SUBSTITUTED UREA NEUROPEPTIDE Y Y5 RECEPTOR ANTAGONISTS

Cross Reference to Related Applications

This application claims the benefit of U.S. Provisional Application No. 60/308,433 filed on July 26, 2001.

Field of the Invention

The present invention relates to neuropeptide Y Y5 receptor antagonists useful in the treatment of obesity and eating disorders, pharmaceutical compositions containing the compounds, and methods of treatment using the compounds.

Background of the Invention

Neuropeptide Y (NPY) is a 36 amino acid neuropeptide that is widely distributed in the central and peripheral nervous systems. NPY is a member of the pancreatic polypeptide family that also includes peptide YY and pancreatic polypeptide (Wahlestedt, C., and Reis, D., Ann. Rev. Toxicol., 32, 309, 1993). NPY elicits its physiological effects by activation of at least six receptor subtypes designated Y1, Y2, Y3, Y4, Y5 and Y6 (Gehlert, D., Proc. Soc. Exp. Biol. Med., 218, 7, 1998; Michel, M. et al., Pharmacol. Rev., 50, 143, 1998). Central administration of NPY to animals causes dramatically increased food intake and decreased energy expenditure (Stanley, B. and Leibowitz, S., Proc. Natl. Acad. Sci. USA 82: 3940, 1985; Billington et al., Am J. Physiol., 260, R321, 1991). These effects are believed to be mediated at least in part by activation of the NPY Y5 receptor subtype. The isolation and characterization of the NPY Y5 receptor subtype has been reported (Gerald, C. et al., Nature, 1996, 382, 168; Gerald, C. et al. WO 96/16542). Additionally, it has been reported that activation of the NPY Y5 receptor by administration of the Y5 – selective agonist [D-Trp^{32}]NPY to rats stimulates feeding and decreases energy expenditure (Gerald, C. et al., Nature, 1996, 382, 168; Hwa, J. et al., Am. J. Physiol., 277 (46), R1428, 1999). Hence, compounds that block binding of NPY to the NPY Y5 receptor subtype should have utility in the treatment of obesity, disorders such as, bulimia nervosa, anorexia nervosa, and in the treatment of

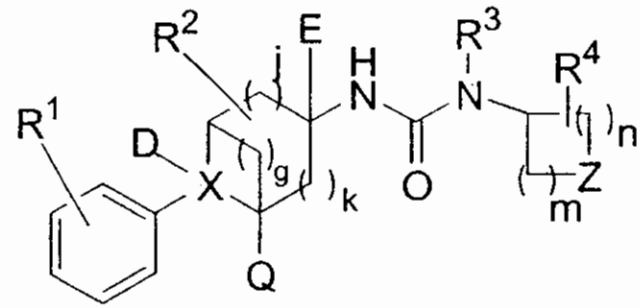
disorders associated with obesity such as type II diabetes, insulin resistance, hyperlipidemia, and hypertension.

PCT patent application WO 00/27845 describes a class of compounds, characterized therein as spiro-indolines, said to be selective neuropeptide Y Y5 receptor antagonists and useful for the treatment of obesity and the complications associated therewith. Urea derivatives indicated as possessing therapeutic activity are described in U.S. Patent Nos. 4,623,662 (antiatherosclerotic agents) and 4,405,644 (treatment of lipometabolism).

Provisional application, U.S. Serial No. 60/232,255 describes a class of substituted urea neuropeptide Y Y5 receptor antagonists.

SUMMARY OF THE INVENTION

In one embodiment, this invention provides novel urea compounds having NPY Y5 receptor antagonist activity. In an embodiment of the invention is a compound represented by the structural formula



I

or a pharmaceutically acceptable salt or solvate thereof, wherein:

X is independently N or C;

Z is independently NR^8 or CR^3R^9;

D is independently H, -OH, -alkyl or substituted -alkyl with the proviso that when X is N, D and the X-D bond are absent;

E is independently H, -alkyl or substituted –alkyl, or D and E can independently be joined together via a $–(CH_2)_p-$ bridge;

Q is independently H, -alkyl or substituted –alkyl, or D, X, Q and the carbon to which Q is shown attached can jointly form a 3 to 7-membered ring;

g, j, k, m and n can be the same or different and are independently selected;

g is 0 to 3 and when g is 0, the carbons to which $(CH_2)_g$ is shown connected are no more linked;

j and k are independently 0 to 3 such that the sum of j and k is 0, 1, 2 or 3;

m and n are independently 0 to 3 such that the sum of m and n is 1, 2,3, 4 or 5;

p is 1 to 3;

R^1 is 1 to 5 substituents which can be the same or different, each R^1 being independently selected from the group consisting of hydrogen, hydroxy, halogen, haloalkyl, -alkyl, substituted –alkyl, -cycloalkyl, CN, alkoxy, cycloalkoxy, alkylthio, cycloalkylthio, $-NR^5R^6$, $-NO_2$, $-CONR^5R^6$, $-NR^5COR^6$, $-NR^5CONR^5R^6$ where the two R^5 moieties can be the same or different, $-NR^6C(O)OR^7$, $-C(O)OR^6$, $-SOR^7$, $-SO_2R^7$, $-SO_2NR^5R^6$, aryl and heteroaryl;

R^2 is 1 to 6 substituents which can be the same or different, each R^2 being independently selected from the group consisting of hydrogen, -alkyl, substituted –alkyl, alkoxy, and hydroxy, with the proviso that when X is N and R^2 is hydroxy or alkoxy, R^2 is not directly attached to a carbon adjacent to X;

R^3 is independently hydrogen, -alkyl or substituted -alkyl;

R^4 is 1 to 6 substituents which can be the same or different, each R^4 being independently selected from hydrogen, -alkyl, substituted –alkyl, alkoxy, and hydroxy, with the proviso that when Z is NR^8 and R^4 is hydroxy or alkoxy, R^4 is not directly attached to a carbon adjacent to the NR^8;

R^5 and R^6 are independently hydrogen, -alkyl, substituted -alkyl or -cycloalkyl;

R^7 is independently –alkyl, substituted -alkyl or -cycloalkyl;

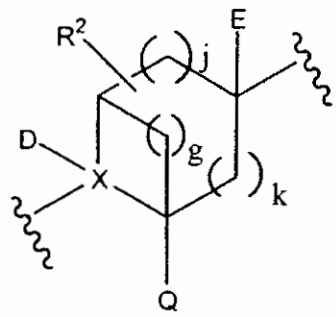
R^8 is independently selected from the group consisting of hydrogen, -alkyl, substituted –alkyl, -cycloalkyl, -alkylcycloalkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, $-SO_2R^{10}$, $-SO_2NR^5R^{11}$, $-C(O)R^{11}$, $-C(O)NR^5R^{11}$ and $-C(O)OR^{10}$;

R^9 is independently hydrogen, -alkyl, substituted –alkyl, hydroxy, alkoxy, $-NR^5R^{11}$, aryl, or heteroaryl; or R^3 and R^9 can be joined together and with the carbon to which they are attached form a carbocyclic or heterocyclic ring having 3 to 7 ring atoms;

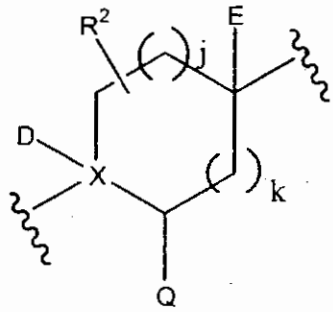
R^{10} is -alkyl, substituted –alkyl, -cycloalkyl, -alkylcycloalkyl, aryl or heteroaryl; and

R^{11} is independently hydrogen, -alkyl, substituted –alkyl, -cycloalkyl, aryl or heteroaryl.

The above statement "when g is 0, the carbons to which $(CH_2)_g$ is shown connected are no more linked" means that when g is 0, then the structural component:



shown in formula I above becomes:



Ureas of formula I or formula III are highly selective, high affinity NPY Y5 receptor antagonists useful for the treatment of obesity.

This invention is also directed to pharmaceutical compositions for the treatment of metabolic disorders such as obesity, and eating disorders such as hyperphagia. In one aspect, this invention is also directed to pharmaceutical compositions for the treatment of obesity which comprise an obesity treating amount of a compound of formula I or formula III thereof, or a pharmaceutically acceptable salt or solvate of said compound, and a pharmaceutically acceptable carrier.

DETAILED DESCRIPTION

The present invention relates to compounds that are represented by structural formula I or formula III or a pharmaceutically acceptable salt or solvate thereof, wherein the various moieties are as described above. The compounds of formula I or formula III can be administered as racemic mixtures or enantiomerically pure compounds.

In a preferred embodiment of the invention is a compound of formula I or a pharmaceutically acceptable salt or solvate thereof, wherein:

R^1 is 1 to 5 substituents which can be the same or different, each R^1 being independently selected from the group consisting of Cl, Br, I or F;

X is N;

D is absent and the X-D bond is absent;

E is H;

g is 0;

j is 1;

k is 1;

m is 2;

n is 2;

R^2 is H;

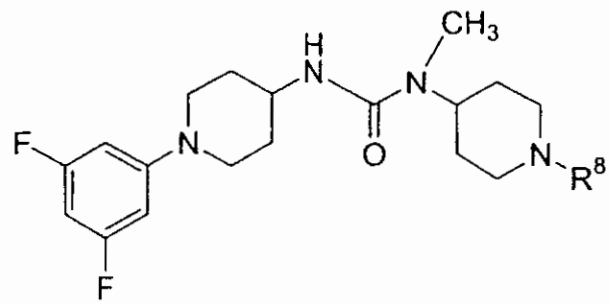
R^3 is methyl;

R^4 is H;

and

Z is NR^8, where R^8 is independently selected from the group consisting of hydrogen, -alkyl, substituted –alkyl, -cycloalkyl, -alkylcycloalkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, $-SO_2R^{10}$, $-SO_2NR^5R^{11}$, $-C(O)R^{11}$, $-C(O)NR^5R^{11}$ and $-C(O)OR^{10}$.

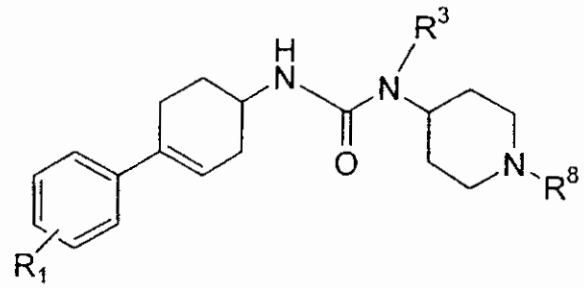
A preferred embodiment of the present invention is a compound of formula II or a pharmaceutically acceptable salt or solvate thereof, wherein:



II

wherein R^8 is defined as herein in the Detailed Description in Table 1.

An additional preferred embodiment of the present invention is a compound of formula III or a pharmaceutically acceptable salt or solvate thereof, wherein:



III

wherein

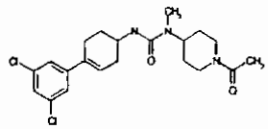
R^1 is 1 to 5 substituents which can be the same or different, each R^1 being independently selected from the group consisting of hydrogen, hydroxy, halogen, haloalkyl, -alkyl, substituted –alkyl, -cycloalkyl, CN, alkoxy, cycloalkoxy, alkylthio, cycloalkylthio, $-NR^5R^6$, $-NO_2$, $-CONR^5R^6$, $-NR^5COR^6$, $-NR^5CONR^5R^6$ where the two R^5 moieties can be the same or different, $-NR^6C(O)OR^7$, $-C(O)OR^6$, $-SOR^7$, $-SO_2R^7$, $-SO_2NR^5R^6$, aryl and heteroaryl;

R^3 is independently hydrogen or –alkyl;

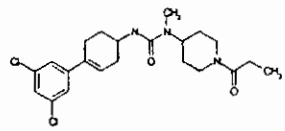
and

R^8 is independently selected from the group consisting of hydrogen, -alkyl, substituted –alkyl, -cycloalkyl, -alkylcycloalkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, $-SO_2R^{10}$, $-SO_2NR^5R^{11}$, $-C(O)R^{11}$, $-C(O)NR^5R^{11}$ and $-C(O)OR^{10}$.

A further preferred group of compounds are compounds of formula III selected from the group consisting of

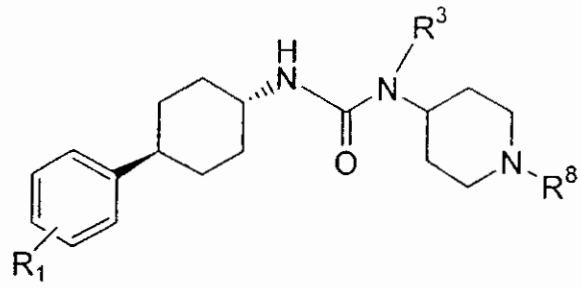


and



or a pharmaceutically acceptable salt or solvate of said compound.

An additional preferred embodiment of the present invention is a compound of formula IV, wherein



IV

or a pharmaceutically acceptable salt or solvate there of, wherein

R^1 is 1 to 5 substituents which can be the same or different, each R^1 being independently selected from the group consisting of hydrogen, hydroxy, halogen, haloalkyl, -alkyl, substituted –alkyl, -cycloalkyl, CN, alkoxy, cycloalkoxy, alkylthio, cycloalkylthio, $-NR^5R^6$, $-NO_2$, $-CONR^5R^6$, $-NR^5COR^6$, $-NR^5CONR^5R^6$ where the two R^5 moieties can be the same or different, $-NR^6C(O)OR^7$, $-C(O)OR^6$, $-SOR^7$, $-SO_2R^7$, $-SO_2NR^5R^6$, aryl and heteroaryl;

R^3 is independently hydrogen or –alkyl;

and

R^8 is independently selected from the group consisting of hydrogen, -alkyl, substituted –alkyl, -cycloalkyl, -alkylcycloalkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, $-SO_2R^{10}$, $-SO_2NR^5R^{11}$, $-C(O)R^{11}$, $-C(O)NR^5R^{11}$ and $-C(O)OR^{10}$.

A set of preferred compounds are listed below in the Detailed Description in Tables 2 and 3, among other preferred compounds.

Except where stated otherwise, the following definitions apply throughout the present specification and claims. These definitions apply regardless of whether a term is used by itself or in combination with other terms. Hence the definition of "alkyl" applies to "alkyl" as well as to the "alkyl" portions of "alkoxy", "alkylamino" etc.

As used above, and throughout the specification, the following terms, unless otherwise indicated, shall be understood to have the following meanings:

"Patient" includes both human and other mammals.

"Mammal" means humans and other animals.

"Alkyl" means an aliphatic hydrocarbon group, which may be straight or branched and comprising about 1 to about 20 carbon atoms in the chain. Preferred alkyl groups contain about 1 to about 12 carbon atoms in the chain. More preferred alkyl groups contain about 1 to about 6 carbon atoms in the chain. Branched means that one or more lower alkyl groups such as methyl, ethyl or propyl, are attached to a linear alkyl chain. "Lower alkyl" means an alkyl group having about 1 to about 6

carbon atoms in the chain, which may be straight or branched. The term "substituted alkyl" means that the alkyl group may be substituted by one or more substituents which may be the same or different, each substituent being independently selected from the group consisting of halo, -alkyl, aryl, -cycloalkyl, cyano, hydroxy, alkoxy, alkylthio, amino, -NH(alkyl), -NH(cycloalkyl), -N(alkyl)$_2$, carboxy and –C(O)O-alkyl. Non-limiting examples of suitable alkyl groups include methyl, ethyl, n-propyl, isopropyl, n-butyl, and t-butyl.

"Alkenyl" means an aliphatic hydrocarbon group comprising at least one carbon-carbon double bond and which may be straight or branched and comprising about 2 to about 15 carbon atoms in the chain. Preferred alkenyl groups have about 2 to about 12 carbon atoms in the chain; and more preferably about 2 to about 6 carbon atoms in the chain. Branched means that one or more lower alkyl groups such as methyl, ethyl or propyl, are attached to a linear alkenyl chain. "Lower alkenyl" means an alkenyl group having about 2 to about 6 carbon atoms in the chain, which may be straight or branched. The term "substituted alkenyl" means that the alkenyl group may be substituted by one or more substituents which may be the same or different, each substituent being independently selected from the group consisting of halo, alkyl, aryl, -cycloalkyl, cyano, and alkoxy. Non-limiting examples of suitable alkenyl groups include ethenyl, propenyl, n-butenyl, and 3-methylbut-2-enyl.

"Alkynyl" means an aliphatic hydrocarbon group comprising at least one carbon-carbon triple bond and which may be straight or branched and comprising about 2 to about 15 carbon atoms in the chain. Preferred alkynyl groups have about 2 to about 12 carbon atoms in the chain; and more preferably about 2 to about 4 carbon atoms in the chain. Branched means that one or more lower alkyl groups such as methyl, ethyl or propyl, are attached to a linear alkynyl chain. "Lower alkynyl" means an alkynyl group having about 2 to about 6 carbon atoms in the chain, which may be straight or branched. Non-limiting examples of suitable alkynyl groups include ethynyl, propynyl and 2-butynyl. The term "substituted alkynyl" means that the alkynyl group may be substituted by one or more substituents which may be the same or different, each substituent being independently selected from the group consisting of alkyl, aryl and -cycloalkyl.

"Aryl" means an aromatic monocyclic or multicyclic ring system comprising about 6 to about 14 carbon atoms, preferably about 6 to about 10 carbon atoms. The aryl group can be unsubstituted or substituted on the ring with one or more

substituents which may be the same or different, each being independently selected from the group consisting of alkyl, aryl, -OCF_3, -OCOalkyl, -OCOaryl, -CF_3, heteroaryl, aralkyl, alkylaryl, heteroaralkyl, alkylheteroaryl, hydroxy, hydroxyalkyl, alkoxy, aryloxy, aralkoxy, acyl, aroyl, halo, haloalkyl, haloalkoxy, nitro, cyano, carboxy, alkoxycarbonyl, aryloxycarbonyl, aralkoxycarbonyl, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, alkylsulfinyl, arylsulfinyl, heteroarylsulfinyl, alkylthio, arylthio, heteroarylthio, aralkylthio, heteroaralkylthio, -cycloalkyl and heterocyclyl. Non-limiting examples of suitable aryl groups include phenyl and naphthyl. The "aryl" group can also be substituted by linking two adjacent carbons on its aromatic ring via a combination of one or more carbon atoms and one or more oxygen atoms such as, for example, methylenedioxy, ethylenedioxy, and the like.

"Heteroaryl" means an aromatic monocyclic or multicyclic ring system comprising about 5 to about 14 ring atoms, preferably about 5 to about 10 ring atoms, in which one or more of the ring atoms is an element other than carbon, for example nitrogen, oxygen or sulfur, alone or in combination. Preferred heteroaryls contain about 5 to about 6 ring atoms. The "heteroaryl" can be optionally substituted on the ring by replacing an available hydrogen on the ring by one or more substituents which may be the same or different, each being independently selected from the group consisting of alkyl, aryl, heteroaryl, aralkyl, alkylaryl, aralkenyl, heteroaralkyl, alkylheteroaryl, heteroaralkenyl, hydroxy, hydroxyalkyl, alkoxy, aryloxy, aralkoxy, acyl, aroyl, halo, nitro, cyano, carboxy, alkoxycarbonyl, aryloxycarbonyl, aralkoxycarbonyl, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, alkylsulfinyl, arylsulfinyl, heteroarylsulfinyl, alkylthio, arylthio, heteroarylthio, aralkylthio, heteroaralkylthio, -cycloalkyl, cycloalkenyl and heterocyclyl. The prefix aza, oxa or thia before the heteroaryl root name means that at least a nitrogen, oxygen or sulfur atom respectively, is present as a ring atom. A nitrogen atom of a heteroaryl can be optionally oxidized to the corresponding N-oxide. Non-limiting examples of suitable heteroaryls include pyridyl, pyrazinyl, furanyl, thienyl, pyrimidinyl, isoxazolyl, isothiazolyl, oxazolyl, thiazolyl, pyrrolyl, triazolyl, and the like.

"Aralkyl" means an aryl-alkyl- group in which the aryl and alkyl are as previously described. Preferred aralkyls comprise a lower alkyl group. Non-limiting examples of suitable aralkyl groups include benzyl, 2-phenethyl and a naphthlenylmethyl. The bond to the parent moiety is through the alkyl.

"Alkylaryl" means an alkyl-aryl- group in which the alkyl and aryl are as previously described. Preferred alkylaryls comprise a lower alkyl group. A non-limiting example of a suitable alkylaryl groups is tolyl. The bond to the parent moiety is through the aryl.

"Cycloalkyl" means a non-aromatic mono- or multicyclic ring system comprising about 3 to about 10 carbon atoms, preferably about 5 to about 10 carbon atoms. Preferred cycloalkyl rings contain about 5 to about 7 ring atoms. The cycloalkyl can be optionally substituted on the ring by replacing an available hydrogen on the ring by one or more substituents which may be the same or different, each being independently selected from the group consisting of alkyl, aryl, heteroaryl, aralkyl, alkylaryl, aralkenyl, heteroaralkyl, alkylheteroaryl, heteroaralkenyl, hydroxy, hydroxyalkyl, alkoxy, aryloxy, aralkoxy, acyl, aroyl, halo, nitro, cyano, carboxy, alkoxycarbonyl, aryloxycarbonyl, aralkoxycarbonyl, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, alkylsulfinyl, arylsulfinyl, heteroarylsulfinyl, alkylthio, arylthio, heteroarylthio, aralkylthio, heteroaralkylthio, cycloalkyl, cycloalkenyl and heterocyclyl. Non-limiting examples of suitable monocyclic cycloalkyls include cyclopropyl, cyclopentyl, cyclohexyl, cycloheptyl and the like. Non-limiting examples of suitable multicyclic cycloalkyls include 1-decalinyl, norbornyl, adamantyl and the like.

"Halo" means fluoro, chloro, bromo or iodo groups. Preferred are fluoro, chloro or bromo, and more preferred are fluoro and chloro.

"Halogen" means fluorine, chlorine, bromine or iodine. Preferred are fluorine, chlorine or bromine, and more preferred are fluorine and chlorine.

"Haloalkyl" means an alkyl as defined above wherein one or more hydrogen atoms on the alkyl is replaced by a halo group defined above.

"Cycloalkenyl" means a non-aromatic mono or multicyclic ring system comprising about 3 to about 10 carbon atoms, preferably about 5 to about 10 carbon atoms which contains at least one carbon-carbon double bond. Preferred cycloalkenyl rings contain about 5 to about 7 ring atoms. The cycloalkenyl can be optionally substituted on the ring by replacing an available hydrogen on the ring by one or more substituents which may be the same or different, each being independently selected from the group consisting of alkyl, aryl, heteroaryl, aralkyl, alkylaryl, aralkenyl, heteroaralkyl, alkylheteroaryl, heteroaralkenyl, hydroxy, hydroxyalkyl, alkoxy, aryloxy, aralkoxy, acyl, aroyl, halo, nitro, cyano, carboxy, alkoxycarbonyl, aryloxycarbonyl, aralkoxycarbonyl, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, alkylsulfinyl,

arylsulfinyl, heteroarylsulfinyl, alkylthio, arylthio, heteroarylthio, aralkylthio, heteroaralkylthio, cycloalkyl, cycloalkenyl and heterocyclyl. Non-limiting examples of suitable monocyclic cycloalkenyls include cyclopentenyl, cyclohexenyl, cycloheptenyl, and the like. Non-limiting example of a suitable multicyclic cycloalkenyl is norbornylenyl.

"Heterocyclyl" means a non-aromatic saturated monocyclic or multicyclic ring system comprising about 3 to about 10 ring atoms, preferably about 5 to about 10 ring atoms, in which one or more of the atoms in the ring system is an element other than carbon, for example nitrogen, oxygen or sulfur, alone or in combination. There are no adjacent oxygen and/or sulfur atoms present in the ring system. Preferred heterocyclyls contain about 5 to about 6 ring atoms. The prefix aza, oxa or thia before the heterocyclyl root name means that at least a nitrogen, oxygen or sulfur atom respectively is present as a ring atom. The heterocyclyl can be optionally substituted on the ring by replacing an available hydrogen on the ring by one or more substituents which may be the same or different, each being independently selected from the group consisting of alkyl, aryl, heteroaryl, aralkyl, alkylaryl, aralkenyl, heteroaralkyl, alkylheteroaryl, heteroaralkenyl, hydroxy, hydroxyalkyl, alkoxy, aryloxy, aralkoxy, acyl, aroyl, halo, nitro, cyano, carboxy, alkoxycarbonyl, aryloxycarbonyl, aralkoxycarbonyl, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, alkylsulfinyl, arylsulfinyl, heteroarylsulfinyl, alkylthio, arylthio, heteroarylthio, aralkylthio, heteroaralkylthio, cycloalkyl, cycloalkenyl and heterocyclyl. The nitrogen or sulfur atom of the heterocyclyl can be optionally oxidized to the corresponding N-oxide, S-oxide or S,S-dioxide. Non-limiting examples of suitable monocyclic heterocyclyl rings include piperidyl, pyrrolidinyl, piperazinyl, pyranyl, tetrahydrothiophenyl, morpholinyl and the like.

"Aralkenyl" means an aryl-alkenyl- group in which the aryl and alkenyl are as previously described. Preferred aralkenyls contain a lower alkenyl group. Non-limiting examples of suitable aralkenyl groups include 2-phenethenyl and 2-naphthylethenyl. The bond to the parent moiety is through the alkenyl.

"Heteroaralkyl" means a heteroaryl-alkyl- group in which the heteroaryl and alkyl are as previously described. Preferred heteroaralkyls contain a lower alkyl group. Non-limiting examples of suitable aralkyl groups include pyridylmethyl, 2-(furan-3-yl)ethyl and quinolin-3-ylmethyl. The bond to the parent moiety is through the alkyl.

"Heteroaralkenyl" means an heteroaryl-alkenyl- group in which the heteroaryl and alkenyl are as previously described. Preferred heteroaralkenyls contain a lower alkenyl group. Non-limiting examples of suitable heteroaralkenyl groups include 2-(pyrid-3-yl)ethenyl and 2-(quinolin-3-yl)ethenyl. The bond to the parent moiety is through the alkenyl.

"Hydroxyalkyl" means a HO-alkyl- group in which alkyl is as previously defined. Preferred hydroxyalkyls contain lower alkyl. Non-limiting examples of suitable hydroxyalkyl groups include hydroxymethyl and 2-hydroxyethyl.

"Acyl" means an H-C(O)-, alkyl-C(O)-, alkenyl-C(O)-, Alkynyl-C(O)-, cycloalkyl-C(O)-, cycloalkenyl-C(O)-, or cycloalkynyl-C(O)- group in which the various groups are as previously described. The bond to the parent moiety is through the carbonyl. Preferred acyls contain a lower alkyl. Non-limiting examples of suitable acyl groups include formyl, acetyl, propanoyl, 2-methylpropanoyl, and cyclohexanoyl.

"Aroyl" means an aryl-C(O)- group in which the aryl group is as previously described. The bond to the parent moiety is through the carbonyl. Non-limiting examples of suitable groups include benzoyl and 1- and 2-naphthoyl.

"Alkoxy" means an alkyl-O- group in which the alkyl group is as previously described. Non-limiting examples of suitable alkoxy groups include methoxy, ethoxy, n-propoxy and isopropoxy. The alkyl group is linked to an adjacent moiety through the ether oxygen.

"Aryloxy" means an aryl-O- group in which the aryl group is as previously described. Non-limiting examples of suitable aryloxy groups include phenoxy and naphthoxy. The bond to the parent moiety is through the ether oxygen.

"Alkylthio" means an alkyl-S- group in which the alkyl group is as previously described. Non-limiting examples of suitable alkylthio groups include methylthio, ethylthio, i-propylthio and heptylthio. The bond to the parent moiety is through the sulfur.

"Arylthio" means an aryl-S- group in which the aryl group is as previously described. Non-limiting examples of suitable arylthio groups include phenylthio and naphthylthio. The bond to the parent moiety is through the sulfur.

"Aralkylthio" means an aralkyl-S- group in which the aralkyl group is as previously described. Non-limiting example of a suitable aralkylthio group is benzylthio. The bond to the parent moiety is through the sulfur.

"Alkoxycarbonyl" means an alkoxy group defined earlier linked to an adjacent moiety through a carbonyl. Non-limiting examples of alkoxycarbonyl groups include -C(O)-CH_3, -C(O)-CH_2CH_3 and the like.

"Aryloxycarbonyl" means an aryl-O-C(O)- group. Non-limiting examples of suitable aryloxycarbonyl groups include phenoxycarbonyl and naphthoxycarbonyl. The bond to the parent moiety is through the carbonyl.

"Aralkoxycarbonyl" means an aralkyl-O-C(O)- group. Non-limiting example of a suitable aralkoxycarbonyl group is benzyloxycarbonyl. The bond to the parent moiety is through the carbonyl.

"Alkylsulfonyl" means an alkyl-S(O_2)- group. Preferred groups are those in which the alkyl group is lower alkyl. The bond to the parent moiety is through the sulfonyl.

"Alkylsulfinyl" means an alkyl-S(O)- group. Preferred groups are those in which the alkyl group is lower alkyl. The bond to the parent moiety is through the sulfinyl.

"Arylsulfonyl" means an aryl-S(O_2)- group. The bond to the parent moiety is through the sulfonyl.

"Arylsulfinyl" means an aryl-S(O)- group. The bond to the parent moiety is through the sulfinyl.

The term "optionally substituted" means optional substitution with the specified groups, radicals or moieties.

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

Solvates of the compounds of the invention are also contemplated herein.

"Solvate" means a physical association of a compound of this invention with one or more solvent molecules. This physical association involves varying degrees of ionic and covalent bonding, including hydrogen bonding. In certain instances the solvate will be capable of isolation, for example when one or more solvent molecules are incorporated in the crystal lattice of the crystalline solid. "Solvate" encompasses both solution-phase and isolatable solvates. Non-limiting examples of suitable solvates include ethanolates, methanolates, and the like. "Hydrate" is a solvate wherein the solvent molecule is H_2O.

"Effective amount" or "therapeutically effective amount" is meant to describe an amount of compound of the present invention effective to treat a mammal (e.g., human) having a disease or condition mediated by Y Y5, and thus producing the desired therapeutic effect.

The compounds of formula I or formula III form salts which are also within the scope of this invention. Reference to a compound of formula I or formula III, herein is understood to include reference to salts thereof, unless otherwise indicated. The term "salt(s)", as employed herein, denotes acidic salts formed with inorganic and/or organic acids, as well as basic salts formed with inorganic and/or organic bases. In addition, when a compound of formula I or formula III contains both a basic moiety, such as, but not limited to a pyridine or imidazole, and an acidic moiety, such as, but not limited to a carboxylic acid, zwitterions ("inner salts") may be formed and are included within the term "salt(s)" as used herein. Pharmaceutically acceptable (i.e., non-toxic, physiologically acceptable) salts are preferred, although other salts are also useful. Salts of the compound of formula I or formula III may be formed, for example, by reacting a compound of formula I or formula III with an amount of acid or base, such as an equivalent amount, in a medium such as one in which the salt precipitates or in an aqueous medium followed by lyophilization.

Exemplary acid addition salts include acetates, adipates, alginates, ascorbates, aspartates, benzoates, benzenesulforiates, bisulfates, borates, butyrates, citrates, camphorates, camphorsulfonates, cyclopentanepropionates, digluconates, dodecylsulfates, ethanesulfonates, fumarates, glucoheptanoates, glycerophosphates, hemisulfates, heptanoates, hexanoates, hydrochlorides, hydrobromides, hydroiodides, 2-hydroxyethanesulfonates, lactates, maleates, methanesulfonates, 2-naphthalenesulfonates, nicotinates, nitrates, oxalates, pectinates, persulfates, 3-phenylpropionates, phosphates, picrates, pivalates, propionates, salicylates, succinates, sulfates, sulfonates (such as those mentioned herein), tartarates, thiocyanates, toluenesulfonates (also known as tosylates,) undecanoates, and the like. Additionally, acids which are generally considered suitable for the formation of pharmaceutically useful salts from basic pharmaceutical compounds are discussed, for example, by S. Berge *et al*, *Journal of Pharmaceutical Sciences* (1977) 66(1) 1-19; P. Gould, *International J. of Pharmaceutics* (1986) 33 201-217; Anderson *et al*, *The Practice of Medicinal Chemistry* (1996), Academic Press, New York; and in *The*

Orange Book (Food & Drug Administration, Washington, D.C. on their website). These disclosures are incorporated herein by reference thereto.

Exemplary basic salts include ammonium salts, alkali metal salts such as sodium, lithium, and potassium salts, alkaline earth metal salts such as calcium and magnesium salts, salts with organic bases (for example, organic amines) such as benzathines, dicyclohexylamines, hydrabamines (formed with N,N-bis(dehydroabietyl)ethylenediamine), N-methyl-D-glucamines, N-methyl-D-glucamides, t-butyl amines, and salts with amino acids such as arginine, lysine and the like. Basic nitrogen-containing groups may be quarternized with agents such as lower alkyl halides (e.g. methyl, ethyl, propyl, and butyl chlorides, bromides and iodides), dialkyl sulfates (e.g. dimethyl, diethyl, dibutyl, and diamyl sulfates), long chain halides (e.g. decyl, lauryl, myristyl and stearyl chlorides, bromides and iodides), aralkyl halides (e.g. benzyl and phenethyl bromides), and others.

All such acid salts and base salts are intended to be pharmaceutically acceptable salts within the scope of the invention and all acid and base salts are considered equivalent to the free forms of the corresponding compounds for purposes of the invention.

Compounds of formula I or formula III, and salts and solvates thereof, may exist in their tautomeric form (for example, as an amide or imino ether). All such tautomeric forms are contemplated herein as part of the present invention.

