The present invention provides an improved process for the synthesis of 2-[2-(2,2,2-trifluoroethoxy)phenoxy]ethanol intermediate, its derivatives and/or its pharmaceutically acceptable salts, useful in the synthesis of α-1 adrenoceptor blockers such as silodosin.

Title: NOVEL PROCESS FOR THE SYNTHESIS OF PHENOXYETHYL DERIVATIVES

Abstract: The present invention provides an improved process for the synthesis of 2-[2-(2,2,2-trifluoroethoxy)phenoxy]ethanol intermediate, its derivatives and/or its pharmaceutically acceptable salts, useful in the synthesis of α-1 adrenoceptor blockers such as silodosin.
NOVEL PROCESS FOR THE SYNTHESIS OF PHENOXYETHYL DERIVATIVES

Field of the invention

The invention relates to the field of organic chemistry and is directed to improved, commercially viable and industrially advantageous processes for the synthesis of compounds useful as intermediates in the synthesis of α1 adrenoceptor blockers, including (R)-1-(3-hydroxypropyl)-5-[2-[2-(2,2,2-trifluoroethoxy) phenoxy] ethylamino] propyl] indoline 7-carboxamide (hereinafter referred to by its generic name "Silodosin") and its pharmaceutically acceptable salts.

Background

The following discussion of the prior art is intended to present the invention in an appropriate technical context and allow its significance to be properly appreciated. Unless clearly indicated to the contrary however reference to any prior art in this specification should be construed as an admission that such art is widely known or forms part of common general knowledge in the field.

Silodosin is a selective α1 adrenergic receptor antagonist, indicated for the treatment of the signs and symptoms of benign prostatic hyperplasia (BPH).

Till date very few processes for the manufacture of Silodosin have become known.

United States patent 5,387,603 assigned to Kissei Pharmaceuticals discloses the synthesis of silodosin from 2-[2-(2,2,2-trifluoroethoxy)phenoxy]ethyl methanesulfonate and 1-acetyl-5-(2-aminopropyl) indoline-7-carbonitrile. It also discloses a multistep synthesis of 2-[2-(2,2,2-trifluoroethoxy)phenoxy] ethanol and its salt, specifically mesylate derivative from 2-methoxy phenol
using expensive and hazardous reagents like 1,1,1-trifluoro ethyl iodide and boron tribromide and Lithium aluminium hydride.

United States patent 5,436,264 assigned to Syntex Inc also discloses a process for the synthesis of 2-[2-(2,2,2-trifluoroethoxy)phenoxy] ethanol using 2-hydroxy-1-(2-hydroxyethyloxy) benzene and 2-iodo-1,1,1-trifluoroethane. The 2-iodo-1,1,1-trifluoroethane is low boiling reagent (Boiling point 53-55°C) and is very difficult to handle while doing reaction at reflux condition to obtain the product, 2-[2-(2,2,2-trifluoroethoxy)phenoxy] ethanol.


Thus, the general strategies for making the target compound exist, they are not practical for large-scale synthesis, because they employ reagents which are either expensive or difficult to handle or both, as well as specialized equipments are required for the desired operating conditions. These drawbacks make them ill-suited to be employed on common multipurpose industrial plants. Specifically these processes utilize components like 1, 1, 1-trifluoro-2-iodoethane and boron tribromide which are very expensive and hence are not economical for use on the industrial scale. Also it is desirable that, impurities introduced during commercial manufacturing processes must be limited to very small amounts, and preferably be substantially absent. Hence there is a need for developing processes which are commercially feasible and have simple process that allow the preparation of highly pure intermediates in a facile manner on an industrial scale, which may yield Silodosin and other end products in high yield and purity.

The present invention provides an improved, commercially viable and industrially advantageous processes for the synthesis of 2-[2-(2,2,2-trifluoroethoxy)phenoxy] ethanol using less expensive starting material and reagents such as pyrocatechol and aluminium chloride and also the synthesis of α1 adrenoceptor blockers such as silodosin using 2-[2-(2,2,2-trifluoroethoxy) phenoxyjethanol synthesized by the process of the present invention. The
intermediates and the final end products obtained through the improved processes of this invention are expected to be obtained in a superior yield and purity.

Summary of the invention

The present invention relates to an improved, commercially viable and industrially advantageous process for the synthesis of 2-[2-(2,2,2-trifluoroethoxy)phenoxy]ethanol and its use in the synthesis of α₁ adrenoceptor blockers such as silodosin.

The present invention specifically relates to an improved, commercially viable and industrially advantageous process for the preparation of 2-[2-(2,2,2-trifluoroethoxy) phenoxy] ethanol of Formula I

\[
\text{Formula I}
\]

or its derivatives and/or its pharmaceutically acceptable salts, which comprises the steps of:

(a) preparation of 1-methoxy-2-(2,2,2-trifluoroethoxy)benzene (Formula IV)

\[
\text{Formula IV}
\]

by reacting 2-methoxy phenol (Formula II)

\[
\text{Formula II}
\]

with 2,2,2-trifluoroethyl p-toluenesulfonate (Formula III);
(b) demethylating the compound of Formula IV to yield 2-(2,2,2-trifluoroethoxy)phenol (Formula VI);

(c) reacting compound of formula VI with 2-bromoethanol (Formula VII)

to yield 2-[2-(2,2,2-trifluoroethoxy)phenoxy]ethanol (Formula I);

(d) optionally converting the product of step (c) to its derivatives and/or its pharmaceutically acceptable salts.

