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Synthesis and biological evaluation of novel undecenoic acid-amino acids-based hybrid molecules

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Abstract
In this study, a few undecenoic acid-amino acid-based hybrid molecules were synthesized and evaluated for their biological activities. Initially, methyl undecenoate was epoxidized using *m*-chloroperbenzoic acid to yield epoxy methyl undecenoate. Later the epoxy ring was opened with amino group of the respective methyl esters of selected amino acids, namely, valine, tyrosine, phenylalanine, methionine and leucine to yield methyl (11-methyl valinyl-10 hydroxy) undecenoate, methyl (11-methyl tyrosinyl-10 hydroxy) undecenoate, methyl (11-methyl phenylalanyl-10 hydroxy) undecenoate, methyl (11-methyl methionyl-10 hydroxy) undecenoate and methyl (11-methyl leucinyl-10 hydroxy) undecenoate, respectively. The hydroxy group in fatty amino ester derivatives were further sulfated using chlorosulfonic acid to yield their sulfated sodium salts. Among the synthesized derivatives the non-sulfated derivatives showed moderate antioxidant activities, while, the sulfated derivatives exhibited promising cytotoxicity specifically against the prostate cancer (DU145) cell line.

Keywords: Amino acids, undecenoic acid, antibacterial, antifungal, anticancer properties

Introduction

Fatty acids are the main component of lipids in plants, animals, and microorganisms. In general, fatty acids are straight chain carbon molecules of varying length with a carboxylic acid group at one end. Fatty acids are known to possess various biological activities such as antibacterial and antifungal properties [1]. It is well known that long-chain unsaturated fatty acid derivatives exhibit greater potency than saturated fatty acid derivatives [2]. 10-undecenoic acid (10-UDA) is a first generation derivative of castor oil, produced by high temperature cracking of ricinoleic acid, the major fatty acid present in castor oil [3]. Similarly, undecenoic acid is one of the well-studied fatty acid bearing anti-fungal activity that finds use in topical creams for the treatment of skin infections such as athletes foot, ring worm, etc [4-6]. 10-UDA is an interesting renewable raw material readily used in insecticidal, fungicidal and perfumery formulations [3, 6]. It is also used as precursor for the synthesis of antitumor compounds, antibiotics and a host of insect pheromones [7, 8]. 10-UDA finds extensive use for the manufacture of pharmaceuticals, anti-dandruff shampoos, antimicrobial powders and some bioactive products. While, some of these derivatives are being used in cosmetic formulations due to their skin biocompatibility and mildness owing to the structural resemblance to the skin and hair proteins. Undecenoic acid's terminal double bond is very reactive and can undergo addition reactions to incorporate epoxy group [9, 10] despite its potential, 10-UDA has not been exploited appropriately. Lipophilic derivatives are well known for their vital role in antioxidant, biological and cosmetic applications. In the recent years, the modification of various molecules by lipophilization has become an important methodology to improve the effectiveness in lipid based products [11].

Amino acids have a wide range of biological functions and provide nitrogen balance in our body and also plays an important role in metabolic functions [12, 13]. Amino acids are the building blocks or basic structural units of peptides and proteins. Some of the amino acids, namely alanine, valine, tyrosine, phenylalanine, methionine and leucine possess unusual structural features used for the synthesis of bioactive molecules. In general, the amino acid derivatives are considered as an important class of surfactants and function as good amphoteric surface active germicides [14] However, there is paucity of information on amino acid-undecenoic acid-based hybrid molecules having multifunctional moieties such as amine, hydroxyl, etc. Considering these facts, some selected amino acids and undecenoic acid were used as raw materials for the synthesis of some bioactive hybrid molecules in the present study. Further, all the synthesized molecules were evaluated for different biological activities.

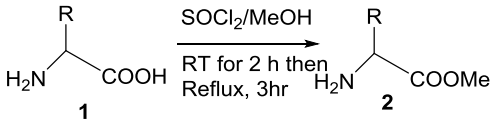
Materials and Methods

All chemicals such as undecylenic acid, valine, tyrosine, phenylalanine, methionine, leucine, alanine, meta-chloroperbenzoic acid, triethyl amine, thionyl chloride and chlorosulfonic acid were purchased from M/s. S.D. Fine Chemical Co. Ltd., Mumbai, India, and were of highest grade of purity. Other commercial solvents were purchased from Merck Group Co., Ltd. All reagents were used without further purification. Infrared spectra were measured on KBr pellets on Perkin Elmer Spectrometer in the range of 4000-400 cm^{-1}. ^{1}H and ^{13}C- NMR spectras was recorded on Avance 300 MHz and Avance 500 MHz NMR spectrometers. Chemical shifts (δ

