

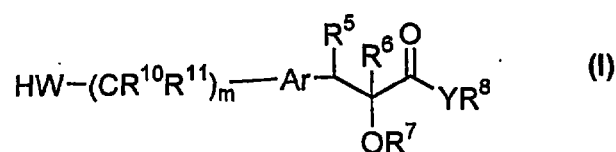


**NOVEL β -PHENYL- α -OXYSUBSTITUTED PROPIONIC DERIVATIVES:
PROCESS FOR ITS PREPARATION AND THEIR USE IN THE
PREPARATION OF PHARMACEUTICALLY IMPORTANT COMPOUNDS**

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Field of the Invention

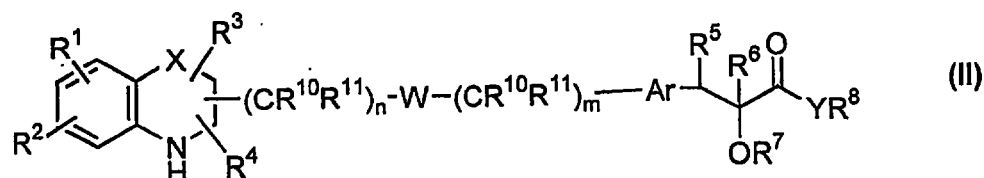
The present invention relates to novel propionic acid derivatives. More particularly, the present invention relates to β -phenyl α -oxysubstituted propionic acids of the general formula (I)



- 10 their derivatives, their analogs, their tautomeric forms, their stereoisomers, their salts, their solvates wherein W represents NR^{12} , R^{12} represents hydrogen, R^{10} and R^{11} may be same or different and represent hydrogen or substituted or unsubstituted group selected from alkyl, alkoxy, aryl or aralkyl group; Ar represents substituted or unsubstituted divalent single or fused aromatic or heterocyclic group; R^5 represents
- 15 hydrogen atom, hydroxy, alkoxy, halogen, alkyl, substituted or unsubstituted aralkyl group or forms a bond together with the adjacent group R^6 ; R^6 represents hydrogen, hydroxy, alkoxy, halogen, lower alkyl group, acyl, substituted or unsubstituted aralkyl or R^6 forms a bond together with R^5 ; R^7 may be hydrogen or substituted or unsubstituted groups selected from alkyl, cycloalkyl, aryl, aralkyl, alkoxyalkyl,
- 20 alkoxycarbonyl, aryloxycarbonyl, alkylaminocarbonyl, arylaminocarbonyl, acyl, heterocyclyl, heteroaryl, heteroaralkyl groups; R^8 may be hydrogen or substituted or unsubstituted groups selected from alkyl, cycloalkyl, aryl, aralkyl, heterocyclyl, heteroaryl or heteroaralkyl groups; Y represents oxygen, sulfur or NR^{13} , where R^{13} represents hydrogen or substituted or unsubstituted groups selected from alkyl, aryl,
- 25 hydroxyalkyl, aralkyl heterocyclyl, heteroaryl, or heteroaralkyl groups; R^8 and R^{13} together may form a substituted or unsubstituted 5 or 6 membered cyclic structure containing carbon atoms, which may optionally contain one or more heteroatoms selected from oxygen, sulfur or nitrogen; m is an integer ranging from 0-6.



The compounds of formula (I) are novel intermediates, useful in the synthesis of novel antidiabetic compounds of the formula (II), which has been made subject matter of our PCT application entitled "New bicyclic compounds and their use in medicine, process for their preparation and pharmaceutical compositions containing them" filed simultaneously on the same day.



wherein R^1 , R^2 and R^3 , R^4 when attached to the carbon atom, may be same or different and represent hydrogen, halogen, hydroxy, nitro, cyano, formyl or substituted or unsubstituted groups selected from alkyl, cycloalkyl, alkoxy, cycloalkoxy, aryl, aryloxy, aralkyl, aralkoxy, heterocyclyl, heteroaryl, heteroaralkyl, heteroaryloxy, heteroaralkoxy, acyl, acyloxy, hydroxyalkyl, amino, acylamino, monoalkylamino, dialkylamino, arylamino, aralkylamino, alkoxycarbonyl, aryloxy, aryloxyalkyl, aralkoxy, aralkoxyalkyl, alkylthio, thioalkyl, alkoxycarbonylamino, aryloxy, aryloxyalkyl, aralkoxy, aralkoxyalkyl, alkylthio, thioalkyl groups, carboxylic acid derivatives, or sulfonic acid derivatives; one or both of R^3 and R^4 may represent oxo or thioxo group when they are attached to carbon atom; R^3 and R^4 when attached to nitrogen atom represent hydrogen, hydroxy, formyl or substituted or unsubstituted groups selected from alkyl, cycloalkyl, alkoxy, cycloalkoxy, aryl, aralkyl, heterocyclyl, heteroaryl, heteroaralkyl, acyl, acyloxy, hydroxyalkyl, amino, acylamino, monoalkylamino, dialkylamino, arylamino, aralkylamino, aminoalkyl, aryloxy, aralkoxy, heteroaryloxy, heteroaralkoxy, alkoxycarbonyl, aryloxy, aryloxyalkyl, aralkoxy, aralkoxyalkyl, alkylthio, thioalkyl groups, carboxylic acid derivatives, or sulfonic acid derivatives; X represents a heteroatom selected from oxygen or sulfur; W represents NR^{12} , $-C(=O)-(CR^{10}R^{11})_o-NR^{12}$, $-O-aryl-(CR^{10}R^{11})_o-NR^{12}$, where R^{12} represents hydrogen or substituted or unsubstituted group selected from alkyl, aryl or aralkyl groups; o is an integer ranging from 0-6; R^{10} and R^{11} may be same or different and represent hydrogen or unsubstituted or unsubstituted group

selected form alkyl, alkoxy, aryl or aralkyl group; Ar represents substituted or unsubstituted divalent single or fused aromatic or heterocyclic group; R⁵ represents hydrogen atom, hydroxy, alkoxy, halogen, alkyl, substituted or unsubstituted aralkyl group or forms a bond together with the adjacent group R⁶; R⁶ represents hydrogen, hydroxy, alkoxy, halogen, alkyl group, acyl, substituted or unsubstituted aralkyl or R⁶ forms a bond together with R⁵; R⁷ may be hydrogen or substituted or unsubstituted groups selected from alkyl, cycloalkyl, aryl, aralkyl, alkoxyalkyl, alkoxy carbonyl, aryloxy carbonyl, alkylaminocarbonyl, arylaminocarbonyl, acyl, heterocyclyl, heteroaryl, heteroaralkyl groups; R⁸ may be hydrogen or substituted or unsubstituted groups selected from alkyl, cycloalkyl, aryl, aralkyl, heterocyclyl, heteroaryl or heteroaralkyl groups; Y represents oxygen, sulfur or NR⁹, where R⁹ represents hydrogen or substituted or unsubstituted groups selected from alkyl, aryl, hydroxyalkyl, aralkyl heterocyclyl, heteroaryl, or heteroaralkyl groups or NR⁹ represents chiral amine, chiral amine alcohols derived from chiral amino acid; R⁸ and R⁹ together may form a substituted or unsubstituted 5 or 6 membered cyclic structure containing carbon atoms, which may optionally contain one or more heteroatoms selected from oxygen, sulfur or nitrogen; m and n are integers ranging from 0-6.

The present invention also relates to processes for the preparation of compounds of the formula (I) and their use in the preparation of compounds of formula (II).

The compounds of general formula (II) are useful in reducing body weight and for the treatment and/or prophylaxis of diseases such as atherosclerosis, stroke, peripheral vascular diseases and related disorders. These compounds are useful for the treatment of hyperlipidemia, hyperglycemia, hypercholesterolemia, lowering of atherogenic lipoproteins, VLDL (very low density lipoprotein) and LDL. The compounds of the present invention can be used for the treatment of renal diseases including glomerulonephritis, glomerulosclerosis, nephrotic syndrome, hypertensive nephrosclerosis and nephropathy. The compounds of general formula (II) are also useful for the treatment and/or prophylaxis of leptin resistance, impaired glucose tolerance, disorders related to syndrome X such as hypertension, obesity, insulin resistance, coronary heart disease and other cardiovascular disorders. These compounds may also be useful as aldose reductase inhibitors, for improving

cognitive functions in dementia, treating diabetic complications, disorders related to endothelial cell activation, psoriasis, polycystic ovarian syndrome (PCOS), inflammatory bowel diseases, osteoporosis, myotonic dystrophy, pancreatitis, arteriosclerosis, retinopathy, xanthoma, eating disorders, inflammation and for the treatment of cancer. The compounds of the present invention are also useful in the treatment and/or prophylaxis of the above said diseases in combination/concomittant with one or more HMG CoA reductase inhibitors; cholesterol absorption inhibitors; antiobesity drugs; lipoprotein disorder treatment drugs; hypoglycemic agents: insulin; biguanides; sulfonylureas; thiazolidinediones; dual PPAR α and γ or a mixture thereof.

Background of the Invention

Atherosclerosis and other peripheral vascular diseases affect the quality of life of millions of people. Therefore, considerable attention has been directed towards understanding the etiology of hypercholesterolemia and hyperlipidemia and development of effective therapeutic strategies.

Hypercholesterolemia has been defined as plasma cholesterol level that exceeds arbitrarily defined value called "normal" level. Recently, it has been accepted that "ideal" plasma levels of cholesterol are much below the "normal" level of cholesterol in the general population and the risk of coronary artery disease (CAD) increases as cholesterol level rises above the "optimum" (or "ideal") value. There is clearly a definite cause and effect-relationship between hypercholesterolemia and CAD, particularly for individuals with multiple risk factors. Most of the cholesterol is present in the esterified forms with various lipoproteins such as Low density lipoprotein (LDL), Intermediate density lipoprotein (IDL), High density lipoprotein (HDL) and partially as Very low density lipoprotein (VLDL). Studies clearly indicate that there is an inverse correlation between CAD and atherosclerosis with serum HDL-cholesterol concentrations, (Stampfer *et al.*, *N. Engl. J. Med.*, 325 (1991), 373-381) and the risk of CAD increases with increasing levels of LDL and VLDL.

In CAD, generally "fatty streaks" in carotid, coronary and cerebral arteries, are found which are primarily free and esterified cholesterol. Miller *et al.*, (*Br. Med. J.*, 282 (1981), 1741 - 1744) have shown that increase in HDL-particles may decrease the number of sites of stenosis in coronary arteries of human, and high level
5 of HDL-cholesterol may protect against the progression of atherosclerosis. Picardo *et al.*, *Arteriosclerosis* 6 (1986) 434 - 441 have shown by *in vitro* experiment that HDL is capable of removing cholesterol from cells. They suggest that HDL may deplete tissues of excess free cholesterol and transfer it to liver, which is known as reverse cholesterol transport, (Macikinnon *et al.*, *J. Biol. chem.* 261 (1986), 2548 -
10 2552). Therefore, agents that increase HDL cholesterol would have therapeutic significance for the treatment of hypercholesterolemia and coronary heart diseases (CHD).

Obesity is a disease highly prevalent in affluent societies and in the developing world and is a major cause of morbidity and mortality. It is a state of
15 excess body fat accumulation. The causes of obesity are unclear. It is believed to be of genetic origin or promoted by an interaction between the genotype and environment. Irrespective of the cause, the result is fat deposition due to imbalance between the energy intake versus energy expenditure. Dieting, exercise and appetite suppression have been a part of obesity treatment. There is a need for efficient
20 therapy to fight this disease since it may lead to coronary heart disease, diabetes, stroke, hyperlipidemia, gout, osteoarthritis, reduced fertility and many other psychological and social problems.

Diabetes and insulin resistance is yet another disease which severely affects the quality of large population in the world. Insulin resistance is the diminished
25 ability of insulin to exert its biological action across a broad range of concentrations. In insulin resistance, the body secretes abnormally high amounts of insulin to compensate for this defect; failing which, the plasma glucose concentration inevitably raises and develops into diabetes. Among the developed countries, diabetes mellitus is a common problem and is associated with a variety of
30 abnormalities including obesity, hypertension, hyperlipidemia (*J. Clin. Invest.*, 75

(1985) 809 - 817; *N. Engl. J. Med* 317 (1987) 350-357; *J. Clin. Endocrinol. Metab.*, 66 (1988) 580 - 583; *J. Clin. Invest.*, 68 (1975) 957 - 969) and other renal complications (patent publication No. WO 95/21608). It is now increasingly being recognized that insulin resistance and relative hyperinsulinemia have a contributory
5 role in obesity, hypertension, atherosclerosis and type 2 diabetes mellitus. The association of insulin resistance with obesity, hypertension and angina has been described as a syndrome having insulin resistance as the central pathogenic link-Syndrome-X.

Hyperlipidemia is the primary cause for cardiovascular (CVD) and other
10 peripheral vascular diseases. High risk of CVD is related to the higher LDL (Low Density Lipoprotein) and VLDL (Very Low Density Lipoprotein) seen in hyperlipidemia. Patients having glucose intolerance/insulin resistance in addition to hyperlipidemia have higher risk of CVD. Numerous studies in the past have shown that lowering of plasma triglycerides and total cholesterol, in particular LDL and
15 VLDL and increasing HDL cholesterol help in preventing cardiovascular diseases.

Peroxisome proliferator activated receptors (PPAR) are members of the nuclear receptor super family. The gamma (γ) isoform of PPAR (PPAR γ) has been implicated in regulating differentiation of adipocytes (*Endocrinology*, 135 (1994) 798-800) and energy homeostasis (*Cell*, 83 (1995) 803-812), whereas the alpha (α)
20 isoform of PPAR (PPAR α) mediates fatty acid oxidation (*Trend. Endocrin. Metab.*, 4 (1993) 291-296) thereby resulting in reduction of circulating free fatty acid in plasma (*Current Biol.* 5 (1995) 618 -621). PPAR α agonists have been found useful for the treatment of obesity (WO 97/36579). It has been recently disclosed that compounds which are agonists for both PPAR α and PPAR γ are suggested to be
25 useful for the treatment of syndrome X (WO 97/25042). Similar effect between the insulin sensitizer (PPAR γ agonist) and HMG CoA reductase inhibitor has been observed which may be useful for the treatment of atherosclerosis and xanthoma (EP 0 753 298).

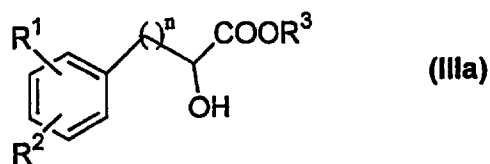
It is known that PPAR γ plays an important role in adipocyte differentiation (*Cell*, 87 (1996) 377-389). Ligand activation of PPAR is sufficient to cause complete terminal differentiation (*Cell*, 79 (1994) 1147-1156) including cell cycle withdrawal. PPAR γ is consistently expressed in certain cells and activation of this nuclear receptor with PPAR γ agonists would stimulate the terminal differentiation of adipocyte precursors and cause morphological and molecular changes characteristics of a more differentiated, less malignant state (*Molecular Cell*, (1998), 465-470; *Carcinogenesis*, (1998), 1949-53; *Proc. Natl. Acad. Sci.*, 94 (1997) 237-241) and inhibition of expression of prostate cancer tissue (*Cancer Research* 58 (1998) 3344-3352). This would be useful in the treatment of certain types of cancer, which express PPAR γ and could lead to a quite nontoxic chemotherapy.

Leptin resistance is a condition wherein the target cells are unable to respond to leptin signal. This may give rise to obesity due to excess food intake and reduced energy expenditure and cause impaired glucose tolerance, type 2 diabetes, cardiovascular diseases and such other interrelated complications. Kallen *et al* (*Proc. Natl. Acad. Sci.* (1996) 93, 5793-5796) have reported that insulin sensitizers which perhaps due to the PPAR agonist expression lower plasma leptin concentrations. However, it has been recently disclosed that compounds having insulin sensitizing property also possess leptin sensitization activity. They lower the circulating plasma leptin concentrations by improving the target cell response to leptin (WO 98/02159).

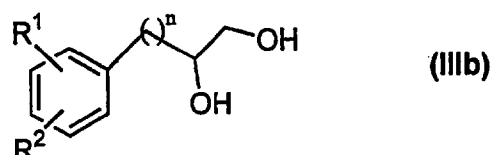
Prior Art

Few β -phenyl α -hydroxysubstituted propionic acid derivatives have been reported which have been used as intermediates for the synthesis of various biologically active molecules. Some of such compounds described in the prior art are outlined below:

- i) European Patent Application EP0816316 discloses compound of formula (IIIa)

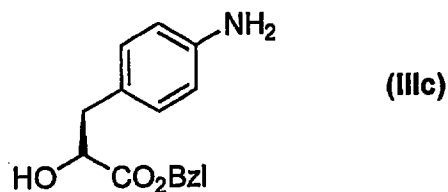


The compound of formula (IIIa) was further converted to 1,2-ethanediol derivative of the formula (IIIb)

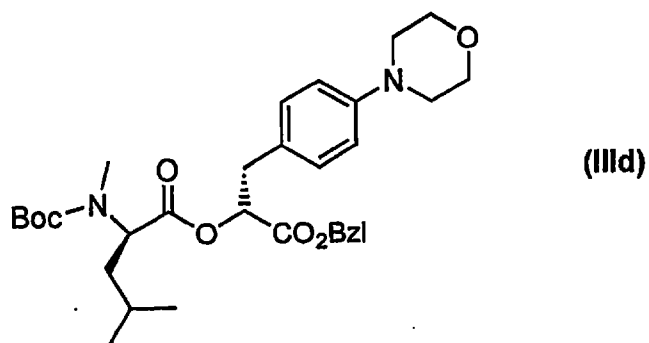


- 5 These 1,2-ethanediol derivatives are useful intermediates for the pharmaceuticals and agricultural chemicals..

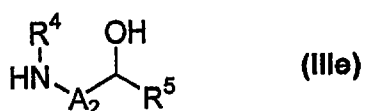
ii) Japanese Patent Application JP 10017540 discloses compound of formula (IIIc)



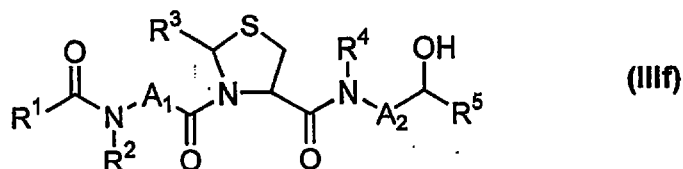
- 10 The compound of formula (IIIc) was further converted to a compound of formula (IIId)



iii) US patent 6410576 discloses compound of formula (IIIe)



wherein A₂ is lower alkylene wherein the alkylene can be substituted phenyl. The compounds of formula were further converted to thiazolidine derivatives of the formula (III_f)



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Summary of the Invention

With an objective to develop novel compounds for reducing blood glucose, lipid levels, lowering cholesterol and reducing body weight with beneficial effects in the treatment and/or prophylaxis of diseases related to increased levels of lipids, atherosclerosis, coronary artery diseases, Syndrome-X, impaired glucose tolerance, insulin resistance, insulin resistance leading to type 2 diabetes and diabetic complications thereof, for the treatment of diseases wherein insulin resistance is the pathophysiological mechanism and for the treatment of hypertension, with better efficacy, potency and lower toxicity, we focused our research to develop new compounds effective in the treatment of the above mentioned diseases. Effort in this direction has led to compounds having general formula (II).

