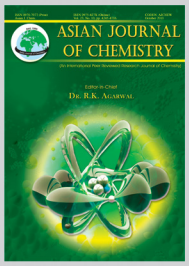
Asian Journal of Chemistry; Vol. 24, No. 3 (2012), 1357-1361

ASIAN JOURNAL OF CHEMISTRY

www.asianjournalofchemistry.co.in



Synthesis and Characterization of Novel Antilipidemic Agents

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(*Received*: 6 May 2011; *Accepted*: 12 November 2011) AJC-10660

Different novel compounds under statin family were synthesized by introduction of more hydrophilic scaffolds in to the statin skeleton by linking the pharmacophore dihydroxy heptanoic acid moiety with more hydrophilic scaffolds to result in compounds, which may be useful as better antilipidemic agents especially as 3-hydroxy-3-methyl glutaryl coenzyme A reductase inhibitors and may improve the level of hepato selectivity and expected to reduce the risk of adverse effects. The target compounds were synthesized starting from *tert*-butyl-2-((4R,6R)-6-(2-aminoethyl)-2,2-dimethyl-1,3-dioxan-4-yl)acetate, a key intermediate of atorvastatin.

Key Words: Antilipidemic, HMG-CoA, Cholesterol, Statin, Oxazolidin, *tert*-Butyl.

INTRODUCTION

Antilipidemic agents are basic drugs for prevention of cardiovascular diseases and have been now in use for more than 4 decades. Antilipidemic agents are categorized into various types like (i) niacin, (ii) fibrates ((fenofibrate [Tricor®], gemfibrozil [Lopid®], clofibrate [Atromid-S®], bezafibrate), (iii) resins that bind bile acid (colestipol [Colestid®] and cholestyramine [Questran®]) and (iv) 3-hydroxy-3-methyl glutaryl coenzyme A (HMG COA) reductase inhibitors (statins). The first class of drugs with an established efficacy in lipid-lowering phenomenon in humans were 3-hydroxy-3-methyl glutaryl coenzyme A reductase inhibitors (statins)[1].

3-Hydroxy-3-methyl glutaryl coenzyme A reductase inhibiting drugs (statins) play significant role in inhibition of the biosynthesis of cholesterol involving the stimulation of the receptor arbitrated by the reduction of the LDL (bad cholesterol). Various statins behave differently to affect the increase of HDL (good cholesterol). However, most of them are able to reduce the levels of triglycerides only to some extent but not fully[2-4]. The list of statins include rosuvastatin[3] (brand name-Crestor; marked by AstraZeneca), lovastatin[5,6] (brand name-Mevacor; marketed by Merck), atorvastatin[7,8] (brand name-Lipitor; marketed by Pfizer), pravastatin[9,10] (brand name-Pravachol; marketed by BMS), fluvastatin[11] (brand name-Lescol; marketed by Novartis), pitavastatin[12,13] (brand name-Livalo) and simvastatin[14,15] (brand name-Zocor, marketed by Merck).

Lipophilicity factor in the statins is found to play an important role because the hepatoselectivity of the statins is directly proportional to the lipophilicity associated with them. The more is the lipophilicity of the statin, the higher are the levels of contact in non-hepatic tissues. On the other hand, the statins with hydrophilic scaffolds possess more hepatoselective nature. Such difference in the hepatoselectivity is because of the fact that statins with lipophilic groups apathetically and non-discriminatively scatter into both of the hepatocyte and non-heptatocyte. Whereas, the statins with groups possessing hydrophilic nature depend highly on rapid transport into hepatocyte to endeavor their effects[17,19]. Higher level of hepatoselectivity is found to result in deminished risk of adverse effects such as diarrhoea, abdominal pain, constipation, flatulence *etc*[18].

In view of the importance of hydrophilicity of statins discussed above, it was an endeavour to invent new HMG-CoA reductase inhibitors, which are easier to synthesize and ensured that all the newly invented inhibitors are retained with key pharmacophore of the statin compounds by embedding the more polar scaffolds to the 'dihydroxy heptanoic acid moiety' when compared to most of the existing statins depicted in Fig. 1. Hence, said novel compounds are considered to possess more hydrophilicity to be useful as better anti-lipidemic agents especially as HMG-CoA reductase inhibitors, which are expected to improve the level of hepatoselectivity and reduce the risk of adverse effects such as diarrhoea, abdominal pain, constipation, flatulence etc.

