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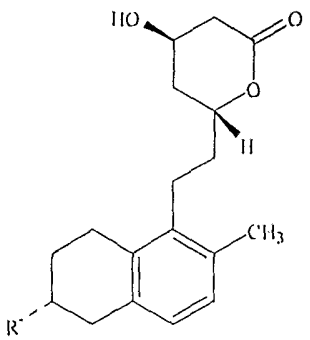
(54) Title: NOVEL STATIN DERIVATIVES



(I)

(57) Abstract: The present invention provides novel statin derivatives and a facile process for preparation thereof selected from a group consisting of a compound of formula (I), wherein R is selected from a group consisting of -OH, -OR_1, $OCOR_1$, -OCHO, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, alkylaryl, heteroaryl, aralkyl, heterocycle having ring size between 3 to 6, -CN, -COOH, -$COOR_1$, -$CONHR_1$, -$CONR_1R_2$, -NH_2, -NHR_1, -NR_1R_2 halogen, -SH and -SR_1; wherein R_1 and R_2 are independently selected from C_1-C_6 alkyl, alkylaryl, heteroaryl, aralkyl, heterocycle having ring size between 3 to 6, C_2-C_6 alkenyl and C_2-C_6 alkynyl, or R_1 and R_2 together with the carbon atom to which they are attached from a heterocycle with a ring size from 3 to 6, ------ represents either α or β-susbstituent, and pharmaceutically acceptable salt thereof. The compounds have anti-hyperlipidimic anti-hypercholesterolemic and antiinflammatory activity.

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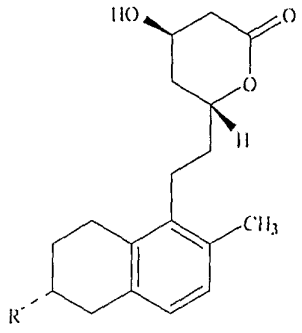
NOVEL STATIN DERIVATIVES

The present invention provides a novel statin derivative selected from a group consisting of a compound of formula I,



Formula I

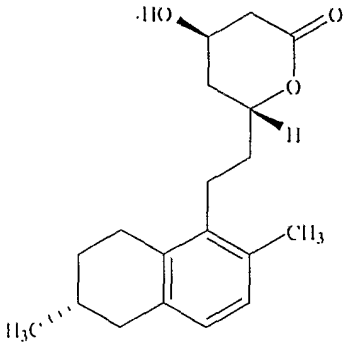
wherein R is selected from a group consisting of –OH, -OR_1, -$OCOR_1$, -OCHO, C_1-C_6 alkyl, C_2-C_6 alkeny, C_2-C_6 alkynyl, alkylaryl, heteroaryl, aralkyl, heterocycle having ring size between 3 to 6, , -CN, -COOH, -$COOR_1$, -$CONHR_1$, -$CONR_1R_2$, -NH_2, -NHR_1, -NR_1R_2, halogen, -SH and -SR_1;

wherein R_1 and R_2 are independently selected from C_1-C_6 alkyl, alkylaryl, heteroaryl, aralkyl, heterocycle having ring size between 3 to 6, C_2-C_6 alkenyl and C_2-C_6 alkynyl, or R_1 and R_2 together with the carbon atom to which they are attached form a heterocycle with a ring size from 3 to 6,

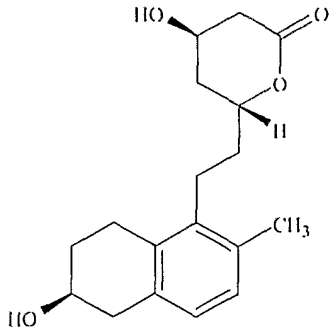
------ represents either α-substituent or β-susbstituent,

and pharmaceutically acceptable salt thereof.

In one aspect the present invention provides a novel statin derivative:



Formula I-A



Formula I-B

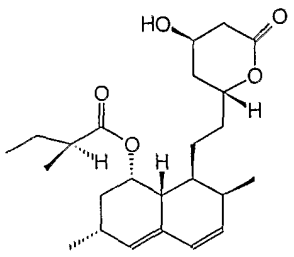
selected from a compound of formula I-A, a compound of formula I-B and pharmaceutically acceptable salt thereof.

The present invention also provides a facile process for preparation of these novel statin derivatives.

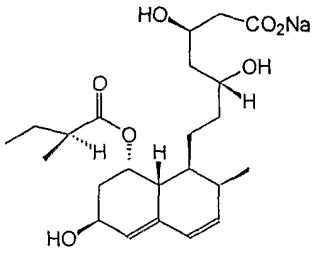
BACKGROUND OF THE INVENTION

Statins are well established drugs for the treatment of hyperlipidemia and are known as cholesterol lowering drugs. Statins reduce cholesterol through competitive inhibition of HMG-CoA reductase, the key enzyme which is involved in the biosynthesis of cholesterol.

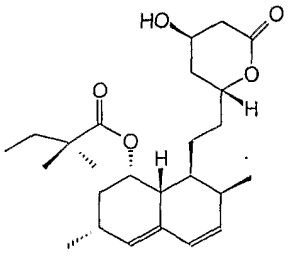
Several members of this class are approved for clinical use in the management of hypercholesterolemia. The first members of HMG-CoA reductase inhibitors, being novel fungal metabolites like lovastatin (II) and pravastatin sodium (III), while simvastatin (IV) is a semisynthetic drug prepared using lovastatin. These were followed by a number of close synthetic analogues like fluvastatin (V), atorvastatin (VI) and rosuvastatin (VII).



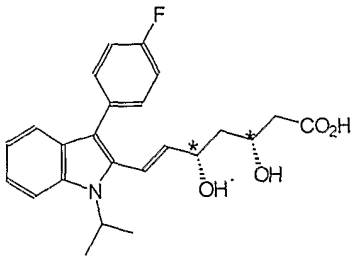
Lovastatin (II)



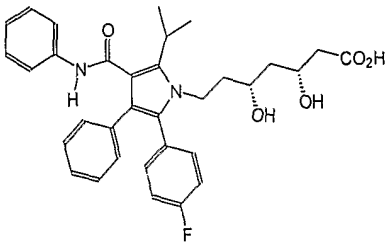
Pravastatin sodium (III)



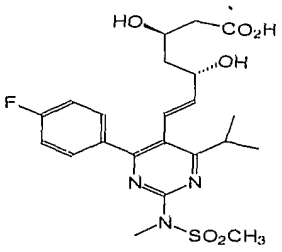
Simvastatin (IV)



Fluvastatin (V)



Atorvastatin (VI)



Rosuvastatin (VII)

The use of statins as lipid-lowering agents has lead to remarkable changes in the treatment and prevention of ischemic heart disease. Results of large clinical trials of patients with ischemic heart disease have demonstrated that statins reduce inflammatory markers such as C-reactive protein, an independent risk factor in the disease.

More interestingly the statin class have been reported to posses several beneficial effects beyond their lipid-lowering effects. It is evident that statins exhibit pleiotropic effects that are independent of their lipid lowering action.

Simvastatin is currently in phase III clinical trials for the treatment of dementia and Alzheimers disease. It is also demonstrated as a potential compound in the treatment of sepsis (Circulation 2004, 109(21), 2560), treatment against relapsing-remitting multiple sclerosis (Lancet 2004,363 (9241), 1607), prevention of brain infarct (Stroke, 2004, 35(6), e211), in the treatment of HIV infection (J. Exp. Med., 2004, 200(4), 541).

