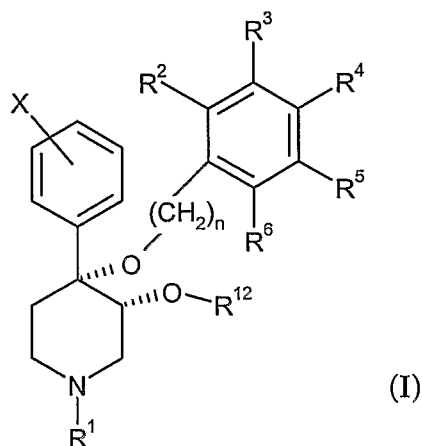


Substituted piperidines as novel MDM2-p53 inhibitors

The present invention provides a novel series of piperidines with *cis*-3,4-dialkoxy substitutions represented by formula (I):



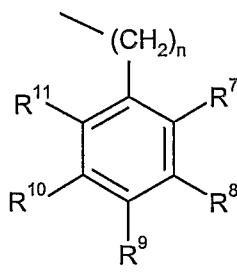
and the pharmaceutically acceptable salts thereof; wherein

5 n is an integer independently selected from 1 or 2;

X is halogen;

R¹ is selected from the group consisting of hydrogen, carbonyl, sulfonyl, lower alkyl, and lower alkyl substituted by carbonyl, sulfonyl, or hydroxy;

10 R¹² is selected from the group consisting of alkyl or alkenyl having from 1 to about 5 carbon atoms, and



wherein R⁷ to R¹¹ are independently selected from the group consisting of hydrogen, halogen, -CN, -NO₂, CF₃, -OCH₃, -COOCH₃, and -C₆H₅;

R² to R⁶ are independently selected from the group consisting of hydrogen, halogen, lower alkyl, -C(CH₃)₃, CF₃, -OCH₃, -NO₂, and -CN;

and in case R¹² is alkyl or alkenyl having from 1 to about 5 carbon atoms, R² to R⁶ are hydrogen.

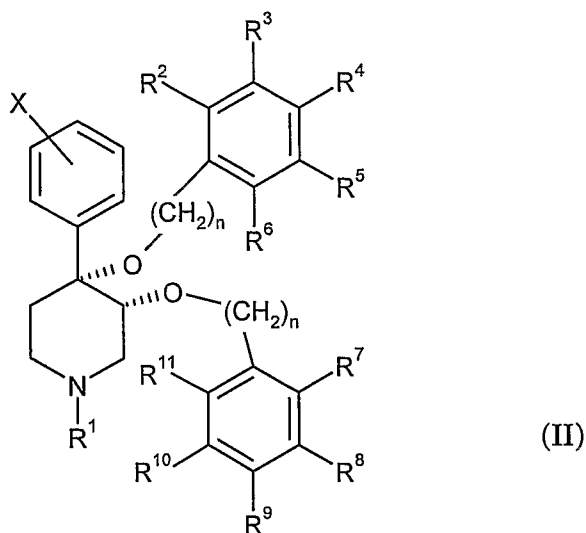
5 The compounds of formula I are small molecule inhibitors of MDM2-p53 interaction. These compounds are useful in the treatment or control of cancer.

p53 is a tumor suppressor protein that plays a central role in protection against the development of cancer. p53 guards cellular integrity and prevents the propagation of permanently damaged clones of cells by the induction of growth arrest or apoptosis. At
10 the molecular level, p53 is a transcription factor that can activate a panel of genes implicated in the regulation of cell cycle and apoptosis. p53 is a potent cell cycle inhibitor, which is tightly regulated by MDM2 at the cellular level. MDM2 and p53 form a feedback control loop. MDM2 can bind p53 and inhibit its ability to transactivate p53-regulated genes. In addition, MDM2 mediates the ubiquitin-dependent degradation of
15 p53. p53 can activate the expression of the MDM2 gene, thus raising the cellular level of MDM2 protein. This feedback control loop insures that both MDM2 and p53 are kept at a low level in normal proliferating cells. MDM2 is also a cofactor for E2F, which plays a central role in cell cycle regulation.

The ratio of MDM2 to p53 (E2F) is dysregulated in many cancers. Frequently
20 occurring molecular defects in the p16INK4/p19ARF locus, for instance, have been shown to affect MDM2 protein degradation. Inhibition of MDM2-p53 interaction in tumor cells with wild-type p53 should lead to accumulation of p53, cell cycle arrest and/or apoptosis. MDM2 antagonists, therefore, can offer a novel approach to cancer
25 therapy as single agents or in combination with a broad spectrum of other antitumor therapies. The feasibility of this strategy has been shown by the use of different macromolecular tools for inhibition of MDM2-p53 interaction (e.g. antibodies, antisense oligonucleotides, peptides). MDM2 also binds E2F through a conserved binding region as p53 and activates E2F-dependent transcription of cyclin A, suggesting that MDM2 antagonists might have effects in p53 mutant cells.

30 The present invention provides a compound represented by formula (II):

- 3 -



and the pharmaceutically acceptable salts thereof; wherein

n is an integer independently selected from 1 or 2;

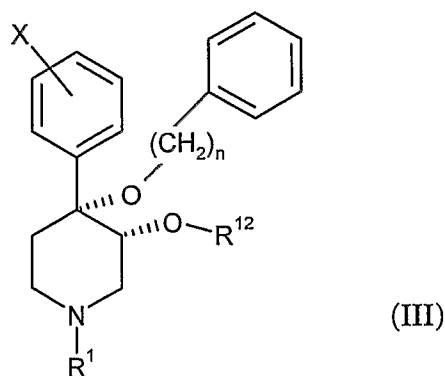
X is halogen;

5 R¹ is selected from the group consisting of hydrogen, carbonyl, sulfonyl, lower alkyl, and lower alkyl substituted by carbonyl, sulfonyl, or hydroxy;

R² to R⁶ are independently selected from the group consisting of hydrogen, halogen, lower alkyl, -C(CH₃)₃, CF₃, -OCH₃, -NO₂, and -CN; and

10 R⁷ to R¹¹ are independently selected from the group consisting of hydrogen, halogen, -CN, -NO₂, -CF₃, -OCH₃, -COOCH₃, and -C₆H₅.

The present invention also provides a compound represented by formula (III):



and the pharmaceutically acceptable salts thereof; wherein

n is an integer from 1 to 2;

X is halogen;

R¹ is selected from the group consisting of hydrogen, carbonyl, sulfonyl, lower alkyl, and lower alkyl substituted by carbonyl, sulfonyl, or hydroxy; and

R¹² is selected from the group consisting of alkyl and alkenyl having from 1 to about 5
5 carbon atoms.

The invention also provides a pharmaceutical composition comprising a therapeutically effective amount of a compound represented by formula (II) or (III) and a pharmaceutically acceptable carrier or excipient. The invention further provides a method for treating cancer comprising administering to a patient in need of such
10 treatment a therapeutically effective amount of a compound represented by formula (II) or (III). Furthermore, the invention provides the use of a compound represented by formula (II) or (III) for the preparation of medicaments for treating cancer.

The present invention provides a novel series of small molecule inhibitors of MDM2-p53 interaction, piperidines with *cis*-3,4-dialkoxy substitutions, which have been
15 tested in ELISA assays. The most potent compounds in this series have been shown to inhibit interaction of MDM2 protein with a p53-like peptide with a potency that is approximately the same as a p53-derived peptide. Binding of these compounds to the p53-binding pocket of MDM2 protein has been confirmed by NMR studies of selected compounds in this series as well as fragments of these compounds. These compounds
20 have been shown to bind the same binding pockets as *cis*-imidazolines, which have demonstrated clear mechanistic activity in cell-based assays as well as antiproliferative activity against wild-type-p53 containing tumor cells both *in vitro* and *in vivo*. Therefore these compounds are useful as anticancer agents.

As used herein, the following terms have the given meanings:

25 "Alkyl" or "lower alkyl group" means a straight-chained or branched saturated aliphatic hydrocarbon having from 1 to 10, preferably 1 to 6 carbon atoms and more preferably 1 to 4 carbon atoms. Typical lower alkyl groups include methyl, ethyl, propyl, and isopropyl.

"Alkenyl" means a straight-chain or branched aliphatic hydrocarbon having from 2
30 to 10, preferably 2 to 6 carbon atoms, and at least one carbon-carbon double bond, for example, vinyl, 2-butenyl, and 3-methyl-2-butenyl.

"Carbonyl" means a divalent -CO- radical.

"Effective amount" means an amount that is effective to prevent, alleviate or ameliorate symptoms of disease or prolong the survival of the subject being treated.

"Halogen" means fluorine, chlorine, bromine, or iodine.

"Hydroxy" means a monovalent -OH group.

5 "Substituted," as in substituted alkyl, means that the substitution can occur at one or more positions and, unless otherwise indicated, that the substituents at each substitution site are independently selected from the specified options.

"Sulfonyl" means the bivalent radical -SO₂-.

10 "IC₅₀" means a concentration of a particular compound required to inhibit 50% of a specific measured activity. IC₅₀ can be measured, *inter alia*, as is described subsequently.

15 "Pharmaceutically acceptable salt" refers to conventional acid-addition salts or base-addition salts that retain the biological effectiveness and properties of the compounds of the present invention and are formed from suitable non-toxic organic or inorganic acids or organic or inorganic bases. Sample acid-addition salts include those derived from inorganic acids such as hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, sulfamic acid, phosphoric acid and nitric acid, and those derived from organic acids such as p-toluenesulfonic acid, salicylic acid, methanesulfonic acid, oxalic acid, succinic acid, citric acid, malic acid, lactic acid, fumaric acid, and the like. Sample
20 base-addition salts include those derived from ammonium, potassium, sodium and, quaternary ammonium hydroxides, such as for example, tetramethylammonium hydroxide. Chemical modification of a pharmaceutical compound (i.e. drug) into a salt is a technique well known to pharmaceutical chemists to obtain improved physical and chemical stability, hygroscopicity, flowability and solubility of compounds. *See, e.g.,* H.
25 Ansel et. al., *Pharmaceutical Dosage Forms and Drug Delivery Systems* (6th Ed. 1995) at pp. 196 and 1456-1457.

"Pharmaceutically acceptable," such as pharmaceutically acceptable carrier, excipient, etc., means pharmacologically acceptable and substantially non-toxic to the subject to which the particular compound is administered.

30 "Therapeutically effective amount" means an amount of at least one compound of formula (II) or (III), or a pharmaceutically acceptable salt thereof, which significantly inhibits proliferation and/or prevents differentiation of a human tumor cell, including human tumor cell lines.

Compounds of the present invention as exemplified advantageously show IC₅₀ values from about 3 μ M to about 100 μ M.

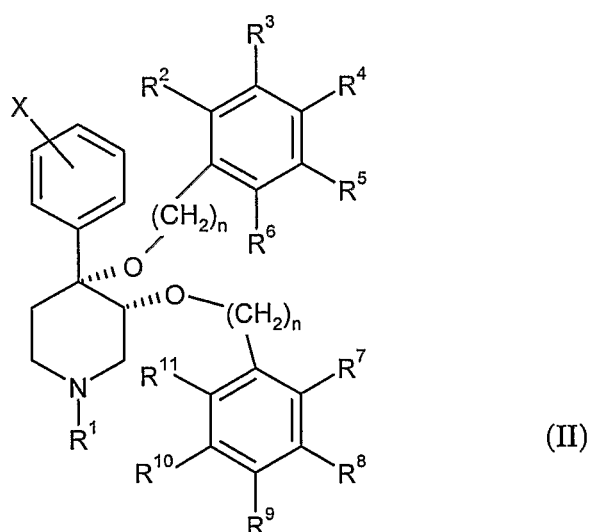
The compounds of the present invention are useful in the treatment or control of cell proliferative disorders, in particular, oncological disorders. These compounds and formulations containing the compounds may be useful in the treatment or control of solid tumors, such as, for example, breast, colon, lung and prostate tumors.

A therapeutically effective amount of a compound in accordance with this invention means an amount of compound that is effective to prevent, alleviate or ameliorate symptoms of disease or prolong the survival of the subject being treated.

Determination of a therapeutically effective amount is within the skill in the art.

The therapeutically effective amount or dosage of a compound according to this invention can vary within wide limits and may be determined in a manner known in the art. Such dosage will be adjusted to the individual requirements in each particular case including the specific compound(s) being administered, the route of administration, the condition being treated, as well as the patient being treated. In general, in the case of oral or parenteral administration to adult humans weighing approximately 70 Kg, a daily dosage of about 10 mg to about 10,000 mg, preferably from about 200 mg to about 1,000 mg, should be appropriate, although the upper limit may be exceeded when indicated. The daily dosage can be administered as a single dose or in divided doses, or for parenteral administration, it may be given as continuous infusion.

In accordance with the present invention, a compound is provided represented by formula (II):



and the pharmaceutically acceptable salts thereof; wherein

n is an integer independently selected from 1 or 2;

X is halogen;

R¹ is selected from the group consisting of hydrogen, carbonyl, sulfonyl, lower alkyl, and lower alkyl substituted by carbonyl, sulfonyl, or hydroxy;

5 R² to R⁶ are independently selected from the group consisting of hydrogen, halogen, lower alkyl, -C(CH₃)₃, CF₃, -OCH₃, -NO₂, and -CN; and

R⁷ to R¹¹ are independently selected from the group consisting of hydrogen, halogen, -CN, -NO₂, CF₃, -OCH₃, -COOCH₃, and -C₆H₅.

In a preferred embodiment of the invention, n is 1.

10 In another preferred embodiment of the invention, X is chloro or fluoro; more preferably chloro. In another preferred embodiment of the invention, X is a *para* substituent.

In another preferred embodiment of the invention, R₁ is selected from the group consisting of hydrogen, -CH₂CH₃, -CH₂CH₂CH₃, -COCH₃, -COCH₂CH₃,
15 -CH₂CHOHCH₂OH, and -SO₂CH₃; more preferably R₁ is hydrogen.

In another preferred embodiment of the invention, R₂ and R₆ are independently selected from the group consisting of hydrogen and halogen; more preferably hydrogen, fluoro, chloro, and bromo.

In another preferred embodiment of the invention, R₃ and R₅ are independently
20 selected from the group consisting of hydrogen, fluoro, chloro, bromo, -CH₃, -OCH₃, -CN, and -NO₂; more preferably R₃ and R₅ are independently selected from the group consisting of hydrogen, fluoro, chloro, and bromo.

In another preferred embodiment of the invention, R₄ is selected from the group consisting of hydrogen, fluoro, chloro, bromo, -C(CH₃)₃, -CH₃, -CN, and -CF₃; more
25 preferably R₄ is selected from the group consisting of hydrogen, fluoro, chloro, and bromo.

In another preferred embodiment of the invention, R₇ and R₁₁ are independently selected from the group consisting of hydrogen, halogen, -CN, -NO₂, and -C₆H₅; more preferably R₇ and R₁₁ are independently selected from the group consisting of hydrogen,
30 fluoro, chloro, and bromo.

In another preferred embodiment of the invention, R₈ and R₁₀ are independently selected from the group consisting of hydrogen, fluoro, chloro, bromo, -CN, -NO₂, and -OCH₃; more preferably R₈ and R₁₀ are independently selected from the group consisting of hydrogen, fluoro, chloro, and bromo.

- 5 In another preferred embodiment of the invention, R₉ is selected from the group consisting of hydrogen, fluoro, chloro, bromo, -OCH₃, -CN, -CF₃, and -COOCH₃; more preferably R₉ is selected from the group consisting of hydrogen, fluoro, chloro, and bromo.

Preferred compounds having formula (II) include:

- 10 *cis*-[rac]-4-Benzylloxy-4-(4-chloro-phenyl)-3-(3,4-difluoro-benzylloxy)-piperidine;
cis-[rac]-4-Benzylloxy-4-(4-chloro-phenyl)-3-(2,6-difluoro-benzylloxy)-piperidine;
cis-[rac]-4-Benzylloxy-3-(biphenyl-2-ylmethoxy)-4-(4-chloro-phenyl)-piperidine;
cis-[rac]-4-[4-Benzylloxy-4-(4-chloro-phenyl)-piperidin-3-yloxymethyl]-benzonitrile;
- 15 *cis*-[rac]-4-Benzylloxy-4-(4-chloro-phenyl)-3-(3-nitro-benzylloxy)-piperidine;
cis-[rac]-4-Benzylloxy-3-(3-bromo-benzylloxy)-4-(4-chloro-phenyl)-piperidine;
cis-[rac]-4-Benzylloxy-4-(4-chloro-phenyl)-3-(2,4-difluoro-benzylloxy)-piperidine;
cis-[rac]-4-Benzylloxy-3-(2-chloro-4-fluoro-benzylloxy)-4-(4-chloro-phenyl)-piperidine;
- 20 *cis*-[rac]-4-[4-Benzylloxy-4-(4-chloro-phenyl)-piperidin-3-yloxymethyl]-benzoic acid methyl ester;
cis-[rac]-4-Benzylloxy-4-(4-chloro-phenyl)-3-(3,5-difluoro-benzylloxy)-piperidine;
cis-[rac]-4-Benzylloxy-3-(3-chloro-2-fluoro-benzylloxy)-4-(4-chloro-phenyl)-piperidine;
- 25 *cis*-[rac]-4-Benzylloxy-4-(4-chloro-phenyl)-3-(2,5-dichloro-benzylloxy)-piperidine;
cis-[rac]-4-Benzylloxy-4-(4-chloro-phenyl)-3-(2,3-difluoro-benzylloxy)-piperidine;
cis-[rac]-4-Benzylloxy-4-(4-chloro-phenyl)-3-(4-trifluoromethyl-benzylloxy)-piperidine;