The present invention further discloses an improved, commercially viable and industrially advantageous process for the preparation of 2-[2-(2,2,2-trifluoroethoxy)phenoxy]ethanol of Formula I, its derivatives and/or its pharmaceutically acceptable salts thereof, which comprises the steps of:

(a) preparation of 2-(2,2,2-trifluoroethoxy)phenol (Formula VI)

by reacting pyrocatechol (Formula V)
with 2,2,2-trifluoroethyl p-toluenesulfonate (Formula III);

\[
\text{TsO-} \quad \text{CF}_3
\]

Formula III

(b) reacting compound of Formula VI with 2-bromoethanol (formula VII)

\[
\text{Br-} \quad \text{OH}
\]

Formula VII
to yield 2-[2-(2,2,2-trifluoroethoxy)phenoxy]ethanol (Formula I);

\[
\text{O} \quad \text{OH}
\quad \text{O} \quad \text{CF}_3
\]

Formula I

(c) optionally converting the product of step (b) to its derivatives and/or its pharmaceutically acceptable salts.

The present invention still further discloses an improved, commercially viable and industrially advantageous process for the preparation of 2-[2-(2,2,2-trifluoroethoxy)phenoxy]ethanol of Formula I, derivatives and/or its pharmaceutically acceptable salts, which comprises the steps of:

(a) preparation of 2-(2-hydroxyethoxy)phenol (Formula VIII)

\[
\text{O} \quad \text{OH}
\quad \text{OH}
\]

Formula VIII

by reacting pyrocatechol (formula V)

\[
\text{OH}
\quad \text{OH}
\]

Formula V

with 2 bromoethanol (formula VII);

\[
\text{Br-} \quad \text{OH}
\]

Formula VII
(b) reacting the compound of Formula VIII with 2,2,2-trifluoroethyl p-toluenesulfonate (Formula III)

\[
\begin{array}{c}
\text{Tscr} \\
\text{CF}_3 \\
\end{array}
\]

Formula III
to yield 2-[2-(2,2,2-trifluoroethoxy)phenoxy]ethanol (Formula I);

\[
\begin{array}{c}
\text{O} \\
\text{CF}_3 \\
\end{array}
\]

Formula I
(c) optionally converting the product of step (b) to its derivative and/or its pharmaceutically acceptable salt.

The present invention further discloses an improved, commercially viable and industrially advantageous process for the preparation of 2-[2-(2,2,2-trifluoroethoxy)phenoxy]ethyl methane sulfonate (Formula IX)

\[
\begin{array}{c}
\text{O} \\
\text{OMs} \\
\text{CF}_3 \\
\end{array}
\]

Formula IX
by reacting 2-[2-(2,2,2-trifluoroethoxy)phenoxy]ethanol (Formula I) obtained by following the processes as disclosed in any of the embodiments of the present invention with methanesulfonyl chloride.

The present invention even further discloses an improved, commercially viable and industrially advantageous process for the preparation of silodosin (Formula XIII)

\[
\begin{array}{c}
\text{N} \\
\text{OH} \\
\text{CONH}_2 \\
\end{array}
\]

Formula XIII
or its pharmaceutically acceptable salt thereof, comprising the following steps
(a) reacting 2-[2-(2,2,2-trifluoroethoxy)phenoxy]ethanol (Formula I) obtained by following the processes as disclosed in any of the embodiments of the present invention with methanesulfonyl chloride to obtain 2-[2-(2,2,2-trifluoroethoxy)phenoxy]ethyl methane sulfonate (Formula IX)

\[ \text{Formula IX} \]

(b) reacting compound of formula IX with Compound represented by the structural formula X

\[ \text{Formula X} \]

to obtain compound of formula XI

\[ \text{Formula XI} \]

wherein R is hydrogen or hydroxyl protecting group selected from a group comprising of acetyl, t-butyl, t-butoxymethyl, methoxymethyl, tetrahydropyranyl, 1-ethoxyethyl, 1-(2-chloroethoxy)ethyl, 2-trimethylsilylethyl, p-chlorophenyl, 2,4-dinitrophenyl, benzyl, benzoyle, p-phenylbenzoyl, 2,6-dichlorobenzyl, diphenylmethyl, p-nitrobenzyl, triphenylmethyl (trityl), 4-methoxytrityl, 4,4'-dimethoxytrityl, trimethylsilyl, triethoxysilyl, t-butylidimethylsilyl, t-butyldiphenylsilyl, triphenylsilyl, triisopropylsilyl, benzoylformate, chloroacetethyl, trichloroacetethyl, trifluoroacetethyl, pivaloyl, 9-fluorenyl-methyl carbonate, mesylate, tosylate, triflate,
trityl, monomethoxytrityl, dimethoxytrityl, trimethoxytrityl or substitutedpixyl, preferred hydroxyl protecting group is benzoyl. 

(c) removing the hydroxyl protecting group of compound of formula XI to yield compound of formula XII

\[\text{Formula XII}\]

(d) hydrolyzing compound of formula XII to obtain silodosin (formula XIII)

These and other features, aspects, and advantages of the present subject matter will become better understood with reference to the following description and appended claims. This summary is provided to introduce a selection of concepts in a simplified form. This summary is not intended to limit the scope of the claimed subject matter.

15 **Detailed description of the invention**

The present invention relates to an improved, commercially viable and industrially advantageous process for the synthesis of 2-[2-(2,2,2-trifluoroethoxy)phenoxy]ethanol, its derivatives and/or its pharmaceutically acceptable salts. 2-[2-(2,2,2-trifluoroethoxy)phenoxy]ethanol, its derivatives and/or its pharmaceutically acceptable salts are useful as intermediates in the synthesis of compounds that act as \(\alpha_1\) adrenoceptor blockers.

Definitions:
The invention described herein in detail using the terms defined below unless otherwise specified.

The term "solvent" refers to solvent selected from the group comprising of polar protic solvents such as n-Butanol, Isopropanol, n-Propanol, ethanol, methanol, water, polar aprotic solvents such as Dichloromethane, Tetrahydrofuran, ethyl acetate, acetone, methyl isobutyl ketone,
dimethylformamide (DMF), dimethylacetamide, acetonitrile (MeCN), dimethyl sulfoxide and non polar solvents such as hexane, benzene, toluene, 1,4-dioxane, chloroform, diethyl ether, methyl t-butyl ether. It may also include inorganic solvents such as ammonia (NH₃), concentrated sulfuric acid (H₂SO₄).

