 mL (0.223 mol) of a 4.0 M HCl in dioxane solution. The mixture was stirred for 15 hours then concentrated to provide 8.45 g (100%) of compound E as a white solid containing 10 wt % of dioxane by ^1H NMR, melting point 123–126° C. A dioxane-free sample of the hydrochloride salt has a melting point of 192–194° C.

F. N-[1-(3,3-Diphenylpropyl)-4-piperidinyl] benzamide

To solution of compound E (100 mg, 0.30 mmol) and triethylamine (152 mg, 0.33 mmol) in dichloromethane (2 mL) was added a solution of benzoyl chloride (46.8 mg, 0.33 mmol) in dichloromethane (0.5 mL) at 0° C. After addition, the reaction was stirred at 0° C. for 10 minutes. The reaction was diluted with dichloromethane (50 mL), the organic layer was washed with saturated sodium bicarbonate solution (10 mL), water (10 mL) and dried over sodium sulfate. The solution was evaporated to dryness. The resulting residue was recrystallized from isopropanol to give compound F (100 mg, 84%) as a white solid (melting point 151–155° C.).

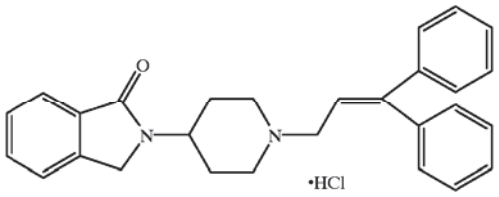
G. N-[1-(3,3-Diphenylpropyl)-4-piperidinyl] benzamide, monohydrochloride

Compound F (100 mg, 0.25 mmol) was dissolved in ethanol (2 mL) and 1 N HCl in diethyl ether (0.5 mL) was added. The mixture was evaporated to give Example 1 (100 mg, 100%) as a white solid, melting point 246–249° C.

Analysis for $C_{27}H_{31}ClN_2O.0.2H_2O$: Calc'd C, 73.94; H, 7.22; N, 6.39; Cl, 8.08 Found: C, 73.90; H, 7.18; N, 6.40; Cl, 8.11

EXAMPLE 2

2-[1-(3,3-Diphenyl-2-propenyl)-4-piperidinyl]-2,3-dihydro-1H-isoindol-1-one, monohydrochloride



A. 2-(4-piperidinyl)-2,3-dihydro-1H-isoindol-1-one

To a solution of compound B from Example 3 (8.5 g, 26.4 mmol) in ethanol (65 mL) was added acetic acid (3.5 mL, 52.8 mmol), followed by 10% palladium on activated carbon (0.7 g) under argon. The slurry was purged with nitrogen and agitated under a pressure of 45 psi of hydrogen gas for 48 hours. The reaction mixture was filtered through Celite® and washed with ethanol. The filtrate was evaporated to dryness. The resulting residue was dissolved in chloroform (100 mL) and washed with 1 N KOH saturated with sodium chloride (2×30 mL) and dried over $MgSO_4$. The resulting clear solution was evaporated to dryness and azeotroped with toluene (2×30 mL) to give compound A (5.0 g, 77%) as a white solid, melting point 137–140° C.

B. 3,3-Diphenyl-2-propen-1-ol

To a solution of b-phenylcinnamaldehyde (5.0 g, 24.0 mmol) in toluene (100 mL) was added 1 M diisobutylaluminum hydride (26.4 mL, 26.4 mmol) at 0° C. The reaction was stirred at 0° C. for 15 minutes, and methanol (5 mL) was added slowly to quench the reaction. 1 M potassium sodium tartrate solution (150 mL) was added and the mixture was stirred at room temperature overnight. The reaction was diluted with ethyl ether (100 mL), and the organic layer was washed with brine (30 mL) and dried over Na_2SO_4. Evaporation gave compound B (3.95 g, 80%) as a pale yellow oil.

C. 1-Chloro-3,3-diphenyl-2-propene

To a solution of N-chlorosuccinimide (1.52 g, 11.4 mmol) in dichloromethane (40 mL) was added dimethyl sulfide (1.1 mL, 14.5 mmol) at −40° C. under argon. The reaction was stirred at −40° C. for 10 minutes then warmed to room temperature for 30 minutes. The white cloudy solution was recooled to −40° C., and a solution of compound B (2.17 g, 10.3 mmol) in dichloromethane (3 mL) was added dropwise. The reaction was stirred at −40° C. for 2 hours and then diluted with hexane (100 mL). The organic layer was washed with water (50 mL), brine (50 mL×2) and dried over Na_2SO_4. Evaporation gave compound C (1.9 g, 81%) as a colorless oil.

D. 2-[1-(3,3-Diphenyl-2-propenyl)-4-piperidinyl]-2,3-dihydro-1H-isoindol-1-one

To a solution of compound A (1.63 g, 7.56 mmol) and compound C (1.90 g, 8.32 mmol) in dimethylformamide (35 mL), potassium carbonate (1.10 g, 7.94 mmol) was added at room temperature. The reaction was stirred at 50° C. overnight. The reaction was evaporated to dryness. The resulting residue was dissolved in dichloromethane (150 mL) and washed with water (50 mL×2), brine (50 mL×2) and dried over $MgSO_4$. Evaporation gave a crude solid. Purification was performed by flash chromatography, loaded and eluted with 3% methanol in dichloromethane. Pure fractions were combined and evaporated to give compound D (1.95 g, 63%) as a white solid, melting point 164–167° C.

Analysis for $C_{28}H_{28}N_2O.0.3\ H_2O$: Calc'd: C, 81.24; H, 6.96; N, 6.77; Found: C, 81.29; H, 6.88; N, 6.79.

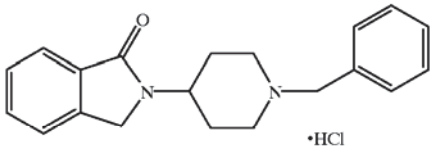
E. 2-[1-(3,3-Diphenyl-2-propenyl)-4-piperidinyl]-2,3-dihydro-1H-isoindol-1-one, monohydrochloride

To a solution of compound D (200 mg, 0.49 mmol) in methanol (2 mL) was added 1 N HCl in ethyl ether (0.5 mL) at room temperature. The resulting salt was filtered and washed with cold methanol (2×0.5 mL). After drying under high vacuum, Example 2 was obtained (160 mg, 80%) as a white solid, melting point 231–235° C.

Analysis for $C_{28}H_{29}ClN_2O.0.9\ H_2O$: Calc'd: C, 72.92; H, 6.73; Cl, 7.69; N, 6.07; Found: C, 72.99; H, 6.91; Cl, 7.36; N, 6.06.

EXAMPLE 3

2,3-Dihydro-2-[1-(phenylmethyl)-4-piperidinyl]-1H-isoindol-1-one, monohydrochloride



A. 2-[1-(Phenylmethyl)-4-piperidinyl]-1H-isoindol-1,3(2H)-dione

A mixture of phthalic anhydride (15.0 g, 101 mmol) and 4-amino-1-benzylpiperidine (19.3 g, 101 mmol) was heated with stirring in an oil bath until the mixture melted (about 125° C.). The reaction was kept at this temperature until the mixture solidified again (about 30 minutes). The reaction was cooled to room temperature. Purification was performed by flash chromatography on 1 kg silica gel, loaded and eluted with 30% ethyl acetate in hexane. Pure fractions were combined and evaporated to give compound A (25 g, 77%) as a white solid, melting point 151–154° C.

B. 2,3-Dihydro-2-[1-(phenylmethyl)-4-piperidinyl]-1H-isoindol-1-one

To a solution of compound A (20.0 g, 62.5 mmol) in acetic acid (248 mL) was added zinc dust (28.6 g, 438 mmol) under argon. With mechanical stirring, the reaction was refluxed overnight. The reaction was filtered through Celite, then evaporated to dryness. Dichloromethane (500 mL) was added, and the organic layer was washed with saturated sodium bicarbonate (2×100 mL), brine (100 mL) and dried over $MgSO_4$. Evaporation gave a crude oil. The resulting residue was azeotroped with toluene (2×30 mL) to afford a white solid. The product was recrystallized from isopropanol to give compound B (16 g, 80%) as a white solid (melting point 130–133° C.)

C. 2,3-Dihydro-2-[1-(phenylmethyl)-4-piperidinyl]-1H-isoindol-1-one, monohydrochloride

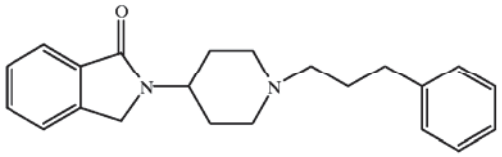
Compound B (200 mg, 0.62 mmol) was dissolved in ethanol (3 mL) and 4 N HCl in dioxane (1 mL) was added.

After 2 minutes at room temperature, a white solid precipitated. The solid was filtered and pumped under high vaccum to give Example 3 (120 mg, 60%) as a white solid, melting point 271–274° C.

Analysis for $C_{20}H_{23}N_2OCl.0.8\ H_2O$: Calc'd. C, 67.22; H, 6.94; N, 7.84; Found: C, 66.99; H, 7.05; N, 8.07.

EXAMPLE 4

2,3-Dihydro-2-[1-(3-phenylpropyl)-4-piperidinyl]-1H-isoindol-1-one, monohydrochloride



• HCl

A. 2,3-Dihydro-2-[1-(3-phenylpropyl)-4-piperidinyl]-1H-isoindol-1-one

To a solution of compound A from Example 2 (300 mg, 1.39 mmol) in dimethylformamide (8 mL) was added 1-bromo-3-phenylpropane (276 mg, 1.39 mmol, Aldrich) and potassium carbonate (201 mg, 1.46 mmol) at room temperature. The reaction was stirred at room temperature for 30 minutes, then the reaction was heated to 50° C. for 4 hours. The reaction was cooled to room temperature. Dichloromethane (100 mL) was added to dilute the reaction, and the organic layer was washed with water (50 mL×2), brine (50 mL×2) and dried over magnesium sulfate. Evaporation under reduced pressure gave a crude oil. Purification was performed by flash chromatography on silica gel (50 g), loaded and eluted with 0.5% methanol in dichloromethane (1.5 L) then 1.2% methanol in dichloromethane (1.0 L). Pure fractions were combined and evaporated to give compound A (400 mg, 84%) as a colorless oil.

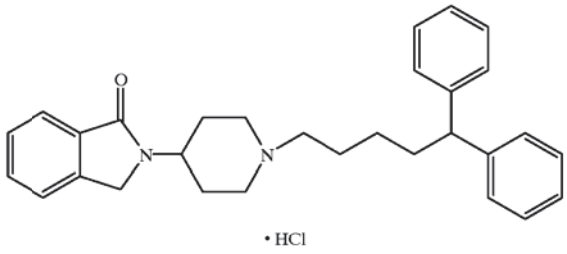
B. 2,3-Dihydro-2-[1-(3-phenylpropyl)-4-piperidinyl]-1H-isoindol-1-one, monohydrochloride

Compound A (400 mg, 1.20 mmol) was dissolved in 20% methanol in ethyl ether (2 mL). A solution of 1 N HCl in ethyl ether (4 mL, 4.0 mmol) was added. The HCl salt precipitated and was filtered and washed with ethyl ether. The resulting solid was dried under high vacuum at 60° C. overnight to give Example 4 (320 mg, 80%) as a white solid, melting point 229–231° C.

Analysis for $C_{22}H_{27}ClN_2O$: Calc'd: C, 71.24; H, 7.34; N, 7.55; Cl, 9.56; Found: C, 70.96; H, 7.42; N, 7.60; Cl, 9.63.

EXAMPLE 5

2-[1-(5,5-Diphenylpentyl)-4-piperidinyl]-2,3-dihydro-1H-isoindol-1-one, monohydrochloride



• HCl

A. b-Phenylbenzenepropanal

To a solution of oxalyl chloride (2.0 M in dichloromethane, 1.53 mL, 30.7 mmol) in dichloromethane (100 mL) was added dropwise a solution of dimethyl sulfoxide (4.35 mL, 61.4 mmol) in dichloromethane (9 mL) at −70° C. After addition, the reaction was stirred at −70° C. for 30 minutes, then a solution of 3,3-diphenyl-1-propanol (5.0 g, 23.6 mmol) in dichloromethane (10 mL) was added dropwise. The reaction was stirred at −70° C. for 1 hour. Triethylamine (27 mL, 141 mmol) was added and the reaction mixture was warmed to room temperature. Ethyl ether (300 mL) was added to dilute the reaction, the organic layer was washed with water (2×100 mL), 1 N HCl (2×100 mL), saturated sodium bicarbonate solution (2×100 mL), brine (2×100 mL) and dried over $MgSO_4$. Evaporation gave compound A (5.0 g, 100%) as a yellowish oil.

B. (E)-5,5-Diphenyl-2-pentenoic acid, ethyl ester

To a suspension of sodium hydride (1.14 g, 28.6 mmol) in tetrahydrofuran (50 mL) was added dropwise a solution of triethyl phosphonoacetate (6.13 mL, 30.9 mmol) in tetrahydrofuran (5 mL) at 0° C. The reaction was stirred at room temperature for 20 minutes (the solution is clear) then recooled to −78° C. A solution of compound A (5.0 g, 23.8 mmol) in tetrahydrofuran (5 mL) was added dropwise. The reaction was warmed to room temperature and quenched with saturated ammonium chloride solution (5 mL). Ethyl ether (200 mL) was added to dilute the reaction, and the organic layer was washed with water (2×50 mL), brine (2×50 mL) and dried over $MgSO_4$. Evaporation gave a crude oil. Purification was performed by flash chromatography on 250 g silica gel, loaded and eluted with 6% ethyl acetate in hexane. Pure fractions were combined and evaporated to give compound B (5.0 g, 75%) as a colorless oil.