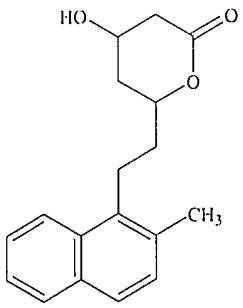
Statins also promote bone formation by affecting the expression of the bone morphogenic protein-2 (BMP-2) thus indicating for the treatment of bone fractures and osteoporosis (Science 199, 286, 1946; Biochem. BiophysRes Commun, 2000, 271, 688). The other

potential therapeutic benefits are in the treatment of glaucoma (Arc Ophthalmol 2004, 122(6), 822), disorders like rheumatoid arthritis (Lancet 2004, 363(9426), 2015) thus exhibiting anti-inflammatory effects apart from their action on HMG-CoA reductase inhibitory activity.

Statins are also found to reduce the risk of colorectal cancer (Scrip, 2004, 2963, June 23rd, p. 30) and improvement of erectile dysfunction in men with hypercholesterolemia (J Urol 2004, 172(1), 255).

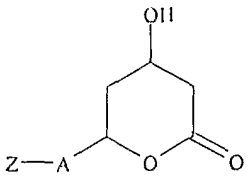
Number of positive beneficial effects of statins makes an attractive area for continued research to find new statin derivatives and their biological functions.

New statin analogues, viz., mevastatin derivatives as cholesterol lowering agents are disclosed by Asahi Denka in Japanese Patent No. 2004 115380. Solistatin (VIII) and statans with cholesterol lowering effect are disclosed by Novozymes in a PCT publication No. WO 03/048148.

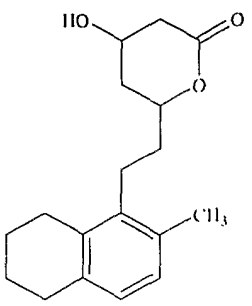


Solistatin (VIII)

United States Patent Number 4255444 (referred to as the '444 patent hereinafter) teaches 4-hydroxy-2-pyrone compounds of a formula IX, including amongst a large number of compounds, a compound of formula IX' and that these can be prepared by cyclization of the corresponding 3,5-dihydroxypentanoic ester derivative under alkaline conditions:



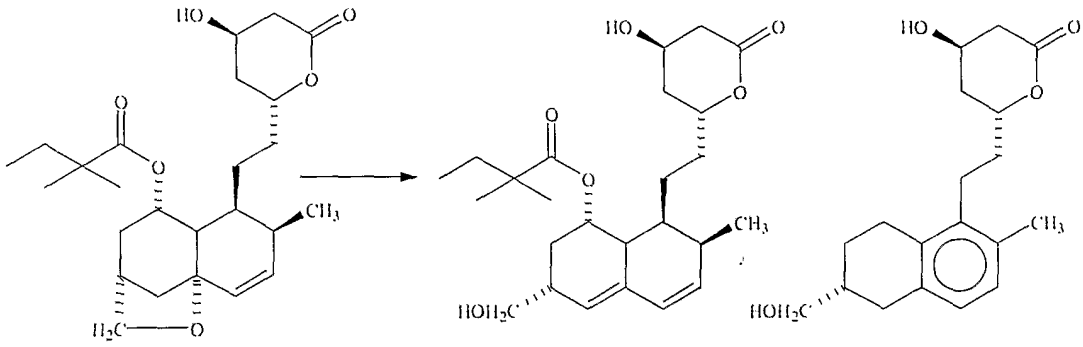
Formula IX



Formula IX'

wherein A represents an alkylene group optionally alkyl substituted or an alkenylene group and Z represents a substituted or unsusbstituted aryl or aryloxy group.

Lee et al. (J. Org. Chem., 1992, 57, 1966) have reported synthesis of 6α-hydroxymethyl metabolite of simvastatin, a compound of formula X, via the treatment of cyclic ether intermediate, a compound of formula XI with 48% HF acid, wherein a compound of formula XII is formed as a by product in trace.

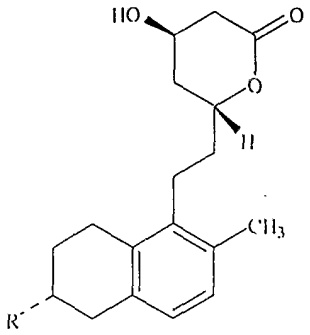


Formula XI Formula X Formula XII

It further teaches that the structural feature of compound of formula XI facilitates the formation of tertiary allylic carbocation upon protonation of the strained ether oxygen attached to the tertiary carbon, thus furnishing trace amount of compound of formula XII.

OBJECT OF THE INVENTION

We have found novel statin derivative, a compound of formula I and pharmaceutically acceptable salt thereof:



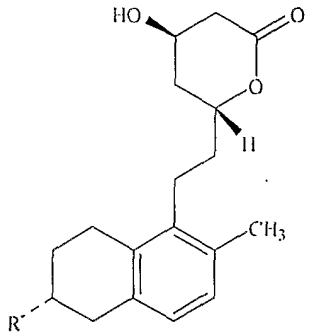
Formula I

and a facile process for preparation thereof.

The compounds are useful antihyperlipedemic compounds as demonstrated by their ability to inhibit cholesterol biosynthesis by inhibiting the 3-hydroxy-3-methyl-glutaryl-CoA or HMG-CoA reductase enzyme.

SUMMARY OF THE INVENTION

The present invention provides a novel statin derivative selected from a group consisting of a compound of formula I,



Formula I

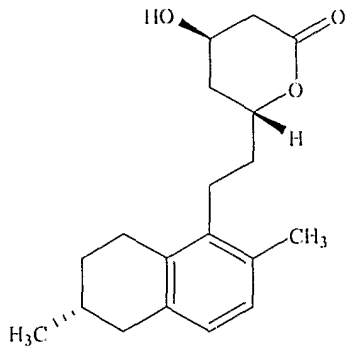
wherein R is selected from a group consisting of –OH, -OR_1, -$OCOR_1$, -OCHO, C_1-C_6 alkyl, C_2-C_6 alkeny, C_2-C_6 alkynyl, alkylaryl, heteroaryl, aralkyl, heterocycle having ring size between 3 to 6, , -CN, -COOH, -$COOR_1$, -$CONHR_1$, -$CONR_1R_2$, -NH_2, -NHR_1, -NR_1R_2, halogen, -SH and -SR_1;

wherein R_1 and R_2 are independently selected from C_1-C_6 alkyl, alkylaryl, heteroaryl, aralkyl, heterocycle having ring size between 3 to 6, C_2-C_6 alkenyl and C_2-C_6 alkynyl, or R_1 and R_2 together with the carbon atom to which they are attached form a heterocycle with a ring size from 3 to 6,

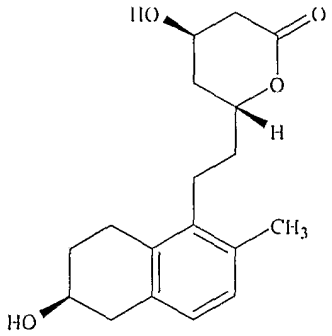
------ represents either α-substituent or β-susbstituent,

and pharmaceutically acceptable salt thereof.