- cis*-[rac]-4-Benzylloxy-4-(4-chloro-phenyl)-3-(4-fluoro-benzylloxy)-piperidine;
- cis*-[rac]-4-Benzylloxy-3-(4-bromo-benzylloxy)-4-(4-chloro-phenyl)-piperidine;
- cis*-[rac]-4-Benzylloxy-4-(4-chloro-phenyl)-3-(3-fluoro-benzylloxy)-piperidine;
- cis*-[rac]-2-[4-Benzylloxy-4-(4-chloro-phenyl)-piperidin-3-yloxymethyl]-
5 benzonitrile;
- cis*-[rac]-3-[4-Benzylloxy-4-(4-chloro-phenyl)-piperidin-3-yloxymethyl]-
benzonitrile;
- cis*-[rac]-4-Benzylloxy-4-(4-chloro-phenyl)-3-(4,5-dimethoxy-2-nitro-benzylloxy)-
piperidine;
- 10 *cis*-[rac]-4-Benzylloxy-3-but-2-enyloxy-4-(4-chloro-phenyl)-piperidine;
- cis*-[rac]-4-Benzylloxy-4-(4-chloro-phenyl)-3-pent-2-enyloxy-piperidine;
- cis*-[rac]-4-Benzylloxy-4-(4-chloro-phenyl)-3-(2,3,6-trifluoro-benzylloxy)-
piperidine;
- cis*-[rac]-4-Benzylloxy-3-butoxy-4-(4-chloro-phenyl)-piperidine;
- 15 *cis*-[rac]-4-Benzylloxy-3-(4-chloro-2-fluoro-benzylloxy)-4-(4-chloro-phenyl)-
piperidine;
- cis*-[rac]-4-Benzylloxy-3-(4-bromo-2-fluoro-benzylloxy)-4-(4-chloro-phenyl)-
piperidine;
- cis*-[rac]-4-Benzylloxy-4-(4-chloro-phenyl)-3-(2,4,6-trifluoro-benzylloxy)-
20 piperidine;
- cis*-[rac]-4-Benzylloxy-4-(4-chloro-phenyl)-3-(2,4,5-trifluoro-benzylloxy)-
piperidine;
- cis*-[rac]-4-Benzylloxy-4-(4-chloro-phenyl)-3-(2,3,4-trifluoro-benzylloxy)-
piperidine;
- 25 *cis*-[rac]-3-Benzylloxy-4-(4-chloro-phenyl)-4-(2,4,6-trifluoro-benzylloxy)-
piperidine;
- cis*-[rac]-3-Benzylloxy-4-(4-chloro-phenyl)-4-(2,5-dichloro-benzylloxy)-piperidine;

- cis*-[rac]-3-Benzylloxy-4-(4-chloro-phenyl)-4-(2,6-dichloro-benzylloxy)-piperidine;
- cis*-[rac]-3-Benzylloxy-4-(4-chloro-phenyl)-4-(2,6-difluoro-benzylloxy)-piperidine;
- cis*-[rac]-3-Benzylloxy-4-(4-chloro-phenyl)-4-(3-methoxy-benzylloxy)-piperidine;
- cis*-[rac]-3-Benzylloxy-4-(4-chloro-phenyl)-4-(2,3,6-trifluoro-benzylloxy)-
5 piperidine;
- cis*-[rac]-3-Benzylloxy-4-(4-chloro-phenyl)-4-(2-fluoro-benzylloxy)-piperidine;
- cis*-[rac]-3-Benzylloxy-4-(4-chloro-phenyl)-4-(2-fluoro-3-methyl-benzylloxy)-
piperidine;
- cis*-[rac]-4-(4-Chloro-phenyl)-3-(3,4-dichloro-benzylloxy)-4-(4-fluoro-benzylloxy)-
10 piperidine;
- cis*-[rac]-4-(4-Bromo-benzylloxy)-4-(4-chloro-phenyl)-3-(3,4-dichloro-benzylloxy)-
piperidine;
- cis*-[rac]-4-(4-Chloro-phenyl)-3-(3,4-dichloro-benzylloxy)-4-(2,4-difluoro-
benzylloxy)-piperidine;
- cis*-[rac]-4-(2-Chloro-4-fluoro-benzylloxy)-4-(4-chloro-phenyl)-3-(3,4-dichloro-
15 benzylloxy)-piperidine;
- cis*-[rac]-4-(2-Bromo-benzylloxy)-4-(4-chloro-phenyl)-3-(3,4-dichloro-benzylloxy)-
piperidine;
- cis*-[rac]-4-(4-tert-Butyl-benzylloxy)-4-(4-chloro-phenyl)-3-(3,4-dichloro-
20 benzylloxy)-piperidine;
- cis*-[rac]-4-[4-(4-Chloro-phenyl)-3-(3,4-dichloro-benzylloxy)-piperidin-4-
yloxymethyl]-benzonitrile;
- cis*-[rac]-4-(3-Chloro-benzylloxy)-4-(4-chloro-phenyl)-3-(3,4-dichloro-
benzylloxy)-piperidine;
- cis*-[rac]-4-(3-Bromo-benzylloxy)-4-(4-chloro-phenyl)-3-(3,4-dichloro-benzylloxy)-
25 piperidine;
- cis*-[rac]-4-(4-Chloro-phenyl)-3-(3,4-dichloro-benzylloxy)-4-(2-fluoro-benzylloxy)-
piperidine;

cis-[rac]-4-(4-Chloro-phenyl)-3-(3,4-dichloro-benzyloxy)-4-(3,5-difluoro-benzyloxy)-piperidine;

cis-[rac]-4-(3-Chloro-2-fluoro-benzyloxy)-4-(4-chloro-phenyl)-3-(3,4-dichloro-benzyloxy)-piperidine;

5 *cis*-[rac]-4-(4-Chloro-phenyl)-3-(3,4-dichloro-benzyloxy)-4-(2,3-difluoro-benzyloxy)-piperidine;

cis-[rac]-4-(4-Chloro-phenyl)-3-(3,4-dichloro-benzyloxy)-4-(4-trifluoromethyl-benzyloxy)-piperidine;

10 *cis*-[rac]-4-(4-Chloro-phenyl)-3-(3,4-dichloro-benzyloxy)-4-(3-fluoro-benzyloxy)-piperidine;

cis-[rac]-3-[4-(4-Chloro-phenyl)-3-(3,4-dichloro-benzyloxy)-piperidin-4-yl]oxymethyl]-benzonitrile;

cis-[rac]-4-(2-Chloro-benzyloxy)-4-(4-chloro-phenyl)-3-(3,4-dichloro-benzyloxy)-piperidine;

15 *cis*-[rac]-4-(4-Chloro-phenyl)-3-(3,4-dichloro-benzyloxy)-4-(4-methyl-benzyloxy)-piperidine;

cis-[rac]-4-(4-Chloro-phenyl)-3,4-bis-(2,4-difluoro-benzyloxy)-piperidine;

cis-[rac]-4-(4-Chloro-phenyl)-3,4-bis-(3-nitro-benzyloxy)-piperidine;

20 *cis*-[rac]-1-[4-Benzyloxy-4-(4-chloro-phenyl)-3-(2,4-difluoro-benzyloxy)-piperidin-1-yl]-ethanone;

cis-[rac]-1-[4-Benzyloxy-3-(3-bromo-benzyloxy)-4-(4-chloro-phenyl)-piperidin-1-yl]-ethanone;

cis-[rac]-1-[4-Benzyloxy-3-(2-chloro-4-fluoro-benzyloxy)-4-(4-chloro-phenyl)-piperidin-1-yl]-ethanone;

25 *cis*-[rac]-1-[4-Benzyloxy-4-(4-chloro-phenyl)-3-(3,5-difluoro-benzyloxy)-piperidin-1-yl]-ethanone;

cis-[rac]-1-[4-Benzyloxy-3-(3-chloro-2-fluoro-benzyloxy)-4-(4-chloro-phenyl)-piperidin-1-yl]-ethanone;

cis-[rac]-1-[4-Benzylloxy-4-(4-chloro-phenyl)-3-(3,4-dichloro-benzylloxy)-piperidin-1-yl]-ethanone;

cis-[rac]-1-[4-Benzylloxy-4-(4-chloro-phenyl)-3-(4-fluoro-benzylloxy)-piperidin-1-yl]-ethanone;

5 *cis*-[rac]-1-[4-Benzylloxy-3-(4-bromo-benzylloxy)-4-(4-chloro-phenyl)-piperidin-1-yl]-ethanone;

cis-[rac]-1-[4-Benzylloxy-4-(4-chloro-phenyl)-3-(3-fluoro-benzylloxy)-piperidin-1-yl]-ethanone;

10 *cis*-[rac]-3-[1-Acetyl-4-benzylloxy-4-(4-chloro-phenyl)-piperidin-3-yloxymethyl]-benzonitrile;

cis-[rac]-1-[4-Benzylloxy-4-(4-chloro-phenyl)-3-(2,6-difluoro-benzylloxy)-piperidin-1-yl]-ethanone;

cis-[rac]-1-[4-Benzylloxy-4-(4-chloro-phenyl)-3-(3-nitro-benzylloxy)-piperidin-1-yl]-ethanone;

15 *cis*-[rac]-1-[4-Benzylloxy-4-(4-chloro-phenyl)-3-(2,3,4-trifluoro-benzylloxy)-piperidin-1-yl]-ethanone;

cis-[rac]-1-[4-(4-Chloro-phenyl)-3-(3,4-dichloro-benzylloxy)-4-(2-fluoro-benzylloxy)-piperidin-1-yl]-ethanone;

20 *cis*-[rac]-1-[4-Benzylloxy-4-(4-chloro-phenyl)-3-(2,3,4-trifluoro-benzylloxy)-piperidin-1-yl]-propan-1-one;

cis-[rac]-1-[4-Benzylloxy-4-(4-chloro-phenyl)-3-(3,4-dichloro-benzylloxy)-piperidin-1-yl]-propan-1-one;

cis-[rac]-4-Benzylloxy-3-(4-bromo-benzylloxy)-4-(4-fluoro-phenyl)-piperidine;

25 *cis*-[rac]-4-Benzylloxy-4-(4-chloro-phenyl)-3-(3,4-dichloro-benzylloxy)-1-ethyl-piperidine;

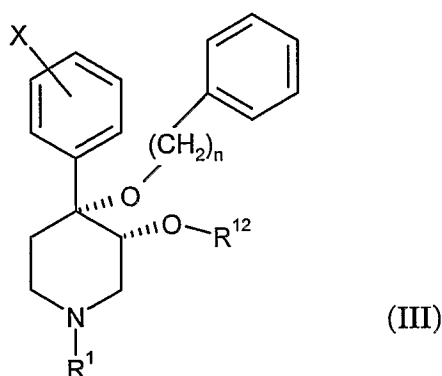
cis-[rac]-4-Benzylloxy-4-(4-chloro-phenyl)-3-(3,4-dichloro-benzylloxy)-1-propyl-piperidine;

cis-[rac]-3-[4-Benzylloxy-4-(4-chloro-phenyl)-3-(2,3,4-trifluoro-benzylloxy)-piperidin-1-yl]-propane-1,2-diol;

cis-[rac]-3-[4-Benzyloxy-3-(4-bromo-benzyloxy)-4-(4-chloro-phenyl)-piperidin-1-yl]-propane-1,2-diol; and

cis-[rac]-3-[4-Benzyloxy-4-(4-chloro-phenyl)-3-(2,3,4-trifluoro-benzyloxy)-piperidin-1-yl]-methane sulfonyl.

- 5 Further in accordance with the present invention, a compound is provided having formula (III):



and the pharmaceutically acceptable salts thereof; wherein

- n is an integer from 1 to 2;
- 10 X is halogen;
- R¹ is selected from the group consisting of hydrogen, carbonyl, sulfonyl, lower alkyl, and lower alkyl substituted by carbonyl, sulfonyl, or hydroxy; and
- R¹² is selected from the group consisting of alkyl and alkenyl having from 1 to about 5 carbon atoms.
- 15 In a preferred embodiment of the invention, n is 1.

In another preferred embodiment of the invention, X is chloro or fluoro; more preferably chloro. In another preferred embodiment of the invention, X is a *para* substituent.

- In another preferred embodiment of the invention, R₁ is selected from the group
- 20 consisting of hydrogen, -CH₂CH₃, -CH₂CH₂CH₃, -COCH₃, -COCH₂CH₃, -CH₂CHOHCH₂OH, and -SO₂CH₃; more preferably R₁ is hydrogen.

In another preferred embodiment of the invention, R₁₂ is selected from the group consisting of -(CH₂)₃CH₃, -(CH₂)₄CH₃, -CH₂CH=CHCH₃, and -CH₂CH=CH CH₂CH₃.

Preferred compounds having formula (III) include:

cis-[rac]-4-Benzylxy-4-(4-fluoro-phenyl)-3-butyloxy-piperidine;

cis-[rac]-4-Benzylxy-4-(4-fluoro-phenyl)-3-pentyloxy-piperidine;

cis-[rac]-4-Benzylxy-4-(4-fluoro-phenyl)-3-(but-2-en)xyloxy-piperidine; and

5 *cis*-[rac]-4-Benzylxy-4-(4-fluoro-phenyl)-3-(pent-2-en)oxy-piperidine.

Other preferred compounds having formula (II) include:

cis-[rac]-4-Benzylxy-4-(4-chloro-phenyl)-3-butyloxy-piperidine;

cis-[rac]-4-Benzylxy-4-(4-chloro-phenyl)-3-pentyloxy-piperidine;

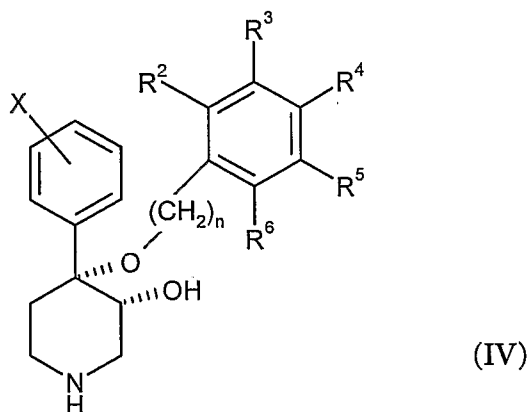
cis-[rac]-4-Benzylxy-4-(4-chloro-phenyl)-3-(but-2-en)xyloxy-piperidine; and

10 *cis*-[rac]-4-Benzylxy-4-(4-chloro-phenyl)-3-(pent-2-en)oxy-piperidine.

The invention also provides a pharmaceutical composition comprising a therapeutically effective amount of a compound represented by formula (II) or (III) and a pharmaceutically acceptable carrier or excipient. The invention further provides a method for treating cancer comprising administering to a patient in need of such
15 treatment a therapeutically effective amount of a compound represented by formula (II) or (III). Preferably, the cancer is breast or colon cancer.

Furthermore, the invention provides a process for the preparation of a compound of formula I of claim 1, which process comprises

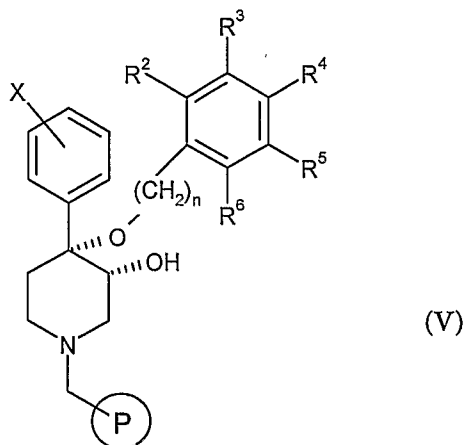
a) coupling a compound of the formula IV



20

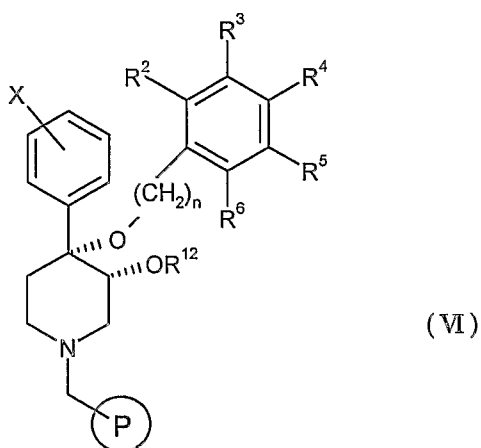
wherein R^2 to R^6 , X and n have the significances as defined hereinbefore, with a suitable linker to a solid phase to obtain a compound of formula V

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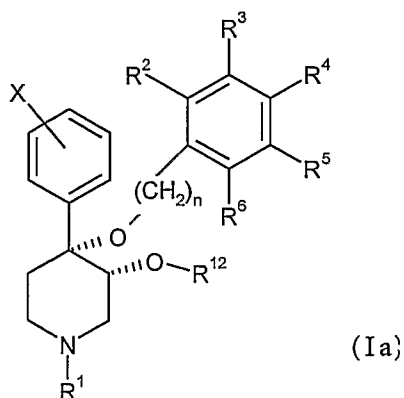
wherein $\textcircled{\text{P}}$ symbolizes the solid phase,

- b) using potassium tert. Butoxide to generate an anion and alkylating the compound of formula V with an alkyl halide of formula R^{12}X to obtain a compound of formula VI



wherein R^{12} is as defined hereinbefore,

- c) cleaving the product from the linker to obtain a compound of formula Ia,



wherein R¹ is H, and if desired,

d) reacting the compound of formula Ia with an acyl halide, alkyl halide or sulfonyl chloride to obtain a compound of formula I, wherein R¹ is carbonyl, sulfonyl, lower alkyl or lower alkyl substituted by carbonyl, sulfonyl or hydroxy.

- 5 The compounds of the present invention, and intermediates thereof, can be prepared according to the schemes set out below. Starting materials are made using known procedures or as illustrated. The abbreviations used in the descriptions of the schemes, preparations, and the examples are set out below.