All stereoisomers (for example, geometric isomers, optical isomers and the like) of the present compounds (including those of the salts and solvates of the compounds), such as those which may exist due to asymmetric carbons on various substituents, including enantiomeric forms (which may exist even in the absence of asymmetric carbons), rotameric forms, atropisomers, and diastereomeric forms, are contemplated within the scope of this invention. Individual stereoisomers of the compounds of the invention may, for example, be substantially free of other isomers, or may be admixed, for example, as racemates or with all other, or other selected, stereoisomers. The chiral centers of the present invention can have the S or R configuration as defined by the *IUPAC* 1974 Recommendations. The use of the terms "salt", "solvate" and the like, is intended to equally apply to the salt and solvate of enantiomers, stereoisomers, rotamers, tautomers, or racemates of the inventive compounds.

When any variable (e.g., aryl, heterocycle, R_1, etc.) occurs more than one time in any constituent or in formula I or formula III, its definition on each occurrence is independent of its definition at every other occurrence. Also, combinations of substituents and/or variables are permissible only if such combinations result in stable compounds.

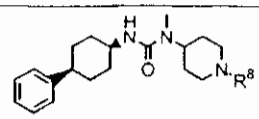
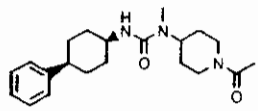
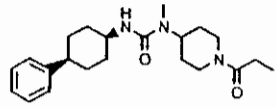
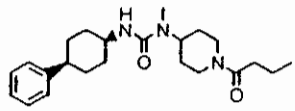
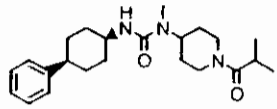
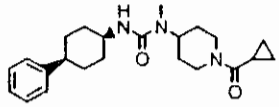
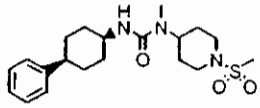
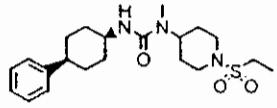
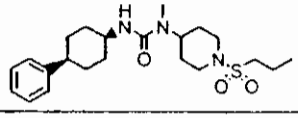
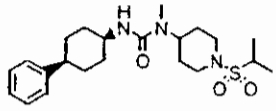
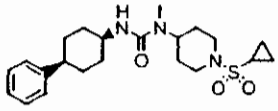
For compounds of the invention having at least one asymmetrical carbon atom, all isomers, including diastereomers, enantiomers and rotational isomers are contemplated as being part of this invention. The invention includes d and l isomers in both pure form and in admixture, including racemic mixtures. Isomers can be prepared using conventional techniques, either by reacting optically pure or optically enriched starting materials or by separating isomers of a compound of formula I or formula III.

Compounds of formula I or formula III can exist in unsolvated and solvated forms, including hydrated forms. In general, the solvated forms, with pharmaceutically acceptable solvents such as water, ethanol and the like, are equivalent to the unsolvated forms for purposes of this invention.

A compound of formula I or formula III may form pharmaceutically acceptable salts with organic and inorganic acids. For example, pyrido-nitrogen atoms may form salts with strong acids, while tertiary amino groups may form salts with weaker acids. Examples of suitable acids for salt formation are hydrochloric, sulfuric, phosphoric, acetic, citric, malonic, salicylic, malic, fumaric, succinic, ascorbic, maleic, methanesulfonic and other mineral and carboxylic acids well known to those skilled in the art. The salts are prepared by contacting the free base forms with a sufficient amount of the desired acid to produce a salt in the conventional manner. The free base forms may be regenerated by treating the salt with a suitable dilute aqueous base solution, such as dilute aqueous sodium hydroxide, potassium carbonate, ammonia or sodium bicarbonate. The free base forms differ from their respective salt forms somewhat in certain physical properties, such as solubility in polar solvents, but the salts are otherwise equivalent to their respective free base forms for purposes of the invention.

A further group of preferred compounds are those listed below in Table 2.

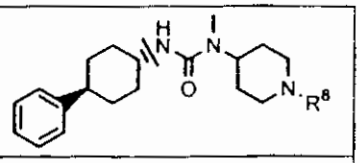
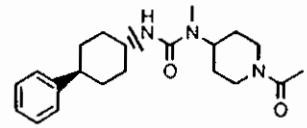
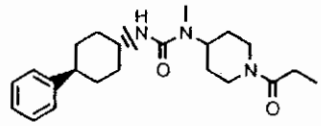
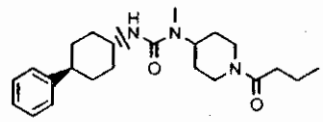
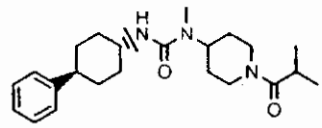
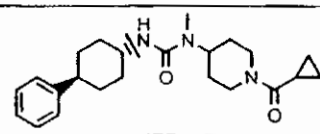
Table 2

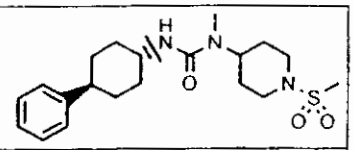
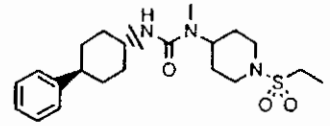
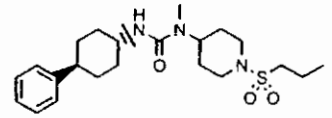
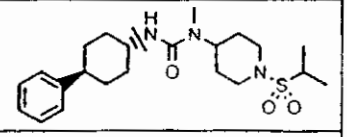
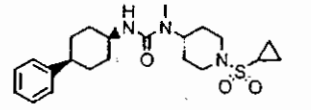
Example	
2A	
2B	
2C	
2D	
2E	
2F	
2G	
2H	
2I	
2J	

as well as their pharmaceutically acceptable salts or solvates.

An even further preferred group of compounds are those listed below in Table 3.

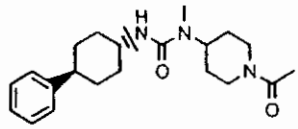
Table 3

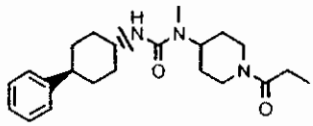
Example	
3A	
3B	
3C	
3D	
3E	

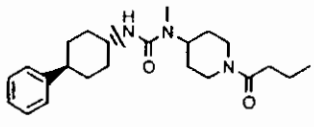
3F	
3G	
3H	
3I	
3J	

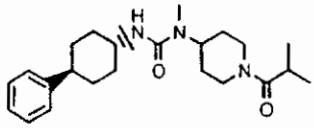
as well as their pharmaceutically acceptable salts or solvates.

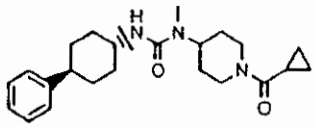
An even further group of preferred compounds are compounds from the group consisting of:

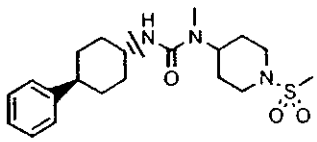


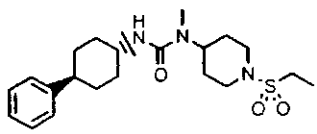


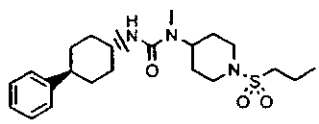


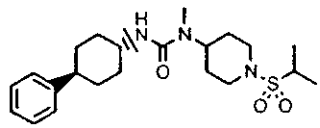


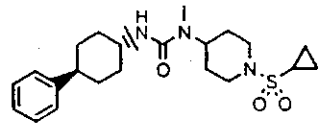


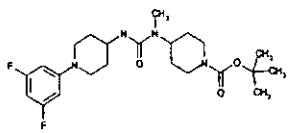


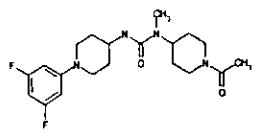


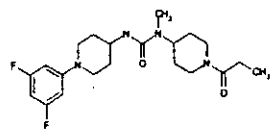


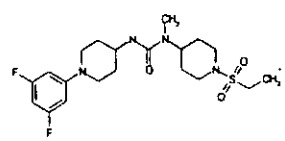


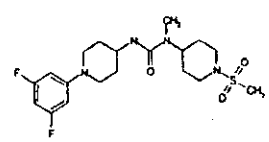


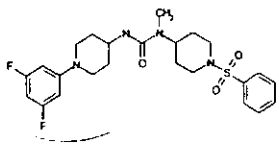


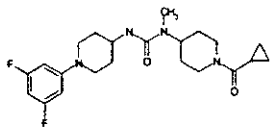


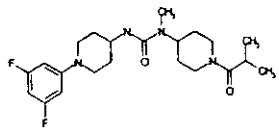


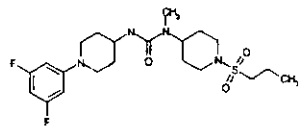


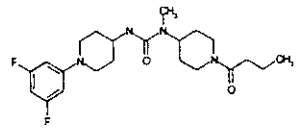


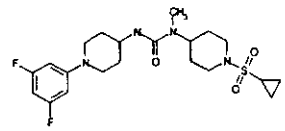


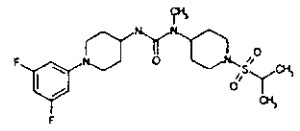


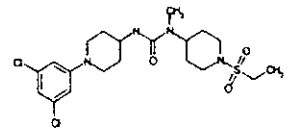


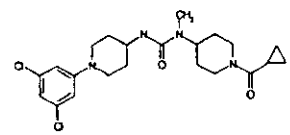


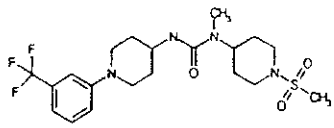


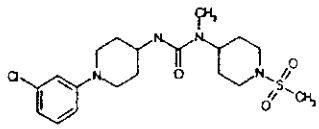


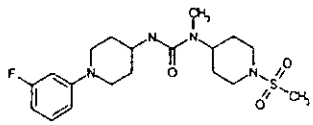


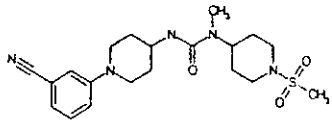


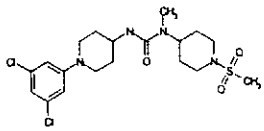


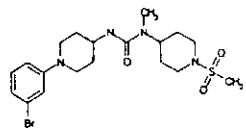


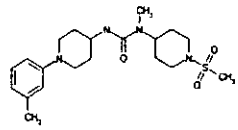


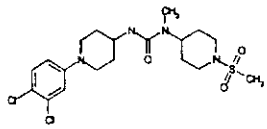


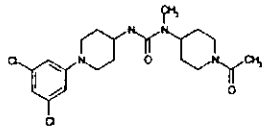


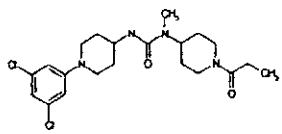


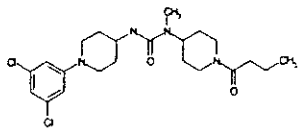


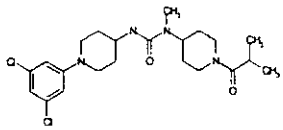


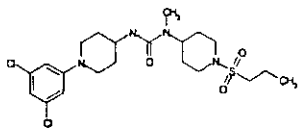


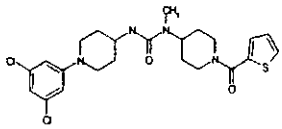


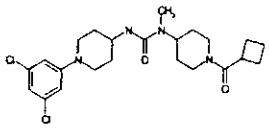


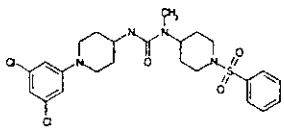


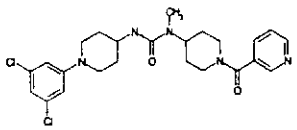


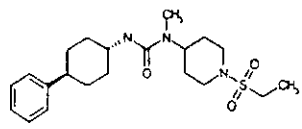


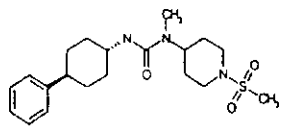


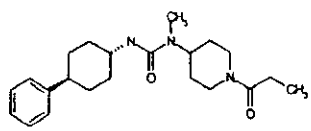


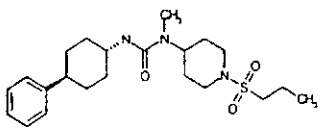


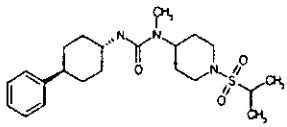


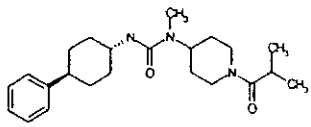


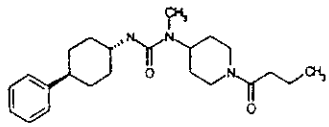


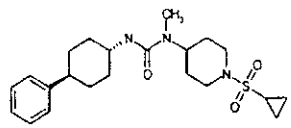


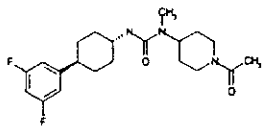


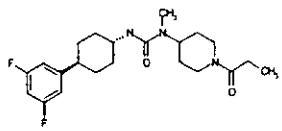


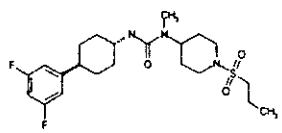


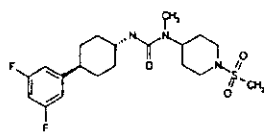


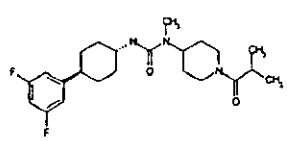


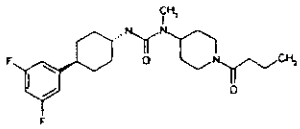


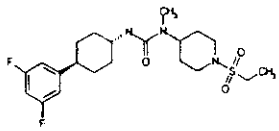


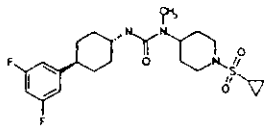


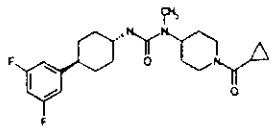


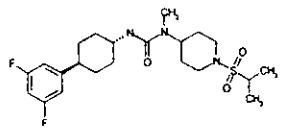


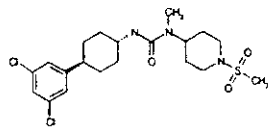


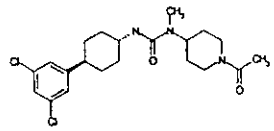


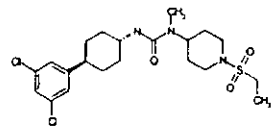


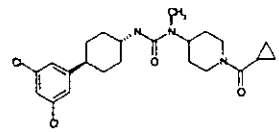


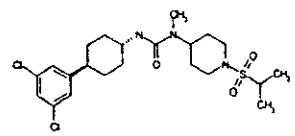


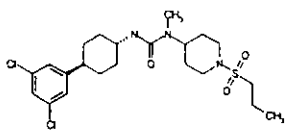


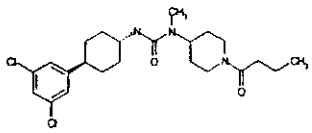


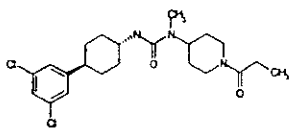


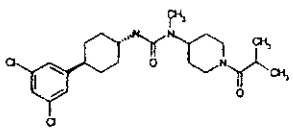


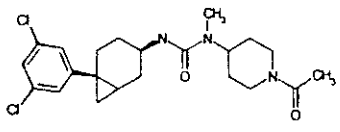


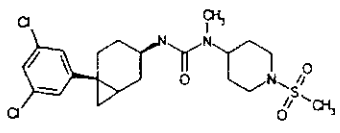


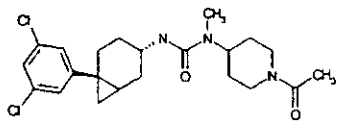


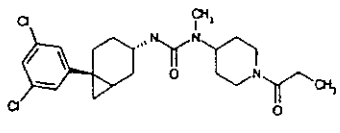


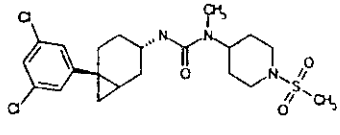


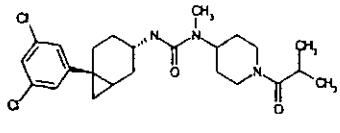


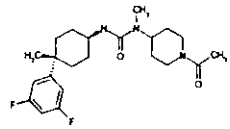


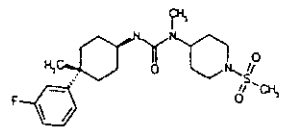


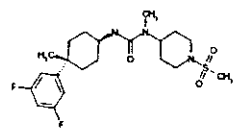


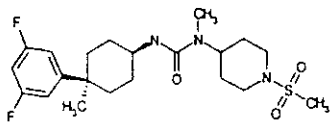


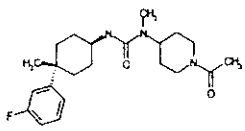


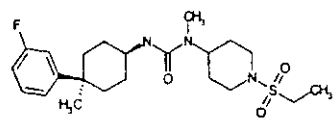


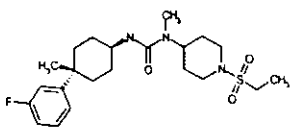


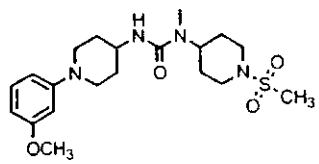


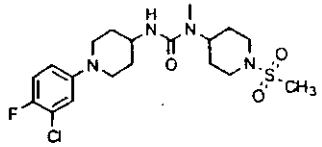


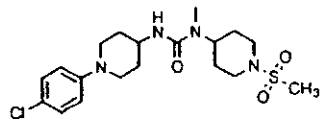


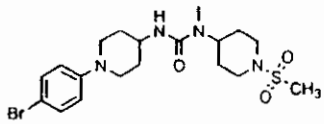


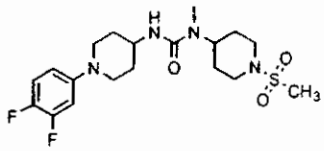


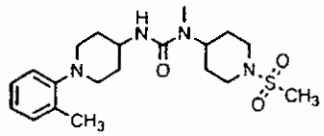


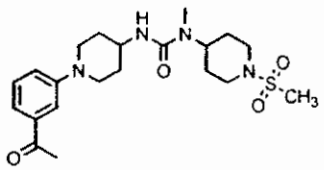


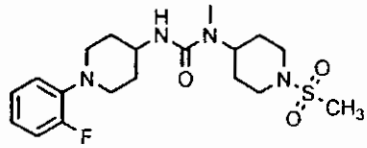


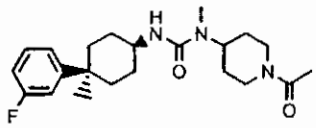


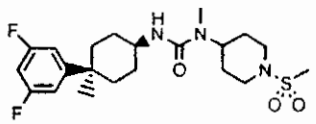


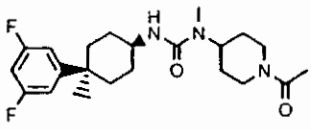


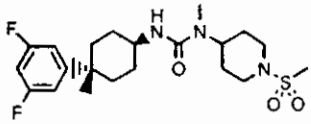




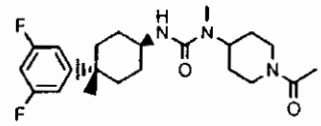








and



as well as their pharmaceutically acceptable salts or solvates.

Another aspect of this invention is a method of treating a mammal (*e.g.*, human) having a disease or condition mediated by the neuropeptide Y Y5 receptor by administering a therapeutically effective amount of a compound of formula I or formula III, or a pharmaceutically acceptable salt of said compound to the mammal.

A dosage for the invention is about 0.001 to 30 mg/kg/day of the formula I or

formula III compound. An additional dosage range is about 0.001 to 3 mg/kg/day of a compound of formula I or formula III, or a pharmaceutically acceptable salt of said compound.

Another aspect of this invention is directed to a method of treating obesity comprising administering to a mammal in need of such treatment a therapeutically effective amount of a compound of formula I or formula III or a pharmaceutically acceptable salt of said compound.

Another aspect of this invention is directed to a method for treating metabolic and eating disorders such as bulimia and anorexia comprising administering to a mammal a therapeutically effective amount of a compound of formula I or formula III, or a pharmaceutically acceptable salt of said compound.

Another aspect of this invention is directed to a method for treating hyperlipidemia comprising administering to a mammal a therapeutically effective amount of a compound of formula I or formula III, or a pharmaceutically acceptable salt of said compound.

Another aspect of this invention is directed to a method for treating cellulite and fat accumulation comprising administering to a mammal a therapeutically effective amount of a compound of formula I or formula III, or a pharmaceutically acceptable salt of said compound.

Another aspect of this invention is directed to a method for treating Type II diabetes comprising administering to a mammal a therapeutically effective amount of a compound of formula I or formula III or a pharmaceutically acceptable salt of said compound.

In addition to the "direct" effect of the compounds of this invention on the neuropeptide Y Y5 receptor subtype, there are diseases and conditions that will benefit from the weight loss such as insulin resistance, impaired glucose tolerance, Type II Diabetes, hypertension, hyperlipidemia, cardiovascular disease, gall stones, certain cancers, and sleep apnea.

This invention is also directed to pharmaceutical compositions, which comprise an amount of a compound of formula I or formula III, or a pharmaceutically acceptable salt of said compound and a pharmaceutically acceptable carrier.

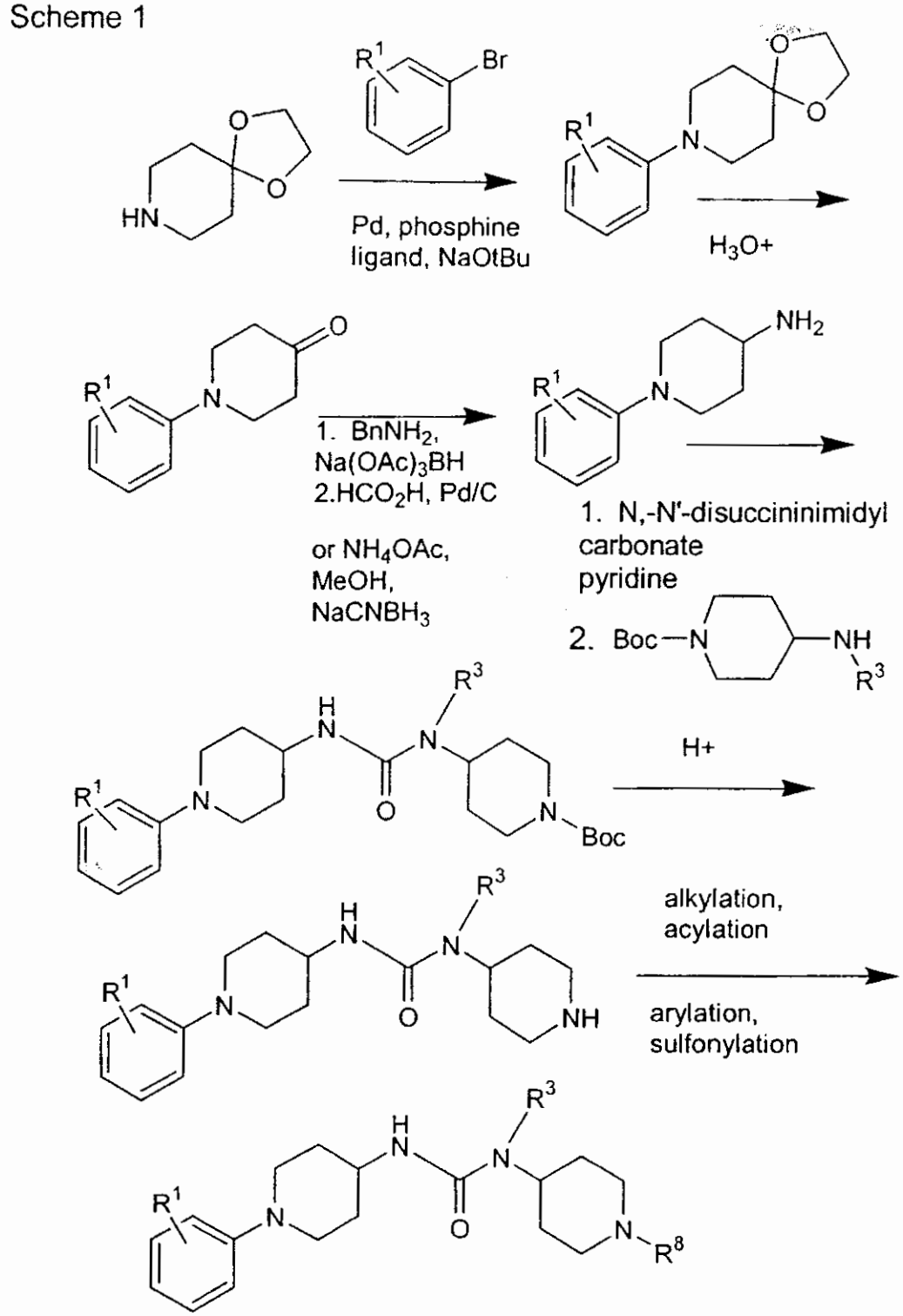
This invention is also directed to pharmaceutical compositions for the treatment of obesity which comprise an obesity treating amount of a compound of

formula I or formula III, or a pharmaceutically acceptable salt of said compound or of said and a pharmaceutically acceptable carrier therefor.

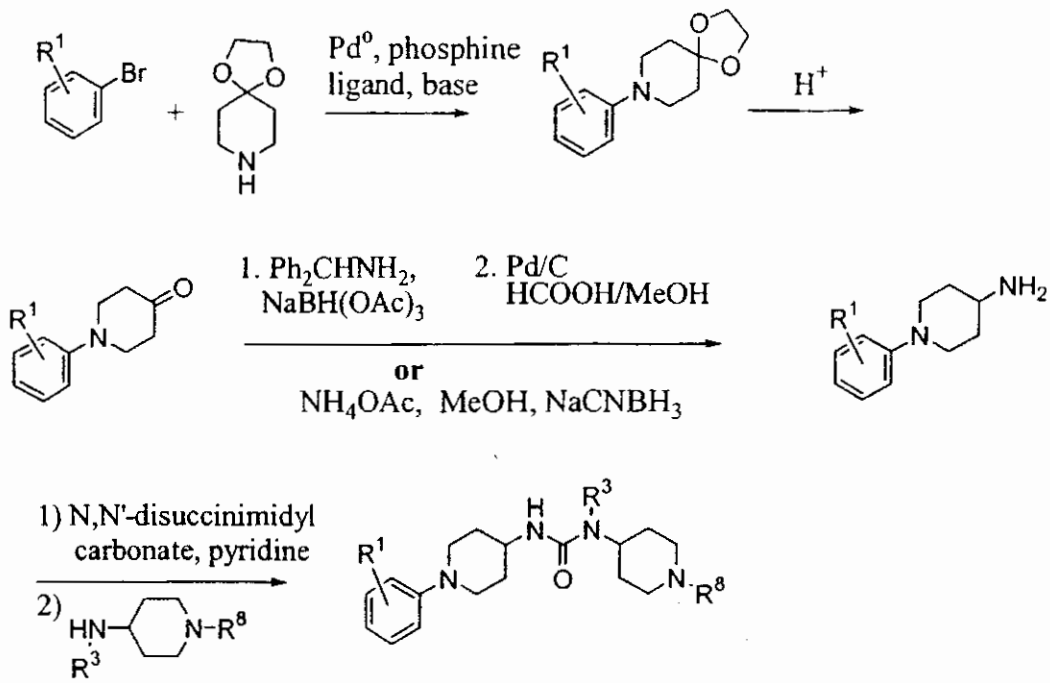
Compounds of formula I or formula III can be produced by processes known to those skilled in the art using either solution phase or solid phase synthesis as shown in the following reaction schemes, in the preparations and examples below.

Compounds of formula I where X is N, D is absent, A is absent, E is H, R^2 is H, R^4 is H, j is 1, k is 1, m is 2, n is 2, and Z is NR^8 can be prepared by Scheme 1, as follows:

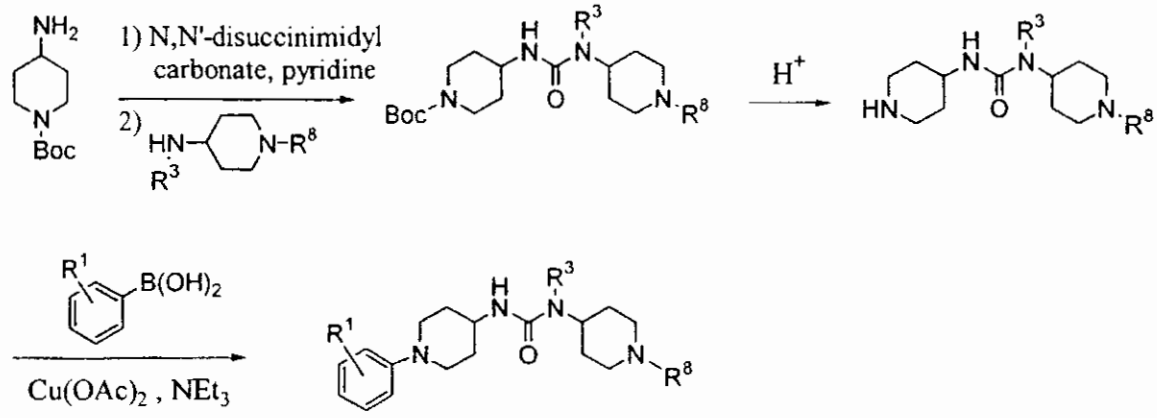
Scheme 1


R1
Br
HN
O
Pd, phosphine ligand, NaOtBu
H3O+
NH2
1. BnNH2, Na(OAc)3BH
2.HCO2H, Pd/C
or NH4OAc, MeOH, NaCNBH3
1. N,-N'-disuccininimidyl carbonate pyridine
2. Boc—N
NH
R3
H+
Boc
alkylation, acylation
arylation, sulfonylation
R8

Scheme 2

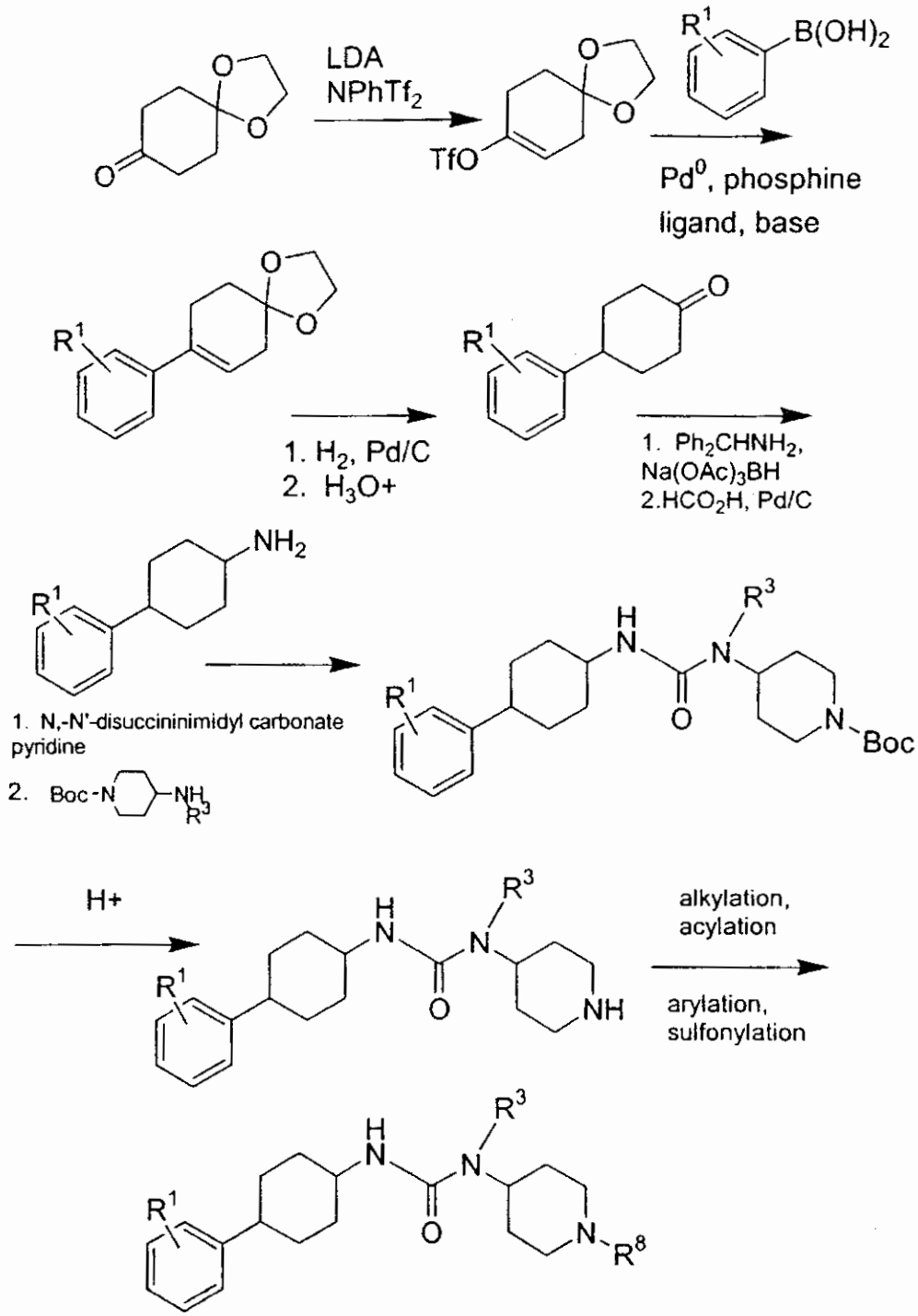


Scheme 3

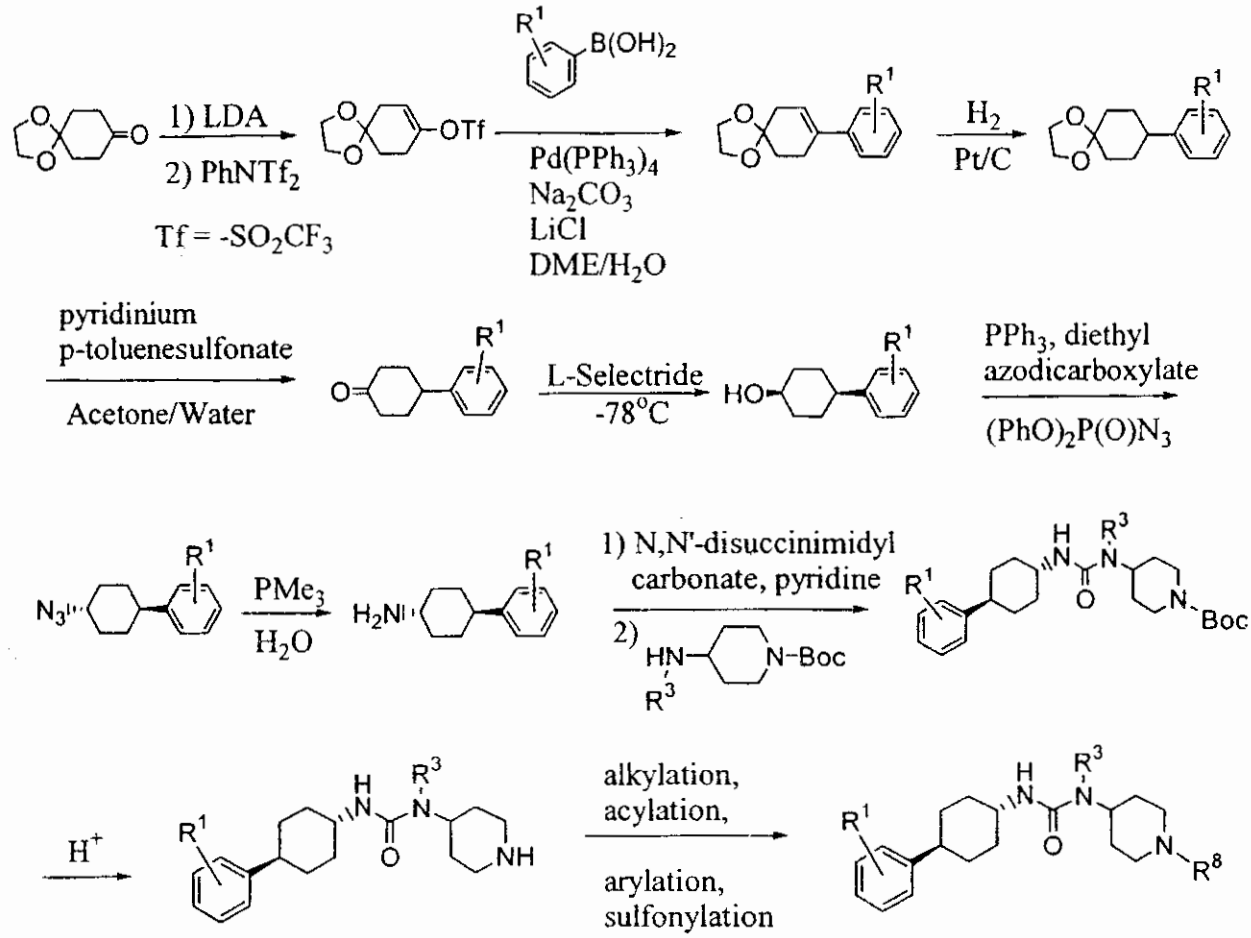


Compounds of formula I wherein X is C, D is H, A is absent, E is H, R^2 is H, R^4 is H, j is 1, k is 1, m is 2, n is 2 and Z is NR^8 can be prepared by Scheme 4, as follows:

Scheme 4

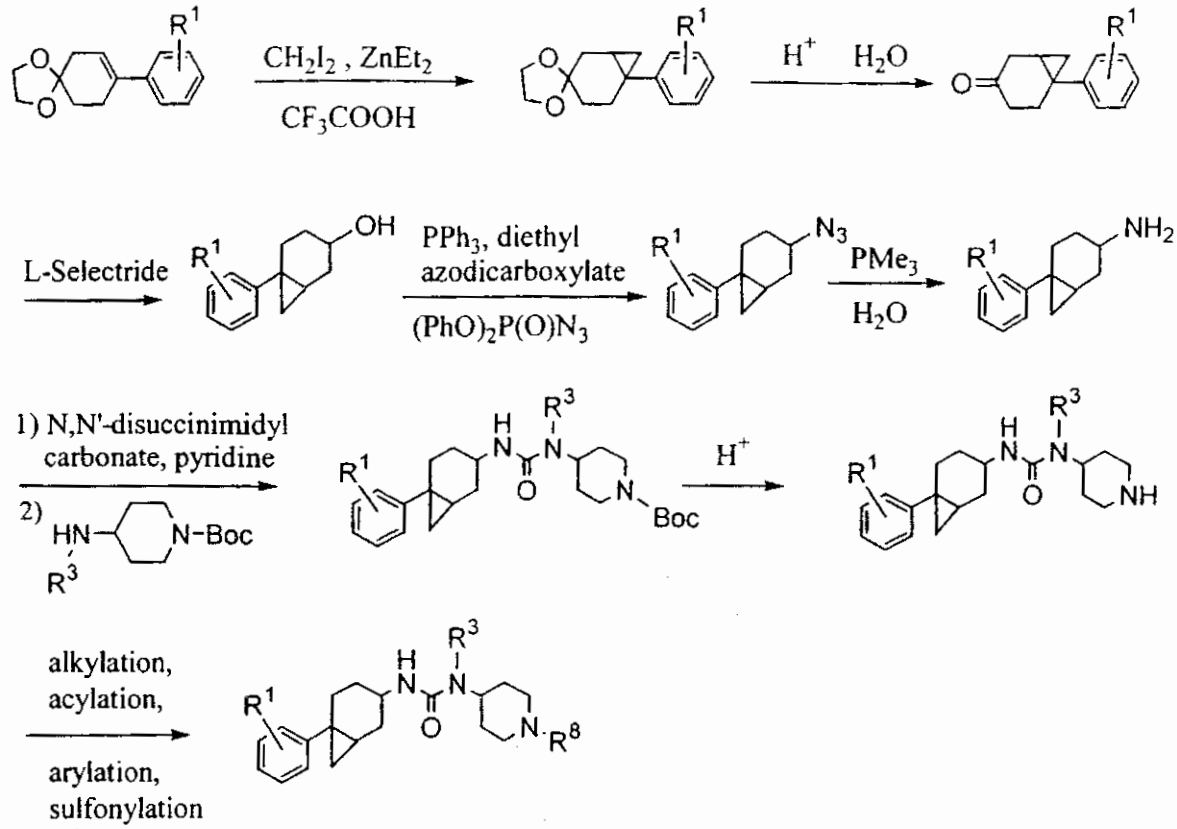


Scheme 5

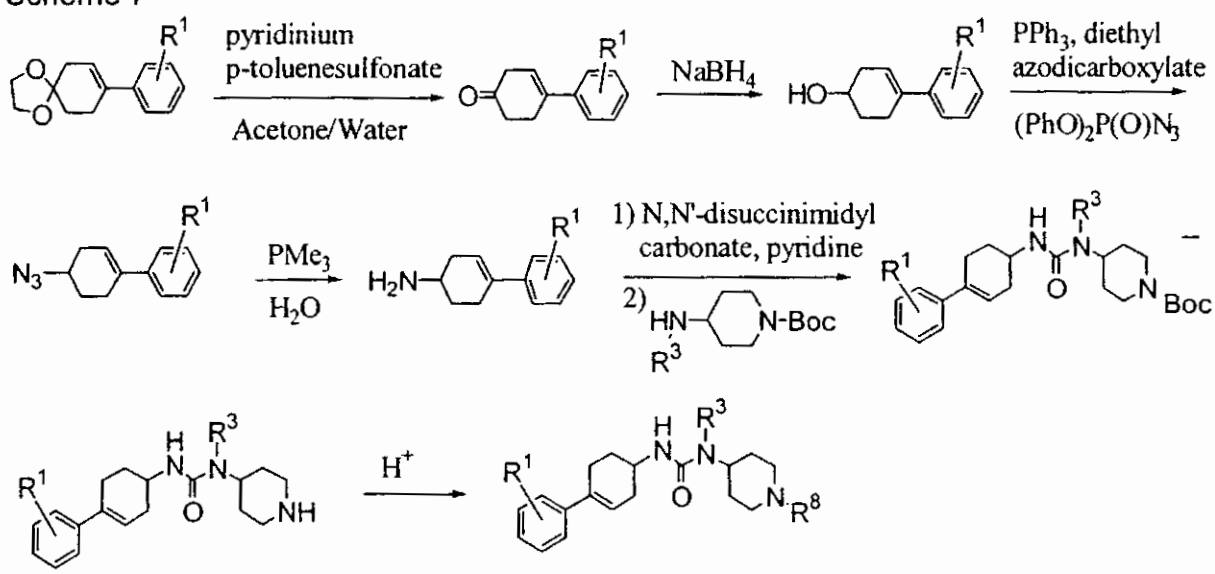

1) LDA
2) PhNTf2
Tf = -SO2CF3
B(OH)2
Pd(PPh3)4
Na2CO3
LiCl
DME/H2O
H2
Pt/C
pyridinium
p-toluenesulfonate
Acetone/Water
L-Selectride
-78°C
PPh3, diethyl
azodicarboxylate
(PhO)2P(O)N3
PMe3
H2O
1) N,N'-disuccinimidyl
carbonate, pyridine
2)
N-Boc
Boc
H+
alkylation,
acylation,
arylation,
sulfonylation

5

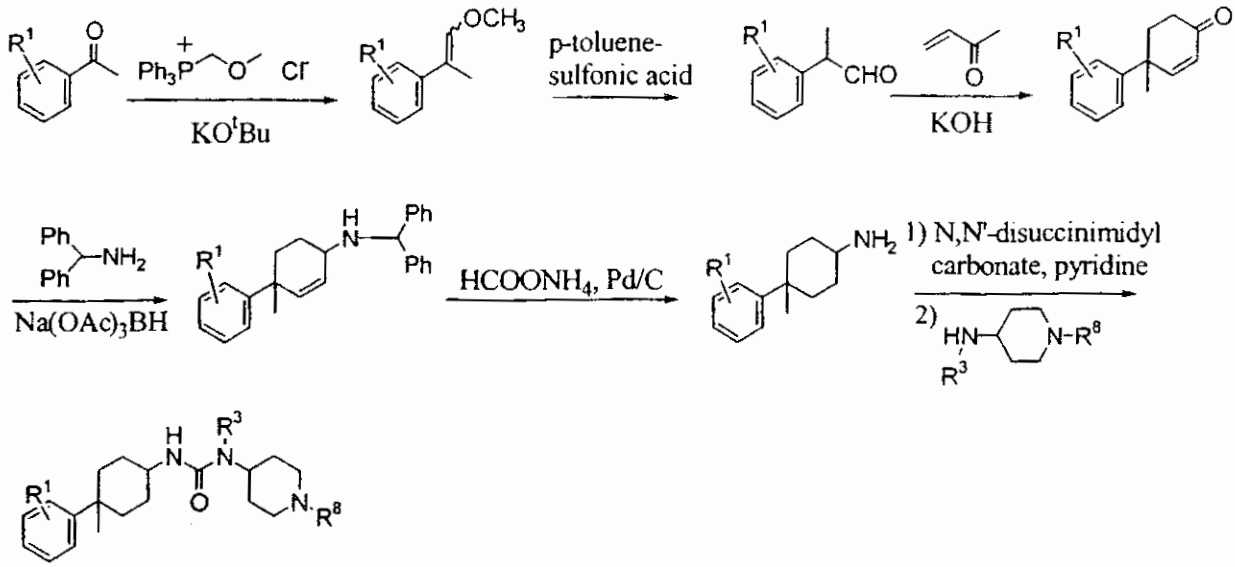
Scheme 6



Scheme 7



Scheme 8



Combinatorial libraries of compounds of formula I can also be prepared using solid phase chemistry as shown in the schemes above.

Alternative mechanistic pathways and analogous structures within the scope of the invention would be apparent to those skilled in the art.

Starting materials are prepared by known methods and/or methods described in the Preparations.

The compounds of formula I or formula III exhibit Y Y5 receptor antagonizing activity, which has been correlated with pharmaceutical activity for treating metabolic disorders, such as obesity, eating disorders such as hyperphagia, and diabetes.

The compounds of formula I or formula III display pharmacological activity in a test procedure designed to demonstrate Y Y5 receptor antagonist activity. The compounds are non-toxic at pharmaceutically therapeutic doses.

cAMP Assay

HEK-293 cells expressing the Y5 receptor subtype were maintained in Dulbecco's modified Eagles' media (Gico-BRL) supplemented with 10% FCS (ICN), 1% penicillin-streptomycin and 200 µg/ml Geneticin®(GibcoBRL #11811-031) under a humidified 5% CO_2 atmosphere. Two days prior to assay, cells were released from T-175 tissue culture flasks using cell dissociation solution (1X; non-enzymatic [Sigma #C-5914]) and seeded into 96-well, flat-bottom tissue culture plates at a density of

15,000 to 20,000 cells per well. After approximately 48 hours, the cell monolayers were rinsed with Hank's balanced salt solution (HBSS) then pre-incubated with approximately 150 µl/well of assay buffer (HBSS supplemented with 4 mM $MgCl_2$, 10 mM HEPES, 0.2% BSA [HH]) containing 1 mM 3-isobutyl-1-methylxanthine ([IBMX] Sigma #1-587) with or without the antagonist compound of interest at 37°C. After 20 minutes the 1 mM IBMX-HH assay buffer (± antagonist compound) was removed and replaced with assay buffer containing 1.5 µM (CHO cells) or 5 µM (HEK-293 cells) forskolin (Sigma #F-6886) and various concentrations of NPY in the presence or absence of one concentration of the antagonist compound of interest. At the end of 10 minutes, the media were removed and the cell monolayers treated with 75 µl ethanol. The tissue culture plates were agitated on a platform shaker for 15 minutes, after which the plates were transferred to a warm bath in order to evaporate the ethanol. Upon bringing all wells to dryness, the cell residues were re-solubilized with 250 µl FlashPlate® assay buffer. The amount of cAMP in each well was quantified using the [^{125}I]-cAMP FlashPlate® kit (NEN #SMP-001) and according to the protocol provided by the manufacturer. Data were expressed as either pmol cAMP/ml or as percent of control. All data points were determined in triplicate and EC_{50}'s (nM) were calculated using a nonlinear (sigmoidal) regression equation (GraphPad Prism™). The K_B of the antagonist compound was estimated using the following formula:

$$K_B = [B] / (1 - \{[A'] / [A]\})$$

where

[A] is the EC_{50} of the agonist (NPY) in the absence of antagonist,

[A'] is the EC_{50} of the agonist (NPY) in the presence of antagonist,

and

[B] is the concentration of the antagonist.

NPY Receptor Binding Assay

Human NPY Y5 receptors were expressed in CHO cells. Binding assays were performed in 50 mM HEPES, pH 7.2, 2.5 mM $CaCl_2$, 1 mM $MgCl_2$ and 0.1% BSA containing 5-10 µg of membrane protein and 0.1 nM ^{125}L-peptide YY in a total volume of 200 µl. Non-specific binding was determined in the presence of 1 µM NPY. The

reaction mixtures were incubated for 90 minutes at room temperature then filtered through Millipore MAFC glass fiber filter plates which had been pre-soaked in 0.5% polyethleneimine. The filters were washed with phosphate-buffered saline, and radioactivity was measured in a Packard TopCount scintillation counter.

For the compounds of this invention, a range of NPY Y5 receptor binding activity (Ki values) of from about 0.2 nM to about 2,000 nM was observed. Compounds of this invention preferably have a binding activity in the range of from about 0.2 nM to about 1,000 nM, more preferably from about 0.2 to about 100 nM, and most preferably from about 0.2 to about 10 nM.

Yet another aspect of this invention are combinations of a compound of formula I or formula III, or a pharmaceutically acceptable salt of said compound and other compounds as described below.

One such aspect of this invention is a method for treating obesity comprising administering to a mammal (*e.g.*, a female or male human)

a. an amount of a first compound, said first compound being a formula I or formula III compound, or a pharmaceutically acceptable salt of said compound; and

b. an amount of a second compound, said second compound being an anti-obesity and/or anorectic agent such as a $ß_3$ agonist, a thyromimetic agent, an anoretic agent, or an NPY antagonist wherein the amounts of the first and second compounds result in a therapeutic effect.

This invention is also directed to a pharmaceutical combination composition comprising: a therapeutically effective amount of a composition comprising

a first compound, said first compound being a formula I or formula III compound, or a pharmaceutically acceptable salt of said compound

a second compound, said second compound being an anti-obesity and/or anorectic agent such as a $ß_3$ agonist, a thyromimetic agent, an anoretic, or an NPY antagonist; and/or optionally a pharmaceutical carrier, vehicle or diluent.

Another aspect of this invention is a kit comprising:

a. an amount of a formula I or formula III compound, or a pharmaceutically acceptable salt of said compound and a pharmaceutically acceptable carrier, vehicle or diluent in a first unit dosage form;

b. an amount of an anti-obesity and/or anorectic agent such as a $ß_3$ agonist, a thyromimetic agent, an anoretic agent, or an NPY antagonist and a

pharmaceutically acceptable carrier, vehicle or diluent in a second unit dosage form; and

c. means for containing said first and second dosage forms wherein the amounts of the first and second compounds result in a therapeutic effect.

Preferred anti-obesity and/or anorectic agents (taken singly or in any combination thereof) in the above combination methods, combination compositions and combination kits are:

phenylpropanolamine, ephedrine, pseudoephedrine, phentermine, a cholecystokinin-A (hereinafter referred to as CCK-A) agonist, a monoamine reuptake inhibitor (such as sibutramine), a sympathomimetic agent, a serotonergic agent (such as dexfenfluramine or fenfluramine), a dopamine agonist (such as bromocriptine), a melanocyte-stimulating hormone receptor agonist or mimetic, a melanocyte-stimulating hormone analog, a cannabinoid receptor antagonist, a melanin concentrating hormone antagonist, the OB protein (hereinafter referred to as "leptin"), a leptin analog, a leptin receptor agonist, a galanin antagonist or a GI lipase inhibitor or decreaser (such as orlistat). Other anorectic agents include bombesin agonists, dehydroepiandrosterone or analogs thereof, glucocorticoid receptor agonists and antagonists, orexin receptor antagonists, urocortin binding protein antagonists, agonists of the glucagon-like peptide-1 receptor such as Exendin and ciliary neurotrophic factors such as Axokine.

Another aspect of this invention is a method treating diabetes comprising administering to a mammal (*e.g.*, a female or male human)

a. an amount of a first compound, said first compound being a formula I or formula III compound, or a pharmaceutically acceptable salt of said compound; and

b. an amount of a second compound, said second compound being an aldose reductase inhibitor, a glycogen phosphorylase inhibitor, a sorbitol dehydrogenase inhibitor, a protein tyrosine phosphatase 1B inhibitor, a dipeptidyl protease inhibitor, insulin (including orally bioavailable insulin preparations), an insulin mimetic, metformin, acarbose, a PPAR-gamma ligand such as troglitazone, rosaglitazone, pioglitazone or GW-1929, a sulfonylurea, glipazide, glyburide, or chlorpropamide wherein the amounts of the first and second compounds result in a therapeutic effect.

This invention is also directed to a pharmaceutical combination composition comprising: a therapeutically effective amount of a composition comprising

a first compound, said first compound being a formula I or formula III compound, or a pharmaceutically acceptable salt of said compound;

a second compound, said second compound being an aldose reductase inhibitor, a glycogen phosphorylase inhibitor, a sorbitol dehydrogenase inhibitor, a protein tyrosine phosphatase 1B inhibitor, a dipeptidyl protease inhibitor, insulin (including orally bioavailable insulin preparations), an insulin mimetic, metformin, acarbose, a PPAR-gamma ligand such as troglitazone, rosaglitazone, pioglitazone, or GW-1929, a sulfonylurea, glipazide, glyburide, or chlorpropamide; and optionally a pharmaceutical carrier, vehicle or diluent.

Another aspect of this invention is a kit comprising:

a. an amount of a formula I or formula III compound, or a pharmaceutically acceptable salt of said compound and a pharmaceutically acceptable carrier, vehicle or diluent in a first unit dosage form;

b. an amount of an aldose reductase inhibitor, a glycogen phosphorylase inhibitor, a sorbitol dehydrogenase inhibitor, a protein tyrosine phosphatase 1B inhibitor, a dipeptidyl protease inhibitor, insulin (including orally bioavailable insulin preparations), an insulin mimetic, metformin, acarbose, a PPAR-gamma ligand such as troglitazone, rosaglitazone, pioglitazone, or GW-1929, a sulfonylurea, glipazide, glyburide, or chlorpropamide and a pharmaceutically acceptable carrier, vehicle or diluent in a second unit dosage form; and

c. means for containing said first and second dosage forms wherein the amounts of the first and second compounds result in a therapeutic effect.

For preparing pharmaceutical compositions from the compounds described by this invention, inert, pharmaceutically acceptable carriers can be either solid or liquid. Solid form preparations include powders, tablets, dispersible granules, capsules, cachets and suppositories. The powders and tablets may be comprised of from about 5 to about 95 percent active ingredient. Suitable solid carriers are known in the art, e.g., magnesium carbonate, magnesium stearate, talc, sugar or lactose. Tablets, powders, cachets and capsules can be used as solid dosage forms suitable for oral administration. Examples of pharmaceutically acceptable carriers and methods of manufacture for various compositions may be found in A. Gennaro (ed.),

Remington's Pharmaceutical Sciences, 18th Edition, (1990), Mack Publishing Co., Easton, Pennsylvania.

Liquid form preparations include solutions, suspensions and emulsions. As an example may be mentioned water or water-propylene glycol solutions for parenteral injection or addition of sweeteners and opacifiers for oral solutions, suspensions and emulsions. Liquid form preparations may also include solutions for intranasal administration.

Aerosol preparations suitable for inhalation may include solutions and solids in powder form, which may be in combination with a pharmaceutically acceptable carrier, such as an inert compressed gas, e.g. nitrogen.

Also included are solid form preparations that are intended to be converted, shortly before use, to liquid form preparations for either oral or parenteral administration. Such liquid forms include solutions, suspensions and emulsions.

The compounds of the invention may also be deliverable transdermally. The transdermal compositions can take the form of creams, lotions, aerosols and/or emulsions and can be included in a transdermal patch of the matrix or reservoir type as are conventional in the art for this purpose.

The compounds of this invention may also be delivered subcutaneously.

Preferably the compound is administered orally.

Preferably, the pharmaceutical preparation is in a unit dosage form. In such form, the preparation is subdivided into suitably sized unit doses containing appropriate quantities of the active component, e.g., an effective amount to achieve the desired purpose.

The quantity of active compound in a unit dose of preparation may be varied or adjusted from about 1 mg to about 100 mg, preferably from about 1 mg to about 50 mg, more preferably from about 1 mg to about 25 mg, according to the particular application.

The actual dosage employed may be varied depending upon the requirements of the patient and the severity of the condition being treated. Determination of the proper dosage regimen for a particular situation is within the skill of the art. For convenience, the total daily dosage may be divided and administered in portions during the day as required.

The amount and frequency of administration of the compounds of the invention and/or the pharmaceutically acceptable salts thereof will be regulated according to

the judgment of the attending clinician considering such factors as age, condition and size of the patient as well as severity of the symptoms being treated. A typical recommended daily dosage regimen for oral administration can range from about 1 mg/day to about 300 mg/day, preferably 1 mg/day to 50 mg/day, in two to four divided doses.

The invention disclosed herein is exemplified by the following preparations and examples which should not be construed to limit the scope of the disclosure. Alternative mechanistic pathways and analogous structures will be apparent to those skilled in the art.

Where NMR data are presented, ^1H spectra were obtained on either a Varian VXR-200 (200 MHz, ^1H), Varian Gemini-300 (300 MHz) or XL-400 (400 MHz) and are reported as ppm down field from Me_4Si with number of protons, multiplicities, and coupling constants in Hertz indicated parenthetically. Where LC/MS data are presented, analyses was performed using an Applied Biosystems API-100 mass spectrometer and Shimadzu SCL-10A LC column: Altech platinum C18, 3 micron, 33mm x 7mm ID; gradient flow: 0 min – 10% CH_3CN, 5 min – 95% CH_3CN, 7 min – 95% CH_3CN, 7.5 min – 10% CH_3CN, 9 min – stop. The retention time and observed parent ion are given.

The following constituents, solvents and reagents may be referred to by their abbreviations in parenthesis:

PTLC (preparative thin-layer chromatography);

N-Phenyltrifluoromethanesulfonimide ($NPhTf_2$);

trifluoromethanesulfonyloxy (TfO);

sodium triacetoxyborohydride ($Na(OAc)_3BH$);

sodium t-butoxide (NaOtBu);

lithium diisopropylamide (LDA);

dppp [1,3-bis(diphenylphosphino)propane];

THF (tetrahydrofuran);

DME (1,2-dimethoxyethane);

EtOAc (ethyl acetate);

Et_3N (triethylamine);

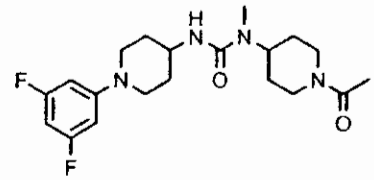
MeOH (methanol);

room temperature (r.t.);

and tert-butoxycarbonyl (Boc).

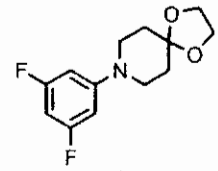
EXPERIMENTAL DETAILS

Example **1A**



1A

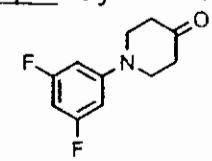
Step 1. Synthesis of **14**:



14

To a solution of 1-bromo-3,5-difluorobenzene (1.76 g, 9.14 mmol), 1,4-dioxa-azaspiro(4,5)decane (1.41 g, 9.8 mmol), $Pd(OAc)_2$ (0.096 g, 0.43 mmol), dppp (0.21 g, 0.50 mmol) in anhydrous toluene (5 ml) was added NaOtBu (2.04 g, 21.2 mmol). The reaction mixture was degassed with nitrogen, then sealed and heated at 90 °C for 16 hours. The mixture was diluted with CH_2Cl_2 (50 ml) and filtered. The filtrate was concentrated *in vacuo* and the residue was separated by flash column chromatography (hexane:EtOAc 100:0→95:5, v/v) to give **14** (2.0 g, 86%). MS m/e 256 $(M+H)^+$.

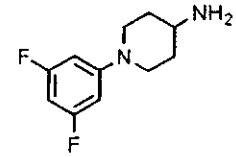
Step 2. Synthesis of **15**:



15

To a solution of **14** (0.1 g, 0.04 mmol) in THF (4 ml) was added 5N HCl (4 ml). The reaction mixture was stirred at room temperature for 16 hours. The mixture was adjusted to pH 10 with saturated sodium bicarbonate solution and extracted with CH_2Cl_2 (2x15 ml). The combined organic layer was washed with brine (30 ml), separated and dried over magnesium sulfate. The concentrated residue was separated by PTLC (hexane:EtOAc 4:1, v/v) to give **15** (0.065 g, 79%). MS m/e 212 $(M+H)^+$.

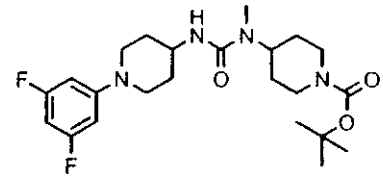
Step 3. Synthesis of **16**:



16

To a solution of **15** (0.80 g, 3.8 mmol), benzylamine (0.64 g, 6.0 mmol) in DME (50 ml) was added $Na(OAc)_3BH$ (1.6 g, 7.5 mmol). After the reaction mixture was stirred at room temperature for 16 hours, 1N NaOH (50 ml) and CH_2Cl_2 (50 ml) were added. The organic layer was separated, washed with water (50 ml) and brine (50 ml), then dried over magnesium sulfate. The concentrated residue was dissolved in MeOH (100 ml). Formic acid (4.50 ml, 119 mmol) and 10% Pd/C (1 g, 0.9 mmol) were added. The reaction mixture was stirred at room temperature for 16 hours. The mixture was filtered via celite. The filtrate was concentrated and diluted with CH_2Cl_2 (50 ml) and 1N NaOH (50 ml). The organic layer was washed with brine (50 ml), dried over magnesium sulfate, and concentrated *in vacuo* to give **16** (0.66 g, 82%). MS m/e 213 $(M+H)^+$.

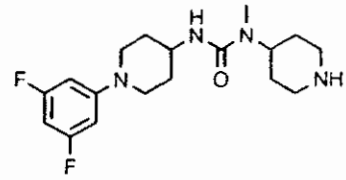
Step 4. Synthesis of **17**:



17

To a solution of **16** (0.21 g, 1.0 mmol) in THF (5 ml) was added pyridine (0.25 ml, 3.0 mmol). The mixture was cooled in an ice water-bath, and N, N'-disuccinimidyl carbonate (0.28 g, 1.1 mmol) was added at 0 °C. The mixture was stirred at room temperature for 3.5 hours, then cooled in an ice water-bath, and a solution of 1-tert-butoxycarbonyl-4-methylaminopiperidine, prepared via the procedure of WO 02/22492, page 17) (0.24 g, 1.1 mmol) in THF (1 ml) was added at 0 °C. The reaction mixture was stirred at room temperature for 16 hours. The concentrated residue was diluted with CH_2Cl_2 (50 ml), then washed with 1N NaOH (50 ml), water (50 ml), and brine (50 ml). The organic layer was separated and dried over potassium carbonate. The concentrated residue was separated by PTLC (CH_2Cl_2:MeOH 20:1, v/v) to give **17** (0.36 g, 80%). MS m/e 453 $(M+H)^+$.

Step 5. Synthesis of **18**:



18

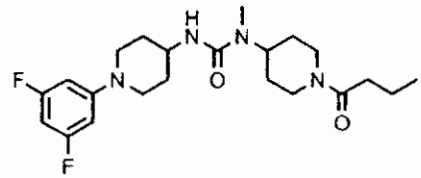
To a solution of **17** (0.33 g, 0.73 mmol) in CH_2Cl_2 (9 ml) was added trifluoroacetic acid (1 ml). The reaction mixture was stirred at room temperature for 16 hours. The concentrated residue was diluted with CH_2Cl_2 (50 ml) and washed with 1N NaOH (50 ml). The organic layer was separated and dried over magnesium sulfate. The concentrated residue was separated by flash column chromatography (1:9 MeOH/CH_2Cl_2→1:4 2M ammonia in MeOH/CH_2Cl_2) to give **18** (0.22 g, 86%). MS m/e 353 $(M+H)^+$.

Step 6.

To a solution of **18** (0.050 g, 0.14 mmol) in CH_2Cl_2 (2 ml) was added acetic anhydride (0.030 ml, 0.32 mmol) and Et_3N (0.20 ml, 1.4 mmol). The reaction mixture was stirred at room temperature for 16 hours. PS-Trisamine resin (100 mg) was added, and the mixture was stirred for 16 hours. The mixture was filtered and washed with 4:1 MeOH/CH_2Cl_2 (50 ml). The filtrate was concentrated and the residue was separated by PTLC (CH_2Cl_2: MeOH 20:1, v/v) to give **1A** (0.057 g, 94%).

Reaction of **18** with propanoyl chloride by the same procedure afforded Example **1B**.

Example **1C**:

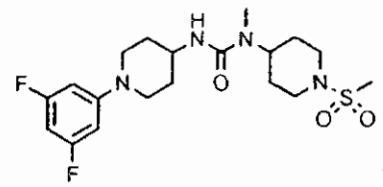


1C

To a solution of **18** (0.050 g, 0.14 mmol) and Et_3N (0.20 ml, 1.4 mmol) in CH_2Cl_2 (2 ml) was added butyryl chloride (0.040 ml, 0.38 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 10 minutes. The concentrated residue was separated by PTLC (CH_2Cl_2:MeOH 10:1, v/v) to give **1C** (0.058 g, 91%).

Using the procedure of Example **1C** and the appropriate acid chloride, Examples **1D** and **1E** were prepared.

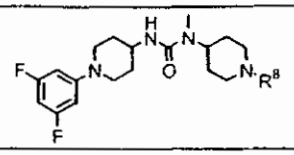
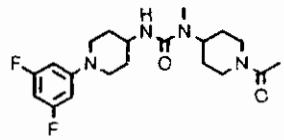
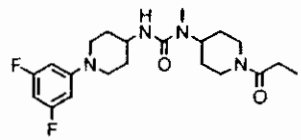
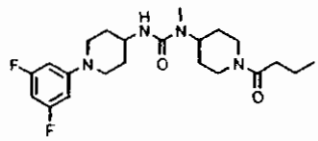
Example **1F**:

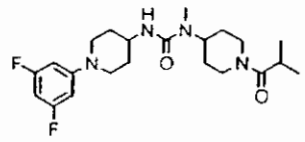
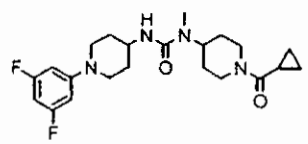
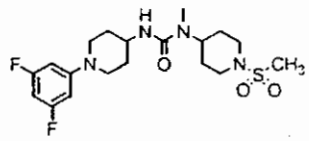
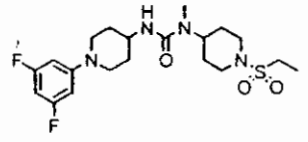
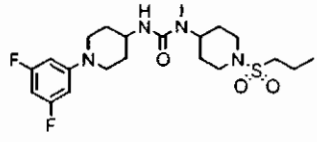
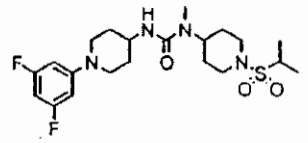


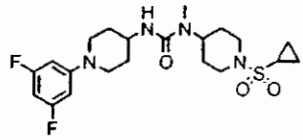
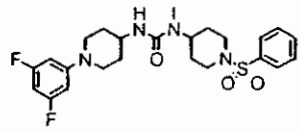
1F

To a solution of **18** (0.050 g, 0.14 mmol) and Et_3N (0.20 ml, 1.4 mmol) in CH_2Cl_2 (2 ml) was added methanesulfonyl chloride (0.040 ml, 0.52 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 10 minutes. The concentrated residue was separated by PTLC (CH_2Cl_2:MeOH 10:1, v/v) to give **1F** (0.052 g, 86%).