In one aspect the present invention provides a novel statin derivative:



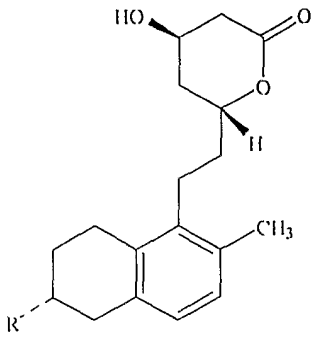
Formula I-A



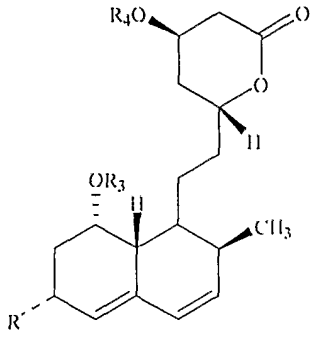
Formula I-B

selected from (4R, 6R)–6[2(2,6(R)-Dimethyl-5,6,7,8-tetrahydronaphthalen-1-yl)ethyl]-4-hydroxytetrahydropyran-2-one, a compound of formula I-A, and (4R, 6R)–6[2(6(S)-Hydroxy-2-methyl-5,6,7,8-tetrahydronaphthalen-1-yl)ethyl]-4- hydroxytetrahydropyran-2-one, a compound of formula I-B and pharmaceutically acceptable salt thereof.

In one aspect the present invention provides a process for preparation of a novel statin derivative selected from a group consisting of a compound of formula I and pharmaceutically acceptable salt thereof, comprising subjecting a compound of formula I':



Formula I



Formula I'

wherein,

R is selected from a group consisting of –OH, -OR_1, -$OCOR_1$, -OCHO, C_1-C_6 alkyl, C_2-C_6 alkeny, C_2-C_6 alkynyl, alkylaryl, heteroaryl, aralkyl, heterocycle having ring size between 3 to 6, , -CN, -COOH, -$COOR_1$, -$CONHR_1$, -$CONR_1R_2$, -NH_2, -NHR_1, -NR_1R_2, halogen, -SH and -SR_1;

wherein R_1 and R_2 are independently selected from C_1-C_6 alkyl, alkylaryl, heteroaryl, aralkyl, heterocycle having ring size between 3 to 6, C_2-C_6 alkenyl and C_2-C_6 alkynyl, or R_1 and R_2 together with the carbon atom to which they are attached form a heterocycle with a ring size from 3 to 6;

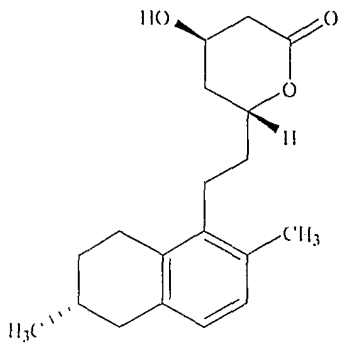
R_3 is selected from group consisting of H, -$COCH(CH_3)CH_2CH_3$ and -$COC(CH_3)_2CH_2CH_3$;

R_4 is selected from group consisting of H, -CH_2OCH_3, -$CH_2OCH_2CH_2OCH_3$, -$CH_2C_6H_5$, -$CH_2OCH_2C_6H_5$, -$CH_2CH_2OCH_3$, -$CH_2C_6H_4OCH_3$, o-$NO_2C_6H_4CH_2$-, allyl, propargyl, tetrahydropyranyl, 1-methoxycyclohexyl, 1-methoxycyclopentyl, 2-methoxy-2-propyl and –methyl-heteroaryl;

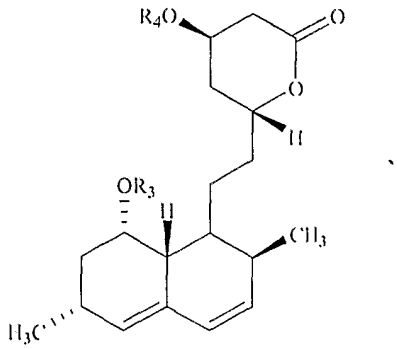
------ represents either α-substituent or β-susbstituent,

to treatment with a silyl compound of formula $(R_5)_3$-Si-L, a compound of formula XIV, wherein R_5 is same or different and selected from a group consisting of C_1 to C_4 alkyl, which may be linear or branched and phenyl; L is selected from a group consisting of chloro, bromo, iodo and trifluoromethanesulfonyl such that the treatment results in conversion of a compound of formula I' into a compound of formula I.

In one aspect the present invention provides a process for preparation of a novel statin derivative, a compound of formula I-A and pharmaceutically acceptable salt thereof comprising subjecting a compound of formula XIII-A:



Formula I-A



Formula XIII-A

wherein,

R_3 is selected from group consisting of H, $-COCH(CH_3)CH_2CH_3$ and $-COC(CH_3)_2CH_2CH_3$;

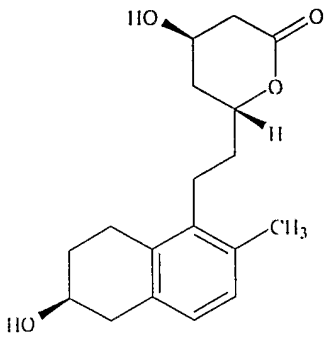
R_4 is selected from group consisting of H, $-CH_2OCH_3$, $-CH_2OCH_2CH_2OCH_3$, $-CH_2C_6H_5$, $-CH_2OCH_2C_6H_5$, $-CH_2CH_2OCH_3$, $-CH_2C_6H_4OCH_3$, $o\text{-}NO_2C_6H_4CH_2$-, allyl, propargyl, tetrahydropyranyl, 1-methoxycyclohexyl, 1-methoxycyclopentyl, 2-methoxy-2-propyl and –methyl-heteroaryl

to treatment with a silyl compound of formula $(R_5)_3$-Si-L, a compound of formula XIV,

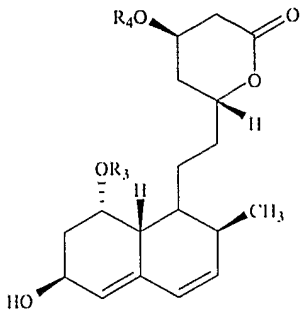
wherein,

R_5 is same or different and selected from a group consisting of C_1-C_4 alkyl, which may be linear or branched and phenyl; L is selected from a group consisting of chloro, bromo, iodo and trifluoromethanesulfonyl such that the treatment results in conversion of a compound of formula XIII-A into a compound of formula I-A.

In another aspect the present invention provides a process for preparation of a novel statin derivative, a compound of formula I-B and pharmaceutically acceptable salt thereof comprising subjecting a compound of formula XIII-B:



Formula I-B



Formula XIII-B

wherein,

R_3 is selected from group consisting of H, $-COCH(CH_3)CH_2CH_3$ and $-COC(CH_3)_2CH_2CH_3$;

R_4 is selected from group consisting of H, $-CH_2OCH_3$, $-CH_2OCH_2CH_2OCH_3$, $-CH_2C_6H_5$, $-CH_2OCH_2C_6H_5$, $-CH_2CH_2OCH_3$, $-CH_2C_6H_4OCH_3$, o-$NO_2C_6H_4CH_2$-, allyl, propargyl, tetrahydropyranyl, 1-methoxycyclohexyl, 1-methoxycyclopentyl, 2-methoxy-2-propyl and –methyl-heteroaryl;

to treatment with a silyl compound of formula $(R_5)_3$-Si-L, a compound of formula XIV, wherein,

R_5 is same or different and selected from a group consisting of C_1-C_4 alkyl, which may be linear or branched and phenyl; L is selected from a group consisting of chloro, bromo, iodo and trifluoromethanesulfonyl such that the treatment results in conversion of a compound of formula XIII-B into a compound of formula I-B.

