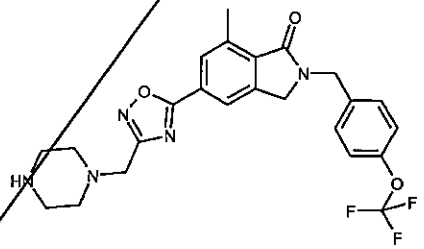
been demonstrated (Meller *et al.*, 1993, Neuroreport, 4: 879; Bordi & Ugolini, 1999, Brain Res., 871:223). In addition, mGluR activation has been suggested to play a modulatory role in a variety of other normal processes including synaptic transmission, neuronal development, apoptotic neuronal death, synaptic plasticity, spatial learning, olfactory memory, central control of cardiac activity, waking, motor control and control of the vestibulo-ocular reflex (Nakanishi, 1994, Neuron, 13:1031; Pin *et al.*, 1995, Neuropharmacology, *supra*; Knopfel *et al.*, 1995, J. Med. Chem., 38:1417).

Recent advances in the elucidation of the neurophysiological roles of mGluRs have established these receptors as promising drug targets in the therapy of acute and chronic neurological and psychiatric disorders and chronic and acute pain disorders. Because of the physiological and pathophysiological significance of the mGluRs, there is a need for new drugs and compounds that can modulate mGluR function.

DESCRIPTION OF THE INVENTION

The schemes and processes described herein illustrate the preparation of 7-methyl-5-(3-piperazin-1-ylmethyl-[1,2,4]oxadiazol-5-yl)-2-(4-trifluoromethoxybenzyl)-2,3-dihydroisoindol-1-one, having the structure below:



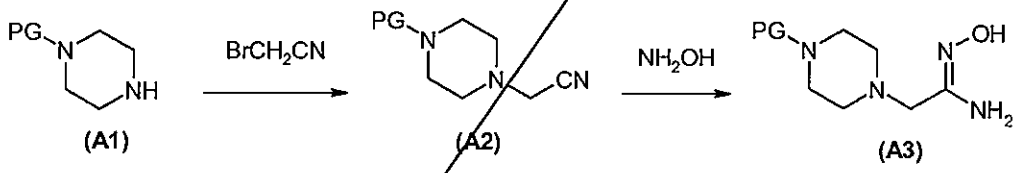
It will be understood by those of skill in the art that the compound made by a process described herein may exist in solvated, for example hydrated, as well as unsolvated forms. It will further be understood that the present invention encompasses all such solvated forms of the compound. Still further, it will be understood by those of skill in the art that the compound may be made by varying, or modifying, the process described herein. Particularly, those of skill in the art will understand that, as examples, solvents, temperatures or specific reagents may be changed or varied and that such changes are within the scope of the present invention.

Within the scope of the invention are also salts of the compound. Generally, pharmaceutically acceptable salts of compound made by the process of the present invention are obtained using standard procedures well known in the art.

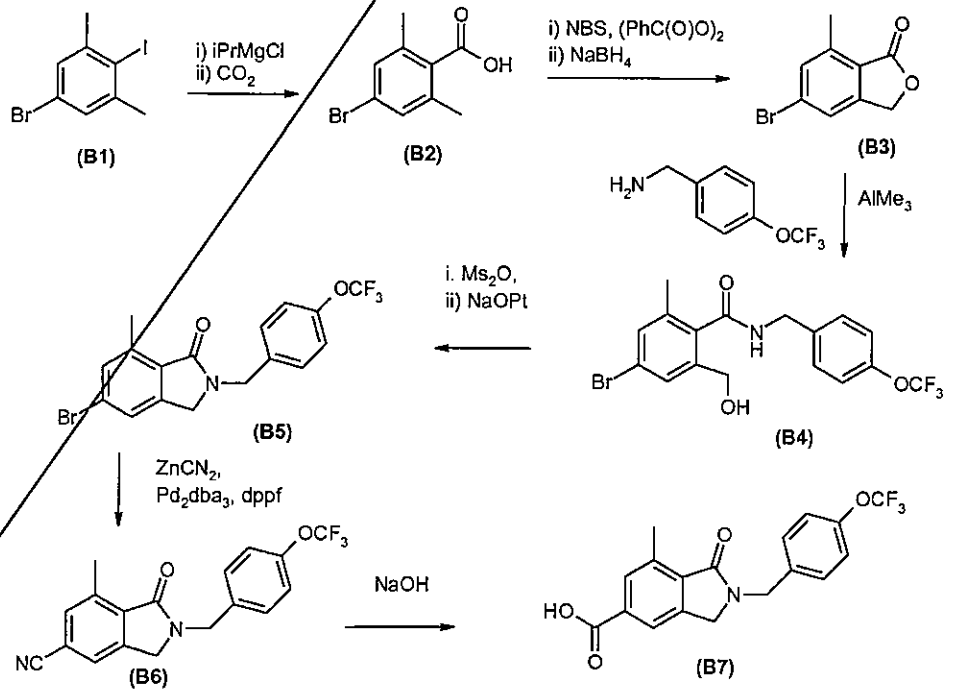
In one embodiment of the present invention, the compound may be a pharmaceutically acceptable salt or a solvate thereof. Particularly, a pharmaceutically acceptable salt may be an acidic addition salt such as a hydrochloride, hydrobromide, phosphate, acetate, fumarate, maleate, tartrate, citrate, methanesulphonate or *p*-toluenesulphonate.