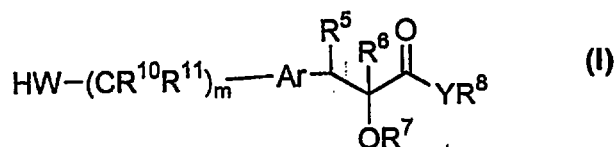
The main objective of the present invention is to provide novel β-phenyl α-oxysubstituted propionic acids of formula (I), their derivatives, their analogs, their tautomeric forms and their stereoisomers which are useful in the synthesis of compounds of formula (II).

Another objective of the present invention is to provide a process for the preparation of compounds of formula (I), their derivatives, their analogs, their tautomers and their stereoisomers.

Detailed Description of the Invention

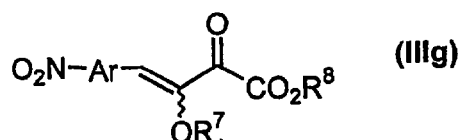
Novel β -phenyl α -oxysubstituted propionic acids having the general formula

(I)



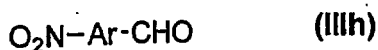
5 their derivatives, their analogs, their tautomeric forms, their stereoisomers, their salts, their solvates wherein W represents NR^{12} , R^{12} represents hydrogen, R^{10} and R^{11} may be same or different and represent hydrogen or substituted or unsubstituted group selected from alkyl, alkoxy, aryl or aralkyl group; Ar represents substituted or unsubstituted divalent single or fused aromatic or heterocyclic group; R^5 represents
 10 hydrogen atom, hydroxy, alkoxy, halogen, alkyl, substituted or unsubstituted aralkyl group or forms a bond together with the adjacent group R^6 ; R^6 represents hydrogen, hydroxy, alkoxy, halogen, lower alkyl group, acyl, substituted or unsubstituted aralkyl or R^6 forms a bond together with R^5 ; R^7 may be hydrogen or substituted or unsubstituted groups selected from alkyl, cycloalkyl, aryl, aralkyl, alkoxyalkyl,
 15 alkoxyacetyl, aryloxyacetyl, alkylaminocarbonyl, arylaminocarbonyl, acyl, heterocyclyl, heteroaryl, heteroaralkyl groups; R^8 may be hydrogen or substituted or unsubstituted groups selected from alkyl, cycloalkyl, aryl, aralkyl, heterocyclyl, heteroaryl or heteroaralkyl groups; Y represents oxygen, sulfur or NR^{13} , where R^{13} represents hydrogen or substituted or unsubstituted groups selected from alkyl, aryl,
 20 hydroxyalkyl, aralkyl heterocyclyl, heteroaryl, or heteroaralkyl groups; R^8 and R^{13} together may form a substituted or unsubstituted 5 or 6 membered cyclic structure containing carbon atoms, which may optionally contain one or more heteroatoms selected from oxygen, sulfur or nitrogen; m is an integer ranging from 0-6.

The novel intermediate of formula (I) where m is 0 and all other symbols are
 25 as defined above may be prepared by reducing the compound of formula (IIIg)

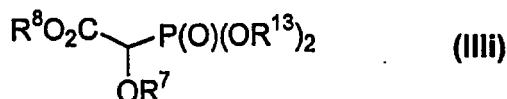


where R^7 , R^8 and Ar are as defined above may be carried out in the presence of gaseous hydrogen and a catalyst such as Pd/C, Rh/C, Pt/C, Raney nickel and the like. Mixtures of catalysts may be used. The reaction may also be conducted in the presence of solvents such as dioxane, acetic acid, ethyl acetate and the like. A pressure between atmospheric pressure and 80 psi may be employed. The catalyst may be preferably 5-10 % Pd/C and the amount of catalyst used may range from 1-50 % w/w. The reaction may also be carried out by employing metal solvent reduction such as magnesium, iron, tin, samarium in alcohol or sodium amalgam in alcohol, preferably methanol. The hydrogenation may be carried out in the presence of metal catalysts containing chiral ligands to obtain a compound of formula (I) in optically active form. The metal catalyst may contain Rhodium, Ruthenium, Indium and the like. The chiral ligands may preferably be chiral phosphines such as (2S,3S)-bis(diphenylphosphino)butane, 1,2-bis(diphenylphosphino)ethane, 1,2-bis(2-methoxyphenylphenylphosphino)ethane, (-)-2,3-isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino) butane and the like.

The compound of formula (IIIg) may be prepared by reacting the compound of formula (IIIh)

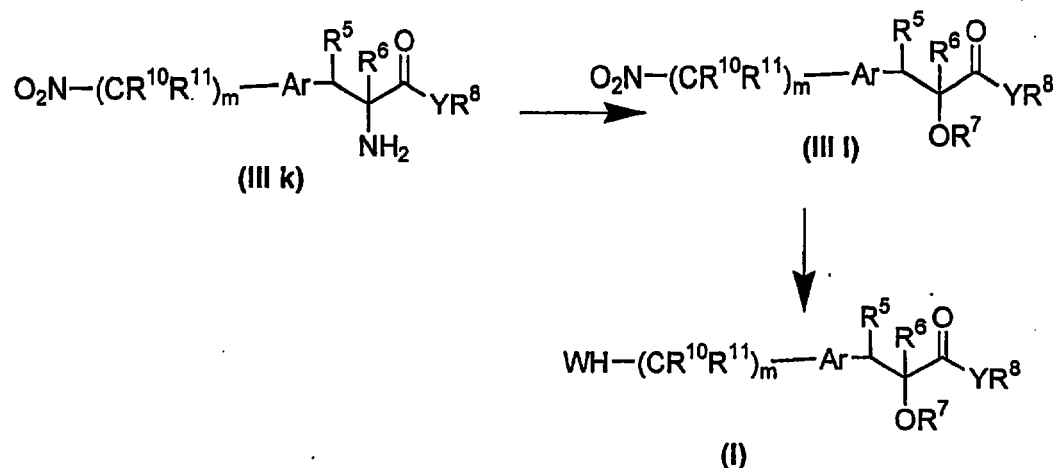


where Ar is as defined above with compound of formula (IIIi)



where R^{13} represents (C_1-C_6) alkyl group and all other symbols are as defined earlier may be carried out in the presence of a base such as metal hydride such as NaH or KH; organolithiums such as CH_3Li , $BuLi$ and the like; alkoxides such as NaOMe, NaOEt, $t-BuOK^+$ and the like or mixtures thereof. The reaction may be carried out in the presence of solvents such as diethyl ether, THF, dioxane, DMF, DMSO, DME, dimethyl acetamide and the like or mixtures thereof. HMPA may be used as cosolvent. The reaction temperature may range from $-78^\circ C$ to $50^\circ C$, preferably at a temperature in the range of $-10^\circ C$ to $30^\circ C$. The reaction is more effective under anhydrous conditions.

In yet another embodiment of the present invention, the compound of formula (I) where m is 0 and all other symbols are as defined above may be prepared by diazotizing the compound of formula (III k) to a compound of formula (III l) and reducing the compound of formula (III l) to yield compound of formula (I). The reaction shown in scheme-III below:



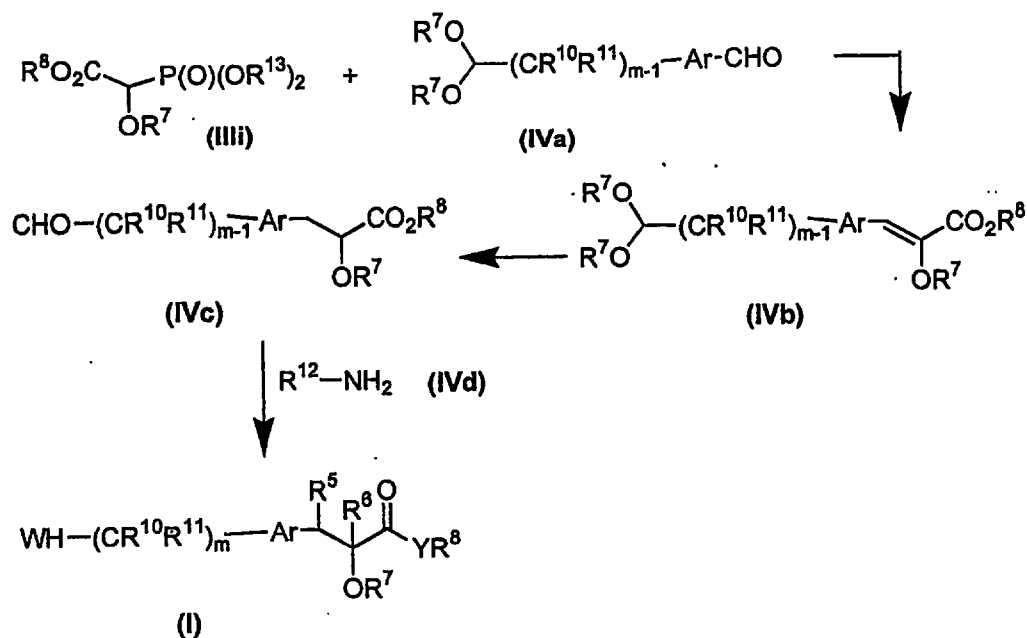
Scheme-III

The diazotiaziaon of the compound of the formula (III k) to obtain compound of formula (III l) may be carried out using diazotizing agent such as sodium nitrite, isoamyl nitrite, potassium nitrite, ammonium nitrite and the like under acidic conditions using acids such as sulfuric acid, HCl, acetic acid and the like, in an organic solvent such as alcohols such as methanol, ethanol, propanol and the like; 1,4-dioxane, THF, acetone and the like. Etherifying the resiude using alkyl sulfates such as diethyl sulphate, dimethylsulphate and the like or alkyl halides such as ethyl iodide, methyl iodide and the like, in the presence of solvents such as hydrocarbons like toluene, benzene and the like or DMF, DMSO, acetonitrile, THF, methyl isobutyl ketone (MIBK) and the like, in alkali bases such as sodium carbonate, potassium carbonate, sodium methoxide, sodium hydride, potassium hydride and the like.

The reduction of compound of the formula (III l) to yield a compound of the general formula (I) may be carried out in the presence of gaseous hydrogen and a catalyst such as Pd/C, Rh/C, Pt/C, Raney nickel and the like. Mixtures of catalysts

may be used. The reaction may also be conducted in the presence of solvents such as dioxane, acetic acid, ethyl acetate and the like. A pressure between atmospheric pressure and 80 psi may be employed. The catalyst may be preferably 5-10 % Pd/C and the amount of catalyst used may range from 1-50 % w/w. The reaction may also
 5 be carried out by employing metal solvent reduction such as magnesium, iron, tin, samarium in alcohol or sodium amalgam in alcohol, preferably methanol. The
 10 hydrogenation may be carried out in the presence of metal catalysts containing chiral ligands to obtain a compound of formula (I) in optically active form. The metal catalyst may contain Rhodium, Ruthenium, Indium and the like. The chiral ligands
 may preferably be chiral phosphines such as (2S,3S)-bis(diphenylphosphino)butane,
 1,2-bis(diphenylphosphino)ethane, 1,2-bis(2-methoxyphenyl
 phenylphosphino)ethane, (-)-2,3-isopropylidene-2,3-dihydroxy-1,4-
 bis(diphenylphosphino) butane and the like.

15 In yet another embodiment of the present invention, the compound of formula (I) where m is 1-6, and all other symbols are as defined above may be prepared by following the process described in scheme-IV below :



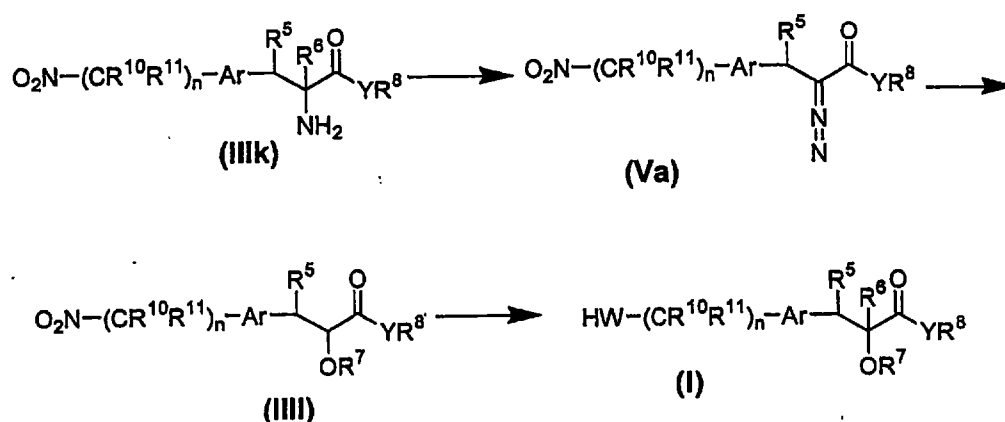
The reaction of a compound of the general formula (IIIi) defined above with a compound of formula (IVa), to yield compound of formula (IVb) may be carried out in the presence of a base such as metal hydride like NaH or KH; organolithiums such as CH₃Li, BuLi and the like; alkoxides such as NaOMe, NaOEt, t-BuOK⁺ and the like or mixtures thereof. The reaction may be carried out in the presence of solvents such as diethyl ether, THF, dioxane, DMF, DMSO, DME, dimethyl acetamide and the like or mixtures thereof. HMPA may be used as cosolvent. The reaction temperature may range from -78 °C to 50 °C, preferably at a temperature in the range of -10 °C to 30 °C.

10 The reduction of compound of the formula (IVb) to yield a compound of the formula (IVc) may be carried out in the presence of gaseous hydrogen and a catalyst such as Pd/C, Rh/C, Pt/C, Raney nickel and the like. Mixtures of catalysts may be used. The reaction may also be conducted in the presence of solvents such as dioxane, acetic acid, ethyl acetate and the like. A pressure between atmospheric pressure and 80 psi may be employed. The catalyst may be preferably 5-10 % Pd/C and the amount of catalyst used may range from 1-50 % w/w. The reaction may also be carried out by employing metal solvent reduction such as magnesium, iron, tin, samarium in alcohol or sodium amalgam in alcohol, preferably methanol. The hydrogenation may be carried out in the presence of metal catalysts containing chiral ligands to obtain a compound of formula (IVc) in optically active form. The metal catalyst may contain Rhodium, Ruthenium, Indium and the like. The chiral ligands may preferably be chiral phosphines such as (2S,3S)-bis(diphenylphosphino)butane, 1,2-bis(diphenylphosphino)ethane, 1,2-bis(2-methoxyphenylphenylphosphino)ethane, (-)-2,3-isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino) butane and the like.

25 The reaction of a compound of general formula (IVc) with a compound of formula (IVd) to provide a compound of formula (I) may be carried out using solvents such as CH₂Cl₂, CHCl₃, chlorobenzene, benzene, THF, in the presence of catalyst such as p-toluenesulfonic acid, methanesulfonic acid, TFA, TfOH, BF₃-OEt₂ and the like. The reaction may also be carried out using activated molecular sieves. The temperature of the reaction may range from 10 °C to 100 °C, preferably at a

temperature in the range from 10 °C to 60 °C. The imine product initially produce may be reducing using $\text{Na}(\text{CN})\text{BH}_3\text{-HCl}$.

In yet another embodiment of the present invention, the compound of formula (I) where m is 0 or 1 and all other symbols are as defined above may be prepared by diazotizing the compound of formula (IIIk) to a compound of formula (Va), decomposition of compound of formula (Va) to a compound of formula (III) in the presence of alcohol such as R^7OH and reducing the compound of formula (III) to yield compound of formula (I). The reaction sequence is shown in scheme-V below:



Scheme-V

The diazotiaziaon of the compound of the formula (IIIk) where m is 0, R^6 is hydrogen and all other symbols are as defined above, to obtain compound of formula (Va) may be carried out using diazotizing agent such as sodium nitrite, isoamyl nitrite, potassium nitrite, ammonium nitrite and the like in the presence of catalytic amount of carboxylic acid such as acetic acid, propionic acid and the like, in suitable solvent such as chloroform, chlorobenzene, dichloroethane and the like or a mixture thereof at a temperature in the range of room temperature and reflux temperature of the solvent employed for a period in the range of 0.5 to 16 h.

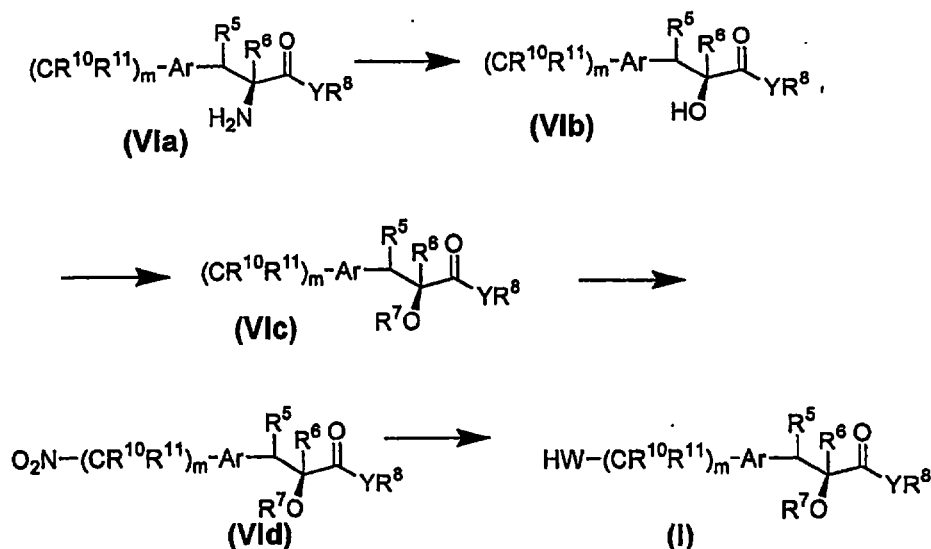
Decomposing the arylalkyl diazo acetate of the formula (Va) to obtain a compound of formula (III) where R^7 is as defined earlier excluding hydrogen and all other symbols are as defined earlier can be promoted by a suitable catalyst such as

Rh(II)acetate, salt/complex of Cu(I) or Rh(II) and the like in the presence of an alcohol of the formula R^7OH .

The reduction of compound of the formula (III) to yield a compound of the general formula (I) where all symbols are as defined earlier may be carried out in the presence of gaseous hydrogen and a catalyst such as Pd/C, Rh/C, Pt/C, Raney nickel and the like. Mixtures of catalysts may be used. The reaction may also be conducted in the presence of solvents such as dioxane, acetic acid, ethyl acetate and the like. A pressure between atmospheric pressure and 80 psi may be employed. The catalyst may be preferably 5-10% Pd/C and the amount of catalyst used may range from 1-50% w/w. The reaction may also be carried out by employing metal solvent reduction such as magnesium, iron, tin, samarium in alcohol or sodium amalgam in alcohol, preferably methanol. The hydrogenation may also be carried out using ammonium formate, cyclohex-1,4-diene type of hydrogen donor under pd/c conditions using solvents such as methanol, ethanol, ethyl acetate and the like.