ACE-Cl = 1-chloroethyl chloroformate (Aldrich)

- 10 BEMP = 2-tert-butylimino-2-diethylamino-1,3-dimethyl-perhydro-1,3,2-diazaphosphorine (Fluka)

Boc = tert-butyloxycarbonyl

t-BuOK = potassium tert-butoxide

CH₂Cl₂ = dichloromethane

- 15 DCE = 1,2-dichloroethane

DMF = N,N-dimethylformamide

Et₂O = diethyl ether

EtOH = ethanol

H₂SO₄ = sulfuric acid

- 20 HCl = hydrogen chloride

H₂O = water

MeOH = methanol

NaH = sodium hydride

NMO = N-methylmorpholine-N-oxide

- 25 NMP = 1-methyl-2-pyrrolidinone

OsO₄ = osmium tetroxide

Polymer (supported) BEMP = 2-*tert*-butylimino-2-diethylamino-1,3-dimethyl-perhydro-1,3,2- diazaphosphorine supported by polystyrene resin (Fluka)

i-Pr₂NEt = N, N-diisopropylethylamine

TEA = triethylamine

5 TFA = trifluoroacetic acid

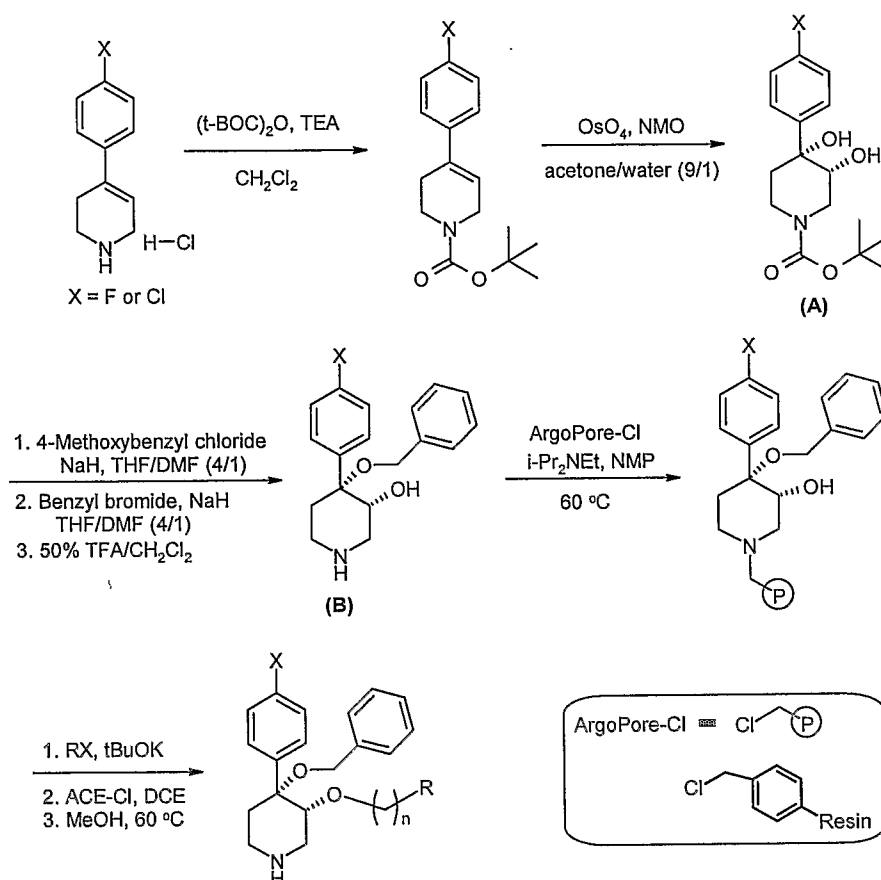
THF = tetrahydrofuran

Schemes 1-3 outline a general method for preparing compounds of the invention having formula (II) and (III) using a novel solid phase synthesis. Scheme 4 outlines a general method for preparing the compounds in solution phase. Scheme 5 illustrates
10 various methods for modifying the R₁ group using a novel polymer supported reagent.

In Scheme 1, the protection of a secondary amine of a commercially available 4-aryl-1,2,3,6-tetrahydropyridine is outlined. The preferred protecting group is a *tert*-butyloxycarbonyl, which can be synthesized from known procedures (Greene, T. W. and Wuts, P. G. M, 2nd Edition, John Wiley & Sons, N. Y. 1991). For liquid phase synthesis,
15 the resulting *tert*-butyl ester can be treated with OsO₄/NMO to form the dihydroxy intermediate A. Selective *o*-alkylation of intermediate A at C3 can be carried out using NaH and 4-methoxybenzyl chloride. The resulting intermediate can be benzylated according to known methods. Deprotection of both 4-methoxybenzyl and *tert*-butyloxycarbonyl groups using 50% TFA/CH₂Cl₂ yields 4-aryl-4-benzyloxy-3-
20 hydroxypiperidine B. For solid phase synthesis, the resulting piperidine B can be coupled to a suitable linker, such as a chloromethyl derivative ArgoPore-Cl linker (Argonaut). Alkylation on solid phase can be accomplished using *t*-BuOK to generate the anion followed by coupling with various alkyl halides (RX). The final reaction product can be cleaved from the N-benzyl linked tertiary amine linker using *alpha*-chloroethyl
25 chloroformat (ACE-Cl)/MeOH to give the piperidine compounds of the invention (Leysen, D. et al. *Tetrahedron Lett.* 1997, 2915-2918).

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Scheme 1

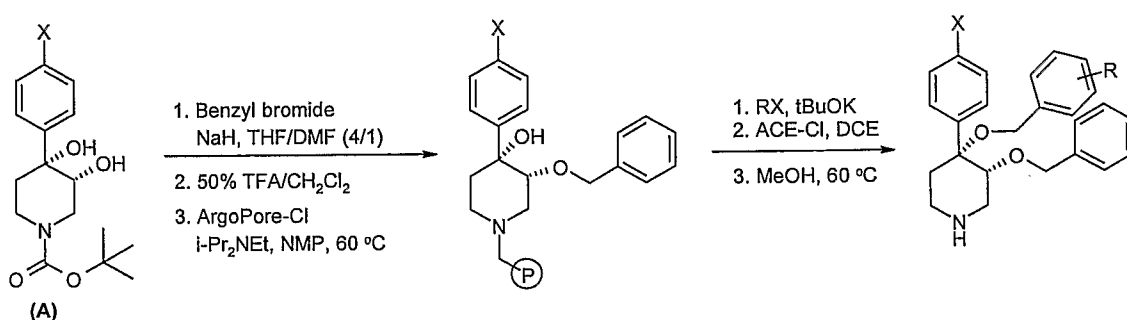


In Scheme 2, a general method is outlined for preparing compounds of formula (II) that feature functionalized R groups derived from intermediate A in Scheme 1.

- 5 Intermediate A can be converted to 4-aryl-3-benzyloxy-3-hydroxypiperidine via alkylation at C3 using NaH and benzylbromide followed by acidic deprotection of a *tert*-butoxycarbonyl group. The subsequent synthesis on solid phase can be accomplished to yield the piperidine compounds of the invention following the described reactions set out in Scheme 1.

10

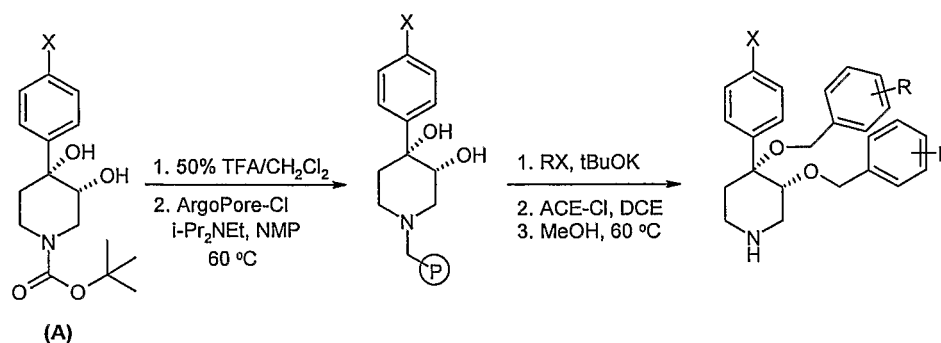
Scheme 2



In Scheme 3, deprotection of a *tert*-butoxycarbonyl from intermediate A can be carried out using 50% TFA/CH₂Cl₂. The synthesis on solid phase commences with the

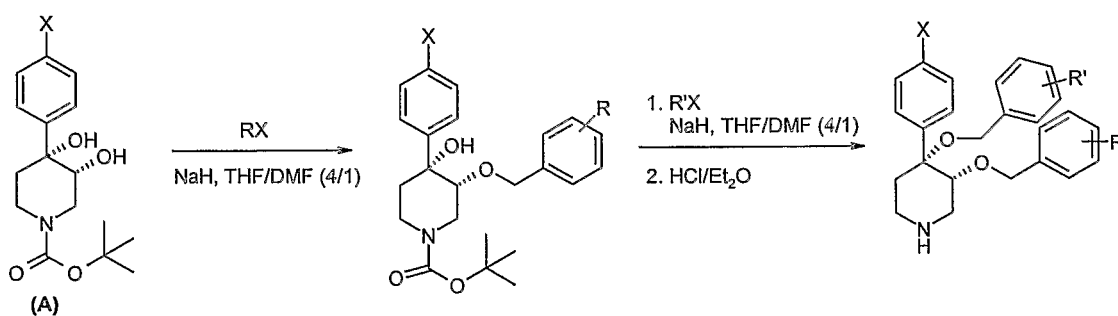
coupling of the resulting 4-aryl-3,4-dihydroxypiperidine with a ArgoPore-Cl linker. Dialkylation using *t*-BuOK and alkyl halides (RX) followed by cleavage of the polymer support according to the described conditions affords the piperidine compounds of the invention.

5

Scheme 3

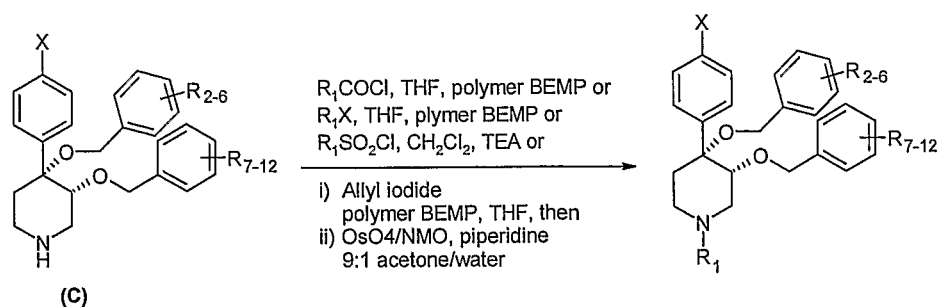
In Scheme 4, a general synthetic method is outlined for preparing compounds of formula (II) and (III) in solution phase. Sequential alkylation of intermediate A using NaH and alkyl halides followed by acidic deprotection of tert-butyloxycarbonyl provides the piperidine compounds of the invention.

10

Scheme 4

In Scheme 5, a general method is outlined for the post-modification of intermediate C. The secondary amine of intermediate C can be treated with a variety of agents such as acyl chlorides, alkyl halides, and sulfonyl chlorides to form the corresponding amide, tert-amine, or sulfonamide. The intermediate C can also be allylated using polymer support BEMP and allyl iodide to form the *N*-allyl substituted intermediate, which can be further treated with OsO₄/NMO to form 3-propane-1,2-diol-substituted piperidines of the invention.

15

Scheme 5

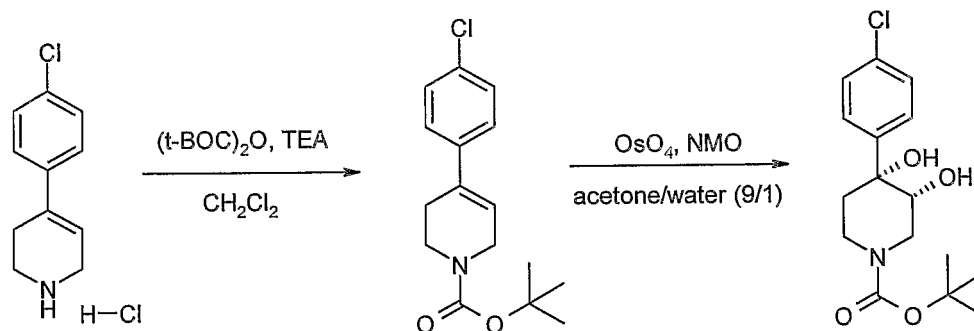
The compounds of the present invention can be prepared according to the examples below. The examples are presented for purposes of demonstrating, but not limiting, the preparation of the compounds and compositions of this invention.

Examples

The inhibitory activity (IC_{50}) of the compounds prepared in the examples below, and represented by formula (II) or (III), is in the range of 3 μ M to 100 μ M.

Example 1

10 *cis*-[rac]-4-(4-Chlorophenyl)-3,4-dihydropiperidine-1-carboxylic acid tert-butyl ester

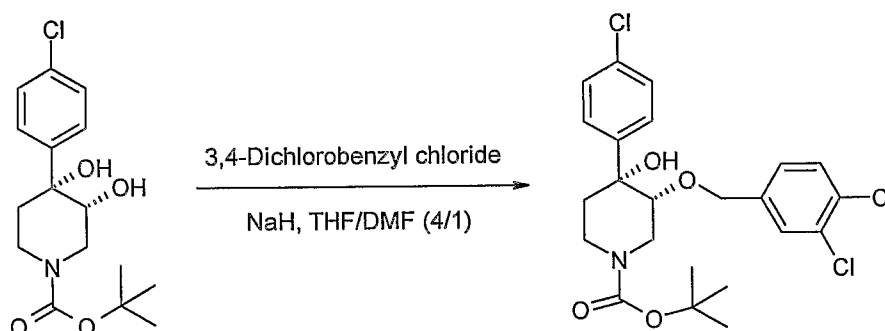


4-(4-Chlorophenyl)-1,2,3,6-tetrahydropyridine hydrochloride (Lancaster, 1.00 g, 4.35 mmol), triethylamine (0.92 g, 9.13 mmol), and di-tert-butyl carbonate (Aldrich, 1.04 g, 4.78 mmol) were combined in dichloromethane (100 mL) and stirred at room temperature for 14 hours. The mixture was washed with saturated aqueous ammonium chloride solution (30 mL), water (30 mL), saturated sodium chloride solution (30 mL) and dried over anhydrous magnesium sulfate. The mixture was filtered and concentrated *in vacuo* to give 4-(4-chlorophenyl)-3,6-dihydro-2H-pyridine-1-carboxylic acid tert-butyl ester (1.41 g, 100%) of as a viscous yellow oil, which was used without further purification. 4-(4-Chlorophenyl)-3,6-dihydro-2H-pyridine-1-carboxylic acid tert-butyl ester (334 mg, 1.14 mmol) was dissolved in acetone/water (1:1, 10 mL), and N-

methymorpholine-N-oxide (Aldrich, 462 mg, 3.42 mmol) and a catalytic amount of osmium tetroxide (Aldrich) were added. The mixture was stirred at room temperature for 3 hours. A saturated aqueous solution of sodium sulfite (2 mL) was added, and the mixture was stirred for 30 minutes at room temperature. The mixture was diluted with ethyl acetate (10 mL) and water (5 mL). The organic layer was separated, and the aqueous layer was extracted with ethyl acetate (2 X 10 mL). The combined organic layers were washed with brine and dried over anhydrous magnesium sulfate. The mixture was filtered and concentrated *in vacuo* to give *cis*-[rac]-4-(4-chlorophenyl)-3,4-dihydroxypiperidine-1-carboxylic acid tert-butyl ester (364 mg, 1.11 mmol, 97%) as a yellow oil.

Example 2

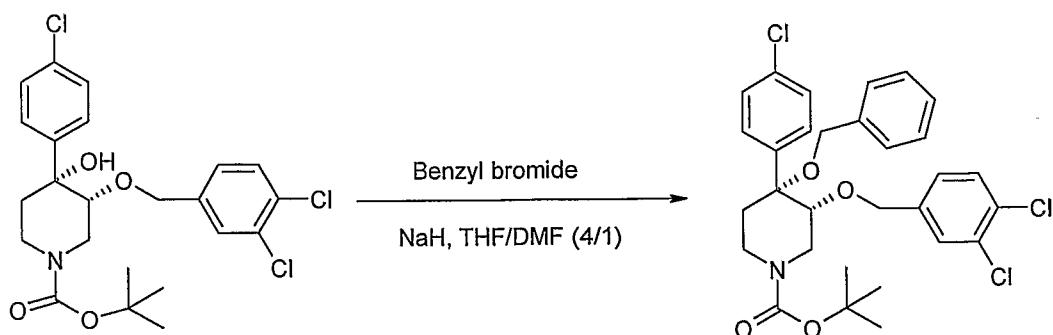
cis-[rac]-4-(4-Chlorophenyl)-3-(3,4-dichlorobenzoyloxy)-4-hydroxypiperidine-1-carboxylic acid tert-butyl ester



To an ice-cold suspension of sodium hydride (62 mg, 2.6 mmol) in a mixture of tetrahydrofuran/N,N-dimethylformamide (4/1, 4 mL) was added dropwise a solution of *cis*-[rac]-4-(4-chlorophenyl)-3,4-dihydroxypiperidine-1-carboxylic acid tert-butyl ester (Example 1, 340 mg, 1.04 mmol) in tetrahydrofuran/N,N-dimethylformamide (1 mL, 4/1). After the addition was complete, the mixture was stirred with ice cooling for 15 minutes. Then 3,4-dichlorobenzyl chloride (Aldrich, 239 mg, 1.14 mmol) was added, and the mixture was warmed to room temperature and stirred for 20 hours. The mixture was poured into a saturated aqueous solution of ammonium chloride (30 mL), and the mixture was extracted with ethyl acetate (3 X 15 mL). The combined organic layers were washed with water (2 X 20 mL), saturated aqueous sodium chloride solution (1 X 20 mL), and dried over anhydrous magnesium sulfate. The mixture was filtered and concentrated *in vacuo* to give a viscous oil (500 mg), which was purified by flash silica gel chromatography (Merck silica gel 60, 230 to 400 mesh) to afford *cis*-[rac]-4-(4-chlorophenyl)-3-(3,4-dichlorobenzoyloxy)-4-hydroxypiperidine-1-carboxylic acid tert-butyl ester (310 mg, 61%) as a colorless oil.

Example 3

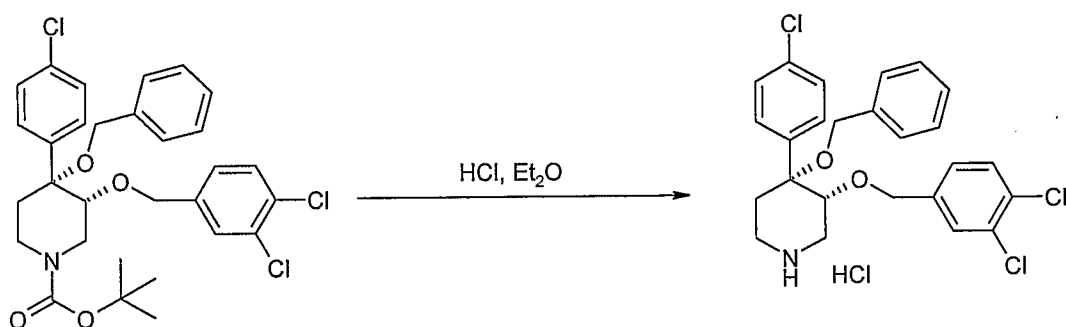
cis-[rac]-4-(Benzyloxy)-4-(4-chlorophenyl)-3-(3,4-dichlorobenzyloxy)-piperidine-1-carboxylic acid tert-butyl ester



- 5 To an ice cold solution of *cis*-[rac]-4-(4-chlorophenyl)-3-(3,4-dichloro-
benzyloxy)-4-hydroxypiperidine-1-carboxylic acid tert-butyl ester (Example 2, 224 mg,
0.46 mmol) in tetrahydrofuran (1.5 mL) was added sodium hydride (22 mg, 0.92 mmol)
portionwise. After stirring with ice cooling for ten minutes, benzyl bromide (86 mg, 0.51
mmol) was added followed by N,N-dimethylformamide (0.5 mL). The cooling bath was
10 removed, and the mixture was warmed to room temperature and stirred for 3 hours.
Several drops of methanol were added, and the mixture was stirred and room
temperature for 1 hour. The mixture was partitioned between ethyl acetate (30 mL) and
saturated aqueous ammonium chloride solution (15 mL). The organic layer was
separated, and the aqueous layer was extracted with ethyl acetate (3 X 15 mL). The
15 combined organic layers were washed with water (3 X 30 mL), saturated aqueous sodium
chloride solution (15 mL) and dried over anhydrous magnesium sulfate. The mixture
was filtered and concentrated *in vacuo* to give *cis*-[rac]-4-(benzyloxy)-4-(4-
chlorophenyl)-3-(3,4-dichlorobenzyloxy)-piperidine-1-carboxylic acid tert-butyl ester
(240 mg), which was used without further purification.

