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REGULAR ARTICLE

The impact of sugar and fatty acid on the bioactivity of *N*-fatty acyl-*L*-tyrosine aglycone

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Abstract. In the present study, a series of fatty acids-based (short, medium and long unsaturated chains) glycosylated *N*-fatty acyl-*L*-tyrosines and *N*-lipoyl-*L*-tyrosine methyl esters were synthesized and evaluated for their cytotoxic and antimicrobial activities. The aglycone moiety was synthesized using different chemical reagents. The glycosylation of aglycone moiety with different carbohydrates was performed using the Lewis acid, $BF_3.Et_2O$. All the synthesized compounds were tested against a panel of four cancer cell lines. The glycosylated *N*-fatty acyl-*L*-tyrosines showed moderate activity against all the cell lines and the IC_{50} values were in the range of 15.6−45.6 μM. However, the oleic acid analogues (**10a, 10d**) exhibited IC_{50} values of 15.6, 17.6 μM, respectively, against MDA-MB-231 cell line. Glycosylated *N*-lipoyl-*L*-tyrosine methyl esters (**6b–6d**) showed promising activity against all the tested cell lines and the IC_{50} values ranged between 9.4−13.8 μM. The compound **6d** exhibited significant cytotoxicity and IC_{50} values were 10.5, 9.4, 10.9 and 12.1 μM against A549, PC3, MDA-MB-231 and HepG2 cell lines, respectively. Moreover, the non-glycosylated *N*-fatty acyl-*L*-tyrosine and methyl *N*-fatty acyl-*L*-tyrosinate derivatives showed excellent and moderate antimicrobial activity against some of the tested bacterial strains.

Keywords. *L*-Tyrosine; *N*-fatty acyl-*L*-tyrosine; fatty acids; α-Lipioic acid; cytotoxicity; carbohydrates.

1. Introduction

In general, glycosides are biologically active compounds and the glycosidic residue dictates their biological activity. In some cases, the glycosidic residue also improves the pharmacokinetic parameters.[1] In some glycosides, the overall molecular structure[1,2] contributes to the biological activity. Especially, the combination of carbohydrate moiety to aglycone plays a functional role in the bioactivity, and to support this statement, a noted example is vancomycin.[1–4] Moreover, most of the glycoprotein and glycolipid carbohydrate antigens find application in the anticancer vaccine research. These carbohydrate antigens are directed to the cell surface either by lipid tail or by an amino acid component linked to the oligosaccharide.[5]

On the other hand, many reports are available on biologically active lipoamino acids and fatty amino acid conjugates.[6–8] These endogenous substances exhibit multiple biological activities[9–12] such as analgesic, anti-inflammatory and inhibition of cell proliferation. Further, a number of microbial secondary metabolites carrying a carbohydrate moiety on the phenolic hydroxyl group of tyrosine or hydroxy phenyl glycine derivatives and phenolic glycosides and its derivatives exhibited good cytotoxicity.[13–17] Earlier, Brady and Clardy isolated long-chain *N*-fatty acyl tyrosine antibiotics from heterologously expressed environmental DNA,[18,19] which exhibited anti-bacterial activities. Further, there are some reports[15,20,21] available on the synthesis of glycosyl-tyrosine and their related derivatives. However, there is a paucity of information on the synthesis and biological activity of lipid derivatives of glycosylated tyrosine.

Nevertheless, the biological activity of *N*-fatty acyl tyrosines is dependent on the fatty acid moiety. Considering this fact, we have included an unusual fatty acid α-lipoic acid (1,2-dithiolane-3-valeric acid or thioctic acid) in the present study. It is well-established that α-lipoic acid acts as an essential coenzyme in several

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enzyme-catalyzed reactions and also exhibits antioxidant activity.[22,23] A recent report on the lipoic acid-based *N*-fatty acyl amino acids showed potential biological applications.[22]

Based on the above facts, it was necessary to place the amino acid acylated with fatty acids and glycosylated with carbohydrates into a separate class of lipid derivatives which are worthy to investigate. Hence, in the present study, the glycosylated *N*-fatty acyl-*L*-tyrosines with short, medium and long chain unsaturated fatty acids and glycosylated *N*-lipoyl-*L*-tyrosine methyl esters were synthesized and further evaluated for their biological activities to examine the impact of sugar and fatty acid on the bioactivity of *N*-fatty acyl-*L*-tyrosine derivatives.