The invention is illustrated by way of the following schemes and examples, which describe several embodiments of the process of the invention. The synthetic schemes and the synthetic procedures provided herein are provided by way of illustration and are not to be construed as limiting the invention. It will be clear to those skilled in the art that the compound or its intermediates may be prepared by modifications of the processes described.

Scheme A



Scheme B



Definitions:

The following definitions are used in the schemes and descriptions herein:

NB from schemes, please check and correct where necessary

"PG" - Protecting Group, for example a BOC group

"$BrCH_2CN$" - Bromoacetonitrile

"NH_2OH" - Hydoxylamine

"iPrMgCl" - Iso-propylmagnesium chloride

"NBS" – N-Bromosuccinimide

"$(PhC(CO)O)_2$" – Benzoyl peroxide

"$AlMe_3$" - Trimethylaluminium

"Ms_2O" – Methanesulphonyl anhydride

"NaOPt" – Sodium t-amylate

"$ZnCN_2$" – Zinc cyanide

"R" - A short chain alkyl group, for example, ethyl

"$POCl_3$" – Phosphorous oxychloride

"DMF" - Dimethyl formamide

"$NaBH_4$" - Sodium borohydride

"$SOCl_2$" – Thionyl Chloride

"NaOEt" – Sodium ethoxide

"TBAF" – Tetrabutylammonium fluoride

"MsOH" - Methane sulfonic acid

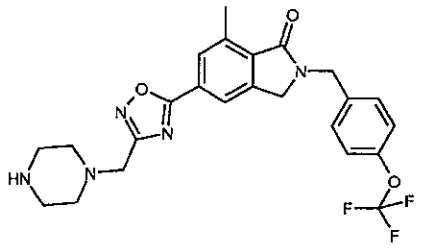
"rel vol" or "rel vols" - Relative volumes

For all the Examples and processes described herein amounts of materials, solvents, volumes, temperatures and times are exemplary and are not to be taken as limiting the manner in which such reactions may be performed or the scope of the invention. Variations in amounts of materials, solvents, volumes, temperatures and times may be made while carrying out the processes described and while practicing the invention described herein.

Example 1: Preparation of 4-(N-hydroxycarbamimidoylmethyl)-piperazine-1-carboxylic acid tert-butyl ester (A3a)

Claims:

Claim 1 A process for preparing 7-methyl-5-(3-piperazin-1-ylmethyl-[1,2,4]oxadiazol-5-yl)-2-(4-trifluoromethoxybenzyl)-2,3-dihydroisoindol-1-one, having the structure below:



or an acid salt thereof, the process comprising:

reacting tert-butyl piperazine-1-carboxylate with bromoacetonitrile, in an organic solvent in the presence of a base and subsequent reaction with hydroxylamine or an acid salt thereof to form 4-(N-hydroxycarbamimidoylmethyl)-piperazine-1-carboxylic acid tert-butyl ester;

reacting 5-bromo-2-iodo-1,3-dimethyl-benzene in an ether solvent with a Grignard reagent and carbon dioxide gas to form 4-bromo-2,6-dimethylbenzoic acid;