values) and coupling constants (*J* values) were reported in parts per million (ppm) and Hertz (Hz), respectively. Chemical shifts were relative to tetramethylsilane (TMS) except for solvents that were used, and the signals were quoted as s (singlet), d (doublet), t (triplet), q (quartet) and m (multiplet). The ESI-MS mass spectra were recorded on Waters 2998 mass spectrometer.

General procedure for the synthesis of amino acid methyl esters

Methanol (100 ml) was added to amino acid (30 mmol) and the contents were cooled to 0 °C. And then, thionyl chloride (2.4 ml, 40 mmol), was added drop wise to these contents and the stirring was continued for 1 h at this temperature. The reaction mixture was magnetically stirred for 2 h at RT followed by refluxing for 3 h. The crude product mixture was concentrated under the reduced pressure to remove excess methanol and thionyl chloride (Scheme 1).



R = -CH_3 **(a)**, -CH (CH_3)$_2$ **(b)**, -CH_2Ph-OH **(c)**, -CH_2Ph **(d)**, -C_2H_4-S-CH_3 **(e)**, -CH_2-CH (CH_3)$_2$ **(f)**

Scheme 1: Synthesis of amino acid methyl esters

Alanine methyl ester (2a)

Yield 90%; $C_4H_9NO_2$; FT-IR (cm^{-1}, neat): 3,425 (N-H str), 1,745 (-C=O str); ^{1}H- NMR ($CDCl_3$, 300 MHz) : δ 3.7 (3H, S, -O-CH_3), 2 (2H, m, -NH_2), 1.2 (3H, d, -CH_3), 3.5 (1H, m, H_2N-CH-); C^{13}-NMR ($CDCl_3$, 300 MHz): 19.6, 49.6, 58.2, 76.9; MS/ESI (*m/z*) Calcd: 103 [M+], found: 103.958 (M+1); HRMS: 104.07053.

Valine methyl ester (2b)

Yield 90%; $C_5H_{11}NO_2$; FT-IR (cm^{-1}, neat): 3,429 (N-H str), 1,741(-C=O str); ^{1}H-NMR ($CDCl_3$, 300 MHz) : δ/ppm 0.98 [6H, dd, (-CH_3)$_2$], 2 (2H, m, -NH_2), 2.7 (1H, m, -CH-), 3.3 (1H, d, H_2N-CH), 3.7 (3H, s, -O-CH_3); ^{13}C-NMR ($CDCl_3$, 300 MHz): 18.6, 30.0, 53.1, 58.8, 169.2; MS/ESI (*m/z*) Calcd: 131 [M+], found:131.94 (M+1); HRMS: 132.10152.

Tyrosine methyl ester (2c)

Yield 90%; $C_{10}H_{13}NO_3$; FT-IR (cm^{-1}, neat): 3,432 (N-H str), 1,635 (-C=O str); H^1- NMR ($CDCl_3$, 300 MHz): δ/ppm 2 (2H, m, H_2N-), 3.1 (2H, d, Ph-CH_2-), 3.67 (3H, s, -O-CH_3), 3.8 (1H, m, H_2N-CH-), 6.7 (2H, d, ortho-2H), 7 (2H, d, meta-2H); C^{13}-NMR ($CDCl_3$, 300 MHz): 34.1, 51.6, 52.57, 114.5, 129.4, 155.8, 168.5; MS/ESI (*m/z*) Calcd: 195 [M+], found: 218(M+23).

Phenyl alanine methyl ester (2d)

Yield 90%; $C_{10}H_{13}NO_2$; FT-IR (cm^{-1}, neat): 3,430 (N-H str), 1,744 (-C=O str); ^{1}H- NMR ($CDCl_3$, 300 MHz): δ/ppm 2 (2H, m, H_2N-), 2.9-3.1 (2H, m, Ph-CH_2-), 3.67 (3H, s, -O-CH_3), 7.2 (5H, m, aromatic-5H); MS/ESI (*m/z*) Calcd: 179 [M+], found: 202 (M+23).