C. (E)-5,5-Diphenyl-2-penten-1-ol

To a solution of compound B (4.97 g, 17.8 mmol) in toluene (30 mL) at 0° C. was added dropwise diisobutyl aluminum hydride (1.0 M in toluene) (39.1 mL, 39.1 mmol). The reaction was stirred at 0° C. for 1 hour. The reaction was quenched with methanol (5 mL). Potassium sodium tartrate solution (1 M, 200 mL) was added, and the reaction mixture was stirred for 3.5 hours. Ethyl ether (200 mL) was added, and the organic layer was washed with water (2×50 mL), brine (2×50 mL) and dried over $MgSO_4$. Evaporation gave a crude oil. Purification was performed by flash chromatography on 300 g silica gel, loaded and eluted with 20% ethyl acetate in hexane. Pure fractions were combined and evaporated to give compound C as a colorless oil (3.6 g, 85%).

D. (E)-1-Chloro-5,5-diphenyl-2-pentene

To a solution of N-chlorosuccinimide (2.22 g, 16.6 mmol) in dichloromethane (50 mL) at −40° C. was added dropwise methyl sulfide (1.55 mL, 21.1 mmol). The reaction was stirred at −40° C. for 10 minutes then warmed to room temperature for 30 minutes. The reaction was recooled to −40° C., and a solution of compound C (3.6 g, 15.1 mmol) in dichloromethane (5 mL) was added dropwise. The reaction was stirred at −40° C. for 2 hours then warmed to room temperature for 30 minutes. Hexane (300 mL) was added to dilute the reaction and the organic layer was washed with water (2×50 mL), brine (2×50 mL) and dried over $MgSO_4$. Evaporation gave compound D (3.4 g, 87%) as a colorless oil.

E. (E)-2-[1-(5,5-Diphenyl-2-pentenyl)-4-piperidinyl]-2,3-dihydro-1H-isoindol-1-one

To a solution of compound A from Example 2 (800 mg, 3.70 mmol) in dimethylformamide (20 mL) was added compound D (952 mg, 3.70 mmol) followed by anhydrous potassium carbonate (536 mg, 3.89 mmol). The reaction was stirred at 50° C. for 3 hours. The reaction was cooled to room temperature. Ethyl acetate (100 mL) was added to dilute the reaction, and the organic layer was washed with water (2×50 mL), brine (2×50 mL) and dried over Na_2SO_4. Evaporation gave a crude oil. Purification was performed by flash chromatography on 100 g of silica gel, loaded and eluted with 2% methanol in dichloromethane. Pure fractions were combined and evaporated to give compound E (1.0 g, 62%) as a white solid (melting point 136–141° C.).

F. 2-[1-(5,5-Diphenylpentyl)-4-piperidinyl]-2,3-dihydro-1H-isoindol-1-one

To a solution of compound E (500 mg, 1.36 mmol) in ethanol (10 mL) was added 10% palladium on activated carbon (50 mg) under argon at room temperature. A hydrogen balloon was connected to the solution. Hydrogenation was maintained overnight. The reaction was filtered through Celite, and the filtrate was evaporated to dryness. Purification was performed by flash chromatography on 100 g silica gel, loaded and eluted with 2.5% methanol in dichloromethane. Pure fractions were combined and evaporated to give compound F (400 mg, 80%) as a white solid, melting point 121–124° C.

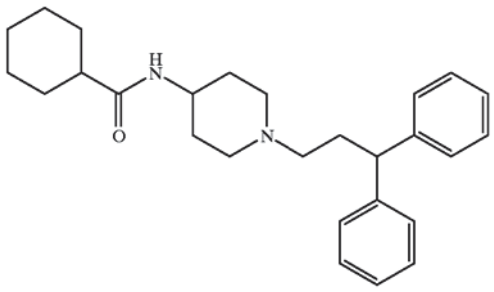
G. 2-[1-(5,5-Diphenylpentyl)-4-piperidinyl]-2,3-dihydro-1H-isoindol-1-one, monohydrochloride

Compound F (400 mg, 0.91 mmol) was dissolved in 20% methanol in ethyl ether (2 mL). A solution of 1 M HCl in ethyl ether (4 mL, 4.0 mmol) was added. The HCl salt precipitated and was filtered and washed with ethyl ether. The resulting solid was dried under high vacuum at 60° C. overnight to give Example 5 (320 mg, 80%) as a white solid (melting point 208–211° C.)

Analysis for $C_{30}H_{35}ClN_2O$: Calc'd: C, 75.85; H, 7.43; N, 7.90; Cl, 7.46; Found: C, 75.54; H, 7.54; N, 7.82; Cl, 7.56.

EXAMPLE 6

N-[1-(3,3-Diphenylpropyl)-4-piperidinyl] cyclohexane-carboxamide, monohydrochloride



• HCl

A. N-[1-(3,3-Diphenylpropyl)-4-piperidinyl]-cyclohexanecarboxamide

To a stirred solution of 405 mg (1.22 mmol) of compound E from Example 1 and 7 mg (5 mol %) of 4-dimethylaminopyridine in 8 mL of methylene chloride at 0° C. under argon were added 296 mL (3.67 mmol) of pyridine and 171 mL (1.28 mmol) of cyclohexylcarbonyl chloride. After warming to room temperature, the mixture was stirred for one hour and diluted with methylene chloride and water. The organics were separated, and the aqueous layer was basified with 1 M KOH and extracted with methylene chloride. The combined organics were dried (sodium sulfate) and concentrated to provide a yellow solid which was dried under high vacuum. The crude product was purified by flash chromatograghy on silica gel (80 g) eluted with 9:1 methylene chloride/methanol. Pure fractions were combined and concentrated to yield 438 mg (88%) of compound A as a clear, glassy solid.

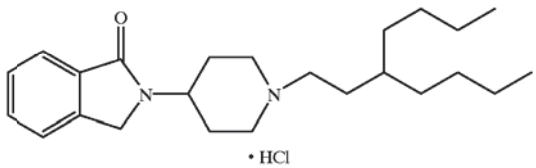
B. N-[1-(3,3-Diphenylpropyl)-4-piperidinyl] cyclohexane-carboxamide, monohydrochloride

To a solution of 430 mg (1.06 mmol) of compound A in 4 mL of methylene chloride was added 2.12 mL (2.12 mmol) of a 1.0 M solution of hydrogen chloride in diethyl ether. The opaque white solution was concentrated and dried under vacuum to provide 375 mg (76%) of Example 6 as a white solid, melting point greater than 250° C.

Analysis for $C_{27}H_{37}N_2OCl$: Calcd.: C, 73.53; H, 8.46; N, 6.35;Cl, 8.04; Found: C, 73.38; H, 8.52; N, 6.16; Cl, 7.97.

EXAMPLE 7

2-[1-(3-Butylheptyl)-4-piperidinyl]-2,3-dihydro-1H-isoindol-1- one, monohydrochloride



• HCl

A. 3-Butyl-2-heptenoic acid, ethyl ester

To a suspension of sodium hydride (60% in mineral oil) (1.01 g, 25.3 mmol) in tetrahydrofuran (40 mL) was added

dropwise a solution of triethyl phosphonoacetate (5.44 mL, 27.4 mmol) in tetrahydrofuran (5 mL) at 0° C. The reaction was warmed to room temperature and stirring was continued until the solution was clear. The reaction was recooled to −78° C., a solution of 5-nonanone (3.0 g, 21.1 mmol) in tetrahydrofuran (5 mL) was added dropwise. The reaction was stirred at −78° C. for 1 hour. The reaction was warmed to room temperature and quenched with saturated ammonium chloride (5 mL). Ethyl ether (200 mL) was added to dilute the reaction, and the organic layer was washed with water (2×50 mL), brine (2×50 mL) and dried over magnesium sulfate. Purification was performed by flash chromatography on 400 g silica gel, loaded and eluted with 15% ethyl acetate in hexane. Pure fractions were combined and evaporated to give compound A (1.63 g, 37%) as a colorless oil.

B. 3-Butyl-2-hepten-1-ol

To a solution of compound A (1.63 g, 7.69 mmol) in toluene (20 mL) at 0° C. was added a solution of diisobutylaluminum hydride (1 M solution in toluene, 16.9 mL, 16.9 mmol). The reaction was stirred at room temperature for 10 minutes and quenched with methanol (5 mL). Potassium sodium tartrate solution (1 M, 100 mL) was added, the mixture was stirred overnight. Ethyl ether (100 mL) was added, and the organic layer was washed with water (2×50 mL), brine (2×50 mL) and dried over magnesium sulfate. Evaporation gave compound B (1.30 g, 99%) as a colorless oil.

C. 3-Butyl-2-hepten-1-yl chloride

To a suspension of N-chlorosuccinimide (1.12 g, 8.42 mmol) in dichloromethane (20 mL) at −40° C. was added dropwise a solution of methyl sulfide (0.79 mL, 10.7 mmol) in dichloromethane (1 mL). After addition, the reaction was warmed to room temperature for 30 minutes. The reaction was recooled to −40° C., and a solution of 3 (1.3 g, 7.65 mmol) in dichloromethane (2 mL) was added. The reaction was stirred at −40° C. for 2 hours and warmed to room temperature. Hexane (150 mL) was added to dilute the reaction, and the organic layer was washed with water (2×50 mL), brine (2×50 mL) and dried over magnesium sulfate. Evaporation gave compound C (860 mg, 60%) as a cololess oil.

D. 2-[1-(3-Butyl-2-heptenyl)-4-piperidinyl]-2,3-dihydro-1H-isoindol-1-one

To a solution of compound A from Example 2 (974 mg, 4.51 mmol) in dimethylformamide (14 mL) was added a solution of compound C (850 mg, 4.51 mmol) in dimethylformamide (2 mL) followed by anhydrous potassium carbonate (653 mg, 4.74 mmol). The reaction was stirred at 50° C. for 3 hours. The reaction was cooled to room temperature. Ethyl acetate (100 mL) was added to dilute the reaction, and the organic layer was washed with water (2×50 mL), brine (2×50 mL) and dried over magnesium sulfate. Evaporation gave a crude oil. Purification was performed by flash chromatography on 100 g of silica gel, loaded and eluted with 2% methanol in dichloromethane. Pure fractions were combined and evaporated to give compound D (1.13 g, 68%) as a cololess oil.

E. 2-[1-(3-Butylheptyl)-4-piperidinyl]-2,3-dihydro-1H-isoindol-1-one

To a solution of compound D (500 mg, 1.36 mmol) in ethanol (10 mL) was added 10% palladium on activated carbon (50 mg) under argon at room temperature. Argon on the reaction was replaced by hydrogen. A hydrogen balloon was connected to the solution. Hydrogenation was maintained overnight. The reaction was filtered through Celite, and the filtrate was evaporated to dryness. Purification was performed by flash chromatography on 100 g silica gel, loaded and eluted with 2.5% methanol in dichloromethane. Pure fractions were combined and evaporated to give compound F (480 mg, 95%) as a waxy solid.

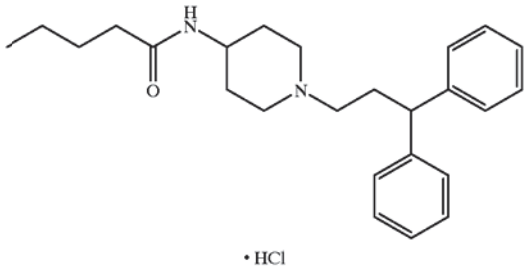
F. 2-[1-(3-Butylheptyl)-4-piperidinyl]-2,3-dihydro-1H-isoindol-1-one, monohydrochloride

Compound E (480 mg, 1.30 mmol) was dissolved in 20% methanol in ethyl ether (2 mL). A solution of 1 M HCl in ethyl ether (4 mL, 4.0 mmol) was added. The HCl salt precipitated and was filtered and washed with ethyl ether. The resulting solid was dried under high vacuum at 60° C. overnight to give Example 7 (300 mg, 62%) as a white solid (melting point 185–187° C.).

Analysis for $C_{24}H_{39}ClN_2O.0.5\ H_2O$: Calc'd: C, 69.29; H, 9.69; N, 6.73; Cl, 8.52; Found: C, 69.17; H, 9.75; N, 6.88; Cl, 8.91.

EXAMPLE 8

N-[1-(3,3-Diphenylpropyl)-4-piperidinyl]pentamide, monohydrochloride



A. N-[1-(3,3-Diphenylpropyl)-4-piperidinyl]-pentamide

To a stirred solution of 385 mg (1.16 mmol) of compound E from Example 1 and 7 mg (5 mol %) of 4-dimethylaminopyridine in 8 mL of methylene chloride at 0° C. under argon were added 282 mL (3.49 mmol) of pyridine and 147 mL (1.22 mmol) of valeryl chloride. After warming to room temperature, the mixture was stirred for one hour and diluted with methylene chloride and water. The organic layers were separated, and the aqueous layer was basified with 1 M KOH and extracted with methylene chloride. The combined organic layers were dried (sodium sulfate) and concentrated to provide a yellow solid which was dried under high vacuum. The crude product was purified by flash chromatography on silica gel (75 g) eluted with 95:5 methylene chloride/methanol. Pure fractions were combined and concentrated to yield 334 mg (76%) of compound A as a clear, glassy solid, melting point 126–128° C.