heating 4-bromo-2,6-dimethylbenzoic acid with N-bromosuccinimide and a radical initiator in an organic solvent and subsequent reduction of over-brominated products with a reducing agent to form 5-bromo-7-methyl-3H-isobenzofuran-1-one;

heating 5-bromo-7-methyl-3H-isobenzofuran-1-one with 4-(trifluoromethoxy)-benzylamine in an anhydrous solvent with trimethylaluminium to form 4-bromo-2-hydroxymethyl-6-methyl-N-(4-trifluoromethoxy-benzyl)-benzamide;

reacting 4-bromo-2-hydroxymethyl-6-methyl-N-(4-trifluoromethoxy-benzyl)-benzamide with methanesulphonyl chloride and a base in an organic solvent to form 5-bromo-7-methyl-2-(4-trifluoromethoxy-benzyl)-2,3-dihydro-isoindol-1-one;

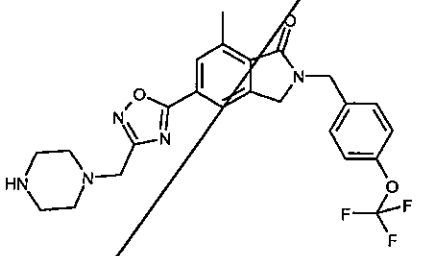
heating 5-bromo-7-methyl-2-(4-trifluoromethoxy-benzyl)-2,3-dihydro-isoindol-1-one in the presence of zinc cyanide, 1,1'-bis(diphenylphospino)ferrocene and tris(dibenzylideneacetone)-dipalladium in an organic solvent to form 7-methyl-1-oxo-2-(4-trifluoromethoxy-benzyl)-2,3-dihydro-1H-isoindole-5-carbonitrile;

hydrolysis of 7-methyl-1-oxo-2-(4-trifluoromethoxy-benzyl)-2,3-dihydro-1H-isoindole-5-carbonitrile in a solvent with a hydroxide solution to form 7-methyl-1-oxo-2-(4-trifluoromethoxy-benzyl)-2,3-dihydro-1H-isoindole-5-carboxylic acid;

reacting 7-methyl-1-oxo-2-(4-trifluoromethoxy-benzyl)-2,3-dihydro-1H-isoindole-5-carboxylic acid in an organic solvent with thionyl chloride or another chlorinating agent and reacting the product with tert-butyl 4-[(2Z)-2-amino-2-hydroxyimino)ethyl]-piperazine-1-carboxylate in the presence of a base to form 4-{5-[7-methyl-1-oxo-2-(4-trifluoromethoxy-benzyl)-2,3-dihydro-1H-isoindol-5-yl]-[1,2,4]oxadiazol-3-ylmethyl}-piperazine-1-carboxylic acid tert-butyl ester, and

decarboxylating 4-{5-[7-methyl-1-oxo-2-(4-trifluoromethoxy-benzyl)-2,3-dihydro-1H-isoindol-5-yl]-[1,2,4]oxadiazol-3-ylmethyl}-piperazine-1-carboxylic acid tert-butyl ester by heating with acid in a solvent, to form 7-methyl-5-(3-piperazin-1-ylmethyl-[1,2,4]oxadiazol-5-yl)-2-(4-trifluoromethoxy-benzyl)-2,3-dihydro-isoindol-1-one or an acid salt thereof.

Claim 2 A process for preparing 7-methyl-5-(3-piperazin-1-ylmethyl-[1,2,4]oxadiazol-5-yl)-2-(4-trifluoromethoxybenzyl)-2,3-dihydroisoindol-1-one, having the structure below:



or an acid salt thereof, the process comprising:

reacting tert-butyl piperazine-1-carboxylate with bromoacetonitrile, in an organic solvent in the presence of a base and subsequent reaction with hydroxylamine or an acid salt thereof to form 4-(N-hydroxycarbamimidoylmethyl)-piperazine-1-carboxylic acid tert-butyl ester;

formylating ethyl-3-furoate with a Vilsmeier reagent formed by reaction of phosphoryl chloride with dimethylformamide or another formylating agent to form 5-formyl-furan-3-carboxylic acid ethyl ester;

reacting 5-formyl-furan-3-carboxylic acid ethyl ester in an organic solvent with 4-(trifluoromethoxy)-benzylamine and reducing the product to form 5-[(4-trifluoromethoxy-benzylamino)-methyl]-furan-3-carboxylic acid ethyl ester or an acid salt thereof ;