2. Experimental

2.1 *Materials and methods*

All the chemicals used in these schemes were of analytical grade and they were obtained from different commercial sources and were used without any further purification. All the dry reactions were carried out under nitrogen atmosphere using anhydrous freshly distilled solvents and 4 Å molecular sieves in flame dried glassware using standard gas-light syringes, cannulas and septa. Reactions were monitored on micro TLC plates (coated with TLC grade silica gel, obtained from Merck) and the spots were detected by iodine vapor. Column chromatography was performed by using silica gel (100–200 mesh) procured from Qualigens (India) using freshly distilled solvents. All the ^{1}H-NMR and ^{13}C-NMR spectra were recorded with a Bruker Avance (operating for ^{1}H-NMR at 300 MHz, 500 MHz, 600 MHz and for ^{13}C-NMR at 75 MHz, 125 MHz, 175 MHz) spectrometer using TMS (δ = 0 ppm) and δ 77.00 ppm as internal standard for chemical shifts (δ) in $CDCl_3$ at 25°C. The chemical shift values are presented in ppm (parts per million) units. Mass spectra were recorded with HRMS (Electron Spray Ionization Technique). IR spectra were recorded in chloroform on a Perkin-Elmer FT-IR spectrum BX. The melting points were determined on a Barnstead Electro Thermal 9200 Instrument. Purity of the compounds was analyzed using HPLC (Agilent Technologies 1200 series with RI detector interfaced with Agilent Chemistation on a Rezex RPM-monosaccharide (Pb^{+2}) column (300 × 7.8 mm), oven temperature at 65°C, 100% water as mobile phase, flow rate at 0.6 mL/min, and optical unit temperature at 35°C. All the purified compounds were obtained with more than 98% purity.

2.2 *Synthesis of methyl-L-tyrosinate (**1**)*

Concentrated (96%) H_2SO_4 (9 mL) was added drop wise to a heterogenic solution of *L*-tyrosine (8 g) in methanol (150 mL). The mixture was refluxed for 4 h, and the solution was concentrated by evaporating the methanol. The solution was brought to pH of about 10 by adding saturated solution of sodium carbonate and extracted with three portions of DCM. The organic phase was evaporated to a white solid (6.03 g, 70% yield).; M.p.: 135−137°C, $[\alpha]_D^{20}$ = +26.98° (C = 2.4 g/dL, MeOH) {Lit.[24,25] M.p.: 135−136°C, $[\alpha]_D^{20}$ = +26.1° (C = 2.4 g/dL, MeOH)}; ^{1}H-NMR ($CDCl_3$, 500MHz): δ 6.95 (d, J = 7.47 Hz, 2H), 6.7 (d, J = 8.24 Hz, 2H), 3.64 (s, 3H), 3.59 (t, J = 6.71 Hz, 1H), 2.88 (dd, J = 5.49, 13.58 Hz, 1H), 2.74 (dd, J = 7.17, 13.12 Hz, 1H); ^{13}C-NMR ($CDCl_3$ + DMSO − d_6, 100 MHz): 174.8(C=O), 155.7(Ar-C-OH), 129.7(Ar-C), 127(Ar-CH), 115(Ar-CH), 55.4(NH-CH), 51.2(CH_3), 39.7(Ar-CH_2); IR(KBr): 3355, 3300, 2928, 1744, 1598, 1514, 1478, 1264, 1175, 1020, 837 cm^{-1}; HRMS (ESI) m/z [M + H]-calc. for $C_{10}H_{14}O_3N$ = 196.0968; Found 196.0961.

2.3 *General procedure for synthesis of methyl N-fattyacyl-L-tyrosinate*

A mixture of 12.3 mmol of fatty acid, 12.3 mmol of EDC and 15.38 mmol of HOBt dissolved in ice-cold anhydrous DCM (50 mL) was kept in ice for 20 min with stirring, followed by the addition of 10.25 mmol of *L*-tyrosine methyl ester and the mixture was left at room temperature for 12 h with stirring. TLC (hexane/ethyl acetate 1:1, v/v) was used to monitor the reaction. At the end of the reaction, the mixture was dissolved in 75 mL of $CHCl_3$, which was then washed with 5% $NaHCO_3$ solution and saturated NaCl solution. The chloroform layer was dried with anhydrous Na_2SO_4. The filtrate was then dried under vaccum. Then, the crude mixture was purified by silica-gel chromatography by using solvent mixture (hexane/ethyl acetate 70:30, v/v), with 80-89% yield of the title compound was obtained as a solid.