20 Example 4

cis-[rac]-4-(Benzyloxy)-4-(4-chlorophenyl)-3-(3,4-dichlorobenzyloxy)-piperidine
hydrochloride

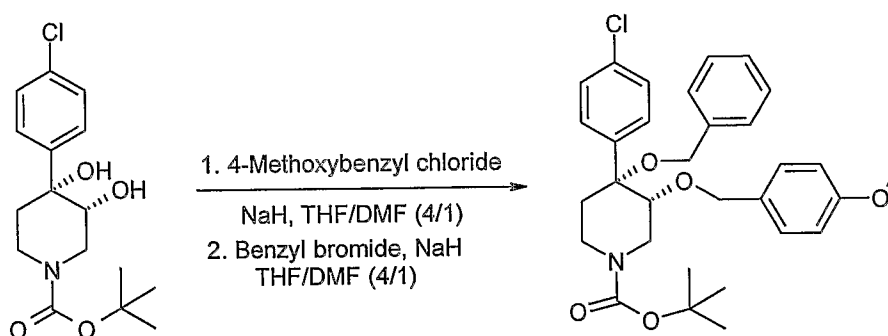


Crude *cis*-[rac]-4-(benzyloxy)-4-(4-chlorophenyl)-3-(3,4-dichlorobenzyloxy)-piperidine-1-carboxylic acid tert-butyl ester (Example 3, 240 mg) was dissolved in anhydrous diethyl ether (10 mL). The mixture was cooled in an ice bath, and hydrogen chloride gas was passed through the solution for 10 minutes. The reaction vessel was tightly stoppered and stored at 0°C for 24 hours. The precipitated solid was collected and washed with diethyl ether to afford *cis*-[rac]-4-(benzyloxy)-4-(4-chlorophenyl)-3-(3,4-dichlorobenzyloxy)-piperidine hydrochloride as a white solid (130 mg, 55%).

HR-FAB m/e calcd for C₂₄H₂₄NO₂Cl: [M+H]⁺ 476.0952, found 476.0931.

Example 5

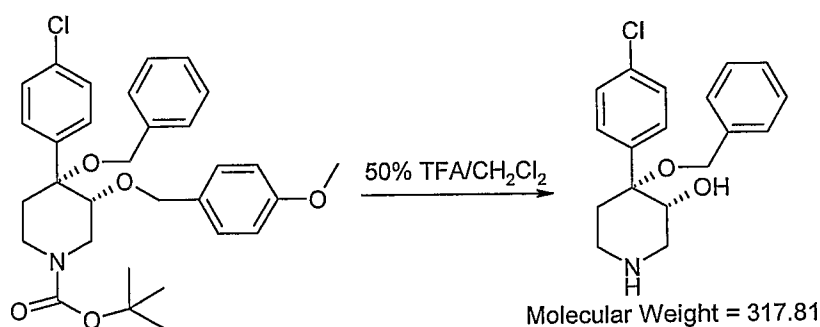
10 *cis*-[rac]-4-Benzyloxy-4-(4-chloro-phenyl)-3-(4-methoxy-benzyloxy)-piperidine-1-carboxylic acid tert-butyl ester



cis-[rac]-4-Benzyloxy-4-(4-chloro-phenyl)-3-(4-methoxy-benzyloxy)-piperidine-1-carboxylic acid tert-butyl ester was prepared from *cis*-[rac]-4-(4-chlorophenyl)-3,4-dihydroxypiperidine-1-carboxylic acid tert-butyl ester (Example 1) and 4-methoxybenzyl chloride (Aldrich) following the procedures used in Examples 2 and 3, which was used without purification.

Example 6

cis-[rac]-4,4-[benzyloxy-(4-chlorophenyl)]-3-hydroxypiperidine

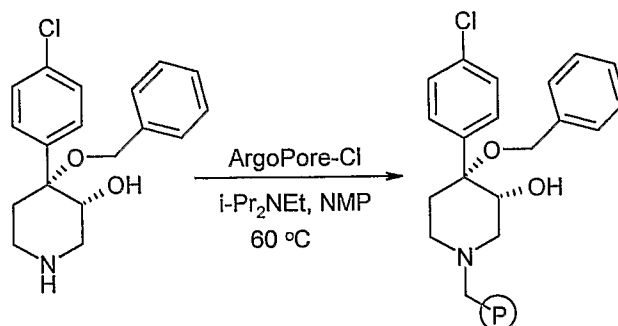


- 24 -

cis-[rac]-4-Benzoyloxy-4-(4-chloro-phenyl)-3-(4-methoxy-benzoyloxy)-piperidine-1-carboxylic acid tert-butyl ester (Example 5, 550 mg, 1.02 mmol) was dissolved in 50% trifluoroacetic acid/dichloromethane (10 mL). After stirring 1.5 hours, the solution was evaporated *in vacuo*. The residue was triturated in 1:1 ethyl acetate/hexane to provide *cis*-[rac]-4,4-[benzyloxy-(4-chlorophenyl)]-3-hydroxypiperidine (150 mg) as a white powder. Mass spectrum (ES) $[M+CH_3CN]^+ = 359$.

Example 7

Resin-bound *cis*-[rac]-4,4-[benzyloxy-(4-chlorophenyl)]-3-hydroxypiperidine

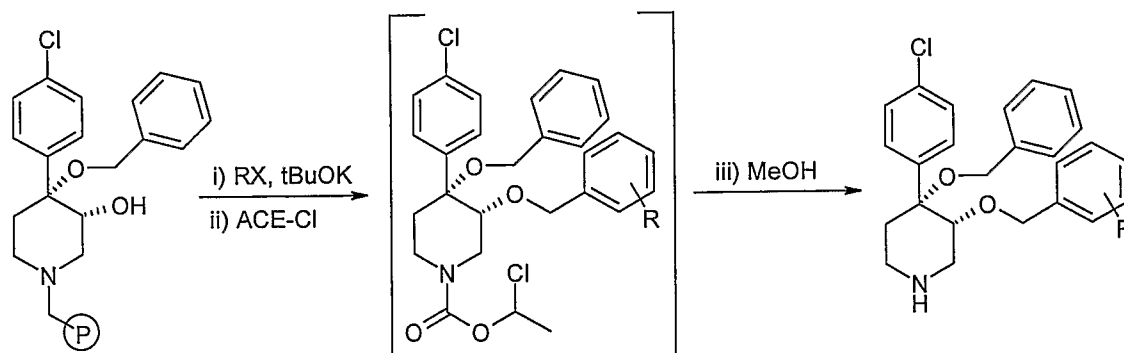


A mixture of *cis*-[rac]-4,4-[benzyloxy-(4-chlorophenyl)]-3-hydroxypiperidine (Example 6, 7.3 g, 23 mmol), ArgoPore-Cl resin (16 g, 15.3 mmol, loading capacity: 0.96 mmol from Argonaut Inc.), and N,N-diisopropylethylamine (13 mL, 76.7 mmol) in N-methylpyrrolinone (12 mL) was heated at 60°C overnight. The resin was filtered and washed successively with CH₂Cl₂, and MeOH. The resin was dried at 40°C/high vacuum overnight to provide resin-bound 4,4-[benzyloxy-(4-chlorophenyl)]-3-hydroxypiperidine.

Example 8

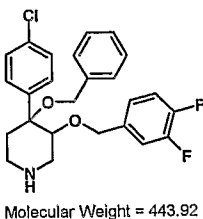
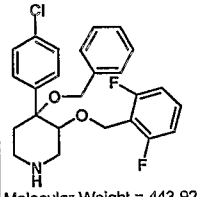
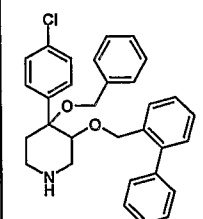
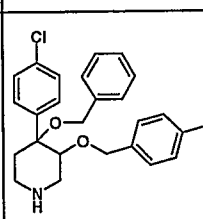
cis-[rac]-4-Benzoyloxy-4-(4-chloro-phenyl)-3-substituted piperidine library:

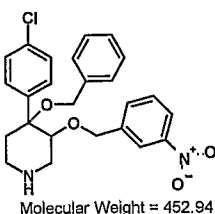
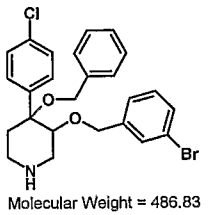
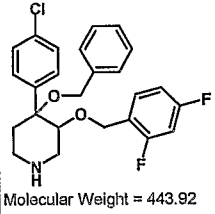
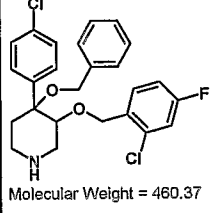
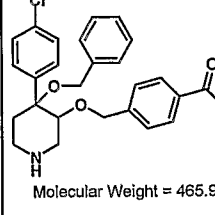
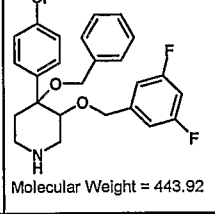
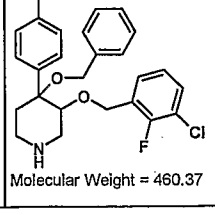
General procedure

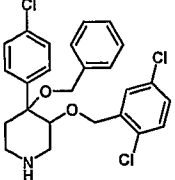
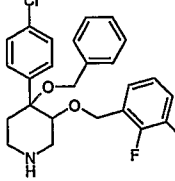
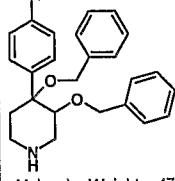
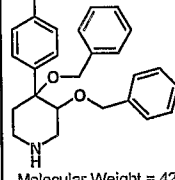
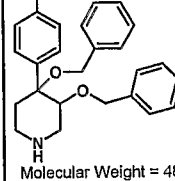
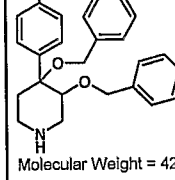
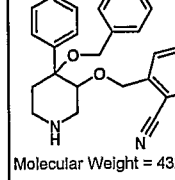


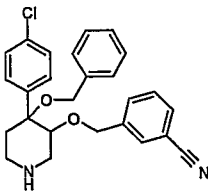
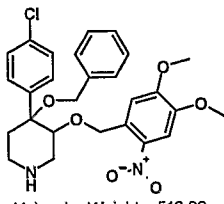
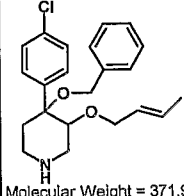
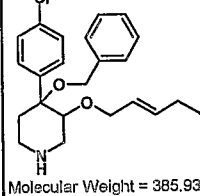
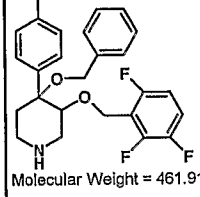
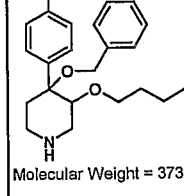
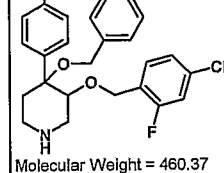
- To a suspension of resin-bound *cis*-[rac]-4,4-[benzyloxy-(4-chlorophenyl)]-3-hydroxypiperidine (Example 7, 200 mg, 0.192 mmol, loading capacity: 0.96 mmol/g) and alkyl halide (RX, 0.58 mmol) in 4:1 THF:DMF solution (2 mL) was added potassium t-butoxide (0.77 M in THF; 1 mL, 0.77 mmol). After stirring at room temperature overnight, the resin was filtered and washed successively with N,N-dimethylformamide, tetrahydrofuran, methanol, dichloromethane, and diethyl ether. The resin was dried at 40°C/high vacuum overnight. 1-Chloroethyl chloroformate (0.2 mL, 1.9 mmol) was added to the resin in 1,2-dichloroethane (2 mL). After shaking 4 hours at room temperature, the resin was filtered off and washed with 1,2-dichloroethane (3 x 2 mL).
- 10 The filtrate was evaporated *in vacuo*. Dry methanol (2 mL) was added to the residue and the solution was heated at 60°C for 3 hours. The solution was evaporated *in vacuo* to provide the desired product.

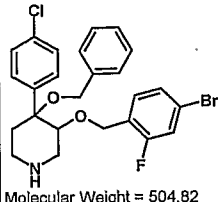
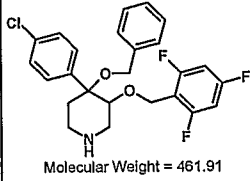
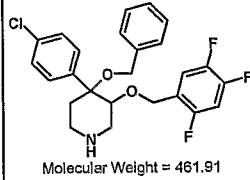
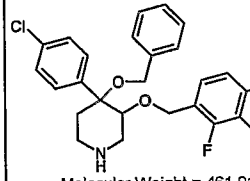
In the manner described above, the following compounds were prepared.

Example	Starting Material: Alkyl halide (RX)	Product	Nomenclature	Mass Spectrum (ES)
8A	3,4-DIFLUOROBENZYL BROMIDE (Aldrich)	 Molecular Weight = 443.92	4-Benzyloxy-4-(4-chloro-phenyl)-3-(3,4-difluoro-benzyloxy)-piperidine	444
8B	2,6-DIFLUOROBENZYL BROMIDE (Aldrich)	 Molecular Weight = 443.92	4-Benzyloxy-4-(4-chloro-phenyl)-3-(2,6-difluoro-benzyloxy)-piperidine	444
8C	2-PHENYLBENZYL BROMIDE (Aldrich)	 Molecular Weight = 484.04	4-Benzyloxy-3-(biphenyl-2-ylmethoxy)-4-(4-chloro-phenyl)-piperidine	484
8D	ALPHA-BROMO-P-TOLUNITRILE (Aldrich)	 Molecular Weight = 432.95	4-[4-Benzyloxy-4-(4-chloro-phenyl)-piperidin-3-yloxymethyl]-benzonitrile	433

Example	Starting Material: Alkyl halide (RX)	Product	Nomenclature	Mass Spectrum (ES)
8E	3-NITROBENZYL BROMIDE (Lancaster)	 Molecular Weight = 452.94	4-Benzyloxy-4-(4-chloro-phenyl)-3-(3-nitro-benzyloxy)-piperidine	453
8F	3-BROMOBENZYL BROMIDE (Aldrich)	 Molecular Weight = 486.83	4-Benzyloxy-3-(3-bromo-benzyloxy)-4-(4-chloro-phenyl)-piperidine	487
8G	2,4-DIFLUOROBENZYL BROMIDE (Lancaster)	 Molecular Weight = 443.92	4-Benzyloxy-4-(4-chloro-phenyl)-3-(2,4-difluoro-benzyloxy)-piperidine	444
8H	2-CHLORO-4-FLUOROBENZYL BROMIDE (Lancaster)	 Molecular Weight = 460.37	4-Benzyloxy-3-(2-chloro-4-fluoro-benzyloxy)-4-(4-chloro-phenyl)-piperidine	460
8I	METHYL 4-(BROMOMETHYL) BENZOATE (Aldrich)	 Molecular Weight = 465.97	4-[4-Benzyloxy-4-(4-chloro-phenyl)-piperidin-3-yloxymethyl]-benzoic acid methyl ester	466
8J	3,5-DIFLUOROBENZYL BROMIDE (Lancaster)	 Molecular Weight = 443.92	4-Benzyloxy-4-(4-chloro-phenyl)-3-(3,5-difluoro-benzyloxy)-piperidine	444
8K	3-CHLORO-2-FLUOROBENZYL BROMIDE (Lancaster)	 Molecular Weight = 460.37	4-Benzyloxy-3-(3-chloro-2-fluoro-benzyloxy)-4-(4-chloro-phenyl)-piperidine	460

Example	Starting Material: Alkyl halide (RX)	Product	Nomenclature	Mass Spectrum (ES)
8L	2,5-DICHLOROBENZYL BROMIDE (Lancaster)	 Molecular Weight = 476.83	4-Benzyloxy-4-(4-chloro-phenyl)-3-(2,5-dichloro-benzyloxy)-piperidine	477
8M	2,3-DIFLUOROBENZYL BROMIDE (Aldrich)	 Molecular Weight = 443.92	4-Benzyloxy-4-(4-chloro-phenyl)-3-(2,3-difluoro-benzyloxy)-piperidine	444
8N	4-(TRIFLUORO-METHYL)BENZYL BROMIDE (Aldrich)	 Molecular Weight = 475.94	4-Benzyloxy-4-(4-chloro-phenyl)-3-(4-trifluoromethyl-benzyloxy)-piperidine	476
8O	4-FLUOROBENZYL BROMIDE (Aldrich)	 Molecular Weight = 425.93	4-Benzyloxy-4-(4-chloro-phenyl)-3-(4-fluoro-benzyloxy)-piperidine	426
8P	4-BROMOBENZYL- BROMIDE (Aldrich)	 Molecular Weight = 486.83	4-Benzyloxy-3-(4-bromo-benzyloxy)-4-(4-chloro-phenyl)-piperidine	487
8Q	3-FLUOROBENZYL BROMIDE (Aldrich)	 Molecular Weight = 425.93	4-Benzyloxy-4-(4-chloro-phenyl)-3-(3-fluoro-benzyloxy)-piperidine	426
8R	ALPHA-BROMO-O- TOLUNITRILE (Aldrich)	 Molecular Weight = 432.95	2-[4-Benzyloxy-4-(4-chloro-phenyl)-piperidin-3-yloxymethyl]-benzonitrile	433