B. N-[1-(3,3-Diphenylpropyl)-4-piperidinyl] pentamide, monohydrochloride

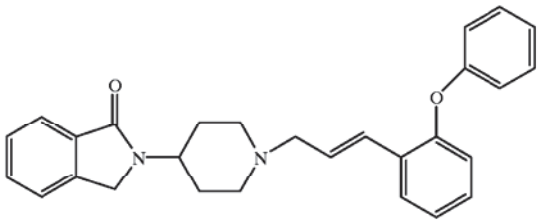
To a solution of 319 mg (0.84 mmol) of compound A in 4 mL of methylene chloride was added 1.68 mL (1.68 mmol) of a 1.0 M solution of hydrogen chloride in diethyl ether and

the heterogeneous mixture was stirred for thirty minutes. The resulting precipitate was filtered, washed with ether, and dried under vacuum to provide 327 mg (72%) of Example 8 as a yellow solid, melting point 189–191° C.

Analysis for $C_{25}H_{35}N_2OCl+0.3\ H_2O$: Calc'd: C, 71.41; H, 8.54; N, 6.66; Cl, 8.43; Found: C, 71.56; H, 8.46; N, 6.51; Cl, 8.66.

EXAMPLE 9

(E)-2,3-Dihydro-2-[1-[3-(2-phenoxyphenyl)-2-propenyl]-4-piperidinyl]-1H-isoindol-1-one, monohydrochloride



• HCl

A. 2-Phenoxybenzenemethanol

To a solution of 2-phenoxybenzoic acid (5.0 g, 23.3 mmol) in tetrahydrofuran (50 mL) was added dropwise at 0° C. lithium aluminum hydride solution (1 M in tetrahydrofuran, 23.3 mL, 23.3 mmol). The reaction was warmed to room temperature and stirring was continued for 8 hours. The reaction was quenched with methanol (5 mL), and 1 M potassium sodium tartrate solution (100 mL) was added. The mixture was stirred at room temperature overnight. Ethyl ether (200 mL) was added, and the organic layer was washed with water (2×50 mL), brine (2×50 mL) and dried over magnesium sulfate. Evaporation gave compound A (4.65 g, 99%) as a colorless oil.

B. 2-Phenoxybenzaldehyde

To a solution of oxalyl chloride (2.0 M in dichloromethane, 15.1 mL, 30.3 mmol) in dichloromethane (100 mL) at −70° C. was added dropwise a solution of dimethyl sulfoxide (4.25 mL, 60.6 mmol) in dichloromethane (5 mL). After addition, the reaction was stirred at −70° C. for 30 minutes, then a solution of compound A (4.65 g, 23.3 mmol) in dichloromethane (10 mL) was added dropwise. The reaction was stirred at −70° C. for 1 hour. Triethylamine (27 mL) was added and the reaction mixture was warmed to room temperature. Ethyl ether (300 mL) was added to dilute the reaction, and the organic layer was washed with water (2×100 mL), 1 N HCl (2×100 mL), saturated sodium bicarbonate solution (2×100 mL) and brine (2×100 mL) and dried over $MgSO_4$. Evaporation gave compound B as a yellowish oil (4.63 g, 100%).

C. (E)-3-(2-Phenoxyphenyl)-2-propenoic acid, ethyl ester

To suspension of sodium hydride (1.12 g, 28.1 mmol) in tetrahydrofuran (50 mL) was added dropwise a solution of triethyl phosphonoacetate (6.04 mL, 30.4 mmol) in tetrahydrofuran (5 mL) at 0° C. Then the reaction was stirred at room temperature for 20 minutes (the solution was clear). The reaction was recooled to −78° C., and a solution of compound A (4.63 g, 23.4 mmol) in tetrahydrofuran (5 mL) was added dropwise. The reaction was warmed to room temperature and quenched with saturated ammonium chloride solution (5 mL). Ethyl ether (200 mL) was added to dilute the reaction, and the organic layer was washed with water (2×50 mL), brine (2×50 mL) and dried over $MgSO_4$. Evaporation gave a crude oil. Purification was performed by flash chromatography on 500 g silica gel, loaded and eluted with 10% ethyl acetate in hexane. Pure fractions were combined and evaporated to give compound C (6.0 g, 96%) as a colorless oil.

D. (E)-3-(2-Phenoxyphenyl)-2-propenol

To a solution of compound C (2.5 g, 9.33 mmol) in toluene at 0° C. was added dropwise a diisobutyl aluminum hydride (1.0 M in toluene) (20.5 mL, 20.5 mmol) solution. The reaction was stirred at 0° C. for 1 hour. The reaction was quenched with methanol (5 mL). 1 M potassium sodium tartrate solution (100 mL) was added, and the reaction mixture was stirred for 3.5 hours. Ethyl ether (200 mL) was added, and the organic layer was washed with water (2×50 mL), brine (2×50 mL) and dried over $MgSO_4$. Evaporation gave a crude oil. Purification was performed by flash chromatography on 300 g silica gel, loaded and eluted with 20% ethyl acetate in hexane. Pure fractions were combined and evaporated to give compound D (1.85 g, 88%) as a colorless oil.

E. (E)-1-(3-Chloro-1-propenyl)-2-phenoxybenzene

To a solution of N-chlorosuccinimide (1.11 g, 8.33 mmol) in dichloromethane (20 mL) was added dropwise methyl sulfide (0.78 mL, 10.6 mmol) at −40° C. The reaction was stirred at −40° C. for 10 minutes then warmed to room temperature for 30 minutes. The reaction was recooled to −40° C., and a solution of compound D (1.71 g, 7.57 mmol) in dichloromethane was added dropwise. The reaction was stirred at −40° C. for 3 hours, then warmed to room temperature for 30 minutes. Hexane (100 mL) was added to dilute the reaction, and the organic layer was washed with water (2×50 mL), brine (2×50 mL) and dried over $MgSO_4$. Evaporation gave compound E (1.72 g, 93%) as a colorless oil.

F. (E)-2,3-Dihydro-2-[1-[3-(2-phenoxyphenyl)-2-propenyl]-4-piperidinyl]-1H-isoindol-1-one

To a solution of compound A from Example 2 (0.88 g, 4.09 mmol) in dimethylformamide (10 mL) was added a solution of compound E (1.0 g, 4.09 mmol)in dimethylformamide (2 mL) followed by potassium carbonate (592 mg, 4.29 mmol). The reaction was stirred at 50° C. for 14 hours. The reaction was cooled to room temperature. Ethyl ether (100 mL) was added to dilute the reaction, and the organic layer was washed with water (2×50 mL), brine (2×50 mL) and dried over $MgSO_4$. Evaporation gave a crude oil. Purification was performed by flash chromatography on 150 g silica gel, loaded and eluted with 2% methanol in dichloromethane. Pure fractions were combined and evaporated to give compound F (1.1 g, 63%) as a colorless oil.

G. (E)-2,3-Dihydro-2-[1-[3-(2-phenoxyphenyl)-2-propenyl]-4-piperidinyl]-1H-isoindol-1-one, monohydrochloride

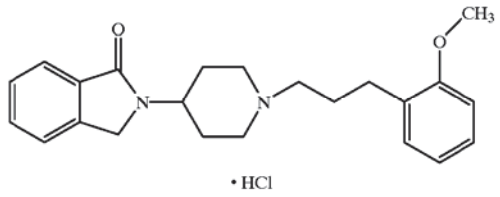
To a solution of compound F (500 mg, 1.15 mmol) in ethyl ether:methanol (2 mL, 5:1) was added 1 M HCl in ethyl ether (1.5 mL, 1.5 mmol). The HCl salt precipitated from the solution. The salt was filtered and dried at 60° C.

under vacuum to give Example 9 (300 mg, 55%) as a white solid, melting point 215–218° C.

Analysis for $C_{28}H_{29}ClN_2O_2$: Calc'd: C, 72.95; H, 6.34; N, 6.08; Cl, 7.69; Found: C, 72.49; H, 6.39; N, 6.04; Cl, 7.37.

EXAMPLE 10

2,3-Dihydro-2-[1-[3-(2-methoxyphenyl)propyl]-4-piperidinyl]-1H-isoindol-1-one, monohydrochloride



A. 2-Methoxybenzenepropanol

To a solution of 3-(2-methoxyphenyl)propionic acid (2.0 g, 11.1 mmol) in tetrahydrofuran (25 mL) was added dropwise at 0° C. lithium aluminum hydride solution (1 M in tetrahydrofuran, 11.1 mL, 11.1 mmol). The reaction was warmed to room temperature and stirring was continued overnight. The reaction was quenched with methanol (5 mL), and 1 M potassium sodium tartrate solution (100 mL) was added. The mixture was stirred at room temperature overnight. Ethyl ether (200 mL) was added, and the organic layer was washed with water (2×50 mL), brine (2×50 mL) and dried over magnesium sulfate. Evaporation gave compound A (1.5 g, 81%) as a colorless oil.

B. 1-(3-Bromopropyl)-2-methoxybenzene

To a solution of compound A (620 mg, 3.73 mmol) and triphenylphosphine (1.08 g, 4.11 mmol) in dichloromethane (10 mL) was added N-bromosuccinimide (731 mg, 4.11 mmol) at 0° C. The reaction was stirred at 0° C. for 2 hours. Dichloromethane (100 mL) was added to dilute the reaction, and the organic layer was washed with water (2×50 mL), brine (2×50 mL) and dried over $MgSO_4$. Purification was performed by flash chromatography on 100 g silica gel, loaded and eluted with 10% dichloromethane in hexane. Pure fractions were combined and evaporation to give compound B (582 mg, 68%) as a colorless oil.

C. 2,3-Dihydro-2-[1-[3-(methoxyphenyl)propyl]-4-piperidinyl]-1H-isoindol-1-one

To a solution of compound A from Example 2 (549 mg, 2.54 mmol) in dimethylformamide (10 mL) was added a solution of compound B (582 mg, 2.54 mmol) in dimethylformamide (1 mL) followed by potassium carbonate (386 mg, 2.80 mmol). The reaction was stirred at 50° C. for 14 hours. The reaction was cooled to room temperature. Ethyl ether (100 mL) was added to dilute the reaction, and the organic layer was washed with water (2×50 mL), brine (2×50 mL) and dried over $MgSO_4$. Evaporation gave a crude oil. Purification was performed by flash chromatography on 150 g silica gel, loaded and eluted with 2% methanol in dichloromethane. Pure fractions were combined and evaporated to give compound C (560 mg, 61%) as a colorless oil.

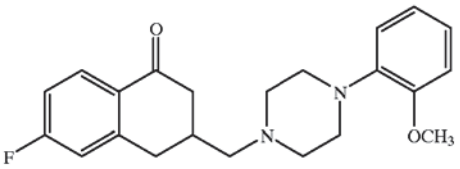
D. 2,3-Dihydro-2-[1-[3-(2-methoxyphenyl)propyl]-4-piperidinyl]-1H-isoindol-1-one, monohydrochloride

To a solution of compound C (500 mg, 1.37 mmol) in methanol (2 mL) was added 1 M HCl in ethyl ether (1.5 mL, 1.5 mmol). The mixture was evaporated and dried at 70° C. under vacuum to give Example 10 (300 mg, 60%) as a yellowish solid, melting point 191–195° C.

Analysis for $C_{23}H_{29}ClN_2O_2$+0.3 mol H_2O: Calc'd: C, 67.98; H, 7.34; N, 6.89; Cl, 8.72; Found: C, 67.92; H, 7.63; N, 6.75; Cl, 8.54

EXAMPLE 11

6-Fluoro-3,4-dihydro-3-[[4-(2-methoxyphenyl)-1-piperazinyl]-methyl]-1(2H)-naphthalenone



A. a-Acetyl-3-fluorobenzenepropanoic acid, ethyl ester

To a solution of 500 mL of 10% dimethylformamide in benzene was added 58.6% NaH (41 g, 1.0 mol) cooled in an ice bath was added ethyl acetoacetate (130 g, 1.0 mol) was added. The reaction was stirred at room temperature for 30 minutes, and m-fluorobenzyl chloride (145 g, 1.0 mol) was added. The reaction was heated to reflux for 3 hours and gave an NaCl precipitate which was then removed by filtration. The filtrated was poured into H_2O, acidified with concentrated HCl and was extracted with a mixture of ether and benzene. The organic layer was washed with H_2O, brine, dried over Na_2SO_4 and concentrated in vacuo. The crude product was purified by distillation (112–119° C./25 mmHg) to give compound A (133 g, 56%).

Analysis for $C_{13}H_{15}FO_3$: Calc'd: C, 65.53; H, 6.35; Found: C, 65.56; H 6.12.

B. 2-Acetyl-2-[(3-fluorophenyl)methyl]butanedioic acid, diethyl ester

This reaction procedure was followed as described above for the preparation of compound A. The reaction scale is as follows: Compound A (130 g, 0.546 mol), ethyl chloroacetate (67 g, 0.546 mol), 58.6% NaH (22.36 g, 0.546 mol) and 400 mL of 20% dimethylformamide in benzene. The reflux time in this reaction was 21 hours and the crude product was purified by distillation at 135–158° C./0.2 mmHg to give compound B (119 g, 67%).