Thus the target compounds were prepared by: (i) reacting epichlorohydrin with *tert*-butyl-2-((4R,6R)-6-(2-aminoethyl)-2,2-dimethyl-1,3-dioxan-4-yl)acetate (compound **1**) to afford

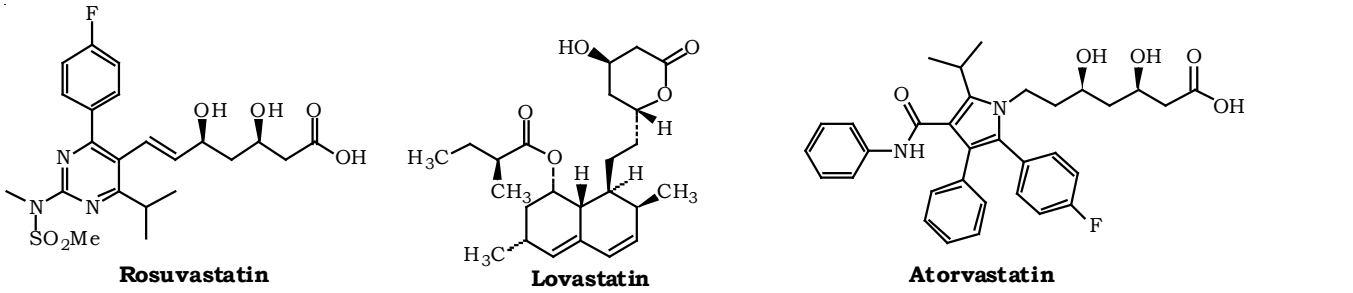
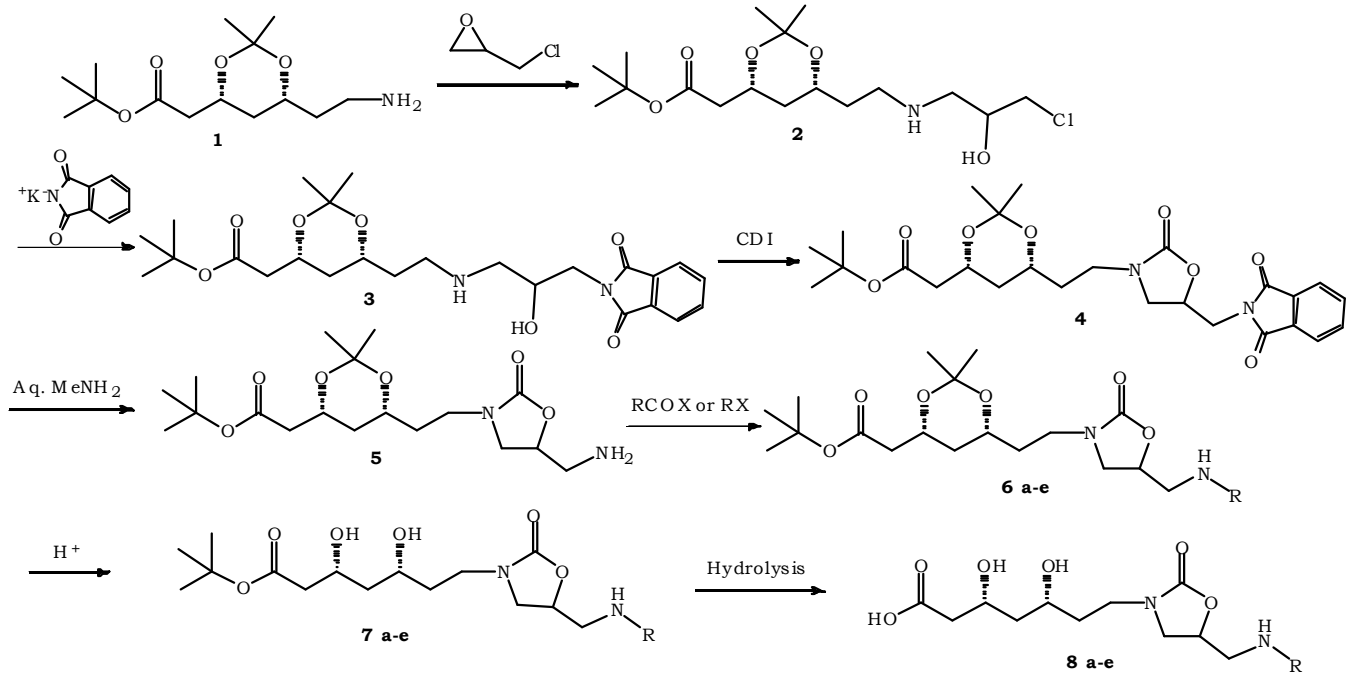