DESCRIPTION OF THE INVENTION

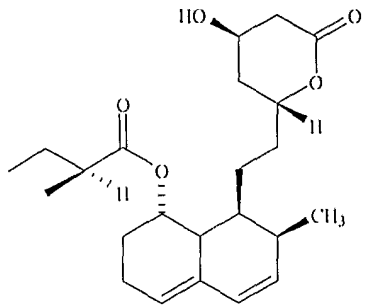
Throughout the specification:

the ''''''''' bond denotes α-substituent ,

the ▬▬ bond denotes the β-substituent and

It is of interest to find new novel agents using the available well studied pharmacophores with minimal side effects. In this respect the natural/semi-synthetic products like

lovastatin (II), pravastatin (III), simvastatin (IV) and mevastatin (XV) are used as therapeutic agents more than a decade in the management of hyperlipidemia.

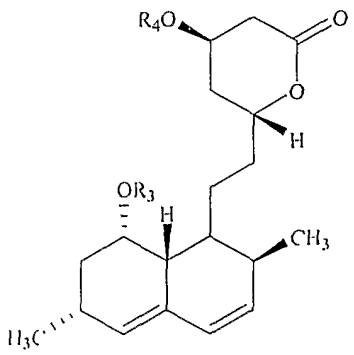


Mevastatin (XV)

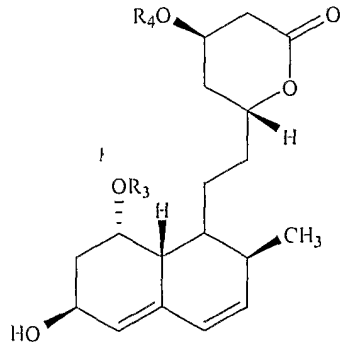
Hence, the use of well established pharmacophore structures derived from natural sources is of immense value to find novel agents.

The structural frame works of statins obtained from fungal origin has the desired side chain of dihydroxyheptanoic acid with defined chirality. However the bicyclic motif modifications can be envisaged to make novel analogs, as Lovastatin as well as all the synthetic analogues III to VII differ in their functionalities, and each of these exhibit unique HMG-CoA inhibitory activity.

In our endeavour to identify novel compounds with biological activity we have studied the utilization of readily available members of statins, for example, compounds of the



Formula XIII-A



Formula XIII-B

formulae XIII-A and XIII-B and derivatives thereof to transform the bicyclic moiety for further functionalization, wherein R_3 and R_4 are as defined above.

As used herein 'alkyl' means an aliphatic hydrocarbon group which may be straight, branched or cyclic having 1 to 6 carbon atoms in the chain. Exemplary alkyl groups include methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, t-butyl, n-pentyl, cyclohexyl cyclopentyl and the like.

As used herein 'alkenyl' means an aliphatic hydrocarbon group containing a carbon-carbon double bond and which may be straight, branched or cyclic having 2 to 6 carbon atoms in the chain. Exemplary alkenyl groups include ethenyl, propenyl, n-butenyl, i-butenyl, 3-methylbut-2-enyl,n-pentenyl.

As used herein 'alkynyl' means an aliphatic hydrocarbon group containing a carbon-carbon triple bond and which may be straight or branched having 2 to 6 carbon atoms in the chain. Exemplary alkynyl groups include ethynyl, propynyl, n-butynyl, 2-butynyl, 3-methylbutynyl, n-pentynyl.

As used herein 'aralkyl' means an aryl-alkyl group wherein the alkyl are as herein described and aryl means an aromatic monocyclic or multicyclic ring system of 6 to 10 carbon atoms like phenyl or naphthyl. Exemplary aralkyl groups include benzyl, 2-phenethyl and naphthalenemethyl and the like.

As used herein 'alkylaryl' means an alkyl-aryl group, wherein the aryl and alkyl are as defined herein. Exemplary 'alkylaryl' groups include tolyl.

As used herein 'heterocyle' means ring systems which, in addition to carbon, also contain heteroatoms, such as, for example, nitrogen, oxygen or sulfur. Exemplary heterocycles include piperazinyl, terahydrofuranyl, pyrrolidinyl, imidazolidinyl, thiazolidinyl and the like.

As used herein 'heteroaryl' means aromatic monocyclic or multicyclic ring system which, in addition to carbon, also contain heteroatoms, such as, for example, nitrogen, oxygen or sulfur. Exemplary heteroaryls include benzimidazolyl, imidazolyl, benzoxazolyl, benzothiazolyl, pyrimidinyl, quinolinyl, isoquinolinyl, indolyl, phthazinyl, benzoxazolyl and the like.

As used herein '-methyl-heteroaryl' denotes the moiety $-CH_2$-heteroaryl, wherein heteroaryl may be any heteroaryl group, for example, furyl, thienyl, tetrazolyl, thiazolyl, imidazolyl, benzimidazolyl, quinolinyl and the like.

The ring present in the alkylaryl, heteroaryl, aralkyl or heterocycle may be optionally substituted with one or more halogen, C_1-C_5 alkyl, -OH, -CN, $-NO_2$, $-NH_2$, -COOH, $-CONH_2$, -SH, $-SR_1$, $-NHR_1$, $-NR_1R_2$, $-CONHR_1$, $-CONR_1R_2$, wherein R_1 and R_2 are as defined above.

The ------ bond represents either α-substituent or β-susbstituent, specifying the stereochemistry at that particular carbon atom and does not relate to a racemic mixture of α-substituent and β-susbstituent.

Compound of formula I' on treatment with a silyl compound of formula $(R_5)_3$-Si-L, a compound of formula XIV, for example, trimethylsilyl chloride produced an hitherto unknown aromatic compound, a compound of formula I. The compound of formula I have the structural feature, which could be utilized to make a variety of novel derivatives by chemical or biological functionalizations.

Compounds of formulae XIII-A and XIII-B on treatment with a silyl compound of formula $(R_5)_3$-Si-L, a compound of formula XIV, for example, trimethylsilyl chloride produced an aromatic compound which was characterized as hitherto unknown compounds of formula I-A and I-B, respectively.

In the manufacture of known statins containing pyranone ring, for example, simvastatin (IV) is made by lactonisation of the corresponding hydroxy acid with mineral acids like aqueous hydrochloric acid. In the presence of a mineral acid like HCl acid, the substituent $-OCOC(CH_3)_2CH_2CH_3$ on C-8 atom of the simvastatin ring remains intact. Thereby one can not envisage that the treatment of compounds such as compound of formulae XIII-A or XIII-B which encompass statin like simvastatin, with aqueous hydrochloric acid would lead to compounds like compounds of formula I-A and I-B.

We have obtained novel statin derivatives, a compound of formulae I by facile conversion of compounds of formula I' on treatment with a silyl compound of formula $(R_5)_3$-Si-L, a compound of formula XIV.