15

In yet another embodiment of the present invention, the compound of formula (I) in its enantiomerically pure form, where m is 0, $R^5 = R^6 = H$ and all other symbols are as defined above may be prepared by following the process described in scheme-VI below:



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Scheme-VI

The diazotization of the compound of the formula (VIa) where all symbols are as defined above to obtain compound of formula (VIb) may be carried out by using diazotizing agent such as sodium nitrite, isoamyl nitrite, potassium nitrite, ammonium nitrite and the like under aqueous acidic conditions using acids such as sulfuric acid, HCl, acetic acid and the like, in an organic solvent such as alcohols such as methanol, ethanol, propanol and the like; 1,4-dioxane, THF, acetone and the like.

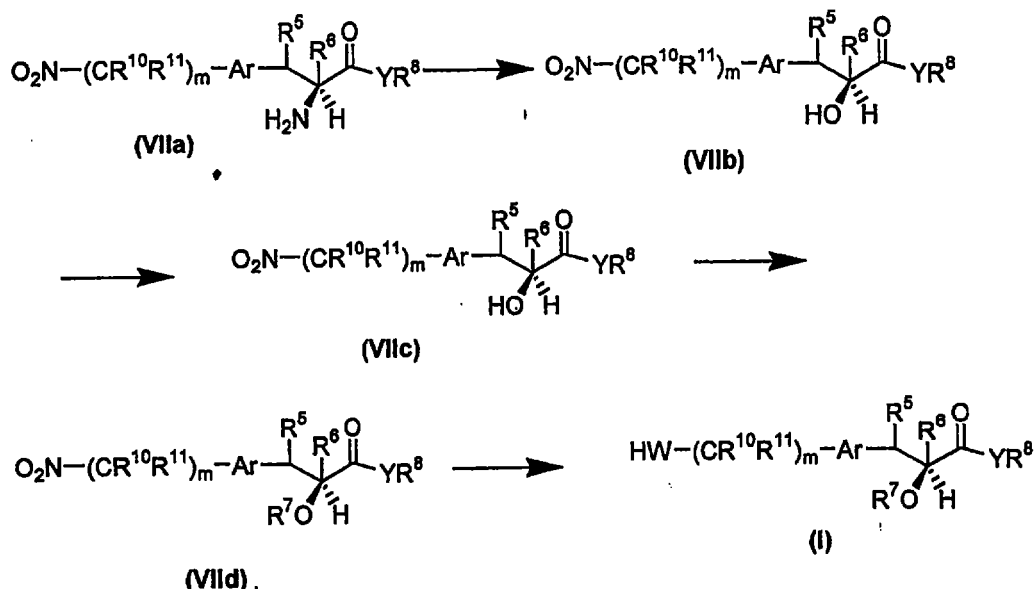
One pot esterification and etherification of compound of general formula (VIb) to a compound of general formula (VIc) may be carried by initial deprotonation of (VIb) using a suitable base such as NaH, KH, KOH or like, in a suitable solvent such as toluene, benzene, diethylether, THF, DMF, DME HMPA, and like, followed by treatment with alkyl halide such as ethyl iodide or methyl iodide and like. Other alkylating agents such as $\text{Et}_3\text{O}^+\text{BF}_4^-$, $\text{Me}_3\text{O}^+\text{BF}_4^-$, dialkylsulfate may also be used. Reaction temperature may vary from 0 °C to 100 °C.

Nitration of the compound of formula (VIc) to a compound of formula (VIId) where n is 0 and all other symbols are as defined above, may be carried out using nitrating agents such as fuming nitric acid, N_2O_5 , a mixture of conc. Nitric acid and conc. Sulfuric acid or a mixture of nitric acid and acetic anhydride in the presence of a solvent or under neat condition at a temperature in the range of -10°C to room temperature for a period in the range of 0.5 to 4 h. (Ref: Org. Synth. Col. Vol. I, 396)

Reduction of compound of the formula (VIId) to a compound of formula (I), may be carried out in the presence of gaseous hydrogen or hydrogen donors such as ammonium formate, cyclohex-1,4-diene and the like and a catalyst such as Pd/C, Rh/C, Pt/C, Raney nickel and the like. Mixtures of catalysts may be used in the presence of solvents such as methanol, ethanol, dioxane, acetic acid, ethyl acetate and the like. A pressure between atmospheric pressure and 80 psi may be employed. The catalyst may be preferably 5-10 % Pd/C and the amount of catalyst used may range from 1-50 % w/w. Alternatively, the reaction may also be carried out by employing metal solvent reduction such as magnesium, iron, tin, samarium, indium, sodium amalgam in alcohol, or other suitable solvents preferably methanol.

In yet another embodiment of the present invention, the compound of formula (I) in its enantiomerically pure form, where m is 0, $\text{R}^5 = \text{R}^6 = \text{H}$ and all other symbols

are as defined above may be prepared by following the process described in scheme-VII below:



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Scheme VII

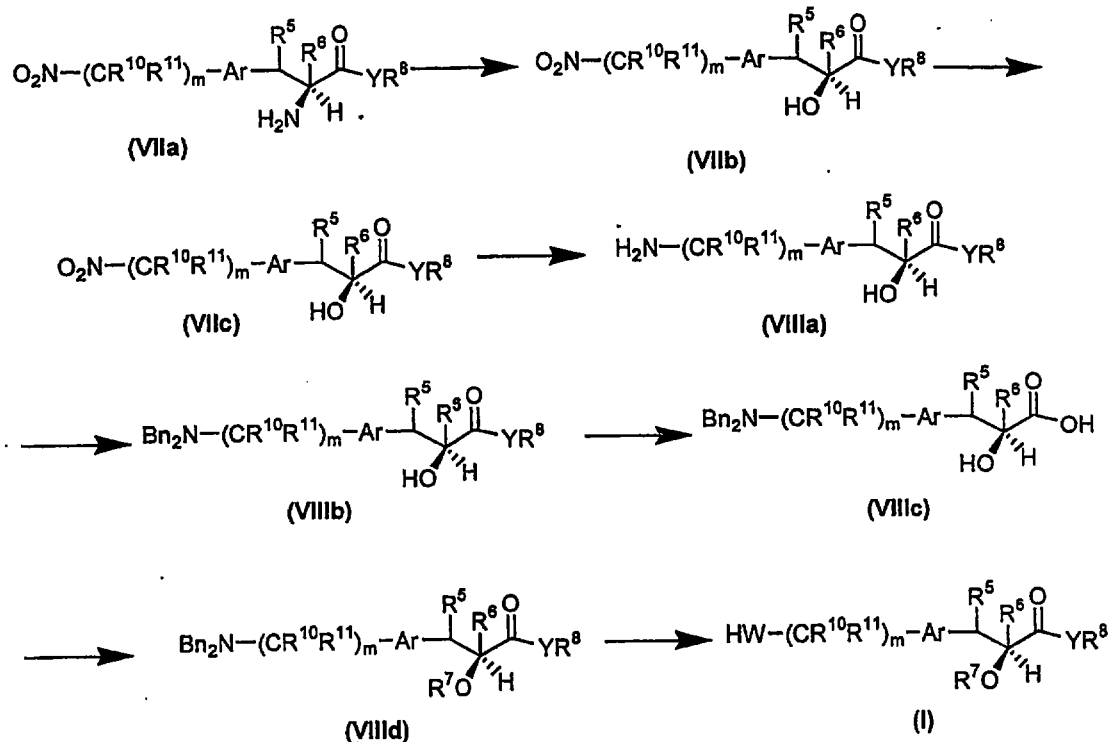
The diazotization of the compound of formula (VIIa) where all symbols are as defined above to obtain a compound of formula (VIIb) may be carried out using diazotizing agents such as sodium nitrite, isoamyl nitrite, potassium nitrite, ammonium nitrite and the like under aqueous acidic conditions using acids such as sulfuric acid, hydrochloric acid, acetic acid and the like, in presence of an optional co solvent like alcohols such as methanol, ethanol, propanol and the like; or ethers such as 1,4-dioxane, THF, and the like; or ketones such as acetone, methyl ethyl ketone and the like.

Esterification of the compound of formula (VIIb) to a compound of formula (VIIc) may be done using an appropriate alcohol of formula R^8-OH where R^8 represents lower alkyl groups such as methyl, ethyl, propyl, isopropyl, n-butyl, t-butyl and the like in presence of suitable catalyst such as, conc. sulfuric acid, dry HCl, BF_3-OEt_2 , and the like. The reaction may be carried out at reflux temperature of the alcohol employed. Alternatively reagents like diazomethane or $\text{Et}_3\text{O}^+\text{BF}_4^-$ or $\text{Me}_3\text{O}^+\text{BF}_4^-$ and the like may also be used for esterification.

Selective O-alkylation of the compound of formula (VIIc) to the compound of formula (VIIId) may be done using alkyl sulfates such as diethyl sulfate, dimethyl sulfate and the like or alkyl halides such as ethyl iodide, methyl iodide, n-propyl iodide, n-propyl bromide, isopropyl iodide and the like, in solvents such as hydrocarbons like toluene, benzene and the like or acetonitrile, tetrahydro furan, dimethyl formamide, dimethyl sulfoxide, and the like, in the presence of molecular sieves and alkali bases such as sodium carbonate, potassium carbonate, cesium carbonate, sodium methoxide, sodium hydride, potassium hydride, sodium or potassium hydroxide and the like. Heavy metal oxides such as Ag_2O , PbO , HgO and the like may be of particular use to carry out alkylation when alkyl halides are used as alkylation reagent. Phase transfer catalysts such as tetraalkylammonium hydroxide or tetraalkylammonium halides such as tetrabutylammonium chloride, tetrabutylammonium bromide and the like may also be employed.

Reduction of compound of the formula (VIIId) to a compound of formula (I), may be carried out in the presence of gaseous hydrogen or hydrogen donors such as ammonium formate, cyclohex-1,4-diene and the like and a catalyst such as Pd/C , Rh/C , Pt/C , Raney nickel and the like. Mixtures of catalysts may be used in the presence of solvents such as methanol, ethanol, dioxane, acetic acid, ethyl acetate, and the like. A pressure between atmospheric pressure and 80 psi may be employed. The catalyst may be preferably 5-10 % Pd/C and the amount of catalyst used may range from 1-50 % w/w. Alternatively, the reaction may also be carried out by employing metal solvent reduction such as magnesium, iron, tin, samarium, indium, sodium amalgam in alcohol, or other suitable solvents preferably methanol.

In yet another embodiment of the present invention, the compound of formula (I) in its enantiomerically pure form, where m is 0, $\text{R}^5 = \text{R}^6 = \text{H}$ and all other symbols are as defined above may be prepared by following the process described in scheme-VIII below:



Scheme VIII

The diazotization of the compound of formula (VIIa) where all symbols are as defined above to obtain a compound of formula (VIIb) may be carried out using diazotizing agents such as sodium nitrite, isoamyl nitrite, potassium nitrite, ammonium nitrite and the like under aqueous acidic conditions using acids such as sulfuric acid, hydrochloric acid, acetic acid and the like, in presence of an optional co solvent like alcohols such as methanol, ethanol, propanol and the like; or ethers such as 1,4-dioxane, THF, and the like; or ketones such as acetone, methyl ethyl ketone and the like.

Esterification of the compound of formula (VIIb) to a compound of formula (VIIc) may be done using an appropriate alcohol of formula $\text{R}^8\text{-OH}$ where R^8 represents lower alkyl groups such as methyl, ethyl, propyl, isopropyl, n-butyl, t-butyl and the like in presence of suitable catalyst such as, conc. sulfuric acid, dry HCl, $\text{BF}_3\text{-OEt}_2$, and the like. The reaction may be carried out at reflux temperature of the alcohol employed. Alternatively, reagents like diazomethane or $\text{Et}_3\text{O}^+\text{BF}_4^-$ or $\text{Me}_3\text{O}^+\text{BF}_4^-$ and the like may also be used for esterification.

Reduction of compound of the formula (VIIc) to a compound of formula (VIIIa), may be carried out in the presence of gaseous hydrogen or hydrogen donors such as ammonium formate, cyclohex-1,4-diene and the like and a catalyst such as Pd/C, Rh/C, Pt/C, Raney nickel and the like. Mixture of catalysts may be used in the presence of solvents such as methanol, ethanol, dioxane, acetic acid, ethyl acetate and the like. A pressure between atmospheric pressure to 80 psi may be employed. The catalyst may be preferably 5-10 % Pd/C and the amount of catalyst used may range from 1-50 % w/w. Alternatively, the reaction may also be carried out by employing metal solvent reduction such as magnesium, iron, tin, samarium, indium, sodium amalgam in alcohol, or other suitable solvents preferably methanol.

N,N-dibenylation of the compound of formula (VIIIa) to the compound of formula (VIIIb) may be done using benzyl halides such as benzyl bromide, benzyl chloride and the like in solvents such as hydrocarbons like toluene, benzene and the like or acetonitrile, tetrahydro furan, dimethyl formamide, dimethyl sulfoxide, and the like, in the presence of alkali bases such as sodium carbonate, potassium carbonate, sodium or potassium hydroxide and the like. Phase transfer catalysts such as tetraalkylammonium hydroxide or tetraalkylammonium halides such as tetrabutylammonium chloride, tetrabutylammonium bromide and the like may also be employed. The reaction may be carried out in the range of room temperature to the reflux temperature of the solvent employed.

Hydrolysis of the compound of the formula (VIIIb) to the compound of formula (VIIIc) using aqueous alkali metal bases such as lithium carbonate, sodium carbonate, potassium carbonate or potassium bicarbonate, lithium hydroxide, sodium hydroxide or potassium hydroxide and the like, in suitable co-solvents such as methanol, ethanol, THF and like or mixtures thereof. The reaction time may range from 0.5 h to 24 h, preferably 0.5 h to 3-4 h and reaction temperature may range from 0 °C to 80 °C.

One pot esterification and etherification of the compound of the formula (VIIIc) to the compound of formula (VIIId) where $R^5 = R^6$, may be done by treating with bases such as sodium hydride, potassium hydride, sodium hydroxide, potassium hydroxide, sodium carbonate, potassium carbonate and the like, in solvents such as hydrocarbons like toluene, benzene and the like, dialkyl ethers such as diethyl ether,

tetrahydro furan and the like or dimethyl formamide, HMPA followed by treatment with alkyl halides such as ethyl iodide, methyl iodide, n-propyl iodide, n-propyl bromide, isopropyl iodide and the like, or alkyl sulfates such as diethyl sulfate, dimethyl sulfate and the like or alkylating agents such as $\text{Et}_3\text{O}^+\text{BF}_4^-$, $\text{Me}_3\text{O}^+\text{BF}_4^-$ and
5 the like. The reaction time may range from 2 h to 20 h and reaction temperature may range from 0 °C to 80 °C.

Debenzylation of the compound of the formula (VIIIId) to the compound of formula (I) may be carried out in the presence of gaseous hydrogen or hydrogen donors such as ammonium formate, cyclohex-1,4-diene and the like and a catalyst
10 such as Pd/C, Rh/C, Pt/C, Raney nickel and the like. Mixture of catalysts may be used in the presence of solvents such as methanol, ethanol, dioxane, acetic acid, ethyl acetate and the like. A pressure between atmospheric pressure and 80 psi may be employed. The catalyst may be preferably 5-10 % Pd/C and the amount of catalyst used may range from 1-50 % w/w.

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Particularly useful compounds according to the present invention include:

(±) Ethyl 2-ethoxy-3-(4-aminophenyl)propanoate

(+) Ethyl 2-ethoxy-3-(4-aminophenyl)propanoate

(-) Ethyl 2-ethoxy-3-(4-aminophenyl)propanoate

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(±) Ethyl 2-ethoxy-3-[4-{N-heptyl-N-(2'-bromoethyl)}aminophenyl]propanoate

(+) Ethyl 2-ethoxy-3-[4-{N-heptyl-N-(2'-bromoethyl)}aminophenyl]propanoate

(-) Ethyl 2-ethoxy-3-[4-{N-heptyl-N-(2'-bromoethyl)}aminophenyl]propanoate

25 (±) Methyl 2-ethoxy-3-[4-(N-heptylaminomethyl)phenyl]propanoate

(+) Methyl 2-ethoxy-3-[4-(N-heptylaminomethyl)phenyl]propanoate

(-) Methyl 2-ethoxy-3-[4-(N-heptylaminomethyl)phenyl]propanoate

(±) Methyl 2-ethoxy-3-(4-aminophenyl)propanoate

30 (+) Methyl 2-ethoxy-3-(4-aminophenyl)propanoate

(-) Methyl 2-ethoxy-3-(4-aminophenyl)propanoate

(±) Methyl 2-ethoxy-3-(3-aminophenyl)propanoate
 (+) Methyl 2-ethoxy-3-(3-aminophenyl)propanoate
 (-) Methyl 2-ethoxy-3-(3-aminophenyl)propanoate

5 (±) Ethyl 2-isopropoxy-3-(4-aminophenyl)propionate
 (+) Ethyl 2-isopropoxy-3-(4-aminophenyl)propionate
 (-) Ethyl 2-isopropoxy-3-(4-aminophenyl)propionate

The compounds of the present invention can be converted to the compounds of the
 10 formula (II) which includes:

(±) Ethyl 3-[4-{3-(3,4-dihydro-2H-benzo[b][1,4]oxazin-4-yl)propylamino}
 phenyl]-2-ethoxypropanoate ;
 (+) Ethyl 3-[4-{3-(3,4-dihydro-2H-benzo[b][1,4]oxazin-4-yl)propylamino}
 15 phenyl]-2-ethoxypropanoate ;
 (-) Ethyl 3-[4-{3-(3,4-dihydro-2H-benzo[b][1,4]oxazin-4-yl)propylamino}
 phenyl]-2-ethoxypropanoate ;

(±) 3-[4-{3-(3,4-Dihydro-2H-benzo[b][1,4]oxazin-4-yl)propylamino}phenyl]-2-
 20 ethoxypropanoic acid or its salts ;
 (+) 3-[4-{3-(3,4-Dihydro-2H-benzo[b][1,4]oxazin-4-yl)propylamino}phenyl]-2-
 ethoxypropanoic acid or its salts ;
 (-) 3-[4-{3-(3,4-Dihydro-2H-benzo[b][1,4]oxazin-4-yl)propylamino}phenyl]-2-
 ethoxypropanoic acid or its salts ;

25 (±) Ethyl 3-[4-N-heptyl-N-{2-(3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-4-
 yl)ethylamino}phenyl]-2-ethoxypropanoate ;
 (+) Ethyl 3-[4-N-heptyl-N-{2-(3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-4-
 yl)ethylamino}phenyl]-2-ethoxypropanoate ;
 30 (-) Ethyl 3-[4-N-heptyl-N-{2-(3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-4-
 yl)ethylamino}phenyl]-2-ethoxypropanoate ;