Preferred solvent is dimethylformamide (DMF) and acetonitrile (MeCN).

The term "base" refers to an organic base or an inorganic base. Suitable organic base include, but are not limited to, lower alkyl amine such as triethylamine, diisopropylethylamine and the like. Suitable inorganic base include, but are not limited to, an alkali metal carbonate (for example, cesium carbonate, potassium carbonate, sodium carbonate, etc.), an alkali phosphate (for examples Sodium hydrogen diphosphate, sodium dihydrogen monophosphate, potassium dihydrogen phosphate, potassium monohydrogen phosphate) an alkali metal alkoxide (for example, potassium t-butoxide, sodium ethoxide, etc.), an alkali metal hydride (for example, potassium hydride, sodium hydride, etc.), or an alkali metal hydroxide (for example, potassium hydroxide, sodium hydroxide, etc.).

The term "appropriate alcohol" refers to alcohol selected from a group comprising of 2-bromoethanol, 2-chloroethanol, 2-iodoethanol, 2-methanesulfonyloxy ethanol, 2-(p-toluenesulfonyloxy) ethanol, 2-(p-trifluromethanesulfonyloxy) ethanol. 2-bromoethanol is preferred alcohol.

The term "pharmaceutically acceptable salt" refers to salts prepared from pharmaceutically acceptable non-toxic inorganic or organic acids. The salts may be prepared during the final isolation and purification of the compounds by making acidic addition salts. Representative salts of basic compounds of the present invention can be prepared by reacting free base form of the compound with a suitable acid, including, but not limited to acetate, trifluoroacetate, adipate, citrate, aspartate, benzoate, benzenesulphonate, bisulfate, besylate, butyrate, camphorsulphonate, difluconae, hemisulfate, heptanoate, formate, fumarate, lactate, maleate, methanesulfonate, naphthylsulfonate, nicotinate, oxalate, picrate, pivalate, succinate, tartrate, tirchloracetat, glutamate, p-toluenesulphonate, hydrochloric, , hydrobromic, sulphuric, phosphoric and the like.
The term "derivatives" refers to any compounds prepared from the Formula I. The term "Lewis acid" refers to any compound that can accept an electron pair. Few examples of lewis acid include, but are not limited to aluminum chloride, aluminum bromide, tribromoborane, stannous chloride.

The term "nucleophile" refers to any molecule possessing an electron rich functional group. Specifically the term nucleophile as used herein would mean "sulphur containing nucleophiles". Few examples of sulphur containing nucleophiles include, but are not limited to, methanethiol, ethanethiol, isopropanethiol, butanethiol, dodecanethiol, benzenethiol or \( C_{1-12} \) thiols.

The term "Lewis acid - nucleophile system" refers to a combination of Lewis acid and a nucleophile used in the reaction system for the demethylation reaction. Lewis acid and nucleophile can be selected from those specifies within the meaning of Lewis acid and nucleophile in the present invention. Specific examples of Lewis acid - nucleophile system include, but are not limited to, \( AlC{l}_3 \)-Ethanethiol system, \( AlC{l}_3 \)-methanethiol system, \( AlC{l}_3 \)-isopropanethiol, \( AlCu \)-dodecanethiol system and the like.

The term "alkylating agent" refers to substituted and unsubstituted linear or cyclic alkyl sulfonates such as 2,2,2-trifluoroethyl tolenesulfonate, 2,2,2-trifluoroethyl methane sulfonate, 2,2,2-trifluoroethyl trifluoromethanesulfonate; substituted and unsubstituted methyl and ethyl benzenesulfonate, 2,2,2-trifluoroethyl chloride, 2,2,2-trifluoroethyl bromide, 2,2,2-trifluoroethyl iodide. These entire alkylating agents may be preferably substituted with one or more halogen atoms.

The term "hydroxyl protecting group" means any moiety that can react with hydroxyl group to form a protected hydroxyl moiety to protect it in a reaction. Suitable examples of hydroxyl protecting group include, but not limited to acetyl, t-butyl, t-butoxymethyl, methoxymethyl, tetrahydropyranyl, 1-ethoxyethyl, 1-(2-chloroethoxy)ethyl, 2-trimethylsilyl ethyl, p-chlorophenyl, 2,4-dinitrophenyl, benzyl, benzoyle, p-phenylbenzoyl, 2,6-dichlorobenzyl, diphenylmethy, p-nitrobenzyl, triphenylmethy (trityl), 4-methoxytrityl, 4,4'-diphenoxycryl, trimethylsilyl, triethoxysilyl, t-butyldimethylysilyl, t-butyldiphenylysilyl, triphenylsilyl, triisopropylsilyl, benzoylformate, chloroacetyl, trichloroacetyl,
trifluoroacetyl, pivaloyi, 9-fluorenyl-methyl carbonate, mesylate, tosylate, triflate, trityl, monomethoxytrityl, dimethoxytrityl, trimethoxytrityl or substitutedpixyl. Preferred hydroxyl protecting group is benzoyl.

It must be noted that as used herein and in the appended claims, the singular forms "a", "an", and "the" include plural reference unless the context clearly dictates otherwise. As well, the terms "a" (or "an"), "one or more" and "at least one" can be used interchangeably herein. It is also to be noted that the terms "comprising", "including", "characterized by" and "having" can be used interchangeably.

In one embodiment, the present invention provides a improved, commercially viable and industrially advantageous process for preparation of 2-[2-(2,2,2-trifluoroethoxy)phenoxy]ethanol comprising:

(a) alkylating 2-methoxy phenol by treating it with a suitable alkylating agent in the presence of a suitable base (s) and solvent to obtain 1-methoxy-2-(2,2,2-trifluoroethoxy)benzene ;

(b) demethylating 1-methoxy-2-(2,2,2-trifluoroethoxy)benzene using a Lewis acid - nucleophile system in a suitable solvent (s) to obtain 2-(2,2,2-trifluoroethoxy)phenol, and

(c) subjecting 2-(2,2,2-trifluoroethoxy)phenol to a condensation reaction with a appropriate alcohol in presence of a suitable base and solvent to yield 2-[2-(2,2,2-trifluoroethoxy) phenoxy]ethanol .