reacting 5-[(4-trifluoromethoxy-benzylamino)-methyl]-furan-3-carboxylic acid ethyl ester or an acid salt thereof with crotonoyl chloride in the presence of a base, with subsequent heating or other conditions so as to affect a Diels Alder transformation and subsequent

dehydration of the product with an acid or base to form 7-methyl-1-oxo-2-(4-trifluoromethoxy-benzyl)-2,3-dihydro-1H-isoindole-5-carboxylic acid ethyl ester;

reacting 7-methyl-1-oxo-2-(4-trifluoromethoxy-benzyl)-2,3-dihydro-1H-isoindole-5-carboxylic acid ethyl ester with tert-butyl 4-[(2Z)-2-amino-2-hydroxyimino)ethyl]-piperazine-1-carboxylate in an organic solvent with a base to form 4-{5-[7-methyl-1-oxo-2-(4-trifluoromethoxy-benzyl)-2,3-dihydro-1H-isoindol-5-yl]-[1,2,4]oxadiazol-3-ylmethyl}-piperazine-1-carboxylic acid tert-butyl ester, and

decarboxylating 4-{5-[7-methyl-1-oxo-2-(4-trifluoromethoxy-benzyl)-2,3-dihydro-1H-isoindol-5-yl]-[1,2,4]oxadiazol-3-ylmethyl}-piperazine-1-carboxylic acid tert-butyl ester by heating with acid in an organic solvent, to form 7-methyl-5-(3-piperazin-1-ylmethyl-[1,2,4]oxadiazol-5-yl)-2-(4-trifluoromethoxy-benzyl)-2,3-dihydro-isoindol-1-one or an acid salt thereof.

Claim 3 A compound selected from the group consisting of:

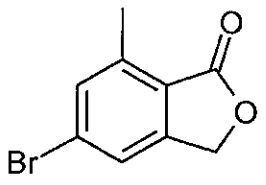
5-bromo-7-methyl-3H-isobenzofuran-1-one;

4-bromo-2-hydroxymethyl-6-methyl-N-(4-trifluoromethoxy-benzyl)-benzamide;

5-[(4-trifluoromethoxy-benzylamino)-methyl]-furan-3-carboxylic acid or an alkyl ester thereof, and

7-methyl-1-oxo-2-(4-trifluoromethoxy-benzyl)-2,3-dihydro-1H-isoindole-5-carboxylic acid or an alkyl ester thereof.

Claim 4 A process for making 5-bromo-7-methyl-3H-isobenzofuran-1-one,

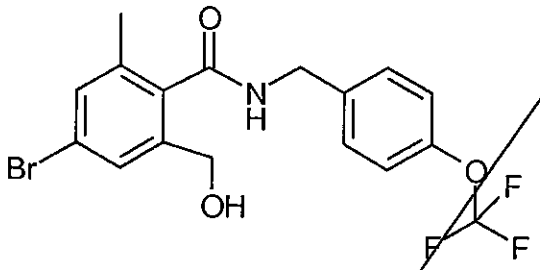


the process comprising:

reacting 5-bromo-2-iodo-1,3-dimethyl-benzene in an ether solvent with a Grignard reagent and carbon dioxide gas to form 4-bromo-2,6-dimethylbenzoic acid, and

heating 4-bromo-2,6-dimethylbenzoic acid with N-bromosuccinimide and a radical initiator in an organic solvent and subsequent reduction of over-brominated products with a reducing agent to form 5-bromo-7-methyl-3H-isobenzofuran-1-one.

Claim 5 A process for making 4-bromo-2-hydroxymethyl-6-methyl-N-(4-trifluoromethoxy-benzyl)-benzamide,



the process comprising:

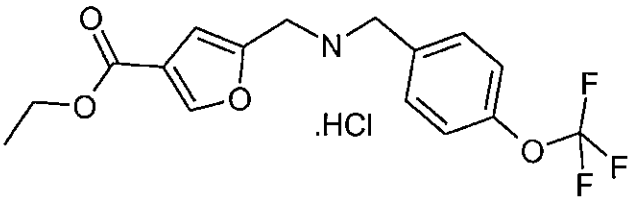
reacting tert-butyl piperazine-1-carboxylate with bromoacetonitrile, in an organic solvent in the presence of a base and subsequent reaction with hydroxylamine or an acid salt thereof to form 4-(N-hydroxycarbamimidoylmethyl)-piperazine-1-carboxylic acid tert-butyl ester;

reacting 5-bromo-2-iodo-1,3-dimethyl-benzene in an ether solvent with a Grignard reagent and carbon dioxide gas to form 4-bromo-2,6-dimethylbenzoic acid;

heating 4-bromo-2,6-dimethylbenzoic acid with N-bromosuccinimide and a radical initiator in an organic solvent and subsequent reduction of over-brominated products with a reducing agent to form 5-bromo-7-methyl-3H-isobenzofuran-1-one;

heating 5-bromo-7-methyl-3H-isobenzofuran-1-one with 4-(trifluoromethoxy)-benzylamine in an anhydrous solvent with trimethylaluminium to form 4-bromo-2-hydroxymethyl-6-methyl-N-(4-trifluoromethoxy-benzyl)-benzamide.

Claim 6 A process for making 5-[(4-trifluoromethoxy-benzylamino)-methyl]-furan-3-carboxylic acid ethyl ester or an acid salt thereof,



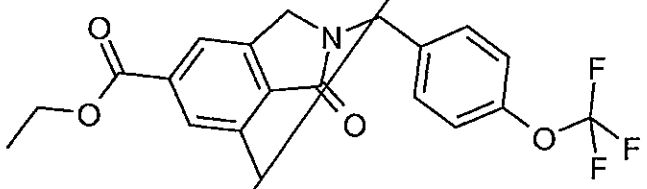
the process comprising:

reacting tert-butyl piperazine-1-carboxylate with bromoacetonitrile, in an organic solvent in the presence of a base and subsequent reaction with hydroxylamine or an acid salt thereof to form 4-(N-hydroxycarbamimidoylmethyl)-piperazine-1-carboxylic acid tert-butyl ester;

formylating ethyl-3-furoate with a Vilsmeier reagent formed by reaction of phosphoryl chloride with dimethylformamide or another formylating agent to form 5-formyl-furan-3-carboxylic acid ethyl ester;

reacting 5-formyl-furan-3-carboxylic acid ethyl ester in an organic solvent with 4-(trifluoromethoxy)-benzylamine and reducing the product to form 5-[(4-trifluoromethoxy-benzylamino)-methyl]-furan-3-carboxylic acid ethyl ester.

Claim 7 A process for making 7-methyl-1-oxo-2-(4-trifluoromethoxy-benzyl)-2,3-dihydro-1H-isoindole-5-carboxylic acid ethyl ester,



the process comprising:

reacting tert-butyl piperazine-1-carboxylate with bromoacetonitrile, in an organic solvent in the presence of a base and subsequent reaction with hydroxylamine or an acid salt thereof to form 4-(N-hydroxycarbamimidoylmethyl)-piperazine-1-carboxylic acid tert-butyl ester;

formylating ethyl-3-furoate with a Vilsmeier reagent formed by reaction of phosphoryl chloride with dimethylformamide or another formylating agent to form 5-formyl-furan-3-carboxylic acid ethyl ester;

reacting 5-formyl-furan-3-carboxylic acid ethyl ester in an organic solvent with 4-(trifluoromethoxy)-benzylamine and reducing the product to form 5-[(4-trifluoromethoxy-benzylamino)-methyl]-furan-3-carboxylic acid ethyl ester or an acid salt thereof;

reacting 5-[(4-trifluoromethoxy-benzylamino)-methyl]-furan-3-carboxylic acid ethyl ester or an acid salt thereof with crotonoyl chloride in the presence of a base, with subsequent heating or other conditions so as to affect a Diels Alder transformation and subsequent

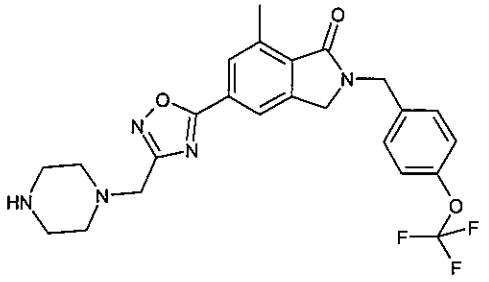
dehydration of the product with an acid or base to form 7-methyl-1-oxo-2-(4-trifluoromethoxy-benzyl)-2,3-dihydro-1H-isoindole-5-carboxylic acid ethyl ester.