- (±) 3-[4-N-Heptyl-N-{2-(3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-4-yl)ethylamino}phenyl]-2-ethoxypropanoic acid or its salts ;
- (+) 3-[4-N-Heptyl-N-{2-(3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-4-yl)ethylamino}phenyl]-2-ethoxypropanoic acid or its salts ;
- 5 (-) 3-[4-N-Heptyl-N-{2-(3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-4-yl)ethylamino}phenyl]-2-ethoxypropanoic acid or its salts ;
- (±) Methyl 2-ethoxy-3-[4-{N-heptyl-N-(2-(3,4-dihydro-2H-benzo[b]oxazin-4-yl)-2-oxoethyl)aminomethyl}phenyl]propanoate ;
- 10 (+) Methyl 2-ethoxy-3-[4-{N-heptyl-N-(2-(3,4-dihydro-2H-benzo[b]oxazin-4-yl)-2-oxoethyl)aminomethyl}phenyl]propanoate ;
- (-) Methyl 2-ethoxy-3-[4-{N-heptyl-N-(2-(3,4-dihydro-2H-benzo[b]oxazin-4-yl)-2-oxoethyl)aminomethyl}phenyl]propanoate ;
- 15 (±) 2-Ethoxy-3-[4-{N-heptyl-N-(2-(3,4-dihydro-2H-benzo[b]oxazin-4-yl)-2-oxoethyl)aminomethyl}phenyl]propanoic acid or its salts ;
- (+) 2-Ethoxy-3-[4-{N-heptyl-N-(2-(3,4-dihydro-2H-benzo[b]oxazin-4-yl)-2-oxoethyl)aminomethyl}phenyl]propanoic acid or its salts ;
- (-) 2-Ethoxy-3-[4-{N-heptyl-N-(2-(3,4-dihydro-2H-benzo[b]oxazin-4-yl)-2-oxoethyl)aminomethyl}phenyl]propanoic acid or its salts ;
- 20 (±) Methyl 3-[4-{5-(3,4-dihydro-2H-benzo[b][1,4]oxazin-4-yl)-5-oxopentylamino}phenyl]-2-ethoxypropanoate ;
- (+) Methyl 3-[4-{5-(3,4-dihydro-2H-benzo[b][1,4]oxazin-4-yl)-5-oxopentylamino}phenyl]-2-ethoxypropanoate ;
- 25 (-) Methyl 3-[4-{5-(3,4-dihydro-2H-benzo[b][1,4]oxazin-4-yl)-5-oxopentylamino}phenyl]-2-ethoxypropanoate ;
- (±) 3-[4-{5-(3,4-Dihydro-2H-benzo[b][1,4]oxazin-4-yl)-5-oxopentylamino} phenyl]-2-ethoxypropanoic acid or its salts ;
- 30

- (+) 3-[4-{5-(3,4-Dihydro-2H-benzo[b][1,4]oxazin-4-yl)-5-oxopentylamino} phenyl]-2-ethoxypropanoic acid or its salts ;
- (-) 3-[4-{5-(3,4-Dihydro-2H-benzo[b][1,4]oxazin-4-yl)-5-oxopentylamino} phenyl]-2-ethoxypropanoic acid or its salts ;
- 5 (±) Methyl 3-[3-{3-(3,4-dihydro-2H-benzo[b][1,4]oxazin-4-yl)propylamino} phenyl]-2-ethoxypropanoate ;
- (+) Methyl 3-[3-{3-(3,4-dihydro-2H-benzo[b][1,4]oxazin-4-yl)propylamino} phenyl]-2-ethoxypropanoate ;
- 10 (-) Methyl 3-[3-{3-(3,4-dihydro-2H-benzo[b][1,4]oxazin-4-yl)propylamino} phenyl]-2-ethoxypropanoate ;
- (±) 3-[3-{3-(3,4-Dihydro-2H-benzo[b][1,4]oxazin-4-yl)propylamino} phenyl]-2-ethoxypropanoic acid or its salts ;
- 15 (+) 3-[3-{3-(3,4-Dihydro-2H-benzo[b][1,4]oxazin-4-yl)propylamino} phenyl]-2-ethoxypropanoic acid or its salts ;
- (-) 3-[3-{3-(3,4-Dihydro-2H-benzo[b][1,4]oxazin-4-yl)propylamino} phenyl]-2-ethoxypropanoic acid or its salts ;
- 20 (±) Methyl 3-[4-{3-(7-fluoro-3,4-dihydro-2H-benzo[b][1,4]oxazin-4-yl)propylamino} phenyl]-2-ethoxypropanoate ;
- (+) Methyl 3-[4-{3-(7-fluoro-3,4-dihydro-2H-benzo[b][1,4]oxazin-4-yl)propylamino} phenyl]-2-ethoxypropanoate ;
- (-) Methyl 3-[4-{3-(7-fluoro-3,4-dihydro-2H-benzo[b][1,4]oxazin-4-yl)propylamino} phenyl]-2-ethoxypropanoate ;
- 25 (±) 3-[4-{3-(7-Fluoro-3,4-dihydro-2H-benzo[b][1,4]oxazin-4-yl)propylamino} phenyl]-2-ethoxypropanoic acid or its salts ;
- (+) 3-[4-{3-(7-Fluoro-3,4-dihydro-2H-benzo[b][1,4]oxazin-4-yl)propylamino} phenyl]-2-ethoxypropanoic acid or its salts ;
- 30

- (-) 3-[4-{3-(7-Fluoro-3,4-dihydro-2H-benzo[b][1,4]oxazin-4-yl)propylamino}phenyl]-2-ethoxypropanoic acid or its salts ;
- (±) Methyl 2-ethoxy-3-[4-{4-(3-(3,4-dihydro-2H-benzo[b][1,4]oxazin-4-yl)propyloxy)benzyl}aminophenyl]propanoate ;
- 5 (+) Methyl 2-ethoxy-3-[4-{4-(3-(3,4-dihydro-2H-benzo[b][1,4]oxazin-4-yl)propyloxy)benzyl}aminophenyl]propanoate ;
- (-) Methyl 2-ethoxy-3-[4-{4-(3-(3,4-dihydro-2H-benzo[b][1,4]oxazin-4-yl)propyloxy)benzyl}aminophenyl]propanoate ;
- 10 (±) Methyl 2-ethoxy-3-[3-{4-(3-(3,4-dihydro-2H-benzo[b][1,4]oxazin-4-yl)propyloxy)benzyl}aminophenyl]propanoate ;
- (+) Methyl 2-ethoxy-3-[3-{4-(3-(3,4-dihydro-2H-benzo[b][1,4]oxazin-4-yl)propyloxy)benzyl}aminophenyl]propanoate ;
- 15 (-) Methyl 2-ethoxy-3-[3-{4-(3-(3,4-dihydro-2H-benzo[b][1,4]oxazin-4-yl)propyloxy)benzyl}aminophenyl]propanoate ;
- (±) 2-Ethoxy-3-[4-{4-(3-(3,4-dihydro-2H-benzo[b][1,4]oxazin-4-yl)propyloxy)benzyl}aminophenyl]propanoic acid or its salts ;
- 20 (+) 2-Ethoxy-3-[4-{4-(3-(3,4-dihydro-2H-benzo[b][1,4]oxazin-4-yl)propyloxy)benzyl}aminophenyl]propanoic acid or its salts ;
- (-) 2-Ethoxy-3-[4-{4-(3-(3,4-dihydro-2H-benzo[b][1,4]oxazin-4-yl)propyloxy)benzyl}aminophenyl]propanoic acid or its salts ;
- 25 (±) 2-Ethoxy-3-[3-{4-(3-(3,4-dihydro-2H-benzo[b][1,4]oxazin-4-yl)propyloxy)benzyl}aminophenyl]propanoic acid or its salts ;
- (+) 2-Ethoxy-3-[3-{4-(3-(3,4-dihydro-2H-benzo[b][1,4]oxazin-4-yl)propyloxy)benzyl}aminophenyl]propanoic acid or its salts ;
- (-) 2-Ethoxy-3-[3-{4-(3-(3,4-dihydro-2H-benzo[b][1,4]oxazin-4-yl)propyloxy)benzyl}aminophenyl]propanoic acid or its salts ;
- 30

- (±) Ethyl 2-ethoxy-3-[4-{3-(3,4-dihydro-2H-benzo[b][1,4]thiazin-4-yl)propylamino}phenyl]propanoate ;
- (+) Ethyl 2-ethoxy-3-[4-{3-(3,4-dihydro-2H-benzo[b][1,4]thiazin-4-yl)propylamino}phenyl]propanoate ;
- 5 (-) Ethyl 2-ethoxy-3-[4-{3-(3,4-dihydro-2H-benzo[b][1,4]thiazin-4-yl)propylamino}phenyl]propanoate ;
- (±) 2-Ethoxy-3-[4-{3-(3,4-dihydro-2H-benzo[b][1,4]thiazin-4-yl)propylamino}phenyl]propanoic acid or its salts ;
- 10 (+) 2-Ethoxy-3-[4-{3-(3,4-dihydro-2H-benzo[b][1,4]thiazin-4-yl)propylamino}phenyl]propanoic acid or its salts ;
- (-) 2-Ethoxy-3-[4-{3-(3,4-dihydro-2H-benzo[b][1,4]thiazin-4-yl)propylamino}phenyl]propanoic acid or its salts ;
- 15 (±) Ethyl 2-ethoxy-3-[4-{2-(3,4-dihydro-2H-benzo[b][1,4]oxazin-4-yl)ethylamino}phenyl]propanoate ;
- (+) Ethyl 2-ethoxy-3-[4-{2-(3,4-dihydro-2H-benzo[b][1,4]oxazin-4-yl)ethylamino}phenyl]propanoate ;
- (-) Ethyl 2-ethoxy-3-[4-{2-(3,4-dihydro-2H-benzo[b][1,4]oxazin-4-yl)ethylamino}phenyl]propanoate ;
- 20 (±) 2-Ethoxy-3-[4-{2-(3,4-dihydro-2H-benzo[b][1,4]oxazin-4-yl)ethylamino}phenyl]propanoic acid or its salts ;
- (+) 2-Ethoxy-3-[4-{2-(3,4-dihydro-2H-benzo[b][1,4]oxazin-4-yl)ethylamino}phenyl]propanoic acid or its salts ;
- 25 (-) 2-Ethoxy-3-[4-{2-(3,4-dihydro-2H-benzo[b][1,4]oxazin-4-yl)ethylamino}phenyl]propanoic acid or its salts ;

- (±) Methyl 2-ethoxy-3-[4-[4-{2-(3,4-dihydro-2H-benzo[b][1,4]oxazin-4-yl)ethoxy} phenylaminomethyl]phenyl]propanoate ;
- (+) Methyl 2-ethoxy-3-[4-[4-{2-(3,4-dihydro-2H-benzo[b][1,4]oxazin-4-yl)ethoxy} phenylaminomethyl]phenyl]propanoate ;
- 5 (-) Methyl 2-ethoxy-3-[4-[4-{2-(3,4-dihydro-2H-benzo[b][1,4]oxazin-4-yl)ethoxy} phenylaminomethyl]phenyl]propanoate ;
- (±) 2-Ethoxy-3-[4-[4-{2-(3,4-dihydro-2H-benzo[b][1,4]oxazin-4-yl)ethoxy} phenylaminomethyl]phenyl]propanoic acid or its salts ;
- 10 (+) 2-Ethoxy-3-[4-[4-{2-(3,4-dihydro-2H-benzo[b][1,4]oxazin-4-yl)ethoxy} phenylaminomethyl]phenyl]propanoic acid or its salts ;
- (-) 2-Ethoxy-3-[4-[4-{2-(3,4-dihydro-2H-benzo[b][1,4]oxazin-4-yl)ethoxy} phenylaminomethyl]phenyl]propanoic acid or its salts ;
- 15 (±) Ethyl 3-[4-{3-(7-fluoro-3,4-dihydro-2H-benzo[b][1,4]oxazin-4-yl) propylamino}phenyl]-2-ethoxypropanoate
- (+) Ethyl 3-[4-{3-(7-fluoro-3,4-dihydro-2H-benzo[b][1,4]oxazin-4-yl) propylamino}phenyl]-2-ethoxypropanoate
- (-) Ethyl 3-[4-{3-(7-fluoro-3,4-dihydro-2H-benzo[b][1,4]oxazin-4-yl) propylamino}phenyl]-2-ethoxypropanoate
- 20 (±) Ethyl 3-[4-{3-(7-fluoro-3,4-dihydro-2H-benzo[b][1,4]oxazin-4-yl) propylamino}phenyl]-2-methoxypropanoate
- (+) Ethyl 3-[4-{3-(7-fluoro-3,4-dihydro-2H-benzo[b][1,4]oxazin-4-yl) propylamino}phenyl]-2-methoxypropanoate
- 25 (-) Ethyl 3-[4-{3-(7-fluoro-3,4-dihydro-2H-benzo[b][1,4]oxazin-4-yl) propylamino}phenyl]-2-methoxypropanoate
- (±) 3-[4-{3-(7-Fluoro-3,4-dihydro-2H-benzo[b][1,4]oxazin-4-yl)propylamino} phenyl]-2-methoxypropanoic acid or its salts
- 30

- (+) 3-[4-{3-(7-Fluoro-3,4-dihydro-2H-benzo[b][1,4]oxazin-4-yl)propylamino}phenyl]-2-methoxypropanoic acid or its salts
- (-) 3-[4-{3-(7-Fluoro-3,4-dihydro-2H-benzo[b][1,4]oxazin-4-yl)propylamino}phenyl]-2-methoxypropanoic acid or its salts
- 5 (±) Ethyl 3-[4-{3-(2-methyl-7-fluoro-3,4-dihydro-2H-benzo[b][1,4]oxazin-4-yl)propylamino}phenyl]-2-ethoxypropanoate
- (+) Ethyl 3-[4-{3-(2-methyl-7-fluoro-3,4-dihydro-2H-benzo[b][1,4]oxazin-4-yl)propylamino}phenyl]-2-ethoxypropanoate
- 10 (-) Ethyl 3-[4-{3-(2-methyl-7-fluoro-3,4-dihydro-2H-benzo[b][1,4]oxazin-4-yl)propylamino}phenyl]-2-ethoxypropanoate
- (±) 3-[4-{3-(2-methyl-7-Fluoro-3,4-dihydro-2H-benzo[b][1,4]oxazin-4-yl)propylamino}phenyl]-2-ethoxypropanoic acid or its salts
- 15 (+) 3-[4-{3-(2-methyl-7-Fluoro-3,4-dihydro-2H-benzo[b][1,4]oxazin-4-yl)propylamino}phenyl]-2-ethoxypropanoic acid or its salts
- (-) 3-[4-{3-(2-methyl-7-Fluoro-3,4-dihydro-2H-benzo[b][1,4]oxazin-4-yl)propylamino}phenyl]-2-ethoxypropanoic acid or its salts
- 20 (±) Ethyl 3-[4-{3-(2-methyl-3,4-dihydro-2H-benzo[b][1,4]oxazin-4-yl)propylamino}phenyl]-2-ethoxypropanoate
- (+) Ethyl 3-[4-{3-(2-methyl-3,4-dihydro-2H-benzo[b][1,4]oxazin-4-yl)propylamino}phenyl]-2-ethoxypropanoate
- (-) Ethyl 3-[4-{3-(2-methyl-3,4-dihydro-2H-benzo[b][1,4]oxazin-4-yl)propylamino}phenyl]-2-ethoxypropanoate
- 25 (±) 3-[4-{3-(2-methyl-3,4-dihydro-2H-benzo[b][1,4]oxazin-4-yl)propylamino}phenyl]-2-ethoxypropanoic acid or its salts
- (+) 3-[4-{3-(2-methyl-3,4-dihydro-2H-benzo[b][1,4]oxazin-4-yl)propylamino}phenyl]-2-ethoxypropanoic acid or its salts
- 30

- (-) 3-[4-{3-(2-methyl-3,4-dihydro-2H-benzo[b][1,4]oxazin-4-yl)propylamino}phenyl]-2-ethoxypropanoic acid or its salts
- (±) Ethyl 3-[4-{3-(2-methyl-3,4-dihydro-2H-benzo[b][1,4]oxazin-4-yl)propylamino}phenyl]-2-methoxypropanoate
- 5 (+) Ethyl 3-[4-{3-(2-methyl-3,4-dihydro-2H-benzo[b][1,4]oxazin-4-yl)propylamino}phenyl]-2-methoxypropanoate
- (-) Ethyl 3-[4-{3-(2-methyl-3,4-dihydro-2H-benzo[b][1,4]oxazin-4-yl)propylamino}phenyl]-2-methoxypropanoate
- 10 (±) 3-[4-{3-(2-methyl-3,4-dihydro-2H-benzo[b][1,4]oxazin-4-yl)propylamino}phenyl]-2-methoxypropanoic acid or its salts
- (+) 3-[4-{3-(2-methyl-3,4-dihydro-2H-benzo[b][1,4]oxazin-4-yl)propylamino}phenyl]-2-methoxypropanoic acid or its salts
- 15 (-) 3-[4-{3-(2-methyl-3,4-dihydro-2H-benzo[b][1,4]oxazin-4-yl)propylamino}phenyl]-2-methoxypropanoic acid or its salts
- (±) Ethyl 3-[4-{3-(2-propyl-3,4-dihydro-2H-benzo[b][1,4]oxazin-4-yl)propylamino}phenyl]-2-ethoxypropanoate
- 20 (+) Ethyl 3-[4-{3-(2-propyl-3,4-dihydro-2H-benzo[b][1,4]oxazin-4-yl)propylamino}phenyl]-2-ethoxypropanoate
- (-) Ethyl 3-[4-{3-(2-propyl-3,4-dihydro-2H-benzo[b][1,4]oxazin-4-yl)propylamino}phenyl]-2-ethoxypropanoate
- 25 (±) 3-[4-{3-(2-propyl-3,4-dihydro-2H-benzo[b][1,4]oxazin-4-yl)propylamino}phenyl]-2-ethoxypropanoic acid or its salts
- (+) 3-[4-{3-(2-propyl-3,4-dihydro-2H-benzo[b][1,4]oxazin-4-yl)propylamino}phenyl]-2-ethoxypropanoic acid or its salts
- (-) 3-[4-{3-(2-propyl-3,4-dihydro-2H-benzo[b][1,4]oxazin-4-yl)propylamino}phenyl]-2-ethoxypropanoic acid or its salts
- 30

- (±) Ethyl (2*S*)-3-[4-{3-(2-propyl-3,4-dihydro-2H-benzo[b][1,4]oxazin-4-yl)propylamino}phenyl]-2-methoxypropanoate
- (+) Ethyl (2*S*)-3-[4-{3-(2-propyl-3,4-dihydro-2H-benzo[b][1,4]oxazin-4-yl)propylamino}phenyl]-2-methoxypropanoate
- 5 (-) Ethyl (2*S*)-3-[4-{3-(2-propyl-3,4-dihydro-2H-benzo[b][1,4]oxazin-4-yl)propylamino}phenyl]-2-methoxypropanoate
- (±) 3-[4-{3-(2-propyl-3,4-dihydro-2H-benzo[b][1,4]oxazin-4-yl)propylamino}phenyl]-2-methoxypropanoic acid and its salts
- 10 (+) 3-[4-{3-(2-propyl-3,4-dihydro-2H-benzo[b][1,4]oxazin-4-yl)propylamino}phenyl]-2-methoxypropanoic acid and its salts
- (-) 3-[4-{3-(2-propyl-3,4-dihydro-2H-benzo[b][1,4]oxazin-4-yl)propylamino}phenyl]-2-methoxypropanoic acid and its salts
- 15 (±) Ethyl 2-isopropoxy-3-[4-{3-(7-fluoro-3,4-dihydro-2H-benzo[b][1,4]oxazin-4-yl)propylamino}phenyl] propanoate
- (+) Ethyl 2-isopropoxy-3-[4-{3-(7-fluoro-3,4-dihydro-2H-benzo[b][1,4]oxazin-4-yl)propylamino}phenyl] propanoate
- (-) Ethyl 2-isopropoxy-3-[4-{3-(7-fluoro-3,4-dihydro-2H-benzo[b][1,4]oxazin-4-yl)propylamino}phenyl] propanoate
- 20 (±) 2-Isopropoxy-3-[4-{3-(7-fluoro-3,4-dihydro-2H-benzo[b][1,4]oxazin-4-yl)propylamino}phenyl]propanoic acid and its salts
- (+) 2-Isopropoxy-3-[4-{3-(7-fluoro-3,4-dihydro-2H-benzo[b][1,4]oxazin-4-yl)propylamino}phenyl]propanoic acid and its salts
- 25 (-) 2-Isopropoxy-3-[4-{3-(7-fluoro-3,4-dihydro-2H-benzo[b][1,4]oxazin-4-yl)propylamino}phenyl]propanoic acid and its salts
- (±) Ethyl 3-[4-{3-(2-methyl-7-fluoro-3,4-dihydro-2H-benzo[b][1,4]oxazin-4-yl)propylamino}phenyl]-2-methoxypropanoate
- 30