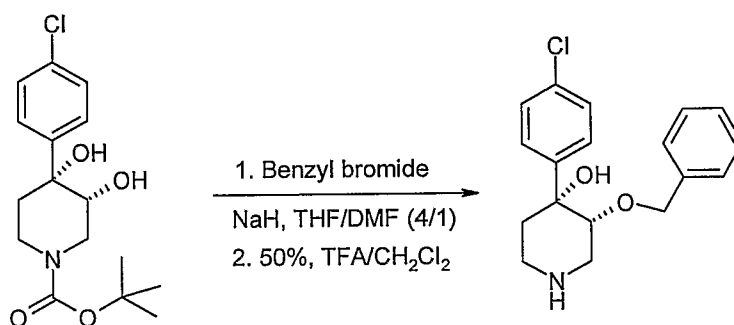
Example	Starting Material: Alkyl halide (RX)	Product	Nomenclature	Mass Spectrum (ES)
8S	ALPHA-BROMO-M-TOLUNITRILE (Aldrich)	 Molecular Weight = 432.95	3-[4-Benzyloxy-4-(4-chloro-phenyl)-piperidin-3-yloxymethyl]-benzonitrile	433
8T	4,5-DIMETHOXY-2-NITROBENZYL BROMIDE (Aldrich)	 Molecular Weight = 512.99	4-Benzyloxy-4-(4-chloro-phenyl)-3-(4,5-dimethoxy-2-nitro-benzyloxy)-piperidine	513
8U	CROTYL BROMIDE (Aldrich)	 Molecular Weight = 371.91	4-Benzyloxy-3-but-2-enyloxy-4-(4-chloro-phenyl)-piperidine	372
8V	1-BROMO-2-PENTENE (Aldrich)	 Molecular Weight = 385.93	4-Benzyloxy-4-(4-chloro-phenyl)-3-pent-2-enyloxy-piperidine	386
8W	2,3,6-TRIFLUORO-BENZYL BROMIDE (Aldrich)	 Molecular Weight = 461.91	4-Benzyloxy-4-(4-chloro-phenyl)-3-(2,3,6-trifluoro-benzyloxy)-piperidine	462
8X	1-IODOBUTANE (Aldrich)	 Molecular Weight = 373.92	4-Benzyloxy-3-butoxy-4-(4-chloro-phenyl)-piperidine	374
8Y	4-CHLORO-2-FLUOROBENZYL BROMIDE (Maybridge)	 Molecular Weight = 460.37	4-Benzyloxy-3-(4-chloro-2-fluoro-benzyloxy)-4-(4-chloro-phenyl)-piperidine	460

Example	Starting Material: Alkyl halide (RX)	Product	Nomenclature	Mass Spectrum (ES)
8Z	4-BROMO-2-FLUOROBENZYL BROMIDE (Aldrich)	 Molecular Weight = 504.82	4-Benzyloxy-3-(4-bromo-2-fluorobenzyloxy)-4-(4-chloro-phenyl)-piperidine	505
8Aa	2,4,6-TRIFLUORO- BENZYL BROMIDE (Lancaster)	 Molecular Weight = 461.91	4-Benzyloxy-4-(4-chloro-phenyl)-3-(2,4,6-trifluoro-benzyloxy)-piperidine	462
8Ab	2,4,5-TRIFLUORO BENZYL BROMIDE (Lancaster)	 Molecular Weight = 461.91	4-Benzyloxy-4-(4-chloro-phenyl)-3-(2,4,5-trifluoro-benzyloxy)-piperidine	462
8Ac	2,3,4-TRIFLUORO BENZYL BROMIDE (Lancaster)	 Molecular Weight = 461.91	4-Benzyloxy-4-(4-chloro-phenyl)-3-(2,3,4-trifluoro-benzyloxy)-piperidine	462

In the assay described in Example 28 the compound of Example 8O showed an IC_{50} of 19,8 μM .

Example 9

5 *cis*-[rac]-3-benzyloxy-4,4-[(4-chlorophenyl)-hydroxy]piperidine

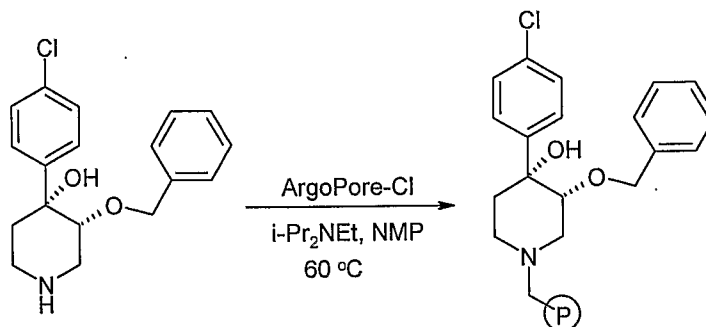


cis-[rac]-3-benzyloxy-4,4-[(4-chlorophenyl)-hydroxy]piperidine was prepared from *cis*-[rac]-4-(4-chlorophenyl)-3,4-dihydropiperidine-1-carboxylic acid tert-butyl

ester (Example 1) and benzyl bromide (Aldrich) following the procedure used in Examples 2 and 6.

Example 10

Resin-bound *cis*-[rac]-3-benzyloxy-4,4-[(4-chlorophenyl)-hydroxy]piperidine



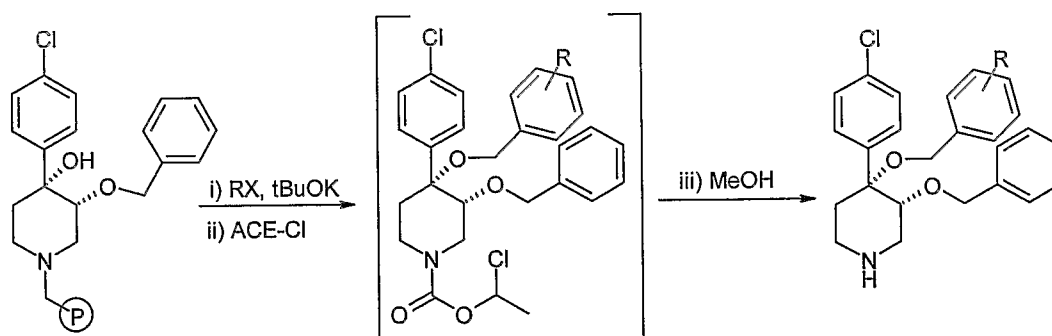
5

This resin-bound compound was prepared from *cis*-[rac]-3-benzyloxy-4,4-[(4-chlorophenyl)-hydroxy]piperidine (Example 9) following the procedure used in Example 7.

Example 11

10 *cis*-[rac]-3-Benzyloxy-4-(4-chlorophenyl)-4-substituted piperidine library:

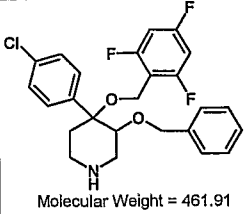
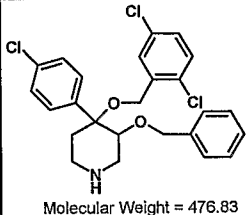
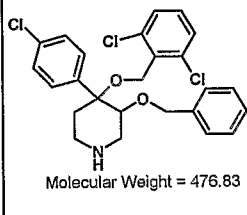
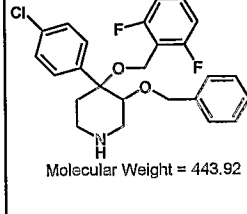
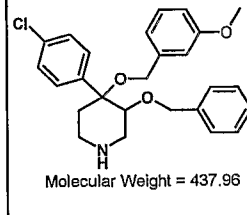
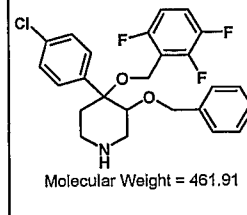
General procedure

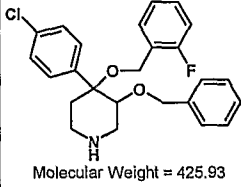
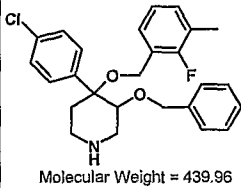


cis-[rac]-3-Benzyloxy-4-(4-chlorophenyl)-4-substituted piperidine was prepared from resin-bound *cis*-[rac]-3-benzyloxy-4,4-[(4-chlorophenyl)-hydroxy]piperidine (Example 10) and alkyl bromide following the procedure used in Example 8.

15

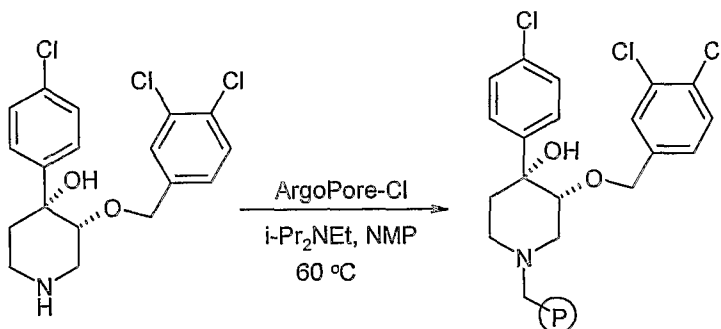
In the manner described above, the following compounds were prepared.

Example	Starting Material: Alkyl halide (RX)	Product	Nomenclature	Mass Spectrum (ES)
11A	2,4,6-TRIFLUORO BENZYL BROMIDE (Lancaster)	 Molecular Weight = 461.91	3-Benzyloxy-4-(4-chloro-phenyl)-4-(2,4,6-trifluoro-benzyloxy)-piperidine	462
11B	2,5-DICHLOROBENZYL BROMIDE (Lancaster)	 Molecular Weight = 476.83	3-Benzyloxy-4-(4-chloro-phenyl)-4-(2,5-dichloro-benzyloxy)-piperidine	477
11C	2,6-DICHLOROBENZYL BROMIDE (Aldrich)	 Molecular Weight = 476.83	3-Benzyloxy-4-(4-chloro-phenyl)-4-(2,6-dichloro-benzyloxy)-piperidine	477
11D	2,6-DIFLUOROBENZYL BROMIDE (Aldrich)	 Molecular Weight = 443.92	3-Benzyloxy-4-(4-chloro-phenyl)-4-(2,6-difluoro-benzyloxy)-piperidine	444
11E	3-METHOXYBENZYL BROMIDE (Aldrich)	 Molecular Weight = 437.96	3-Benzyloxy-4-(4-chloro-phenyl)-4-(3-methoxy-benzyloxy)-piperidine	438
11F	2,3,6-TRIFLUORO BENZYL BROMIDE (Aldrich)	 Molecular Weight = 461.91	3-Benzyloxy-4-(4-chloro-phenyl)-4-(2,3,6-trifluoro-benzyloxy)-piperidine	462

Example	Starting Material: Alkyl halide (RX)	Product	Nomenclature	Mass Spectrum (ES)
11G	2-FLUOROBENZYL BROMIDE (Aldrich)	 Molecular Weight = 425.93	3-Benzyloxy-4-(4-chloro-phenyl)-4-(2-fluoro-benzyloxy)-piperidine	426
11H	2-FLUORO-3-METHYLBENZYL BROMIDE (Maybridge)	 Molecular Weight = 439.96	3-Benzyloxy-4-(4-chloro-phenyl)-4-(2-fluoro-3-methyl-benzyloxy)-piperidine	440

Example 12

Resin-bound 3-(3,4-dichlorobenzyloxy)-4,4-[(4-chlorophenyl)-hydroxy]piperidine

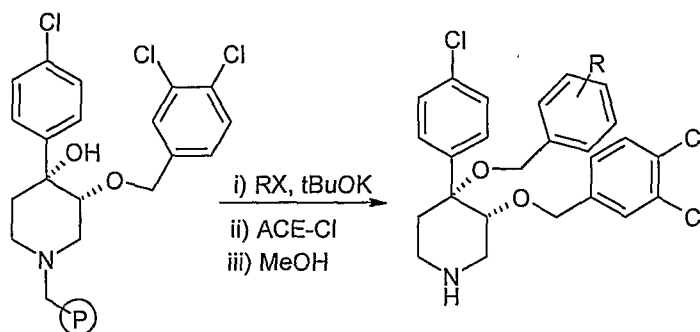


- 5 This resin-bound compound was prepared following the procedure used in Examples 2, 6, and 7.

Example 13

4-(4-Chloro-phenyl)-3-(3,4-dichloro-benzyloxy)-4-substituted piperidine:

General procedure

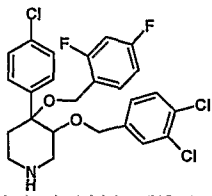
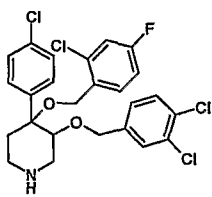
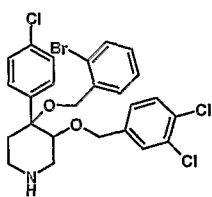
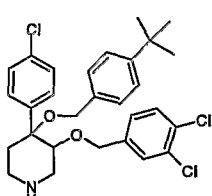
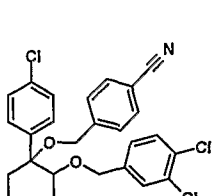
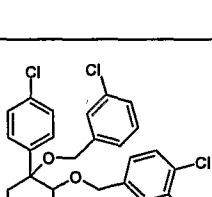


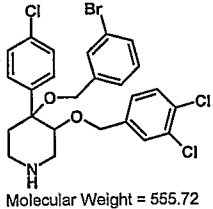
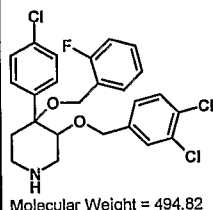
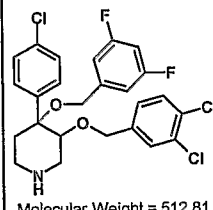
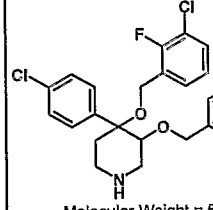
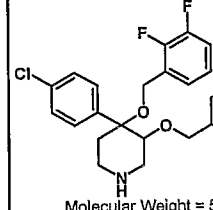
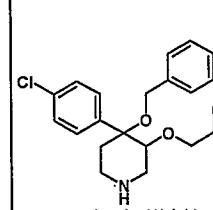
- 5 4-(4-Chloro-phenyl)-3-(3,4-dichloro-benzyloxy)-4-substituted piperidine was prepared from resin-bound 3-(3,4-dichlorobenzyloxy)-4,4-[(4-chlorophenyl)-hydroxy]piperidine (Example 12) and alkyl bromide following the procedure used in Example 8.

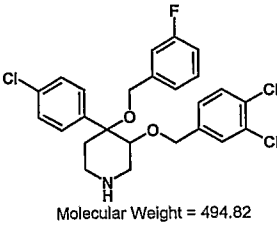
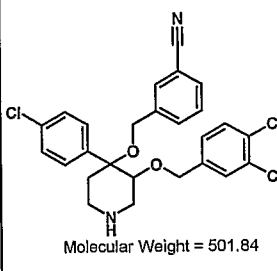
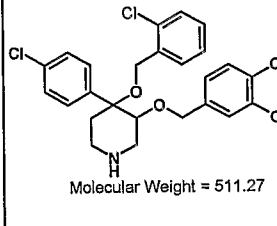
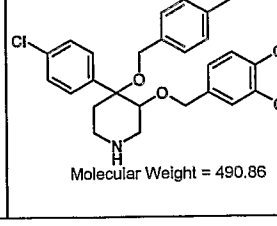
In the manner described above, the following compounds were prepared.

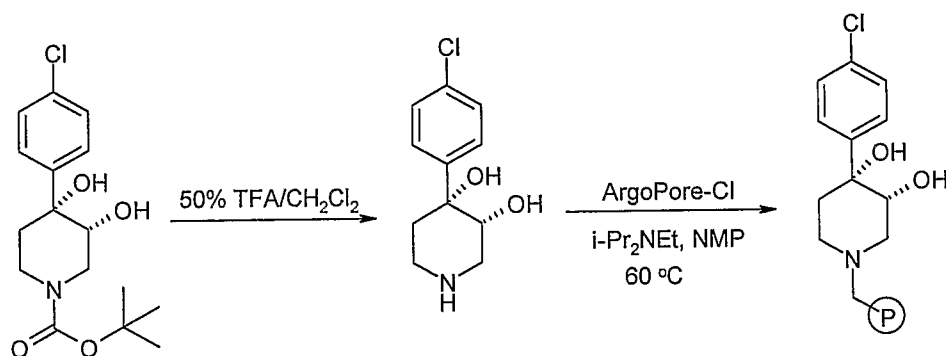
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Example	Starting Material: Alkyl halide (RX)	Product	Nomenclature	Mass Spectrum (ES)
13A	4-FLUOROBENZYL BROMIDE (Aldrich)	 Molecular Weight = 494.82	4-(4-Chloro-phenyl)- 3-(3,4-dichloro- benzyloxy)-4-(4- fluoro-benzyloxy)- piperidine	496
13B	4-BROMOBENZYL BROMIDE (Aldrich)	 Molecular Weight = 555.72	4-(4-Bromo- benzyloxy)-4-(4- chloro-phenyl)-3- (3,4-dichloro- benzyloxy)-piperidine	556

Example	Starting Material: Alkyl halide (RX)	Product	Nomenclature	Mass Spectrum (ES)
13C	2,4-DIFLUOROBENZYL BROMIDE (Lancaster)	 Molecular Weight = 512.81	4-(4-Chloro-phenyl)- 3-(3,4-dichloro- benzyloxy)-4-(2,4- difluoro-benzyloxy)- piperidine	514
13D	2-CHLORO-4- FLUOROBENZYLBR OMIDE (Lancaster)	 Molecular Weight = 529.26	4-(2-Chloro-4-fluoro- benzyloxy)-4-(4- chloro-phenyl)-3- (3,4-dichloro- benzyloxy)-piperidine	530
13E	2-BROMOBENZYL BROMIDE (Aldrich)	 Molecular Weight = 555.72	4-(2-Bromo- benzyloxy)-4-(4- chloro-phenyl)-3- (3,4-dichloro- benzyloxy)-piperidine	556
13F	4-(TERT- BUTYL)BENZYL BROMIDE (Fluka)	 Molecular Weight = 532.94	4-(4-tert-Butyl- benzyloxy)-4-(4- chloro-phenyl)-3- (3,4-dichloro- benzyloxy)-piperidine	533
13G	ALPHA-BROMO-P- TOLUNITRILE (Aldrich)	 Molecular Weight = 501.84	4-[4-(4-Chloro- phenyl)-3-(3,4- dichloro-benzyloxy)- piperidin-4- yloxymethyl]- benzonitrile	502
13H	3-CHLOROBENZYL BROMIDE (Aldrich)	 Molecular Weight = 511.27	4-(3-Chloro- benzyloxy)-4-(4- chloro-phenyl)-3- (3,4-dichloro- benzyloxy)-piperidine	512