been demonstrated (Meller *et al.*, 1993, Neuroreport, 4: 879; Bordi & Ugolini, 1999, Brain Res., 871:223). In addition, mGluR activation has been suggested to play a modulatory role in a variety of other normal processes including synaptic transmission, neuronal development, apoptotic neuronal death, synaptic plasticity, spatial learning, olfactory memory, central control of cardiac activity, waking, motor control and control of the vestibulo-ocular reflex (Nakanishi, 1994, Neuron, 13:1031; Pin *et al.*, 1995, Neuropharmacology, *supra*; Knopfel *et al.*, 1995, J. Med. Chem., 38:1417).

Recent advances in the elucidation of the neurophysiological roles of mGluRs have established these receptors as promising drug targets in the therapy of acute and chronic neurological and psychiatric disorders and chronic and acute pain disorders (see for example WO2008/150233 and WO2008/150232 which both describe oxadiazole derivatives; and US2009/0111830 which describes substituted isoindolones. Each of these documents also describe the use of the respective compounds that they describe as metabotropic glutamate receptor potentiators). Because of the physiological and pathophysio-logical significance of the mGluRs, there is a need for new drugs and compounds that can modulate mGluR function.

DESCRIPTION OF THE INVENTION

The schemes and processes described herein illustrate the preparation of 7-methyl-5-(3-piperazin-1-ylmethyl-[1,2,4]oxadiazol-5-yl)-2-(4-trifluoromethoxybenzyl)-2,3-dihydroisoindol-1-one, having the structure below:

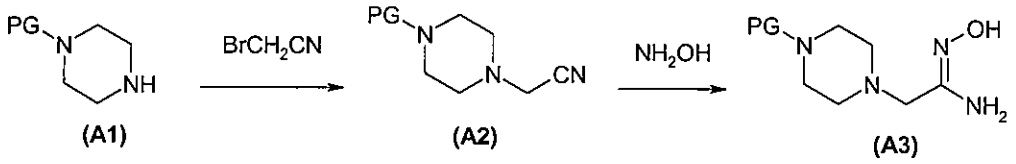


Within the scope of the invention are also acid salts of the compound. Generally, pharmaceutically acceptable salts of compound made by the process of the present invention are obtained using standard procedures well known in the art.

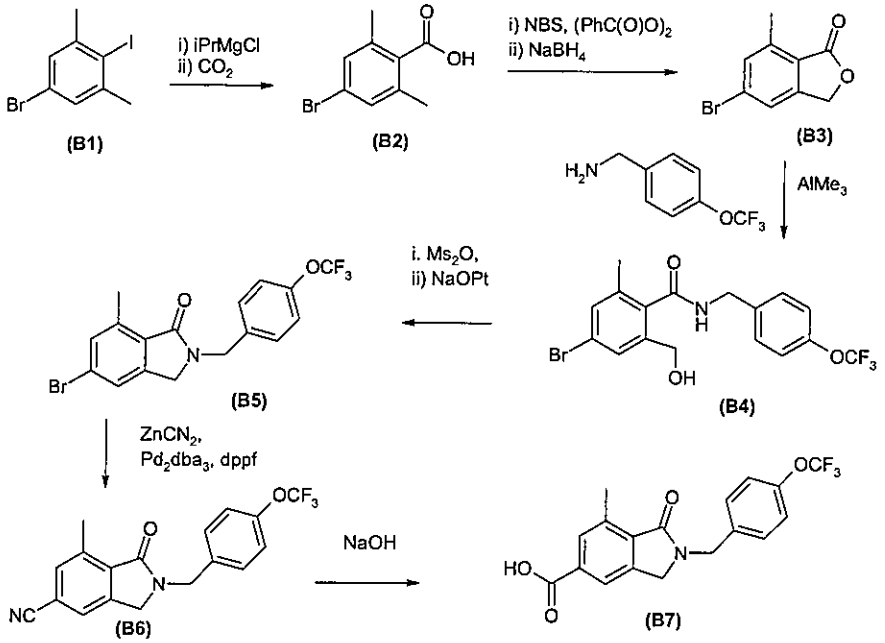
In one embodiment of the present invention, the compound may be a pharmaceutically acceptable salt or a solvate thereof. Particularly, a pharmaceutically acceptable salt may be an acidic addition salt such as a hydrochloride, hydrobromide, phosphate, acetate, fumarate, maleate, tartrate, citrate, methanesulphonate or *p*-toluenesulphonate.