(+) Ethyl 3-[4-{3-(2-methyl-7-fluoro-3,4-dihydro-2H-benzo[b][1,4]oxazin-4-yl)propylamino}phenyl]-2-methoxypropanoate

(-) Ethyl 3-[4-{3-(2-methyl-7-fluoro-3,4-dihydro-2H-benzo[b][1,4]oxazin-4-yl)propylamino}phenyl]-2-methoxypropanoate

5

(±) 3-[4-{3-(2-methyl-7-fluoro-3,4-dihydro-2H-benzo[b][1,4]oxazin-4-yl)propylamino}phenyl]-2-methoxypropanoic acid and its salts

(+) 3-[4-{3-(2-methyl-7-fluoro-3,4-dihydro-2H-benzo[b][1,4]oxazin-4-yl)propylamino}phenyl]-2-methoxypropanoic acid and its salts

10 (-) 3-[4-{3-(2-methyl-7-fluoro-3,4-dihydro-2H-benzo[b][1,4]oxazin-4-yl)propylamino}phenyl]-2-methoxypropanoic acid and its salts

[2*S*,N(1*R*)]-N-(2-hydroxy-1-phenylethyl)-2-ethoxy-3-[4-{3-(3,4-dihydro-2H-benzo[b][1,4]oxazin-4-yl)propylamino}phenyl]propanamide ;

15

[2*R*,N(1*R*)]-N-(2-hydroxy-1-phenylethyl)-2-ethoxy-3-[4-{3-(3,4-dihydro-2H-benzo[b][1,4]oxazin-4-yl)propylamino}phenyl]propanamide ;

2*S*,N(1*R*)]-N-(2-hydroxy-1-phenylethyl)-2-ethoxy-3-[4-{3-(7-fluoro-3,4-dihydro-2H-benzo[b][1,4]oxazin-4-yl)propylamino}phenyl]propanamide

20

[2*R*,N(1*R*)]-N-(2-hydroxy-1-phenylethyl)-2-ethoxy-3-[4-{3-(7-fluoro-3,4-dihydro-2H-benzo[b][1,4]oxazin-4-yl)propylamino}phenyl]propanamide

25 [2*S*,N(1*R*)]-N-(2-hydroxy-1-phenylethyl)-2-ethoxy-3-[4-{3-(3,4-dihydro-2H-benzo[b][1,4]oxazin-4-yl)propylamino}phenyl]propanamide hydrochloride salt ;

[2*R*,N(1*R*)]-N-(2-hydroxy-1-phenylethyl)-2-ethoxy-3-[4-{3-(3,4-dihydro-2H-benzo[b][1,4]oxazin-4-yl)propylamino}phenyl]propanamide hydrochloride salt ;

30

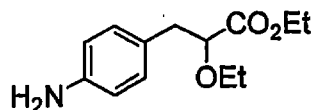
The novel antidiabetic compounds of formula (II) and process for preparing them are described and claimed in our PCT application entitled "New bicyclic

compounds and their use in medicine, process for their preparation and pharmaceutical compositions containing them" filed simultaneously on the same day.

5 It is appreciated that in any of the above mentioned reactions, any reactive group in the substrate molecule may be protected according to conventional chemical practice. Suitable protecting groups in any of the above mentioned reactions are tertiarybutyl dimethyl silylchloride, methoxymethyl chloride etc, to protect hydroxyl group, N-Boc, N-Cbz, N-Fmoc etc, for protection of amino group, acetal protection
10 for aldehyde, ketal protection for ketone and the like. The methods of formation and removal of such protecting groups are those conventional methods appropriate to the molecule being protected.

The stereoisomers of the compounds forming part of this invention may be prepared by using reactants in their single enantiomeric form in the process wherever
15 possible or by conducting the reaction in the presence of reagents or catalysts in their single enantiomer form or by resolving the mixture of stereoisomers by conventional methods. Some of the preferred methods include use of microbial resolution, resolving the diastereomeric salts formed with chiral acids such as mandelic acid, camphorsulfonic acid, tartaric acid, lactic acid, and the like wherever applicable or
20 chiral bases such as brucine, cinchona alkaloids and their derivatives and the like. Commonly used methods are compiled by Jaques et al in "Enantiomers, Racemates and Resolution" (Wiley Interscience, 1981). More specifically the compound of formula (I) where YR^8 represents OH may be converted to a 1:1 mixture of diastereomeric amides by treating with chiral amines, amino acids, amino alcohols
25 derived from aminoacids; conventional reaction conditions may be employed to convert acid into an amide; the diastereomers may be separated either by fractional crystallization or chromatography and the stereoisomers of compound of formula (I) may be prepared by hydrolyzing the pure diastereomeric amide.

The invention is explained in detail in the examples given below which are
30 provided by way of illustration only and therefore should not be construed to limit the scope of the invention.

Example 1**Ethyl 2-ethoxy-3-(4-aminophenyl)propanoate****Step (i)**

- 5 Wittig salt from triethyl 2-ethoxyphosphonoacetate (26.5 g, 1.5 eq, 99.3 mmol) and NaH (50 % in oil) (5.3 g, 2 eq, 132.4 mmol) was prepared in THF (350 ml) at 0 °C. To this solid 4-nitrobenzaldehyde (10 g, 1 eq, 66.2 mmol) was added in portions at 0 °C and the resulting solution was stirred at RT for 16 h. The reaction mixture was diluted with ethyl acetate and washed with aqueous NH₄Cl. The crude contains ethyl
10 4-nitro-2-ethoxycinnamate in both Z and E stereoisomers (11 g).

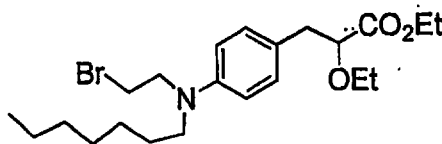
Step (ii)

- Ethyl 4-nitro-2-ethoxycinnamate obtained in step (i) was hydrogenated using Pd (10%)/C - H₂ (60 psi) (11 g) in ethyl acetate (150 ml) at RT and chromatographed
15 using ethyl acetate / hexane to yield the title compound as viscous oil (9.41 g, yield 60%).

¹H NMR (200 MHz, CDCl₃) δ: 1.16 (t, J=7.0Hz, 3H), 1.22 (t, J=7.0Hz, 3H), 2.90 (d, J=6.3Hz, 2H), 3.30 (bs, 2H, NH₂), 3.35 (m, 1H), 3.55 (m, 1H), 3.94 (t, J=6.3Hz, 1H), 4.15 (q, J=7.0Hz, 2H), 6.62 (d, J=8.3Hz, 2H), 7.03 (d, J = 8.0Hz, 2H).

- 20 IR (neat) cm⁻¹: 3372, 1738.

Mass m/z (CI): 238 (M+1), 192 (M - OC₂H₅).

Example 2**Ethyl 2-ethoxy-3-[4-{N-heptyl-N-(2'-bromoethyl)}aminophenyl]propanoate**

25

Step (i)

A mixture of ethyl 2-ethoxy-3-(4-aminophenyl)propanoate (5 g, 1 eq, 21 mmol) obtained in preparation 1, heptylbromide (18.8 g, 5 eq, 105 mmol), and anhydrous

K₂CO₃ (14.5 g, 5 eq, 105 mmol), was heated at 70 °C in DMF (100 ml), for 16 h. The reaction mixture was diluted with ethyl acetate, washed with water and brine. The residue was chromatographed using a mixture of ethyl acetate and hexane as diluent to afford monoheptylated product as thick liquid (3.85 gm, yield 55%).

5 ¹H NMR (200 MHz, CDCl₃) δ: 0.88 (bt, J=6.3Hz, 3H), 1.05-1.42 (m, 15H), 1.42-1.68 (m, 2H), 2.90 (d, J=6.6Hz, 2H), 3.08 (t, J=6.8Hz, 2H), 3.22-2.42 (m, 1H), 3.44-3.64 (m, 1H), 3.94 (t, J=6.8Hz, 1H), 4.1 (q, J=7.0Hz, 2H), 6.55 (d, J=8.3Hz, 2H), 7.04 (d, J=8.3Hz, 2H).

IR (neat) cm⁻¹: 3396, 1747.

10 Mass m/z (CI): 335 (M+1), 290 (M-OC₂H₅).

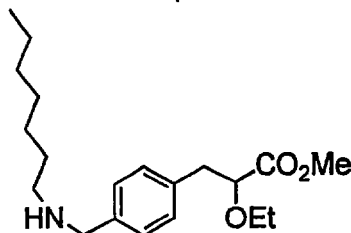
Step (ii)

The mono heptylated product (3 g, 1 eq, 8.98 mmol) obtained in step (i) was treated with excess dibromoethane (10 eq) in presence of anhydrous K₂CO₃ (3.72 g, 3 eq, 27 mmol), in DMF (40 ml), and heated at 70 °C for 16 h. The reaction mixture was diluted with ethyl acetate, washed with water and brine. The residue was chromatographed using a mixture of ethyl acetate and hexane as diluent to yield ethyl 2-ethoxy-3-[4-{N-heptyl-N-(2'-bromoethyl)}aminophenyl]propanoate as thick liquid (1.98 g, yield 50%).

20 ¹H NMR (200 MHz, CDCl₃) δ: 0.88 (bt, J=6.3Hz, 3H), 1.05-1.42 (m, 14H), 1.42-1.68 (m, 2H), 2.90 (d, J=6.6Hz, 2H), 3.28 (t, J=7.3Hz, 2H), 3.30-3.45 (m, 3H), 3.50-3.70 (m, 3H), 3.96 (t, J=6.8Hz, 1H), 4.17 (q, J=7.0Hz, 2H), 6.57 (d, J=8.3Hz, 2H), 7.09 (d, J=8.3Hz, 2H).

IR (neat) cm⁻¹: 1747.

25 Mass m/z (CI): 442 (M(⁷⁹Br)+1), 444 (M(Br⁸¹)+1).

Example 3**Methyl 2-ethoxy-3-[4-(N-heptylaminomethyl)phenyl]propanoate****Step (i)**

- 5 Methyl 3-[4-formylphenyl]-2-ethoxypropanoate (2 g, 1 eq, 8.51 mmol) obtained in preparation 5, heptylamine (978 mg, 1 eq, 8.51 mmol) and cat. amount of p-TsOH.H₂O were taken in DCM (40 ml), along with few pieces of activated molecular sieves (4 Å). The reaction mixture was filtered through celite after 24 h, at RT and the filtrate was diluted with DCM and was washed with aqueous sodium
10 bicarbonate and dried over anhydrous sodium sulfate to yield crude methyl 2-ethoxy-3-[4-(N-heptylaminomethyl)phenyl]propanoate

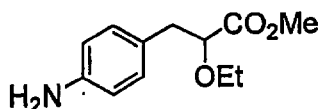
Step (ii)

- The crude methyl 2-ethoxy-3-[4-(N-heptylaminomethyl)phenyl]propanoate obtained
15 in step (i) above (2.95 g), was dissolved in methanol (40 ml), and treated with conc. HCl (850 µl, 1 eq, 8.51 mmol) and sodium cyanoborohydride (535 mg, 1 eq, 8.51 mmol) at 0 °C. The progress of the reaction was monitored by TLC. After 2-3 h, the reaction mixture was diluted with ethyl acetate, washed with aqueous sodium bicarbonate and dried over anhydrous sodium sulfate. The residue was
20 chromatographed using methanol and chloroform to afford the title compound (1.71 g, yield 60%) as viscous liquid.

- ¹H NMR (200 MHz, CDCl₃) δ: 0.86 (bt, J=6.3Hz, 3H), 1.14 (t, J=6.8Hz, 3H), 1.20-1.40 (m, 9H), 1.50-1.70 (m, 2H), 2.60 (t, J=7.4Hz, 2H), 2.98 (d, J=6.3Hz, 2H), 3.22-3.41 (m, 1H), 3.48-3.67 (m, 1H), 3.71 (s, 3H), 3.89 (s, 2H), 4.02 (t, J=6.3Hz, 1H),
25 7.23 (d, J=7.8Hz, 2H), 7.30 (d, J=7.8Hz, 2H).

IR (neat) cm⁻¹: 3500 (br), 1748.

Mass m/z (CI): 336 [M+1].

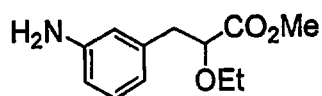
Example 4**Methyl 2-ethoxy-3-(4-aminophenyl)propanoate**

- 5 Ethyl 4-nitro-2-ethoxycinnamate (10 g, 1 eq, 37.7 mmol) obtained in step (i) of preparation 1, was treated with activated magnesium turnings (18 g, 20 eq, 754 mmol) in dry methanol (400 ml). The reaction mixture was refluxed for 2-3 h, and allowed to stir at room temperature for 16 h. The reaction mixture was diluted with ethyl acetate and quenched with cold aqueous ammonium chloride. The organic layer
10 was washed with water and brine. The residue was chromatographed using ethyl acetate and hexane to afford the title compound as liquid (6 g, yield 72%).

¹H NMR (200 MHz, CDCl₃) δ: 1.64 (t, J=6.8Hz, 3H), 2.90 (d, J = 6.3 Hz, 2H), 3.22 - 3.42 (m, 1H), 3.42 - 3.65 (m, 2H), 3.70 (s, 3H), 3.96 (t, J = 6.8 Hz, 1H), 6.61 (d, J = 8.3 Hz, 2H), 7.00 (d, J = 8.3 Hz, 2H).

- 15 IR (neat) cm⁻¹: 3350 (br), 1735.

Mass m/z (CI): 224 [M+1].

Example 5**Methyl 2-ethoxy-3-(3-aminophenyl)propanoate**

20

Step (i)

- Wittig salt from triethyl 2-ethoxyphosphonoacetate (34.3 ml, 2 eq, 132 mmol) and NaH (50 % in oil) (6.28 g, 2 eq, 132 mmol) was prepared in THF (350 ml) at 0 °C. To this solid 3-nitrobenzaldehyde (10 g, 1 eq, 66 mmol) was added in portions at 0
25 °C. The resulting solution was stirred at RT for 16 h. The reaction mixture was diluted with ethyl acetate and washed with aqueous NH₄Cl. The crude contains ethyl 4-nitro-2-ethoxycinnamate in both Z and E stereoisomers (15 g, yield 86%).

Step (ii)

The crude compound (15 g, 1 eq, 56.6 mmol) obtained in step (i) was dissolved in methanol (250 ml). To this ammonium formate (35.6 g, 10 eq, 566 mmol) and 10 %
5 Pd/C (40 g) was added and the reaction mixture was stirred at RT for 16 h. The catalyst was filtered and the methanol was condensed on rotavapour. The reaction mixture was diluted with ethyl acetate and washed with water and brine. The residue was chromatographed to yield methyl 2-ethoxy meta amino cinnamate as (E) and (Z) isomers (10 g, yield 75%).

10

Step (iii)

Methyl 2-ethoxy meta amino cinnamate (10 g, 1 eq, 42.5 mmol) obtained in step (ii) was treated with magnesium (20.4 g, 20 eq, 850 mmol) and dry methanol (500 ml). The reaction mixture was refluxed for 2-3 h, and allowed to stir at room temperature
15 for 16 h. The reaction mixture was diluted with ethyl acetate and quenched with cold aqueous ammonium chloride. The organic layer was washed with water and brine. The residue was chromatographed using ethyl acetate and hexane to afford the title compound as viscous liquid (8.06 g, yield 80%).

20 ^1H NMR (200 MHz, CDCl_3) δ : 1.15 (t, $J=6.8\text{Hz}$, 3H), 2.96 (d, $J=6.9\text{Hz}$, 2H), 3.22 – 3.42 (m, 1H), 3.42 – 3.65 (m, 2H), 3.70 (s, 3H), 4.01 (t, $J=6.4\text{Hz}$, 1H), 6.50 – 6.62 (aromatics, 3H), 7.06 (t, $J=7.8\text{Hz}$, 1H).

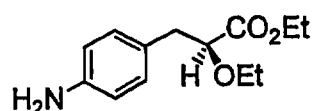
IR (neat) cm^{-1} : 3360, 1738.

Mass m/z (CI): 224 ($M+1$).

25

Example 6

(S)-Ethyl 2-ethoxy-3-(4-aminophenyl)propionate



30

Step (i)

To a solution of (*S*)-(4-nitrophenyl) alanine (10g, 47.6 mmol) in a mixture of water (50 mL), H₂SO₄ (1M, 60 mL) and acetone (150 mL) at -5 °C, was added under stirring, a solution of sodium nitrite (9.85g, 142.8 mmol) in water (40 mL) drop wise
5 over a period of 30 min. The reaction mixture was stirred at -5 to 0 °C for another 1.5 h, followed by stirring at room temperature for 16 h. Acetone was removed and then the reaction mixture was diluted with 500 mL ethyl acetate. Organic layer was washed with brine, dried over anhydrous Na₂SO₄, and concentrated. The crude mass was purified by crystallization from isopropyl acetate (9.0 g, 96 %).

10 Mp: 134-136 °C

[α]_D: -25° (c 1.0, MeOH)

¹H NMR (CDCl₃) δ: 3.04 (dd, J = 14, 7.8 Hz, 1H), 3.24 (dd, J = 14, 4, Hz, 1H), 4.39 (dd, J = 7.3, 4.1 Hz, 1H), 7.42 (d, J = 8.7 Hz, 2H), 8.16 (d, J = 8.7 Hz, 2H).

IR (neat) cm⁻¹: 3485, 3180, 2927, 1715, 1515, 1343.

15 Mass m/z (CI) : 212 (M+1).

Step (ii)

(*S*)-2-Hydroxy-3-(4-nitrophenyl)propionic acid (9.0 g, 42.6 mmol), obtained from step (i) above, was dissolved in dry EtOH (300 mL). To this solution was added conc. H₂SO₄ (326 mL, 5.9 mmol), and refluxed for 5 to 6 h. The reaction mixture
20 was neutralized with aqueous sodium bicarbonate. Ethanol was condensed on rotavapor, and the residue was dissolved in ethyl acetate. Organic layer was washed with aqueous sodium bicarbonate, water, brine, and then dried over anhydrous Na₂SO₄, and concentrated. Desired product was obtained from the crude mass by crystallizing from diisopropylether (8.0 g, 78.5 %).