We have obtained novel statin derivatives, a compound of formulae I-A and I-B by facile conversion of compounds of formulae XIII-A or XIII-B, which encompass known statins like lovastatin, pravastatin or simvastatin and derivatives thereof, on treatment with a silyl compound of formula $(R_5)_3$-Si-L, a compound of formula XIV.

In one embodiment, a compound of formula XIV, may be selected from trimethyl silyl halide, like trimethylsilyl chloride, t-butyldimethylsilyl halide, diphenylmethylsilyl halide, trimethylsilyl triflate.

Our study in this direction with a view to optimize yields resulted in the identification of additives, the compounds in presence of which the conversion of compounds of formula I' to compound of formula I was facilitated.

In one embodiment the process for preparation of a novel statin derivative, a compound of formula I, by subjecting a compound of formula I' to treatment with a silyl compound such as trimethylsilyl chloride is carried out in presence of an additive, which facilitates this conversion.

In one embodiment the process for preparation of a novel statin derivative, a compound of formula I-A or a compound of formula I-B, by subjecting a compound of formula XIII-A or a compound of formula XIII-B, respectively, to treatment with a silyl compound such as trimethylsilyl chloride is carried out in presence of an additive, which facilitates this conversion.

The additive may be advantageously selected from a group consisting of a metallic halide and a Lewis acid. Examples of a metallic halide are sodium iodide, lithium iodide, potassium iodide, lithium bromide, magnesium chloride and the like. Example of Lewis acid are $AlCl_3$, $TiCl_4$, $BF_3.Et_2O$, $SnCl_4$ and the like. In a preferred embodiment the metallic halide is an alkali earth metal halide or an alkaline earth metal halide, for example, sodium iodide, lithium iodide, potassium iodide, lithium bromide, magnesium chloride and the like.

The reaction of a compound of formula I' (for example, a compound of formula XIII-A or a compound of formulae XIII-B) with a a silyl compound of formula $(R_5)_3$-Si-L, a compound of formula XIV, can be carried out in a suitable inert solvent at a temperature between the range of about -5°C to about 100°C till the desired conversion is achieved. The solvent used may be any neutral solvent, for example, ester such as ethyl acetate, an ether such as tetrahydrofuran, a nitrile such as acetonitrile, amide such as acetamide solvent. In one preferred embodiment, the reaction is carried out in acetonitrile at a temperature between the range of about -5°C to about 30°C.

The compounds of formula I', wherein R_4 is H, R is CH_3 or OH and R_3 is as defined above are known in the art and include statins like lovastatin, simvastatin or pravastatin etc and can be prepared by any method known in the art.

The compounds of formula I', wherein R_4 is H, R is other than CH_3 or OH and R_3 is as defined above can be prepared from known statins like lovastatin, simvastatin or pravastatin etc. by following the known methodologies in synthetic chemistry by conversion of the compound having R as $-CH_3$ or -OH to compounds wherein R is any

other desired substituent, for example the various functionalities like -OR_1, -$OCOR_1$, alkenyl, alkynyl, -COOH, -$CONH_2$, -NH_2, heterocycle, aralkyl etc. could be introduced via a suitable neucleophilic substitution/addition reaction on the mesylate, tosylate, triflate or keto derivative of the hydroxyl function.

The compounds of formula XIII-A or XIII-B, wherein R_4 is H and R_3 is as defined above are known in the art and include statins like lovastatin, simvastatin or pravastatin etc and can be prepared by any method known in the art.

The ether derivatives of formulae I', XIII-A or XIII-B, wherein R_4 is other than H can be prepared from the corresponding compounds of formulae I', XIII-A or XIII-B, respectively, wherein R_4 is H by treatment with a reagent R_4-Z, a compound of formula XVI, in presence of a base, wherein R_4 is selected from a group consisting of -CH_2OCH_3, -$CH_2OCH_2CH_2OCH_3$, -$CH_2C_6H_5$, -$CH_2OCH_2C_6H_5$, -$CH_2CH_2OCH_3$, -$CH_2C_6H_4OCH_3$, o-$NO_2C_6H_4CH_2$-, allyl, propargyl, tetrahydropyranyl, 1-methoxycyclohexyl, 1-methoxycyclopentyl, 2-methoxy-2-propyl and –methyl-heteroaryl; Z is a suitable leaving group such as halide. Any suitable organic or inorganic base, for example, N,N-diisopropylethyl amine, trimethyl amine may be used. The reaction may be advantageously carried out in any non protic solvent such as dichloromethane at about ambient to reflux temperature.

The resultant ether derivatives of formulae I', XIII-A or XIII-B wherein R_4 is other than H can be further subjected to treatment with a silyl compound of formula $(R_5)_3$-Si-L, a compound of formula XIV, such that the treatment results in conversion of the ether derivatives of formulae I', XIII-A or XIII-B into a compound of formulae I, I-A or I-B, respectively.

If desired the ether derivatives, wherein R_4 is other than H, may be isolated and then subjected to further treatment with a compound of formula XIV or it may be formed *in-situ* and converted further to compound of formulae I, I-A or I-B.

Pharmaceutically acceptable salts may be particularly suitable for medical applications, due to their greater solubility in water compared with the starting or base compounds. Said salts usually have a pharmaceutically acceptable anion or cation. Suitable pharmaceutically acceptable basic salts of the compounds of the invention are ammonium salts, alkali metal salts (such as sodium salts and potassium salts) and alkaline earth metal salts (such as magnesium salts and calcium salts). The pharmaceutically acceptable salts of the compounds of the invention can be prepared by reacting the compounds of the invention with alkali metals, whereas alkaline earth metal salts can be obtained directly or by exchange of alkaline metal salts of carboxylate with Ca^{+2}, Mg^{+2} salts in a suitable solvents like in polar protic or polar aprotic solvents like MeOH, EtOH, acetone etc.

The compounds of the present invention are useful in human in particular as anti-hyperlipidemics/antihypercholesterolemic.

There is thus provided as a further aspect of the invention a compounds of the invention and pharmaceutically acceptable salt thereof for use in human, particularly in the treatment of patients with hyperlipidemia, arteriosclerosis, stroke, type-2-diabetes, glaucoma, sepsis, colorectal cancer and potentiation of anticancer activity of cytotoxic agents and HIV.

According to another aspects of the invention, there is provide the use of a compounds of the invention and pharmaceutically acceptable salt thereof for the manufacture of a medicament for the treatment of patients with hyperlipidemia, arteriosclerosis, stroke, type-2-diabetes, glaucoma, sepsis, colorectal cancer and potentiation of anticancer activity of cytotoxic agents and HIV.

In a further aspect, there is provided a method for the treatment of a human or animal subject with an hyperlipidemic, hypercholesterolemic, osteoporosis, glaucoma, or inflammatory condition, which method comprises administering to said human or animal subject an effective amount of a compound selected from, a compound of formula I-A, a compound of formula I-B and pharmaceutically acceptable salt thereof.

As used herein, treating or treatment includes the treating of, for example, a patient inflicted with a disease or condition, as well as the prevention, prophylaxis, or protective treatment of a patient.

The compounds of the invention have potentially beneficial anti-hyperlipidemic effects, which are demonstrated by, for example, their ability to inhibit cholesterol biosynthesis via inhibition of HMG-CoA reductase enzyme. The compounds of the invention are useful in the treatment of hyperlipidemia, arteriosclerosis, stroke, type-2-diabetes, glaucoma, sepsis, colorectal cancer and potentiation of anticancer activity of cytotoxic agents and HIV.