The invention is illustrated by way of the following schemes and examples, which describe several embodiments of the process of the invention. It will be clear to those skilled in the art that the compound or its intermediates may be prepared by modifications of the processes described.

Scheme A



Scheme B



Definitions:

The following definitions are used in the schemes and descriptions herein:

NB from schemes, please check and correct where necessary

"PG" - Protecting Group, for example a BOC group

"$BrCH_2CN$" - Bromoacetonitrile

"NH_2OH" - Hydoxylamine

"iPrMgCl" - Iso-propylmagnesium chloride

"NBS" – N-Bromosuccinimide

"$(PhC(CO)O)_2$" – Benzoyl peroxide

"$AlMe_3$" - Trimethylaluminium

"Ms_2O" – Methanesulphonyl anhydride

"NaOPt" – Sodium t-amylate

"$ZnCN_2$" – Zinc cyanide

"R" - A short chain alkyl group, for example, ethyl

"$POCl_3$" – Phosphorous oxychloride

"DMF" - Dimethyl formamide

"$NaBH_4$" - Sodium borohydride

"$SOCl_2$" – Thionyl Chloride

"NaOEt" – Sodium ethoxide

"TBAF" – Tetrabutylammonium fluoride

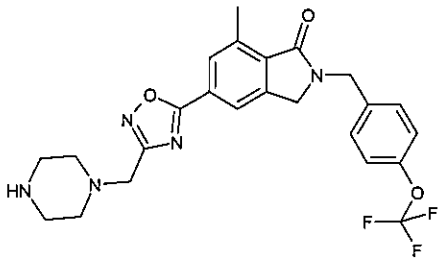
"MsOH" - Methane sulfonic acid

"rel vol" or "rel vols" - Relative volumes

Example 1: Preparation of 4-(N-hydroxycarbamimidoylmethyl)-piperazine-1-carboxylic acid tert-butyl ester (A3a)

Claims:

1. A process for preparing 7-methyl-5-(3-piperazin-1-ylmethyl-[1,2,4]oxadiazol-5-yl)-2-(4-trifluoromethoxybenzyl)-2,3-dihydroisoindol-1-one, having the structure below:



or an acid salt thereof, the process comprising:

reacting tert-butyl piperazine-1-carboxylate with bromoacetonitrile, in an organic solvent in the presence of a base and subsequent reaction with hydroxylamine or an acid salt thereof to form 4-(N-hydroxycarbamimidoylmethyl)-piperazine-1-carboxylic acid tert-butyl ester;

reacting 5-bromo-2-iodo-1,3-dimethyl-benzene in an ether solvent with a Grignard reagent and carbon dioxide gas to form 4-bromo-2,6-dimethylbenzoic acid;

heating 4-bromo-2,6-dimethylbenzoic acid with N-bromosuccinimide and a radical initiator in an organic solvent and subsequent reduction of over-brominated products with a reducing agent to form 5-bromo-7-methyl-3H-isobenzofuran-1-one;

heating 5-bromo-7-methyl-3H-isobenzofuran-1-one with 4-(trifluoromethoxy)-benzyl-amine in an anhydrous solvent with trimethylaluminium to form 4-bromo-2-hydroxymethyl-6-methyl-N-(4-trifluoromethoxy-benzyl)-benzamide;

reacting 4-bromo-2-hydroxymethyl-6-methyl-N-(4-trifluoromethoxy-benzyl)-benzamide with methanesulphonyl chloride and a base in an organic solvent to form 5-bromo-7-methyl-2-(4-trifluoromethoxy-benzyl)-2,3-dihydro-isoindol-1-one;

heating 5-bromo-7-methyl-2-(4-trifluoromethoxy-benzyl)-2,3-dihydro-isoindol-1-one in the presence of zinc cyanide, 1,1'-bis(diphenylphospino)ferrocene and tris(dibenzylidene-acetone)-dipalladium in an organic solvent to form 7-methyl-1-oxo-2-(4-trifluoromethoxy-benzyl)-2,3-dihydro-1H-isoindole-5-carbonitrile;