Fig.1



Scheme-I; a: isobutyryl; **b**: acetyl; **c**:benzoyl; **d**: benzyl; **e**: 4-methyl benzyl

tert-butyl-2-((4R,6R)-6-(2-((3-chloro-2-hydroxypropyl)-amino)ethyl)-2,2-dimethyl-1,3-dioxan-4-yl)acetate (compound **2**); (ii) compound (**2**) was converted to *tert*-butyl-2-((4R,6R)-6-(2-(5-((1,3-dioxoisoindolin-2-yl)methyl)-2-oxooxazolidin-3-yl)ethyl)-2,2-dimethyl-1,3-dioxan-4-yl)acetate (compound **4**) by reacting compound (**2**) with potassium phthalimide to afford *tert*-butyl-2-((4R,6R)-6-(2-((3-(1,3-dioxoisoindolin-2-yl)-2-hydroxypropyl)amino) ethyl)-2,2-dimethyl-1,3-dioxan-4-yl)acetate (compound **3**) followed by reaction with carbonyldiimidazole to build the heterocycle oxazolidinone to get compound (**4**); (iii) hydrolysis of compound (**4**) resulted in *tert*-butyl-2-((4R,6R)-6-(2-(5-(aminomethyl)-2-oxooxazolidin-3-yl)ethyl)-2,2-dimethyl-1,3-dioxan-4-yl)acetate (compound **5**); (iv) derivatization of the amino group of compound (**5**) by acylation or alkylation lead to compounds of formula (6); wherein R is alkyl or acyl group; (v) deprotection of acetonide moiety resulted in dihydroxy ester compounds of formula (7); wherein R is alkyl or acyl group; (vi) hydrolysis of the resulting ester afforded the targeted statin compounds of formula (**8**); wherein R is alkyl or acyl group either in their free acid form or in the form of their base addition salts.

EXPERIMENTAL

Melting points were determined in open capillaries and are uncorrected. All the reactions were monitored by TLC and IR spectra were recorded on Perkin-Elmer model-1600 spectrophotometer. ^{1}H NMR spectra of the compounds were recorded on Perkin-Elmer EM-390-200 MHz spectrophotometer, using TMS as an internal standard.

Tert-butyl-2-((4R,6R)-6-(2-aminoethyl)-2,2-dimethyl-1,3-dioxan-4-yl)acetate (compound **1**) was prepared from ethyl(R)-4-cyano-3- hydroxy butyrate by a procedure similar to that described[16] in the US patent 5,003,080.

Synthesis of *tert*-butyl-2-((4R,6R)-6-(2-((3-chloro-2-hydroxypropyl)amino)ethyl)-2,2-dimethyl-1,3-dioxan-4-yl)acetate (compound 2): A solution of *tert*-butyl-2-((4R,6R)-6-(2-aminoethyl)-2,2-dimethyl-1,3-dioxan-4-yl)acetate compound (**1**) (1.0 g, 0.0036 mol) and epichlorohydrin (0.43 g, 0.0046 mol) in isopropanol and mixture was refluxed for 5 h and evaporated under reduced pressure. The resultant compound (**2**) was purified by flash-LC (mixture of *n*-hexane and ethyl acetate in the 7:3 ratio) to give the title compound (**2**) (1.0 g, 78 % yield) as a pale yellow syrup.