The treatment includes reducing and/or maintaining the symptoms of a subject who is inflicted with or is susceptible to the conditions that are treatable with the compounds of the invention. The treatment also includes inhibiting and/or slowing the symptoms of a subject who is inflicted with the conditions or is susceptible to it. Treatment also includes treating a subject susceptible to or predisposed to developing the conditions, which could include patients in whom the conditions has not yet presented as well as patients in whom the disease has been successfully treated but could redevelop or reoccur.

The compounds of the invention can be administered orally, intravenously, or by any other conventional means and they are preferably formulated with carriers or diluents. The posology would be dependent on age, weight, severity of the symptoms. The daily dosage for adults is generally from 0.5 mg to 500 mg/day, can be administered in divided doses.

The pharmaceutical formulation of the compounds of the invention is desirably provided in a form suitable for adsorption in gastrointestinal tract. Tablets and capsules for oral administration are normally in unit dosage form and contain conventional vehicles, for example, lactose, cornstarch, microcrystalline cellulose, calcium/magnesium silicate, croscarmellose sodium, carboxymethyl cellulose, silicon dioxide, povidone, hydroxypropylmethyl cellulose, magnesium stearate or talc. Tablets may be coated by

any method known in the art. The compounds of the present invention can be incorporated into a food product or a liquid.

Liquid formulations for administration include sterile aqueous or non-aqueous solutions, suspensions and emulsions or may be in dried form for redissolution in water or another suitable vehicle. The liquid compositions may also include conventional additives like binders, viscosity enhancers, buffers, preservatives, chelating agents, sweetening, flavoring and coloring agents, and the like. Non-aqueous solvents include alcohols, propylene glycol, polyethylene glycol, vegetable oils such as olive oil, and organic esters, such as ethyl oleate.

Injectable preparations may be provided in unit dosage ampoules with added preservatives. These preparations may be in form of suspensions, solutions or emulsions in oily or aqueous vehicles and may contain conventional additives.

Formulations suitable for rectal administration are preferably presented as unit dose suppositories, with a solid based carrier such as cocoa butter, and may include a salicylate.

The pharmaceutical formulation of the invention preferably contain not les than 0.1% by weight, more preferably from 10% to 70% by weight of the active ingredient, depending upon the rote of administration. A unit dosage form of the formulation preferably contains from 5 mg to 500 mg of the active ingredient.

The present invention provides a pharmaceutical composition comprising as active ingredient an effective amount of a compound of formula I or pharmaceutically acceptable salt thereof; and a pharmaceutically acceptable carrier or excipient.

The present invention provides a pharmaceutical anti-hyperlipidimic composition comprising as active ingredient an effective amount of a compound of formula selected from (4R, 6R)–6[2(2,6(R)-Dimethyl-5,6,7,8-tetrahydronaphthalen-1-yl)ethyl]-4-

hydroxytetrahydropyran-2-one, a compound of formula I-A, and (4R, 6R)-6[2(6(S)-Hydroxy-2-methyl-5,6,7,8-tetrahydronaphthalen-1-yl)ethyl]-4- hydroxytetrahydropyran-2-one, a compound of formula I-B and pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier or excipient.

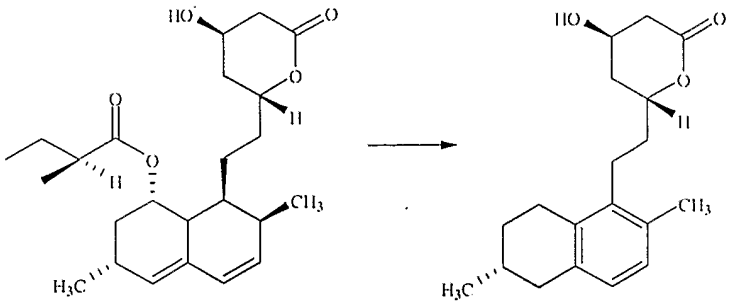
The present invention provides a method of treating a subject suffering from a condition selected from hyperlipidemia, arteriosclerosis, stroke, type-2-diabetes, glaucoma, sepsis, colorectal cancer comprising a step of administering to said subject suffering from said condition, a therapeutically effective amount of a compound selected from a compound of formula I-A, a compound of formula I-B or a pharmaceutically acceptable salt thereof.

The present invention provides a method of treating a subject suffering from a condition selected from hyperlipidemia, arteriosclerosis, stroke, type-2-diabetes, glaucoma, sepsis, colorectal cancer comprising a step of administering to said subject suffering from said condition, a therapeutically effective amount of a compound of formula I or a pharmaceutically acceptable salt thereof.

The invention is further illustrated but not restricted by the description in the following examples

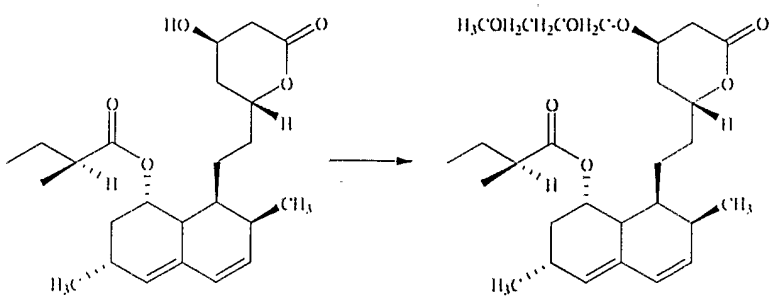
EXAMPLES

Example I: Preparation of compound of formula I-A from lovastatin (a compound of formula XIII-A, wherein R_3 is $-COCH(CH_3)CH_2CH_3$ and R_4 is H)



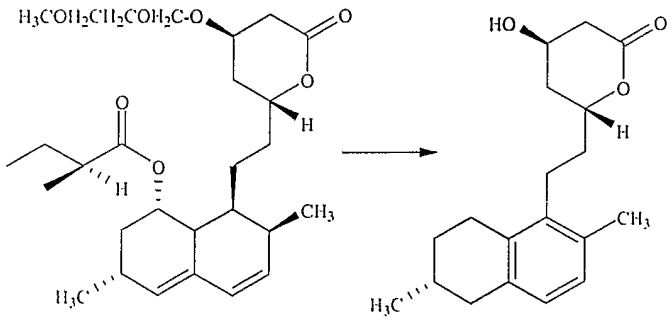
To a stirred solution of Lovastatin (12 g, 29.6 mmoles) in acetonitrile (60 ml) at –5°C to -10°C was added sodium iodide (8 g, 53.4 mmoles) and trimethyl silyl chloride (6.75 g, 53.4 mmoles). The reaction mixture was then allowed to stir at room temperature for 2.0 hours. D.M water (50 ml) added to the reaction mixture and stirred for 10 minutes. Acetonitrile was removed under vacuum at about 50°C and aqueous solution was extracted with ethyl acetate. The combined organic layer was washed with 10 % sodium thiosulphate solution, followed by water and brine solution, and dried over sodium sulphate and filtered. The solvent was removed under vacuum to obtain crude product. The crude product was purified by column chromatography to get a compound of formula I-A.