C. 2-[(3-Fluorophenyl)methyl]butanedioic acid, diethyl ester

To a solution of compound B (119.3 g, 0.368 mol) in 550 mL H_2O was added NaOH (45 g, 1.10 mol) and the reaction was reflux for 23 hours. The reaction was cooled to room temperature, and the reaction mixture was washed with ether. The aqueous layer was placed in the ice bath, acidified with concentrated HCl and gave a precipitate. The crude product was removed by filtration and recrystallized in hot benzene to give compound C (57.8 g, 69%), melting point 120.5–121.5° C.

Analysis for $C_{11}H_{11}FO_4$: Calc'd: C, 58.41; H, 4.90; Found: C, 58.91; H, 5.10.

D. 3-[(3-Fluorophenyl)methyl]-3,4-dihydro-2,5-furandione

To a solution of compound C (43.0 g, 0.19 mol) in 100 mL acetic anhydride was added 8 mL acetic acid. The reaction

was heated to reflux for 20 minutes and concentrated in vacuo with dry benzene. The crude product was dissolved in 10 mL benzene, 70 mL skelly B was added and upon cooling in an ice bath, a crystalline solid formed. The crystals were collected by filtration and recrystallized in isopropanol/skelly B to give compound D (24.0 g, 61%), melting point 55–57° C.

Analysis for $C_{11}H_9FO_3$: Calc'd: C, 63.46; H, 4.36; Found: C, 63.92; H, 5.25.

E. 7-Fluoro-1,2,3,4-tetrahydro-4-oxo-2-naphthalene-carboxylic acid

To 500 mL of nitrobenzene was slowly added $AlCl_3$ (30.66 g, 0.23 mol) and compound D (23.85 g, 0.115 mol) keeping the temperature between 20–25° C. The reaction was stirred at room temperature for 67 hours and was poured into a mixture of 360 g ice and 170 mL concentrated HCl. The nitrobenzene was then removed by distillation. The crude product was crystallized in the ice bath and was recrystallized from benzene/skelly B to give compound E (20.0 g, 84%), melting point 146–147° C.

Analysis for $C_{11}H_9FO_3$: Calc'd: C, 63.46; H, 4.36 Found:C, 63.54; H, 4.48.

F. 7-Fluoro-1,2,3,4-tetrahydro-4-oxo-2-naphthalene-carboxylic acid, methyl ester

To a solution of compound E (5.0 g, 0.024 mol) in 25 mL methanol was added 1 mL concentrated H_2SO_4. The reaction mixture heated to reflux for 40 hours. The reaction mixture was concentrated in vacuo and was partitioned between ethyl acetate and 5% $NaHCO_3$. The organic layer was washed further with H_2O, brine, dried over Na_2SO_4 and was concentrated in vacuo. The crude product was crystallized in a mixture of ethyl acetate and skelly B and was recrystallized in hot skelly B to give compound F (4.9 g, 92%), melting point 90–92° C.

Analysis for $C_{12}H_{11}FO_3$: Calc'd: C, 64.86; H, 4.99; Found: C, 65.21; H, 5.21.

G. 6-Fluoro-3',4'-dihydrospiro[1,3-dioxolane-2,1'(2'H)-naphthalene]-3'-carboxylic acid, methyl ester

To a solution of compound F (103.4 g, 0.465 mol) in 700 mL of dry benzene was added ethylene glycol (78.5 mL, 1.395 mol), followed by a catalytic amount of p-toluenesulfonic acid. The reaction was heated to reflux for 66 hours. The reaction mixture was concentrated in vacuo, and the crude product was crystallized in methanol to give compound G (82 g, 66%), melting point 79–81° C.

Analysis for $C_{14}H_{15}FO_4$: Calc'd: C, 63.15; H, 5.67; Found: C, 63.13; H, 5.82.

H. 6-Fluoro-3',4'-dihydrospiro[1,3-dioxolane-2,1'(2'H)-naphthalene]-3'-methanol

To a suspension of lithium aluminum hydride (11.25 g, 0.296 mol) in 700 mL of dry tetrahydrofuran was added a solution of compound G (78.8 g, 0.296 mol) in 300 mL tetrahydrofuran. The reaction was heated to reflux for 17 hours and 22.5 mL H_2O and 18 mL 10% NaOH was added with cooling. The reaction was stirred at room temperature for 2 hours. The reaction mixture was filtered and the filtrate was concentrated in vacuo to give compound H (69.4 g, 78%).

Analysis for $C_{13}H_{15}FO_3$ Calc'd: C, 65.53; H, 6.35 Found: C, 65.82; H, 6.72.

I. 6-Fluoro-3',4'-dihydrospiro[1,3-dioxolane-2,1'(2'H)-naphthalene]-3'-methanol, methanesulfonate ester

To a solution of compound H (61.1 g, 0.256 mol) in 175 mL dry pyridine under nitrogen was added methanesulfonyl chloride (27.15 mL, 0.358 mol) maintaining the temperature between 10 and 15° C. The reaction was stirred between 5–10° C. for 30 minutes and room temperature for 2.5 hours. The reaction mixture was poured into ice-water and extracted with CH_2Cl_2. The organic layer was further washed with H_2O, brine, dried over Na_2SO_4 and was concentrated in vacuo. The crude product was further evaporated with toluene at 35° C. under water pressure to give compound I (83.7 g, quant.).

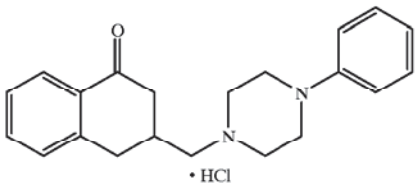
J. 6-Fluoro-3,4-dihydro-3-[[4-(2-methoxyphenyl)-1-piperazinyl]-methyl]-1(2H)-naphthalenone

To a solution of compound I (10.0 g, 0.0316 mmol) in 150 mL of 25% methyl isobutyl ketone in absolute ethanol was added Na_2CO_3 (2.7 g, 0.0316 mol) and 1-(2-methoxyphenyl)piperazine followed by a catalytic amount of KI. The reaction was heated to reflux for 25 hours and the mixture was filtered. The filtrate was concentrated in vacuo and dissolved in CH_2Cl_2. The organic layer was washed with H_2O, $NaHCO_3$, brine, dried over Na_2SO_4 and was concentrated in vacuo. 15% HCl (100 mL) was added to the crude and stirred at room temperature for 4 hours. The solution was filtered and was extracted with ethyl ether. The aqueous solution was then basified and extracted with ethyl ether. The final ethyl ether layer was washed with H_2O, brine, dried over Na_2SO_4 and was concentrated in vacuo. The crude product was recrystallized from methanol twice to give Example 11 (6.57 g, 56%), melting point 111–113° C.

Analysis for $C_{22}H_{25}N_2O_2F$: Calc'd: C, 71.72; H, 6.84; N, 7.60; Found: C, 70.11; H, 7.06, N, 7.83.

EXAMPLE 12

3,4-Dihydro-3-[(4-phenyl-1-piperazinyl)-methyl]-1-(2H)-naphthalenone, monohydrochloride



A. 2-Acetyl-2-(phenylmethyl)butanedioic acid, diethyl ester

This reaction procedure followed the procedure described in the preparation of compound B of Example 11. The reaction scale is as follows: Benzyl acetoacetate (180 g, 0.86 mol), ethyl chloroacetate (105 g, 0.86 mol), 58.6% NaH (35.2 g, 0.86 mol) and 300 mL of 10% dimethylformamide in dry benzene. The reflux time in this reaction was 3 hours and the crude product was purified by distillation at 148–159° C./0.3 mmHg to give compound A (164.7 g, 63%).

B. 2-(Phenylmethyl)butanedioic acid

This reaction procedure followed the procedure described in the preparation of compound C of Example 11. The

reaction scale is as follows: compound A (164.7 g, 0.54 mol) and 1.5 L of 2 N NaOH. The reaction was reflux for 20 hours and gave compound B (95.8 g, 85%), melting point 152–156° C.

C. 3,4-Dihydro-3-(phenylmethyl)-2,5-furandione

This reaction procedure was followed as described in the preparation of compound D of Example 11. 95.8 g of compound B gave 72 g (82%) of compound C, boiling point 156° C. (0.4 mm), and the resulting solid was recrystallzed from hot benzene, melting point 94–96° C.

D. 1,2,3,4-Tetrahydro-4-oxo-2-naphthalene-carboxylic acid

This reaction procedure was followed as described in the preparation of compound E of Example 11. The reaction scale is as follows: compound C (55.7 g, 0.29 mol), $AlCl_3$ (80 g, 0.6 mol) and 280 mL nitrobenzene. The nitrobenzene was removed by distillation and the aqueous was crystallized to give compound D (50.8 g, 91%), melting point 145–148° C.

E. 1,2,3,4-Tetrahydro-4-oxo-2-naphthalene-carboxylic acid, methyl ester

To a solution of N-nitro-N-methyl urea in 500 mL ether was added 135 mL of 40% KOH, followed by compound D (50.8 g, 0.27 mol), while cooling in an ice bath. The reaction was stirred at room temperature for 1 hour and acetic acid was added to react with excess diazomethane. The ethyl ether layer was washed with 200 mL of 5% NaOH, 200 mL of dilute acetic acid, 200 mL of dilute $NaHCO_3$, brine, dried over Na_2SO_4 and was concentrated in vacuo. The crude product was isolated by distillation at 124° C./0.15 mmHg to give compound E (50.3 g, 91%).

F. 3',4'-Dihydrospiro[1,3-dioxolane-2,1'(2'H)-naphthalene]-3'-carboxylic acid, methyl ester

This reaction procedure was followed as described in the preparation of compound G of Example 11. The reaction scale is as follows: compound E (5.0 g, 0.025 mol), ethylene glycol (4.8 Ml, 0.075 mol), 40 mL dry benzene and a catatalytic amount p-toluenesulfonic acid. The reaction was reflux for 64 hours and was concentrated in vacuo to give compound F (6.0 g, 95%).

G. 3',4'-Dihydrospiro[1,3-dioxolane-2,1'(2'H)-naphthalene]-3'-methanol

This reaction procedure was followed as described in the preparation of compound H of Example 11. The reaction scale is as follows: compound F (7.3 g, 0.028 mol), lithium aluminum hydride (1.06 g, 0.028 mol) and 50 mL dry tetrahydrofuran. The crude product was isolated by distillation at 152–153° C./0.15 mmHg to give compound G (4.0 g, 62%).

Analysis for $C_{13}H_{16}O_3$: Calc'd: C, 70.89; H, 7.32; Found: C, 70.73; H 7.33.

H. 3',4'-Dihydrospiro[1,3-dioxolane-2,1'(2'H)-naphthalene]-3'-methanol, methanesulfonate ester

This reaction procedure was followed as described in the preparation of compound I of Example 11. The reaction scale is as follows: compound G (3.16 g, 0.144 mol), methanesulfonyl chloride (1.6 mL, 0.202 mol) and 30 mL pyridine. The reaction was stirred at room temperature for 2 hours and the crude product was precipitated by pouring onto ice to give compound H (3.35 g, 78%), melting point 75–79° C.

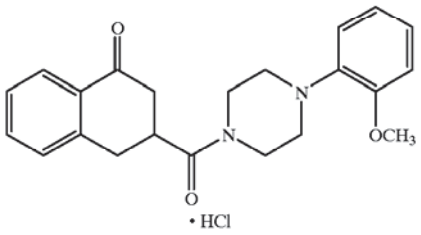
I. 3,4-Dihydro-3-[(4-phenyl-1-piperazinyl)methyl]-1-(2H)-naphthalenone, monohydrochloride

To a solution of compound H (1.43 g, 0.048 mmol) in 50 mL of a mixture of methyl isobutyl ketone and absolute ethanol was added Na_2CO_3 (0.71 g, 0.048 mol) and 1-phenylpiperazine (1.77 g, 0.011 mol). The reaction was heated to reflux for 20 hours and the particles was removed by filtration. The filtrate was concentrated in vacuo and dissolved in ethyl acetate. The organic layer was washed with H_2O, 5% $NaHCO_3$ and was concentrated in vacuo to dryness. 100 mL of 10% HCl was added to the crude and stirred at room temperature for 4 hours. The mixture was extracted with ethyl ether and the aqueous solution was then basified with concentrated NH_4OH to pH 9 and extracted with ethyl ether. The ethyl ether layer was combined, washed with H_2O, brine, dried over Na_2SO_4 and concentrated in vacuo. The crude product was redissolved in 200 mL ethyl ether, saturated with HCl, and the solid precipitate was recrystallized from hot ethanol to give Example 12 (0.43 g, 23%), melting point 243–246° C.

Analysis for $C_{21}H_{24}N_2O.HCl$: Calc'd: C, 64.09; H, 6.67; N, 7.13; Cl, 9.95; Found: C, 70.77; H, 7.10; N, 7.69; Cl, 10.69.

EXAMPLE 13

3,4-Dihydro-3-[[4-(2-methoxyphenyl)-1-piperazinyl]-carbonyl]-1(2H)-naphthalenone, monohydrochloride



A. 1,2,3,4-Tetrahydro-4-oxo-2-naphthalene-carboxylic acid

To a solution of KOH (6.7 g, 0.12 mol) in 60 mL H_2O was added compound E from Example 12 (10.0 g, 0.049 mol). The reaction was warmed gently for 30 minutes and was then cooled to room temperature and was acidified with 1 N HCl. The crude product was filtered, washed with cold H_2O and dried over P_2O_5 to give compound A (8.68 g, 93%), melting point 148–150° C.