The obtained product was characterized as *tert*-butyl-2-((4R,6R)-6-(2-((3-chloro-2-hydroxypropyl)amino)ethyl)-2,2-dimethyl-1,3-dioxan-4-yl)acetate (compound **2**) based on (C,H,N) analytical data, FT-IR, mass and ^{1}H NMR spectral data as depicted in Tables 1 and 2.

Synthesis of *tert*-butyl-2-((4R,6R)-6-(2-((3-(1,3-dioxoisoindolin-2-yl)-2-hydroxypropyl)amino)ethyl)-2,2-dimethyl-1,3-dioxan-4-yl)acetate (compound 3): A mixture of *tert*-butyl 2-((4R,6R)-6-(2-((3-chloro-2-hydroxypropyl)-amino)ethyl)-2,2-dimethyl-1,3-dioxan-4-yl)acetate (compound **2**) (0.5 g, 1.14 mmol) and potassium phthalimide (0.33 g, 1.78 mmol) in triethylamine (2.5 mL). The reaction mixture was stirred for 4 h at 70 ºC. The reaction mixture was allowed to cool to room temperature and stirred for 1 h before water (10 mL) was added. After addition of dichloromethane and phase separation, the aqueous phase was extracted with dichloromethane. The combined organic phases were dried with anhyd. sodium sulfate, filtered and evaporated under reduced pressure. The residue was purified by Flash-LC (mixtures of dichloromethane/methanol) to give the title compound **5** (0.46 g, 70 % yield) as a colourless solid. m.p. 230 ºC.

The obtained product was characterized as *tert*-butyl-2-((4R,6R)-6-(2-((3-(1,3-dioxoisoindolin-2-yl)-2-hydroxypropyl)amino)ethyl)-2,2-dimethyl-1,3-dioxan-4-yl)acetate (compound **3**) based on (C,H,N) analytical data, FT-IR, mass and ^{1}H NMR spectral data as depicted in Tables 1 and 2.

Synthesis of *tert*-butyl 2-((4R,6R)-6-(2-(5-((1,3-dioxoisoindolin-2-yl)methyl)-2-oxooxazolidin-3-yl)ethyl)-2,2-dimethyl-1,3-dioxan-4-yl)acetate (compound 4): *N,N'*-Carbonyldiimidazole (0.7 g, 4.31 mmol) and 4-(dimethylamino)pyridine (0.24 mmol) were added to a suspension of compound (**3**) (0.5 g, 1.68 mmol) in tetrahydrofuran (8.4 mL). The reaction mixture was stirred for 3 h at room temperature and 3 h at 60 ºC. The precipitate was filtered, washed with tetrahydrofuran and dried *in vacuo*. The combined mother liquors were evaporated and the resulting residue was purified by Flash-LC (mixtures of dichloromethane/methanol). The title compound **4** (0.46 g, 55 % yield) was obtained as a colourless solid.

The obtained product was characterized as isopropyl 2-((4R,6R)-6-(2-(5-((1,3-dioxoisoindolin-2-yl)methyl)-2-oxooxazolidin-3-yl)ethyl)-2,2-dimethyl-1,3-dioxan-4-yl)acetate (compound **4**) based on (C,H,N) analytical data, FT-IR, mass and ^{1}H NMR spectral data as depicted in Tables 1 and 2.

Synthesis of *tert*-butyl 2-((4R,6R)-6-(2-(5-(aminomethyl)-2-oxooxazolidin-3-yl)ethyl)-2,2-dimethyl-1,3-dioxan-4-yl)acetate (compound 5): Methylamine (40 % in water, 0.77 mL, 9.9 mol) was added to a suspension of compound (**4**) (0.5 g, 0.99 mmol) in methanol (8 mL). The reaction mixture was refluxed for 1 h and evaporated under reduced pressure. The resultant compound was purified by Flash-LC (mixtures of dichloromethane/methanol) to give the title compound **5** (0.70 g, 70 % yield) as a colourless solid.

The obtained product was characterized as *tert*-butyl-2-((4R,6R)-6-(2-(5-(aminomethyl)-2-oxooxazolidin-3-yl)ethyl)-2,2-dimethyl-1,3-dioxan-4-yl)acetate (compound **5**) based on (C,H,N) analytical data, FT-IR, mass and ^{1}H NMR spectral data as depicted in Tables 1 and 2.