2.3a *Synthesis of methyl N-hexanoyl-L-tyrosinate (**2**)*: The crude mixture was purified by silica-gel chromatography by using solvent mixture (hexane/ethyl acetate 70:30, v/v), with 85% yield of the title compound, which was obtained as a solid. ^{1}H-NMR ($CDCl_3$, 500 MHz): δ 7.14 (br s, 1H), 6.93 (d, J = 8.39 Hz, 2H), 6.73 (d, J = 8.54 Hz, 2H), 6.05 (d, J = 7.93 Hz, 1H), 4.86–4.9 (m, 1H), 3.73 (s, 3H), 3.08 (dd, J = 5.49, 14.03 Hz, 1H), 2.97 (dd, J = 6.25, 14.03 Hz, 1H), 2.17 (t, J = 7.32 Hz, 2H), 1.54–1.6 (m, 2H), 1.2–1.32 (m, 4H), 0.86 (t, J = 6.71 Hz, 3H); ^{13}C-NMR ($CDCl_3$, 125 MHz): δ 173.6(C=O), 172.3(C=O), 155.7(Ar-C-OH), 130(Ar-C), 126.5(Ar-CH), 115.5(Ar-CH), 53.1(NH-CH), 52.3(CH_3), 37(Ar-CH_2), 36.3(O = C-$\underline{CH_2}$), 31.1(CH_2), 25.1(CH_2), 22.2(CH_2), 13.7(CH_3); IR(KBr): 3330, 2958, 2928, 1725, 1656, 1271, 1223, 829 cm^{-1}; HRMS (ESI) m/z [M + Na]-calc. for $C_{16}H_{23}O_4NNa$ = 316.1519; Found: 316.1507.

2.3b *Synthesis of methyl N-undec-10-enoyl-L-tyrosinate (**3**)*: The crude mixture was purified by silica-gel chromatography by using solvent mixture (hexane/ethyl acetate 70:30, v/v) (89% yield) of the title compound which was obtained as a white solid. ^{1}H-NMR ($CDCl_3$, 300MHz): δ

6.93 (d, J = 8.3 Hz, 2H), 6.83 (br s, 1H), 6.73 (d, J = 8.49 Hz, 2H), 6.02 (d, J = 7.93 Hz, 1H), 5.73–5.87 (m, 1H), 4.94–5.01 (m, 2H), 4.84–4.91 (m, 1H), 3.73 (s, 3H), 3.08 (dd, J = 5.66, 13.97 Hz, 1H), 2.98 (dd, J = 6.04, 13.97 Hz, 1H), 2.17 (t, J = 7.36 Hz, 2H), 1.57 (m, 2H), 1.25 (m, 10H); ^{13}C-NMR ($CDCl_3$, 100 MHz): δ 173.6(C=O), 172.3(C=O), 155.7(Ar-C-OH), 139.1(H_2C-CH = CH_2), 130.1(Ar-C), 126.5(Ar-CH), 115.5(Ar-CH), 114.1(CH = CH_2), 53.2(NH-CH), 52.3(CH_3), 37.1(Ar-CH_2), 36.4(O = C-CH_2), 33.7(H_2C-CH = CH_2), 29.2(CH_2), 29(CH_2), 28.9(CH_2), 28.8(CH_2), 25.5(CH_2); IR(KBr): 3413, 3317, 2921, 2851, 1719, 1650, 1520, 1263, 1220, 1022, 913, 824 cm^{-1}; HRMS (ESI) m/z [M + Na]-calc. for $C_{21}H_{31}O_4$NNa = 384.2145; Found: 384.2135.

2.3c *Synthesis of methyl N-tetradecanoyl-L-tyrosinate (4)*: The crude mixture was purified by silica-gel chromatography by using a gradient of (hexane/ethyl acetate 70:30, v/v) (89% yield) of the title compound which was obtained as a light brown solid. ^{1}H-NMR ($CDCl_3$, 500MHz): δ 7.39 (br s, 1H), 6.92 (d, J = 8.54 Hz, 2H), 6.73 (d, J = 8.39 Hz, 2H), 6.09 (d, J = 8.08 Hz, 1H), 4.85–4.89 (m, 1H), 3.72 (s, 3H), 3.07 (dd, J = 5.64, 14.03 Hz, 1H), 2.98 (dd, J = 6.1, 14.03 Hz, 1H), 2.18 (t, J = 7.47 Hz, 2H), 1.56–1.59 (m, 2H), 1.24 (m, 21H), 0.87 (t, J = 6.86 Hz, 3H); ^{13}C-NMR ($CDCl_3$, 100 MHz): δ 173.5(C=O), 172.3(C=O), 155.6(Ar-C-OH), 130.1(Ar-C), 126.6(Ar-CH), 115.5(Ar-CH), 53.1(NH-CH), 52.3(CH_3), 37.1(Ar-CH_2), 36.4(O = C-CH_2), 31.8(O = C-CH_2-CH_2), 29.5(CH_2), 29.4(CH_2), 29.3(CH_2), 29.2(CH_2), 29.1(CH_2), 25.5(CH_2), 22.6(CH_2), 14(CH_3); IR(KBr): 3309, 2919, 2850, 1741, 1641, 1542, 1240, 1018, 825 cm^{-1}; HRMS (ESI) m/z [M + Na]-calc. for $C_{24}H_{39}O_4$NNa = 428.2771; Found: 428.2745.