B. 3,4-Dihydro-3-[[4-(2-methoxyphenyl)-1-piperazinyl]-carbonyl]-1(2H)-naphthalenone, monohydrochloride

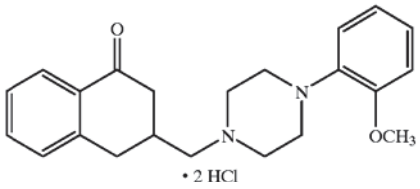
To a solution of compound A (9.5 g, 0.05 mmol) and triethylamine (8.38 mL, 0.05 mol) in 125 mL CH_2Cl_2 was added isobutyl chloroformate (6.58 mL, 0.05 mol) at −10° C. The reaction was stirred at −5 to −10° C. for 10 minutes and was followed by 1-(2-methoxyphenyl)piperazine (9.61 g, 0.05 mol) in 25 mL CH_2Cl_2. The ice bath was removed and the reaction was stirred at room temperature for 17

hours. The reaction mixture was washed with 5% $NaHCO_3$, H_2O, brine, dried over Na_2SO_4 and concentrated in vacuo. The crude product was dissolved in ethyl ether, bubbled with HCl and was filtered to give Example 13 (15.45 g, 85%), melting point 197–199° C.

Analysis for $C_{22}H_{24}N_2O_3$.HCl: Calc'd: C, 65.89; H, 6.28; N, 6.99; Cl, 8.85; Found: C, 66.27; H, 6.41; N, 7.35; Cl, 9.58.

EXAMPLE 14

3,4-Dihydro-3-[[4-(2-methoxyphenyl)-1-piperazinyl] methyl]-1(2H)-naphthalenone, dihydrochloride



• 2 HCl

A. 1,2,3,4-Tetrahydro-3-[[4-(2-methoxyphenyl)-1-piperazinyl]methyl]-1-naphthalenone

To a solution of the free base of compound B of Example 13 (11.74 g, 0.0322 mol) in 50 mL of dry tetrahydrofuran was added lithium aluminum hydride (2.45 g, 0.0644 mol) in 50 mL of dry tetrahydrofuran. The reaction was heated to reflux for 22 hours. The reaction was mixed with 5 mL H_2O, 4 mL of 10% NaOH and was stirred at room temperature for 2 hours. The solids were removed by filtration, washed with tetrahydrofuran and concentrated in vacuo to give compound A (10.1 g, 89%).

Analysis for $C_{22}H_{28}N_2O_2$.2 HCl.H_2O: Calc'd: C, 59.59; H, 7.27; N, 6.32; Cl, 15.99; KF, 4.06; Found: C, 59.45; H, 7.10; N, 6.50; Cl, 16.49; KF, 4.36.

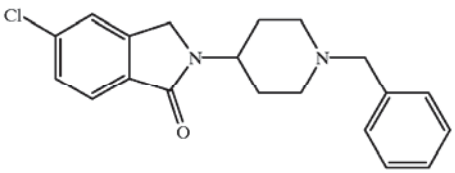
B. 3,4-Dihydro-3-[[4-(2-methoxyphenyl)-1-piperazinyl]methyl]-1(2H)-naphthalenone, dihydrochloride

To a solution of compound A (4.91 g, 0.014 mmol) in 120 mL benzene was added potassium tert-butoxide (3.93 g, 0.035 mol) and benzophenone (11.8 g, 0.065 mol). The reaction was refluxed for 16 hours and washed with H_2O. The organic layer was washed further with brine, dried over Na_2SO_4 and concentrated in vacuo to dryness. The crude product was dissolved in ethyl ether, bubbled with HCl salt, recrystallized from methanol/ethyl ether to give Example 14 (5.2 g, 87%), melting point 218–219° C.

Analysis for $C_{22}H_{26}N_2O_2$.2 HCl Calc'd: C, 62.41; H, 6.67; N, 6.62; Cl, 16.75; Found: C, 62.61; H, 6.87; N, 6.37.

EXAMPLE 15

5-Chloro-2,3-dihydro-2-[1-(phenylmethyl)-4-piperidinyl]-1H-isoindol-1-one, monohydrochloride



• HCl

A. 5-Chloro-1,3-isobenzofurandione

4-Chlorophthalic acid (446.5 g, 2.23 mol) was heated neat until H_2O was no longer released to give compound A (415.9 g, quantitative), melting point 138–140° C.

B. 5-Chloro-1H-isoindole-1,3(2H)-dione

A solution of compound A (415.9 g, 2.28 mol) and 1000 mL of 28% ammonium hydroxide was heated at 300° C. until H_2O was no longer released to give compound B (361.0 g, 8%).

C. 5-Chloro-2-[1-(phenylmethyl)-4-piperidinyl]-1H-isoindole-1,3(2H)-dione

To a solution of compound B (10.0 g, 55.2 mmol) in 100 mL amyl alcohol was added 4-amino-1-benzylpiperidine (10.5 g, 55.2 mmol). The reaction was heated to reflux for 16 hours. The reaction mixture was concentrated in vacuo and dissolved in 250 mL $CHCl_3$. The $CHCl_3$ layer was washed with H_2O, dried over Mg_2SO_4 and was concentrated in vacuo. The crude product was dissolved in 400 mL isopropyl ether, treated with charcoal and filtered. The filtrate was acidified with 4 N HCl in dioxane to give compound C (19.0 g, 97%) as a white solid, melting point 233–234.5° C.

Analysis for $C_{20}H_{19}ClN_2O_2$.HCl: Calc'd: C, 61.40; H, 5.16; N, 7.16; Found: C, 62.04; H, 5.64; N, 7.31.

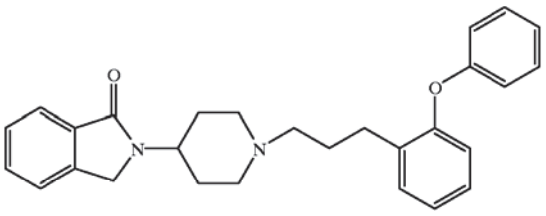
D. 5-Chloro-2,3-dihydro-2-[1-(phenylmethyl)-4-piperidinyl]-1H-isoindol-1-one, monohydrochloride

To a solution of compound C (5.5 g, 14.1 mmol) in 40 mL acetic acid and 8.25 mL concentrated HCl was added tin (4.2 g, 35.3 mmol). The reaction was heated at 95–100° C. for 16 hours, treated with 5% NaOH to pH greater than 9, and extracted with $CHCl_3$. The organic layer was dried over Mg_2SO_4 and was concentrated in vacuo to the dryness. The crude product was dissolved in 200 mL H_2O and treated with HCl in dioxane to give Example 15 (4.64 g, 87%), melting point 269–271° C.

Analysis for $C_{20}H_{21}ClN_2O$+0.8 HCl+0.2 H_2O: Calc'd: C, 64.29; H, 5.99; N, 7.50; Cl, 17.08; H_2O, 0.96; Found: C, 64.19; H, 6.05; N, 7.54; Cl, 16.96; H_2O, 0.95.

EXAMPLE 16

2,3-Dihydro-2-[1-[3-(2-phenoxyphenyl)propyl]-4-piperidinyl]-1H-isoindol-1-one, monohydrochloride



• HCl

A. 2,3-Dihydro-2-[1-[3-(2-phenoxyphenyl)propyl]-4-piperidinyl]-1H-isoindol-1-one

To a solution of compound F from Example 9 (450 mg, 1.06 mmol) in ethanol (10 mL) was added 10% palladium on activated carbon (45 mg) under argon at room temperature. Argon on the reaction was replaced by hydrogen. A hydrogen balloon was connected to the solution. Hydrogenation was maintained overnight. The reaction was filtered through Celite, and the filtrate was evaporated to dryness. Purification was performed by flash chromatography on 100 g silica gel, loaded and eluted with 1.5% methanol in dichloromethane. Pure fractions were combined and evaporated to give compound A (450 mg, 100%) as a colorless oil.

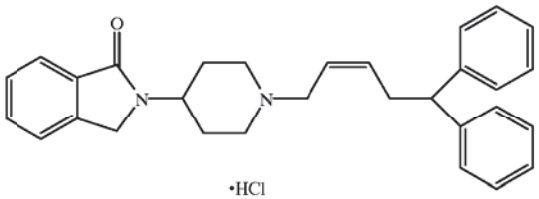
B. 2,3-Dihydro-2-[1-[3-(2-phenoxyphenyl)propyl]-4-piperidinyl]-1H-isoindol-1-one, monohydrochloride

Compound A (450 mg, 1.06 mmol) was dissolved in 20% methanol in ethyl ether (2 mL). A solution of 1 M HCl in ethyl ether (2 mL, 2.0 mmol) was added. The HCl salt precipitated and was filtered and washed with ethyl ether. Dichloromethane (80 mL) was added to dissolve the solid, and the organic layer was washed with saturated sodium bicarbonate solution (2×30 mL). Evaporation gave a colorless oil. Purification was performed by flash chromatography, loaded and eluted with 1.5% methanol in dichloromethane. Pure fractions were combined and evaporated to give a colorless oil. The resulting oil was dissolved in 20% methanol in hexane. A solution of 1 M HCl in ethyl ether (1 mL, 1.0 mmol) was added. The HCl salt precipitated and was filtered and washed ethyl ether. The resulting solid was dried under high vacuum at 60° C. overnight to give Example 16 (160 mg, 35%) as a white solid, melting point 199–202° C.

Analysis. for $C_{28}H_{31}ClN_2O_2.0.5\ H_2O$: Calc'd: C, 71.25; H, 6.83; N, 5.93; Found: C, 71.13; H, 6.78; N, 5.93.

EXAMPLE 17

(Z)-2,3-Dihydro-2-[1-(5,5-diphenyl-2-pentenyl)-4-piperidinyl]-1H-isoindol-1-one, monohydrochloride



•HCl

A. (Z)-5,5-Diphenyl-2-pentenoic acid, methyl ester

To a suspension of bis(2,2,2-trifluoroethyl)-(methoxycarbonylmethyl)phosphonate (4.16 g, 13.1 mmol) and 18-crown-6 (3.46 g, 13.1 mmol) in tetrahydrofuran (65 mL) at 0° C. was added dropwise 0.5 M potassium bis(trimethylsilyl)amide in toluene (26.2 mL, 13.1 mmol). The reaction was stirred at 0° C. for 15 minutes, then cooled to −78° C. A solution of compound A from Example 5 (5.0 g, 23.8 mmol) in tetrahydrofuran (5 mL) was added dropwise. The reaction was stirred at −78° C. for 1 hour, then warmed to room temperature and quenched with saturated ammonium chloride solution (5 mL). Ethyl ether (200 mL) was added to dilute the reaction, and the organic layer was washed with water (2×50 mL), brine (2×50 mL) and dried over $MgSO_4$. Evaporation gave a crude oil. Purification was performed by flash chromatography on 250 g silica gel, loaded and eluted with 6% ethyl acetate in hexane. Pure fractions were combined and evaporated to give compound A (2.2 g, 70%) as a colorless oil.

B. (Z)-5,5-Diphenyl-2-penten-1-ol

To a solution of compound A (2.2 g, 8.27 mmol) in toluene (20 mL) at 0° C. was added dropwise diisobutylaluminum hydride (1.0 M in toluene, 18.2 mL, 18.2 mmol). The reaction was stirred at 0° C. for 1 hour. The reaction was quenched with methanol (5 mL). Potassium sodium tartrate solution (1 M, 200 mL) was added, and the reaction mixture was stirred for 3.5 hours. Ethyl ether (200 mL) was added, and the organic layer was washed with water (2×50 mL), brine (2×50 mL) and dried over $MgSO_4$. Evaporation gave a crude oil. Purification was performed by flash chromatography on 300 g silica gel, loaded and eluted with 20% ethyl acetate in hexane. Pure fractions were combined and evaporated to give compound B as a colorless oil (1.9 g, 97%).

C. (Z)-1-Chloro-5,5-diphenyl-2-pentene

To a solution of N-chlorosuccinimide (0.56 g, 4.16 mmol) in dichloromethane (12 mL) at −40° C. was added dropwise methyl sulfide (0.4 mL, 5.29 mmol). The reaction was stirred at −40° C. for 10 minutes then warmed to room temperature for 30 minutes. The reaction was recooled to −40° C., and a solution of compound B (0.9 g, 3.78 mmol) in dichloromethane (5 mL) was added dropwise. The reaction was stirred at −40° C. for 2 hours then warmed to room temperature for 30 minutes. Hexane (300 mL) was added to dilute the reaction and the organic layer was washed with water (2×50 mL), brine (2×50 mL) and dried over $MgSO_4$. Evaporation gave compound C (0.9 g, 93%) as a colorless oil.

D. (Z)-2,3-Dihydro-2-[1-(5,5-diphenyl-2-pentenyl)-4-piperidinyl]-1H-isoindol-1-one

To a solution of compound A from Example 2 (756 mg, 3.50 mmol) in dimethylformamide (12 mL) was added

compound C (900 mg, 3.50 mmol) followed by anhydrous potassium carbonate (531 mg, 3.85 mmol). The reaction was stirred at 50° C. overnight. The reaction was cooled to room temperature. Ethyl ether (100 mL) was added to dilute the reaction, and the organic layer was washed with water (2×50 mL), brine (2×50 mL) and dried over Na_2SO_4. Evaporation gave a crude oil. Purification was performed by flash chromatography on 100 g of silica gel, loaded and eluted with 2% methanol in dichloromethane. Pure fractions were combined and evaporated to give compound D (950 mg, 62%) as a white solid, melting point 138–140° C.