Synthesis of *tert*-butyl-2-((4R,6R)-6-(2-(5-(isobutyramidomethyl)-2-oxooxazolidin-3-yl)ethyl)-2,2-dimethyl-1,3-dioxan-4-yl)acetate (compound 6a): Isobutyric anhydride (0.44 g, 2.8 mmol) was added drop-wise to a solution of the compound (**5**) in pyridine (8 mL) at 0 ºC. The reaction mixture was allowed to warm to room temperature and stirred for 1 h before water was added. After addition of dichloromethane and phase separation, the aqueous phase was extracted with dichloromethane. The combined organic phases were dried with anhyd. sodium sulfate, filtered and evaporated *in vacuo*. The residue was purified by Flash-LC (mixtures of dichloromethane/methanol) to give the title compound **6a** (0.41 g, 62 % yield) as a colourless solid.

The obtained product was characterized as *tert*-butyl-2-((4R,6R)-6-(2-(5-(isobutyramidomethyl)-2-oxooxazolidin-3-yl)ethyl)-2,2-dimethyl-1,3-dioxan-4-yl)acetate (compound **6a**) based on (C,H,N) analytical data, FT-IR, mass and ^{1}H NMR spectral data as depicted in Tables 1 and 2.

By following the similar procedure involving the use of appropriate conventional reagents, four other derivatives of *tert*-butyl-2-((4R,6R)-6-(2-(5-(aminomethyl)-2-oxooxazolidin-3-yl)ethyl)-2,2-dimethyl-1,3-dioxan-4-yl)acetate (**6 b-e**) were synthesized.

Synthesis of (3R,5R)-*tert*-butyl 3,5-dihydroxy-7-(5-(isobutyramidomethyl)-2-oxooxazolidin-3-yl)heptanoate (compound 7a): A stirred mixture of (0.5 g, 1.1 mmol) of *tert*-butyl-2-((4R,6R)-6-(2-(5-(isobutyramidomethyl)-2-oxooxazolidin-3-yl)ethyl)-2,2-dimethyl-1,3-dioxan-4-yl)acetate (compound **6a**) in 10 mL acetonitrile was added a diluted solution of 2.5 mL (2.2 mmol) of conc. HCl in 5 mL of water slowly at room temperature. Aged at room temperature for 45 min and pH of the reaction mixture was adjusted to 8 with aqueous sodium carbonate solution by controlling temperature at room temperature. The product was extracted with dichloromethane and the organic layer was washed with water. Solvent was distilled under reduced pressure and the resulting compound was purified by flash-LC (mixtures of dichloromethane/methanol) to give the title compound **7a** (0.2 g, 44 % yield) as a colourless solid.

The obtained product was characterized as (3R,5R)-*tert*-butyl-3,5-dihydroxy-7-(5-(isobutyramidomethyl)-2-oxooxazolidin-3-yl)heptanoate (compound **7a**) based on (C,H,N) analytical data, FT-IR, mass and ^{1}H NMR spectral data as depicted in Tables 1 and 2.