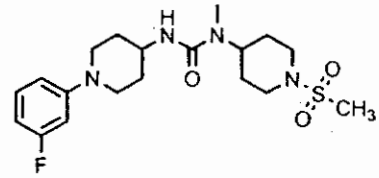
Using the same procedure, reaction of **18** with the appropriate sulfonyl chloride afforded **1G**, **1H**, **1I**, **1J**, and **1K** .

Example		^{1}H NMR	MS $(M+H)^+$
1A		($CDCl_3$) δ 6.35 (m, 2H), 6.20 (m, 1H), 4.70 (m, 1H), 4.42 (m, 1H), 4.29 (m, 1H), 3.84 (m, 2H), 3.61 (m, 2H), 3.12 (m, 1H), 2.90 (m, 2H), 2.66 (s, 3H), 2.55 (m, 1H), 2.07 (s, 3H), 2.03 (m, 2H), 1.68 (m, 2H), 1.48 (m, 4H).	395
1B		($CDCl_3$) δ 6.36 (m, 2H), 6.20 (m, 1H), 4.76 (m, 1H), 4.43 (m, 1H), 4.25 (m, 1H), 3.88 (m, 2H), 3.62 (m, 2H), 3.10 (m, 1H), 2.91 (m, 2H), 2.67 (s, 3H), 2.59 (m, 1H), 2.34 (q, J=7.6Hz, 2H), 2.04 (m, 2H), 1.70 (m, 2H), 1.50 (m, 4H), 1.13 (t, J=7.6Hz, 3H).	409
1C		($CDCl_3$) δ 6.38 (m, 2H), 6.22 (m, 1H), 4.78 (m, 1H), 4.42 (m, 1H), 4.21 (m, 1H), 3.90 (m, 2H), 3.63 (m, 2H), 3.10 (m, 1H), 2.91 (m, 2H), 2.68 (s, 3H), 2.58 (m, 1H), 2.31 (q, J=6.8Hz, 2H), 2.06 (m, 2H), 1.78-1.58 (m, 4H), 1.58-1.42 (m, 4H), 0.99 (t, J=7.6Hz, 3H).	423

1D		($CDCl_3$) δ 6.36 (m, 2H), 6.21 (m, 1H), 4.78 (m, 1H), 4.42 (m, 1H), 4.21 (m, 1H), 3.98 (m, 1H), 3.83 (m, 1H), 3.63 (m, 2H), 3.10 (m, 1H), 2.90 (m, 2H), 2.78 (m, 1H), 2.67 (s, 3H), 2.56 (m, 1H), 2.06 (m, 2H), 1.80-1.60 (m, 2H), 1.60-1.40 (m, 4H), 1.11 (d, J=7.2 Hz, 6H).	423
1E		($CDCl_3$) δ 6.34 (m, 2H), 6.20 (m, 1H), 4.70 (m, 1H), 4.42 (m, 1H), 4.27 (m, 2H), 3.82 (m, 1H), 3.60 (m, 2H), 3.18 (m, 1H), 2.90 (m, 2H), 2.67 (s, 3H), 2.60 (m, 1H), 2.04 (m, 2H), 1.73 (m, 2H), 1.64 (m, 1H), 1.47 (m, 4H), 0.95 (m, 2H), 0.73 (m, 2H).	421
1F		($CDCl_3$) δ 6.37 (m, 2H), 6.20 (m, 1H), 4.40 (m, 1H), 4.22 (m, 1H), 3.90 (m, 3H), 3.64 (m, 2H), 2.90 (m, 2H), 2.78 (s, 3H), 2.75 (m, 2H), 2.71 (s, 3H), 2.08 (m, 2H), 1.74 (m, 4H), 1.50 (m, 2H).	431
1G		($CDCl_3$) δ 6.34 (m, 2H), 6.20 (m, 1H), 4.38 (m, 1H), 4.27 (m, 1H), 3.90 (m, 3H), 3.62 (m, 2H), 3-2.8 (m, 6H), 2.69 (s, 3H), 2.05 (m, 2H), 1.69 (m, 4H), 1.47 (m, 2H), 1.34 (t, J=7.6Hz, 3H).	445
1H		($CDCl_3$) δ 6.36 (m, 2H), 6.21 (m, 1H), 4.38 (m, 1H), 4.23 (m, 1H), 3.88 (m, 3H), 3.62 (m, 2H), 3.00-2.80 (m, 6H), 2.70 (s, 3H), 2.04 (m, 2H), 1.85 (m, 2H), 1.73 (m, 4H), 1.48 (m, 2H), 1.05 (t, J=7.6Hz, 3H).	459
1I		($CDCl_3$) δ 6.35 (m, 2H), 6.21 (m, 1H), 4.40 (m, 1H), 4.23 (m, 1H), 3.90 (m, 3H), 3.62 (m, 2H), 3.16 (m, 1H), 2.94 (m, 4H), 2.70 (s, 3H), 2.04 (m, 2H),	459

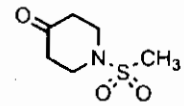
		1.67 (m, 4H), 1.48 (m, 2H), 1.32 (d, J=6.4Hz, 6H).	
1J		($CDCl_3$) δ 6.36 (m, 2H), 6.23 (m, 1H), 4.40 (m, 1H), 4.22 (m, 1H), 3.88 (m, 3H), 3.64 (m, 2H), 3.00-2.80 (m, 4H), 2.71 (s, 3H), 2.25 (m, 1H), 2.05 (m, 2H), 1.73 (m, 4H), 1.49 (m, 2H), 1.17 (m, 2H), 0.98 (m, 2H).	457
1K		($CDCl_3$) δ 7.75 (m, 2H), 7.59 (m, 1H), 7.57 (m, 2H), 6.34 (m, 2H), 6.20 (m, 1H), 4.22 (m, 1H), 4.18 (m, 1H), 3.88 (m, 2H), 3.80 (m, 1H), 3.60 (m, 2H), 2.87 (m, 2H), 2.66 (s, 3H), 2.33 (m, 2H), 1.99 (m, 2H), 1.80-1.60 (m, 4H), 1.45 (m, 2H).	493

Example **2A**



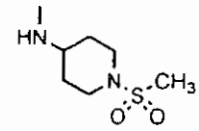
2A

Step 1. Synthesis of 1-Methylsulfonyl-4-piperidone



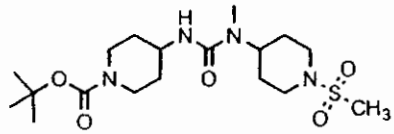
To a stirred solution of 4-piperidone hydrate hydrochloride (40.00 g, 0.260 mol) and THF (320 ml) was added CH_3SO_2Cl (31.0 ml, 0.402 mol) and 15% aq. NaOH (156 ml) such that the temperature of the reaction mixture was maintained at 26-32 °C. After this addition, the reaction mixture was stirred at RT for 2 hours and transferred to a separatory funnel. The organic layer was collected and the aqueous layer was extracted with THF (2x250 ml). The combined organic layers were dried over Na_2SO_4. After filtration, the concentrated residue was washed with hexane to give the product (46.0 g, 100%). ^1H NMR ($CDCl_3$) δ 3.59 (t, J=6.00 Hz, 4H), 2.89 (s, 3H), 2.59 (t, J=5.6 Hz, 4H).

Step 2. Synthesis of N-Methyl-1-(methylsulfonyl)-4-piperidineamine



1-Methylsuylfonyl-4-piperidone (40.00 g, 0.226 mol), CH_3CN (240 ml) and 40% CH_3NH_2 (20.4 ml, 0.263 mol) were added to a round bottom flask, and the mixture was stirred at room temperature for 1 hour. To another round bottom flask, $NaBH(OAc)_3$ (60.00 g, 0.283 mol) and 120 ml of CH_3CN were added. This solution was stirred at –10 °C, to which the first mixture (derived from 1-methylsulfonyl-4-piperidone) was added slowly via an additional funnel. After the addition, the reaction was allowed to warm to room temperature and stirred overnight. The reaction mixture was concentarted to a small volume, to which 1N aq. NaOH (282 ml) was added. This resulting solution was extracted with CH_2Cl_2 (3x500 ml) followed by extraction with toluene until no product remained in the extraction solution. The combined organic layers were dried over Na_2SO_4. After filtration, the solution was concentrated in vacuo to give the product (29.0 g, 63%). ^1H NMR ($CDCl_3$) δ 3.66 (m, 2H), 2.84 (m, 2H), 2.76 (s, 3H), 2.52 (m, 1H), 2.42 (s, 3H), 1.96 (m, 2H), 1.45 (m, 2H). MS *m/e* 193 $(M+H)^+$.

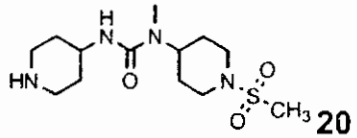
Step 3. Synthesis of **19**



19

To a solution of 4-amino-N-Boc-piperidine (3.60 g, 18.0 mmol) and pyridine (5.0 ml, 61 mmol) in THF (70 ml) in an ice-water bath was added N, N'-disuccinimidyl carbonate (5.06 g, 19.8 mmol). The mixture was stirred at RT for 2 hours and cooled in an ice-water bath. N-Methyl-1-(methylsulfonyl)-4-piperidineamine (3.62 g, 18.9 mmol) was added and the mixture was stirred at RT for 16 hours. The mixture was diluted with CH_2Cl_2 (300 ml) and washed with 1N NaOH (200 ml), 1N HCl (100 ml), water, and brine sequentially. The organic portion was dried ($MgSO_4$), concentrated, and purified by chromatography (CH_3OH:CH_2Cl_2 2:100) to give **19** (4.80 g, 64%). MS m/e 419 $(M+H)^+$.

Step 4. Synthesis of **20**



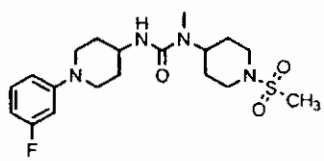
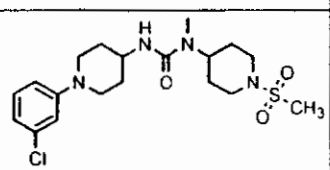
20

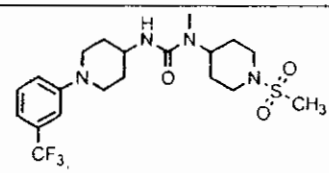
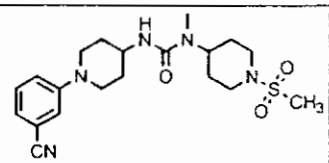
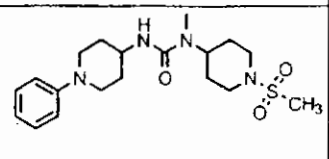
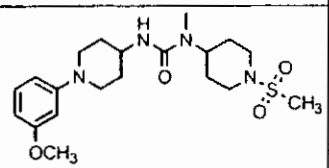
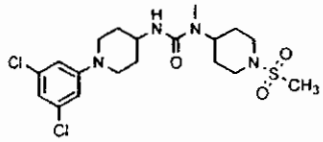
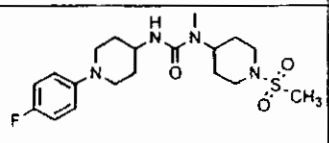
A mixture of **19** (4.80 g, 11.5 mmol) and 4N HCl/dioxane (100 ml) in THF (100 ml) was stirred at RT for 40 hours. The mixture was concentrated and the residue was purified by chromatography (CH_3OH:CH_2Cl_2 1:10 gradient to 2M NH_3/ CH_3OH:CH_2Cl_2 1:1) to give **20** (1.90 g, 52%). MS m/e 319 $(M+H)^+$.

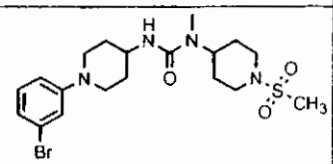
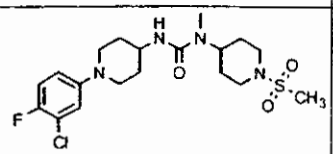
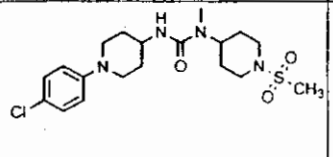
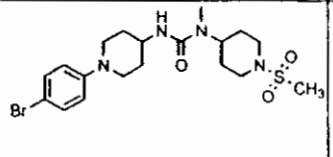
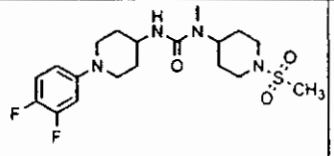
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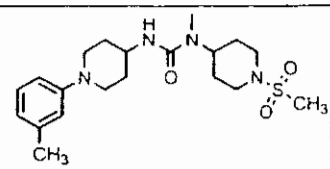
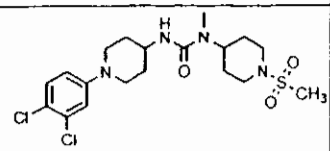
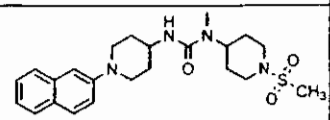
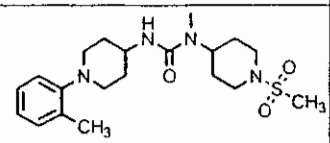
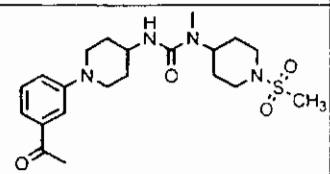
A mixture of **20** (0.096g, 0.30 mmol), 3-fluorophenylboronic acid (0.063 g, 0.45 mmol), copper(II) acetate (0.055g, 0.30 mmol), and pyridine (0.048g, 0.61 mmol) in CH_2Cl_2 (2.5 ml) was stirred at RT for 17 hours. The mixture was diluted with CH_2Cl_2 (20 ml) and washed with water and aqueous sodium bicarbonate. The organic portion was dried (K_2CO_3), concentrated, and purified by PTLC (CH_3OH:CH_2Cl_2 1:10) to give **2A** (0.024g, 19%).

Using essentially the same procedure, examples **2B** through **2R** were prepared.

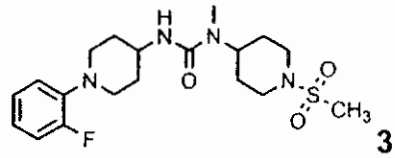
Example		^{1}H NMR	MS $(M+H)^+$
2A		($CDCl_3$) δ 7.16 (m, 1H), 6.69 (m, 1H), 6.60 (m, 1H), 6.51 (m, 1H), 4.38 (m, 1H), 4.25 (m, 1H), 3.88 (m, 3H), 3.64 (m, 2H), 2.90 (m, 2H), 2.79 (s, 3H), 2.75 (m, 2H), 2.71 (s, 3H), 2.06 (m, 2H), 1.74 (m, 4H), 1.53 (m, 2H).	413
2B		($CDCl_3$) δ 7.14 (m, 1H), 6.87 (m, 1H), 6.78 (m, 2H), 4.36 (m, 1H), 4.27 (m, 1H), 3.86 (m, 3H), 3.63 (m, 2H), 2.88 (m, 2H), 2.78 (s, 3H), 2.75 (m, 2H), 2.70 (s, 3H), 2.05 (m, 2H), 1.73 (m, 4H), 1.51	429

		(m,2H).	
2C		($CDCl_3$) δ 7.33 (m, 1H), 7.05 (m, 3H), 4.37 (m, 1H), 4.27 (m, 1H), 3.87 (m, 3H), 3.69 (m, 2H), 2.91 (m, 2H), 2.78 (s, 3H), 2.75 (m, 2H), 2.71 (s, 3H), 2.09 (m, 2H), 1.74 (m, 4H), 1.53 (m, 2H).	463
2D		($CDCl_3$) δ 7.30 (m, 1H), 7.10 (m, 3H), 4.38 (m, 1H), 4.26(m, 1H), 3.88 (m, 3H), 3.67 (m, 2H), 2.93 (m, 2H), 2.79 (s, 3H), 2.76 (m, 2H), 2.72 (s, 3H), 2.07 (m, 2H), 1.74 (m, 4H), 1.52 (m, 2H).	420
2E		($CDCl_3$) δ 7.25 (m, 2H), 6.94 (m, 2H), 6.84 (m, 1H), 4.37 (m, 1H), 4.26 (m, 1H), 3.86 (m, 3H), 3.63 (m, 2H), 2.88 (m, 2H), 2.78 (s, 3H), 2.75 (m, 2H), 2.71 (s, 3H), 2.05 (m, 2H), 1.75 (m, 4H), 1.56 (m, 2H).	395
2F		($CDCl_3$) δ 7.15 (t, J=8.2 Hz, 1H), 6.54 (m, 1H), 6.48 (m, 1H), 6.39 (m, 1H), 4.37 (m, 1H), 4.26 (m, 1H), 3.87 (m, 3H), 3.78 (s, 3H), 3.64 (m, 2H), 2.91 (m, 2H), 2.78 (s, 3H), 2.75 (m, 2H), 2.71 (s, 3H), 2.04 (m, 2H), 1.74 (m, 4H), 1.54 (m, 2H).	425
2G		($CDCl_3$) δ 6.76 (m, 3H), 4.37 (m, 1H), 4.24 (m, 1H), 3.88 (m, 3H), 3.63 (m, 2H), 2.91 (m, 2H), 2.82 (s, 3H), 2.75 (m, 2H), 2.71 (s, 3H), 2.05 (m, 2H), 1.74 (m, 4H), 1.48 (m, 2H).	463
2H		($CDCl_3$) δ 6.93 (m, 4H), 4.37 (m, 1H), 4.27 (m, 1H), 3.87 (m, 2H), 3.81 (m, 1H), 3.50 (m, 2H), 2.84	413

		(m, 2H), 2.78 (s, 3H), 2.75 (m, 2H), 2.72 (s, 3H), 2.05 (m, 2H), 1.74 (m, 4H), 1.59 (m, 2H).	
2I		($CDCl_3$) δ 7.09 (m, 2H), 6.97 (m, 1H), 6.88 (m, 1H), 4.37 (m, 1H), 4.30 (m, 1H), 3.87 (m, 3H), 3.63 (m, 2H), 2.91 (m, 2H), 2.78 (s, 3H), 2.75 (m, 2H), 2.71 (s, 3H), 2.06 (m, 2H), 1.75 (m, 4H), 1.58 (m, 2H).	473
2J		($CDCl_3$) δ 7.03 (m, 1H), 6.95 (m, 1H), 6.81 (m, 1H), 4.37 (m, 1H), 4.27 (m, 1H), 3.87 (m, 2H), 3.81 (m, 1H), 3.52 (m, 2H), 2.85 (m, 2H), 2.78 (s, 3H), 2.75 (m, 2H), 2.72 (s, 3H), 2.07 (m, 2H), 1.74 (m, 4H), 1.57 (m, 2H).	447
2K		($CDCl_3$) δ 7.18 (m, 2H), 6.87 (m, 2H), 4.36 (m, 1H), 4.28 (m, 1H), 3.87 (m, 3H), 3.58 (m, 2H), 2.86 (m, 2H), 2.77 (s, 3H), 2.74 (m, 2H), 2.70 (s, 3H), 2.05 (m, 2H), 1.73 (m, 4H), 1.56 (m, 2H).	429
2L		($CDCl_3$) δ 7.32 (m, 2H), 6.82 (m, 2H), 4.37 (m, 1H), 4.27 (m, 1H), 3.85 (m, 3H), 3.59 (m, 2H), 2.87 (m, 2H), 2.78 (s, 3H), 2.74 (m, 2H), 2.71 (s, 3H), 2.06 (m, 2H), 1.73 (m, 4H), 1.56 (m, 2H).	473
2M		($CDCl_3$) δ 7.02 (m, 1H), 6.74 (m, 1H), 6.62 (m, 1H), 4.37 (m, 1H), 4.27 (m, 1H), 3.87 (m, 2H), 3.81 (m, 1H), 3.52 (m, 2H), 2.86 (m, 2H), 2.78 (s, 3H), 2.75 (m, 2H), 2.72 (s, 3H), 2.08 (m, 2H), 1.74 (m, 4H), 1.56 (m, 2H).	431

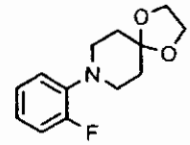
2N		($CDCl_3$) δ 7.15 (m, 1H), 6.74 (m, 3H), 4.33 (m, 2H), 3.87 (m, 3H), 3.62 (m, 2H), 2.89 (m, 2H), 2.78 (s, 3H), 2.75 (m, 2H), 2.72 (s, 3H), 2.31 (s, 3H), 2.08 (m, 2H), 1.75 (m, 4H), 1.61 (m, 2H).	409
2O		($CDCl_3$) δ 7.26 (m, 1H), 7.00 (m, 1H), 6.79 (m, 1H), 4.37 (m, 1H), 4.27 (m, 1H), 3.87 (m, 3H), 3.60 (m, 2H), 2.90 (m, 2H), 2.78 (s, 3H), 2.75 (m, 2H), 2.71 (s, 3H), 2.08 (m, 2H), 1.74 (m, 4H), 1.56 (m, 2H).	463
2P		($CDCl_3$) δ 7.72 (m, 3H), 7.40 (m, 1H), 7.28 (m, 2H), 7.18 (m, 1H), 4.34 (m, 2H), 3.88 (m, 3H), 3.77 (m, 2H), 2.99 (m, 2H), 2.78 (s, 3H), 2.75 (m, 2H), 2.72 (s, 3H), 2.13 (m, 2H), 1.74 (m, 4H), 1.65 (m, 2H).	445
2Q		($CDCl_3$) δ 7.18 (m, 2H), 7.00 (m, 2H), 4.35 (m, 2H), 3.85 (m, 3H), 3.12 (m, 2H), 2.80 (s, 3H), 2.77 (m, 2H), 2.74 (s, 3H), 2.31 (s, 3H), 2.06 (m, 2H), 1.75 (m, 4H), 1.65 (m, 2H).	409
2R		($CDCl_3$) δ 7.59 (m, 1H), 7.44 (m, 1H), 7.35 (m, 1H), 7.24 (m, 1H), 4.34 (m, 2H), 3.89 (m, 3H), 3.71 (m, 2H), 2.97 (m, 2H), 2.80 (s, 3H), 2.76 (m, 2H), 2.72 (s, 3H), 2.61 (s, 3H), 2.10 (m, 2H), 1.74 (m, 4H), 1.62 (m, 2H).	437

Example 3



3

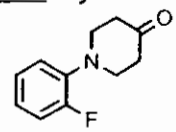
Step 1. Synthesis of **21**



21

A mixture of 2-bromofluorobenzene (3.04 g, 17.4 mmol), 1,4-dioxa-8-azaspiro(4.5)decane (2.13 g, 14.9 mmol), palladium dibenzylideneacetone (0.657 g, 0.717 mmol), 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (0.678 g, 1.09 mmol), and sodium t-butoxide (3.54 g, 36.8 mmol) in toluene (20 ml) was heated to 95°C for 16 hours. The mixture was diluted with CH_2Cl_2 (50 ml) and filtered. The filtrate was evaporated and purified by column chromatography (CH_2Cl_2 gradient to CH_3OH: CH_2Cl_2 1:500) to give **21** (3.27 g, 93%). MS m/e 238 $(M+H)^+$.

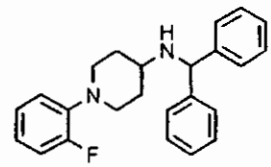
Step 2. Synthesis of **22**



22

A mixture of **21** (3.27 g, 13.8 mmol) in THF (50 ml) and aqueous 5N HCl (50 ml) was stirred at RT for 16 hours and then at 85°C for 4 hours. The volatiles were removed under reduced pressure and the residue was partitioned between CH_2Cl_2 (2x100 ml) and aqueous ammonium hydroxide (80 ml). The combined organic portion was dried ($MgSO_4$), evaporated, and purified by column chromatography (Hexanes gradient to EtOAc:Hexanes 2:100) to give **22** (1.54 g, 58%). MS m/e 194 $(M+H)^+$.

Step 3. Synthesis of **23**

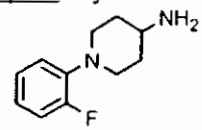


23

A mixture of **22** (1.54 g, 8.00 mmol), aminodiphenylmethane (1.43 g, 7.48 mmol), and sodium triacetoxyborohydride (2.57 g, 12.1 mmol) in dichloroethane (20 ml) was stirred at RT for 16 hours. The mixture was diluted with CH_2Cl_2 (80 ml) and washed with 1N NaOH (40 ml). The organic portion was dried ($MgSO_4$), evaporated,

and purified by column chromatography (Hexanes gradient to EtOAc:Hexanes 4:100) to give **23** (2.41 g, 90%). MS m/e 361 $(M+H)^+$.

Step 4. Synthesis of **24**



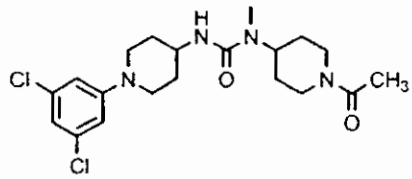
24

A mixture of **23** (2.41 g, 6.70 mmol), formic acid (4.4 ml), and 10% Pd/C (1.12 g) in CH_3OH (100 ml) was stirred for 3 hours. The mixture was filtered through a celite pad and the filtrate was evaporated to dryness. The residue was partitioned between CH_2Cl_2 (100 ml) and aqueous ammonium hydroxide (50 ml). The organic portion was dried ($MgSO_4$), evaporated, and purified by column chromatography (CH_2Cl_2 gradient to CH_3OH: CH_2Cl_2 1:4) to give **24** (1.15 g, 88%). MS m/e 195 $(M+H)^+$.

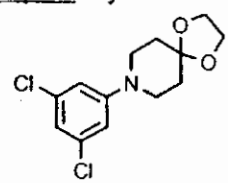
Step 5

A mixture of **24** (0.087 g, 0.45 mmol), N, N'-disuccinimidyl carbonate (0.138 g, 0.538 mmol), and pyridine (0.199 g, 2.52 mmol) in THF (7 ml) was stirred in an ice-water bath for 30 minutes and then at RT for 3 hours. N-Methyl-1-(methylsulfonyl)-4-piperidineamine (0.098 g, 0.51 mmol) was added and the mixture was stirred at RT for 20 hours. The volatiles were removed under reduced pressure and the residue was partitioned between aqueous ammonium chloride (15 ml) and CH_2Cl_2 (40 ml). The organic portion was dried ($MgSO_4$), evaporated, and purified by PTLC (CH_3OH: CH_2Cl_2 3:100) to give **3** (0.051 g, 27%). ^{1}H-NMR ($CDCl_3$) δ 7.02 (m, 4H), 4.33 (m, 2H), 3.87 (m, 3H), 3.42 (m, 2H), 2.86 (m, 2H), 2.78 (s, 3H), 2.75 (m, 2H), 2.73 (s, 3H), 2.08 (m, 2H), 1.74 (m, 6H). MS m/e 413 $(M+H)^+$.

Example **4A**



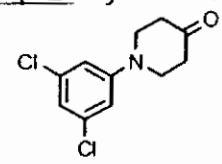
Step 1. Synthesis of **25**



25

A mixture of 1-bromo-3,5-dichlorobenzene (7.43 g, 32.9 mmol), 1,4-dioxa-8-azaspiro(4.5)decane (3.90 g, 27.2 mmol), palladium dibenzylideneacetone (0.591 g, 0.645 mmol), 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (0.598 g, 0.960 mmol), and sodium t-butoxide (4.33 g, 45.0 mmol) in toluene (30 ml) was heated to 100°C for 16 hours. The mixture was diluted with CH_2Cl_2 (20 ml) and filtered. The filtrate was concentrated and purified by column chromatography (Hexanes gradient to EtOAc:Hexanes 1:40) to give **25** (6.67 g, 85%). MS m/e 288 $(M+H)^+$.

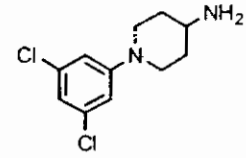
Step 2. Synthesis of **26**



26

A mixture of **25** (6.67 g, 23.2 mmol) in THF (20 ml) and aqueous 5N HCl (100 ml) was stirred at RT for 64 hours. The mixture was basified with conc. NH_4OH and extracted with CH_2Cl_2 (3x200 ml). The combined organic portion was washed with brine, dried ($MgSO_4$), and concentrated to give **26** (5.50g, 97%). MS m/e 244 $(M+H)^+$.

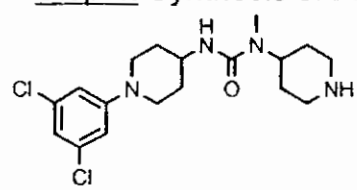
Step 3. Synthesis of **27**



27

A mixture of **26** (2.44 g, 10.0 mmol), ammonium acetate (76 g, 0.99 mol), and sodium cyanoborohydride (0.500 g, 7.96 mmol) in CH_3OH (200 ml) was stirred at RT for 66 hours. The mixture was concentrated and the residue was partitioned between conc. NH_4OH (150 ml) and CH_2Cl_2 (2x150 ml). The combined organic portion was washed with water (150 ml) and brine (150 ml), dried (K_2CO_3), concentrated, and purified by column chromatography (CH_2Cl_2 gradient to 2M NH_3/CH_3OH: CH_2Cl_2 1:10) to give **27** (1.66 g, 68%). MS m/e 245 $(M+H)^+$.

Step 4. Synthesis of **28**



28

To a solution of **27** (1.23 g, 5.02 mmol) and pyridine (3 ml) in THF (100 ml) in an ice-water bath was added N, N'-disuccinimidyl carbonate (1.54 g, 6.03 mmol). The mixture was stirred at RT for 4 hours and a solution of 4-methylamino-1-Boc-

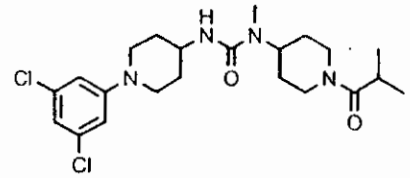
piperidine (1.18 g, 5.51 mmol) was added at 0°C. The reaction was stirred at RT for 16 hours and concentrated. The residue was dissolved in CH_2Cl_2 (200 ml), washed with 1N NaOH (150 ml) and brine, dried (K_2CO_3) and concentrated. The crude material and trifluoroacetic acid (8 ml) in CH_2Cl_2 (72 ml) was stirred at RT for 21 hours. The mixture was concentrated and partitioned between CH_2Cl_2 (200 ml) and conc. NH_4OH (50 ml). The organic portion was washed in sodium bicarbonate and brine, dried (K_2CO_3), concentrated, and purified by column chromatography (CH_2Cl_2 gradient to 2M NH_3/CH_3OH: CH_2Cl_2 1:10) to give **28** (1.20 g, 62%). MS m/e 385 $(M+H)^+$.

Step 5.

A mixture of **28** (0.077 g, 0.20 mmol), acetic anhydride (50 µl, 0.53 mmol), and triethylamine (200 µl, 1.42 mmol) in CH_2Cl_2 (5 ml) was stirred at RT for 3 hours. 1N NaOH (2 ml) was added and the organic portion was dried ($MgSO_4$), concentrated, and purified by PTLC (CH_3OH: CH_2Cl_2 1:10) to give **4A** (0.080 g, 94%).

Using essentially the same procedure, **4B** was prepared.

Example **4C**

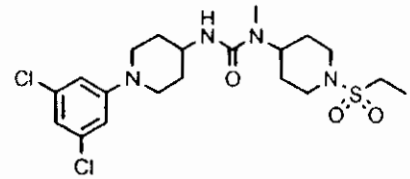


4C

A mixture of **28** (0.077 g, 0.20 mmol), isobutyryl chloride (45 µl, 0.43 mmol), and triethylamine (200 µl, 1.42 mmol) in CH_2Cl_2 (5 ml) was stirred at RT for 2 hours. The mixture was washed with 1N NaOH (2 ml), dried ($MgSO_4$), concentrated, and purified by PTLC (CH_3OH: CH_2Cl_2 1:10) to give **4C** (0.085 g, 93%).

Using essentially the same procedure, **4D**, **4E**, **4F**, **4G**, and **4H** were prepared.

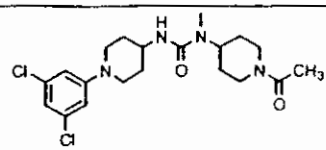
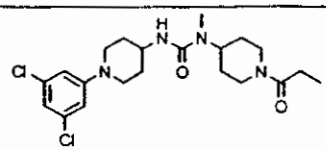
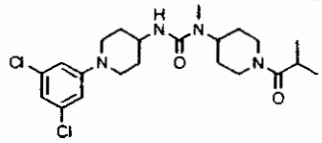
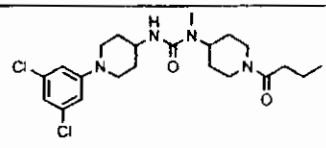
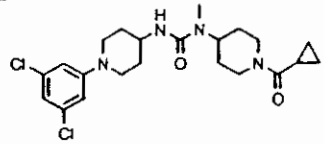
Example **4I**

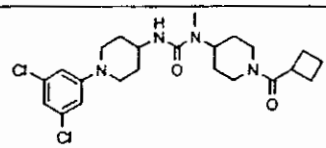
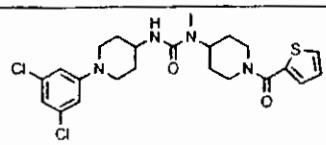
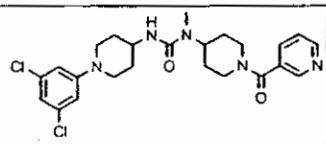
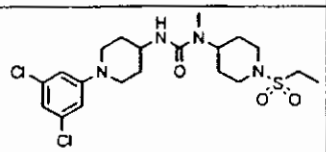
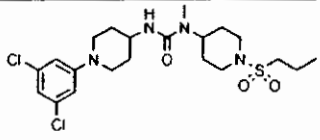
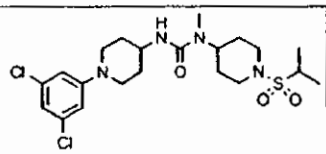


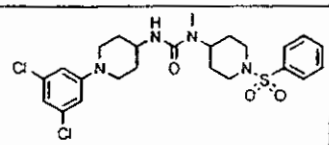
4I

A mixture of **28** (0.077 g, 0.20 mmol), ethanesulfonyl chloride (45 µl, 0.47 mmol), and triethylamine (200 µl, 1.42 mmol) in CH_2Cl_2 (5 ml) was stirred at RT for 2 hours. The mixture was washed with 1N NaOH, dried ($MgSO_4$), concentrated, and purified by PTLC (CH_3OH: CH_2Cl_2 1:10) to give **4I** (0.082 g, 86%).