The starting material 2-methoxy phenol can be obtained commercially.

In another embodiment the present invention relates to an improved, commercially viable and industrially advantageous process for preparation of 2-[2-(2,2,2-trifluoroethoxy) phenoxy]ethanol of Formula I

\[
\text{Formula I}
\]

or its derivatives and/or its pharmaceutically acceptable salts thereof, which comprises the steps of:

(a) preparation of 1-methoxy-2-(2,2,2-trifluoroethoxy)benzene (Formula IV)
by reacting 2-methoxy phenol (Formula II)

with suitable alkylating agent (Formula IMA);

(b) treating the compound of Formula IV with aluminium chloride in the presence of ethanethiol and methylene chloride to yield 2-(2,2,2-trifluoroethoxy)phenol (Formula VI);

(c) reacting compound of formula VI with 2 substituted ethanol (formula VIIA);

to yield 2-[2-(2,2,2-trifluoroethoxy)phenoxy]ethanol (Formula I);

(d) optionally converting the product of step (c) to its derivatives and/or its pharmaceutically acceptable salts.

wherein X is selected from a group comprising of substituted or unsubstituted linear or cyclic group such as toluenesulfonate, trifluoromethanesulfonate, ethylbenzenesulphonate, chlorine, bromine and the like.
wherein Y is selected from a group comprising of bromine, chlorine, iodine and the like.

In a preferred embodiment the present invention relates to an improved, commercially viable and industrially advantageous process for preparation of 2-[2-(2,2,2-trifluoroethoxy) phenoxyl]ethanol of Formula I

```
\[
\text{Formula I}
\]
```

or its derivatives and/or its pharmaceutically acceptable salts thereof, which comprises the steps of:

(a) preparation of 1-methoxy-2-(2,2,2-trifluoroethoxy)benzene (Formula IV)

```
\[
\text{Formula IV}
\]
```

by reacting 2-methoxy phenol (Formula II)

```
\[
\text{Formula II}
\]
```

with 2,2,2-trifluoroethyl p-toluenesulfonate (Formula III);

```
\[
\text{Formula III}
\]
```

(b) treating the compound of Formula IV with aluminium chloride in the presence of ethanethiol and methylene chloride to yield 2-(2,2,2-trifluoroethoxy)phenol (Formula VI);

```
\[
\text{Formula VI}
\]
```

(c) reacting compound of formula VI with 2 bormoethanol (Formula VIII)
to yield 2-[2-(2,2,2-trifluoroethoxy)phenoxy]ethanol (Formula I);

(d) optionally converting the product of step (c) to its derivatives and/or its pharmaceutically acceptable salts.

In another embodiment, the present invention provides a improved, commercially viable and industrially advantageous process of preparation of 2-[2-(2,2,2-trifluoroethoxy) phenoxy] ethanol comprising the steps of : 

(a) alkylation of pyrocatechol to corresponding aralkylether by reacting it with an alkylation agent in the presence of a suitable base and a solvent; and

(b) reacting the aralkylether with an appropriate alcohol in the presence of a suitable base and solvent.

In still another embodiment, the present invention relates to an improved, commercially viable and industrially advantageous process for the preparation of 2-[2-(2,2,2-trifluoroethoxy)phenoxy]ethanol of Formula I or its derivatives and/or its pharmaceutically acceptable salts, which comprises the steps of:

(a) preparation of 2-(2,2,2-trifluoroethoxy)phenol (Formula VII)

by reacting pyrocatechol (Formula V) with suitable alkylation agent (Formula IIIA );

Formulas are shown as follows:

**Formula I**

**Formula II**

**Formula III**

**Formula IV**

**Formula V**

**Formula VI**

**Formula VII**

**Formula IIIA**
(b) reacting compound of Formula VII with 2 substituted ethanol (formula VIIA);

\[
\text{Y} - \text{OH}
\]

Formula VIIA

to yield 2-\[2-(2,2,2\text{-trifluoroethoxy})\text{phenoxy}]\text{ethanol} \text{ (Formula I)};

\[
\begin{array}{c}
\text{O} \\
\text{CF}_3 \\
\text{O} \\
\end{array}
\]

Formula I

(c) optionally converting the product of step (b) to its derivatives and/or its pharmaceutically acceptable salts.

wherein X is selected from a group comprising of substituted or unsubstituted linear or cyclic group such as toluenesulfonate, trifluoromethanesulfonate, ethylbenzenesulphonate, chlorine, bromine and the like.

wherein Y is selected from a group comprising of bromine, chlorine, iodine and the like.

In another preferred embodiment, the present invention relates to an improved, commercially viable and industrially advantageous process for the preparation of 2-\[2-(2,2,2\text{-trifluoroethoxy})\text{phenoxy}]\text{ethanol} \text{ of Formula I or its derivatives and/or its pharmaceutically acceptable salts, which comprises the steps of:}

(a) preparation of 2-(2,2,2-trifluoroethoxy)phenol \text{ (Formula VII)}

\[
\begin{array}{c}
\text{OH} \\
\text{CF}_3 \\
\end{array}
\]

Formula VI

by reacting pyrocatechol \text{ (Formula V)}

\[
\begin{array}{c}
\text{OH} \\
\text{OH} \\
\end{array}
\]

Formula V

with 2,2,2-trifluoroethyl p-toluenesulfonate \text{ (Formula III)};
(b) reacting compound of Formula VII with 2 bromoethanol (formula VIII)

\[
\begin{align*}
\text{O} & \quad \text{C} \quad \text{F}_3 \\
\text{Br} & \quad \text{O} \\
\text{O} & \quad \text{C} \quad \text{F}_3
\end{align*}
\]

Formula VII
to yield 2-[2-(2,2,2-trifluoroethoxy)phenoxy]ethanol (Formula I);

\[
\begin{align*}
\text{O} & \quad \text{C} \quad \text{F}_3 \\
\text{O} & \quad \text{C} \quad \text{F}_3
\end{align*}
\]

Formula I
(c) optionally converting the product of step (b) to its derivatives and/or its pharmaceutically acceptable salts.