Methionine methyl ester (2e)

Yield 90%; $C_6H_{13}NO_2S$; FT-IR (cm^{-1}, neat) data: 3,429 (N-H str), 1,741 (-C=O str); ^{1}H- NMR ($CDCl_3$, 300 MHz); δ/ppm 2 (2H, m, H_2N-), 2.1 (3H, s, -S-CH_3), 2.6 (2H, t, -S-CH_2-), 3.6 (1H, m, H_2N-CH-), 3.75 (3H, s, -O-CH_3); MS/ESI (*m/z*) Calcd: 163 [M+], found: 186 (M+23).

Leucine methyl ester (2f)

Yield 90%; $C_7H_{15}NO_2$; FT-IR (cm^{-1}, neat): 3,418 (N-H str), 1,742 (-C=O str); ^{1}H- NMR ($CDCl_3$, 300 MHz): δ 2 (2H, m, -NH_2), 3.45 (1H, m, H_2N-CH-), 2.5 [1H, m,-CH (CH_3)-], 1.8 (1H, m, -CH-CH_3), 1 [9H, d, (-CH_3)$_3$]; C^{13}-NMR ($CDCl_3$, 300 MHz): 15.8, 49.1, 49.8, 53.2, 170.4; MS/ESI (*m/z*) Calcd: 145 [M+], found: 146 (M+1); HRMS: 146.11689.

Synthesis of undecenoic acid methyl ester

Undecylenic acid (50 g) was dissolved in 200 ml of 2% sulphuric acid in methanol. The reaction mixture was refluxed at 65 ºC for 2 h. The product mixture was concentrated on rotary evaporator and the product was extracted using ethyl acetate. Later, ethyl acetate was removed and the crude product was passed through activated basic alumina to remove unconverted undecylenic acid. The yield obtained was up to 95%.

Methyl undecenoate (4)

Yield 95%; $C_{12}H_{22}O_2$; FT-IR (cm^{-1}, neat) data: 1,743 (-C=O str), 1,641 (-C=C- str); ^{1}H-NMR ($CDCl_3$, 300 MHz):δ 3.6 (3H, s, -O-CH_3), 2.3 (2H, t,-CH_2-C=O), 5.03 (2H, m, H_2C=), 5.7 (1H, m, =CH), 1.4 [14H, m, (-CH_2-) $_7$]; C^{13}-NMR ($CDCl_3$, 300 MHz): 24.9, 28.9, 34.0, 51.3, 114.1, 139.0, 174.1; MS/ESI (*m/z*) Calcd: 198 [M+], found: 199 (M+1).

Synthesis of epoxy methyl undecenoate

Methyl undecenoate (11.88 g, 1 eq) was dissolved in dichloromethane (100 ml) and mCPBA (15.5 gr, 1.5 eq) was taken in dichloromethane, added slowly to reaction mixture at 4 °C for 0.5 h with stirring. Stirring was continued at same temperature for 6 h and the crude reaction mixture was filtered under high vacuum to remove mCBA formed during reaction. And then dichloromethane was removed by rotary evaporation and again the crude product mixture was dissolved in ethyl acetate and washed with aq. $NaHCO_3$, aq. $NaHSO_3$ and aq. NaCl solutions, respectively. The pure product was obtained through column chromatography where 2% ethyl acetate in hexane was used as eluent. The yield obtained was up to 90%.

Epoxy methyl undecanoate (5)

Yield 85%; $C_{12}H_{22}O_3$; FT-IR (cm^{-1}, neat): 1,738 (-C=O str), 912 (epoxy ring); ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 2.3 (2H, t,-CH_2-C=O), 3.67 (3H, s,--CH_3), 1.4 (2H, m, epoxy-CH_2-), 1.3 [12H, m, (-CH_2-)], 2.4-2.7 (2H, m, epoxy-CH_2); MS/ESI (*m/z*) Calcd: 214 [M+], found: 237 (M+23).

General procedures for the epoxy methyl undecanoate ring opening with amino acid methyl esters

10–epoxy undecanoate (2.4 g, 1 eq) and methyl valine (1.865 g, 1.5 eq) were dissolved in methanol (50 ml). Then catalytic amount of triethylamine was added to the contents and magnetically stirred for overnight under reflux conditions. After completion of the reaction, the methanol was removed using reduced pressure and the product was extracted with ethyl acetate.