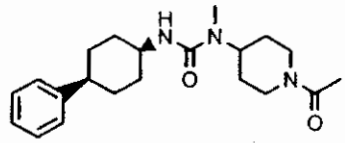
Using essentially the same procedure, **4J**, **4K**, and **4L** were prepared.

Example		^{1}H NMR	MS (M+H)$^+$
4A		($CDCl_3$) δ 6.77 (m, 3H), 4.74 (m, 1H), 4.44 (m, 1H), 4.21 (m, 1H), 3.86 (m, 2H), 3.63 (m, 2H), 3.15 (m, 1H), 2.93 (m, 2H), 2.68 (s, 3H), 2.58 (m, 1H), 2.11 (s, 3H), 2.08 (m, 2H), 1.68 (m, 2H), 1.53 (m, 4H).	427
4B		($CDCl_3$) δ 6.75 (m, 3H), 4.75 (m, 1H), 4.43 (m, 1H), 4.22 (m, 1H), 3.89 (m, 2H), 3.63 (m, 2H), 3.09 (m, 1H), 2.92 (m, 2H), 2.68 (s, 3H), 2.58 (m, 1H), 2.35 (q, J=7.4 Hz, 2H), 2.05 (m, 2H), 1.69 (m, 2H), 1.49 (m, 4H), 1.15 (t, J=7.4 Hz, 3H).	441
4C		($CDCl_3$) δ 6.75 (m, 3H), 4.75 (m, 1H), 4.44 (m, 1H), 4.22 (m, 1H), 4.00 (m, 1H), 3.86 (m, 1H), 3.63 (m, 2H), 3.11 (m, 1H), 2.92 (m, 2H), 2.80 (m, 1H), 2.68 (s, 3H), 2.56 (m, 1H), 2.06 (m, 2H), 1.71 (m, 2H), 1.49 (m, 4H), 1.12 (m, 6H).	455
4D		($CDCl_3$) δ 6.74 (m, 3H), 4.74 (m, 1H), 4.43 (m, 1H), 4.24 (m, 1H), 3.89 (m, 2H), 3.63 (m, 2H), 3.09 (m, 1H), 2.92 (m, 2H), 2.66 (s, 3H), 2.56 (m, 1H), 2.31 (m, 2H), 2.06 (m, 2H), 1.69 (m, 4H), 1.47 (m, 4H), 0.96 (t, J=7.2 Hz, 3H).	455
4E		($CDCl_3$) δ 6.75 (m, 3H), 4.72 (m, 1H), 4.46 (m, 1H), 4.28 (m, 1H), 4.22 (m, 1H), 3.89 (m, 1H), 3.63 (m, 2H), 3.16 (m, 1H), 2.92 (m, 2H), 2.68 (s, 3H), 2.62 (m, 1H), 2.06 (m,	453

		2H), 1.42-1.78 (m, 7H), 0.97 (m, 2H), 0.75 (m, 2H).	
4F		($CDCl_3$) δ 6.72 (m, 3H), 4.69 (m, 1H), 4.41 (m, 1H), 4.27 (m, 1H), 3.84 (m, 1H), 3.74 (m, 1H), 3.62 (m, 2H), 3.24 (m, 1H), 2.83-3.05 (m, 4H), 2.65 (s, 3H), 2.56 (m, 1H), 2.34 (m, 2H), 1.74-2.20 (m, 5H), 1.65 (m, 2H), 1.46 (m, 4H).	467
4G		($CDCl_3$) δ 7.46 (m, 1H), 7.30 (m, 1H), 7.05 (m, 1H), 6.78 (m, 3H), 4.55 (m, 3H), 4.24 (m, 1H), 3.87 (m, 1H), 3.64 (m, 2H), 2.97 (m, 4H), 2.71 (s, 3H), 2.08 (m, 2H), 1.37-1.78 (m, 6H).	495
4H		($CDCl_3$) δ 8.66 (m, 2H), 7.77 (m, 1H), 7.37 (m, 1H), 6.75 (m, 3H), 4.81 (m, 1H), 4.51 (m, 1H), 4.25 (m, 1H), 3.84 (m, 2H), 3.63 (m, 2H), 3.18 (m, 1H), 2.89 (m, 3H), 2.71 (s, 3H), 2.05 (m, 2H), 1.4-2.0 (m, 6H).	490
4I		($CDCl_3$) δ 6.74 (m, 3H), 4.37 (m, 1H), 4.23 (m, 1H), 3.88 (m, 3H), 3.64 (m, 2H), 2.95 (m, 5H), 2.71 (s, 3H), 2.05 (m, 2H), 1.71 (m, 5H), 1.49 (m, 2H), 1.36 (t, J=7.4 Hz, 3H).	477
4J		($CDCl_3$) δ 6.74 (m, 3H), 4.37 (m, 1H), 4.25 (m, 1H), 3.87 (m, 3H), 3.63 (m, 2H), 2.87 (m, 5H), 2.71 (s, 3H), 2.05 (m, 2H), 1.83 (m, 2H), 1.69 (m, 5H), 1.49 (m, 2H), 1.05 (t, J=7.8 Hz, 3H).	491
4K		($CDCl_3$) δ 6.74 (m, 3H), 4.39 (m, 1H), 4.24 (m, 1H), 3.90 (m, 3H), 3.61 (m, 2H), 3.16 (m, 1H), 2.93 (m, 4H), 2.71 (s, 3H), 2.05 (m, 2H),	491

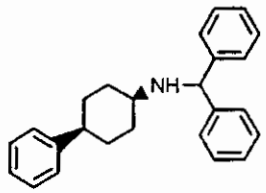
		1.68 (m, 4H), 1.49 (m, 2H), 1.33 (d, J=6.4 Hz, 6H).	
4L		($CDCl_3$) δ 7.77 (m, 2H), 7.56 (m, 3H), 6.74 (m, 3H), 4.18 (m, 2H), 3.84 (m, 3H), 3.62 (m, 2H), 2.92 (m, 2H), 2.68 (s, 3H), 2.36 (m, 2H), 2.03 (m, 2H), 1.69 (m, 4H), 1.47 (m, 2H).	525

Example **5A**:

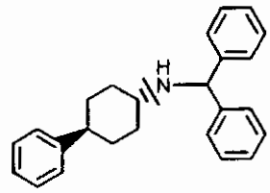


5A

Step 1. Synthesis of **29** and **30**:



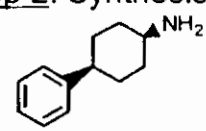
29



30

A mixture of 4-phenylcyclohexanone (1.7 g, 10 mmol) and benzhydrylamine (2.0 g, 11 mmol) in DME (60 ml) was stirred at room temperature for 2 hours. Then $Na(OAc)_3BH$ (3.2 g, 15 mmol) was added. After the reaction mixture was stirred at room temperature for 2 days, 1N NaOH (100 ml) was added. The solution was extracted with CH_2Cl_2 (3x100 ml). The combined organic layer was separated and dried over potassium carbonate. The concentrated residue was separated by flash column chromatography (CH_2Cl_2:hexane 1:9→100:0, v/v) to give **29** (2.13 g) and **30** (0.68 g), total yield being 82%. MS m/e 342 $(M+H)^+$.

Step 2. Synthesis of **31**:

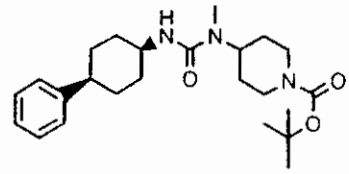


31

To a solution of **29** (1.9 g, 5.6 mmol) in MeOH (100 ml) was added formic acid (4.50 ml, 119 mmol) and 10% Pd/C (1.9 g. 1.8 mmol). The reaction mixture was stirred at room temperature for 16 hours. It was filtered via celite and the celite was washed with 2M ammonia/ MeOH. The filtrate was concentrated, then diluted with

CH_2Cl_2 (100 ml), and washed with water (50 ml). The aqueous layer was adjusted to pH 11 with ammonia hydroxide solution, then extracted with CH_2Cl_2 (3x100 ml). The combined organic layer was separated, dried over magnesium sulfate and concentrated to give **31** (0.90 g, 92%). MS m/e 176 $(M+H)^+$.

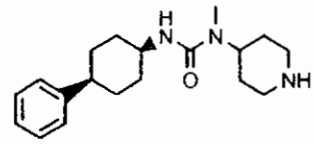
Step 3. Synthesis of **32**:



32

To a solution of **31** (0.90 g, 5.1 mmol) in THF (80 ml) was added pyridine (2.0 ml, 24 mmol). The mixture was cooled in an ice water-bath, and N,N'-disuccinimidyl carbonate (1.45 g, 5.66 mmol) was added at 0 °C. The mixture was stirred at room temperature for 3.5 hours and cooled to 0 °C, 1-tert-butoxycarbonyl-4-methylaminopiperidine (1.15 g, 5.37 mmol) was added. The reaction mixture was stirred at room temperature for 16 hours. The mixture was concentrated to give crude **32** (2.1 g, 96%). MS m/e 416 $(M+H)^+$.

Step 4. Synthesis of **33**:



33

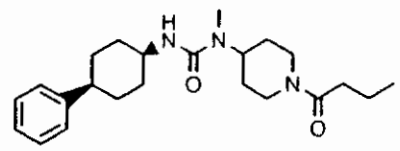
A solution of **32** (2.05 g, 4.94 mmol) in 4N HCl/1,4-dioxane (100 ml) was stirred at room temperature for 5 hours. The concentrated residue was washed with ether to give **33** (1.83 g, 100%). MS m/e 316 $(M+H)^+$.

Step 5.

To a solution of **33** (0.07 g, 0.2 mmol) and Et_3N (0.20 ml, 1.4 mmol) in CH_2Cl_2 (2 ml) was added acetic anhydride (0.040 ml, 0.43 mmol) at 0°C and the reaction mixture was stirred for another 1 hour at 0°C. The concentrated residue was separated by PTLC (CH_2Cl_2: MeOH 20:1, v/v) to give **5A** (0.055g, 77%).

Using essentially the same procedure, **5B** was prepared.

Example **5C**:

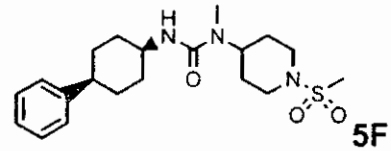


5C

To a solution of **33** (0.07 g, 0.2 mmol) and Et_3N (0.20 ml, 1.4 mmol) in CH_2Cl_2 (2 ml) was added butyryl chloride (0.040 ml, 0.38 mmol) at 0°C. The reaction mixture was stirred at room temperature for 30 minutes. PS-Trisamine resin (100 mg) was added and the mixture was stirred for another 2 hours, then filtered. The filtrate was concentrated and the residue was separated by PTLC (CH_2Cl_2: MeOH 20:1, v/v) to give **5C** (0.055 g, 71%).

Using essentially the same procedure, **5D** and **5E** were prepared.

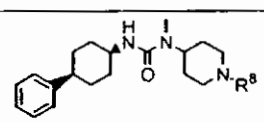
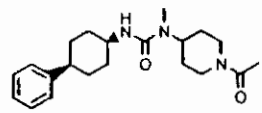
Example **5F**:

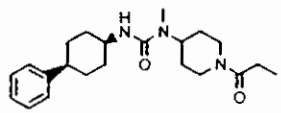
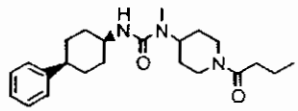
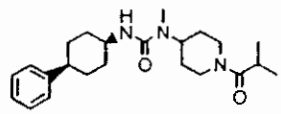
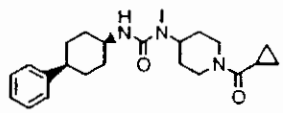
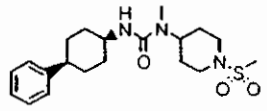
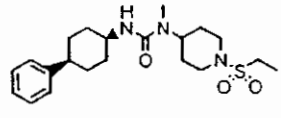
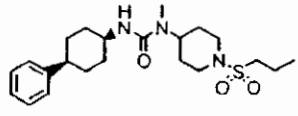


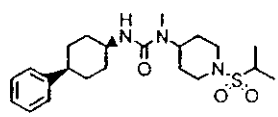
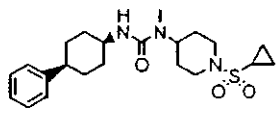
5F

To a solution of **33** (0.07 g, 0.2 mmol) and Et_3N (0.20 ml, 1.4 mmol) in CH_2Cl_2 (2 ml) was added methanesulfonyl chloride (0.040 ml, 0.52 mmol) at 0°C. The reaction mixture was stirred at room temperature for 1 hour. PS-Trisamine (100 mg) was added and the mixture was stirred for another hour. It was filtered and the filtrate was concentrated. The residue was separated by PTLC (CH_2Cl_2: MeOH 20:1, v/v) to give **5F** (0.046 g, 59%).

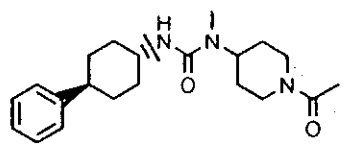
Using essentially the same procedure, Examples **5G**, **5H**, **5I**, and **5J** were prepared.

Example		^{1}H NMR	MS (M+H)
5A		($CDCl_3$) δ 7.31 (m, 2H), 7.20 (m, 3H), 4.72 (m, 1H), 4.58 (m, 1H), 4.48 (m, 1H), 4.10 (m, 1H), 3.85 (m, 1H), 3.18 (m, 1H), 2.73 (s, 3H), 2.60 (m, 2H), 2.09 (s, 3H), 1.90-1.44 (m, 11H).	358

5B		($CDCl_3$) δ 7.31 (m, 2H), 7.20 (m, 3H), 4.75 (m, 1H), 4.58 (m, 1H), 4.48 (m, 1H), 4.08 (m, 1H), 3.90 (m, 1H), 3.10 (m, 1H), 2.72 (s, 3H), 2.60 (m, 2H), 2.36 (m, 2H), 1.90-1.40 (m, 11H), 1.12 (m, 3H).	372
5C		($CDCl_3$) δ 7.31 (m, 2H), 7.20 (m, 3H), 4.78 (m, 1H), 4.58 (m, 1H), 4.42 (m, 1H), 4.08 (m, 1H), 3.90 (m, 1H), 3.10 (m, 1H), 2.72 (s, 3H), 2.60 (m, 2H), 2.30 (m, 2H), 1.95-1.40 (m, 13H), 0.96 (t, J=7.6Hz, 3H).	386
5D		($CDCl_3$) δ 7.31 (m, 2H), 7.20 (m, 3H), 4.78 (m, 1H), 4.54 (m, 1H), 4.45 (m, 1H), 4.08 (m, 1H), 3.98 (m, 1H), 3.10 (m, 1H), 2.80 (m, 1H), 2.73 (s, 3H), 2.60 (m, 2H), 1.98-1.40 (m, 11H), 1.11 (dd, J=6.8Hz, J=12Hz, 6H).	386
5E		($CDCl_3$) δ 7.29 (m, 2H), 7.21 (m, 3H), 4.70 (m, 1H), 4.50 (m, 2H), 4.28 (m, 1H), 4.10 (m, 1H), 3.18 (m, 1H), 2.74 (s, 3H), 2.81 (m, 2H), 1.98-1.42 (m, 12H), 0.97 (m, 2H), 0.75 (m, 2H).	384
5F		($CDCl_3$) δ 7.32 (m, 2H), 7.22 (m, 3H), 4.57 (m, 1H), 4.40 (m, 1H), 4.08 (m, 1H), 3.88 (m, 2H), 2.80-2.65 (m, 8H), 2.60 (m, 1H), 1.90-1.52 (m, 11H).	394
5G		($CDCl_3$) δ 7.30 (m, 2H), 7.21 (m, 3H), 4.58 (m, 1H), 4.40 (m, 1H), 4.05 (m, 1H), 3.90 (m, 2H), 2.94 (m, 3H), 2.86 (m, 1H), 2.76 (s, 3H), 2.60 (m, 1H), 1.98-1.50 (m, 11H), 1.34 (t, J=7.6Hz, 3H).	408
5H		(CD_3OD) δ 6.93 (m, 4H), 6.82 (m, 1H), 3.88 (m, 1H), 3.60 (m, 1H), 3.48 (m, 2H), 2.97 (m, 1H), 2.65 (m, 2H), 2.55 (m, 2H), 2.47 (s, 3H), 2.30 (m,	422

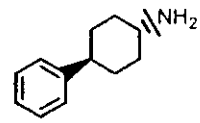
		1H), 1.60-1.20 (m, 13H), 0.72 (t, J=7.2Hz, 3H).	
5I		(CD_3OD) δ 7.26 (m, 4H), 7.18 (m, 1H), 4.22 (m, 1H), 4.00-3.80 (m, 3H), 3.30 (m, 2H), 2.98 (m, 2H), 2.80 (s, 3H), 2.62 (m, 1H), 1.98-1.58 (m, 11H), 1.30 (d, J=7.2Hz, 6H).	422
5J		(CD_3OD) δ 7.29(m, 2H), 7.21 (m, 3H), 4.78 (m, 1H), 4.40 (m, 1H), 4.08 (m, 1H), 3.85 (m, 2H), 2.88 (m, 2H), 2.77 (s, 3H), 2.60 (m, 1H), 2.26 (m, 1H), 1.98-1.50 (m, 11H), 1.16 (m, 2H), 0.98 (m, 2H).	420

Example **6A**:



6A

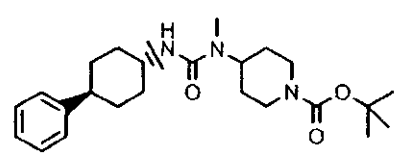
Step 1. Synthesis of **34**



34

A mixture of **30** (2.0 g, 5.8 mmol) and 10% Pd/C (2.0 g) in 4.4% HCOOH/MeOH (100 ml) was stirred at room temperature for 16 hours. The mixture was filtered through a pad of celite and the pad was washed with MeOH. The filtrate was concentrated and the residue was purified by column chromatography (gradient of CH_2Cl_2 to 1:9 MeOH/CH_2Cl_2 to 1:5 2M NH_3/MeOH in CH_2Cl_2) to give **34** (0.86 g, 84%). MS m/e 176 $(M+H)^+$.

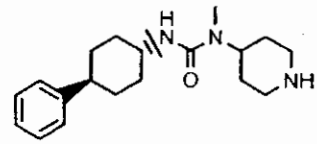
Step 2. Synthesis of **35**



35

To an ice-cold solution of **34** (0.86 g, 4.9 mmol) and pyridine (2.0 ml, 24 mmol) in THF (60 ml) was added N,N'-disuccinimidylcarbonate (1.38 g, 5.39 mmol). The mixture was stirred at room temperature for 3 hours and then cooled in an ice-water bath. 1-tert-Butoxycarbonyl-4-methylaminopiperidine (1.10 g, 5.14 mmol) was added and the mixture was stirred at room temperature for 16 hours. The reaction mixture was evaporated to dryness and the residue was partitioned between CH_2Cl_2 (200 ml) and 1N NaOH (100 ml). The organic layer was washed with water and brine, dried over $MgSO_4$, and concentrated. The crude product was purified by column chromatography (CH_2Cl_2, then 2:98 MeOH/CH_2Cl_2) to give **35** (1.8 g, 88%). MS m/e 416 $(M+H)^+$.

Step 3. Synthesis of **36**



36

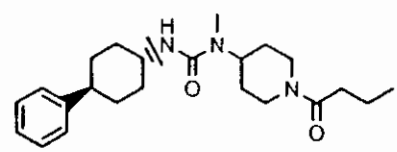
A solution of **35** (1.7 g, 4.1 mmol) in 4N HCl/1,4-dioxane (150 ml) was stirred at room temperature for 3 hours. The concentrated residue was triturated with ether to give **36** (1.38 g, 95%). MS m/e 316 $(M+H)^+$.

Step 4

A solution of **36** (70 mg, 0.22 mmol), acetic anhydride (40 µl, 0.43 mmol), and Et_3N (200 µl, 1.43 mmol) in CH_2Cl_2 (2.5 ml) was stirred at room temperature for 1 hour. The concentrated residue was purified by PTLC (20:1 CH_2Cl_2/MeOH) to give **6A** (60 mg, 76%).

Using essentially the same procedure, **6B** was prepared.

Example **6C**:



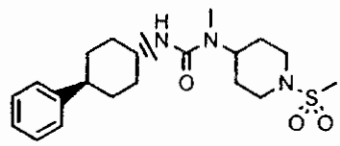
6C

To a solution of **36** (70 mg, 0.22 mmol) and Et_3N (200 µl, 1.43 mmol) in CH_2Cl_2 (2.5 ml) in an ice-water bath was added butyryl chloride (40 µl, 0.38 mmol). The

mixture was warmed to room temperature and stirred for 1 hour. PS-Trisamine resin (100 mg) was added and the mixture was stirred for another 2 hours, then filtered. The filtrate was concentrated and the residue was purified by PTLC (10:1 CH_2Cl_2/MeOH) to give **6C** (60 mg, 71%).

Using essentially the same procedure, **6D** and **6E** were prepared.

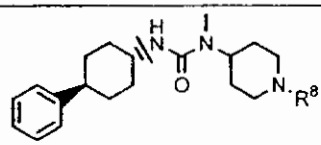
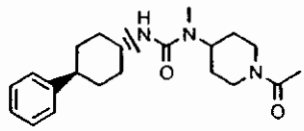
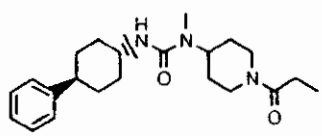
Example **6F**:

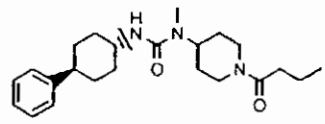
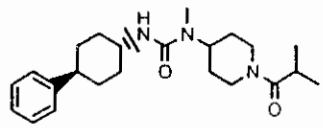
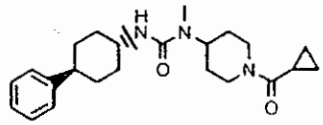
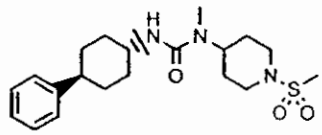
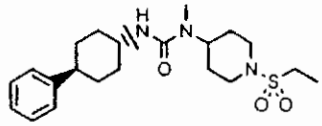


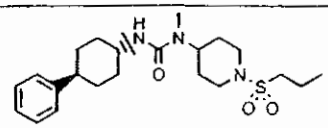
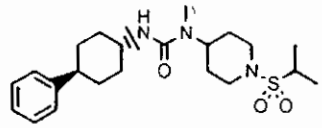
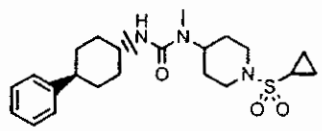
6F

To a solution of **36** (70 mg, 0.22 mmol) and Et_3N (200 µl, 1.43 mmol) in CH_2Cl_2 (2.5 ml) in an ice-water bath was added methanesulfonyl chloride (40 µl, 0.52 mmol). The mixture was stirred at room temperature for 1 hour. PS-Trisamine (100 mg) was added and the mixture was stirred for 2 hours, then filtered. The filtrate was concentrated and the residue was purified by PTLC (10:1 CH_2Cl_2/MeOH) to give **6F** (35 mg, 40%).

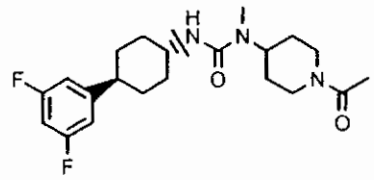
Using essentially the same procedure, examples **6G**, **6H**, **6I**, and **6J** were prepared.

Example		^{1}H NMR	MS (M+H)
6A		($CDCl_3$) δ 7.18-7.31 (m, 5H), 4.73 (m, 1H), 4.47 (m, 1H), 4.20 (m, 1H), 3.87 (m, 1H), 3.74 (m, 1H), 3.15 (m, 1H), 2.69 (s, 3H), 2.59 (m, 1H), 2.48 (m, 1H), 2.14 (m, 2H), 2.10 (s, 3H), 1.94 (m, 2H), 1.4-1.8 (m, 6H), 1.27 (m, 2H).	358
6B		($CDCl_3$) δ 7.16-7.29 (m, 5H), 4.73 (m, 1H), 4.45 (m,1H), 4.23 (m, 1H), 3.89 (m, 1H), 3.70 (m, 1H), 3.07 (m, 1H), 2.67 (s, 3H), 2.4-2.6 (m, 2H), 2.37	372

		(m, 2H), 2.13 (m, 2H), 1.92 (m, 2H), 1.4-1.8 (m, 6H), 1.26 (m, 2H), 1.13 (m, 3H).	
6C		($CDCl_3$) δ 7.16-7.29 (m, 5H), 4.73 (m, 1H), 4.42 (m,1H), 4.22 (m, 1H), 3.90 (m, 1H), 3.69 (m, 1H), 3.06 (m, 1H), 2.67 (s, 3H), 2.4-2.6 (m, 2H), 2.30 (m, 2H), 2.13 (m, 2H), 1.90 (m, 2H), 1.4-1.8 (m, 8H), 1.22 (m, 2H), 0.95 (m, 3H).	386
6D		($CDCl_3$) δ 7.17-7.26 (m, 5H), 4.73 (m, 1H), 4.43 (m,1H), 4.22 (m, 1H), 3.97 (m, 1H), 3.70 (m, 1H), 3.06 (m, 1H), 2.78 (m, 1H), 2.67 (s, 3H), 2.4-2.6 (m, 2H), 2.12 (m, 2H), 1.90 (m, 2H), 1.4-1.8 (m, 6H), 1.24 (m, 2H), 1.10 (m, 6H).	386
6E		($CDCl_3$) δ 7.18-7.27 (m, 5H), 4.70 (m, 1H), 4.46 (m, 1H), 4.27 (m, 2H), 3.71 (m, 1H), 3.14 (m, 1H), 2.68 (m, 3H), 2.61 (m, 1H), 2.45 (m, 1H), 2.13 (m, 2H), 1.92 (m, 2H), 1.4-1.8 (m, 7H), 1.24 (m, 2H), 0.97 (m, 2H), 0.73 (m, 2H).	384
6F		($CDCl_3$) δ 7.18-7.28 (m, 5H), 4.40 (m, 1H), 4.21 (m, 1H), 3.87 (m, 2H), 3.69 (m, 1H), 2.6-2.8 (m, 8H), 2.46 (m, 1H), 2.14 (m, 2H), 1.93 (m, 2H), 1.74 (m, 4H), 1.61 (m, 2H), 1.26 (m, 2H).	394
6G		($CDCl_3$) δ 7.18-7.28 (m, 5H), 4.39 (m, 1H), 4.22 (m, 1H), 3.88 (m, 2H), 3.65 (m, 1H), 2.95 (m, 2H), 2.86 (m, 2H), 2.70 (s, 3H), 2.46 (m, 1H), 2.13 (m, 2H), 1.92 (m, 2H), 1.5-1.8 (m, 6H), 1.2-1.4 (m, 5H).	408
6H		($CDCl_3$) δ 7.18-7.28 (m, 5H), 4.39 (m, 1H), 4.21 (m, 1H), 3.88 (m, 2H), 3.72	

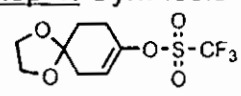
		(m, 1H), 2.88 (m, 4H), 2.71 (s, 3H), 2.46 (m, 1H), 2.14 (m, 2H), 1.5-2.0 (m, 10H), 1.26 (m, 2H), 1.04 (m, 3H).	422
6I		($CDCl_3$) δ 7.19-7.28 (m, 5H), 4.41 (m, 1H), 4.21 (m,1H), 3.91 (m, 2H), 3.72 (m, 1H), 3.17 (m, 1H), 2.96 (m, 2H), 2.71 (s, 3H), 2.47 (m, 1H), 2.14 (m, 2H), 1.93 (m, 2H), 1.5-1.8 (m, 6H), 1.33 (d, J=6.8 Hz, 6H), 1.26 (m, 2H).	422
6J		($CDCl_3$) δ 7.16-7.30 (m, 5H), 4.37 (m, 1H), 4.24 (m, 1H), 3.87 (m, 2H), 3.71 (m, 1H), 2.89 (m, 2H), 2.71 (s, 3H), 2.47 (m, 1H), 2.25 (m, 1H), 2.13 (m, 2H), 1.93 (m, 2H), 1.5-1.8 (m, 6H), 1.28 (m, 2H), 1.15 (m, 2H), 0.98 (m, 2H).	420

Example **7A**



7A

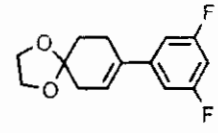
Step 1. Synthesis of **37**



37

To a solution of diisopropylamine (3.75 g, 37.1 mmol) in THF (20 ml) in dry ice-acetone bath was added 2.5 M butyllithium in hexanes (14.4 ml). The mixture was stirred for 10 min and a solution of 1,4-dioxa-spiro[4,5]decan-8-one (5.00 g, 32.0 mmol) in THF (25 ml) was added. After 1 hour, N-phenyltrifluoromethanesulfonimide (11.5 g, 32.3 mmol) in THF (25 ml) was added and the mixture was kept in an ice-water bath. The reaction was allowed to warm to RT slowly and stirred for 16 hours. The volatiles were removed under reduced pressure and the residue was purified by column chromatography (Hexanes gradient to EtOAc:Hexanes 9:1000) to give **37** (6.86 g, 74%). ^{1}H-NMR ($CDCl_3$) 5.66 (m, 1H), 3.99 (m, 4H), 2.54 (m, 2H), 2.41 (m, 2H), 1.90 (m, 2H).

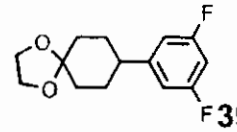
Step 2. Synthesis of **38**



38

A mixture of **37** (4.33 g, 15.0 mmol), 3,5-difluorophenyl boronic acid (3.63 g, 23.0 mmol), lithium chloride (2.60 g, 61.3 mmol), sodium carbonate (6.44 g, 60.8 mmol), and palladium tetrakis(triphenylphosphine) (1.30 g, 1.13 mmol) in DME (50 ml) and water (27 ml) was refluxed under nitrogen for 5 hours. The mixture was cooled down to RT and partitioned between CH_2Cl_2 (300 ml) and 2N sodium carbonate (200 ml). The aqueous layer was extracted with CH_2Cl_2 (200 ml) and the combined organic portion was dried, concentrated, and purified by column chromatography (Hexanes gradient to EtOAc:Hexanes 1:40) to give **38** (2.90 g, 90%). ^{1}H-NMR ($CDCl_3$) δ 6.87 (m, 2H), 6.65 (m, 1H), 6.04 (m, 1H), 4.02 (s, 4H), 2.59 (m, 2H), 2.46 (m, 2H), 1.90 (m, 2H).

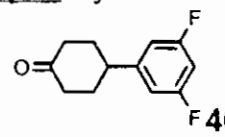
Step 3. Synthesis of **39**



39

A mixture of **38** (0.692 g, 2.75 mmol) and 10% Pd/C (0.100 g) in CH_3OH (30 ml) was stirred under 1 atm hydrogen for 4 hours. The mixture was filtered and concentrated to give **39** (0.650 g, 93%). MS m/e 255 $(M+H)^+$.

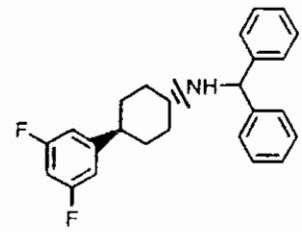
Step 4. Synthesis of **40**



40

A solution of **39** (3.50 g, 13.8 mmol) in THF (60 ml) and 5N HCl (60 ml) was refluxed for 4 hours. The volatiles were removed under reduced pressure and the residue was partitioned between CH_2Cl_2 and sodium carbonate. The organic portion was dried ($MgSO_4$), concentrated, and purified by column chromatography (Hexanes gradient to EtOAc:Hexanes 1:10) to give **40** (2.00 g, 66%). ^{1}H-NMR ($CDCl_3$) δ 6.78 (m, 2H), 6.66 (m, 1H), 3.02 (m, 1H), 2.52 (m, 4H), 2.21 (m, 2H), 1.90 (m, 2H).

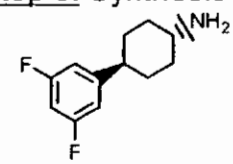
Step 5. Synthesis of **41**



41

A mixture of the **40** (2.00 g, 9.52 mmol), diphenylmethylamine (2.09 g, 11.4 mmol), and sodium triacetoxyborohydride (2.40 g, 11.3 mmol) in dichloroethane (100 ml) was stirred for 16 hours. The mixture was diluted with CH_2Cl_2 (100 ml) and washed with 1N NaOH (100 ml). The organic portion was passed through a pad of silica, concentrated, and purified by column chromatography (Hexanes gradient to EtOAc:Hexanes 1:50) to give **41** (0.660 g, 18%). MS m/e 378 $(M+H)^+$.