In a further embodiment, the present invention provides an improved, commercially viable and industrially advantageous process of preparation of 2-[2-(2,2,2-trifluoroethoxy) phenoxy] ethanol comprising the steps of:

(a) reaction between pyrocatechol and a appropriate alcohol in the presence of a suitable base and solvent to obtain a hydroxylated aralkylether;
(b) alkylating the hydroxylated aralkylether by reacting it with an alkylating agent in the presence of a suitable base and solvent.

In a still further embodiments the present invention is to provide an improved, commercially viable and industrially advantageous process for the preparation of 2-[2-(2,2,2-trifluoroethoxy)phenoxy]ethanol of Formula I or its derivatives and/or its pharmaceutically acceptable salts, comprising the steps of:

(a) preparation of 2-(2-hydroxyethoxy)phenol (Formula VIII)

\[
\begin{align*}
\text{O} & \quad \text{C} \\
\text{O} & \quad \text{C}
\end{align*}
\]

Formula VIII
by reacting pyrocatechol (Formula V)
Formula V

with 2 substituted ethanol (formula VIIA);

\[ \text{Y} \quad \begin{array}{c} \text{OH} \\ \end{array} \]

Formula VIIA

(b) reacting the compound of Formula VIII with suitable alkylation agent (Formula IMA)

\[ \text{X} \quad \begin{array}{c} \text{CF}_3 \\ \end{array} \]

Formula IMA

to yield 2-[2-(2,2,2-trifluoroethoxy)phenoxy]ethanol (Formula I);

\[
\begin{array}{c}
\text{O} \\
\text{O} \\
\text{CF}_3 \\
\end{array}
\]

(c) optionally converting the product of step (b) to its derivatives and/or its pharmaceutically acceptable salts.

wherein X is selected from a group comprising of substituted or unsubstituted linear or cyclic group such as toluenesulfonate, trifluoromethanesulfonate, ethylbenzenesulphonate, chlorine, bromine and the like.

wherein Y is selected from a group comprising of bromine, chlorine, iodine and the like.

In a further preferred embodiments the present invention is to provide an improved, commercially viable and industrially advantageous process for the preparation of 2-[2-(2,2,2-trifluoroethoxy)phenoxy]ethanol of Formula I or its derivatives and/or its pharmaceutically acceptable salts, comprising the steps of:

(a) preparation of 2-(2-hydroxyethoxy)phenol (Formula VIII)

\[
\begin{array}{c}
\text{O} \\
\text{OH} \\
\end{array}
\]

Formula VIII

by reacting pyrocatechol (Formula V)
with 2 bormoethanol (formula VII);

(b) reacting the compound of Formula VIII with 2,2,2-trifluoroethyl p-toluenesulfonate (Formula III)

\[
\text{TsO}^+\text{CF}_3
\]

Formula III

to yield 2-[2-(2,2,2-trifluoroethoxy)phenoxy]ethanol (Formula I);

(c) optionally converting the product of step (b) to its derivatives and/or its pharmaceutically acceptable salts.

The present invention further discloses an improved, commercially viable and industrially advantageous process for the preparation of 2-[2-(2,2,2-trifluoroethoxy)phenoxy]ethyl methane sulfonate (Formula IX)

\[
\text{OMs}
\]

Formula IX

by reacting 2-[2-(2,2,2-trifluoroethoxy)phenoxy]ethanol (Formula I) obtained by following the processes as disclosed in any of the embodiments of the present invention with methanesulfonyl chloride.

The 2-[2-(2,2,2-trifluoroethoxy)phenoxyjethanol (Formula I) or its derivatives and/or its pharmaceutically acceptable salt obtained by following the process of any of the embodiments of the present invention, can be used as
intermediate for the synthesis of a1 adrenoceptor blockers such as silodosin, either by isolating it or without the need of isolating it as intermediate (one pot process).
The above compound of formula I can be used in preparation of silodosin with or without isolating it.
In a particularly preferred embodiment, the present invention provides an improved, commercially viable and industrially advantageous process for the synthesis of silodosin (Formula XIII)

```
Formula XIII
```

```
10
or its pharmaceutically acceptable salt thereof, comprising the steps of ;
(a) reacting 2-[2-(2,2,2-trifluoroethoxy)phenoxy]ethanol (Formula I) obtained by following the processes as claimed in any of the preceding claim , with methanesulfonyl chloride to obtain 2-[2-(2,2,2-trifluoroethoxy)phenoxy]ethyl methane sulfonate (Formula IX)

```
Formula IX
```

```
(b) reacting compound of formula IX with Compound represented by the structural formula X
```