Example II: Preparation of lovastatin-MEM ether (a compound of formula XIII-A, wherein R_3 is $-COCH(CH_3)CH_2CH_3$ and R_4 is $-CH_2OCH_2CH_2OCH_3$) from lovastatin



Diisopropylethylamine (12.82 ml, 74.1 mmoles) was added to a stirred solution of lovastatin (10 g, 24.7 mmoles) in methylenedichloride. 2-Methoxyethoxy methyl chloride (8.3 ml, 80%) was introduced into the reaction mixture and heated at 45°C for six hours. The reaction mixture was cooled to room temperature and quenched with water (75 ml). Methylenedichloride layer was separated and aqueous layer was extracted with methylenedichloride (100 ml). The combined organic layer was washed with water followed by brine solution and then dried over sodium sulphate. Removal of organic layer gave crude liquid product. Further purified by column chromatography to yield lovastatin MEM ether.

Example III: Preparation of compound of formula I-A from Lovastatin-MEM ether



Trimethyl silylchloride (0.207g, 1.907 mmoles) was added to a stirred solution of lovastatin-MEM ether (0.5 g, 1.015mmoles) in acetonitrile (5 ml) at –10°C to –15°C and stirring was continued for 5.0 hours. At the same temperature water (10 ml) was added and stirred for 10 minutes. Acetonitrile was removed and aqueous solution was extracted with ethyl acetate (40 ml). The combined organic layer was washed with water (20 ml) and dried over sodium sulphate. The solvent was removed under vacuum to obtain crude

compound. It was purified by column chromatography to obtain compound of formula I-A.

Example IV: The biological activity of the compound of invention was demonstrated by the following test:

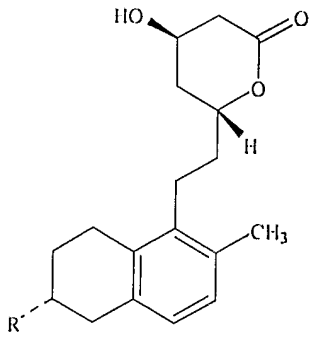
METHODS- HMG-CoA Enzyme Assay

Source:	Wistar Rat Liver
Substrate:	2.5 µM[^{14}C]HMG-CoA
Vehicle	1% DMSO
Pre-Incubation Time/Temp:	15 minutes @ 37^{0}C
Incubation Time/Temp:	15 minutes @ 37^{0}C
Incubation Buffer:	100 mM KH_2PO_4, pH 7.5, 20 mM G-6-P, 2.5 nM NADP, 10 mM EDTA, 5 mM DTT, 1.4 U G-6-P-DH
Quantitation Method:	Quantitation of [^{14}C] Mevalonate

The IC_{50} = 36.2 nM for compound of formula I-A

Claims:

1. A novel statin derivative selected from a group consisting of a compound of formula I,



Formula I

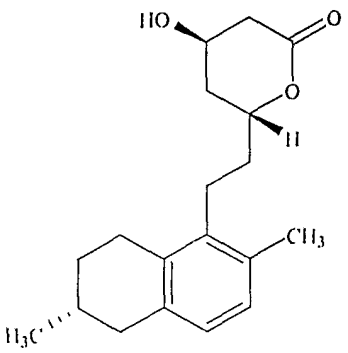
wherein R is selected from a group consisting of –OH, -OR_1, -$OCOR_1$, -OCHO, C_1-C_6 alkyl, C_2-C_6 alkeny, C_2-C_6 alkynyl, alkylaryl, heteroaryl, aralkyl, heterocycle having ring size between 3 to 6, , -CN, -COOH, -$COOR_1$, -$CONHR_1$, -$CONR_1R_2$, -NH_2, -NHR_1, -NR_1R_2, halogen, -SH and -SR_1;

wherein R_1 and R_2 are independently selected from C_1-C_6 alkyl, alkylaryl, heteroaryl, aralkyl, heterocycle having ring size between 3 to 6, C_2-C_6 alkenyl and C_2-C_6 alkynyl, or R_1 and R_2 together with the carbon atom to which they are attached form a heterocycle with a ring size from 3 to 6,

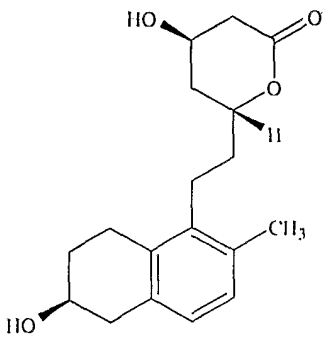
------ represents either α-substituent or β-susbstituent,

and pharmaceutically acceptable salt thereof.

2. A novel statin derivative:



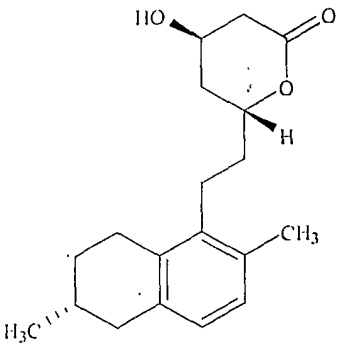
Formula I-A



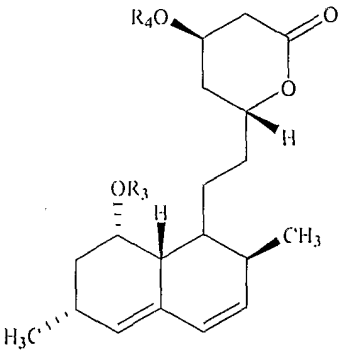
Formula I-B

selected from (4R, 6R)–6[2(2,6(R)-Dimethyl-5,6,7,8-tetrahydronaphthalen-1-yl)ethyl]-4- hydroxytetrahydropyran-2-one, a compound of formula I-A, and (4R, 6R)–6[2(6(S)-Hydroxy-2-methyl-5,6,7,8-tetrahydronaphthalen-1-yl)ethyl]-4-hydroxytetrahydropyran-2-one, a compound of formula I-B and pharmaceutically acceptable salt thereof.

3. A process for preparation of a novel statin derivative, a compound of formula I-A and pharmaceutically acceptable salt thereof comprising subjecting a compound of formula XIII-A:



Formula I-A



Formula XIII-A

wherein,

R_3 is selected from group consisting of H, $-COCH(CH_3)CH_2CH_3$ and $-COC(CH_3)_2CH_2CH_3$;

R_4 is selected from group consisting of H, $-CH_2OCH_3$, $-CH_2OCH_2CH_2OCH_3$, $-CH_2C_6H_5$, $-CH_2OCH_2C_6H_5$, $-CH_2CH_2OCH_3$, $-CH_2C_6H_4OCH_3$, o-$NO_2C_6H_4CH_2$-, allyl,

propargyl, tetrahydropyranyl, 1-methoxycyclohexyl, 1-methoxycyclopentyl, 2-methoxy-2-propyl and –methyl-heteroaryl,

to treatment with a silyl compound of formula $(R_1)_3$-Si-L, a compound of formula XIV,

wherein,

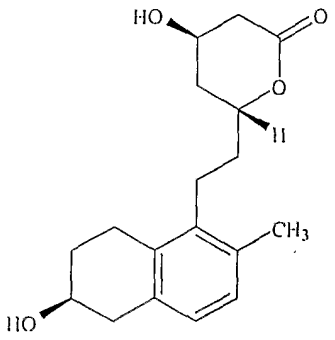
R_1 is same or different and selected from a group consisting of C1 to C4 alkyl, which may be linear or branched and phenyl; L is selected from a group consisting of chloro, bromo, iodo, and trifluoromethanesulfonyl such that the treatment results in conversion of a compound of formula XIII-A into a compound of formula I-A.