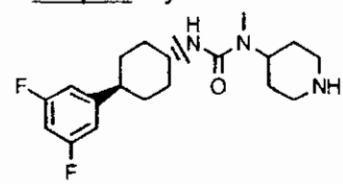
Step 6. Synthesis of **42**



42

A mixture of **41** (0.640 g, 1.70 mmol), ammonium formate (1.90 g, 30.1 mmol), and 10% Pd/C (0.130 g) in CH_3OH (30 ml) was stirred at RT for 1 hour. The mixture was filtered through a pad of celite and concentrated. The residue was partitioned between CH_2Cl_2 (150 ml) and conc. NH_4OH (50 ml). The organic portion was dried (K_2CO_3), concentrated, and purified by column chromatography (CH_2Cl_2 gradient to 2M NH_3/ CH_3OH:CH_2Cl_2 1:10) to give **42** (0.250 g, 70%). MS m/e 212 $(M+H)^+$.

Step 7. Synthesis of **43**



43

To a solution of **42** (0.250 g, 1.18 mmol) and pyridine (1.0 ml, 12 mmol) in an ice-water bath was added N, N'-disuccinimidyl carbonate (0.362 g, 1.42 mmol). The mixture was stirred at RT for 2.5 hours and cooled in an ice-water bath. A solution of 4-methylamino-1-Boc-piperidine (0.278 g, 1.30 mmol) was added and the mixture was stirred at RT for 16 hours. The volatiles were removed under reduced pressure and the residue was partitioned between CH_2Cl_2 (100 ml) and 1N NaOH (50 ml). The organic portion was washed with 1N HCl, brine, dried (K_2CO_3), and concentrated. The resulting solid was taken up in CH_2Cl_2 (25 ml) and 4N HCl/dioxane (25 ml) and the solution was stirred at RT for 2.5 hours. The mixture was concentrated and the

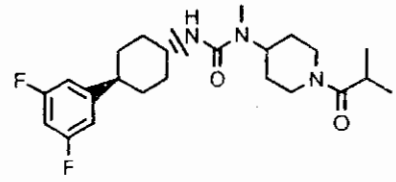
residue was partitioned between CH_2Cl_2 (150 ml) and conc. NH_4OH (50 ml). The organic portion was dried (K_2CO_3), concentrated, and purified by column chromatography (CH_2Cl_2 gradient to 2M NH_3/ CH_3OH:CH_2Cl_2 1:10) to give **43** (0.43 g, 96%). MS m/e 352 $(M+H)^+$.

Step 8

A solution of **43** (0.058 g, 0.15 mmol), acetic anhydride (40 µl, 0.42 mmol), and triethylamine (200 µl, 1.42 mmol) in CH_2Cl_2 (2 ml) was stirred at RT for 2 hours. 1N NaOH (2 ml) was added and the organic portion was washed with brine, dried ($MgSO_4$), concentrated, and purified by PTLC (CH_3OH: CH_2Cl_2 1:20) to give **7A** (0.036 g, 61%).

Using essentially the same procedure, **7B** was prepared.

Example **7C**

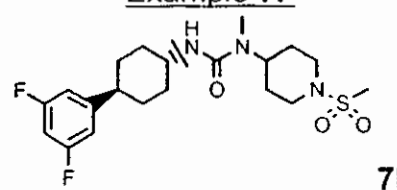


7C

A solution of **43** (0.058 g, 0.15 mmol), isobutyryl chloride (40 µl, 0.38 mmol), and triethylamine (200 µl, 1.42 mmol) in CH_2Cl_2 (2 ml) was stirred at RT for 16 hours. The mixture was diluted with CH_2Cl_2 (5 ml) and washed with 1N NaOH (2 ml). The organic portion was dried ($MgSO_4$), concentrated, and purified by PTLC (CH_3OH: CH_2Cl_2 1:20) to give **7C** (0.041 g, 65%).

Using essentially the same procedure, **7D** and **7E** were prepared.

Example **7F**

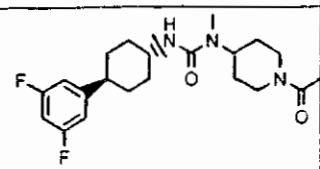
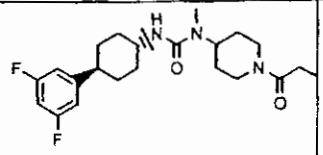
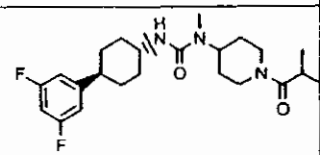
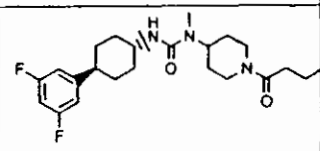


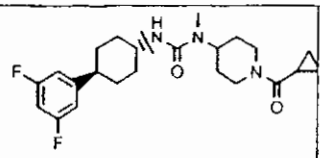
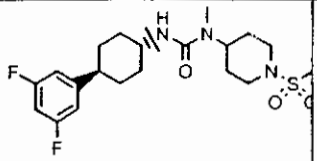
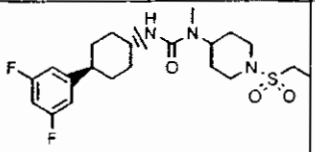
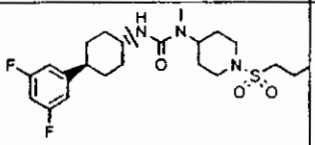
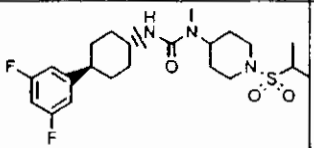
7F

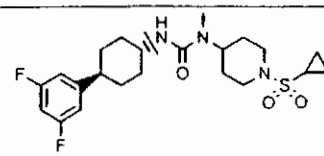
A solution of **43** (0.058 g, 0.15 mmol), methanesulfonyl chloride (40 µl, 0.52 mmol), and triethylamine (200 µl, 1.42 mmol) in CH_2Cl_2 (2 ml) was stirred at RT for 16 hours. The mixture was diluted with CH_2Cl_2 (5 ml) and washed with 1N NaOH (2 ml).

The organic portion was dried ($MgSO_4$), concentrated, and purified by PTLC (CH_3OH: CH_2Cl_2 1:20) to give **7F** (0.030 g, 47%).

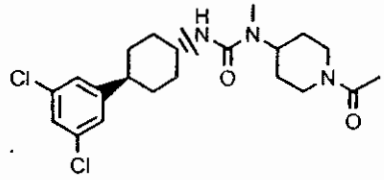
Using essentially the same procedure, **7G**, **7H**, **7I**, and **7J** were prepared.

Example		^{1}H NMR	MS (M+H)$^+$
7A		($CDCl_3$) δ 6.71 (m, 2H), 6.61 (m, 1H), 4.72 (m, 1H), 4.46 (m, 1H), 4.22 (m, 1H), 3.86 (m, 1H), 3.69 (m, 1H), 3.14 (m, 1H), 2.68 (s, 3H), 2.58 (m, 1H), 2.46 (m, 1H), 2.12 (m, 2H), 2.09 (s, 3H), 1.92 (m, 2H), 1.68 (m, 2H), 1.52 (m, 4H), 1.25 (m, 2H).	394
7B		($CDCl_3$) δ 6.71 (m, 2H), 6.62 (m, 1H), 4.75 (m, 1H), 4.46 (m, 1H), 4.18 (m, 1H), 3.91 (m, 1H), 3.71 (m, 1H), 3.09 (m, 1H), 2.68 (s, 3H), 2.59 (m, 1H), 2.47 (m, 1H), 2.34 (m, 2H), 2.15 (m, 2H), 1.93 (m, 2H), 1.4-1.8 (m, 6H), 1.27 (m, 2H), 1.15 (t, J=7.8 Hz, 3H).	408
7C		($CDCl_3$) δ 6.71 (m, 2H), 6.58 (m, 1H), 4.74 (m, 1H), 4.44 (m, 1H), 4.21 (m, 1H), 3.97 (m, 1H), 3.69 (m, 1H), 3.09 (m, 1H), 2.78 (m, 1H), 2.66 (s, 3H), 2.56 (m, 1H), 2.44 (m, 1H), 2.14 (m, 2H), 1.93 (m, 2H), 1.4-1.8 (m, 6H), 1.25 (m, 2H), 1.10 (m, 6H).	422
7D		($CDCl_3$) δ 6.71 (m, 2H), 6.62 (m, 1H), 4.75 (m, 1H), 4.46 (m, 1H), 4.18 (m, 1H), 3.91 (m, 1H), 3.71 (m, 1H), 3.11 (m, 1H), 2.68 (s, 3H), 2.58 (m, 1H), 2.46 (m, 1H), 2.31 (m, 2H), 2.16 (m, 2H), 1.93 (m, 2H), 1.4-1.8 (m, 8H), 1.27 (m, 2H), 0.97 (t, J=7.6 Hz, 3H).	422

7E		($CDCl_3$) δ 6.72 (m, 2H), 6.62 (m, 1H), 4.71 (m, 1H), 4.49 (m, 1H), 4.28 (m, 1H), 4.19 (m, 1H), 3.72 (m, 1H), 3.16 (m, 1H), 2.69 (s, 3H), 2.62 (m, 1H), 2.47 (m, 1H), 2.16 (m, 2H), 1.93 (m, 2H), 1.4-1.8 (m, 7H), 1.27 (m, 2H), 0.98 (m, 2H), 0.75 (m, 2H).	420
7F		($CDCl_3$) δ 6.72 (m, 2H), 6.62 (m, 1H), 4.39 (m, 1H), 4.21 (m, 1H), 3.89 (m, 2H), 3.71 (m, 1H), 2.78 (s, 3H), 2.75 (m, 2H), 2.71 (s, 3H), 2.46 (m, 1H), 2.15 (m, 2H), 1.93 (m, 2H), 1.72 (m, 4H), 1.56 (m, 2H), 1.27 (m, 2H).	430
7G		($CDCl_3$) δ 6.72 (m, 2H), 6.62 (m, 1H), 4.40(m, 1H), 4.18 (m, 1H), 3.90 (m, 2H), 3.69 (m, 1H), 2.96 (q, J=7.2 Hz, 2H), 2.87 (m, 2H), 2.71 (s, 3H), 2.47 (m, 1H), 2.15 (m, 2H), 1.92 (m, 2H), 1.4-1.8 (m, 6H), 1.36 (t, J=7.2 Hz, 3H), 1.24 (m, 2H).	444
7H		($CDCl_3$) δ 6.71 (m, 2H), 6.60 (m, 1H), 4.38 (m, 1H), 4.20 (m, 1H), 3.87 (m, 2H), 3.68 (m, 1H), 2.85 (m, 4H), 2.70 (s, 3H), 2.46 (m, 1H), 2.14 (m, 2H), 1.6-2.0 (m, 8H), 1.55 (m, 2H), 1.25 (m, 2H), 1.05 (t, J=7.2 Hz, 3H).	458
7I		($CDCl_3$) δ 6.72 (m, 2H), 6.62 (m, 1H), 4.41 (m, 1H), 4.19 (m, 1H), 3.92 (m, 2H), 3.71 (m, 1H), 3.17 (m, 1H), 2.96 (m, 2H), 2.71 (s, 3H), 2.47 (m, 1H), 2.15 (m, 2H), 1.92 (m, 2H), 1.4-1.8 (m, 6H), 1.33 (d, J=7.6 Hz, 6H), 1.25 (m, 2H).	458

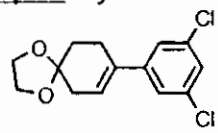
7J		($CDCl_3$) δ 6.72 (m, 2H), 6.62 (m, 1H), 4.39 (m, 1H), 4.20 (m, 1H), 3.88 (m, 2H), 3.71 (m, 1H), 2.90 (m, 2H), 2.71 (s, 3H), 2.47 (m, 1H), 2.26 (m, 1H), 2.15 (m, 2H), 1.92 (m, 2H), 1.4-1.8 (m, 6H), 1.25 (m, 2H), 1.15 (m, 2H), 0.98 (m, 2H).	456

Example **8A**



8A

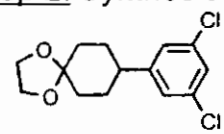
Step 1. Synthesis of **44**



44

A mixture of **37** (6.42 g, 22.3 mmol), 3,5-dichlorophenyl boronic acid (12.8 g, 33.5 mmol), lithium chloride (4.02 g, 94.8 mmol), sodium carbonate (11.7 g, 110 mmol), and palladium tetrakis(triphenylphosphine) (2.01 g, 1.74 mmol) in DME (75 ml) and water (50 ml) was refluxed under nitrogen for 22 hours. The mixture was cooled to RT, diluted with CH_2Cl_2 (200 ml), and washed with 1N NaOH (250 ml). The aqueous portion was extracted with CH_2Cl_2 (2x150 ml) and the combined organic portion was dried (K_2CO_3), concentrated, and purified by column chromatography (Hexanes gradient to EtOAc:Hexanes 1:20) to give **44** (3.60 g, 57%). ^{1}H-NMR ($CDCl_3$) δ 7.25 (m, 2H), 7.21 (m, 1H), 6.02 (m, 1H), 4.02 (s, 4H), 2.60 (m, 2H), 2.46 (m, 2H), 1.90 (m, 2H).

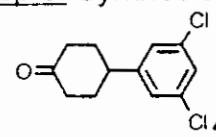
Step 2. Synthesis of **45**



45

A mixture of **44** (3.57 g, 12.5 mmol) and 10% Pt/C (0.357 g) in ethanol (120 ml) was stirred under 1 atm hydrogen for 3 hours. The mixture was filtered, concentrated, and purified by column chromatography (Hexanes gradient to EtOAc:Hexanes 1:100) to give **45** (1.70 g, 47%). ^{1}H-NMR ($CDCl_3$) δ 7.18 (m, 1H), 7.11 (m, 2H), 3.98 (s, 4H), 2.51 (m, 1H), 1.6-1.9 (m, 8H).

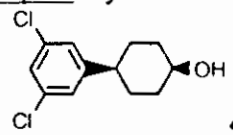
Step 3. Synthesis of **46**



46

A mixture of **45** (1.54 g, 5.36 mmol) and pyridinium p-toluenesulfonate (0.337 g, 1.34 mmol) in acetone (45 ml) and water (5 ml) was refluxed for 24 hours. The mixture was concentrated and the residue was partitioned between CH_2Cl_2 (150 ml) and water (100 ml). The organic portion was washed with 1N HCl (20 ml), 1N NaOH (20 ml), brine (50 ml), dried (K_2CO_3), and concentrated to give **46** (1.30 g, 95%). ^{1}H-NMR ($CDCl_3$) δ 7.24 (m, 1H), 7.12 (m, 2H), 2.99 (m, 1H), 2.51 (m, 4H), 2.19 (m, 2H), 1.92 (m, 2H).

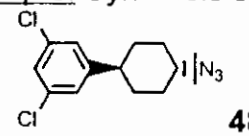
Step 4. Synthesis of **47**



47

A solution of **46** (1.20 g, 4.93 mmol) and 1.0M L-selectride (5.5 ml) in THF (15 ml) was stirred in dry ice-acetone bath for 2 hours and then at RT for 16 hours. The reaction was quenched with drops of water, followed by 1N NaOH (10 ml) and aqueous H_2O_2 (10 ml). The mixture was diluted with saturated Na_2CO_3 (150 ml) and extracted by ether (3x50 ml). The combined organic portion was dried (Na_2SO_4), concentrated, and purified by column chromatography (Hexanes gradient to EtOAc:Hexanes 4.5:100) to give **47** (0.764 g, 63%). ^{1}H-NMR ($CDCl_3$) δ 7.18 (m, 1H), 7.12 (m, 2H), 4.13 (m, 1H), 2.50 (m, 1H), 1.86 (m, 4H), 1.65 (m, 4H).

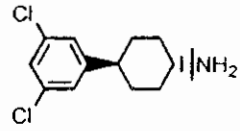
Step 5. Synthesis of **48**



48

To a solution **47** (0.764 g, 3.11 mmol) and triphenylphosphine (0.863 g, 3.29 mmol) in THF (10 ml) in an ice-water bath were added diethyl azodicarboxylate (0.649 g, 3.72 mmol) and diphenylphosphoryl azide (0.978 g, 3.55 mmol). The mixture was allowed to warm to RT slowly and stirred for 16 hours. The volatiles were removed under reduced pressure and the residue was purified by column chromatography (Hexanes gradient to EtOAc:Hexanes 0.75:100) to give **48** (0.626 g, 75%). ^{1}H-NMR ($CDCl_3$) δ 7.20 (m, 1H), 7.07 (m, 2H), 3.33 (m, 1H), 2.48 (m, 1H), 2.14 (m, 2H), 1.96 (m, 2H), 1.48 (m, 4H).

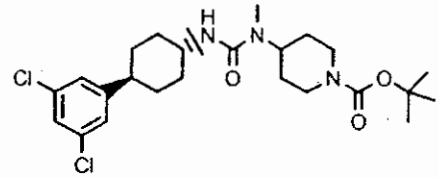
Step 6. Synthesis of **49**



49

A mixture of **48** (0.626 g, 2.32 mmol) in EtOAc (10 ml) and water (0.2 ml) in an ice-water bath was treated with 1.0M trimethylphosphine in toluene (4.6 ml). The mixture was warmed to RT and stirred for 16 hours. The mixture was evaporated to dryness and purified by column chromatography (CH_2Cl_2 gradient to 7M NH_3/CH_3OH: CH_2Cl_2 6:1000) to give **49** (0.417 g, 74%). MS m/e 244 $(M+H)^+$.

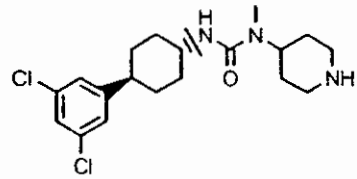
Step 7. Synthesis of **50**



50

To a solution of **49** (0.417 g, 1.71 mmol) and pyridine (0.492 g, 6.22 mmol) in THF (30 ml) in an ice-water bath was added N, N'-disuccinimidyl carbonate (0.493 g, 1.93 mmol). The mixture was stirred for 30 minutes and more pyridine (0.40 ml, 4.9 mmol) was added. The mixture was then stirred at RT for 3 hours. A solution of 4-methylamino-1-Boc-piperidine (0.456 g, 2.13 mmol) in THF (10 ml) was added and the mixture was stirred at RT for 16 hours. The volatiles were removed under reduced pressure and the residue was partitioned between CH_2Cl_2 (65 ml) and 1N NaOH (50 ml). The organic portion was washed sequentially with 1N HCl (30 ml) and water (30 ml), dried ($MgSO_4$), concentrated, and purified by column chromatography (CH_2Cl_2 gradient to CH_3OH: CH_2Cl_2 0.75:100) to give **50** (0.618 g, 75%). MS m/e 484 $(M+H)^+$.

Step 8. Synthesis of **51**



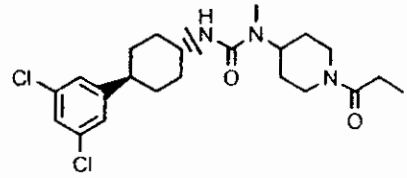
51

A solution of **50** (0.618 g, 1.28 mmol) in 4N HCl/dioxane (15 ml) was stirred at RT for 16 hours. The volatiles were removed under reduced pressure and the residue was partitioned between CH_2Cl_2 (2x40 ml) and conc. NH_4OH (40 ml). The organic portion was dried ($MgSO_4$) and concentrated to give **51** (0.446 g, 91%). MS m/e 384 $(M+H)^+$.

Step 9.

A solution of **51** (0.049 g, 0.13 mmol), acetic anhydride (0.015 g, 0.15 mmol), and triethylamine (0.035 g, 0.35 mmol) in CH_2Cl_2 (5 ml) was stirred at RT for 16 hours. The solution was diluted with CH_2Cl_2 (50 ml) and washed with 1N NaOH (25 ml) and 1N HCl (25 ml). The organic portion was dried ($MgSO_4$), concentrated, and purified by PTLC (CH_3OH: CH_2Cl_2 1:20) to give **8A** (0.049 g, 89%).

Example **8B**

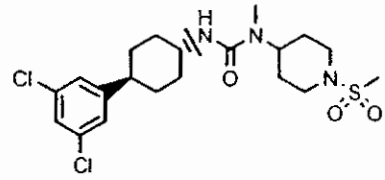


8B

A solution of **51** (0.035 g, 0.090 mmol), propionyl chloride (0.010 g, 0.11 mmol), and triethylamine (0.020 g, 0.20 mmol) in CH_2Cl_2 (2.5 ml) was stirred at RT for 16 hours. The mixture was purified by PTLC (CH_3OH: CH_2Cl_2 7:100) to give **8B** (0.034 g, 86%).

Using essentially the same procedure, **8C**, **8D**, and **8E** were prepared.

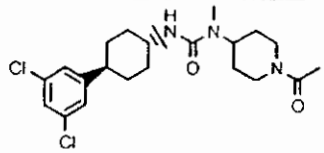
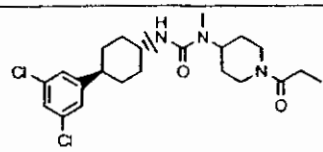
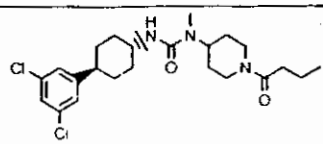
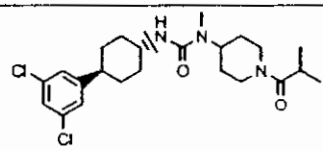
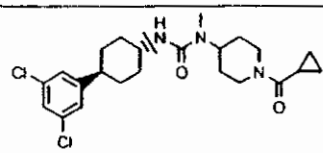
Example **8F**

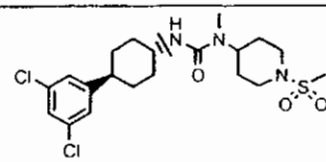
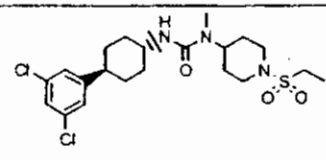
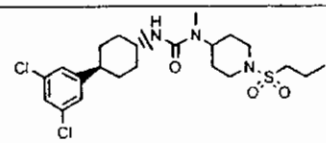
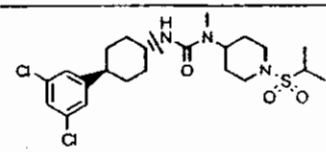


8F

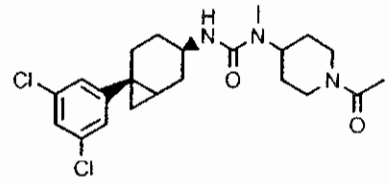
A solution of **51** (0.048 g, 0.13 mmol), methanesulfonyl chloride (0.015 g, 0.13 mmol), and triethylamine (0.033 g, 0.33 mmol) in CH_2Cl_2 (5 ml) was stirred at RT for 64 hours. The solution was diluted with CH_2Cl_2 (40 ml) and washed with 1N NaOH (20 ml). The organic portion was dried ($MgSO_4$), concentrated, and purified by PTLC (CH_3OH: CH_2Cl_2 1:20) to give **8F** (0.053 g, 91%).

Using essentially the same procedure, **8G**, **8H**, and **8I** were prepared.

Example		^{1}H NMR	MS (M+H)$^+$
8A		($CDCl_3$) δ 7.18 (m, 1H), 7.07 (m, 2H), 4.73 (m, 1H), 4.46 (m, 1H), 4.21 (m, 1H), 3.86 (m, 1H), 3.69 (m, 1H), 3.14 (m, 1H), 2.68 (s, 3H), 2.58 (m, 1H), 2.44 (m, 1H), 2.14 (m, 2H), 2.10 (s, 3H), 1.90 (m, 2H), 1.4-1.8 (m, 6H), 1.26 (m, 2H).	426
8B		($CDCl_3$) δ 7.18 (m, 1H), 7.08 (m, 2H), 4.75 (m, 1H), 4.46 (m, 1H), 4.19 (m, 1H), 3.92 (m, 1H), 3.71 (m, 1H), 3.10 (m, 1H), 2.68 (s, 3H), 2.59 (m, 1H), 2.44 (m, 1H), 2.35 (q, J=7.6 Hz, 2H), 2.15 (m, 2H), 1.91 (m, 2H), 1.4-1.8 (m, 6H), 1.26 (m, 2H), 1.15 (t, J=7.6 Hz, 3H).	440
8C		($CDCl_3$) δ 7.18 (m, 1H), 7.08 (m, 2H), 4.76 (m, 1H), 4.46 (m, 1H), 4.18 (m, 1H), 3.93 (m, 1H), 3.72 (m, 1H), 3.10 (m, 1H), 2.68 (s, 3H), 2.57 (m, 1H), 2.44 (m, 1H), 2.29 (m, 2H), 2.16 (m, 2H), 1.90 (m, 2H), 1.4-1.8 (m, 8H), 1.26 (m, 2H), 0.97 (t, J=7.4 Hz, 3H).	454
8D		($CDCl_3$) δ 7.18 (m, 1H), 7.07 (m, 2H), 4.75 (m, 1H), 4.46 (m, 1H), 4.19 (m, 1H), 3.99 (m, 1H), 3.72 (m, 1H), 3.11 (m, 1H), 2.80 (m, 1H), 2.68 (s, 3H), 2.57 (m, 1H), 2.44 (m, 1H), 2.17 (m, 2H), 1.91 (m, 2H), 1.4-1.8 (m, 6H), 1.26 (m, 2H), 1.12 (m, 6H).	454
8E		($CDCl_3$) δ 7.18 (m, 1H), 7.07 (m, 2H), 4.71 (m, 1H), 4.48 (m, 1H), 4.30 (m, 1H), 4.21 (m, 1H), 3.71 (m, 1H), 3.15 (m, 1H), 2.69 (s, 3H), 2.63 (m, 1H), 2.45 (m, 1H), 2.16	452

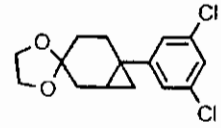
		(m, 2H), 1.92 (m, 2H), 1.4-1.8 (m, 7H), 1.26 (m, 2H), 0.98 (m, 2H), 0.75 (m, 2H).	
8F		($CDCl_3$) δ 7.18 (m, 1H), 7.07 (m, 2H), 4.39 (m, 1H), 4.23 (m, 1H), 3.88 (m, 2H), 3.69 (m, 1H), 2.79 (s, 3H), 2.76 (m, 2H), 2.72 (s, 3H), 2.45 (m, 1H), 2.15 (m, 2H), 1.92 (m, 2H), 1.75 (m, 4H), 1.56 (m, 2H), 1.25 (m, 2H).	462
8G		($CDCl_3$) δ 7.18 (m, 1H), 7.07 (m, 2H), 4.39 (m, 1H), 4.22 (m, 1H), 3.90 (m, 2H), 3.69 (m, 1H), 2.95 (q, J=7.4 Hz, 2H), 2.87 (m, 2H), 2.71 (s, 3H), 2.45 (m, 1H), 2.15 (m, 2H), 1.91 (m, 2H), 1.72 (m, 4H), 1.56 (m, 2H), 1.36 (t, J=7.4 Hz, 3H), 1.25 (m, 2H).	476
8H		($CDCl_3$) δ 7.18 (m, 1H), 7.07 (m, 2H), 4.39 (m, 1H), 4.21 (m, 1H), 3.89 (m, 2H), 3.69 (m, 1H), 2.86 (m, 4H), 2.71 (s, 3H), 2.44 (m, 1H), 2.15 (m, 2H), 1.87 (m, 4H), 1.71 (m, 4H), 1.55 (m, 2H), 1.25 (m, 2H), 1.06 (t, J=7.6 Hz, 3H).	490
8I		($CDCl_3$) δ 7.18 (m, 1H), 7.08 (m, 2H), 4.41 (m, 1H), 4.21 (m, 1H), 3.92 (m, 2H), 3.70 (m, 1H), 3.18 (m, 1H), 2.96 (m, 2H), 2.71 (s, 3H), 2.45 (m, 1H), 2.15 (m, 2H), 1.91 (m, 2H), 1.68 (m, 4H), 1.56 (m, 2H), 1.33 (d, J=6.4 Hz, 6H), 1.27 (m, 2H).	490

Example **9A**



9A

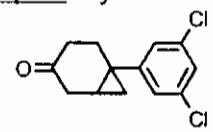
Step 1. Synthesis of **52**



52

To a solution of 1M $ZnEt_2$ in hexanes (7.3 ml) in CH_2Cl_2 (8 ml) in an ice-water bath was added TFA (0.842 g, 7.38 mmol) in CH_2Cl_2 (6 ml) dropwise. Upon stirring for 20 minutes, a solution of CH_2I_2 (2.08 g, 7.78 mmol) in CH_2Cl_2 (4 ml) was added. After an additional 20 minutes, **44** (1.01 g, 3.53 mmol) in CH_2Cl_2 (5 ml) was added and the reaction was stirred at RT for 40 hours. The mixture was cooled in an ice-water bath and quenched with CH_3OH (5 ml), washed with 1N NaOH (60 ml), dried ($MgSO_4$), and purified by column chromatography (Hexanes gradient to EtOAc:Hexanes 1:200) to give **52** (0.608 g, 57%). ^{1}H-NMR ($CDCl_3$) δ 7.17 (m, 2H), 7.15 (m, 1H), 3.90 (m, 4H), 2.19 (m, 3H), 1.80 (m, 1H), 1.63 (m, 1H), 1.46 (m, 1H), 1.24 (m, 1H), 1.01 (m, 1H), 0.78 (m, 1H).

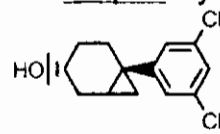
Step 2. Synthesis of **53**



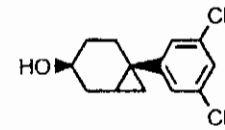
53

A mixture of **52** (0.606 g, 2.03 mmol) and water (1 ml) in 1:1 TFA-CH_2Cl_2 (10 ml) was stirred at RT for 2 hours. The volatiles were removed under reduced pressure and the residue was partitioned between EtOAc (50 ml) and saturated Na_2CO_3 (40 ml). The organic portion was dried ($MgSO_4$) and purified by column chromatography (Hexanes gradient to EtOAc:Hexanes 1:50) to give **53** (0.460 g, 89%). ^{1}H-NMR ($CDCl_3$) δ 7.20 (m, 1H), 7.17 (m, 2H), 2.84 (m, 1H), 2.68 (m, 1H), 2.42 (m, 2H), 2.26 (m, 2H), 1.49 (m, 1H), 1.07 (m, 1H), 0.88 (m, 1H).

Step 3. Synthesis of **54** and **55**



54



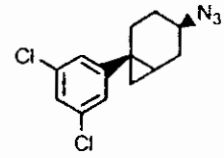
55

A solution of **53** (0.460 g, 1.80 mmol) and 1M L-selectride (2.0ml) in THF (7.5 ml) was stirred in a dry ice-acetone bath for 2 hours and then at RT for 3 hours. More 1M L-selectride (0.6 ml) was added and the solution was stirred at RT for 16 hours. The reaction was quenched with several drops of water, 1N NaOH (5ml), and aqueous H_2O_2 (5 ml). The mixture was diluted with saturated Na_2CO_3 (80 ml) and extracted with ether (2x50 ml). The combined organic portion was dried ($MgSO_4$) and purified by PTLC (CH_3OH: CH_2Cl_2 1:100) to give **54** (0.210 g, 45%) and **55** (0.216 g, 47%).

54 ^{1}H-NMR ($CDCl_3$) δ 7.15 (m, 1H), 7.09 (m, 2H), 3.69 (m, 1H), 2.47 (m, 1H), 2.22 (m, 1H), 1.98 (m, 1H), 1.74 (m, 1H), 1.68 (m, 1H), 1.48 (m, 1H), 1.22 (m, 2H), 0.98 (m, 1H), 0.78 (m, 1H).

55 ^{1}H-NMR ($CDCl_3$) δ 7.17 (m, 3H), 3.81 (m, 1H), 2.23 (m, 1H), 1.98 (m, 3H), 1.60 (m, 1H), 1.49 (m, 2H), 1.22 (m, 1H), 1.00 (m, 1H), 0.58 (m, 1H).

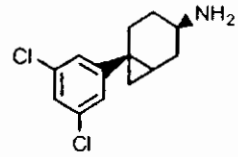
Step 4. Synthesis of **56**



56

To a solution of **54** (0.209 g, 0.813 mmol) and triphenylphosphine (0.226 g, 0.862 mmol) in THF (5 ml) in an ice-water bath were added diethyl azodicarboxylate (0.222 g, 1.27 mmol) and diphenylphosphoryl azide (0.293 g, 1.06 mmol). The ice-water bath was removed and the mixture was stirred at RT for 16 hours. The volatiles were removed under reduced pressure and the residue was purified by PTLC (EtOAc:Hexanes 1:20) to give **56** (0.113 g, 49%). ^{1}H-NMR ($CDCl_3$) δ 7.17 (m, 3H), 3.56 (m, 1H), 2.16 (m, 2H), 1.98 (m, 2H), 1.67 (m, 1H), 1.50 (m, 1H), 1.24 (m, 1H), 1.03 (m, 1H), 0.59(m, 1H).

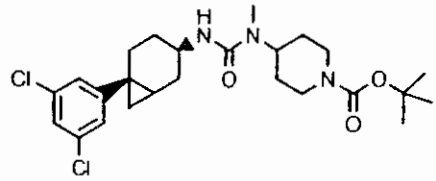
Step 5. Synthesis of **57**



57

A mixture of **56** (0.112 g, 0.397 mmol) and 1M trimethylphosphine in toluene (0.8 ml) in EtOAc (5 ml) and water (50 µl) was stirred at RT for 16 hours. The mixture was evaporated to dryness and purified by PTLC (7M NH_3/CH_3OH:CH_2Cl_2 1:50) to give **57** (0.093 g, 92%). MS m/e 256 $(M+H)^+$.