Methyl(11-methyl alanine-10-hydroxy) undecanoate (6a)
Yield 45%; $C_{16}H_{31}NO_5$; FT-IR (cm^{-1}, neat): 3,645 (N-H str), 3,645 (O-H str), 1,729 (-C=O str); ^{1}H-NMR ($CDCl_3$, 300 MHz): δ/ppm 3.8 (3H, s, -O-CH_3), 1.4 [14H, m, (-CH_2-)], 2 (2H, m, H_2N-), 3.6 (1H, -NH-CH-), 2.9 (2H, dd, -NH-CH_2-), 2.3 (2H, t, -CH_2-C=O) 3.45 [1H, m, -CH (OH)-]; MS/ESI (*m/z*) Calcd: 317 [M+], found: 318 (M+1).

Methyl(11-methyl valinyl-10-hydroxy) undecanoate (6b)
Yield 55%; $C_{18}H_{35}NO_5$; FT-IR (cm^{-1}, neat): 3,408 (N-H str), 3,408 (O-H str), 1,736 (-C=O str); ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 0.9 [6H, t, - $(CH_3)_2$], 3.67 [6H, t, (-O-CH_3)$_2$], 3.5 (1H, -CH-NH-), 3 [2H, dd, -NH-CH_2-CH (OH)-], 2.3 (2H, t, -CH_2-C=O), 1.2 (14H, m, -$(CH_2)_7$-], 2 (1H, m, -NH-); C^{13} NMR ($CDCl_3$, 300 MHz: 18.8, 24.4, 29.1, 34.1, 50.9, 53.3, 66.1, 69.7, 76.7, 173.5, 174.9; MS/ESI (*m/z*) Calcd: 345 [M+], found: 346 (M+1); HRMS: 346.25796.

Methyl-(11-methyl tyrosinyl-10-hydroxy) undecanoate (6c)
Yield 55%; $C_{22}H_{35}NO_6$; FT-IR (cm^{-1}, neat): 3,389 (N-H str), 3,389 (O-H str), 1,734(-C=O str); ^{1}H-NMR ($CDCl_3$, 300 MHz): δ/ppm 3.67 [6H, s, (-O-CH_3)], 2.1 (1H, m, -NH-), 3 [2H, dd, -NH-CH_2-CH (OH)-], 3.6 [1H, m, -CH (OH)-], 1.4 [14H, m, - $(CH_2)_7$ -], 2.3 (2H, t, -CH_2-C=O), 6.7 (2H, m, meta –H), 7 (2H, m, ortho-H); MS/ESI (*m/z*) Calcd: 409 [M+], found: 432 (M+23);

Methyl-(11-methyl phenylalanyl-10-hydroxy) undecanoate (6d)
Yield 60%; $C_{22}H_{35}NO_5$; FT-IR (cm^{-1}, neat): 3,472 (N-H str), 3,472 (O-H str), 1,740 (-C=O str); H^1-NMR ($CDCl_3$, 300 MHz) : δ 0.98 [6H, dd, (-CH_3)$_2$], 2 (2H, m, -NH_2), 2.7 (1H, m, -CH-), 3.3 (1H, d, H_2N-CH), 3.7 (3H, s, -O-CH_3); MS/ESI (*m/z*) Calcd: 393 [M+], found: 416 (M+23).

Methyl-(11-methyl methionine-10-hydroxy) undecanoate (6e)
Yield 50%; $C_{18}H_{35}NO_5S$; FT-IR (cm^{-1}, neat): 3,448 (N-H str), 3,448 (O-H str), 1,735 (-C=O str); H^1-NMR ($CDCl_3$, 300 MHz) : δ/ppm 0.98 [6H, dd, (-CH_3)$_2$], 2 (2H, m, -NH_2), 2.7 (1H, m, -CH-), 3.3 (1H, d, H_2N-CH), 3.7 (3H, s, -O-CH_3); MS/ESI (*m/z*) Calcd: 377 [M+], found: 378 (M+1).

Methyl(11-methyl leucinyl-10-hydroxy) undecanoate (6f)
Yield 46%; $C_{19}H_{37}NO_5$; FT-IR (cm^{-1}, neat): 3,429 (N-H str), 3,429 (O-H str), 1,741(-C=O str); H^1-NMR ($CDCl_3$, 300 MHz) : δ/ppm 0.98 [6H, dd, (-CH_3)$_2$], 2 (2H, m, -NH_2), 2.7 (1H, m, -CH-), 3.3 (1H, d, H_2N-CH), 3.7 (3H, s, -O-CH_3); MS/ESI (*m/z*) Calcd: 359.27 [M+], found: 382 (M+23).