```
Formula X
```

to obtain compound of formula XI
(c) removing the hydroxyl protecting group of compound of formula XI to yield compound of formula XII

(d) hydrolyzing compound of formula XII to obtain silodosin, and optionally converting to its pharmaceutically acceptable salts.

The compounds of Formula X can be prepared by methods disclosed in any of the prior art.

wherein R is hydrogen or hydroxyl protecting group selected from a group comprising of acetyl, t-butyl, t-butoxymethyl, methoxymethyl, tetrahydropyranyl, 1-ethoxyethyl, 1-(2-chloroethoxy)ethyl, 2-trimethylsilylethyl, p-chlorophenyl, 2,4-dinitrophenyl, benzyl, benzoyle, p-phenylbenzoyl, 2,6-dichlorobenzyl, diphenylmethyl, p-nitrobenzyl, triphenylmethyl (trityl), 4-methoxytrityl, 4,4'-dimethoxytrityl, trimethylsilyl, triethylsilyl, t-butyldimethylsilyl, t-butyldiphenylsilyl, triphenylsilyl, triisopropylsilyl, benzoylformate, chloroacetyl, trichloroacetyl, trifluoroacetyl, pivaloyl, 9-fluorenyl-methyl carbonate, mesylate, tosylate, triflate, trityl, monomethoxytrityl, dimethoxytrityl, trimethoxytrityl or substitutedpixyl.

Examples:
The invention is explained in detail in the following examples which are given solely for the purpose of illustration only and therefore should not be construed to limit the scope of the invention.
The following terms/symbols/abbreviations/chemical formulae are employed in the examples:

- ml : Millilitre
- g : Gram
- mg : Milligram
- h : Hours
- min : Minute
- mM : Millimole
- µM : Micromole
- DMF : Dimethyl formamide
- K₂CO₃ : Potassium Carbonate

**Example 1:**
Preparation of 1-methoxy-2-(2,2,2-trifluoroethoxy)benzene (IV)

To a solution of 2-methoxy phenol (II) (1.75 g, 14.1 mmol) in DMF (10 ml) was added K₂CO₃ (3.9 g, 28.2 mmol) and 2,2,2-trifluoroethyl p-toluenesulfonate (III) (3.58 g, 14.1 mmol) at room temperature. The mixture was stirred at 100°C in a sealed vessel for 12 h. The mixture was diluted with water (30 ml) and extracted with ethyl acetate (50 ml). The solvent was evaporated under vacuum and purified by column chromatography to give 1.7 g of 1-methoxy-2-(2,2,2-trifluoroethoxy)benzene (IV) as an oil.

**Example 2:**
Preparation of 2-(2,2,2-Trifluoroethoxy)phenol (VI):

a) Route-1: To a mixture of ethanethiol (2 ml) in methylene chloride (4 ml) was added aluminum chloride (6.77 g, 50.9 mmol) slowly at 0 °C. The resulting solution was stirred for 10 min and 1-methoxy-2-(2,2,2-trifluoroethoxy) benzene (IV) (3.5 g, 16.9 mmol) in methylene chloride (4 ml) was added at 0°C. The mixture was warmed to room temperature and stirred for 4 h. The mixture was diluted with water (50 ml), extracted with methylene chloride (3 X 100 ml) and concentrated under reduced pressure. The product was purified by column
chromatography to give 3 g of 2-(2,2,2-trifluoroethoxy) phenol (VI) as a thick gel.

b) Route-2: To a solution of Pyrocatechol (50 g, 454.5 mmol) in DMF (400 ml) was added K$_2$CO$_3$ (188.1 g, 1363 mmol) and 2,2,2-trifluoroethyl p-toluenesulfonate (III) (115.4 g, 454.5 mmol) at room temperature. The mixture was stirred at 110°C in a sealed vessel for 24 hrs. The mixture was diluted with water (750 ml) and extracted with ethyl acetate (250 ml). The ethyl acetate layer was washed with water (500 ml) and the solvent was evaporated under vacuum. The obtained crude material was purified by column chromatography to give 37 g of 2-(2,2,2-trifluoroethoxy)phenol (VI) as a thick gel.

**Example 3:**
Preparation of 2-(2-Hydroxyethoxy)phenol (VIII):
To a solution of Pyrocatechol (100 g, 909.09 mmol) in acetonitrile (800 ml) was added K$_2$CO$_3$ (376.3 g, 2727.27 mmol) and followed by addition of 2-bromoethanol (VII) (227.2 gm, 1818.18 mmol) at room temperature. The mixture was stirred for 24 hrs at 110-120°C. The reaction mixture was filtered and washed the solid with acetonitrile (200 ml). The filtrate was concentrated under reduced pressure. The obtained crude was dissolved in ethyl acetate (750 ml) and washed with water (1000 ml). The water layer was extracted twice with ethyl acetate (2 X 750 ml). The combined organic layers were distilled at 40-45°C to become thick mass and added mixture of ethyl acetate and pet ether (3:7) (200 ml). The obtained solid was filtered and washed with mixture of ethyl acetate and pet ether (3:7) (100 ml) and dried the solid under vacuum at 45°C to give 45 g of 2-(2-hydroxyethoxy) phenol (VIII) as a white solid.

**Example 4:**
Preparation of 2-[2-(2,2,2-trifluoroethoxy)phenoxy]ethanol (I):
a) Route-1: To a solution of 2-(2,2,2-trifluoroethoxy) phenol (VI) (37 g, 192.7 mmol) in acetonitrile (370 ml) was added K$_2$CO$_3$ (79.7 g, 578.1 mmol) and followed by addition of 2-bromoethanol (VII) (48.17 g, 385.1 mmol) at room temperature. The mixture was stirred for 66 hrs at 90-100°C. The reaction
mixture was filtered and the solvent was evaporated under vacuum. The crude was diluted with ethyl acetate (400 ml) and washed with water (200 ml). The solvent was evaporated under vacuum to give 35 g of 2-[2-(2,2,2-trifluoroethoxy)phenoxy]ethanol (I) as an oil. (HPLC purity is 85-90%).

b) Route-2: To a solution of 2-(2-hydroxyethoxy) phenol (VIII) (250 g, 1623 mmol) in DMF (1250 ml) was added K₂CO₃ (676 g, 4899 mmol) and 2,2,2-trifluoroethyl p-toluenesulfonate (III) (414 g, 1623 mmol) at room temperature. The mixture was stirred at 120°C for 24-30 hrs and was diluted with water (9370 ml). The product was extracted twice with ethyl acetate (2 x 1500 ml) and the combined organic layers were washed with water (500 ml). The solvent was evaporated under vacuum to give 225 g of 2-[2-(2,2,2-trifluoroethoxy)phenoxy]ethanol (I) as a colourless oil (HPLC purity is 95-98%).