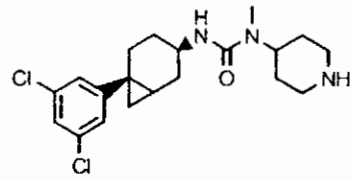
Step 6. Synthesis of **58**



58

To a mixture of **57** (0.093 g, 0.364 mmol) and N, N'-disuccinimidyl carbonate (0.120 g, 0.469 mmol) in THF (5 ml) in an ice-water bath was added pyridine (0.190 g, 2.40 mmol). The mixture was stirred at 0°C for 30 minutes then at RT for 3 hours. A solution of 4-methylamino-1-Boc-piperidine (0.098 g, 0.458 mmol) in THF (5 ml) was added and the mixture was stirred at RT for 16 hours. The volatiles were removed under reduced pressure and the residue was partitioned between CH_2Cl_2 (40 ml) and 1N NaOH (30 ml). The organic portion was dried ($MgSO_4$) and purified by PTLC (CH_3OH:CH_2Cl_2 1:33) to give **58** (0.169 g, 94%). MS m/e 496 $(M+H)^+$.

Step 7. Synthesis of **59**



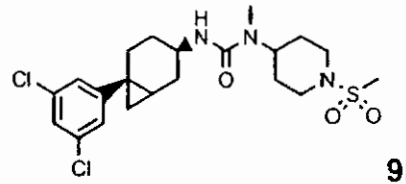
59

A solution of **58** (0.169 g, 0.341 mmol) in 1:1 TFA-CH_2Cl_2 (10 ml) in an ice-water bath was stirred for 30 minutes and then stirred at RT for 16 hours. The volatiles were removed under reduced pressure and the residue was partitioned between CH_2Cl_2 (50 ml) and conc. NH_4OH (25 ml). The organic portion was dried ($MgSO_4$) and evaporated to give **59** (0.114 g, 84%). MS m/e 396 $(M+H)^+$.

Step 8.

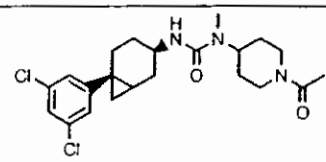
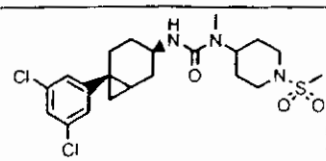
A solution of **59** (0.027 g, 0.069 mmol), acetic anhydride (0.0088 g, 0.086 mmol), and triethylamine (0.013 g, 0.13 mmol) in CH_2Cl_2 (5 ml) was stirred at RT for 16 hours. The mixture was evaporated to dryness and purified by PTLC (CH_3OH:CH_2Cl_2 1:20) to give **9A** (0.029 g, 97%).

Example **9B**

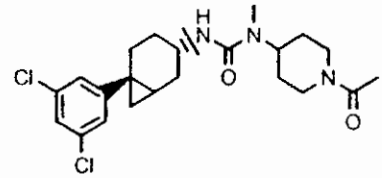


9B

A solution of **59** (0.033 g, 0.082 mmol), methanesulfonyl chloride (0.011 g, 0.096 mmol), and triethylamine (0.020 g, 0.20 mmol) in CH_2Cl_2 (5 ml) was stirred at RT for 16 hours. The mixture was evaporated to dryness and purified by PTLC (CH_3OH:CH_2Cl_2 1:20) to give **9B** (0.037 g, 95%).

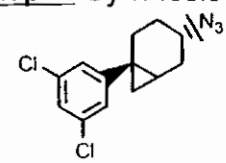
Example		^{1}H NMR	MS $(M+H)^+$
9A		($CDCl_3$) δ 7.15 (m, 1H), 7.11 (m, 2H), 4.73 (m, 1H), 4.43 (m, 1H), 4.28 (m, 1H), 3.87 (m, 1H), 3.70 (m, 1H), 3.13 (m, 1H), 2.69 (s, 3H), 2.57 (m, 1H), 2.10 (m, 6H), 1.2-1.9 (m, 8H), 1.04 (m, 1H), 0.71 (m, 1H).	438
9B		($CDCl_3$) δ 7.15 (m, 1H), 7.10 (m, 2H), 4.34 (m, 2H), 3.88 (m, 2H), 3.69 (m, 1H), 2.78 (s, 3H), 2.75 (m, 2H), 2.72 (s, 3H), 2.09 (m, 3H), 1.74 (m, 5H), 1.43 (m, 2H), 1.29 (m, 1H), 1.03 (m, 1H), 0.71 (m, 1H).	474

Example **10A**



10A

Step 1. Synthesis of **60**

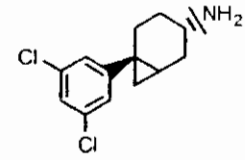


60

To a solution of **55** (0.216 g, 0.842 mmol) and triphenylphosphine (0.246 g, 0.938 mmol) in THF (5 ml) in an ice-water bath were added diethyl azodicarboxylate (0.200 g, 1.15 mmol) and diphenylphosphoryl azide (0.268 g, 0.974 mmol). The ice-water bath was removed and the mixture was stirred at RT for 16 hours. The volatiles were removed under reduced pressure and the residue was purified by PTLC (EtOAc:Hexanes 1:20) to give **60** (0.142 g, 60%). ^{1}H-NMR ($CDCl_3$) δ 7.17 (m, 1H),

7.10 (m, 2H), 3.37 (m, 1H), 2.47 (m, 1H), 2.27 (m, 1H), 1.97 (m, 1H), 1.83 (m, 1H), 1.58 (m, 1H), 1.28 (m, 2H), 1.03 (m, 1H), 0.77 (m, 1H).

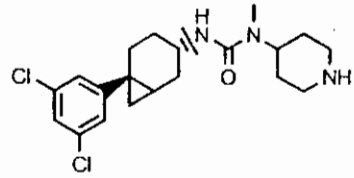
Step 2. Synthesis of **61**



61

A mixture of the **60** (0.142 g, 0.504 mmol) and 1M trimethylphosphine in toluene (1.0 ml) in EtOAc (5 ml) and water (100 µl) was stirred at RT for 16 hours. The mixture was evaporated to dryness and purified by PTLC (7M $NH_3/CH_3OH:CH_2Cl_2$ 1:33) to give **61** (0.102 g, 79%). MS m/e 256 $(M+H)^+$.

Step 3. Synthesis of **62**



62

To a mixture of **61** (0.102 g, 0.398 mmol) and N, N'-disuccinimidyl carbonate (0.134 g, 0.524 mmol) in THF (5 ml) in an ice-water bath was added pyridine (0.280 g, 3.54 mmol). The mixture was stirred at 0°C for 30 minutes then at RT for 3 hours. A solution of 4-methylamino-1-Boc-piperidine (0.120 g, 0.561 mmol) in THF (4 ml) was added and the mixture was stirred at RT for 16 hours. The volatiles were removed under reduced pressure and the residue was partitioned between CH_2Cl_2 (50 ml) and 0.5N HCl (30 ml). The organic portion was washed with 1N NaOH (30 ml), dried ($MgSO_4$), and concentrated. The resulting solid was taken up in 4N HCl/dioxane (5 ml) and stirred at RT for 16 hours. The volatiles were removed under reduced pressure and the residue was partitioned between EtOAc (2x40 ml) and conc. NH_4OH (35 ml). The organic portion was dried (K_2CO_3), concentrated, and purified by PTLC (2.3M $NH_3/CH_3OH:CH_2Cl_2$ 3:17) to give **62** (0.089 g, 56%). ^{1}H-NMR (CD_3OD) δ 7.21 (m, 3H), 4.15 (m, 1H), 3.60 (m, 1H), 3.11 (m, 2H), 2.73 (s, 3H), 2.67 (m, 2H), 2.44 (m, 1H), 2.23 (m, 1H), 2.04 (m, 1H), 1.64 (m, 5H), 1.45 (m, 1H), 1.26 (m, 2H), 0.97 (m, 1H), 0.79 (m, 1H).

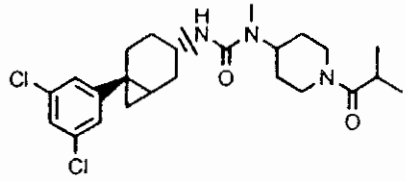
Step 4.

A solution of the **62** (0.022 g, 0.055 mmol), acetic anhydride (0.0069 g, 0.067 mmol), and triethylamine (0.012 g, 0.12 mmol) in CH_2Cl_2 (5 ml) was stirred at RT for

16 hours. The mixture was evaporated to dryness and purified by PTLC (CH_3OH:CH_2Cl_2 1:20) to give **10A** (0.024 g, 98%).

Using essentially the same procedure, **10B** was prepared.

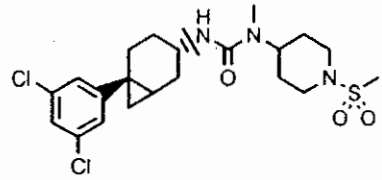
Example **10C**



10C

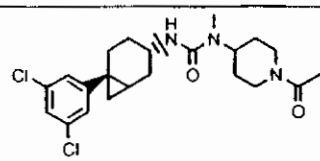
A solution of **62** (0.026 g, 0.068 mmol), isobutyryl chloride (0.0075 g, 0.070 mmol), and triethylamine (0.012 g, 0.12 mmol) in CH_2Cl_2 (3 ml) was stirred at RT for 16 hours. The mixture was evaporated to dryness and purified by PTLC (CH_3OH:CH_2Cl_2 1:20) to give **10C** (0.029 g, 90%).

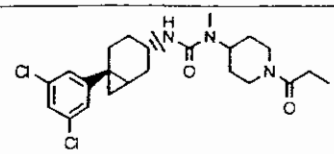
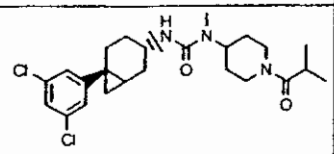
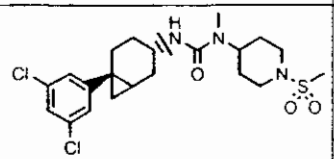
Example **10D**



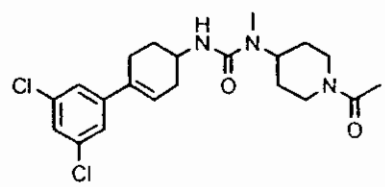
10D

A solution of **62** (0.022 g, 0.056 mmol), methanesulfonyl chloride (0.0087 g, 0.075 mmol), and triethylamine (0.011 g, 0.11 mmol) in CH_2Cl_2 (5 ml) was stirred at RT for 16 hours. The mixture was evaporated to dryness and purified by PTLC (CH_3OH:CH_2Cl_2 1:20) to give **10D** (0.027 g, 100%).

Example		^{1}H NMR	MS $(M+H)^+$
10A		($CDCl_3$) δ 7.15 (m, 1H), 7.12 (m, 2H), 4.72 (m, 1H), 4.44 (m, 1H), 4.08 (m, 1H), 3.86 (m, 1H), 3.65 (m, 1H), 3.14 (m, 1H), 2.66 (s, 3H), 2.57 (m, 2H), 2.21 (m, 1H), 2.10 (s, 3H), 2.05 (m, 1H), 1.83 (m, 1H), 1.68 (m, 2H), 1.51 (m, 2H), 1.27 (m, 2H), 1.08 (m, 1H), 0.98 (m, 1H), 0.70 (m, 1H).	438

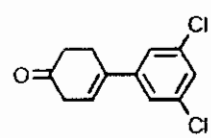
10B		($CDCl_3$) δ 7.15 (m, 1H), 7.11 (m, 2H), 4.75 (m, 1H), 4.43 (m, 1H), 4.08 (m, 1H), 3.90 (m, 1H), 3.66 (m, 1H), 3.09 (m, 1H), 2.66 (s, 3H), 2.57 (m, 2H), 2.35 (q, J=7.2 Hz, 2H), 2.21 (m, 1H), 2.05 (m, 1H), 1.83 (m, 1H), 1.68 (m, 2H), 1.47 (m, 2H), 1.28 (m, 2H), 1.14 (t, J=7.2 Hz, 3H), 1.06 (m, 1H), 0.98 (m, 1H), 0.70 (m, 1H).	452
10C		($CDCl_3$) δ 7.15 (m, 1H), 7.12 (m, 2H), 4.76 (m, 1H), 4.45 (m, 1H), 4.07 (m, 1H), 3.99 (m, 1H), 3.65 (m, 1H), 3.10 (m, 1H), 2.80 (m, 1H), 2.66 (s, 3H), 2.57 (m, 2H), 2.21 (m, 1H), 2.06 (m, 1H), 1.4-1.9 (m, 5H), 1.29 (m, 2H), 1.12 (m, 7H), 0.98 (m, 1H), 0.71 (m, 1H).	466
10D		($CDCl_3$) δ 7.15 (m, 1H), 7.12 (m, 2H), 4.38 (m, 1H), 4.10 (m, 1H), 3.88 (m, 2H), 3.66 (m, 1H), 2.79 (s, 3H), 2.75 (m, 2H), 2.70 (s, 3H), 2.57 (m, 1H), 2.23 (m, 1H), 2.06 (m, 1H), 1.76 (m, 5H), 1.29 (m, 2H), 1.09 (m, 1H), 0.99 (m, 1H), 0.71 (m, 1H).	474

Example **11A**



11A

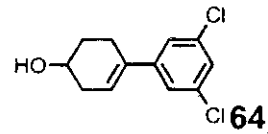
Step 1. Synthesis of **63**



63

A solution of **44** (2.85 g, 10.0 mmol) and pyridinium p-toluenesulfonate (0.628 g, 2.50 mmol) in acetone (90 ml) and water (10 ml) was refluxed for 20 hours. The mixture was concentrated and the residue was partitioned between CH_2Cl_2 (200 ml) and water (100 ml). The organic portion was washed with 1N HCl (30 ml), 1N NaOH (30 ml), brine (50 ml), dried (K_2CO_3), concentrated, and purified by column chromatography (Hexanes gradient to EtOAc:Hexanes 3:100) to give **63** (1.82 g, 76%). ^{1}H-NMR ($CDCl_3$) δ 7.27 (m, 3H), 6.15 (m, 1H), 3.08 (m, 2H), 2.84 (m, 2H), 2.64 (m, 2H).

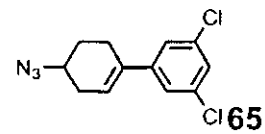
Step 2. Synthesis of **64**



64

A mixture of **63** (1.20 g, 4.98 mmol) and sodium borohydride (0.230 g, 6.08 mmol) in MeOH (50 ml) was stirred at 0°C for 2 hours. Water (2.5 ml) was added and the mixture was stirred for 30 minutes. The mixture was then concentrated and the residue was partitioned between CH_2Cl_2 (150 ml) and water (100 ml). The organic portion was dried (K_2CO_3) and concentrated to give **64** (1.15 g, 95%). ^{1}H-NMR ($CDCl_3$) δ 7.23 (m, 2H), 7.20 (m, 1H), 6.03 (m, 1H), 4.05 (m, 1H), 2.54 (m, 2H), 2.44 (m, 1H), 2.20 (m, 1H), 1.98 (m, 1H), 1.83 (m, 1H).

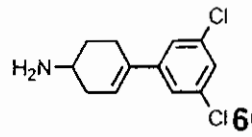
Step 3. Synthesis of **65**



65

To a solution of **64** (1.00 g, 4.12 mmol) and triphenylphosphine (1.13 g, 4.30 mmol) in THF (12 ml) in an ice-water bath were added diethyl azodicarboxylate (0.857 g, 4.92 mmol) and diphenylphosphoryl azide (1.30 g, 4.72 mmol). The ice-water bath was removed and the mixture was stirred at RT for 16 hours. The volatiles were removed under reduced pressure and the residue was taken up in CH_2Cl_2 (100 ml), washed with water and saturated sodium bicarbonate, dried (K_2CO_3), and purified by column chromatography (Hexanes) to give **65** (0.272 g, 25%). ^{1}H-NMR ($CDCl_3$) δ 7.23 (m, 3H), 6.04 (m, 1H), 3.76 (m, 1H), 2.54 (m, 2H), 2.45 (m, 1H), 2.30 (m, 1H), 2.07 (m, 1H), 1.88 (m, 1H).

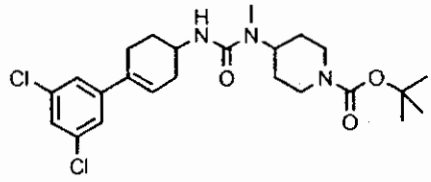
Step 4. Synthesis of **66**



66

A mixture of the **65** (0.300 g, 1.12 mmol) and 1M trimethylphosphine in toluene (2.24 ml) in EtOAc (5 ml) and water (100 μl) was stirred at RT for 16 hours. The mixture was evaporated to dryness and purified by column chromatography (2M NH_3/CH_3OH:CH_2Cl_2 1:20) to give **66** (0.266 g, 98%). MS m/e 242 $(M+H)^+$.

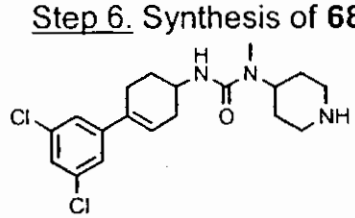
Step 5. Synthesis of **67**



67

To a mixture of **66** (0.266 g, 1.10 mmol) and N, N'-disuccinimidyl carbonate (0.338 g, 1.32 mmol) in THF (20 ml) in an ice-water bath was added pyridine (0.70 ml, 8.6 mmol). The mixture was stirred at 0°C for 30 minutes then at RT for 2 hours. A solution of 4-methylamino-1-Boc-piperidine (0.259 g, 1.21 mmol) in THF (5 ml) was added and the mixture was stirred at RT for 16 hours. The volatiles were removed under reduced pressure and the residue was partitioned between CH_2Cl_2 (100 ml) and 1N NaOH (50 ml). The organic portion was washed with water and brine, dried (K_2CO_3), concentrated, and purified by column chromatography (CH_2Cl_2 gradient to MeOH:CH_2Cl_2 1:50) to give **67** (0.520 g, 98%). ^{1}H-NMR ($CDCl_3$) δ 7.24 (m, 2H), 7.22 (m, 1H), 6.09 (m, 1H), 4.34 (m, 2H), 4.18 (m, 2H), 4.05 (m, 1H), 2.78 (m, 2H), 2.69 (s, 3H), 2.63 (m, 1H), 2.48 (m, 2H), 2.06 (m, 2H), 1.72 (m, 1H), 1.61 (m, 2H), 1.51 (m, 2H), 1.46 (s, 9H).

Step 6. Synthesis of **68**



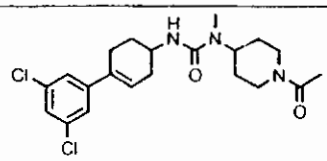
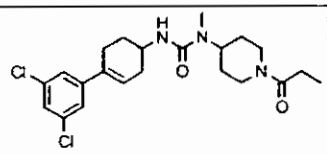
68

A solution of **67** (0.420 g, 0.871 mmol) in 4N HCl/dioxane (10 ml) and CH_2Cl_2 (10 ml) stirred at RT for 2 hours. The mixture was concentrated to give **68** (0.360 g, 99%). ^{1}H-NMR (CD_3OD) δ 7.34 (m, 2H), 7.27 (m, 1H), 6.16 (m, 1H), 4.34 (m, 1H), 3.89 (m, 1H), 3.48 (m, 2H), 3.10 (m, 2H), 2.81 (s, 3H), 2.52 (m, 3H), 1.6-2.3 (m, 7H).

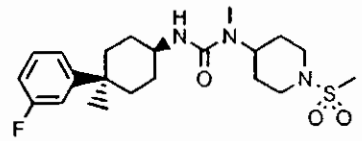
Step 7.

A solution of the **68** (0.050 g, 0.12 mmol), acetic anhydride (40 µl, 0.42 mmol), and triethylamine (200 µl, 1.42 mmol) in CH_2Cl_2 (5 ml) was stirred at RT for 4 hours. The mixture was evaporated to dryness and purified by PTLC (CH_3OH:CH_2Cl_2 1:10) to give **11A** (0.038 g, 75%).

Using essentially the same procedure, **11B** was prepared.

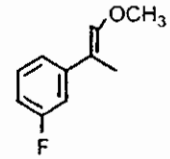
Example		^{1}H NMR	MS $(M+H)^+$
11A		($CDCl_3$) δ 7.24 (m, 2H), 7.22 (m, 1H), 6.09 (m, 1H), 4.73 (m, 1H), 4.47 (m, 1H), 4.32 (m, 1H), 4.04 (m, 1H), 3.86 (m, 1H), 3.14 (m, 1H), 2.68 (s, 3H), 2.4-2.65 (m, 4H), 2.10 (s, 3H), 2.06 (m, 2H), 1.69 (m, 3H), 1.52 (m, 2H).	424
11B		($CDCl_3$) δ 7.23 (m, 2H), 7.20 (m, 1H), 6.07 (m, 1H), 4.74 (m, 1H), 4.46 (m, 1H), 4.34 (m, 1H), 4.04 (m, 1H), 3.90 (m, 1H), 3.08 (m, 1H), 2.67 (s, 3H), 2.4-2.65 (m, 4H), 2.34 (q, J=7.2 Hz, 2H), 2.06 (m, 2H), 1.69 (m, 3H), 1.49 (m, 2H), 1.13 (t, J=7.2 Hz, 3H).	438

Example **12A**



12A

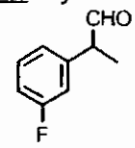
Step 1. Synthesis of **69**



69

To a suspension of methoxymethylenetriphenylphosphonium chloride (16.4 g, 47.8 mmol) in THF (30 ml) in an ice-water bath was added potassium t-butoxide (6.72 g, 60.0 mmol) in t-butanol (40 ml). The mixture was stirred at 0°C for 1 hour. 3'-Fluoroacetophenone (5.00 g, 36.2 mmol) was added and the mixture was stirred at RT for 3 hours. The reaction was diluted with water (100 ml) and extracted wit ether (2x100 ml). The organic portion was washed with brine, dried ($MgSO_4$), concentrated, and purified by column chromatography (Hexanes) to give **69** (4.80 g, 80%). ^{1}H-NMR ($CDCl_3$) δ 7.2-7.5 (m, 2H), 7.08 (m, 0.5H), 6.99 (m, 0.5H), 6.86 (m, 1H), 6.46 (m, 0.5H), 6.16 (m, 0.5H), 3.74 (s, 1.5H), 3.71 (s, 1.5H), 1.97 (m, 1.5H), 1.91 (m, 1.5H).

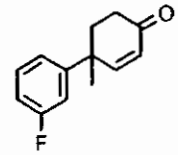
Step 2. Synthesis of **70**



70

A solution of **69** (4.80 g, 28.9 mmol) and p-toluenesulfonic acid (0.338 g, 1.78 mmol) in dioxane (90 ml) and water (18 ml) was refluxed for 20 hours. The mixture was diluted with water (100 ml) and extracted with ether (2x200 ml). The combined organic portion was washed with brine, dried ($MgSO_4$), and purified by column chromatography (Hexanes gradient to EtOAc:Hexanes 1:100) to give **70** (1.90 g, 43%). ^{1}H-NMR ($CDCl_3$) δ 9.68 (d, J=1.6 Hz, 1H), 7.35 (m, 1H), 7.01 (m, 2H), 6.93 (m, 1H), 3.64 (m, 1H), 1.45 (d, J=7.6 Hz, 3H).

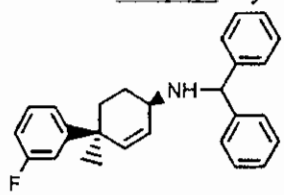
Step 3. Synthesis of **71**



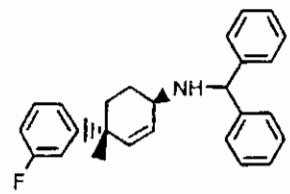
71

To a solution of **70** (1.90 g, 12.5 mmol) in EtOH (120 ml) and ether (60 ml) in an ice-water bath were added potassium hydroxide (0.21 g, 3.7 mmol) and methyl vinyl ketone (1.31 g, 18.7 mmol). The mixture was then warmed to RT and stirred for 16 hours. The mixture was neutralized with 5% citric acid, concentrated, and partitioned between CH_2Cl_2 (2x150 ml) and aqueous sodium bicarbonate. The combined organic portion was washed with brine, dried ($MgSO_4$), and purified by column chromatography (Hexanes gradient to EtOAc:Hexanes 1:20) to give **71** (2.00 g, 78%). MS m/e 205 $(M+H)^+$.

Step 4. Synthesis of **72** and **73**



72



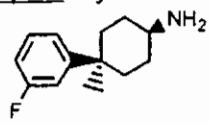
73

A mixture of **71** (1.02 g, 5.00 mmol), aminodiphenylmethane (1.10 g, 6.00 mmol), and sodium triacetoxyborohydride (2.56 g, 12.1 mmol) in dichloroethane (150 ml) was stirred at RT for 48 hours. The mixture was diluted with CH_2Cl_2 (150 ml) and washed with conc. NH_4OH (100 ml). The organic portion was washed with brine, dried (K_2CO_3), and purified by column chromatography (Hexanes gradient to EtOAc:Hexanes 1:200) to give **72** (0.960 g, 52%) and **73** (0.320 g, 18%).

72 ^{1}H-NMR ($CDCl_3$) δ 7.42 (m, 3H), 7.0-7.35 (m, 10H), 6.86 (m, 1H), 5.97 (m, 1H), 5.70 (m, 1H), 5.06 (s, 1H), 3.11 (m, 1H), 1.90 (m, 2H), 1.57 (m, 2H), 1.31 (s, 3H), 1.21 (m, 1H).

73 ^{1}H-NMR ($CDCl_3$) δ 7.42 (m, 3H), 7.15-7.35 (m, 8H), 7.05 (m, 2H), 6.85 (m, 1H), 5.97 (m, 1H), 5.70 (m, 1H), 5.06 (s, 1H), 3.09 (m, 1H), 1.4-2.0 (m, 4H), 1.38 (s, 3H), 1.21 (m, 1H).

Step 5. Synthesis of **74**



74

A mixture of **72** (0.660 g, 1.78 mmol), ammonium formate (1.90 g, 30.2 mmol), and 10% Pd/C (0.120 g) in CH_3OH (50 ml) was stirred at RT for 2 days. The mixture was filtered and concentrated. The residue was taken up in CH_2Cl_2 (150 ml) and washed with conc. NH_4OH (20 ml), saturated sodium bicarbonate, and brine. The organic portion was dried (K_2CO_3), concentrated, and purified by column chromatography (CH_2Cl_2 gradient to 2M NH_3/CH_3OH: CH_2Cl_2 1:20) to give **74** (0.400 g, 100%). MS m/e 208 $(M+H)^+$.

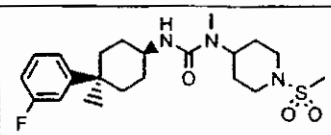
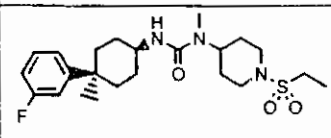
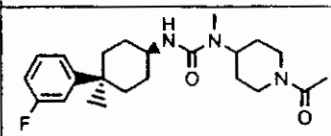
Step 6.

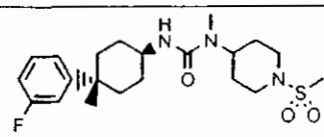
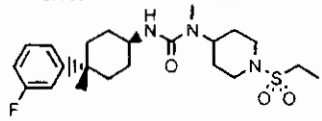
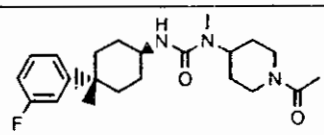
To an ice-cooled solution of **74** (0.041 g, 0.20 mmol) and pyridine (200 µl, 2.45 mmol) in THF (5 ml) was added N, N'-disuccinimidyl carbonate (0.072 g, 0.28 mmol). The mixture was stirred at RT for 6 hours. N-Methyl-1-(methylsulfonyl)-4-piperidineamine (0.042 g, 0.22 mmol) was added at 0°C and the mixture was stirred at RT for 16 hours. The mixture was diluted with CH_2Cl_2 (50 ml) and washed with 1N NaOH (20 ml), 1N HCl (20 ml), saturated sodium bicarbonate, and brine sequentially.

The organic portion was dried ($MgSO_4$), concentrated, and purified by PTLC (CH_3OH: CH_2Cl_2 1:20) to give **12A** (0.045 g, 53%).

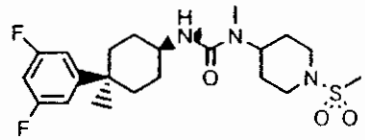
Using essentially the same procedure, **12B** and **12C** were prepared from **74**.

Using essentially the same procedure, **12D**, **12E**, and **12F** were prepared from **73**.

Example		^{1}H NMR	MS $(M+H)^+$
12A		($CDCl_3$) δ 7.30 (m, 1H), 7.14 (m, 1H), 7.05 (m, 1H), 6.89 (m, 1H), 4.34 (m, 1H), 4.02 (m, 1H), 3.86 (m, 2H), 3.74 (m, 1H), 2.77 (s, 3H), 2.72 (m, 2H), 2.61 (s, 3H), 2.29 (m, 2H), 1.85 (m, 2H), 1.5-1.8 (m, 6H), 1.14 (s, 3H), 1.10 (m, 2H).	426
12B		($CDCl_3$) δ 7.30 (m, 1H), 7.14 (m, 1H), 7.05 (m, 1H), 6.89 (m, 1H), 4.33 (m, 1H), 4.03 (m, 1H), 3.87 (m, 2H), 3.74 (m, 1H), 2.94 (q, J=7.4 Hz, 2H), 2.84 (m, 2H), 2.60 (s, 3H), 2.28 (m, 2H), 1.85 (m, 2H), 1.5-1.8 (m, 6H), 1.34 (t, J=7.4 Hz, 3H), 1.14 (s, 3H), 1.10 (m, 2H).	440
12C		($CDCl_3$) δ 7.30 (m, 1H), 7.14 (m, 1H), 7.05 (m, 1H), 6.89 (m, 1H), 4.70 (m, 1H), 4.40 (m, 1H), 4.01 (m, 1H), 3.83 (m, 1H), 3.74 (m, 1H), 3.11 (m, 1H), 2.57 (s, 3H), 2.54 (m, 1H), 2.28 (m, 2H), 2.08 (s, 3H), 1.87 (m, 2H), 1.4-1.8 (m, 6H), 1.14 (s, 3H), 1.10 (m, 2H).	390

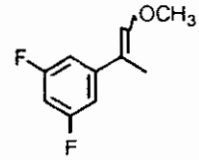
12D		($CDCl_3$) δ 7.27 (m, 1H), 7.15 (m, 1H), 7.06 (m, 1H), 6.88 (m, 1H), 4.40 (m, 1H), 4.31 (m, 1H), 3.88 (m, 2H), 3.68 (m, 1H), 2.79 (s, 3H), 2.76 (m, 2H), 2.74 (s, 3H), 1.4-2.0 (m, 11H), 1.26 (s, 3H), 1.20 (m, 1H).	426
12E		($CDCl_3$) δ 7.27 (m, 1H), 7.15 (m, 1H), 7.06 (m, 1H), 6.88 (m, 1H), 4.40 (m, 1H), 4.29 (m, 1H), 3.91 (m, 2H), 3.66 (m, 1H), 2.96 (q, J=7.4 Hz, 2H), 2.86 (m, 2H), 2.73 (s, 3H), 1.92 (m, 2H), 1.81 (m, 4H), 1.71 (m, 4H), 1.49 (m, 2H), 1.36 (t, J=7.4 Hz, 3H), 1.26 (s, 3H).	440
12F		($CDCl_3$) δ 7.27 (m, 1H), 7.15 (m, 1H), 7.06 (m, 1H), 6.88 (m, 1H), 4.73 (m, 1H), 4.47 (m, 1H), 4.28 (m, 1H), 3.86 (m, 1H), 3.68 (m, 1H), 3.14 (m, 1H), 2.71 (s, 3H), 2.57 (m, 1H), 2.10 (s, 3H), 1.93 (m, 2H), 1.81 (m, 3H), 1.68 (m, 3H), 1.51 (m, 4H), 1.26 (s, 3H).	390

Example **13A**



13A

Step 1. Synthesis of **75**

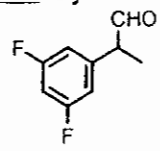


75

To an ice-cooled suspension of methoxymethylenetriphenylphosphonium chloride (13.2 g, 38.4 mmol) in THF (30 ml) was added potassium t-butoxide (5.38 g,

48.0 mmol) in t-butanol (40 ml). The mixture was stirred at 0°C for 1.5 hours. 3',5'-Difluoroacetophenone (5.00 g, 32.0 mmol) was added and the mixture was stirred at RT for 16 hours. The reaction was diluted with water (100 ml) and extracted with ether (2x200 ml). The organic portion was washed with brine, dried (Na_2SO_4), concentrated, and purified by column chromatography (Hexanes) to give **75** (4.80 g, 68%). ^{1}H-NMR ($CDCl_3$) δ 7.17 (m, 1H), 6.79 (m, 1H), 6.61 (m, 1H), 6.49 (m, 0.5H), 6.20 (m, 0.5H), 3.75 (s, 1.5H). 3.73 (s, 1.5H), 1.93 (m, 1.5H), 1.88 (m, 1.5H).

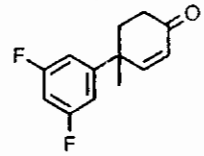
Step 2. Synthesis of **76**



76

A solution of **75** (4.80 g, 26.1 mmol) and p-toluenesulfonic acid (0.338 g, 1.78 mmol) in dioxane (90 ml) and water (18 ml) was refluxed for 20 hours. The mixture was diluted with water (100 ml) and extracted with ether (2x200 ml). The combined organic portion was washed with brine, dried (Na_2SO_4), filtered and purified by column chromatography (Hexanes gradient to EtOAc:Hexanes 1:100) to give **76** (1.80 g, 41%). ^{1}H-NMR ($CDCl_3$) δ 9.66 (d, J=1.2 Hz, 1H), 6.74 (m, 3H), 3.63 (m, 1H), 1.45 (d, J=6.8 Hz, 3H).