25 Mp: 74-76 °C.

[α]_D: -13° (c 1.0, MeOH)

¹H NMR (CDCl₃) δ: 1.30 (t, J = 7 Hz, 3H), 3.06 (dd, J = 14, 7, Hz, 1H), 3.25 (dd, J = 14, 4.3, Hz, 1H), 4.25 (q, J = 7 Hz, 2H), 4.25 (dd, J = 7, 4.3 Hz, 1H), 7.42 (d, J = 8.7 Hz, 2H), 8.16 (d, J = 8.7 Hz, 2H).

30 IR (neat) cm⁻¹: 3432, 2924, 1736, 1518, 1347.

Mass m/z (CI): 240 (M+1).

Step (iii)

To a mixture of (*S*)-Ethyl 2-Hydroxy-3-(4-nitrophenyl)propionate (4.77g, 19.95 mmol), obtained in step ii above, molecular sieves (4 A) (5.0 g) and powdered Ag₂O (13.8g, 59.8 mmol) in dry acetonitrile (100 mL), was added ethyl iodide (6.4 mL, 79.8 mmol) at room temperature. The reaction mixture was heated at 60 °C for 16h. The reaction mixture was filtered through celite, and concentrated. The crude mass was chromatographed using ethyl acetate and hexanes to obtain the desired product as viscous liquid (3.5g, 67% isolated yield). Unreacted starting material was recovered (900 mg) which could be reused.

10

[α]_D: -26° (c 1.0, MeOH)

¹H NMR (CDCl₃) δ : 1.15 (t, J = 7 Hz, 3H); 1.26 (t, J = 7.1 Hz, 3H); 3.10 (d, J = 3.8 Hz, 1H); 3.13 (s, 1H); 3.16-3.35 (m, 1H); 3.45-3.65 (m, 1H); 4.03 (dd, J = 7.5, 5.4 Hz, 1H); 4.21 (q, J = 7.2 Hz, 2H); 7.43 (d, J = 8.6 Hz, 2H); 8.15 (d, J = 8.6 Hz, 2H).

15

IR (neat) cm⁻¹: 2980, 1747, 1604, 1521, 1347.

Mass m/z (CI) : 268 (M+1).

Step (iv)

(*S*)-Ethyl 2-ethoxy-3-(4-nitrophenyl)propionate (6.0, 25.3 mmol), obtained in step (iii) above, was dissolved in dry methanol (100 mL). To this solution was added 20 10% Pd/C (2.0 g), and was hydrogenated using hydrogen gas (20 psi) for 3-4 h. The reaction mixture was filtered through celite, and the filtrate was concentrated to provide a syrupy mass. The product was obtained in quantitative yield.

[α]_D: -14.2° (c 1.0, MeOH).

Chiral HPLC: >98 % ee.

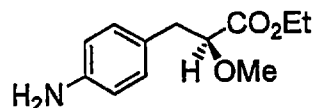
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¹H NMR (CDCl₃) δ : 1.16 (t, J = 7.0Hz, 3H), 1.22 (t, J = 7.0Hz, 3H), 2.90 (d, J = 6.3Hz, 2H), 3.30 (bs, 2H, NH₂), 3.24-3.42(m, 1H), 3.50-3.70 (m, 1H), 3.94 (t, J = 6.3Hz, 1H), 4.15 (q, J = 7.0Hz, 2H), 6.62 (d, J = 8.3Hz, 2H), 7.03 (d, J = 8.0Hz, 2H).

IR (neat) cm⁻¹ : 3372, 1738.

Mass m/z (CI) : 238 (M+1), 192 (M - OC₂H₅).

30

Example 7**(S)-Ethyl 2-methoxy-3-(4-aminophenyl)propionate**

5

Step (i)

To a mixture of (S)-Ethyl 2-Hydroxy-3-(4-nitrophenyl)propionate (12.5 g, 52.3 mmol), obtained in step (ii) of preparation 20, and powdered Ag_2O (36.3 g, 157 mmol) in dry acetonitrile (260 mL) was added methyl iodide (13 mL, 209.2 mmol) at room temperature. Activated molecular sieves (4 Å) (12.5 g) were added and then the reaction mixture was stirred at room temperature for 16 h. The reaction mixture was filtered through celite, and concentrated. The crude mass was chromatographed using ethyl acetate and hexanes to obtain the desired product as viscous liquid (10.0 g, 75%).

15 $[\alpha]_D^{25}$: -30.1° (c 1.0, MeOH)

^1H NMR (CDCl_3) δ : 1.24 (t, J = 7.1 Hz, 3H); 3.09 (d, J = 5.4 Hz, 1H); 3.12 (d, J = 2.7 Hz, 1H); 3.35 (s, 3H); 3.96 (dd, J = 7.5, 5.1 Hz, 1H); 4.19 (q, J = 7.1 Hz, 2H); 7.39 (d, J = 8.6 Hz, 2H); 8.13 (d, J = 8.6 Hz, 2H).

IR (neat) cm^{-1} : 2995, 1747, 1604, 1521, 1343.

20 Mass m/z (CI): 254 (M+1).**Step (ii)**

(S)-Ethyl 2-methoxy-3-(4-nitrophenyl)propionate (8.0, 31.6 mmol), obtained in step (i) above, was dissolved in dry methanol (200 mL). To this solution was added 10% Pd/C (2.5 g), and hydrogenated using hydrogen gas (20 psi) for 3–4 h. The reaction mixture was filtered through celite, and concentrated to a syrupy mass. After column chromatography using ethyl acetate / hexanes the desired product was isolated as thick liquid (7.0 g, quantitative).

25 $[\alpha]_D^{25}$: -14.1° (c 1.0, MeOH).

Chiral HPLC: >98 % ee.

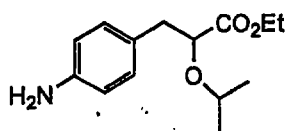
^1H NMR (CDCl_3) δ : 1.23 (t, $J = 7.2\text{Hz}$, 3H), 2.91 (d, $J = 6.1\text{Hz}$, 2H), 3.30 (bs, 2H, NH_2), 3.34 (s, 3H), 3.88 (t, $J = 6.2\text{Hz}$, 1H), 4.17 (q, $J = 7.2\text{Hz}$, 2H), 6.62 (d, $J = 8.3\text{Hz}$, 2H), 7.01 (d, $J = 8.1\text{Hz}$, 2H).

IR (neat) cm^{-1} : 3372, 2985, 2932, 1739, 1627, 1519.

5 Mass m/z (CI): 223 (M), 234 ($M+1$), 192 ($M - \text{OMe}$).

Example 8

Ethyl 2-isopropoxy-3-(4-aminophenyl)propionate



10

Step (i):

4-nitrophenylalanine (5 g, 1 eq, mmol) was added in portions to a solution of dry ethanol (mL) and thionylchloride (mL) at -5°C . It was stirred at that temperature for another one hour, followed by stirring at RT for 16h. The reaction mixture was condensed on rotavapour, azeotroped with toluene, and then dried over high vacuum pump to obtain 4-nitrophenylalanine ethyl ester hydrochloride as white solid (quantitative yield).

20 Step (ii):

4-nitrophenylalanine ethyl ester hydrochloride (2 g, 1.0 eq, 7.28 mmol) obtained in step(i) was dissolved in ethyl acetate (150 mL). To that Na_2CO_3 (386 mg, 0.5 eq, 3.64 mmol) was added and was stirred for 15 min. The reaction mixture was washed with aq. NaHCO_3 . The organic layer was dried (Na_2SO_4), and condensed to obtain 4-nitrophenylalanine ethyl ester as thick oil (1.55 g, 89%).

25

Step (iii):

4-nitrophenylalanine ethyl ester (1.55 g, 1.0 eq, 6.51 mmol), obtained in step(ii) above was dissolved in chloroform (33 mL). To that glacial acetic acid (20 μL , 0.05 eq, 0.33 mmol), and isoamyl nitrite (958 μL , 1.1 eq, 7.16 mmol) were added and the

30

reaction mixture was heated at reflux for 30 min. The reaction mixture was diluted with chloroform, and was washed with aq. NaHCO_3 . The organic layer was dried (Na_2SO_4) and condensed (caution!) to a yellowish liquid.

5 **Step (iv):**

The liquid (1.54 g, 1.0 eq, 6.18 mmol) thus obtained in step (iii), was dissolved in dry isopropanol (31 mL), and to that catalytic amount of $\text{Rh}_2(\text{OAc})_4 \cdot 2\text{H}_2\text{O}$ (38 mg, 0.02 eq, 0.12 mmol) was added and the reaction mixture was stirred at room temperature for 16h. Isopropanol was condensed, and the reaction mixture was
10 diluted with ethyl acetate. The organic layer was washed with water and brine, dried (Na_2SO_4), and concentrated. Column chromatography, using ethyl acetate and hexanes, provided the desired compound ethyl 2-isopropoxy-3-(4-nitrophenyl)propionate (1.25 g, 61% overall).

^1H NMR (200 MHz, CDCl_3) δ : 0.92 (d, $J = 5.8$ Hz, 3H), 1.16 (d, $J = 5.8$ Hz, 3H),
15 1.27 (t, $J = 7.4$ Hz, 3H), 3.00-3.10 (m, 2H), 3.52 (quintet, 1H); 4.08 (dd, $J = 8.7$ and 4.8 Hz, 1H), 4.21 (q, $J = 7.4$ Hz, 2H), 7.43 (d, $J = 8.7$ Hz, 2H), 8.16 (d, $J = 8.7$ Hz, 2H).

IR (neat) cm^{-1} : 2975, 1747, 1602, 1522, 1347.

Mass m/z (CI): 282 $[\text{M}+1]$

20 **Step (v):**

Ethyl 2-isopropoxy-3-(4-nitrophenyl)propionate (1.52 g, 5.4 mmol) obtained in step (v) was hydrogenated under 10 psi pressure of molecular hydrogen using 10% Pd/C (700 mg) as catalyst in ethyl acetate (200 mL) at room temperature for 3-4 h. The desired product was isolated after filtering the reaction mixture and concentrating the
25 filtrate under reduced pressure. Column chromatography of the crude mass using ethyl acetate and hexanes provided the desired compound ethyl 2-isopropoxy-3-(4-aminophenyl)propionate (1.16 g, 86% overall).

^1H NMR (200 MHz, CDCl_3) δ : 0.97 (d, $J = 5.8$ Hz, 3H), 1.15 (d, $J = 5.8$ Hz, 3H),
1.23 (t, $J = 7.0$ Hz, 3H), 2.80-2.95 (m, 2H), 3.49 (quintet, 1H); 3.98 (dd, $J = 8.1$ and
30 5.7 Hz, 1H), 4.16 (q, $J = 7.0$ Hz, 2H), 6.61 (d, $J = 8.3$ Hz, 2H), 7.03 (d, $J = 8.3$ Hz, 2H).

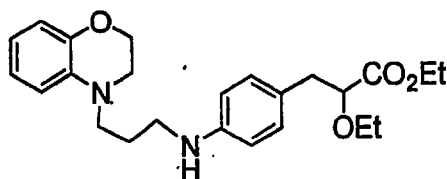
IR (neat) cm^{-1} : 3455, 3371, 2975, 2929, 1737, 1626, 1519.

Mass m/z (CI): 252 [M+1]

Representative examples wherein compounds of the formula (I) have been converted
5 to compounds of formula (II)

Example 9

**Ethyl 3-[4-{3-(3,4-dihydro-2H-benzo[b][1,4]oxazin-4-yl)propylamino}
phenyl]-2-ethoxypropanoate**



10 **Step (i):**

A mixture of 3,4-dihydro-2H-benzo[b][1,4]oxazine (3.0 g, 1 eq, 22.2 mmol), 1,3-dibromopropane (22.5 ml, 10 eq, 222 mmol) and anhydrous sodium carbonate (7.05 g, 3 eq, 66.6 mmol) in dry DMF (200 ml) was heated at 70 °C for 16 h. The reaction mixture was diluted with ethyl acetate and washed with water and brine. The residue
15 was chromatographed using ethyl acetate and hexane to yield 3-(3,4-Dihydro-2H-benzo[b][1,4]oxazin-4-yl)propyl bromide as liquid mass (2.6 g, 47%).

^1H NMR (200 MHz, CDCl_3) δ : 2.10 – 2.30 (m, 2H), 3.37 (t, $J=4.4\text{Hz}$, 2H), 3.40 – 3.56 (m, 4H), 4.25 (t, $J=4.3\text{Hz}$, 2H), 6.60 – 6.90 (m, aromatics, 4H).

Mass m/z (CI): 255 ($\text{M}(^{79}\text{Br})$), 256 ($\text{M}(^{79}\text{Br})+1$), 257 ($\text{M}(\text{Br}^{81})$), 258 ($\text{M}(\text{Br}^{81})+1$).

20

Step (ii):

Ethyl 2-ethoxy-3-(4-aminophenyl)propanoate (2 g, 1 eq, 8.4 mmol) obtained in example 1, 3-(3,4-dihydro-2H-benzo[b][1,4]oxazin-4-yl)propyl bromide (2.36 g, 1.1 eq, 9.3 mmol), obtained in step (i) above, and anhydrous K_2CO_3 (3.5 g, 3 eq, 25
25 mmol), were heated at 70 °C in DMF (40 ml) for 24 h. The reaction mixture was diluted with ethyl acetate, washed with water and brine. The residue was chromatographed using a mixture of ethyl acetate and hexane as eluent to afford the title compound as a viscous liquid (1.04 g, yield 30%).

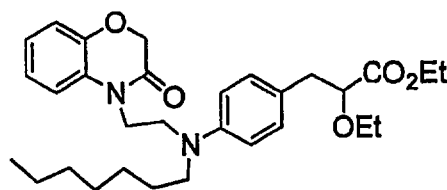
^1H NMR (200 MHz, CDCl_3) 1.17 (t, $J=7.0\text{Hz}$, 3H), 1.23 (t, $J=7.0\text{Hz}$, 3H), 1.92 (q, $J=7.0\text{Hz}$, 2H), 2.90 (d, $J=6.8\text{Hz}$, 2H), 3.20 (t, $J=7.0\text{Hz}$, 2H), 3.22 - 3.41 (m, 5H), 3.45 - 3.62 (m, 1H), 3.95 (t, $J=6.4\text{Hz}$, 1H), 4.05 - 4.37 (m, 4H), 6.65 (d, $J=8.3\text{Hz}$, 2H), 6.61 - 6.85 (m, 4H), 7.05 (d, $J=8.3\text{Hz}$, 2H).

5 IR (neat) cm^{-1} : 3396 (br), 1740.

Mass m/z (CI): 413 ($M+1$).

Example 10

Ethyl 3-[4-N-heptyl-N-{2-(3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazin-4-yl)ethylamino}phenyl]-2-ethoxypropanoate



3-Oxo-3,4-dihydro-2H-benzo[b][1,4]oxazine (185 mg, 1.24 mmol), ethyl 2-ethoxy-3-[4-{N-heptyl-N-(2'-bromoethyl)}aminophenyl]propanoate (500 mg, 1 eq, 1.13 mmol) obtained in example 2, and anhydrous K_2CO_3 (468 mg, 3 eq, 3.39 mmol),
 15 were heated at 70°C in DMF (6 ml) for 16 h. The reaction mixture was diluted with ethyl acetate, washed with water and brine. The residue was chromatographed using a mixture of ethyl acetate and hexanes as diluent to afford the title compound as thick liquid (363 mg, yield 63%).

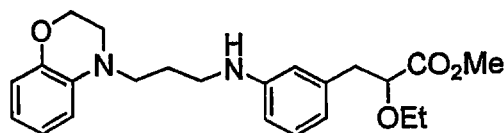
^1H NMR (200 MHz, CDCl_3) δ : 0.88 (bt, $J=6.3\text{Hz}$, 3H), 1.05-1.42 (m, 14H), 1.42-1.68 (m, 2H), 2.92 (d, $J=6.8\text{Hz}$, 2H), 3.25 (t, $J=7.3\text{Hz}$, 2H), 3.30-3.45 (m, 1H), 3.50-3.70 (m, 3H), 3.97 (t, $J=6.6\text{Hz}$, 1H), 4.08 (t, $J=7.3\text{Hz}$, 2H), 4.17 (q, $J=7.0\text{Hz}$, 2H), 4.57 (s, 2H), 6.57 (d, $J=8.3\text{Hz}$, 2H), 6.99 (s, 4H), 7.10 (d, $J=8.0\text{Hz}$, 2H).

IR (neat) cm^{-1} : 1747.

Mass m/z (CI): 511 ($M+1$).

Example 11

Methyl 3-[3-{3-(3,4-dihydro-2H-benzo[b][1,4]oxazin-4-yl)propylamino} phenyl]-2-ethoxypropanoate

**5 Step (i):**

A mixture of 3,4-dihydro-2H-benzo[b][1,4]oxazine (3.0 g, 1 eq, 22.2 mmol), 1,3-dibromopropane (22.5 ml, 10 eq, 222 mmol) and anhydrous sodium carbonate (7.05 g, 3 eq, 66.6 mmol) in dry DMF (200 ml) was heated at 70 °C for 16 h. The reaction mixture was diluted with ethyl acetate and washed with water and brine. The residue
10 was chromatographed using ethyl acetate and hexane to yield 3-(3,4-Dihydro-2H-benzo[b][1,4]oxazin-4-yl)propyl bromide as liquid mass (2.6 g, 47%).

¹H NMR (200 MHz, CDCl₃) δ: 2.10 – 2.30 (m, 2H), 3.37 (t, J=4.4Hz, 2H), 3.40 – 3.56 (m, 4H), 4.25 (t, J=4.3Hz, 2H), 6.60 – 6.90 (m, aromatics, 4H).

Mass m/z (CI): 255 (M(⁷⁹Br)), 256 (M(⁷⁹Br)+1), 257 (M(Br⁸¹)), 258 (M(Br⁸¹)+1).

15 Step (ii):

Methyl 2-ethoxy-3-(3-aminophenyl)propanoate (200 mg, 1 eq, 0.89 mmol) obtained in example 5, 3-(3,4-dihydro-2H-benzo[b][1,4]oxazin-4-yl)propylbromide (253 mg, 1.1 eq, 0.98 mmol) obtained in step (i) above, and anhydrous Na₂CO₃ (285 mg, 3 eq, 2.68 mmol) were heated at 70 °C in DMF (5 ml), for 24 h. The reaction mixture was
20 diluted with ethyl acetate, washed with water and brine. The residue was chromatographed using ethyl acetate and hexane to afford the title compound (304 mg, yield 86%) as viscous liquid.

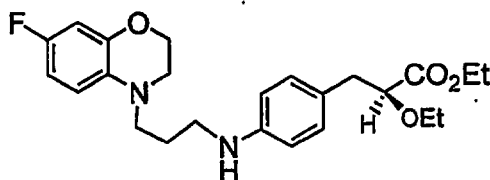
¹H NMR (200 MHz, CDCl₃) δ: 1.17 (t, J=7 Hz, 3H), 1.98 (q, J=7 Hz, 2H), 2.92 (d, J=6.8 Hz, 2H), 3.19 (t, J=7 Hz, 2H), 3.22-3.41 (m, 5H), 3.45-3.62 (m, 1H), 3.70 (s, 3H), 4.02 (t, J=6.4 Hz, 1H), 4.22 (t, J=4.3 Hz, 2H), 6.40-6.82 (m, aromatics, 6H),
25 6.75 (d, J=7.8Hz, 1H), 7.08 (t, J=7.8 Hz, 1H).

IR (neat) cm⁻¹: 3380 (br), 1743, 1680.

Mass m/z (CI): 399 (M+1).