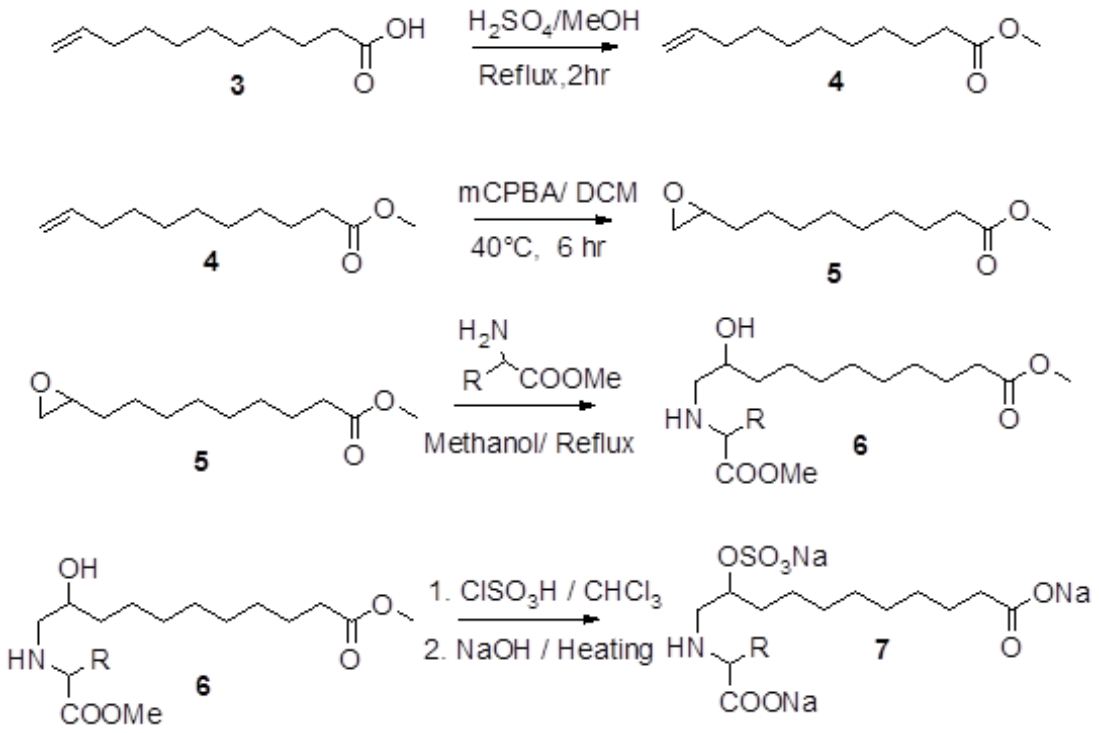
General procedure for the sulfation of methyl (11-methyl amino acid-10-hydroxy) undecanoate
Chlorosulfonic acid (0.17 g, 1.2 mmol) was added drop wise to methyl (11-methyl amino acid-10-hydroxy) undecanoate (0.318 g, 1 mmol) dissolved in chloroform (50 ml) at 5 °C for 30 min, while the mixture was magnetically stirred. Stirring was continued for an additional 3.5 h at the same temperature. The contents were diluted with n-butanol and neutralised with 16 N aqueous sodium hydroxide solution. The water and butanol was removed using a rotary evaporator, and the residue was dried under reduced pressure at 80 °C. The product was treated with diethyl ether to separate the unconverted reactant as ether solubles. The sulfated methyl (11-methyl alanine-10-hydroxy) undecanoate was dried in a vacuum desiccator. The product yield was 0.390 g (90%) (Scheme 2)