Example	Starting Material: Alkyl halide (RX)	Product	Nomenclature	Mass Spectrum (ES)
13I	3-BROMOBENZYL BROMIDE (Aldrich)	 Molecular Weight = 555.72	4-(3-Bromo-benzyloxy)-4-(4-chloro-phenyl)-3-(3,4-dichloro-benzyloxy)-piperidine	556
13J	2-FLUOROBENZYL BROMIDE (Aldrich)	 Molecular Weight = 494.82	4-(4-Chloro-phenyl)-3-(3,4-dichloro-benzyloxy)-4-(2-fluoro-benzyloxy)-piperidine	496
13K	3,5-DIFLUOROBENZYL BROMIDE (Lancaster)	 Molecular Weight = 512.81	4-(4-Chloro-phenyl)-3-(3,4-dichloro-benzyloxy)-4-(3,5-difluoro-benzyloxy)-piperidine	514
13L	3-CHLORO-2-FLUOROBENZYL BROMIDE (Lancaster)	 Molecular Weight = 529.26	4-(3-Chloro-2-fluoro-benzyloxy)-4-(4-chloro-phenyl)-3-(3,4-dichloro-benzyloxy)-piperidine	530
13M	2,3-DIFLUOROBENZYL BROMIDE (Aldrich)	 Molecular Weight = 512.81	4-(4-Chloro-phenyl)-3-(3,4-dichloro-benzyloxy)-4-(2,3-difluoro-benzyloxy)-piperidine	514
13N	4-(TRIFLUORO-METHYL)BENZYL BROMIDE (Aldrich)	 Molecular Weight = 544.83	4-(4-Chloro-phenyl)-3-(3,4-dichloro-benzyloxy)-4-(4-trifluoromethyl-benzyloxy)-piperidine	546

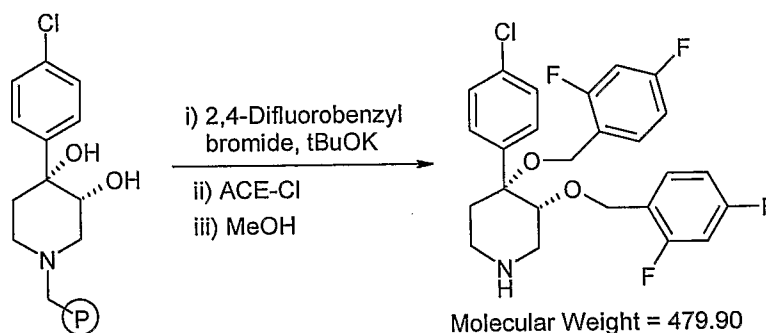
Example	Starting Material: Alkyl halide (RX)	Product	Nomenclature	Mass Spectrum (ES)
13O	3-FLUOROBENZYL BROMIDE (Aldrich)	 Molecular Weight = 494.82	4-(4-Chloro-phenyl)- 3-(3,4-dichloro- benzyloxy)-4-(3- fluoro-benzyloxy)- piperidine	496
13P	ALPHA-BROMO-M- TOLUNITRILE (Aldrich)	 Molecular Weight = 501.84	3-[4-(4-Chloro- phenyl)-3-(3,4- dichloro-benzyloxy)- piperidin-4- yl]oxymethyl]- benzonitrile	503
13Q	2-CHLOROBENZYL BROMIDE (Aldrich)	 Molecular Weight = 511.27	4-(2-Chloro- benzyloxy)-4-(4- chloro-phenyl)-3- (3,4-dichloro- benzyloxy)-piperidine	512
13R	4-METHYLBENZYL BROMIDE (Fluka)	 Molecular Weight = 490.86	4-(4-Chloro-phenyl)- 3-(3,4-dichloro- benzyloxy)-4-(4- methyl-benzyloxy)- piperidine	492

Example 14Resin-bound *cis*-[rac]-4-(4-Chloro-phenyl)-piperidine-3,4-diol

This resin-bound compound was prepared from *cis*-[rac]-4-(4-chlorophenyl)-3,4-dihydropiperidine-1-carboxylic acid tert-butyl ester (Example 1) following the procedure used in Example 6 and 7.

Example 15

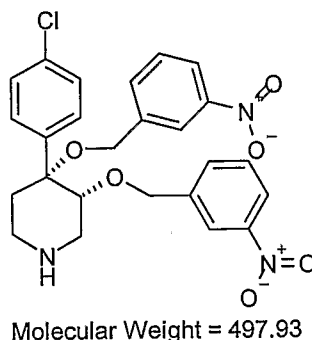
5 *cis*-[rac]-4-(4-Chloro-phenyl)-3,4-bis-(2,4-difluoro-benzyloxy)-piperidine



To a suspension of resin-bound 4-(4-Chloro-phenyl)-piperidine-3,4-diol (Example 14, 200 mg, 0.192 mmol, loading capacity: 0.96 mmol/g) and 2,4-difluorobenzyl bromide (Lancaster, 1.54 mmol) in 4:1 THF:DMF solution (2 mL) was added potassium t-butoxide (0.77 M in THF; 1 mL, 0.77 mmol). After stirring at room temperature overnight, the resin was filtered and washed successively with N,N-dimethylformamide, tetrahydrofuran, methanol, dichloromethane, and diethyl ether. The resin was dried at 40°C/high vacuum overnight. 1-Chloroethyl chloroformate (0.2 mL, 1.9 mmol) was added to the resin in 1,2-dichloroethane (2 mL). After shaking 4 hours at room temperature, the resin was filtered off and washed with 1,2-dichloroethane (3 x 2 mL). The filtrate was evaporated *in vacuo*. Dry methanol (2 mL) was added to the residue and the solution was heated at 60°C for 3 hours. The solution was evaporated *in vacuo* to provide the desired product. Mass spectrum (ES) $M^+ = 480$.

Example 16

20 *cis*-[rac]-4-(4-Chloro-phenyl)-3,4-bis-(3-nitro-benzyloxy)-piperidine

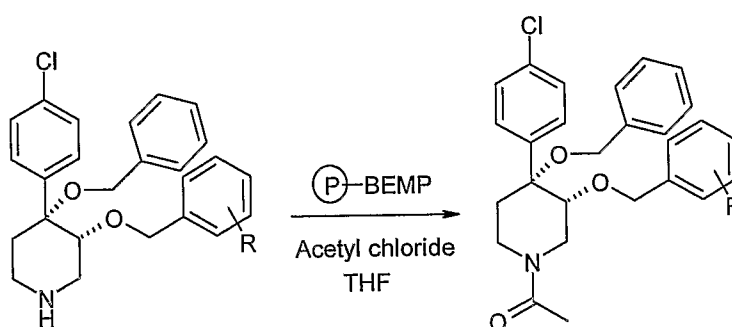


cis-[*rac*]-4-(4-Chloro-phenyl)-3,4-bis-(3-nitro-benzyloxy)-piperidine was prepared from resin-bound 4-(4-Chloro-phenyl)-piperidine-3,4-diol (Example 14) and 3-nitrobenzyl bromide (Lancaster) following the procedure used in Example 15. Mass spectrum (ES) $M^+ = 498$.

5 Example 17

cis-[*rac*]-1-[4-Benzyloxy-4-(4-chloro-phenyl)-3-substituted-piperidin-1-yl]-ethanone library:

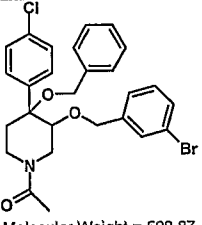
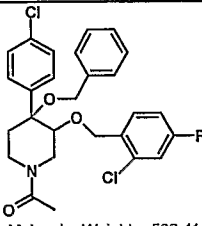
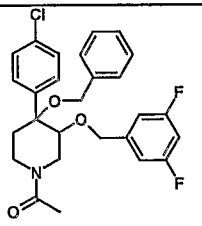
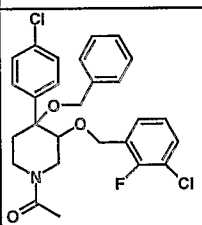
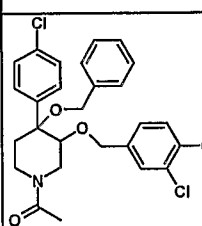
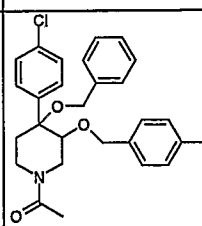
General procedure

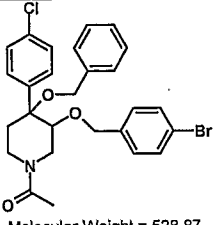
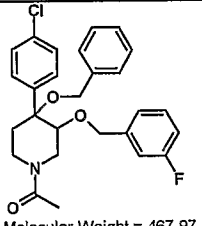
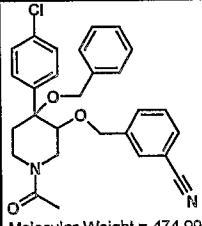
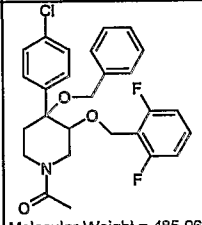
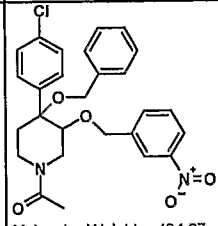
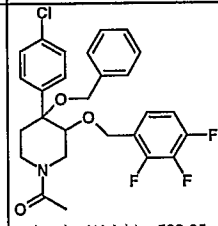


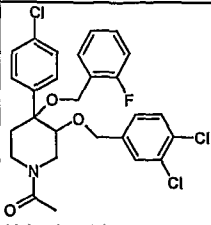
10 A mixture of 4,4-[benzyloxy-(4-chlorophenyl)]-3-aryloxypiperidine (Example 8, 0.012 mmol), polymer-supported BEMP (10 mg, 0.023 mmol, loading capacity: 2.3 mmol/g from Fluka Inc.), and acetyl chloride (0.01 mL, 0.14 mmol) in tetrahydrofuran (1 mL) was shaken at room temperature overnight. The resin was filtered and washed successively with CH_2Cl_2 , and MeOH. The filtrate was evaporated *in vacuo* to provide
15 the desired product.

In the manner described above, the following compounds were prepared.

Example	Starting Material	Product	Nomenclature	Mass Spectrum (ES)
17A	Example 8G	 Molecular Weight = 485.96	1-[4-Benzyloxy-4-(4-chloro-phenyl)-3-(2,4-difluoro-benzyloxy)-piperidin-1-yl]-ethanone	486

Example	Starting Material	Product	Nomenclature	Mass Spectrum (ES)
17B	Example 8F	 Molecular Weight = 528.87	1-[4-Benzyloxy-3-(3-bromo-benzyloxy)-4-(4-chloro-phenyl)-piperidin-1-yl]-ethanone	530
17C	Example 8H	 Molecular Weight = 502.41	1-[4-Benzyloxy-3-(2-chloro-4-fluoro-benzyloxy)-4-(4-chloro-phenyl)-piperidin-1-yl]-ethanone	502
17D	Example 8D	 Molecular Weight = 485.96	1-[4-Benzyloxy-4-(4-chloro-phenyl)-3-(3,5-difluoro-benzyloxy)-piperidin-1-yl]-ethanone	486
17E	Example 8K	 Molecular Weight = 502.41	1-[4-Benzyloxy-3-(3-chloro-2-fluoro-benzyloxy)-4-(4-chloro-phenyl)-piperidin-1-yl]-ethanone	502
17F	Example 4	 Molecular Weight = 518.87	1-[4-Benzyloxy-4-(4-chloro-phenyl)-3-(3,4-dichloro-benzyloxy)-piperidin-1-yl]-ethanone	518
17G	Example 8O	 Molecular Weight = 467.97	1-[4-Benzyloxy-4-(4-chloro-phenyl)-3-(4-fluoro-benzyloxy)-piperidin-1-yl]-ethanone	468

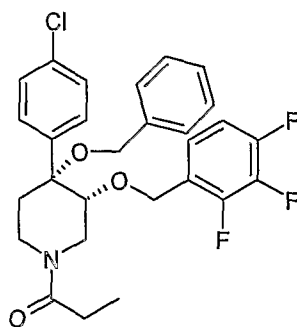
Example	Starting Material	Product	Nomenclature	Mass Spectrum (ES)
17H	Example 8P	 Molecular Weight = 528.87	1-[4-Benzyloxy-3-(4-bromo-benzyloxy)-4-(4-chloro-phenyl)-piperidin-1-yl]-ethanone	530
17I	Example 8Q	 Molecular Weight = 467.97	1-[4-Benzyloxy-4-(4-chloro-phenyl)-3-(3-fluoro-benzyloxy)-piperidin-1-yl]-ethanone	468
17J	Example 8S	 Molecular Weight = 474.99	3-[1-Acetyl-4-benzyloxy-4-(4-chloro-phenyl)-piperidin-3-yloxymethyl]-benzonitrile	475
17K	Example 8B	 Molecular Weight = 485.96	1-[4-Benzyloxy-4-(4-chloro-phenyl)-3-(2,6-difluoro-benzyloxy)-piperidin-1-yl]-ethanone	486
17L	Example 8E	 Molecular Weight = 494.97	1-[4-Benzyloxy-4-(4-chloro-phenyl)-3-(3-nitro-benzyloxy)-piperidin-1-yl]-ethanone	495
17M	Example 8Ac	 Molecular Weight = 503.95	1-[4-Benzyloxy-4-(4-chloro-phenyl)-3-(2,3,4-trifluoro-benzyloxy)-piperidin-1-yl]-ethanone	504

Example	Starting Material	Product	Nomenclature	Mass Spectrum (ES)
17N	Example 13J	 Molecular Weight = 536.86	1-[4-(4-Chloro-phenyl)-3-(3,4-dichloro-benzyloxy)-4-(2-fluoro-benzyloxy)-piperidin-1-yl]-ethanone	538

Example 17K has an IC_{50} of 5.5 μM in the assay described in Example 28.

Example 18

cis-[rac]-1-[4-Benzyloxy-4-(4-chloro-phenyl)-3-(2,3,4-trifluoro-benzyloxy)-piperidin-1-yl]-propan-1-one

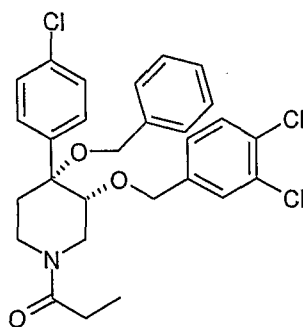


Molecular Weight = 517.97

cis-[rac]-1-[4-Benzyloxy-4-(4-chloro-phenyl)-3-(2,3,4-trifluoro-benzyloxy)-piperidin-1-yl]-propan-1-one was prepared from 4-Benzyloxy-4-(4-chloro-phenyl)-3-(2,3,4-trifluoro-benzyloxy)-piperidine (Example 8Ad) and propionyl chloride (Aldrich) following the procedure used in Example 17. Mass spectrum (ES) $M^+ = 518$.

Example 19

cis-[rac]-1-[4-Benzyloxy-4-(4-chloro-phenyl)-3-(3,4-dichloro-benzyloxy)-piperidin-1-yl]-propan-1-one

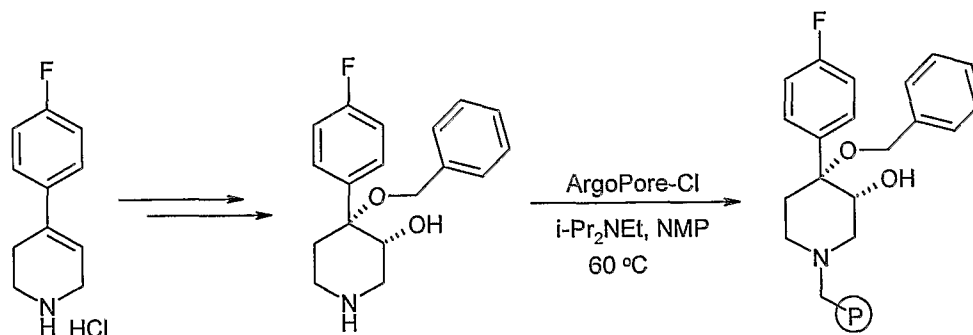


Molecular Weight = 532.89

- 5 *cis*-[rac]-1-[4-Benzyloxy-4-(4-chloro-phenyl)-3-(3,4-dichloro-benzyloxy)-piperidin-1-yl]-propan-1-one was prepared from *cis*-[rac]-4-(benzyloxy)-4-(4-chlorophenyl)-3-(3,4-dichlorobenzoyloxy)-piperidine (Example 4) following the procedure used in Example 18. Mass spectrum (ES) $M^+ = 533$.

Example 20

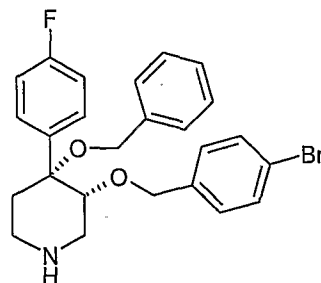
- 10 Resin-bound *cis*-[rac]-4-benzyloxy-4-(4-fluoro-phenyl)-piperidin-3-ol



This resin-bound compound was prepared from 4-(4-fluorophenyl)-1,2,3,6-tetrahydropyridine hydrochloride (Acros) following the procedure used in Examples 1, 5, 6, and 7.

Example 21

cis-[rac]-4-Benzoyloxy-3-(4-bromo-benzyloxy)-4-(4-fluoro-phenyl)-piperidine

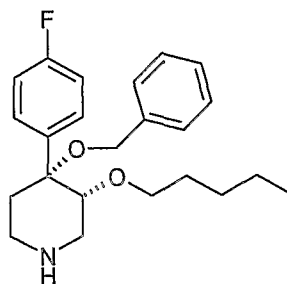


Molecular Weight = 470.38

cis-[rac]-4-Benzoyloxy-3-(4-bromo-benzyloxy)-4-(4-fluoro-phenyl)-piperidine was prepared from resin-bound *cis*-[rac]-4-benzyloxy-4-(4-fluoro-phenyl)-piperidin-3-ol (Example 20) and 4-bromobenzyl bromide (Aldrich) following the procedure used in Example 8. Mass spectrum (ES) MH^+ = 471.