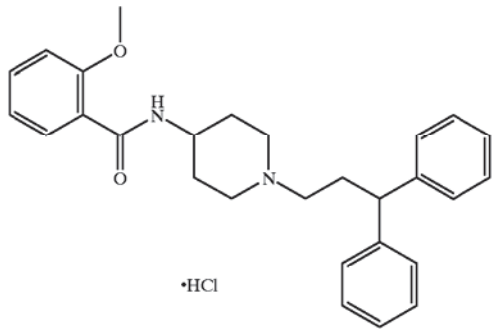
E. (Z)-2,3-Dihydro-2-[1-(5,5-diphenyl-2-pentenyl)-4-piperidinyl]-1H-isoindol-1-one, monohydrochloride

To a solution of compound D (500 mg, 1.15 mmol) in methanol (2 mL) was added 1 M HCl in ethyl ether (1.5 mL, 1.5 mmol). The mixture was evaporated to dryness. The resulting white solid was dried at 60° C. under vacuum to give Example 17 (300 mg, 80%) as a white solid, melting point 174–177° C.

Analysis for $C_{30}H_{33}ClN_2O+1.2\ H_2O$: Calc'd: C, 72.84; H, 7.21; N, 5.66; Cl, 7.17; Found: C, 72.74; H, 6.88; N, 5.70; Cl, 7.42.

EXAMPLE 18

N-[1-(3,3-Diphenylpropyl)-4-piperidinyl]-2-methoxybenzamide, monohydrochloride



A. N-[1-(3,3-Diphenylpropyl)-4-piperidinyl]-2-methoxybenzamide

To a stirred solution of 503 mg (1.52 mmol) of compound E from Example 1 in 8 mL of methylene chloride at 0° C. were added 370 μL (4.52 mmol) of pyridine and 238 μL (1.59 mmol) of o-anisoyl chloride. After warming to room temperature, the mixture was stirred for 1 h then diluted with methylene chloride and water. The organics were separated and the aqueous layer basified with 1 N KOH and extracted with methylene chloride. The combined organics were dried (sodium sulfate) and concentrated to provide a yellow oil which was dried under high vacuum. Flash chromatography on silica gel (180 g) eluted with 2% methanol in ethyl acetate afforded 336 mg (56%) of title compound A as a yellow solid, melting point 96–98° C.

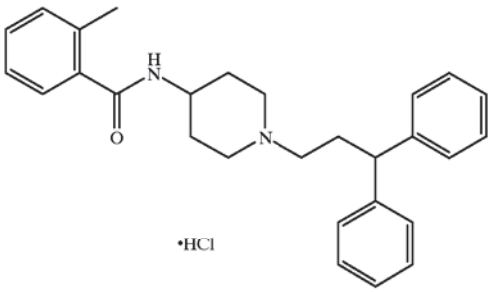
B. N-[1-(3,3-Diphenylpropyl)-4-piperidinyl]-2-methoxybenzamide, monohydrochloride

To a solution of 364 mg (0.85 mmol) of compound A in 4 mL of methylene chloride was added a freshly prepared saturated solution of hydrogen chloride in diethyl ether. The opaque white mixture was concentrated and dried to provide 329 mg (83%) of Example 18 as an off-white solid, melting point 170–172° C.

Analysis for $C_{28}H_{33}N_2O_2Cl+1.11\ H_2O$: Calcd. C, 69.34; H, 7.32; N, 5.78; Found C, 69.41; H, 7.31; N, 5.71.

EXAMPLE 19

N-[1-(3,3-Diphenylpropyl)-4-piperidinyl]-2-methylbenzamide, monohydrochloride



A. N-[1-(3,3-Diphenylpropyl)-4-piperidinyl]-2-methylbenzamide

Compound A was prepared as described for compound A in Example 18, using 485 mg (1.46 mmol) of compound E from Example 18, 336 mL (4.38 mmol) of pyridine, and 200 mL (1.54 mmol) of o-toluoyl chloride. The crude product was purified by flash chromatography on silica gel eluted with 98:2 ethyl acetate/methanol to provide 345 mg (67%) of compound A as a yellow solid.

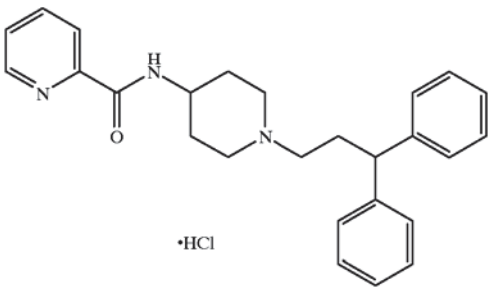
B. N-[1-(3,3-Diphenylpropyl)-4-piperidinyl]-2-methylbenzamide, monohydrochloride

To a solution of 342 mg (0.83 mmol) of compound A in 2 mL of methylene chloride was added a freshly prepared saturated solution of hydrogen chloride in diethyl ether. The opaque white mixture was concentrated, evaporated from methylene chloride to remove residual ether, and dried under vacuum to provide 348 mg (94%) of Example 19 as a white solid, melting point 237–239° C.

Analysis for $C_{28}H_{33}N_2OCl.1.15\ H_2O$: Calc'd: C, 71.60; H, 7.57; N, 5.96, Cl, 7.55; Found: C, 71.59; H, 7.31; N, 5.97, Cl, 7.86.

EXAMPLE 20

N-[1-(3,3-Diphenylpropyl)-4-piperidinyl]-2-pyridine-amide, monohydrochloride



A. N-[1-(3,3-Diphenylpropyl)-4-piperidinyl]-2-pyridine-amide

To a stirred suspension of 199 mg (1.62 mmol) of picolinic acid in 2.5 mL of methylene chloride at 0° C. was

added 225 mL (1.62 mmol) of triethylamine. After all the solids had dissolved, the solution was treated with 412 mg (1.62 mmol) of bis(2-oxo-3-oxazolidinyl)phosphinic chloride, and stirred for 30 minutes. A methylene chloride solution of 535 mg (1.62 mmol) of compound E from Example 1 was converted to the free amine by washing with sodium bicarbonate and concentrating the organic layer to a brown oil which was redissolved in 1 mL of dry methylene chloride and added to the reaction mixture. After stirring at room temperature for 16 hours, the reaction was quenched with water and 4 M HCl and diluted with methylene chloride. The aqueous layer was basified with 1 N KOH and extracted two times. The combined organics were dried (sodium sulfate) and concentrated to provide 554 mg of a brown oil. The crude product was purified by flash chromatography on silica gel eluted with 98:2 ethyl acetate/methanol to provide 316 mg (58%) of compound A as a brown glass.

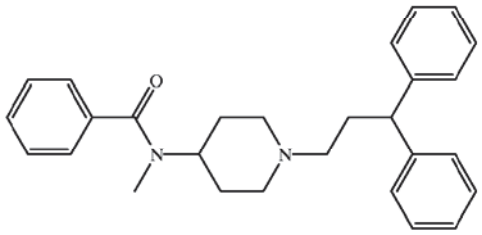
B. N-[1-(3,3-Diphenylpropyl)-4-piperidinyl]-2-pyridin-amide, monohydrochloride

The hydrochloride salt of compound A was prepared by the procedure used for compound B in Example 18, using 316 mg (0.83 mmol) of compound A, to afford 336 mg (83%) of Example 20 as a yellow solid, melting point 109–116° C.

Analysis for $C_{26}H_{30}N_3OCl+1.42\ H_2O$ Calc'd: C 67.65, H 7.17, N 9.10; Found: C 67.53, H 7.10, N 9.22.

EXAMPLE 21

N-[1-(3,3-Diphenylpropyl)-4-piperidinyl]-N-methyl-benzamide, monohydrochloride



•HCl

A. N-[1-(3,3-Diphenylpropyl)-4-piperidinyl]-N-methyl-amine

To a solution of 550 mg (1.4 mmol, 1 eq) of compound D from Example 1 in 5 mL of tetrahydrofuran at 0° C. was added 8.4 mL (8.4 mmol, 6 eq) of a 1 M solution of lithium aluminum hydride in tetrahydrofuran and the reaction was allowed to warm to room temperature. After 15 hours, the reaction was heated at 60° C. for 4 hours, then quenched by slow addition of a saturated aqueous solution of Na_2SO_4. To the resulting heterogeneous mixture was added solid Na_2SO_4 and the mixture was stirred for 30 minutes. The solids were removed by filtration and rinsed well with ethyl acetate. Concentration of the organic filtrate afforded 400 mg (93%) of compound A as a viscous pale yellow oil which was used without further purification.

B. N-[1-(3,3-Diphenylpropyl)-4-piperidinyl]-N-methyl-benzamide

Compound B was prepared from 390 mg (1.3 mmol) of compound A, 158 μL (1.4 mmol) of pyridine and 166 μL (1.4 mmol) of benzoyl chloride as described for compound A in Example 18. Flash chromatography on silica gel (75 g) eluted with 1.5% methanol in t-butylmethylether afforded 472 mg (88%) of compound B as a pale yellow oil.

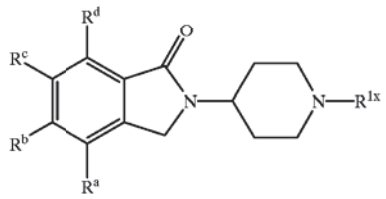
C. N-[1-(3,3-Diphenylpropyl)-4-piperidinyl]-N-methyl-benzamide, monohydrochloride

To a solution of 460 mg (1.1 mmol, 1 eq) of compound B in 5 mL of ether and 1 mL of CH_2Cl_2 was added an excess of HCl as a saturated solution in ether and the resulting heterogeneous mixture was stirred for 20 min. The solid was isolated by filtration, rinsed well with ether, concentrated and the solvent remnants were removed in a vacuum oven at 52° C. and full vacuum to afford 540 mg (82%) of Example 21 as a white solid; melting point 216–217° C.

Analysis for $C_{34}H_{37}N_2OCl$: Calc'd: C 74.90, H 7.41, N 6.24, Cl 7.90 Found: C 74.64, H 7.38, N 6.35, Cl 7.75

Additional compounds falling within the scope of the present invention are described by the following structures. Substituents for each example are identified in the table following each structure.

TABLE A



where R^{1x} is

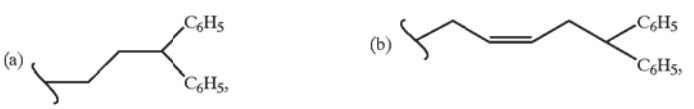
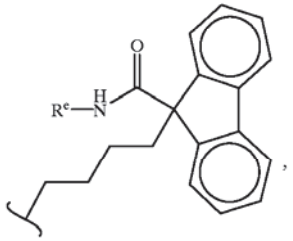


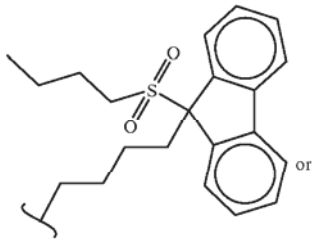
TABLE A-continued

(c)

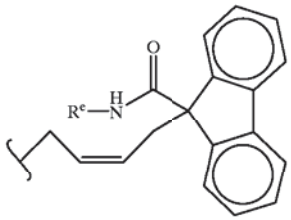


(R^e = C_3H_7 or CF_3CH_2)

(d)



or



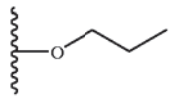
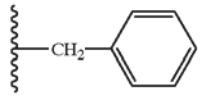
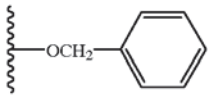
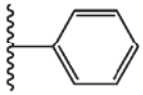
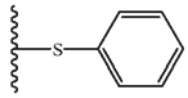
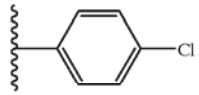
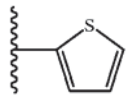
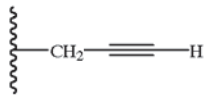
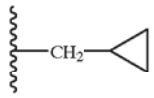
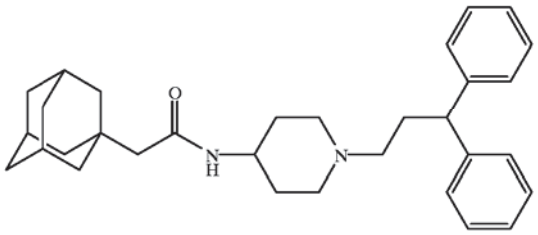
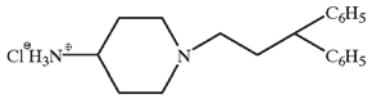
R^a	R^b	R^c	R^d
H	H	H	F
H	H	H	
H	H	F	Cl
H	H	CF_3	H
H	OCH_3	H	H
H	H	H	
	H	H	H
H	H		H
F	Cl	H	H
H	H	H	
H	H	Cl	H
H	H	H	
H	H	H	H
H	H	H	Cl
H	H	CH_3	H

TABLE A-continued

H	CH_3	H	
SCH_3	H	H	H
H	H	OCH_3	H
H	H	H	SCH_3
H	H	H	H
H	H	H	
H		H	H
H	H	H	



A. 1-(3,3-Diphenylpropyl)-4-piperidinamine hydrochloride

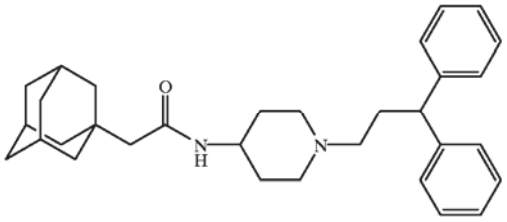


The title compound was prepared as described in Example 1, Part E.