Biology
Antimicrobial activity of the different prepared undecenoic acid-amino acids based hybrid molecules (6a-f and 7a-f) was screened using well diffusion method [15] against a panel of pathogenic bacterial strains including *Escherichia coli* MTCC 739, *Staphylococcus aureus* MLS16, *Bacillus subtilis* MTCC 121, *Klebsiella planticola* MTCC 530, *Pseudomonas aeruginosa* MTCC 2453 and *Candida albicans* MTCC 3017 which were procured from the Microbial Type Culture Collection (MTCC), CSIR-Institute of Microbial Technology, Chandigarh, India. The pathogenic reference strains were seeded on the surface of the media Petri plates, containing Muller-Hinton agar with 0.1 ml of previously prepared microbial suspensions individually containing 1.5×10^8 cfu ml^{-1} (equal to 0.5 McFarland). Wells of 6.0 mm diameter were prepared in the media plates using a cork borer and the prepared molecules at a dose range of 125-0.48 µg $well^{-1}$ were added in each well under sterile conditions in a laminar air flow chamber. Standard antibiotic solution of ciprofloxacin and miconazole at a dose range of 125-0.48 µg $well^{-1}$ and the well containing methanol served as positive and negative controls, respectively. The plates were incubated for 24 h at 37 °C for bacterial and 30 °C for *Candida albicans* and the well containing the least concentration showing the inhibition zone was considered as the minimum inhibitory concentration. All experiments were carried out in duplicates and mean values are represented.
Antioxidant activity of prepared undecenoic acid-amino acid-based derivatives were assessed on the basis of the free radical scavenging effect on the stable 1, 1-diphenyl-2-picrylhydrazyl (DPPH) by a modified method [16] and the DPPH radical scavenging activity was calculated using the formula [17].
DPPH radical scavenging activity (%) = [(Absorbance of control–Absorbance of test sample)/(Absorbance of control)] ×100
The radical scavenging potential was expressed as EC_{50} value, which represents the test compound concentration at which 50% of the DPPH radicals were scavenged. All tests were performed in triplicate and values are represented as mean.
Cytotoxicity data was assessed on the basis of measurement of *in vitro* growth of tumor cell lines in 96 well plates by cell mediated reduction of tetrazolium salt to water insoluble formazan crystals using doxorubicin as a standard control. The cytotoxicity was assessed against a panel of four different tumor cell lines: A549 derived from human alveolar adenocarcinoma epithelial cells (ATCC No. CCL-185), HeLa derived from human cervical cancer cells (ATCC No. CCL-2), DU145 derived from human prostate (HTB-81) adenocarcinoma cells (ATCC No. HTB-81) and HepG2 derived from human hepatocellular carcinoma cells (ATCC No. HB-8065) using the MTT assay [18]. The IC_{50} values (50% inhibitory concentration) were calculated from the plotted absorbance data for the dose response curves. IC_{50} values (in µM) are expressed as the average of two independent experiments.

Results and discussion

Chemistry

Initially, the methyl undecenoate was prepared from undecenoic acid by using 2% sulfuric acid in methanol [IR, 1735 cm^{-1} (ester carbonyl); ^{1}H-NMR, 3.6 ppm (OCH_3); ESI-MS, 198 (M^+); yield, 95%]



R = -CH_3 **(a)**, -CH (CH_3)$_2$ **(b)**, -CH_2Ph- OH **(c)**, -CH_2Ph **(d)**,-C_2H_4-S-CH_3 **(e)**, -CH_2-CH (CH_3)$_2$ **(f)**

Scheme 2: Synthesis of undecenoic acid-amino acid-based hybrid molecules

Methyl undecenoate was epoxidized using metachloroperbenzoic acid to yield epoxy methyl undecanoate [IR, 1250 cm^{-1} (epoxy gp); ^{1}H-NMR, 2.3 ppm (epoxy protons); ESI-MS, 237 (M+23); yield, 90 %]. Later, the amino acid methyl esters were prepared by treating with some selected amino acids, namely, valine, tyrosine, phenylalanine, methionine, leucine with thionyl chloride in methanol [IR, 1735 cm^{-1} (ester carbonyl); ^{1}H-NMR, 3.6 ppm (OCH_3); ESI-MS of alanine analogue,103 (M^+); yield, 95%] (Scheme 1).

Epoxy methyl undecanoate was opened with amino group of the respective amino acid-based methyl esters to yield the corresponding fatty amino ester derivatives [presence of OH, NH peaks in IR (3350-3500 cm^{-1}) and ^{1}H-NMR (2 ppm), ESI-MS of alanine analogue, 318 (M+1); yield, 20 %]. Finally, the hydroxy group in fatty amino ester derivatives were sulphated using chlorosulfonic acid to yield their corresponding sulphated sodium salts [yield, 80%] (Scheme 2).