Example 22

cis-[rac]- 4-Benzoyloxy-4-(4-fluoro-phenyl)-3-pentyloxy-piperidine



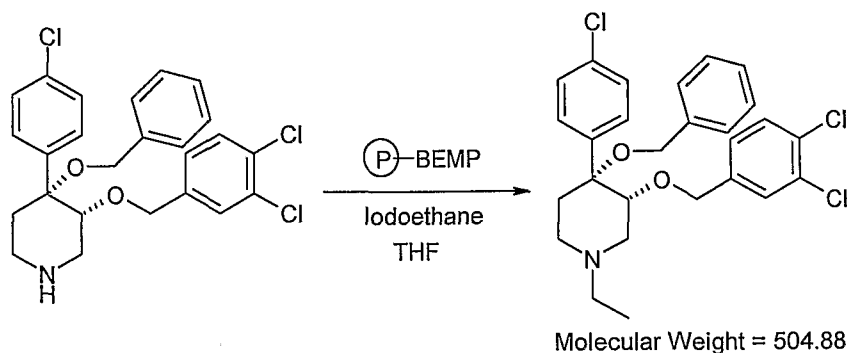
Molecular Weight = 371.49

10

cis-[rac]- 4-Benzoyloxy-4-(4-fluoro-phenyl)-3-pentyloxy-piperidine was prepared from resin-bound *cis*-[rac]-4-benzyloxy-4-(4-fluoro-phenyl)-piperidin-3-ol (Example 20) and 1-iodopentane (Aldrich) following the procedure used in Example 8. Mass spectrum (ES) MH^+ = 372. IC_{50} = 56 μ M (in the assay described in Example 28).

Example 23

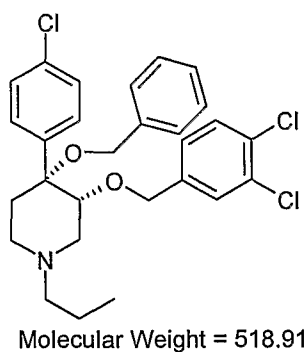
cis-[rac]-4-Benzyloxy-4-(4-chloro-phenyl)-3-(3,4-dichloro-benzyloxy)-1-ethyl-piperidine



- 5 A mixture of 4-benzyloxy-4-(4-chloro-phenyl)-3-(3,4-dichloro-benzyloxy)-piperidine (Example 4, 0.01 mmol), polymer-supported BEMP (6.5 mg, 0.015 mmol, loading capacity: 2.3 mmol/g from Fluka Inc.), iodoethane (Aldrich, 0.015 mmol) in tetrahydrofuran (1 mL) was shaken at room temperature overnight. The resin was filtered and washed successively with CH_2Cl_2 , and MeOH. The filtrate was evaporated *in*
- 10 *vacuo* to provide the desired product. Mass spectrum (ES) $\text{MH}^+ = 506$. $\text{IC}_{50} = 4.9 \mu\text{M}$ (in the assay described in Example 28).

Example 24

cis-[rac]- 4-Benzyloxy-4-(4-chloro-phenyl)-3-(3,4-dichloro-benzyloxy)-1-propyl-piperidine

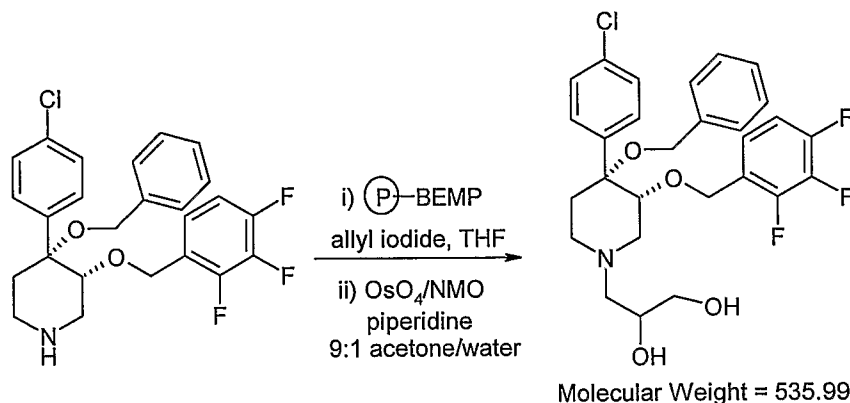


15

cis-[rac]- 4-Benzyloxy-4-(4-chloro-phenyl)-3-(3,4-dichloro-benzyloxy)-1-propyl-piperidine was prepared from 4-benzyloxy-4-(4-chloro-phenyl)-3-(3,4-dichloro-benzyloxy)-piperidine (Example 4) and 1-iodopropane (Aldrich) following the procedure used in Example 23. Mass spectrum (ES) $\text{M}^+ = 519$.

Example 25

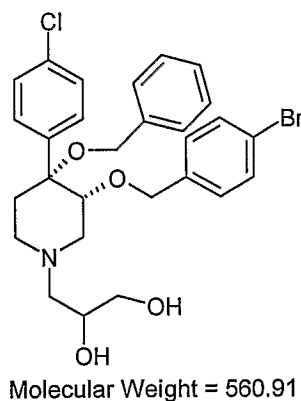
cis-[rac]-3-[4-Benzyloxy-4-(4-chloro-phenyl)-3-(2,3,4-trifluoro-benzyloxy)-piperidin-1-yl]-propane-1,2-diol



- 5 A mixture of 4-benzyloxy-4-(4-chloro-phenyl)-3-(2,3,4-trifluoro-benzyloxy)-piperidine (Example 8Ac, 6 mg, 0.013 mmol), polymer-supported BEMP (10 mg, 0.023 mmol, loading capacity: 2.3 mmol/g from Fluka Inc.), allyl iodide (Aldrich, 3 μ L, 0.003 mmol) in tetrahydrofuran (1 mL) was shaken at room temperature for 2 hours. The resin was filtered and washed successively with CH_2Cl_2 , and MeOH. The filtrate was
- 10 evaporated *in vacuo*. Without purification, the residue was dissolved in 9:1 acetone/water solution (1 mL). To the solution was added osmium tetroxide (Aldrich, 10 μ L, 0.008 mmol) and 4-methylmorpholine *N*-oxide (Aldrich, 12 mg, 0.1 mmol). The mixture was stirred overnight and Na_2SO_3 was added. After stirring for 2 hours, the mixture was filtered through a silica gel pad. The filtrate was evaporated *in vacuo* to provide the
- 15 desired product. Mass spectrum (ES) $M^+ = 536$.

Example 26

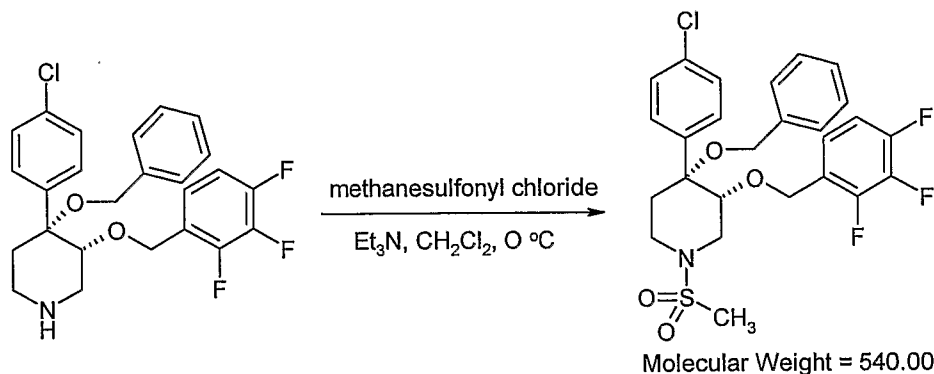
cis-[rac]-3-[4-Benzyloxy-3-(4-bromo-benzyloxy)-4-(4-chloro-phenyl)-piperidin-1-yl]-propane-1,2-diol



This compound was prepared from 4-benzyloxy-3-(4-bromo-benzyloxy)-4-(4-chloro-phenyl)-piperidine (Example 8P) followed the procedure used in Example 25. Mass spectrum (ES) $MH^+ = 562$. $IC_{50} = 25.8 \mu M$ (in the assay described in Example 28).

Example 27

- 5 *cis*-[rac]-3-[4-Benzyloxy-4-(4-chloro-phenyl)-3-(2,3,4-trifluoro-benzyloxy)-piperidin-1-yl]-methane sulfonyl



- To a solution of 4-benzyloxy-4-(4-chloro-phenyl)-3-(2,3,4-trifluoro-benzyloxy)-piperidine (Example 8Ac, 4 mg, 0.008 mmol) and triethylamine (6 μL , 0.08 mmol) in dichloromethane (0.5 mL) at 0 °C was added dropwise methanesulfonyl chloride (Aldrich, 2.5 μL , 0.015 mmol). After stirring for 2 hours, the mixture was filtered through an amino silica gel pad (Silicycle). The filtrate was evaporated *in vacuo* to provide the desired product. Mass spectrum (ES) $MH^+ = 541$.

Example 28

15 *In Vitro* Activity Assay

- The ability of the substituted piperidine compounds of the invention to inhibit the interaction between p53 and MDM2 proteins was measured by an ELISA (Enzyme-Linked Immuno Sorbent Assay) in which recombinant GST-tagged MDM2 binds to a peptide that resembles the MDM2-interacting region of p53 (Böttger et al., J. Mol. Bio. 1997, Vol. 269, pgs. 744-756). This peptide is immobilized to the surface of a 96 well plate via N-terminal biotin, which binds to streptavidin-coated wells. MDM2 is added to each well in the presence of anti-MDM2 mouse monoclonal antibody (SMP-14, Santa Cruz Biotech). After removal of the unbound MDM2 protein, a peroxidase-linked secondary antibody (anti-mouse IgG, Roche Molecular Biochemicals) and the amount of peptide-bound MDM2 is determined colorimetrically by the addition of a peroxidase substrate (MTB Microwell Peroxidase Substrate System, Kirkegaard & Perry Labs).

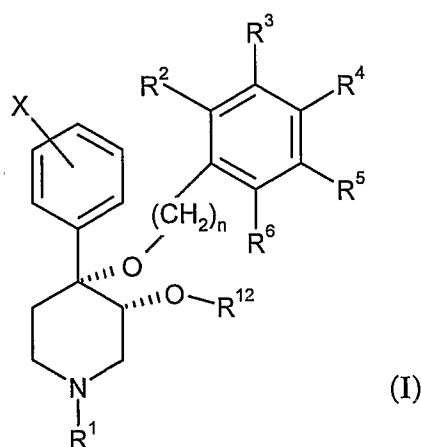
Test plates were prepared by coating with streptavidin (5 mg/ml in PBS) for 2 hours followed by a PBS (phosphate-buffered saline) wash and overnight blocking with 150 μ l of blocking buffer containing 2 mg/ml bovine serum albumin (Sigma) and 0.05% Tween 20 (Sigma) in PBS at 4°C. Biotinylated peptide (1 μ M) is added to each well in 50 μ l of blocking buffer and washed extensively after a 1-hour incubation. Test compounds were diluted in a separate 96 well plate and added in triplicate to a compound incubation plate containing a mix of the MDM2 protein and anti-MDM2 antibody. After 20 minutes incubation, the content of the plate is transferred to the test plate and incubated for an additional 1 hour. The secondary anti-mouse IgG antibody is added to the test plate preceded and followed by a triple wash with 0.05% Tween 20 in PBS. Finally, peroxidase substrate is added to each well and the absorption was read using a plate reader (MR7000, Dynatech) at 450nm. The inhibitory activity of the test compounds was measured as a percentage of the bound MDM2 in treated vs. untreated wells and IC₅₀ was calculated.

15 The inhibitory activity (IC₅₀) of the compounds prepared in the examples above, and represented by formula (I) or (II), is in the range of 3 μ M to 100 μ M.

20 While a number of embodiments of this invention have been represented, it is apparent that the basic construction can be altered to provide other embodiments that utilize the invention without departing from the spirit and scope of the invention. All such modifications and variations are intended to be included within the scope of the invention as defined in the appended claims rather than the specific embodiments that have been presented by way of example.

Claims

1. Compounds represented by formula (I):



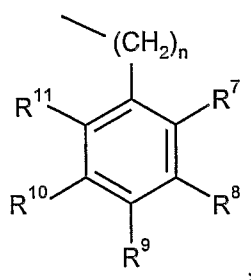
and the pharmaceutically acceptable salts thereof; wherein

5 n is an integer independently selected from 1 or 2;

X is halogen;

R¹ is selected from the group consisting of hydrogen, carbonyl, sulfonyl, lower alkyl, and lower alkyl substituted by carbonyl, sulfonyl, or hydroxy;

10 R¹² is selected from the group consisting of alkyl or alkenyl having from 1 to about 5 carbon atoms, and

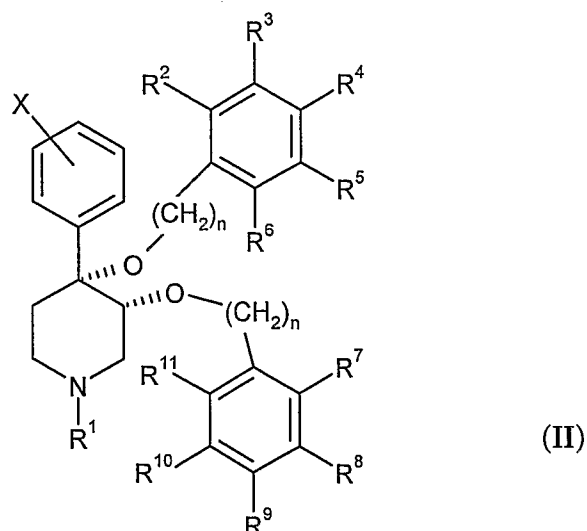


wherein R⁷ to R¹¹ are independently selected from the group consisting of hydrogen, halogen, -CN, -NO₂, CF₃, -OCH₃, -COOCH₃, and -C₆H₅;

15 R² to R⁶ are independently selected from the group consisting of hydrogen, halogen, lower alkyl, -C(CH₃)₃, CF₃, -OCH₃, -NO₂, and -CN;

and in case R¹² is alkyl or alkenyl having from 1 to about 5 carbon atoms, R² to R⁶ are hydrogen.

2. Compounds of formula I according to claim 1 represented by formula (II):



and the pharmaceutically acceptable salts thereof; wherein

n is an integer independently selected from 1 or 2;

5 X is halogen;

R¹ is selected from the group consisting of hydrogen, carbonyl, sulfonyl, lower alkyl, and lower alkyl substituted by carbonyl, sulfonyl, or hydroxy;

R² to R⁶ are independently selected from the group consisting of hydrogen, halogen, lower alkyl, -C(CH₃)₃, CF₃, -OCH₃, -NO₂, and -CN; and

10 R⁷ to R¹¹ are independently selected from the group consisting of hydrogen, halogen, -CN, -NO₂, CF₃, -OCH₃, -COOCH₃, and -C₆H₅.

3. Compounds of formula II according to claim 2, wherein n is 1.

4. Compounds of formula II according to claim 2, wherein X is chloro.

5. Compounds of formula II according to claim 2, wherein X is a *para* substituent.

15 6. Compounds of formula II according to claim 2, wherein R¹ is selected from the group consisting of hydrogen, -CH₂CH₃, -CH₂CH₂CH₃, -COCH₃, -COCH₂CH₃, -CH₂CHOHCH₂OH, and -SO₂CH₃.

7. Compounds of formula II according to claim 2, wherein R² and R⁶ are independently selected from the group consisting of hydrogen, fluoro, chloro, and

20 bromo.

8. Compounds of formula II according to claim 2, wherein R³ and R⁵ are independently selected from the group consisting of hydrogen, fluoro, chloro, bromo, -CH₃, -OCH₃, -CN, and -NO₂.

9. Compounds of formula II according to claim 2, wherein R⁴ is selected from the group consisting of hydrogen, fluoro, chloro, bromo, -C(CH₃)₃, -CH₃, -CN, and -CF₃.

10. Compounds of formula II according to claim 2, wherein R⁷ and R¹¹ are independently selected from the group consisting of hydrogen, fluoro, chloro, -CN, -NO₂, and -C₆H₅.

11. Compounds of formula II according to claim 2, wherein R⁸ and R¹⁰ are independently selected from the group consisting of hydrogen, fluoro, chloro, bromo, -CN, -NO₂, and -OCH₃.

12. Compounds of formula II according to claim 2, wherein R⁹ is selected from the group consisting of hydrogen, fluoro, chloro, bromo, -OCH₃, -CN, -CF₃, and -COOCH₃.