\(^1\)H NMR: δ 7.06-6.91 (m, 4H), 4.37 (q, 2H), 4.12 (t, 2H), 3.94 (t, 2H)

Example 5:

Preparation of 2-[2-(2,2,2-trifluoroethoxy)phenoxy]ethyl methane sulfonate (IX):

To a solution of 2-[2-(2,2,2-trifluoroethoxy)phenoxy]ethanol (287 g, 1216 mmol) in methylene chloride (1435 ml) were added triethyl amine (307 g, 3040 mmol) and methane sulfonyl chloride (145.5 g, 1276 mmol) under ice cooling. The mixture was stirred at room temperature for 1 hrs and water (700 ml) was added to it. The organic layer was separated and washed with water (700 ml). The solvent was evaporated under reduced pressure and the obtained thick gel was crystallized from Hexane (860 ml) at low temperature to give 193 g of 2-[2-(2,2,2-trifluoroethoxy)phenoxy] ethyl methane sulfonate (IX) as a white solid (HPLC purity is 97-98%).

Example 6:

Preparation of Silodosin

The conversion of 2-[2-(2,2,2-trifluoroethoxy)phenoxy] ethyl methane sulfonate (IX) to Silodosin was followed by procedures disclosed in any of the prior art including United States patent application 20070197627 and United States patent 5,387,603.
CLAIRMS

1. A process for preparation of 2-[2-(2,2,2-trifluoroethoxy) phenoxy]ethanol of Formula I

\[
\text{Formula I}
\]

or its derivatives and/or its pharmaceutically acceptable salts thereof, comprising the steps of:

(a) preparation of 1-methoxy-2-(2,2,2-trifluoroethoxy)benzene (Formula IV)

\[
\text{Formula IV}
\]

by reacting 2-methoxy phenol (Formula II)

\[
\text{Formula II}
\]

with suitable alkylating agent of formula IMA

\[
\text{Formula IMA}
\]

(b) demethylating the compound of Formula IV to yield 2-(2,2,2-trifluoroethoxy)phenol (Formula VI);

\[
\text{Formula VI}
\]

(c) reacting compound of formula VI with 2 substituted ethanol (Formula VIIA)

\[
\text{Formula VIIA}
\]

24
to yield 2-[(2,2,2-trifluoroethoxy)phenoxy]ethanol (Formula I);

(d) optionally converting the product of step (c) to its derivatives and/or its pharmaceutically acceptable salts.

wherein X is selected from a group comprising of substituted or unsubstituted linear or cyclic group such as toluenesulfonate, trifluoromethanesulfonate, ethylbenzenesulphonate, chlorine, bromine and the like.

wherein Y is selected from a group comprising of bromine, chlorine, iodine and the like.

2. A process as claimed in claim 1, wherein suitable alkylation agent of formula MIA is 2,2,2-trifluoroethyl p-toluenesulfonate (Formula III);

3. A process as claimed in claim 1, wherein 2 substituted ethanol (Formula V|IA) is 2 bromoethanol (formula VII)

4. A process as claimed in claim 1, wherein either or both of step (a) and step (c) are carried out in presence of a base selected from a group comprising of lower alkyl amine such as triethylamine, diisopropylethylamine and the like, an alkali metal carbonate such as cesium carbonate, potassium carbonate, sodium carbonate and the like, an alkali metal alkoxide such as potassium t-butoxide, sodium ethoxide and the like, an alkali metal hydride such as potassium hydride, sodium hydride and the like, or an alkali metal hydroxide such as potassium hydroxide, sodium hydroxide and the like.
5. A process as claimed in claim 4, wherein either or both of step (a) and step (c) are carried out in presence of potassium carbonate.

6. A process as claimed in claim 1, wherein step (b) is carried out in presence of a Lewis acid - nucleophile system selected from a group comprising of AlCl$_3$-Ethanethiol system, AlCb-methanethiol system, AlCb-isopropanethiol, AlCl$_3$-dodecanethiol system and the like.

7. A process as claimed in claim 6, wherein step (b) is carried out in presence of AlCl$_3$-Ethanethiol system.

8. A process as claimed in claim 1, wherein either or both of step (a) and step (c) are carried out in presence of potassium carbonate and wherein the step (b) is carried out in presence of AlCl$_3$-Ethanethiol system.

9. A process for preparation of 2-[2-(2,2,2-trifluoroethoxy)phenoxy]ethanol of Formula I or its derivatives and/or its pharmaceutically acceptable salts thereof, comprising the steps of:

(a) preparation of 2-(2,2,2-trifluoroethoxy)phenol (Formula VI)

\[
\begin{align*}
\text{Formula VI} \\
\text{by reacting pyrocatechol (Formula V)}
\end{align*}
\]

(b) with suitable alkylating agent of formula IIIA

\[
\begin{align*}
\text{Formula IIIA} \\
\end{align*}
\]
(b) reacting compound of Formula VI with 2 substituted ethanol (formula VIIA);

\[
\begin{align*}
\text{Formula VIIA} \\
\text{to yield 2-[2-(2,2,2-trifluoroethoxy)phenoxy]ethanol (Formula I)};
\end{align*}
\]

(c) optionally converting the product of step (b) to its derivatives and/or its pharmaceutically acceptable salts.

wherein \( X \) is selected from a group comprising of substituted or unsubstituted linear or cyclic group such as toluenesulfonate, trifluoromethanesulfonate, ethylbenzenesulphonate, chlorine, bromine and the like.

wherein \( Y \) is selected from a group comprising of bromine, chlorine, iodine and the like.

10. A process as claimed in claim 9, wherein suitable alkylating agent of formula IMA is 2,2,2-trifluoroethyl p-toluenesulfonate (Formula III);

\[
\begin{align*}
\text{Formula III} \\