Example 12

Ethyl 3-[4-{3-(7-fluoro-3,4-dihydro-2H-benzo[b][1,4]oxazin-4-yl)propylamino}phenyl]-2-ethoxypropanoate

**Step (i):**

To a solution of 2-nitro-5-fluorophenol (5 g, 1 eq, 31.6 mmol) and ethyl 2-bromoacetate (3.8 ml, 1.1 eq, 34.8 mmol) in dry acetone (160 ml) was added anhydrous potassium carbonate (8.7 g, 2 eq, 63.2 mmol) and stirred at RT for 16 h. The reaction mixture was filtered through celite and then condensed on rotavapour.
 10 The residue was diluted with ethyl acetate and washed with water and brine to yield crude compound (6 g, yield 78%), which was used in step (ii).

Step (ii):

The crude compound obtained in step (i) (6 g, 1 eq, 28.8 mmol) was taken in dry
 15 methanol (150 ml). To this iron powder (8.06 g, 5 eq, 144 mmol) and glacial acetic acid (25 ml, 15 eq, 432 mmol) was added and heated at 110 °C for 4 h. The solvents were removed from the reaction mixture and diluted with ethyl acetate. The ethyl acetate layer was washed with aqueous ammonium chloride, water and brine. The residue was chromatographed to yield 3-oxo-7-fluoro-3,4-dihydro-2H-benzo[b][1,4]oxazine as solid (2.2 g, mp : 204-206 °C, yield 46%).
 20

¹H NMR (200 MHz, CDCl₃+DMSO-d₆) δ: 4.52 (s, 2H), 6.60 – 6.70 (m, 2H), 6.88 (dd, J=8.3 and 5.8Hz, 1H), 10.63 (bs, 1H).

IR (KBr) cm⁻¹: 1677, 1622.

Mass m/z (CI): 168 (M+1).

25

Step (iii):

3-Oxo-7-fluoro-3,4-dihydro-2H-benzo[b][1,4]oxazine (2.2 g, 1 eq, 13.1 mmol) obtained in step (ii) in dry THF (10 ml) was added drop wise to a refluxing THF (60 ml) containing LAH (1.5 g, 3 eq, 39.5 mmol). It was further refluxed for 3 h and

quenched with ethyl acetate. To this water (1.5 ml), 15 % sodium hydroxide (1.5 ml) and water (4.5 ml) were added sequentially. Once $\text{Al}(\text{OH})_3 \cdot \text{H}_2\text{O}$ precipitated out, it was filtered through celite. The filtrate was condensed on rotavapour and chromatographed (ethyl acetate and hexane) to yield 7-fluoro-3,4-dihydro-2H-benzo[b][1,4]oxazine (1.3 g, yield 65%) as yellow oil.

^1H NMR (200 MHz, CDCl_3) δ : 2.80 (bs, 1H), 3.38 (t, $J=4.4\text{Hz}$, 2H), 4.24 (t, $J=4.4\text{Hz}$, 2H), 6.48 – 6.56 (aromatics, 3H).

IR (neat) cm^{-1} : 3395 (br), 2957, 1606.

Mass m/z (CI) : 154 ($M+1$).

10

Step (iv):

A mixture of 7-fluoro-3,4-dihydro-2H-benzo[b][1,4]oxazine (1.3 g, 1 eq, 8.49 mmol) obtained in step (iii) above, 1,3-dibromo propane (8.6 ml, 10 eq, 84.9 mmol) and anhydrous sodium carbonate (2.7 g, 3 eq, 25.4 mmol) in dry DMF (85 ml) was heated at 70 °C for 16 h. The reaction mixture was diluted with ethyl acetate and washed with water and brine. The residue was chromatographed using ethyl acetate and hexane to afford 3-(7-fluoro-3,4-dihydro-2H-benzo[b][1,4]oxazin-4-yl)propylbromide (1.1 g, yield 47%) as viscous oil.

^1H NMR (200 MHz, CDCl_3) δ : 2.10-2.28 (m, 2H), 3.30 (t, $J=4.4\text{Hz}$, 2H), 3.38 (t, $J=6.7\text{Hz}$, 2H), 3.49 (t, $J=6.2\text{Hz}$, 2H), 4.24 (t, $J=4.4\text{Hz}$, 2H), 6.50 – 6.70 (aromatics, 3H).

Mass m/z (CI) : 274 [$M(^{79}\text{Br})+1$], 276 [$M(^{81}\text{Br})+1$].

Step (v):

(S)-Ethyl 2-ethoxy-3-(4-aminophenyl)propanoate (2.20 g, 1 eq, 9.28 mmol) obtained in example 6, 3-(7-fluoro-3,4-dihydro-2H-benzo[b][1,4]oxazin-4-yl)propylbromide (3.30 g, 1.3 eq, 12.06 mmol) obtained in step (iv) above, anhydrous K_2CO_3 (3.84 g, 3 eq, 27.84 mmol), and tetrabutyl ammonium bromide (597 mg, 0.2 eq., 1.85 mmol) were heated at 90 °C in dry toluene (47 mL) for 20 h. The reaction mixture was diluted with ethyl acetate, washed with water and brine. The residue was

30

chromatographed using ethyl acetate and hexane to afford the title compound (1.78 g, yield 44.5%) as viscous liquid.

$[\alpha]_D$: -9.2° (c 1.0, MeOH).

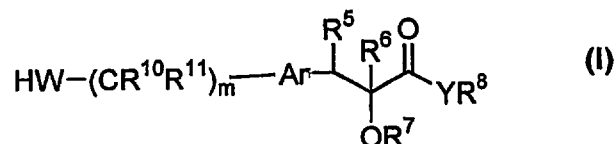
¹H NMR (200 MHz, CDCl₃) δ: 1.17 (t, J=7 Hz, 3H), 1.23 (t, J=7 Hz, 3H), 1.89 (q, J=6.8 Hz, 2H), 2.90 (d, J=6.5 Hz, 2H), 3.10-3.42 (m, 7H), 3.45-3.65 (m, 1H), 3.95 (t, J=6.7 Hz, 1H), 4.10-4.30 (m, 4H), 6.40-6.70 (m, aromatics, 5H), 7.05 (d, J=8.4 Hz, 2H).

IR (neat) cm⁻¹: 3394 (br), 2978, 1740, 1617, 1514.

Mass m/z (CI): 431 (M+1).

We claim:

1. Novel compounds of formula (I)

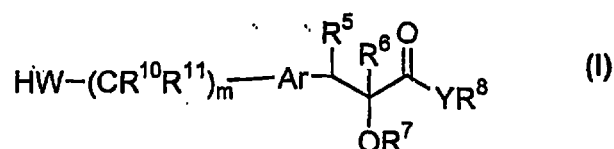


- 5 their derivatives, their analogs, their tautomeric forms, their stereoisomers, their salts, their solvates wherein W represents NR^{12} , R^{12} represents hydrogen, R^{10} and R^{11} may be same or different and represent hydrogen or substituted or unsubstituted group selected from alkyl, alkoxy, aryl or aralkyl group; Ar represents substituted or unsubstituted divalent single or fused aromatic or heterocyclic group; R^5 represents
 10 hydrogen atom, hydroxy, alkoxy, halogen, alkyl, substituted or unsubstituted aralkyl group or forms a bond together with the adjacent group R^6 ; R^6 represents hydrogen, hydroxy, alkoxy, halogen, lower alkyl group, acyl, substituted or unsubstituted aralkyl or R^6 forms a bond together with R^5 ; R^7 may be hydrogen or substituted or unsubstituted groups selected from alkyl, cycloalkyl, aryl, aralkyl, alkoxyalkyl,
 15 alkoxycarbonyl, aryloxy carbonyl, alkylaminocarbonyl, arylaminocarbonyl, acyl, heterocyclyl, heteroaryl, heteroaralkyl groups; R^8 may be hydrogen or substituted or unsubstituted groups selected from alkyl, cycloalkyl, aryl, aralkyl, heterocyclyl, heteroaryl or heteroaralkyl groups; Y represents oxygen, sulfur or NR^{13} , where R^{13} represents hydrogen or substituted or unsubstituted groups selected from alkyl, aryl,
 20 hydroxyalkyl, aralkyl heterocyclyl, heteroaryl, or heteroaralkyl groups; R^8 and R^{13} together may form a substituted or unsubstituted 5 or 6 membered cyclic structure containing carbon atoms, which may optionally contain one or more heteroatoms selected from oxygen, sulfur or nitrogen; m is an integer 0-6.

2. A compound according to claim 1, which is selected from:

- 25 (±) Ethyl 2-ethoxy-3-(4-aminophenyl)propanoate
 (+) Ethyl 2-ethoxy-3-(4-aminophenyl)propanoate
 (-) Ethyl 2-ethoxy-3-(4-aminophenyl)propanoate

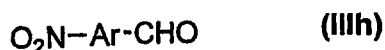
- (±) Ethyl 2-ethoxy-3-[4-{N-heptyl-N-(2'-bromoethyl)}aminophenyl]propanoate
 (+) Ethyl 2-ethoxy-3-[4-{N-heptyl-N-(2'-bromoethyl)}aminophenyl]propanoate
 (-) Ethyl 2-ethoxy-3-[4-{N-heptyl-N-(2'-bromoethyl)}aminophenyl]propanoate
- 5 (±) Methyl 2-ethoxy-3-[4-(N-heptylaminomethyl)phenyl]propanoate
 (+) Methyl 2-ethoxy-3-[4-(N-heptylaminomethyl)phenyl]propanoate
 (-) Methyl 2-ethoxy-3-[4-(N-heptylaminomethyl)phenyl]propanoate
- (±) Methyl 2-ethoxy-3-(4-aminophenyl)propanoate
 10 (+) Methyl 2-ethoxy-3-(4-aminophenyl)propanoate
 (-) Methyl 2-ethoxy-3-(4-aminophenyl)propanoate
- (±) Methyl 2-ethoxy-3-(3-aminophenyl)propanoate
 (+) Methyl 2-ethoxy-3-(3-aminophenyl)propanoate
 15 (-) Methyl 2-ethoxy-3-(3-aminophenyl)propanoate
- (±) Ethyl 2-isopropoxy-3-(4-aminophenyl)propionate
 (+) Ethyl 2-isopropoxy-3-(4-aminophenyl)propionate
 (-) Ethyl 2-isopropoxy-3-(4-aminophenyl)propionate
- 20 3. Process for the preparation of compound of formula (I)



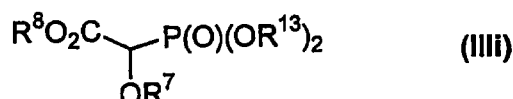
- their derivatives, their analogs, their tautomeric forms, their stereoisomers, their salts, their solvates wherein W represents NR^{12} , R^{12} represents hydrogen, R^{10} and R^{11} may be same or different and represent hydrogen or substituted or unsubstituted group
- 25 selected from alkyl, alkoxy, aryl or aralkyl group; Ar represents substituted or unsubstituted divalent single or fused aromatic or heterocyclic group; R^5 represents hydrogen atom, hydroxy, alkoxy, halogen, alkyl, substituted or unsubstituted aralkyl group or forms a bond together with the adjacent group R^6 ; R^6 represents hydrogen, hydroxy, alkoxy, halogen, lower alkyl group, acyl, substituted or unsubstituted
- 30 aralkyl or R^6 forms a bond together with R^5 ; R^7 may be hydrogen or substituted or

unsubstituted groups selected from alkyl, cycloalkyl, aryl, aralkyl, alkoxyalkyl, alkoxycarbonyl, aryloxy carbonyl, alkylaminocarbonyl, arylaminocarbonyl, acyl, heterocyclyl, heteroaryl, heteroaralkyl groups; R^8 may be hydrogen or substituted or unsubstituted groups selected from alkyl, cycloalkyl, aryl, aralkyl, heterocyclyl, heteroaryl or heteroaralkyl groups; Y represents oxygen, sulfur or NR^{13} , where R^{13} represents hydrogen or substituted or unsubstituted groups selected from alkyl, aryl, hydroxyalkyl, aralkyl heterocyclyl, heteroaryl, or heteroaralkyl groups; R^8 and R^{13} together may form a substituted or unsubstituted 5 or 6 membered cyclic structure containing carbon atoms, which may optionally contain one or more heteroatoms selected from oxygen, sulfur or nitrogen; m is an integer 0-6 which comprises:

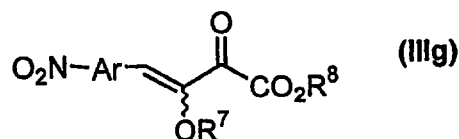
a. i. Reacting compound of formula (IIIh)



where Ar is as defined above with compound of formula (IIIi)



where R^{13} represents (C_1-C_6) alkyl group and all other symbols are as defined earlier in the presence of a base selected from metal hydride like NaH or KH; organolithiums like CH_3Li or $BuLi$; alkoxides like NaOMe, NaOEt or $t-BuOK^+$ or a mixture thereof and a solvent selected from diethyl ether, THF, dioxane, DMF, DMSO, DME, dimethyl acetamide or a mixture thereof. The reaction can be carried out in the presence or absence of HMPA as a cosolvent at a temperature in the range from $-78^\circ C$ to $50^\circ C$, preferably at a temperature in the range of $-10^\circ C$ to $30^\circ C$ under anhydrous conditions to obtain a compound of formula (IIIg)



where R^7 , R^8 and Ar are as defined above.

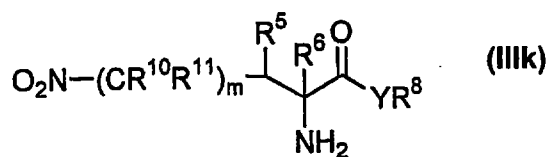
25

ii. Reduction of the compound of formula (IIIg) to a compound of formula (I) where m is 0 and all other symbols are as defined above in the presence of gaseous hydrogen and a catalyst selected from Pd/C, Rh/C, Pt/C, Raney nickel or

a mixture thereof preferably 5-10 % Pd/C and a solvent selected from such as dioxane, acetic acid, ethyl acetate or a mixture thereof. The reaction is carried out at a pressure between atmospheric pressure and 80 psi. The amount of catalyst used is in the range of 1-50 % w/w. Alternatively, the reduction can also be carried out by
 5 employing metal solvent reduction like magnesium, iron, tin, samarium or sodium amalgam in alcohol like methanol, ethanol or propanol preferably methanol. The reduction can be carried out in the presence of metal catalysts selected from Rhodium, Ruthenium or Indium containing chiral ligands selected from (2S,3S)-bis(diphenylphosphino)butane, 1,2-bis(diphenylphosphino)ethane, 1,2-bis(2-methoxyphenylphenylphosphino)ethane or (-)-2,3-isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino) butane to obtain a compound of formula (IIIb) in optically
 10 active form.

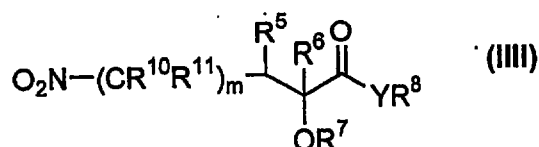
or

b. i. Diazotization of the compound of formula (IIIk)



15

where m is 0 and all other symbols are as defined above, to a compound of formula (III)



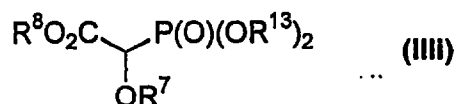
where m is 0 and all other symbols are as defined above in the presence of
 20 diazotizing agent selected from sodium nitrite, isoamyl nitrite, potassium nitrite or ammonium nitrite under acidic conditions using acids selected from sulfuric acid, HCl or acetic acid, in an organic solvent selected from alcohol like methanol, ethanol or propanol; 1,4-dioxane, THF or acetone and the like. Etherifying the residue using alkylating agent selected from alkyl sulfate like diethyl sulphate or dimethylsulphate;
 25 alkyl halide like ethyl iodide or methyl iodide, in solvent selected from hydrocarbons like toluene or benzene; DMF, DMSO, acetonitrile, THF or methyl isobutyl ketone

(MIBK), in an alkali base selected from sodium carbonate, potassium carbonate, sodium methoxide, sodium hydride or potassium hydride.

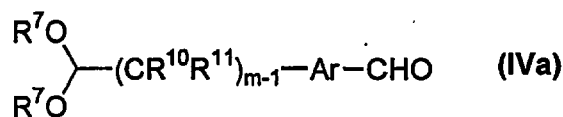
- ii. Reduction of compound of formula (III) to a compound of formula (I) where m is 0 and all other symbols are as defined above in the presence of gaseous hydrogen and a catalyst selected from Pd/C, Rh/C, Pt/C, Raney nickel or a mixture thereof preferably 5-10 % Pd/C and a solvent selected from such as dioxane, acetic acid, ethyl acetate or a mixture thereof. The reaction is carried out at a pressure between atmospheric pressure and 80 psi. The amount of catalyst used is in the range of 1-50 % w/w. Alternatively, the reduction can also be carried out by employing metal solvent reduction like magnesium, iron, tin, samarium or sodium amalgam in alcohol like methanol, ethanol or propanol preferably methanol. The reduction can be carried out in the presence of metal catalysts selected from Rhodium, Ruthenium or Indium containing chiral ligands selected from (2S,3S)-bis(diphenylphosphino)butane, 1,2-bis(diphenylphosphino)ethane, 1,2-bis(2-methoxyphenylphenylphosphino)ethane or (-)-2,3-isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino) butane to obtain a compound of formula (I) in optically active form.

or

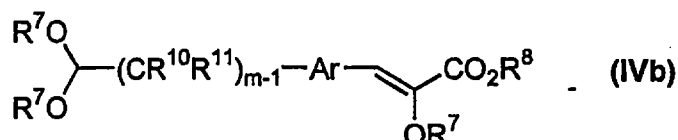
- c. i. Reaction of compound of formula (IIIi)



where all symbols are as defined above with a compound of formula (IVa)

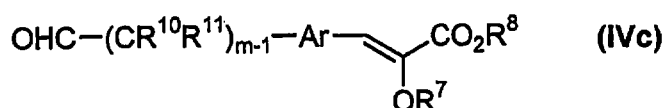


where m is 1-6 and all other symbols are as defined above to yield a compound of formula (IVb)



where m is 1-6 and all other symbols are as defined above in the presence of a base selected from metal hydride like NaH or KH; organolithiums like CH₃Li or BuLi; alkoxides like NaOMe, NaOEt or t-BuOK⁺ or a mixture thereof and a solvent selected from diethyl ether, THF, dioxane, DMF, DMSO, DME, dimethyl acetamide
 5 or a mixture thereof. The reaction can be carried out in the presence or absence of HMPA as a cosolvent at a temperature in the range from -78 °C to 50 °C, preferably at a temperature in the range of -10 °C to 30 °C

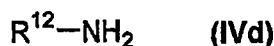
ii. Reduction of the compound of formula (IVb) to yield a compound of formula (IVc)



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where m is 1-6 and all other symbols are as defined above in the presence of gaseous hydrogen and a catalyst selected from Pd/C, Rh/C, Pt/C, Raney nickel or a mixture thereof preferably 5-10 % Pd/C and a solvent selected from such as dioxane, acetic acid, ethyl acetate or a mixture thereof. The reaction is carried out at a pressure
 15 between atmospheric pressure and 80 psi. The amount of catalyst used is in the range of 1-50 % w/w. Alternatively, the reduction can also be carried out by employing metal solvent reduction like magnesium, iron, tin, samarium or sodium amalgam in alcohol like methanol, ethanol or propanol preferably methanol. The reduction can be carried out in the presence of metal catalysts selected from Rhodium, Ruthenium
 20 or Indium containing chiral ligands selected from (2S,3S)-bis(diphenylphosphino)butane, 1,2-bis(diphenylphosphino)ethane, 1,2-bis(2-methoxyphenylphenylphosphino)ethane or (-)-2,3-isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino) butane to obtain a compound of formula (IVc) in optically active form.