B. 1-(3,3-Diphenylpropyl)-4-piperidinamine

A 2.2 g sample of Part A compound was suspended in CH_2Cl_2 (25 mL) and washed with 1 N KOH (15 mL). The organic solution was filtered through cotton and concentrated to afford 1.68 g (95%) of Part B amine as a clear oil which was used without further purification or characterization.

C.



The coupling of carboxylic acid to the Part B amine was carried out using a standard carbodiimide mediated coupling. The process was automated by using a Zymark Benchmate® robotic workstation to carry out the acid-amine coupling and the purification of the resulting amide products. An IBM PC was used to run the Zymark Benchmate® workstation operating program and to write the Benchmate® procedures. The standard protocol for preparation of amides from the Part B free diamine and a carboxylic acid was as follows:

A 16 mm×100 mm tube was charged with 47 mg (0.24 mmol, 4 eq) of adamantane acetic acid and capped loosely with a plastic cap/column holder. The Benchmate® then carried out the following steps on the tube:

1) Added 500 μL (12.5 mg, 0.092 mmol, 1.5 eq) of a 25 mg/mL solution of 1-hydroxybenzotriazole in DMF
2) Added 500 μL (11.5 mg, 0.092 mmol, 1.5 eq) of a 23 mg/mL solution of diisopropylcarbodiimide in CH_2Cl_2
3) Added 500 μL (18 mg, 0.061 mmol, 1 eq) of a 36 mg/mL solution of Part B diamine in CH_2Cl_2
4) Washed syringe with 3mL of CH_2Cl_2
5) Mixed tube contents by vortexing at speed 3 for 15 sec.

After 19 h, the reaction was complete (no starting Part B diamine remained as determined by TLC; 10% MeOH+1% NH_4OH in CH_2Cl_2, I_2; R_f[diamine]=0.13).

The reaction mixture contents were then purified by ion exchange chromatography on a solid phase extraction cartridge mediated by the Benchmate® robotic workstation using the following protocol:

1) Condition a Varian solid phase extraction column (500 mg, SCX cation exchange) with 10 mL of MeOH at 0.25 mL/sec
2) Load reaction contents onto column at 0.05 mL/sec
3) Wash column with 2×10 mL of MeOH at 0.1 mL/sec
4) Wash column with 2 mL of 0.1 M ammonia in MeOH at 0.1 mL/sec
5) Elute column with 2 mL of 1 M ammonia in MeOH and collect into a tared receiving tube at 0.1 mL/sec.

All solution/solvent deliveries were followed by 1.8 mL of air and a 10 sec push delay was used after loading reaction contents onto the ion exchange column.

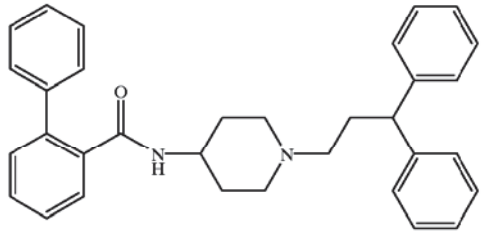
The product solution was concentrated on a Savant Speed Vac (approx. 2 mm Hg for 5 h) and final solvent remnants were removed by further exposure to high vac (0.015 mm Hg, 14 h) to afford 22 mg (77% yield) of title compound. Products were characterized by HPLC and MS.

M.S. (electrospray, pos. ions) 471 (M+H).

EXAMPLES 206 TO 276

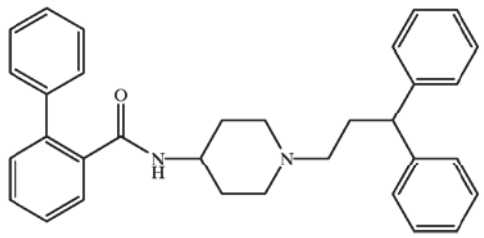
Following the procedure of Example 205, the following compounds of the invention were prepared.

206.



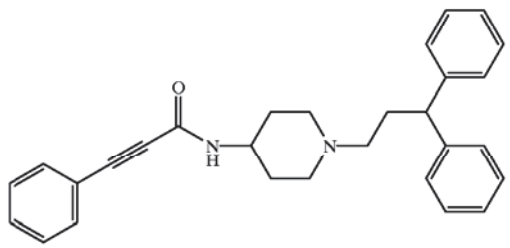
M.S. (electrospray, pos. ions) 475 (M + H).

206.



M.S. (electrospray, pos. ions) 475 (M + H).

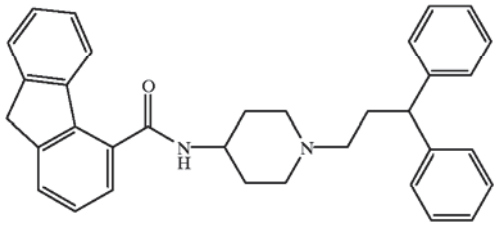
207.



-continued

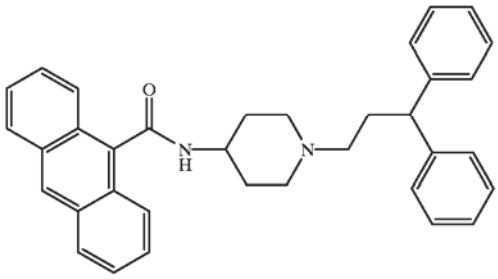
M.S. (electrospray, pos. ions) 423 (M + H).

208.



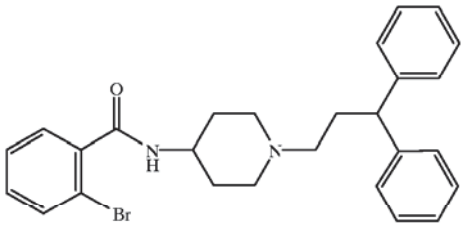
M.S. (electrospray, pos. ions) 487 (M + H).

209.



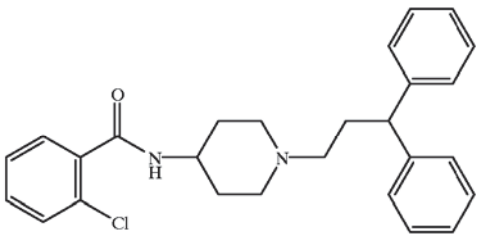
M.S. (electrospray, pos. ions) 499 (M + H).

210.



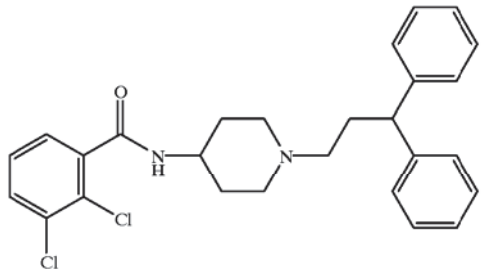
M.S. (electrospray, pos. ions) 477 (M + H), 479 (M + H + 2).

211.



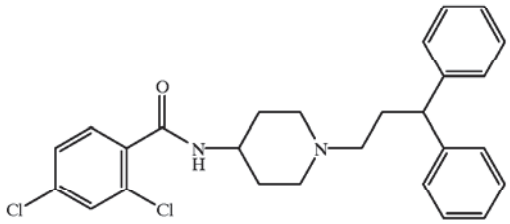
M.S. (electrospray, pos. ions) 433 (M + H).

212.



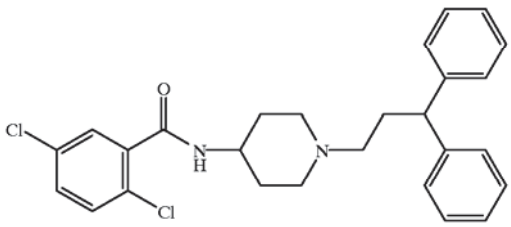
M.S. (electrospray, pos. ions) 467 (M + H), 469 (M + H + 2).

213.



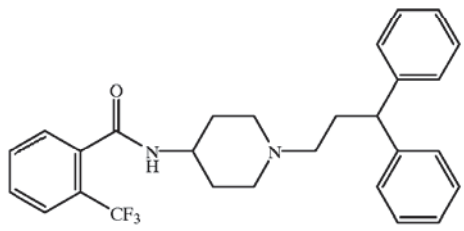
M.S. (electrospray, pos. ions) 467 (M + H), 469 (M + H + 2).

214.



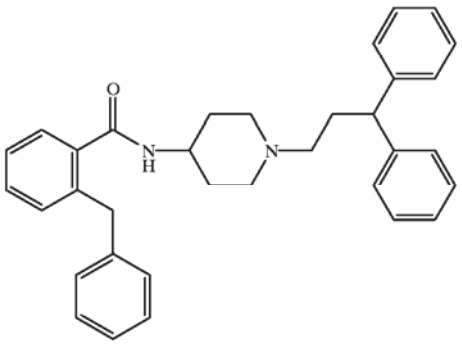
M.S. (electrospray, pos. ions) 467 (M + H), 469 (M + H + 2).

215.



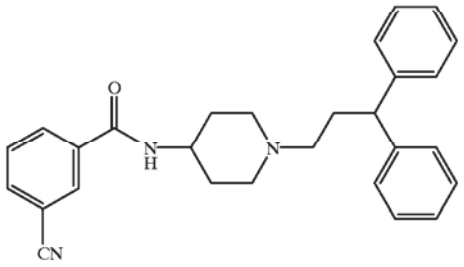
M.S. (electrospray, pos. ions) 467 (M + H).

216.



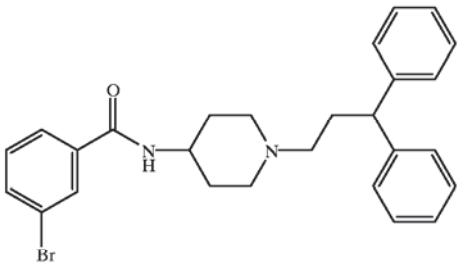
M.S. (electrospray, pos. ions) 489 (M + H).

217.



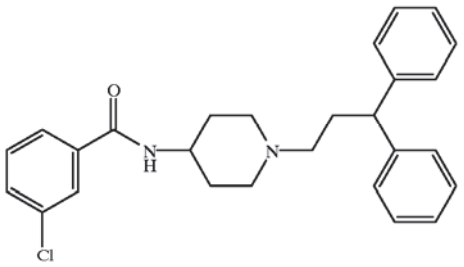
M.S. (electrospray, pos. ions) 424 (M + H).

218.



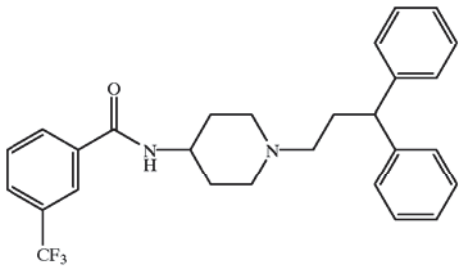
M.S. (electropsray, pos. ions) 477 (M + H), 479 (M + H + 2).

219.



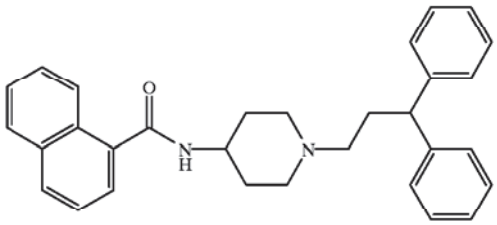
M.S. (electrospray, pos. ions) 433 (M + H).

220.



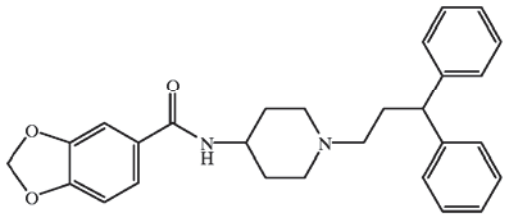
M.S. (electrospray, pos. ions) 467 (M + H).

221.



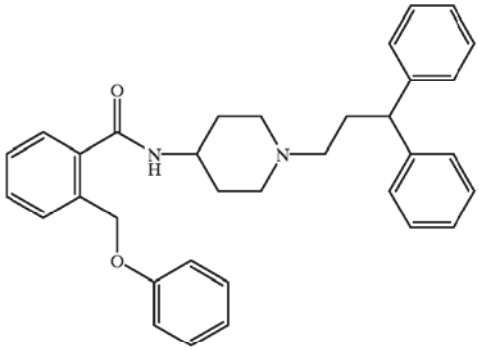
M.S. (electrospray, pos. ions) 449 (M + H).

222.



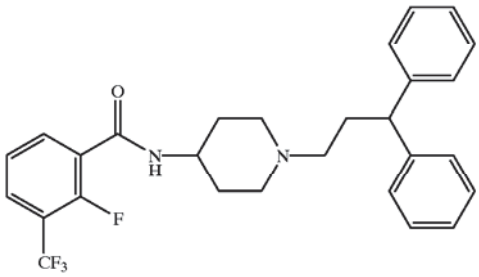
M.S. (electrospray, pos. ions) 443 (M + H).

223.