\end{align*}
\]

11. A process as claimed in claim 9, wherein 2 substituted ethanol (Formula VIIA) is 2 bromoethanol (formula VII)

\[
\begin{align*}
\text{Formula VII} \\
\end{align*}
\]

12. A process as claimed in claim 9, wherein either or both of step (a) and step (b) are carried out in presence of a base selected from a group comprising of lower alkyl amine such as triethylamine, diisopropylethylamine and the like, an alkali metal carbonate such as cesium carbonate, potassium carbonate, sodium carbonate and the like, an alkali metal alkoxide such as potassium t-
butoxide, sodium ethoxide and the like, an alkali metal hydride such as potassium hydride, sodium hydride and the like, or an alkali metal hydroxide such as potassium hydroxide, sodium hydroxide and the like.

13. A process as claimed in claim 12, wherein either or both of step (a) and step (b) are carried out in presence of potassium carbonate.

14. A process for preparation of 2-[2-(2,2,2-trifluoroethoxy)phenoxy]ethanol of Formula I or its derivatives and/or its pharmaceutically acceptable salts thereof, comprising the steps of:

(a) preparation of 2-(2-hydroxyethoxy)phenol (Formula VIII)

\[
\text{Formula VIII}
\]

by reacting pyrocatechol (formula V)

\[
\text{Formula V}
\]

with 2 substituted ethanol (formula VIIA):

\[
\text{Formula VIIA}
\]

(b) reacting the compound of Formula VIII with suitable alkylating agent of formula MIA

\[
\text{Formula IIIA}
\]

to yield 2-[2-(2,2,2-trifluoroethoxy)phenoxy]ethanol (Formula I):
(c) optionally converting the product of step (b) to its derivative and/or its pharmaceutically acceptable salts.

wherein X is selected from a group comprising of substituted or unsubstituted linear or cyclic group such as toluenesulfonate, trifluoromethanesulfonate, ethylbenzenesulphonate, chlorine, bromine and the like.

wherein Y is selected from a group comprising of bromine, chlorine, iodine and the like.

15. A process as claimed in claim 14, wherein suitable alkylating agent of formula IMA is 2,2,2-trifluoroethyl p-toluenesulfonate (Formula III);

\[
\text{TsO} - \bigg\| - \text{CF}_3
\]

Formula III

16. A process as claimed in claim 14, wherein 2 substituted ethanol (Formula VIIA) is 2 bromoethanol (formula VII)

\[
\text{Br} - \bigg\| - \text{OH}
\]

Formula VII

17. A process as claimed in claim 14, wherein either or both of step (a) and step (b) are carried out in presence of a base selected from a group comprising of lower alkyl amine such as triethylamine, diisopropylethylamine and the like, an alkali metal carbonate such as cesium carbonate, potassium carbonate, sodium carbonate and the like, an alkali metal alkoxide such as potassium t-butoxide, sodium ethoxide and the like, an alkali metal hydride such as potassium hydride, sodium hydride and the like, or an alkali metal hydroxide such as potassium hydroxide, sodium hydroxide and the like.

18. A process as claimed in claim 17, wherein either or both of step (a) and step (b) are carried out in presence of potassium carbonate.
19. A process for preparation of 2-[2-(2,2,2-trifluoroethoxy)phenoxy]ethyl methane sulfonate (Formula IX)

\[ \text{Formula IX} \]

by reacting 2-[2-(2,2,2-trifluoroethoxy)phenoxy]ethanol (Formula I) obtained by the processes claimed in any of the preceding claim

\[ \text{Formula I} \]

with methanesulfonyl chloride.

20. A process for preparation of silodosin (Formula XIII)

\[ \text{Formula XIII} \]

or its pharmaceutically acceptable salts thereof, comprising the steps of ;

(a) reacting 2-[2-(2,2,2-trifluoroethoxy)phenoxy]ethanol (Formula I) obtained by following the processes as disclosed in any of the preceding claim with methanesulfonyl chloride to obtain 2-[2-(2,2,2-trifluoroethoxy)phenoxy]ethyl methane sulfonate (Formula IX)

\[ \text{Formula IX} \]

(b) reacting compound of formula IX with Compound represented by the structural formula X
to obtain compound of formula XI

wherein R is hydrogen or hydroxyl protecting group selected from a group comprising of acetyl, t-butyl, t-butoxymethyl, methoxymethyl, tetrahydropyranyl, 1-ethoxyethyl, 1-(2-chloroethoxy)ethyl, 2-trimethylsilylethyl, p-chlorophenyl, 2,4-dinitrophenyl, benzyl, benzoxy, p-phenylbenzoxy, 2,6-dichlorobenzyl, diphenylmethyl, p-nitrobenzyl, triphenylmethyl (trityl), 4-methoxytrityl, 4,4'-dimethoxytrityl, trimethylsilyl, triethyldimethylsilyl, t-butyldiphenylsilyl, triphenylsilyl, triisopropylsilyl, benzyloformate, chloroacetyl, trichloroacetyl, trifluoroacetyl, pivaloyi, 9-fluorenylethyl carbonate, mesylate, tosylate, triflate, trityl, monomethoxytrityl, dimethoxytrityl, trimethoxytrityl or substitutedpixyl and the like.

(c) removing the hydroxyl protecting group of compound of formula XI to yield compound of formula XII

\[ \text{Formula XII} \]
(d) hydrolyzing compound of formula XII to obtain silodosin (formula XIII) and optionally converting to its pharmaceutically acceptable salts.

21. A process as claimed in claim 20, wherein the compound of formula X is 3-{7-cyano-5-[(2R)-2-aminopropyl]-2,3-dihydro-1H-indol-1-yl}propyl benzoate.
X

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Scheme 4, compound 27a

Date of the actual completion of the international search
13 April 2011

Date of mailing of the international search report
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Authorized officer
Seelmann, Ingo
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