TABLE-1
CHN ANALYSIS DATA FOR COMPOUNDS **2-5, 6a-e, 7a-e** AND **8a-e**

Compound no.	Mol. formula	Calculated			Observed		
		C	H	N	C	H	N
2	$C_{17}H_{32}ClNO_5$	55.75	8.74	3.82	55.88	8.79	3.78
3	$C_{25}H_{36}N_2O_7$	63.05	7.60	5.87	63.03	7.59	5.86
4	$C_{26}H_{34}N_2O_8$	62.09	6.90	5.57	62.12	6.80	5.55
5	$C_{18}H_{32}N_2O_6$	58.01	8.62	7.51	57.98	8.62	7.50
6a	$C_{22}H_{38}N_2O_7$	59.70	8.62	6.32	59.70	8.63	6.30
6b	$C_{20}H_{34}N_2O_7$	57.92	8.23	6.75	57.93	8.25	6.74
6c	$C_{25}H_{36}N_2O_7$	62.99	7.63	5.87	63.00	7.60	5.86
6d	$C_{25}H_{38}N_2O_6$	64.89	8.26	6.05	64.90	8.25	6.06
6e	$C_{26}H_{40}N_2O_6$	65.50	8.43	5.87	65.49	8.43	5.86
7a	$C_{19}H_{34}N_2O_7$	56.71	8.49	6.95	56.69	8.50	6.94
7b	$C_{17}H_{30}N_2O_7$	54.50	8.05	7.47	54.51	8.06	7.46
7c	$C_{22}H_{32}N_2O_7$	60.51	7.35	6.41	60.50	7.36	6.40
7d	$C_{22}H_{34}N_2O_6$	62.52	8.09	6.62	62.51	8.10	6.61
7e	$C_{23}H_{36}N_2O_6$	63.22	8.29	6.41	63.26	8.30	6.40
8a	$C_{15}H_{26}N_2O_7$	52.02	7.53	8.08	52.04	7.56	8.10
8b	$C_{13}H_{22}N_2O_7$	49.04	6.94	8.79	49.06	6.98	8.78
8c	$C_{18}H_{24}N_2O_7$	56.81	6.35	7.36	56.80	6.35	7.35
8d	$C_{18}H_{26}N_2O_6$	58.99	7.13	7.64	59.02	7.13	7.63
8e	$C_{19}H_{28}N_2O_6$	59.96	7.40	7.36	59.97	7.41	7.34

TABLE-2
CHARACTERIZATION DATA FOR COMPOUNDS **2-5**, **6a**, **7a** AND **8a**

Compd. No.	IR (cm^{-1})	Mass (m/z)	1H NMR (δ ppm)
2	3350 (O-H str), 3200 (N-H str) 1680 (C=O str)	366 (M+1)	3.60 (s, 1H, OH); 2.09 (s, 1H, NH); 4.46 (m, 1H, CH β to C=O); 3.76 (m, 2H); 3.42-3.68 (m, 2H, CH_2-Cl); 2.28-2.85 (m, 6H); 1.46-1.76 (m, 4H); 1.36 (s, 9H, CH_3 of ter-butyl); 1.29 (s, 6H, CH_3 of acetonide)
3	3250 (OH str); 3100 (NH str); 1750 (C=O str, ester); 1700 (C=O str, amide)	478 (M+2)	7.84-7.89 (m, 4H, Ar); 3.61 (s, 1H, OH); 2.07 (s, 1H, NH); 4.45 (m, 1H); 4.06 (m, 1H); 3.66-3.89 (m, 3H); 2.29-2.87 (m, 6H); 1.45-1.77 (m, 4H); 1.38 (s, 9H, CH_3 of ter-butyl); 1.28 (s, 6H, CH_3 of acetonide)
4	1750 (C=O str, ester); 1700 (C=O str, amide)	503 (M+1)	7.5-7.8 (m, 4H, Ar-H); 5.0 (m, 1H, CH oxazolidinone); 4.4 (m, 1H, one CH of acetonide); 3.5 (m, 1H, second CH of acetonide); 3.1 (m, 2H, CH_2, attached to phthalimide); 2.9 (m, 2H, CH_2 of oxazolidinone); 2.2 (m, 2H, CH_2 adjascent to oxazolidinone); 1.7 (m, 2H, CH_2 adjascent to CO of ester); 1.5 (m, 2H, CH_2 adjascent to acetonide); 1.4 (m, 2H, CH_2 of acetonide); 1.2 (m, 15H, CH_3)
5	3400 (NH str); 1700 (C=O str, ester); 1690 (C=O str, amide);	373 (M+1)	5.4 (m, 2H, NH_2); 4.9 (m, 1H, CH oxazolidinone); 4.4 (m, 1H, one CH of acetonide); 3.7 (m, 1H, second CH of acetonide); 3.1-3.3 (m, 4H, CH_2 attached to phthalimide & CH_2 of oxazolidinone); 2.1 (m, 2H, CH_2 adjascent to NH_2); 2.0 (m, 2H, CH_2 adjascent to CO of ester); 1.7 (m, 2H, CH_2 adjascent to acetonide); 1.5 (m, 2H, CH_2 of acetonide); 1.3 (m, 15H, CH_3)
6a	1720 (C=O str, ester); 1680 (C=O str, amide); 3400 (NH str)	443 (M+1)	8.1 (m, 1H, NH); 4.7 (m, 1H, CH oxazolidinone); 4.5 (m, 1H, one CH of acetonide); 3.2 (m, 1H, second CH of acetonide); 3.1 (m, 4H, CH_2 attached to phthalimide & CH_2 of oxazolidinone); 2.1 (m, 3H, CH_2 adjascent to NH & CH of i-Pr); 2.0 (m, 2H, CH_2 adjascent to CO of ester); 1.7 (m, 2H, CH_2 adjascent to acetonide); 1.5 (m, 2H, CH_2 of acetonide); 1.3 (m, 21H, CH_3)
7a	3350 (O-H str); 3200 (N-H str); 1690 (C=O str, ester); 1650 (C=O str, amide)	403 (M+1)	7.8 (m, 1H, NH); 4.7 (m, 1H, CH oxazolidinone); 4.5 (m, 1H, one CH of CHOH); 3.7 (m, 1H, second CH of CHOH); 3.5 (s, 2H, OH); 1.6-3.1 (m, 13H, CH_2 & CH of i-Pr); 1.3 (m, 15H, CH_3)
8a	3650 (O-H str, COOH); 3200 (N-H str); 1700 (C=O str, ester); 1650 (C=O str, amide)	347 (M+1)	7.7 (m, 1H, NH); 7.5 (s, 1H, COOH); 5.2 (m, 1H, CH oxazolidinone); 3.6 (m, 1H, CH of one CH-OH); 3.5 (s, 2H, OH); 3.3 (m, 1H, CH of second CH-OH); 1.4-3.1 (m, 13H, CH_2 & CH of i-Pr); 1.3 (m, 6H, CH_3)