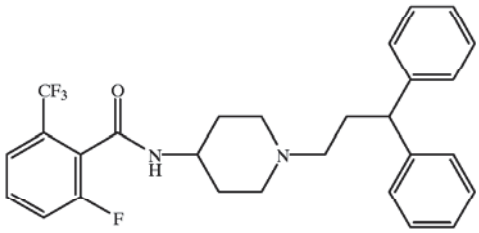
M.S. (electrospray, pos. ions) 505 (M + H).

224.



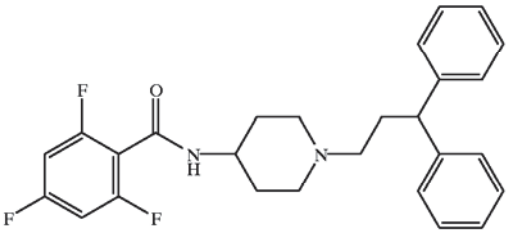
M.S. (electrospray, pos. ions) 485 (M + H).

225.



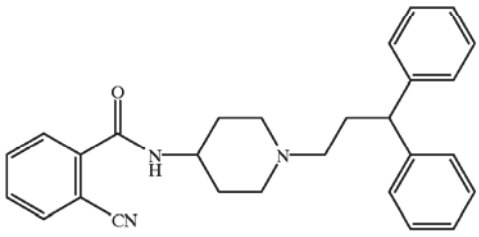
M.S. (electrospray, pos. ions) 485 (M + H).

226.



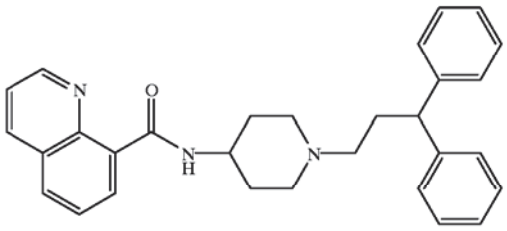
M.S. (electrospray, pos. ions) 453 (M + H).

227.



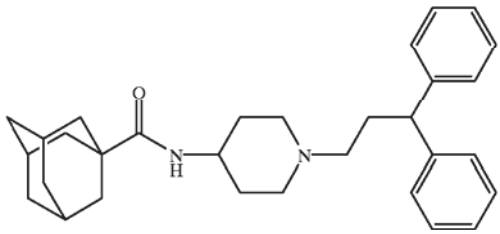
M.S. (electrospray, pos. ions) 424 (M + H).

228.



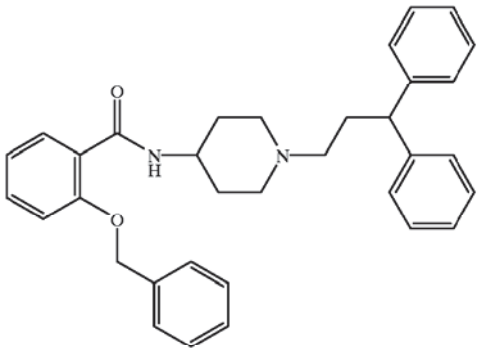
M.S. (electrospray, pos. ions) 450 (M + H).

229.



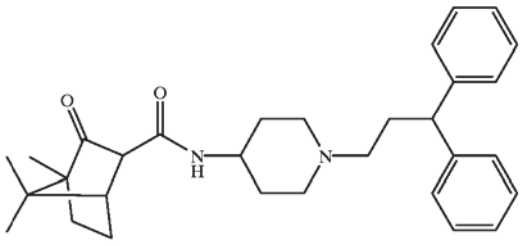
M.S. (electrospray, pos. ions) 457 (M + H).

230.



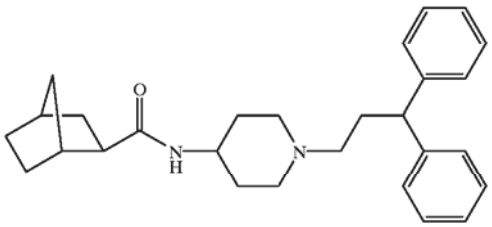
M.S. (electrospray, pos. ions) 505 (M + H).

231.



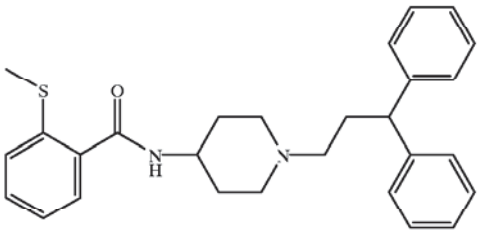
M.S. (electrospray, pos. ions) 473 (M + H).

232.



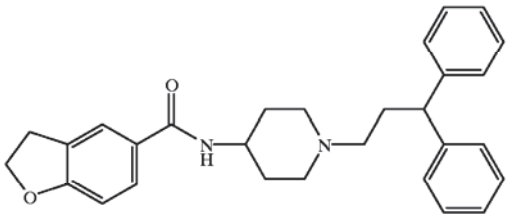
M.S. (electrospray, pos. ions) 417 (M + H).

233.



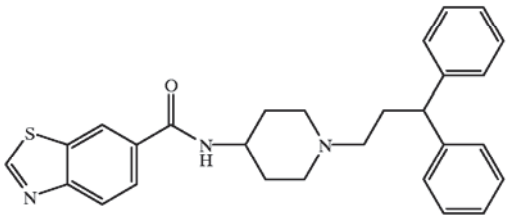
M.S. (electrospray, pos. ions) 445 (M + H).

234.



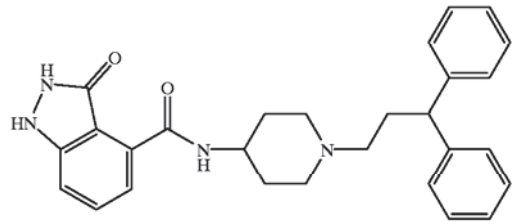
M.S. (electrospray, pos. ions) 441 (M + H).

235.



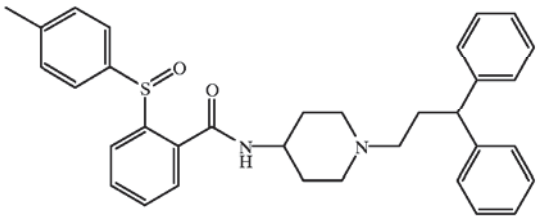
M.S. (electrospray, pos. ions) 456 (M + H).

236.



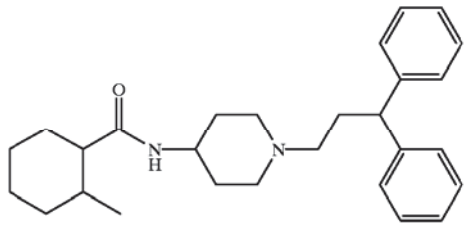
M.S. (electrospray, pos. ions) 455 (M + H).

237.



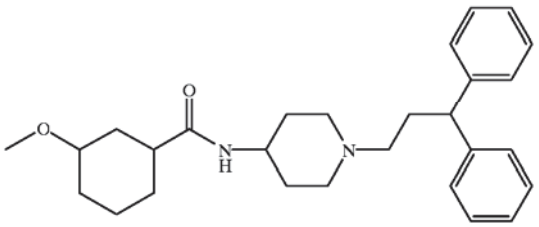
M.S. (electrospray, pos. ions) 537 (M + H).

238.



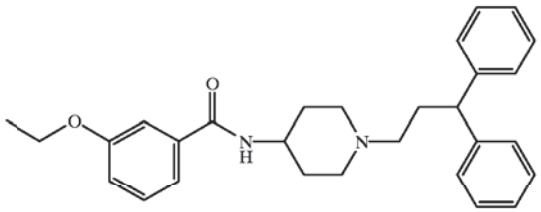
mixture of cis and trans
M.S. (electrospray, pos. ions) 419 (M + H).

239.



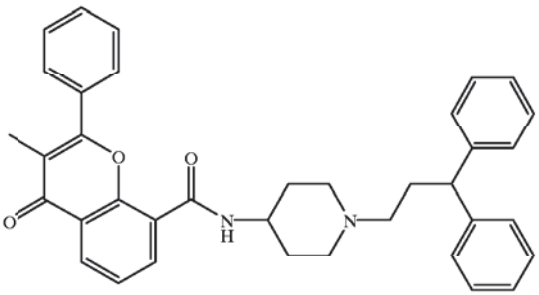
mixture of cis and trans
M.S. (electrospray, pos. ions) 435 (M + H).

240.



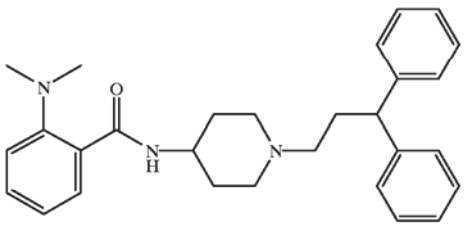
M.S. (electrospray, pos. ions) 443 (M + H).

241.



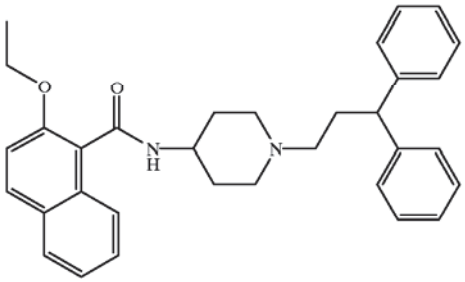
M.S. (electrospray, pos. ions) 557 (M + H).

242.



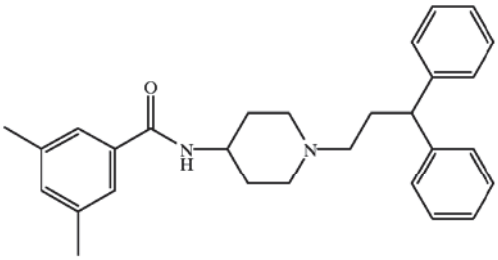
M.S. (electrospray, pos. ions) 442 (M + H).

243.



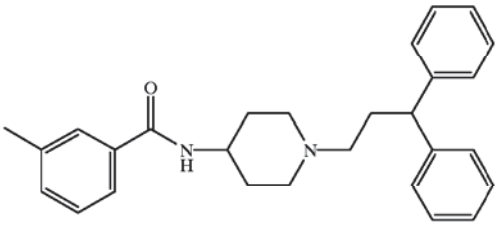
M.S. (electrospray, pos. ions) 493 (M + H).

244.



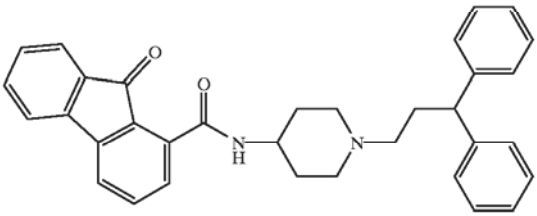
M.S. (electrospray, pos. ions) 427 (M + H).

245.



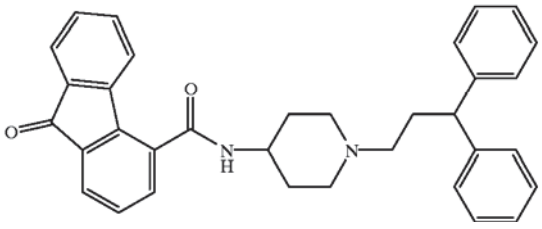
M.S. (electrospray, pos. ions) 413 (M + H).

246.



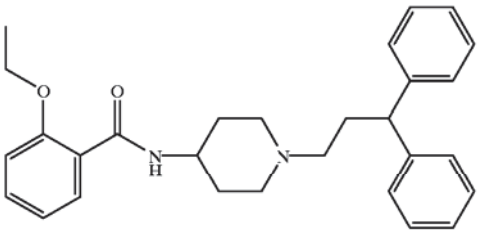
M.S. (electrospray, pos. ions) 501 (M + H).

247.



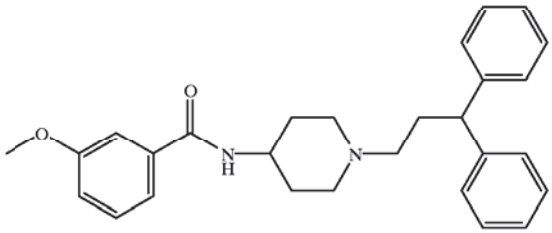
M. S. (electrospray, pos. ions) 501 (M + H).

248.



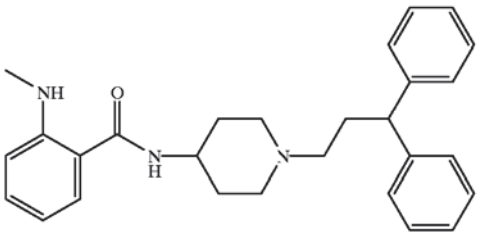
M.S. (elecrospray, pos. ions) 443 (M + H).

249.



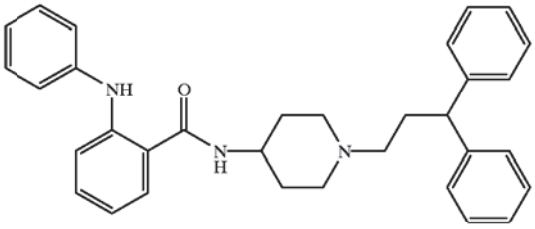
M.S. (elecrospray, pos. ions) 429 (M + H).

250.



M.S. (elecrospray, pos. ions) 428 (M + H).

251.



M.S. (elecrospray, pos. ions) 490 (M + H).