hydrolysis of 7-methyl-1-oxo-2-(4-trifluoromethoxy-benzyl)-2,3-dihydro-1H-isoindole-5-carbonitrile in a solvent with a hydroxide solution to form 7-methyl-1-oxo-2-(4-trifluoro-methoxy-benzyl)-2,3-dihydro-1H-isoindole-5-carboxylic acid;

reacting 7-methyl-1-oxo-2-(4-trifluoromethoxy-benzyl)-2,3-dihydro-1H-isoindole-5-carboxylic acid in an organic solvent with thionyl chloride or another chlorinating agent and reacting the product with tert-butyl 4-[(2Z)-2-amino-2-hydroxyimino)ethyl]-piperazine-1-carboxylate in the presence of a base to form 4-{5-[7-methyl-1-oxo-2-(4-trifluoromethoxy-benzyl)-2,3-dihydro-1H-isoindol-5-yl]-[1,2,4]oxadiazol-3-ylmethyl}-piperazine-1-carboxylic acid tert-butyl ester, and

decarboxylating 4-{5-[7-methyl-1-oxo-2-(4-trifluoromethoxy-benzyl)-2,3-dihydro-1H-isoindol-5-yl]-[1,2,4]oxadiazol-3-ylmethyl}-piperazine-1-carboxylic acid tert-butyl ester by heating with acid in a solvent, to form 7-methyl-5-(3-piperazin-1-ylmethyl-[1,2,4]oxadiazol-5-yl)-2-(4-trifluoromethoxy-benzyl)-2,3-dihydro-isoindol-1-one or an acid salt thereof.

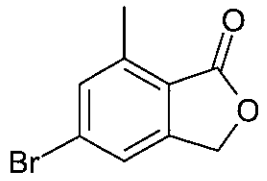
2. A compound selected from the group consisting of:

5-bromo-7-methyl-3H-isobenzofuran-1-one;

4-bromo-2-hydroxymethyl-6-methyl-N-(4-trifluoromethoxy-benzyl)-benzamide; and

7-methyl-1-oxo-2-(4-trifluoromethoxy-benzyl)-2,3-dihydro-1H-isoindole-5-carboxylic acid.

3. A process for making 5-bromo-7-methyl-3H-isobenzofuran-1-one,



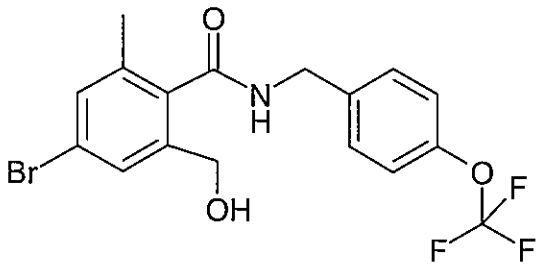
the process comprising:

reacting 5-bromo-2-iodo-1,3-dimethyl-benzene in an ether solvent with a Grignard reagent and carbon dioxide gas to form 4-bromo-2,6-dimethylbenzoic acid, and

heating 4-bromo-2,6-dimethylbenzoic acid with N-bromosuccinimide and a radical initiator in an organic solvent and subsequent reduction of over-brominated products with a reducing agent to form 5-bromo-7-methyl-3H-isobenzofuran-1-one.

4. A process for making 4-bromo-2-hydroxymethyl-6-methyl-N-(4-trifluoromethoxy-

benzyl)-benzamide,



the process comprising:

reacting 5-bromo-2-iodo-1,3-dimethyl-benzene in an ether solvent with a Grignard reagent and carbon dioxide gas to form 4-bromo-2,6-dimethylbenzoic acid;

heating 4-bromo-2,6-dimethylbenzoic acid with N-bromosuccinimide and a radical initiator in an organic solvent and subsequent reduction of over-brominated products with a reducing agent to form 5-bromo-7-methyl-3H-isobenzofuran-1-one;

heating 5-bromo-7-methyl-3H-isobenzofuran-1-one with 4-(trifluoromethoxy)-benzyl-amine in an anhydrous solvent with trimethylaluminium to form 4-bromo-2-hydroxymethyl-6-methyl-N-(4-trifluoromethoxy-benzyl)-benzamide.