13. Compounds of formula II according to claim 2, wherein the compound is selected from the group consisting of:

cis-[rac]-4-benzyloxy-4-(4-chloro-phenyl)-3-(3,4-difluoro-benzyloxy)-piperidine;

cis-[rac]-4-benzyloxy-4-(4-chloro-phenyl)-3-(2,6-difluoro-benzyloxy)-piperidine;

cis-[rac]-4-benzyloxy-3-(biphenyl-2-ylmethoxy)-4-(4-chloro-phenyl)-piperidine;

cis-[rac]-4-[4-benzyloxy-4-(4-chloro-phenyl)-piperidin-3-yloxymethyl]-benzonitrile;

20 *cis*-[rac]-4-benzyloxy-4-(4-chloro-phenyl)-3-(3-nitro-benzyloxy)-piperidine;

cis-[rac]-4-benzyloxy-3-(3-bromo-benzyloxy)-4-(4-chloro-phenyl)-piperidine;

cis-[rac]-4-benzyloxy-4-(4-chloro-phenyl)-3-(2,4-difluoro-benzyloxy)-piperidine;

cis-[rac]-4-benzyloxy-3-(2-chloro-4-fluoro-benzyloxy)-4-(4-chloro-phenyl)-piperidine;

25 *cis*-[rac]-4-[4-benzyloxy-4-(4-chloro-phenyl)-piperidin-3-yloxymethyl]-benzoic acid methyl ester;

cis-[rac]-4-benzyloxy-4-(4-chloro-phenyl)-3-(3,5-difluoro-benzyloxy)-piperidine;

cis-[rac]-4-benzyloxy-3-(3-chloro-2-fluoro-benzyloxy)-4-(4-chloro-phenyl)-piperidine;

- cis*-[rac]-4-benzyloxy-4-(4-chloro-phenyl)-3-(2,5-dichloro-benzyloxy)-piperidine;
- cis*-[rac]-4-benzyloxy-4-(4-chloro-phenyl)-3-(2,3-difluoro-benzyloxy)-piperidine;
- cis*-[rac]-4-benzyloxy-4-(4-chloro-phenyl)-3-(4-trifluoromethyl-benzyloxy)-piperidine;
- cis*-[rac]-4-benzyloxy-4-(4-chloro-phenyl)-3-(4-fluoro-benzyloxy)-piperidine;
- 5 *cis*-[rac]-4-benzyloxy-3-(4-bromo-benzyloxy)-4-(4-chloro-phenyl)-piperidine;
- cis*-[rac]-4-benzyloxy-4-(4-chloro-phenyl)-3-(3-fluoro-benzyloxy)-piperidine;
- cis*-[rac]-2-[4-benzyloxy-4-(4-chloro-phenyl)-piperidin-3-yloxymethyl]-benzonitrile;
- cis*-[rac]-3-[4-benzyloxy-4-(4-chloro-phenyl)-piperidin-3-yloxymethyl]-benzonitrile;
- cis*-[rac]-4-benzyloxy-4-(4-chloro-phenyl)-3-(4,5-dimethoxy-2-nitro-benzyloxy)-
- 10 piperidine;
- cis*-[rac]-4-benzyloxy-3-but-2-enyloxy-4-(4-chloro-phenyl)-piperidine;
- cis*-[rac]-4-benzyloxy-4-(4-chloro-phenyl)-3-pent-2-enyloxy-piperidine;
- cis*-[rac]-4-benzyloxy-4-(4-chloro-phenyl)-3-(2,3,6-trifluoro-benzyloxy)-piperidine;
- cis*-[rac]-4-benzyloxy-3-butoxy-4-(4-chloro-phenyl)-piperidine;
- 15 *cis*-[rac]-4-benzyloxy-3-(4-chloro-2-fluoro-benzyloxy)-4-(4-chloro-phenyl)-piperidine;
- cis*-[rac]-4-benzyloxy-3-(4-bromo-2-fluoro-benzyloxy)-4-(4-chloro-phenyl)-piperidine;
- cis*-[rac]-4-benzyloxy-4-(4-chloro-phenyl)-3-(2,4,6-trifluoro-benzyloxy)-piperidine;
- cis*-[rac]-4-benzyloxy-4-(4-chloro-phenyl)-3-(2,4,5-trifluoro-benzyloxy)-piperidine;
- cis*-[rac]-4-benzyloxy-4-(4-chloro-phenyl)-3-(2,3,4-trifluoro-benzyloxy)-piperidine;
- 20 *cis*-[rac]-3-benzyloxy-4-(4-chloro-phenyl)-4-(2,4,6-trifluoro-benzyloxy)-piperidine;
- cis*-[rac]-3-benzyloxy-4-(4-chloro-phenyl)-4-(2,5-dichloro-benzyloxy)-piperidine;
- cis*-[rac]-3-benzyloxy-4-(4-chloro-phenyl)-4-(2,6-dichloro-benzyloxy)-piperidine;
- cis*-[rac]-3-benzyloxy-4-(4-chloro-phenyl)-4-(2,6-difluoro-benzyloxy)-piperidine;
- cis*-[rac]-3-benzyloxy-4-(4-chloro-phenyl)-4-(3-methoxy-benzyloxy)-piperidine;

cis-[rac]-3-benzyloxy-4-(4-chloro-phenyl)-4-(2,3,6-trifluoro-benzyloxy)-piperidine;

cis-[rac]-3-benzyloxy-4-(4-chloro-phenyl)-4-(2-fluoro-benzyloxy)-piperidine; and

cis-[rac]-3-benzyloxy-4-(4-chloro-phenyl)-4-(2-fluoro-3-methyl-benzyloxy)-piperidine.

14. Compounds of formula II according to claim 2, wherein the compound is
5 selected from the group consisting of:

cis-[rac]-4-(4-chloro-phenyl)-3-(3,4-dichloro-benzyloxy)-4-(4-fluoro-benzyloxy)-
piperidine;

cis-[rac]-4-(4-bromo-benzyloxy)-4-(4-chloro-phenyl)-3-(3,4-dichloro-benzyloxy)-
piperidine;

- 10 *cis*-[rac]-4-(4-chloro-phenyl)-3-(3,4-dichloro-benzyloxy)-4-(2,4-difluoro-benzyloxy)-
piperidine;

cis-[rac]-4-(2-chloro-4-fluoro-benzyloxy)-4-(4-chloro-phenyl)-3-(3,4-dichloro-
benzyloxy)-piperidine;

- 15 *cis*-[rac]-4-(2-bromo-benzyloxy)-4-(4-chloro-phenyl)-3-(3,4-dichloro-benzyloxy)-
piperidine;

cis-[rac]-4-(4-tert-butyl-benzyloxy)-4-(4-chloro-phenyl)-3-(3,4-dichloro-benzyloxy)-
piperidine;

cis-[rac]-4-[4-(4-chloro-phenyl)-3-(3,4-dichloro-benzyloxy)-piperidin-4-yloxymethyl]-
benzonitrile;

- 20 *cis*-[rac]-4-(3-chloro-benzyloxy)-4-(4-chloro-phenyl)-3-(3,4-dichloro-benzyloxy)-
piperidine;

cis-[rac]-4-(3-bromo-benzyloxy)-4-(4-chloro-phenyl)-3-(3,4-dichloro-benzyloxy)-
piperidine;

- 25 *cis*-[rac]-4-(4-chloro-phenyl)-3-(3,4-dichloro-benzyloxy)-4-(2-fluoro-benzyloxy)-
piperidine;

cis-[rac]-4-(4-chloro-phenyl)-3-(3,4-dichloro-benzyloxy)-4-(3,5-difluoro-benzyloxy)-
piperidine;

cis-[rac]-4-(3-chloro-2-fluoro-benzyloxy)-4-(4-chloro-phenyl)-3-(3,4-dichloro-
benzyloxy)-piperidine;

cis-[rac]-4-(4-chloro-phenyl)-3-(3,4-dichloro-benzyloxy)-4-(2,3-difluoro-benzyloxy)-piperidine;

cis-[rac]-4-(4-chloro-phenyl)-3-(3,4-dichloro-benzyloxy)-4-(4-trifluoromethyl-benzyloxy)-piperidine;

- 5 *cis*-[rac]-4-(4-chloro-phenyl)-3-(3,4-dichloro-benzyloxy)-4-(3-fluoro-benzyloxy)-piperidine;

cis-[rac]-3-[4-(4-chloro-phenyl)-3-(3,4-dichloro-benzyloxy)-piperidin-4-yloxymethyl]-benzonitrile;

- 10 *cis*-[rac]-4-(2-chloro-benzyloxy)-4-(4-chloro-phenyl)-3-(3,4-dichloro-benzyloxy)-piperidine; and

cis-[rac]-4-(4-chloro-phenyl)-3-(3,4-dichloro-benzyloxy)-4-(4-methyl-benzyloxy)-piperidine.

15 15. Compounds of formula II according to claim 2, wherein the compound is selected from the group consisting of:

- 15 *cis*-[rac]-4-(4-chloro-phenyl)-3,4-bis-(2,4-difluoro-benzyloxy)-piperidine; and
cis-[rac]-4-(4-chloro-phenyl)-3,4-bis-(3-nitro-benzyloxy)-piperidine.

16. Compounds of formula II according to claim 2, wherein the compound is selected from the group consisting of:

- 20 *cis*-[rac]-1-[4-benzyloxy-4-(4-chloro-phenyl)-3-(2,4-difluoro-benzyloxy)-piperidin-1-yl]-ethanone;

cis-[rac]-1-[4-benzyloxy-3-(3-bromo-benzyloxy)-4-(4-chloro-phenyl)-piperidin-1-yl]-ethanone;

cis-[rac]-1-[4-benzyloxy-3-(2-chloro-4-fluoro-benzyloxy)-4-(4-chloro-phenyl)-piperidin-1-yl]-ethanone;

- 25 *cis*-[rac]-1-[4-benzyloxy-4-(4-chloro-phenyl)-3-(3,5-difluoro-benzyloxy)-piperidin-1-yl]-ethanone;

cis-[rac]-1-[4-benzyloxy-3-(3-chloro-2-fluoro-benzyloxy)-4-(4-chloro-phenyl)-piperidin-1-yl]-ethanone;

cis-[rac]-1-[4-benzyloxy-4-(4-chloro-phenyl)-3-(3,4-dichloro-benzyloxy)-piperidin-1-yl]-ethanone;

cis-[rac]-1-[4-benzyloxy-4-(4-chloro-phenyl)-3-(4-fluoro-benzyloxy)-piperidin-1-yl]-ethanone;

- 5 *cis*-[rac]-1-[4-benzyloxy-3-(4-bromo-benzyloxy)-4-(4-chloro-phenyl)-piperidin-1-yl]-ethanone;

cis-[rac]-1-[4-benzyloxy-4-(4-chloro-phenyl)-3-(3-fluoro-benzyloxy)-piperidin-1-yl]-ethanone;

- 10 *cis*-[rac]-3-[1-acetyl-4-benzyloxy-4-(4-chloro-phenyl)-piperidin-3-yloxymethyl]-benzonitrile.

cis-[rac]-1-[4-benzyloxy-4-(4-chloro-phenyl)-3-(2,6-difluoro-benzyloxy)-piperidin-1-yl]-ethanone;

cis-[rac]-1-[4-benzyloxy-4-(4-chloro-phenyl)-3-(3-nitro-benzyloxy)-piperidin-1-yl]-ethanone;

- 15 *cis*-[rac]-1-[4-benzyloxy-4-(4-chloro-phenyl)-3-(2,3,4-trifluoro-benzyloxy)-piperidin-1-yl]-ethanone;

cis-[rac]-1-[4-(4-chloro-phenyl)-3-(3,4-dichloro-benzyloxy)-4-(2-fluoro-benzyloxy)-piperidin-1-yl]-ethanone;

- 20 *cis*-[rac]-1-[4-benzyloxy-4-(4-chloro-phenyl)-3-(2,3,4-trifluoro-benzyloxy)-piperidin-1-yl]-propan-1-one;

cis-[rac]-1-[4-benzyloxy-4-(4-chloro-phenyl)-3-(3,4-dichloro-benzyloxy)-piperidin-1-yl]-propan-1-one; and

cis-[rac]-4-benzyloxy-3-(4-bromo-benzyloxy)-4-(4-fluoro-phenyl)-piperidine.

17. Compounds of formula II according to claim 2, wherein the compound is
25 selected from the group consisting of:

cis-[rac]-4-benzyloxy-4-(4-chloro-phenyl)-3-(3,4-dichloro-benzyloxy)-1-ethyl-piperidine;

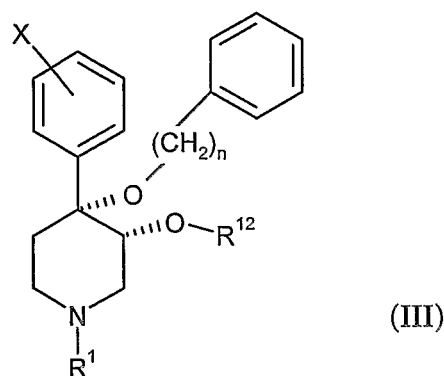
cis-[rac]-4-benzyloxy-4-(4-chloro-phenyl)-3-(3,4-dichloro-benzyloxy)-1-propyl-piperidine;

cis-[rac]-3-[4-benzyloxy-4-(4-chloro-phenyl)-3-(2,3,4-trifluoro-benzyloxy)-piperidin-1-yl]-propane-1,2-diol;

cis-[rac]-3-[4-benzyloxy-3-(4-bromo-benzyloxy)-4-(4-chloro-phenyl)-piperidin-1-yl]-propane-1,2-diol; and

- 5 *cis*-[rac]-3-[4-benzyloxy-4-(4-chloro-phenyl)-3-(2,3,4-trifluoro-benzyloxy)-piperidin-1-yl]-sulfonyl methane.

18. Compounds of formula I according to claim 1 represented by formula (III):



and the pharmaceutically acceptable salts thereof; wherein

- 10 n is an integer from 1 to 2;

X is halogen;

R^1 is selected from the group consisting of hydrogen, carbonyl, sulfonyl, lower alkyl, and lower alkyl substituted by carbonyl, sulfonyl, or hydroxy; and

- 15 R^{12} is selected from the group consisting of alkyl and alkenyl having from 1 to about 5 carbon atoms.

19. Compounds of formula III according to claim 18, wherein n is 1.

20. Compounds of formula III according to claim 18, wherein X is chloro.

21. Compounds of formula III according to claim 18, wherein X is a *para* substituent.

- 20 22. Compounds of formula III according to claim 18, wherein R^1 is selected from the group consisting of hydrogen, $-CH_2CH_3$, $-CH_2CH_2CH_3$, $-COCH_3$, $-COCH_2CH_3$, $-CH_2CHOHCH_2OH$, and $-SO_2CH_3$.

23. Compounds of formula III according to claim 18, wherein R¹² is selected from the group consisting of -(CH₂)₃CH₃, -(CH₂)₄CH₃, -CH₂CH=CHCH₃, and -CH₂CH=CH-CH₂CH₃.

24. Compounds of formula III according to claim 18, wherein the compound is
5 selected from the group consisting of:

cis-[rac]-4-benzyloxy-4-(4-fluoro-phenyl)-3-butyloxy-piperidine;

cis-[rac]-4-benzyloxy-4-(4-fluoro-phenyl)-3-pentyloxy-piperidine;

cis-[rac]-4-benzyloxy-4-(4-fluoro-phenyl)-3-(but-2-en)oxy-piperidine;

cis-[rac]-4-benzyloxy-4-(4-fluoro-phenyl)-3-(pent-2-en)oxy-piperidine;

10 *cis*-[rac]-4-benzyloxy-4-(4-chloro-phenyl)-3-butyloxy-piperidine;

cis-[rac]-4-benzyloxy-4-(4-chloro-phenyl)-3-pentyloxy-piperidine;

cis-[rac]-4-benzyloxy-4-(4-chloro-phenyl)-3-(but-2-en)oxy-piperidine; and

cis-[rac]-4-benzyloxy-4-(4-chloro-phenyl)-3-(pent-2-en)oxy-piperidine.

25. A pharmaceutical composition comprising a therapeutically effective amount of
15 a compound of formula I according to claim 1 and a pharmaceutically acceptable carrier or excipient.

26. The pharmaceutical composition according to claim 25 comprising a therapeutically effective amount of a compound of formula II according to claim 2 and a pharmaceutically acceptable carrier or excipient.

20 27. The pharmaceutical composition according to claim 25 comprising a therapeutically effective amount of a compound of formula III according to claim 18 and a pharmaceutically acceptable carrier or excipient.

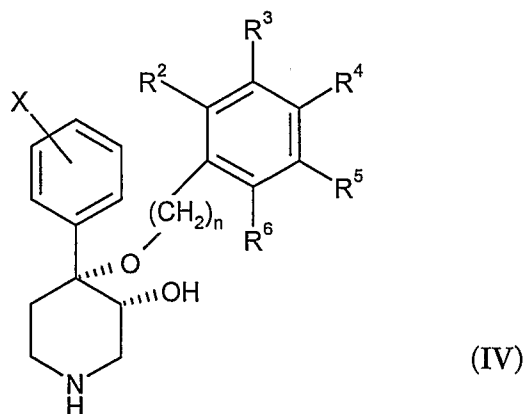
28. The pharmaceutical composition according to claim 25, wherein the compound is suitable for administration to a patient having cancer.

25 29. Compounds of any one of claims 1 to 24 for use as medicaments.

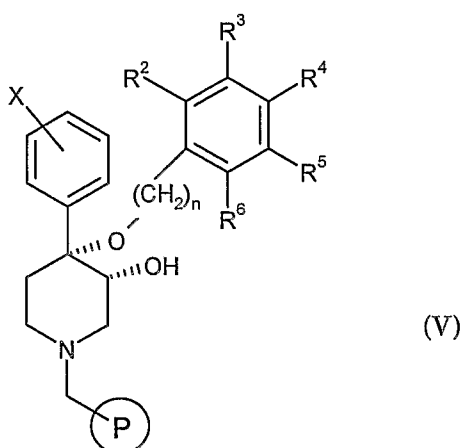
30. A process for the preparation of a compound of formula I of claim 1, which process comprises

a) coupling a compound of the formula IV

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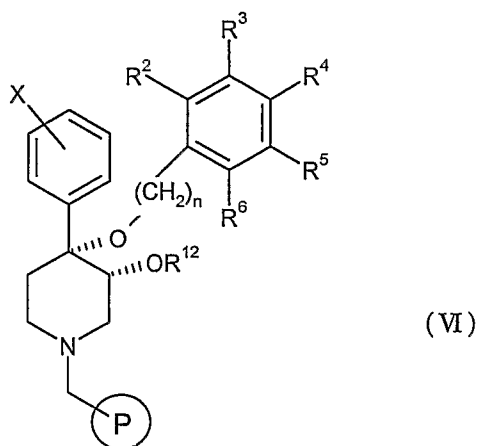


wherein R^2 to R^6 , X and n are as defined in claim 1,
with a suitable linker to a solid phase to obtain a compound of formula V



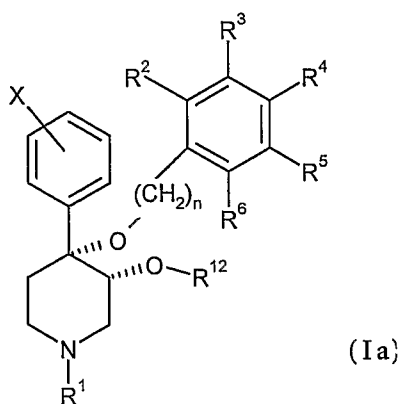
5 wherein P symbolizes the solid phase,

b) using potassium tert. Butoxide to generate an anion and alkylating the compound of formula V with an alkyl halide of formula R^{12}X to obtain a compound of formula VI



wherein R^{12} is as defined in claim 1,

c) cleaving the product from the linker to obtain a compound of formula Ia;



wherein R^1 is H, and if desired,

- 5 d) reacting the compound of formula Ia with an acyl halide, alkyl halide or sulfonyl chloride to obtain a compound of formula I, wherein R^1 is carbonyl, sulfonyl, lower alkyl or lower alkyl substituted by carbonyl, sulfonyl or hydroxy.

31. A compound of formula I of any one of claims 1 to 24 prepared by a process according to claim 30.

- 10 32. Use of compounds of formula I according to any one of claims 1 to 24 for the preparation of medicaments for the treatment and control of cancer.

33. The use according to claim 32 for the treatment and control of breast or colon cancer.

- 15 34. The novel compounds, pharmaceutical compositions, processes, and uses as described herein before.