Biological activities

The prepared amino acid-based undecanoic acid derivatives were further subjected to antimicrobial and antioxidant activities following established protocols. Based on the antimicrobial activity results, it was observed that the minimum inhibitory concentration (MIC) values for all the compounds exhibited >125 µg/mL against the tested microbial strains. The antioxidant results obtained by the DPPH method are given as their EC_{50} (µg ml^{-1}) values and the results to this regard are shown in the Table 1 and the results were compared with BHT and α-tocopherol as standard antioxidants. Among the tested amino acid-based undecenoic acid derivatives, the presence of the following functional moieties such as phenolic hydroxyl, phenolic group, branched alkyl chain, thionyl group in alkyl chain exhibited the antioxidant activity which supports the earlier published work [19]. In view of these facts, the antioxidant activities for the synthesized derivatives were performed.

Table 1: Antioxidant activity of the synthesized undecenoic acid-amino acid based derivatives

Test compounds	EC_{50} (µg ml^{-1}) (Mean ± S.D.)
6a	123.0 ± 0.35
6b	82.6 ± 0.19
6c	113.7 ± 0.17
6d	368.3 ± 0.38
6e	76.5 ± 0.62
6f	128.8 ± 0.32
7a	-[a]
7b	-
7c	606.5 ± 0.22
7d	-[a]
7e	-[a]
7f	260.4 ± 0.28
BHT	28.7 ± 0.24
α-Tocopherol	10.6 ± 0.32

-[a] – No activity

Further, in the present study it was noticed that the aliphatic hydroxylamine-based compounds (6 series compounds – non-sulfated) with free hydroxyl group functioned as good antioxidants which corroborates with the observations recorded in the earlier studies [20]. While, the 7 series compounds (sulfated) did not show significant antioxidant activity.

Compounds 6a-f, 7a-f were screened for *in vitro* cytotoxicity against four human cancer cell lines such as A549, HeLa, DU145 and HepG2 cancer cell lines using Doxorubicin as standard. The results to this regard are shown in Table 2. Among all the compounds screened, the compounds 6e, 7b, 7c, 7d, 7e and 7f showed good cytotoxicity at micromolar concentration towards DU145 cell line. However, compounds 6a, 6b, 6c, 6d, 6f and 7a did not exhibit cytotoxicity against any of the tested cell lines.

Table 2: Cytotoxic activity of the synthesized undecenoic acid-amino acid based derivatives

Test compound	IC_{50} values in (μM)			
	A549	HeLa	DU145	HepG2
6a	-[a]	-[a]	66.5±0.11	-[a]
6b	-[a]	-[a]	-[a]	-[a]
6c	-[a]	-[a]	-[a]	-[a]
6d	-[a]	-[a]	-[a]	-[a]
6e	-[a]	112.8±0.22	27.7±0.26	39.3±0.18
6f	-[a]	-[a]	-[a]	-[a]
7a	-[a]	-[a]	-[a]	-[a]
7b	-[a]	-[a]	31.8±0.22	-[a]
7c	-[a]	-[a]	32.1±0.28	-[a]
7d	-[a]	-[a]	39.3±0.14	-[a]
7e	-[a]	-[a]	25.5±0.09	-[a]
7f	-[a]	-[a]	27.5±0.32	-[a]
Doxorubicin (Standard control)	0.7±0.11	0.6±0.21	0.6±0.13	0.8±0.14

-[a] – No activity

From a structure-activity relationship perspective, it was observed that the cytotoxicity for compound 6e is attributed to the presence of thio group which is an electron withdrawing group, while compounds 7b, 7c, 7d, 7e and 7f are sulphated in nature having a strong electron withdrawing sulphate group which contributed to the cytotoxicity. In some of the earlier studies, it was also reported that the sulphate group attached to the parent scaffold tends to exhibit a strong electron withdrawing property which plays a pivotal role in contributing to the cytotoxicity [21], which corroborates the above observation. While in case of compound 6a, the methyl group which is a moderate electron donating group exhibited cytotoxicity specifically against the DU145 cell line.

Conclusions

In conclusion, various undecenoic acid-amino acid based derivatives were prepared by using the different amino acids and undecenoic acid as starting materials and these prepared derivatives were further evaluated for different biological activities. These synthesized derivatives showed no significant antimicrobial activity against any the tested microbial strains. Further, the non-sulfated derivatives showed moderate antioxidant activities. While, the sulfated derivatives exhibited promising cytotoxicity against the prostate cancer (DU145) cell line. Further studies on the preparation of derivatives involving undecenoic acid and other amino acids may provide interesting bioactive lead molecules.

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