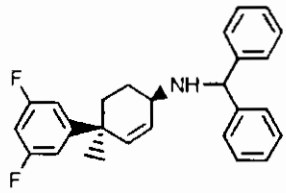
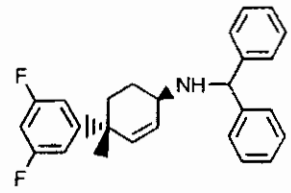
Step 3. Synthesis of **77**



77

To a solution of **76** (1.80 g, 10.6 mmol) in EtOH (120 ml) and ether (60 ml) in an ice-water bath were added potassium hydroxide (0.178 g, 3.17 mmol) and methyl vinyl ketone (1.11 g, 15.8 mmol). The mixture was then warmed to RT and stirred for 16 hours. The mixture was neutralized with 5% citric acid, concentrated, and partitioned between CH_2Cl_2 (2x150 ml) and aqueous sodium bicarbonate. The combined organic portion was washed with brine, dried (Na_2SO_4), and purified by column chromatography (Hexanes gradient to EtOAc:Hexanes 1:20) to give **77** (1.50 g, 64%). MS m/e 223 $(M+H)^+$.

Step 4. Synthesis of **78** and **79**

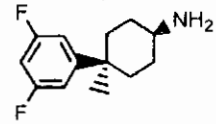
78 **79**

A mixture of **77** (1.50 g, 6.76 mmol), aminodiphenylmethane (1.49 g, 8.11 mmol), and sodium triacetoxyborohydride (3.46 g, 16.4 mmol) in dichloroethane (150 ml) was stirred at RT for 18 hours. The mixture was diluted with CH_2Cl_2 (150 ml) and washed with conc. NH_4OH (100 ml). The organic portion was dried (K_2CO_3) and purified by column chromatography (Hexanes gradient to EtOAc:Hexanes 1:33) to give **78** (0.440 g, 16%) and **79** (0.322 g, 12%).

78 ^{1}H-NMR ($CDCl_3$) δ 7.42 (m, 4H), 7.30 (m, 4H), 7.21 (m, 2H), 6.87 (m, 2H), 6.62 (m, 1H), 5.98 (m, 1H), 5.67 (m, 1H), 5.06 (s, 1H), 3.12 (m, 1H), 1.88 (m, 2H), 1.60 (m, 1H), 1.29 (s, 3H), 1.20 (m, 2H).

79 ^{1}H-NMR ($CDCl_3$) δ 7.46 (m, 4H), 7.32 (m, 4H), 7.23 (m, 2H), 6.83 (m, 2H), 6.62 (m, 1H), 5.99 (m, 1H), 5.69 (m, 1H), 5.08 (s, 1H), 3.10 (m, 1H), 1.70 (m, 4H), 1.50 (m, 1H), 1.38 (s, 3H).

Step 5. Synthesis of **80**



80

A mixture of **78** (0.440 g, 1.13 mmol), ammonium formate (1.30 g, 20.7 mmol), and 10% Pd/C (0.090 g) in CH_3OH (30 ml) was stirred at RT for 16 hours. The mixture was filtered and concentrated. The residue was taken up in CH_2Cl_2 (100 ml), washed with conc. NH_4OH (20 ml), dried (K_2CO_3), concentrated, and purified by column chromatography (CH_2Cl_2 gradient to 2M NH_3/CH_3OH: CH_2Cl_2 1:20) to give **80** (0.200 g, 79%). ^{1}H-NMR ($CDCl_3$) δ 6.87 (m, 2H), 6.61 (m, 1H), 2.73 (m, 1H), 2.21 (m, 2H), 1.73 (m, 2H), 1.50 (m, 2H), 1.12 (s, 3H), 1.07 (m, 4H).

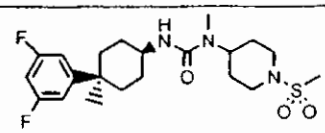
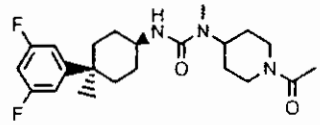
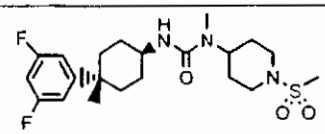
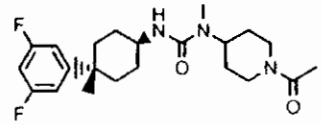
Step 6

To an ice-cooled solution of **80** (0.045 g, 0.20 mmol) and pyridine (200 μl, 2.45 mmol) in THF (5 ml) was added N, N'-disuccinimidyl carbonate (0.072 g, 0.28 mmol). The mixture was stirred at RT for 4 hours. N-Methyl-1-(methylsulfonyl)-4-piperidineamine (0.042 g, 0.22 mmol) was added at 0°C and the mixture was stirred at RT for 16 hours. The mixture was diluted with CH_2Cl_2 (50 ml) and washed with 1N NaOH (20 ml), 1N HCl (20 ml), saturated sodium bicarbonate, and brine sequentially.

The organic portion was dried ($MgSO_4$), concentrated, and purified by PTLC (CH_3OH: CH_2Cl_2 1:20) to give **13A** (0.005 g, 6%).

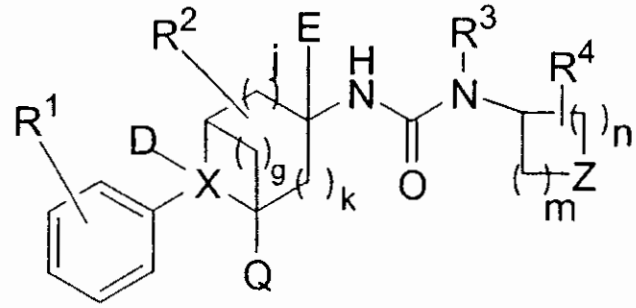
Using essentially the same procedure, **13B** was prepared from **80**.

Using essentially the same procedure, **13C** and **13D** were prepared from **79**.

Example		^{1}H NMR	MS $(M+H)^+$
13A		($CDCl_3$) δ 6.87 (m, 2H), 6.64 (m, 1H), 4.34 (m, 1H), 4.05 (m, 1H), 3.86 (m, 2H), 3.72 (m, 1H), 2.77 (s, 3H), 2.72 (m, 2H), 2.62 (s, 3H), 2.22 (m, 2H), 1.87 (m, 2H), 1.5-1.8 (m, 6H), 1.13 (s, 3H), 1.10 (m, 2H).	444
13B		($CDCl_3$) δ 6.85 (m, 2H), 6.64 (m, 1H), 4.69 (m, 1H), 4.40 (m, 1H), 4.03 (m, 1H), 3.84 (m, 1H), 3.73 (m, 1H), 3.11 (m, 1H), 2.59 (s, 3H), 2.55 (m, 1H), 2.22 (m, 2H), 2.08 (s, 3H), 1.87 (m, 2H), 1.4-1.7 (m, 6H), 1.13 (s, 3H), 1.09 (m, 2H).	408
13C		($CDCl_3$) δ 6.87 (m, 2H), 6.63 (m, 1H), 4.39 (m, 1H), 4.29 (m, 1H), 3.89 (m, 2H), 3.66 (m, 1H), 2.79 (s, 3H), 2.76 (m, 2H), 2.74 (s, 3H), 1.94 (m, 2H), 1.6-1.9 (m, 8H), 1.48 (m, 2H), 1.25 (s, 3H).	444
13D		($CDCl_3$) δ 6.87 (m, 2H), 6.63 (m, 1H), 4.74 (m, 1H), 4.47 (m, 1H), 4.27 (m, 1H), 3.87 (m, 1H), 3.68 (m, 1H), 3.14 (m, 1H), 2.70 (s, 3H), 2.58 (m, 1H), 2.10 (s, 3H), 1.94 (m, 2H), 1.4-1.9 (m, 10H), 1.25 (s, 3H).	408

What is claimed is:

1. A compound represented by the structural formula



I

or a pharmaceutically acceptable salt or solvate thereof, wherein:

X is independently N or C;

Z is independently NR^8 or CR^3R^9;

D is independently H, -OH, -alkyl or substituted -alkyl with the proviso that when X is N, D and the X-D bond are absent;

E is independently H, -alkyl or substituted –alkyl, or D and E can independently be joined together via a $-(CH_2)_p-$ bridge;

Q is independently H, -alkyl or substituted –alkyl, or D, X, Q and the carbon to which Q is attached can jointly form a 3 to 7-membered ring;

g, j, k, m and n can be the same or different and are independently selected;

g is 0 to 3 and when g is 0, the carbons to which $(CH_2)_g$ is shown connected are no more linked;

j and k are independently 0 to 3 such that the sum of j and k is 0, 1, 2 or 3;

m and n are independently 0 to 3 such that the sum of m and n is 1, 2,3, 4 or 5;

p is 1 to 3;

R^1 is 1 to 5 substituents which can be the same or different, each R^1 being independently selected from the group consisting of hydrogen, hydroxy, halogen, haloalkyl, -alkyl, substituted –alkyl, -cycloalkyl, CN, alkoxy, cycloalkoxy, alkylthio, cycloalkylthio, $-NR^5R^6$, $-NO_2$, $-CONR^5R^6$, $-NR^5COR^6$, $-NR^5CONR^5R^6$ where the two R^5 moieties can be the same or different, $-NR^6C(O)OR^7$, $-C(O)OR^6$, $-SOR^7$, $-SO_2R^7$, $-SO_2NR^5R^6$, aryl and heteroaryl;

R^2 is 1 to 6 substituents which can be the same or different, each R^2 being independently selected from the group consisting of hydrogen, -alkyl, substituted –alkyl, alkoxy, and hydroxy, with the proviso that when X is N and R^2 is hydroxy or alkoxy, R^2 is not directly attached to a carbon adjacent to X;

R^3 is independently hydrogen, -alkyl or substituted -alkyl;

R^4 is 1 to 6 substituents which can be the same or different, each R^4 being independently selected from hydrogen, -alkyl, substituted –alkyl, alkoxy, and hydroxy, with the proviso that when Z is NR^8 and R^4 is hydroxy or alkoxy, R^4 is not directly attached to a carbon adjacent to the NR^8;

R^5 and R^6 are independently hydrogen, -alkyl, substituted -alkyl or -cycloalkyl;

R^7 is independently –alkyl, substituted -alkyl or -cycloalkyl;

R^8 is independently selected from the group consisting of hydrogen, -alkyl, substituted –alkyl, -cycloalkyl, -alkylcycloalkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, $-SO_2R^{10}$, $-SO_2NR^5R^{11}$, $-C(O)R^{11}$, $-C(O)NR^5R^{11}$ and $-C(O)OR^{10}$;

R^9 is independently hydrogen, -alkyl, substituted –alkyl, hydroxy, alkoxy, $-NR^5R^{11}$, aryl, or heteroaryl; or R^3 and R^9 can be joined together and with the carbon to which they are attached form a carbocyclic or heterocyclic ring having 3 to 7 ring atoms;

R^{10} is -alkyl, substituted –alkyl, -cycloalkyl, -alkylcycloalkyl, aryl or heteroaryl; and

R^{11} is independently hydrogen, -alkyl, substituted –alkyl, -cycloalkyl, aryl or heteroaryl.

2. The compound of claim 1 or a pharmaceutically acceptable salt or solvate thereof, wherein

R^1 is 1 to 5 substituents which can be the same or different, each R^1 being independently selected from the group consisting of Cl, Br, I or F;

X is N;

D is absent and the X-D bond is absent;

E is H;

g is 0;

j is 1;

k is 1;

m is 2;

n is 2;

R^2 is H;

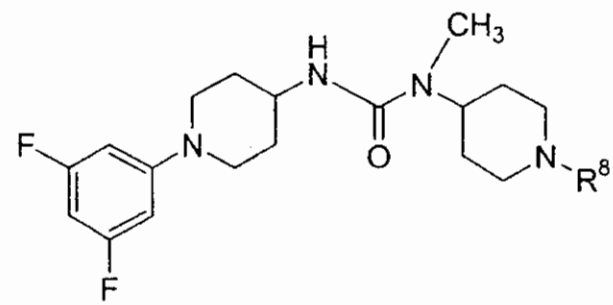
R^3 is methyl;

R^4 is H;

and

Z is NR^8, where R^8 is independently selected from the group consisting of hydrogen, -alkyl, substituted –alkyl, -cycloalkyl, -alkylcycloalkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, $-SO_2R^{10}$, $-SO_2NR^5R^{11}$, $-C(O)R^{11}$, $-C(O)NR^5R^{11}$ and $-C(O)OR^{10}$.

3. A compound represented by the structural formula



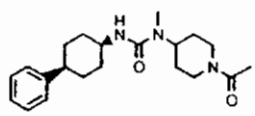
II

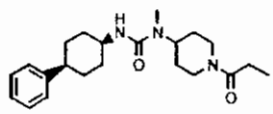
or a pharmaceutically acceptable salt or solvate thereof, wherein R^8 is defined in the following table:

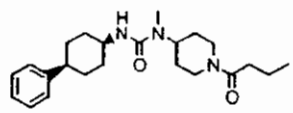
R^8
$-COCH_3$

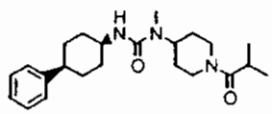
$-COCH_2CH_3$
—CO—
$-COCH(CH_3)_2$
$-CO(CH_2)_2CH_3$
$-COOC(CH_3)_3$
$-SO_2CH_3$
$SO_2CH_2CH_3$
—SO_2—
$-SO_2CH(CH_3)_2$
$-SO_2(CH_2)_2CH_3$
$-SO_2Ph$

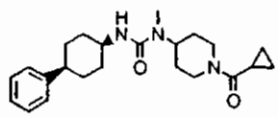
4. A compound of claim 1 selected from the group consisting of

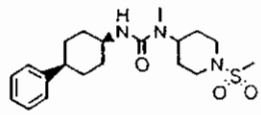


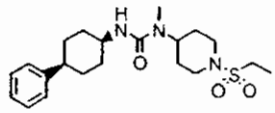


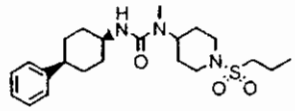


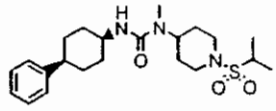




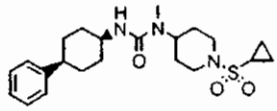






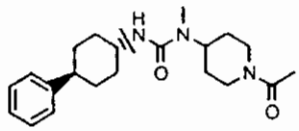


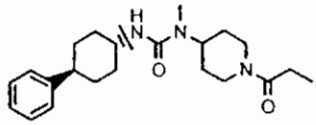
and

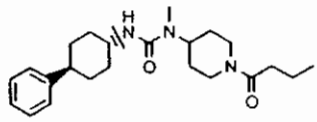


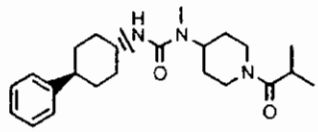
or a pharmaceutically acceptable salt or solvate of said compound.

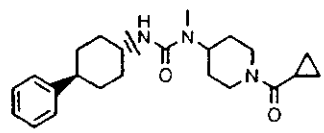
5. A compound of claim 1 selected from the group consisting of

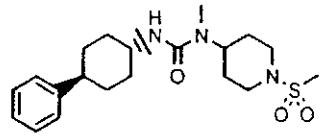


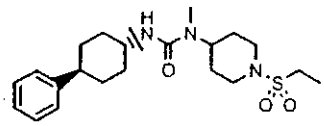


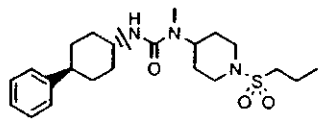


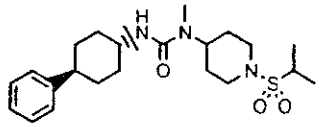


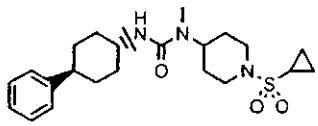


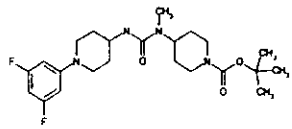


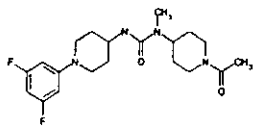


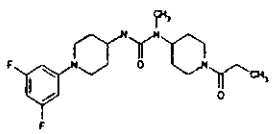


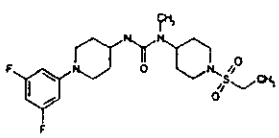


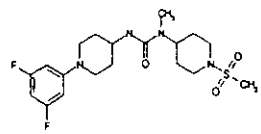


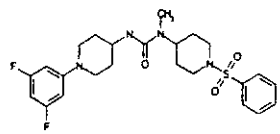


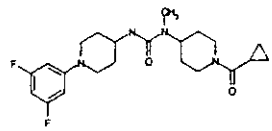


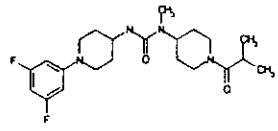


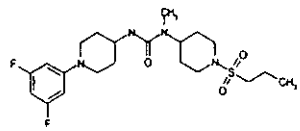


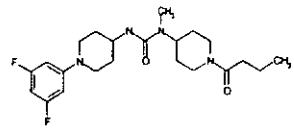


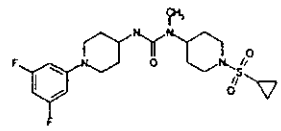


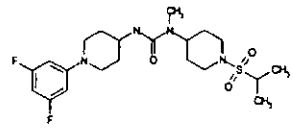


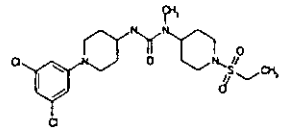


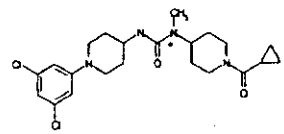


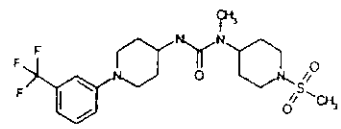


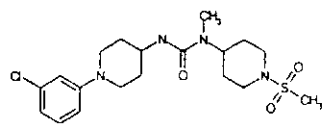


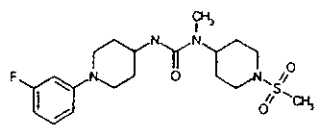


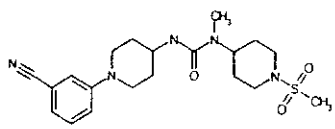


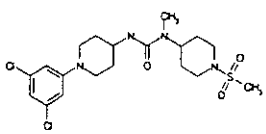


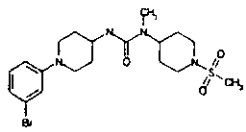


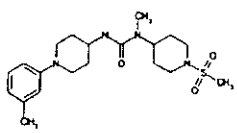


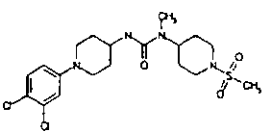


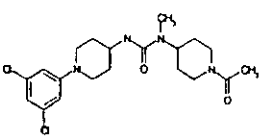


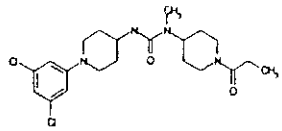


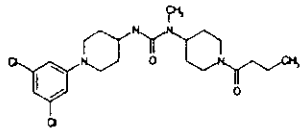


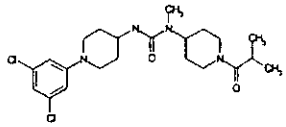


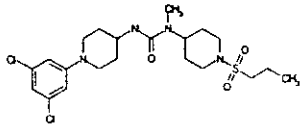


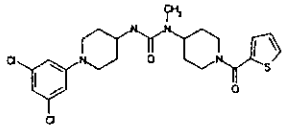


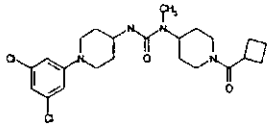


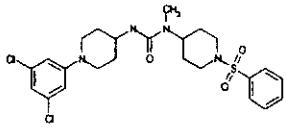


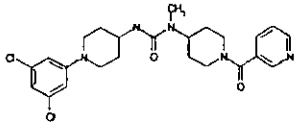


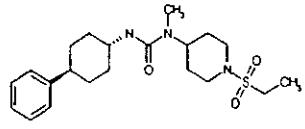


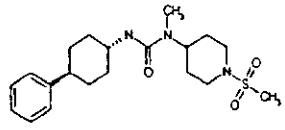


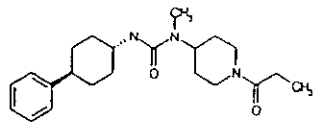


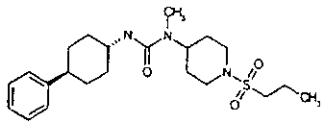


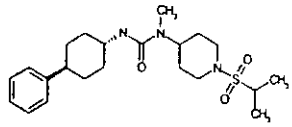


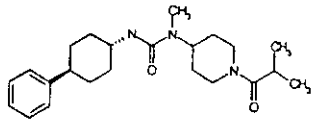


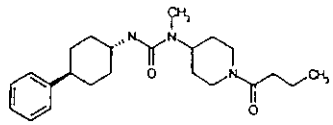


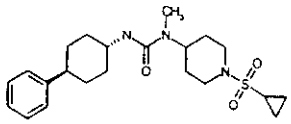


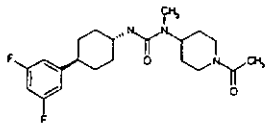


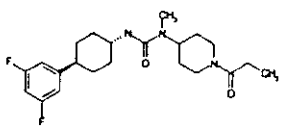


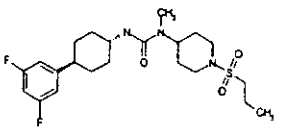


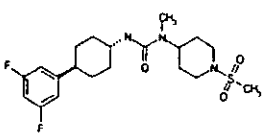


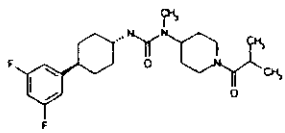


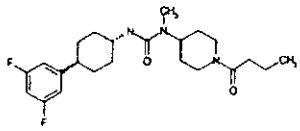


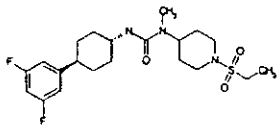


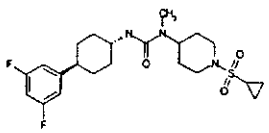


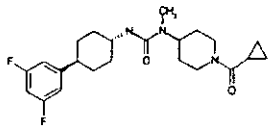


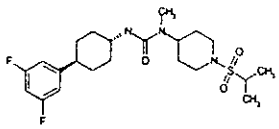


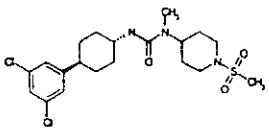


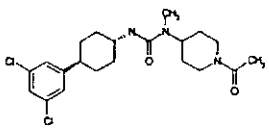


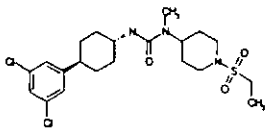


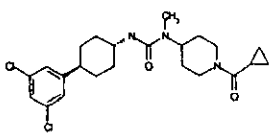


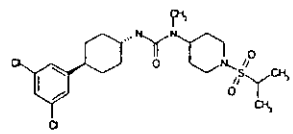


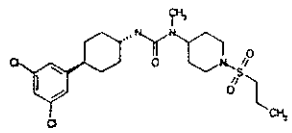


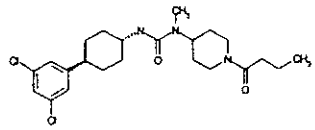


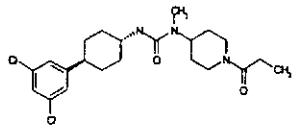


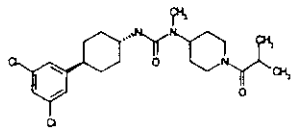


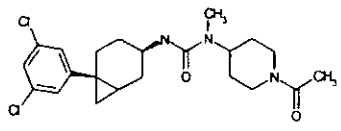


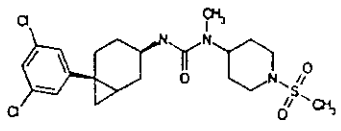


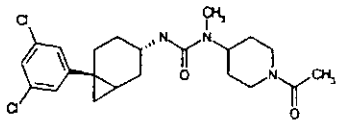


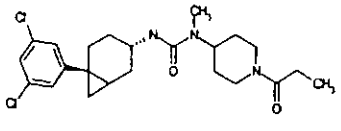


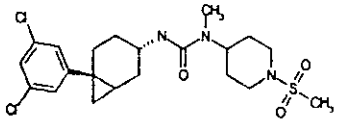


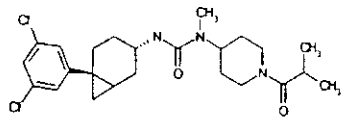


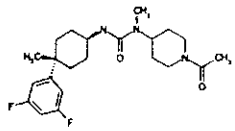


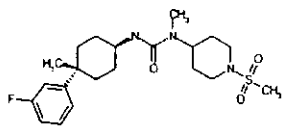


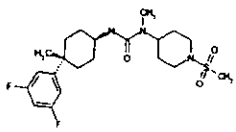


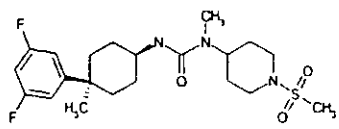


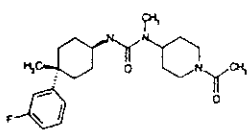


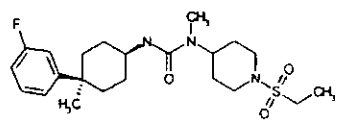


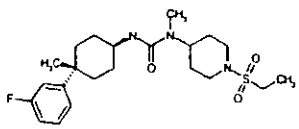


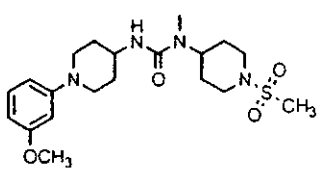


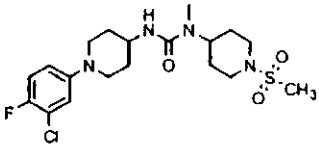


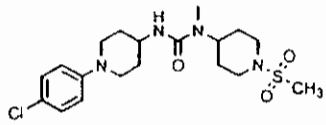


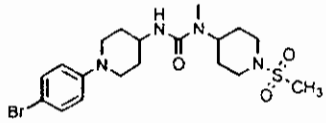


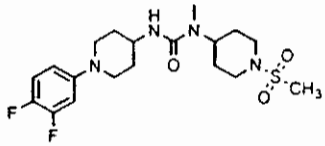


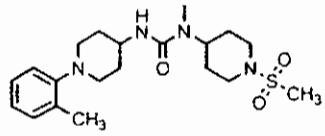


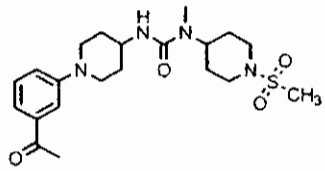


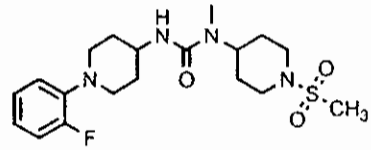


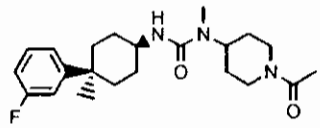


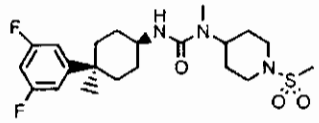


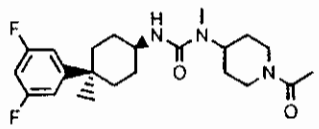


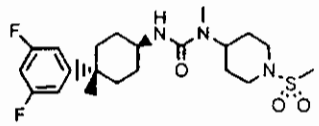




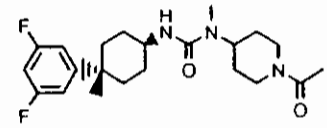






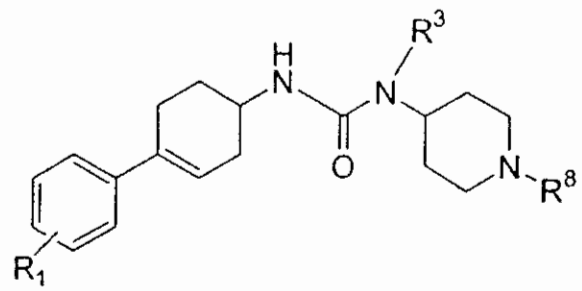


and



or a pharmaceutically acceptable salt or solvate of said compound.

6. A compound represented by the structural formula



III

or a pharmaceutically acceptable salt or solvate thereof, wherein

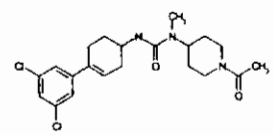
R^1 is 1 to 5 substituents which can be the same or different, each R^1 being independently selected from the group consisting of hydrogen, hydroxy, halogen, haloalkyl, -alkyl, substituted –alkyl, -cycloalkyl, CN, alkoxy, cycloalkoxy, alkylthio, cycloalkylthio, $-NR^5R^6$, $-NO_2$, $-CONR^5R^6$, $-NR^5COR^6$, $-NR^5CONR^5R^6$ where the two R^5 moieties can be the same or different, $-NR^6C(O)OR^7$, $-C(O)OR^6$, $-SOR^7$, $-SO_2R^7$, $-SO_2NR^5R^6$, aryl and heteroaryl;

R^3 is independently hydrogen or –alkyl;

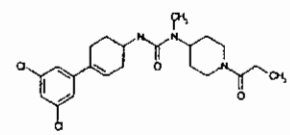
and

R^8 is independently selected from the group consisting of hydrogen, -alkyl, substituted –alkyl, -cycloalkyl, -alkylcycloalkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, $-SO_2R^{10}$, $-SO_2NR^5R^{11}$, $-C(O)R^{11}$, $-C(O)NR^5R^{11}$ and $-C(O)OR^{10}$.

7. A compound of claim 6 selected from the group consisting of

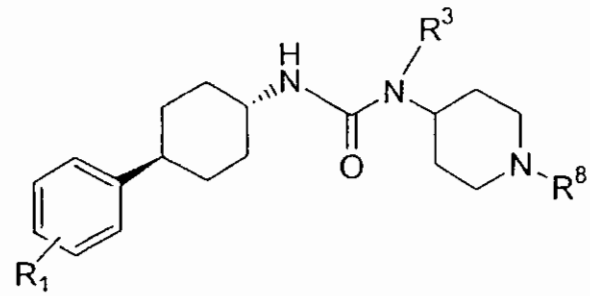


and



or a pharmaceutically acceptable salt or solvate of said compound.

8. A compound represented by the structural formula



IV

or a pharmaceutical acceptable salt or solvate there of, wherein

R^1 is 1 to 5 substituents which can be the same or different, each R^1 being independently selected from the group consisting of hydrogen, hydroxy, halogen, haloalkyl, -alkyl, substituted -alkyl, -cycloalkyl, CN, alkoxy, cycloalkoxy, alkylthio, cycloalkylthio, $-NR^5R^6$, $-NO_2$, $-CONR^5R^6$, $-NR^5COR^6$, $-NR^5CONR^5R^6$ where the two R^5 moieties can be the same or different, $-NR^6C(O)OR^7$, $-C(O)OR^6$, $-SOR^7$, $-SO_2R^7$, $-SO_2NR^5R^6$, aryl and heteroaryl;

R^3 is independently hydrogen or -alkyl;

And

R^8 is independently selected from the group consisting of hydrogen, -alkyl, substituted -alkyl, -cycloalkyl, -alkylcycloalkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, SO_2R^{10}, $-SO_2NR^5R^{11}$, $-C(O)R^{11}$, $-C(O)NR^5R^{11}$ and $-C(O)OR^{10}$.

9. A pharmaceutical composition comprising a therapeutically effective amount of a compound of claim 1 in combination with a pharmaceutically acceptable carrier.

10. Use of an effective amount of a compound of claim 1 for the preparation of a medicament for treating a metabolic disorder, eating disorder or diabetes in a mammal.

11. A pharmaceutical composition, which comprises an effective amount of a compound as, defined in claim 1 and a pharmaceutical acceptable carrier thereof.

12. Use of a therapeutically effective amount of a compound of claim 1 or a pharmaceutically acceptable salt of said compound for the preparation of a medicament for treating metabolic or eating disorders in a mammal.

13. The use of claim 10 wherein said metabolic disorder is obesity.

14. The use of claim 10 wherein said eating disorder is hyperphagia.

15. Use of a therapeutically effective amount of a compound of claim 1 or a pharmaceutical acceptable salt of said compound for the preparation of a medicament for treating disorders associated with obesity in a mammal.

16. The use of claim 15 wherein said disorders associated with obesity are Type II Diabetes, insulin resistance, hyperlipidemia and hypertension.

17. A pharmaceutical composition which comprises a therapeutically effective amount of a composition comprising:

a first compound, said first compound being a compound of claim 1 or a pharmaceutical acceptable salt of said compound;

a second compound, said second compound being an anti-obesity and/or anorectic agent such as a β_3 agonist, a thryomimetic agent, an anorectic agent or an NPY antagonist; and

a pharmaceutical acceptable carrier thereof.

18. Use of an amount of a first compound, said first compound being a compound of claim 1 or a pharmaceutical acceptable salt of said compound;

a second compound, said second compound being an antiobesity and/or anorectic agent such as a β_3 agonist, a thryomimetic agent, an anorectic agent or an NPY antagonist;

wherein the amounts of the first and second compounds result in a therapeutic effect for the preparation of a medicament for treating a metabolic or eating disorder in a mammal.

19. A pharmaceutical composition which comprises a therapeutically effective amount of a composition comprising:

a first compound, said first compound being a compound of claim 1 or a pharmaceutical acceptable salt of said compound;

a second compound, said second compound being an aldose reductase inhibitor, a glycogen phosphorylase inhibitor, a sorbitol dehydrogenase inhibitor, a protein tyrosine phosphatase 1B inhibitor, a dipeptidyl protease inhibitor, insulin (including orally bioavailable insulin preparations), an insulin mimetic, metformin, acarbose, a PPAR-gamma ligand such as troglitazone, rosaglitazone, pioglitazone, or GW-1929, a sulfonylurea, glipazide, glyburide, or chlorpropamide; and

a pharmaceutically acceptable carrier therefor.

20. A pharmaceutical composition made by combining the compound of claim 1 and a pharmaceutical acceptable carrier therefor.

21. A process for making a pharmaceutical composition comprising combining a compound of claim 1 and a pharmaceutically acceptable carrier.