4. The process as claimed in claim 3, wherein the process is carried out in presence of an additive, which facilitates the conversion of a compound of formula XIII-A into a compound of formula I-A.

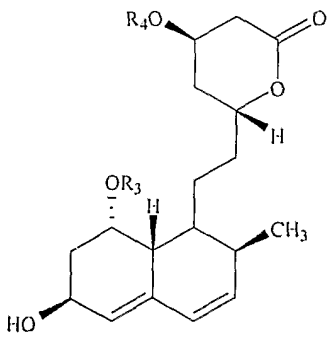
5. The process as claimed in claim 4, wherein the additive is selected from a group consisting of a metallic halide and a Lewis acid.

6. The process as claimed in claim 5, wherein the metallic halide is an alkali earth metal halide or an alkaline earth metal halide.

7. A process for preparation of a novel statin derivative, a compound of formula I-B and pharmaceutically acceptable salt thereof comprising subjecting a compound of formula XIII-B:



Formula I-B



Formula XIII-B

wherein,

R_3 is selected from group consisting of H, $-COCH(CH_3)CH_2CH_3$ and $-COC(CH_3)_2CH_2CH_3$;

R_4 is selected from group consisting of H, $-CH_2OCH_3$, $-CH_2OCH_2CH_2OCH_3$, $-CH_2C_6H_5$, $-CH_2OCH_2C_6H_5$, $-CH_2CH_2OCH_3$, $-CH_2C_6H_4OCH_3$, $o\text{-}NO_2C_6H_4CH_2-$, allyl, propargyl, tetrahydropyranyl, 1-methoxycyclohexyl, 1-methoxycyclopentyl, 2-methoxy-2-propyl and –methyl-heteroaryl

to treatment with a silyl compound of formula $(R_1)_3$-Si-L, a compound of formula XIV,

wherein,

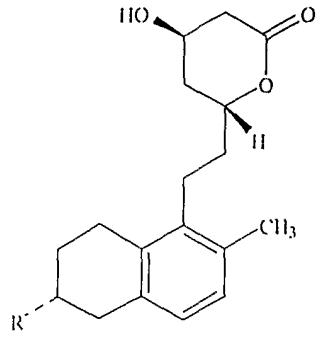
R_1 is same or different and selected from a group consisting of C1 to C4 alkyl, which may be linear or branched and phenyl; L is selected from a group consisting of chloro, bromo, iodo and trifluoromethanesulfonyl such that the treatment results in conversion of a compound of formula XIII-B into a compound of formula I-B.

8. The process as claimed in claim 7, wherein the process is carried out in presence of an additive, which facilitates the conversion of a compound of formula XIII-B into a compound of formula I-B.

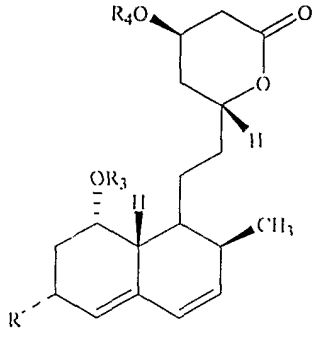
9. The process as claimed in claim 8, wherein the additive is selected from a group consisting of a metallic halide and a Lewis acid.

10. The process as claimed in claim 9, wherein the metallic halide is an alkali earth metal halide or an alkaline earth metal halide.

11. A process for preparation of a novel satin derivative selected from a group consisting of a compound of formula I and pharmaceutically acceptable salt thereof, comprising subjecting a compound of formula I':



Formula I



Formula I'

wherein,

R is selected from a group consisting of –OH, -OR_1, -$OCOR_1$, -OCHO, C_1-C_6 alkyl, C_2-C_6 alkeny, C_2-C_6 alkynyl, alkylaryl, heteroaryl, aralkyl, heterocycle having ring size between 3 to 6, , -CN, -COOH, -$COOR_1$, -$CONHR_1$, -$CONR_1R_2$, -NH_2, -NHR_1, -NR_1R_2, halogen, -SH and -SR_1;

wherein R_1 and R_2 are independently selected from C_1-C_6 alkyl, alkylaryl, heteroaryl, aralkyl, heterocycle having ring size between 3 to 6, C_2-C_6 alkenyl and C_2-C_6 alkynyl, or R_1 and R_2 together with the carbon atom to which they are attached form a heterocycle with a ring size from 3 to 6;

R_3 is selected from group consisting of H, -$COCH(CH_3)CH_2CH_3$ and -$COC(CH_3)_2CH_2CH_3$;

R_4 is selected from group consisting of H, -CH_2OCH_3, -$CH_2OCH_2CH_2OCH_3$, -$CH_2C_6H_5$, -$CH_2OCH_2C_6H_5$, -$CH_2CH_2OCH_3$, -$CH_2C_6H_4OCH_3$, o-$NO_2C_6H_4CH_2$-, allyl, propargyl, tetrahydropyranyl, 1-methoxycyclohexyl, 1-methoxycyclopentyl, 2-methoxy-2-propyl and –methyl-heteroaryl;

------ represents either α-substituent or β-susbstituent,

to treatment with a silyl compound of formula $(R_5)_3$-Si-L, a compound of formula XIV,

wherein R_5 is same or different and selected from a group consisting of C_1 to C_4 alkyl, which may be linear or branched and phenyl; L is selected from a group consisting of chloro, bromo, iodo and trifluoromethanesulfonyl such that the treatment results in conversion of a compound of formula I' into a compound of formula I.

12. The process as claimed in claim 11, wherein the process is carried out in presence of an additive, which facilitates the conversion of a compound of formula I' into a compound of formula I.

13. The process as claimed in claim 12, wherein the additive is selected from a group consisting of a metallic halide and a Lewis acid.

14. The process as claimed in claim 13, wherein the metallic halide is an alkali earth metal halide or an alkaline earth metal halide.

15. A pharmaceutical anti-hyperlipidimic composition comprising as active ingredient an effective amount of a compound of formula selected from (4R, 6R)–6[2(2,6(R)-Dimethyl-5,6,7,8-tetrahydronaphthalen-1-yl)ethyl]-4- hydroxytetrahydropyran-2-one, a compound of formula I-A, and (4R, 6R)–6[2(6(S)-Hydroxy-2-methyl-5,6,7,8-tetrahydronaphthalen-1-yl)ethyl]-4- hydroxytetrahydropyran-2-one, a compound of formula I-B and pharmaceutically acceptable salts thereof and a pharmaceutically acceptable carrier or excipient.

16. A pharmaceutical composition comprising as active ingredient an effective amount of a compound according to claim 1 or a pharmaceutically acceptable salts thereof; and a pharmaceutically acceptable carrier or excipient.

17.A method of treating a subject suffering from a condition selected from hyperlipidemia, arteriosclerosis, stroke, type-2-diabetes, glaucoma, sepsis, colorectal cancer comprising a step of administering to said subject suffering from said condition, a therapeutically effective amount of a compound according to claim 1 or a pharmaceutically acceptable salt thereof.

18. A method of treating a subject suffering from a condition selected from hyperlipidemia, arteriosclerosis, stroke, type-2-diabetes, glaucoma, sepsis, colorectal cancer comprising a step of administering to said subject suffering from said

condition, a therapeutically effective amount of a compound according to claim 2 or a pharmaceutically acceptable salt thereof.

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