25 iii. Reaction of the compound of formula (IVc) with a compound of formula (IVd)

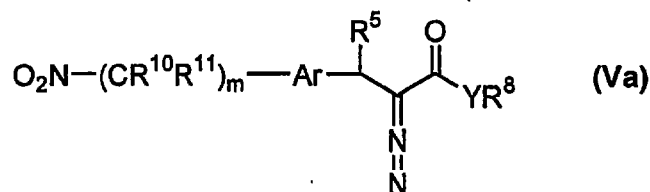


where R¹² is defined above in a solvent selected from CH₂Cl₂, CHCl₃, chlorobenzene, benzene or THF, in the presence of catalyst selected from p-toluenesulfonic acid, methanesulfonic acid, TFA, TfOH or BF₃-OEt₂ or activated
 30

molecular sieves at a temperature in the range of 10 °C to 100 °C, preferably at a temperature in the range from 10 °C to 60 °C. The imine product initially produced is reduced using Na(CN)BH₃-HCl, H₂-Pd/C, H₂-Pt/C or H₂-Ph/C in a solvent selected from methanol or ethanol to yield a compound of formula (I) where m is 1-6 and all
 5 other symbols are defined above.

or

d. i. Diazotization of the compound of formula (IIIk) where m is 0, R⁶ is hydrogen and all other symbols are as defined above to obtain a compound of formula (Va)



10

where m is 0, R⁶ is hydrogen and all other symbols are as defined above in the presence of diazotizing agent selected from sodium nitrite, isoamyl nitrite, potassium nitrite or ammonium nitrite, catalytic amount of carboxylic acid selected from acetic acid or propionic acid, in a solvent selected from chloroform, chlorobenzene, dichloroethane or a mixture thereof at a temperature in the range of room
 15 temperature and reflux temperature of the solvent employed for a period in the range of 0.5 to 16 h.

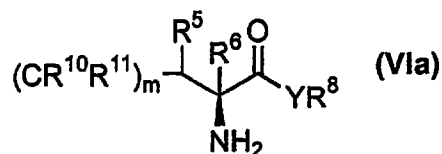
ii. Decomposing the arylalkyl diazo acetate of the formula (Va) to obtain a compound of formula (III) where m is 0, R⁶ is hydrogen, R⁷ is as defined
 20 earlier excluding hydrogen and all other symbols are as defined earlier in the presence of a catalyst selected from Rh(II)acetate, salt/complex of Cu(I) or Rh(II) in the presence of an alcohol of the formula R⁷OH where R⁷ is as defined above.

iii. Reduction of the compound of formula (III) to yield a compound of formula (I) where m is 0, R⁶ is hydrogen, R⁷ is as defined earlier excluding
 25 hydrogen and all other symbols are as defined earlier is carried out in the presence of gaseous hydrogen and a catalyst selected from Pd/C, Rh/C, Pt/C, Raney nickel or a mixture thereof, a solvent selected from dioxane, acetic acid or ethyl acetate at a pressure between atmospheric pressure and 80 psi. The catalyst used is preferably 5-

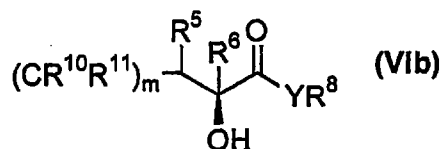
10% Pd/C and the amount of catalyst used is in the range of 1-50% w/w. The hydrogenation can also be carried out using ammonium formate, cyclohex-1,4-diene type of hydrogen donor under pd/c conditions using a solvent selected from methanol, ethanol or ethyl acetate. Alternatively, the reduction can also be carried out by employing metal solvent reduction like magnesium, iron, tin, samarium or sodium amalgam in alcohol like methanol, ethanol or propanol preferably methanol.

or

e. i. Diazotization of the compound of formula (VIa)

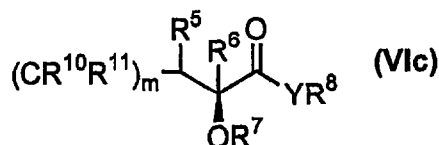


10 where m is 0, $\text{R}^5 = \text{R}^6 = \text{R}^8 = \text{H}$ and all other symbols are as defined above to a compound of formula (VIb)



where m is 0, $\text{R}^5 = \text{R}^6 = \text{R}^8 = \text{H}$, Y is oxygen and all other symbols are as defined above is carried out in the presence of diazotizing agent selected from sodium nitrite, isoamyl nitrite, potassium nitrite or ammonium nitrite under aqueous acidic conditions using acids selected from sulfuric acid, HCl or acetic acid, in an organic solvent selected from alcohols like methanol, ethanol or propanol; 1,4-dioxane, THF or acetone.

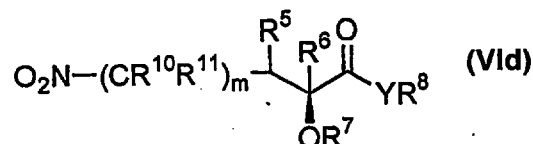
ii. One pot esterification and etherification of compound of formula (VIb) to a compound of formula (VIc)



where m is 0, $\text{R}^5 = \text{R}^6 = \text{H}$, Y is oxygen and all other symbols are as defined above is carried by initial di deprotonation of (VIb) using a base selected from NaH, KH or KOH, in presence of a solvent selected from toluene, benzene, diethylether, THF, DMF, DME or HMPA, followed by treatment with an alkylating agent selected from

alkyl halide like ethyl iodide or methyl iodide; $\text{Et}_3\text{O}^+\text{BF}_4^-$, $\text{Me}_3\text{O}^+\text{BF}_4^-$, dialkylsulfate like dimethyl sulfate or diethyl sulfate at a temperature in the range of 0 °C to 100 °C.

- iii. Nitration of the compound of formula (VIc) to a compound of
5 formula (VIId)

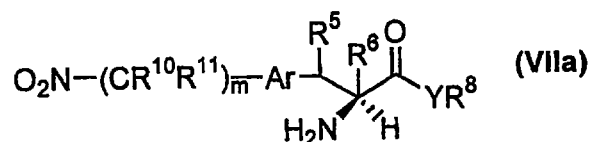


where m is 0, $\text{R}^5 = \text{R}^6 = \text{H}$, Y is oxygen and all other symbols are as defined above is carried out using a nitrating agent selected from fuming nitric acid, N_2O_5 , a mixture of conc. Nitric acid and conc. Sulfuric acid or a mixture of nitric acid and acetic
10 anhydride in the presence of a solvent or under neat condition at a temperature in the range of -10°C to room temperature for a period in the range of 0.5 to 4 h.

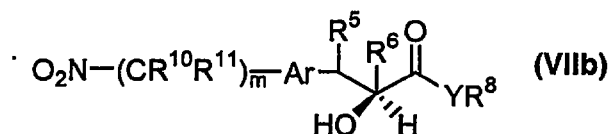
- iv. Reduction of the compound of formula (VIId) to a compound of formula (I) in its enantiomerically pure form where m is 0, $\text{R}^5 = \text{R}^6 = \text{H}$, Y is oxygen and all other symbols are as defined above is carried out in the presence of gaseous
15 hydrogen and a catalyst selected from Pd/C, Rh/C, Pt/C, Raney nickel or a mixture thereof preferably 5-10 % Pd/C and a solvent selected from such as dioxane, acetic acid, ethyl acetate or a mixture thereof. The reaction is carried out at a pressure between atmospheric pressure and 80 psi. The amount of catalyst used is in the range of 1-50 % w/w. Alternatively, the reduction can also be carried out by employing
20 metal solvent reduction like magnesium, iron, tin, samarium or sodium amalgam in alcohol like methanol, ethanol or propanol preferably methanol.

or

- f i. Diazotization of the compound of formula (VIIa)

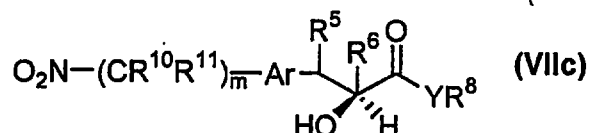


- 25 where m is 0, $\text{R}^1 = \text{R}^2 = \text{H}$ and all other symbols are as defined earlier to a compound of formula (VII b)



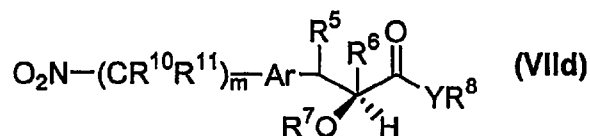
where m is 0, $\text{R}^1 = \text{R}^2 = \text{H}$ and all other symbols are as defined earlier is carried out in the presence of a diazotizing agent selected from sodium nitrite, isoamyl nitrite, potassium nitrite or ammonium nitrite under aqueous acidic conditions using an acid selected from sulfuric acid, hydrochloric acid or acetic acid, in presence of an optional co solvent like an alcohol selected from methanol, ethanol or propanol; ether selected from 1,4-dioxane or THF; ketones selected from acetone or methyl ethyl ketone.

iii. Esterification of the compound of the formula (VII b) to a compound of formula (VII c)



where m is 0, $\text{R}^1 = \text{R}^2 = \text{H}$ and all other symbols are as defined earlier is carried out in the presence of an alcohol $\text{R}^8\text{-OH}$ where R^8 represents lower alkyl groups like methyl, ethyl, propyl, isopropyl, n-butyl or t-butyl and a catalyst like conc. sulfuric acid, dry HCl or $\text{BF}_3\text{-OEt}_2$ at reflux temperature of the alcohol employed. Alternatively reagents like diazomethane, $\text{Et}_3\text{O}^+\text{BF}_4^-$ or $\text{Me}_3\text{O}^+\text{BF}_4^-$ can be used for esterification.

iv. Selective O-alkylation of the compound of formula (VIIc) to the compound of formula (VIId)



where m is 0, $\text{R}^1 = \text{R}^2 = \text{H}$, Y is oxygen and all other symbols are as defined earlier is carried out in the presence of an alkylating agents selected from an alkyl sulfate like diethyl sulfate or dimethyl sulfate; alkyl halides like ethyl iodide, methyl iodide, n-propyl iodide, n-propyl bromide or isopropyl iodide, in a solvent selected from a hydrocarbon like toluene or benzene; acetonitrile, tetrahydro furan, dimethyl

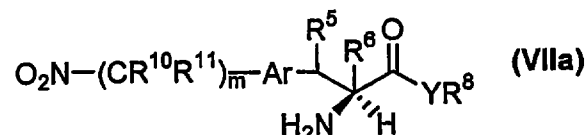
formamide or dimethyl sulfoxide, in the presence of molecular sieves and an alkali base selected from sodium carbonate, potassium carbonate, cesium carbonate, sodium methoxide, sodium hydride, potassium hydride, sodium or potassium hydroxide. Heavy metal oxides selected from Ag_2O , PbO or HgO are of particular
 5 use to carry out alkylation when alkyl halides are used as alkylation reagent. Phase transfer catalysts selected from tetraalkylammonium hydroxide or tetraalkylammonium halides such as tetrabutylammonium chloride or tetrabutylammonium bromide can also be employed.

v. Reduction of compound of the formula (VII d) to a compound of
 10 formula (I) where m is 0, $R^1 = R^2 = \text{H}$, Y is oxygen and all other symbols are as defined earlier, is carried out in the presence of gaseous hydrogen or hydrogen donors selected from ammonium formate or cyclohex-1,4-diene and a catalyst selected from Pd/C , Rh/C , Pt/C , Raney nickel or a mixture thereof in a solvent selected from methanol, ethanol, dioxane, acetic acid or ethyl acetate at a pressure between
 15 atmospheric pressure and 80 psi. The catalyst used is preferably 5-10 % Pd/C and the amount of catalyst used in the range of 1-50 % w/w. Alternatively, the reduction can also be carried out by employing metal solvent reduction like magnesium, iron, tin, samarium or sodium amalgam in alcohol like methanol, ethanol or propanol preferably methanol.

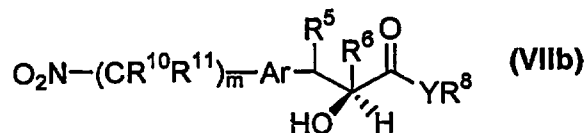
20

or

g i. Diazotization of the compound of formula (VIIa)



where m is 0, $R^1 = R^2 = \text{H}$ and all other symbols are as defined earlier to a compound of formula (VII b)

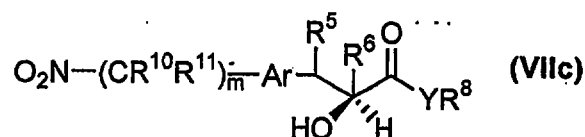


25

where m is 0, $R^1 = R^2 = \text{H}$ and all other symbols are as defined earlier is carried out in the presence of a diazotizing agent selected from sodium nitrite, isoamyl nitrite,

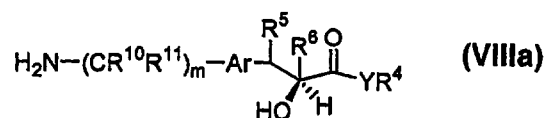
potassium nitrite or ammonium nitrite under aqueous acidic conditions using an acid selected from sulfuric acid, hydrochloric acid or acetic acid, in presence of an optional co solvent like an alcohol selected from methanol, ethanol or propanol; ether selected from 1,4-dioxane or THF; ketones selected from acetone or methyl ethyl ketone.

iii. Esterification of the compound of the formula (VII b) to a compound of formula (VII c)



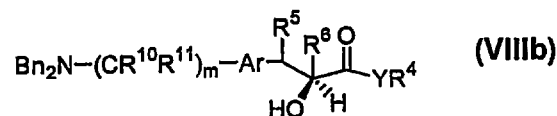
where m is 0, $\text{R}^1 = \text{R}^2 = \text{H}$ and all other symbols are as defined earlier is carried out in the presence of an alcohol $\text{R}^8\text{-OH}$ where R^8 represents lower alkyl groups like methyl, ethyl, propyl, isopropyl, n-butyl or t-butyl and a catalyst like conc. sulfuric acid, dry HCl or $\text{BF}_3\text{-OEt}_2$ at reflux temperature of the alcohol employed. Alternatively reagents like diazomethane, $\text{Et}_3\text{O}^+\text{BF}_4^-$ or $\text{Me}_3\text{O}^+\text{BF}_4^-$ can be used for esterification.

iv. Reduction of compound of the formula (VIIc) to a compound of formula (VIIIa)



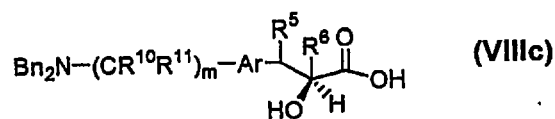
where m is 0, $\text{R}^1 = \text{R}^2 = \text{H}$ and all other symbols are as defined earlier, is carried out in the presence of gaseous hydrogen or hydrogen donors selected from ammonium formate or cyclohex-1,4-diene and a catalyst selected from Pd/C, Rh/C, Pt/C, Raney nickel or a mixture thereof in a solvent selected from methanol, ethanol, dioxane, acetic acid or ethyl acetate at a pressure between atmospheric pressure and 80 psi. The catalyst used is preferably 5-10 % Pd/C and the amount of catalyst used in the range of 1-50 % w/w. Alternatively, the reduction can also be carried out by employing metal solvent reduction like magnesium, iron, tin, samarium or sodium amalgam in alcohol like methanol, ethanol or propanol preferably methanol.

v. N,N-dibenzylation of the compound of formula (VIIIa) to the compound of formula (VIIIb)



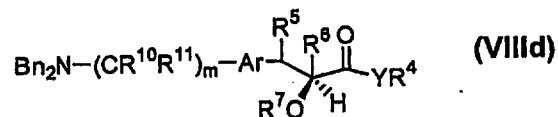
where m is 0, $\text{R}^1 = \text{R}^2 = \text{H}$ and all other symbols are as defined earlier, is carried out by treating with an alkylating agent selected from benzyl halides like benzyl bromide or benzyl chloride in a solvent selected from a hydrocarbon like toluene or benzene or acetonitrile, tetrahydro furan, dimethyl formamide, dimethyl sulfoxide, in the presence of an alkali base selected from sodium carbonate, potassium carbonate, sodium or potassium hydroxide in the absence or presence of a phase transfer catalyst selected from tetraalkylammonium hydroxide or a tetraalkylammonium halide like tetrabutylammonium chloride or tetrabutylammonium bromide at a temperature in the range of room temperature to the reflux temperature of the solvent employed.

vi. Hydrolysis of the compound of the formula (VIIIb) to the compound of formula (VIIIc)



where m is 0, $\text{R}^1 = \text{R}^2 = \text{H}$ and all other symbols are as defined earlier, is carried out using an aqueous alkali metal base selected from lithium carbonate, sodium carbonate, potassium carbonate, potassium bicarbonate, lithium hydroxide, sodium hydroxide or potassium hydroxide, in a suitable co-solvent selected from methanol, ethanol, THF or a mixture thereof at a temperature in the range of 0 °C to 80 °C for a period in the range of 0.5 h to 24 h, preferably 0.5 h to 3-4 h.

vii. One pot esterification and etherification of the compound of the formula (VIIIc) to the compound of formula (VIIId)



where m is 0, $\text{R}^1 = \text{R}^2 = \text{H}$, $\text{R}^5 = \text{R}^6$ and is as defined above and all other symbols are as defined earlier, is carried out by treating with a base selected from sodium hydride, potassium hydride, sodium hydroxide, potassium hydroxide, sodium

carbonate or potassium carbonate, in a solvent selected from a hydrocarbon like toluene or benzene; dialkyl ethers like diethyl ether or tetrahydro furan; dimethyl formamide or HMPA followed by treatment with an alkyl halide selected from ethyl iodide, methyl iodide, n-propyl iodide, n-propyl bromide or isopropyl iodide; an
5 alkyl sulfate like diethyl sulfate or dimethyl sulfate; $\text{Et}_3\text{O}^+\text{BF}_4^-$ or $\text{Me}_3\text{O}^+\text{BF}_4^-$ at a temperature in the range of 0 °C to 80 °C for a period in the range of 2 h to 20 h.

viii. Debenzylation of the compound of the formula (VIIIId) to the compound of formula (I) where m is 0, $\text{R}^1 = \text{R}^2 = \text{H}$, $\text{R}^5 = \text{R}^6$ and is as defined above and all other symbols are as defined earlier, is carried out in the presence of gaseous
10 hydrogen or hydrogen donors selected from ammonium formate or cyclohex-1,4-diene and a catalyst selected from Pd/C, Rh/C, Pt/C, Raney nickel or a mixture thereof in the presence of a solvent selected from methanol, ethanol, dioxane, acetic acid or ethyl acetate. A pressure between atmospheric pressure and 80 psi may be employed. The catalyst used is preferably 5-10 % Pd/C and the amount of catalyst
15 used in the range of 1-50 % w/w.