By following the similar procedure involving the use of appropriate conventional reagents, four other derivatives of (3R,5R)-*tert*-butyl 7-(5-(aminomethyl)-2-oxooxazolidin-3-yl)-3,5-dihydroxyheptanoate (**7 b-e**) were synthesized.

Synthesis of (3R,5R)-3,5-dihydroxy-7-(5-(isobutyramidomethyl)-2-oxooxazolidin-3-yl)heptanoic acid (compound 8a): A stirred mixture of (0.2 g, 0.5 mmol) of (3R,5R)-*tert*-butyl-3,5-dihydroxy-7-(5-(isobutyramidome-thyl)-2-oxooxazolidin-3-yl)heptanoate (compound **7a**) in 10 mL of acetonitrile was slowly added a solution of sodium hydroxide prepared by dissolving (25 mg, 0.6 mmol) of sodium hydroxide in 5 mL of water. The temperature was raised to 45 ºC and aged for 1 h. Reaction mixture was cooled to room temperature and the pH was adjusted to 6 using aqueous acetic acid. The

product was extracted with dichloromethane and the organic layer was washed with water. Solvent was distilled under reduced pressure and the resulting compound was purified by flash-LC (mixtures of dichloromethane/methanol) to give the title compound **8a**.

The resulting compound can be converted to calcium salt by first dissolving the acid in stoichiometric quantity of aqueous sodium hydroxide solution and then treating with stoichiometric quantity of calcium acetate to get the corresponding calcium salt.

The obtained product was characterized as (3R,5R)-3,5-dihydroxy-7-(5-(isobutyramidomethyl)-2-oxooxazolidin-3-yl)heptanoic acid (compound **8a**) based on (C,H,N) analytical data, FT-IR, mass and ^{1}H NMR spectral data as depicted in Tables 1 and 2.

By following the similar procedure involving the use of appropriate conventional reagents, four other derivatives of (3R,5R)-7-(5-(aminomethyl)-2-oxooxazolidin-3-yl)-3,5-dihydroxyheptanoic acid (**8 b-e**) were synthesized.

The analytical data and spectral data of compounds **2, 3, 4, 5, 6a-e, 7a-e** and **8a-e** are presented in Tables 1 and 2.

ACKNOWLEDGEMENTS

The authors are thankful to the management of Dr. Reddy's Lab. Limited for research facilities and encouragement.

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