2.3d *Synthesis of methyl N-oleoyl-L-tyrosinate (**5**)*: The crude mixture was purified by silica-gel chromatography by using as gradient of (hexane/ethyl acetate 70:30, v/v) (87% yield) of the title compound which was obtained as a white solid. ^{1}H-NMR ($CDCl_3$, 500MHz): δ 6.94 (d, J = 8.39 Hz, 2H), 6.73 (d, J = 8.54 Hz, 2H), 6.38 (br s, 1H), 5.95 (d, J = 8.08 Hz, 1H), 5.30–5.37 (m, 2H), 4.86–4.9 (m, 1H), 3.73 (s, 3H), 2.96–3.1 (m, 2H), 2.17 (t, J = 7.47 Hz, 2H), 1.98–2.02 (m, 4H), 1.58 (m, 2H), 1.26 (m, 20H), 0.87 (t, J = 6.86 Hz, 3H); ^{13}C-NMR ($CDCl_3$, 125 MHz): δ 173.3(C=O), 172.3(C=O), 155.5(Ar-C-OH), 130.1(Ar-C), 129.9(HC=CH), 129.6(HC=CH), 126.8(Ar-CH), 115.5(Ar-CH), 53.1(NH-CH), 52.3(CH_3), 37.2(Ar-CH_2), 36.5(O = C-CH_2), 31.8(O = C-CH_2-CH_2, H_2C-CH = CH_2), 29.7(CH_2), 29.6(CH_2), 29.4(CH_2), 29.2(CH_2), 29.1(CH_2), 29(CH_2), 25.5(CH_2), 22.6(CH_2), 14(CH_3); IR(KBr): 3425, 3309, 2923, 2852, 1719, 1648, 1518, 1460, 1218, 1019, 825 cm^{-1}; HRMS (ESI) m/z [M + Na]-calc for .$C_{28}H_{45}O_4$NNa = 482.3240; Found: 482.3221.

2.3e *Synthesis of methyl N-(5-(1, 2-dithiolan-3-yl) pentanoyl)-L-tyrosinate (**6**)*: The crude mixture was purified by silica-gel chromatography by using a gradient of (chloroform/methanol 99:1, v/v) (89% yield) of the title compound which was obtained as a yellowish semi-solid. ^{1}H-NMR ($CDCl_3$, 500MHz): δ 6.94 (d, J = 8.54 Hz, 2H), 6.73 (d, J = 8.34 Hz, 2H), 6.04 (m, 1H), 4.85–4.9 (m, 1H), 3.75 (s, 3H), 3.48–3.55 (m, 1H), 3.07–3.19 (m, 3H), 2.93–2.99 (m, 1H), 2.4–2.46 (m, 1H), 2.13–2.23 (m, 2H), 1.84–1.91 (m, 2H), 1.55–1.68 (m, 4H), 1.3–1.43 (m, 2H); ^{13}C-NMR ($CDCl_3$ + DMSO − d_6, 100 MHz): δ 171.3(C=O), 170.8(C=O), 154.6(Ar-C-OH), 128.5(Ar-C), 125.6(Ar-CH), 113.7(Ar-CH), 54.7(S-CH), 52.2(NH-CH), 50.3(CH_3), 38.5(S-CH-CH_2), 36.7(Ar-CH_2), 35(S-CH_2), 33.7(O = C-CH_2), 32.9(S-CH-CH_2), 26.9(CH_2), 24.7(CH_2), 23.6(CH_2); IR(Neat): 3309, 3016, 2931, 2858, 1739, 1647, 1615, 1515, 1441, 1368, 1220, 754 cm^{-1}; HRMS (ESI) m/z [M + Na]-calc. for $C_{18}H_{25}O_4NNaS_2$ = 406.1117; Found: 406.1104.

2.4 *General procedure for synthesis of N-fatty acyl-L-tyrosine*

N-fatty acyl-*L*-tyrosine methyl esters (**2–6**) (1 eq.) were dissolved in THF: H_2O (7:3) and LiOH added (3 eq.), stirred the reaction mixture at RT for 16 h. After completion of the reaction, the mixture was concentrated under vacuum to obtain a white precipitate. This white precipitate was neutralized with 2 N HCl and the reaction mixture was extracted with ethyl acetate. The organic layer was dried over sodium sulphate and concentrated to yield a white solid. This solid with little impurity was purified by silica gel chromatography using a gradient of chloroform/methanol (95:5, v/v) to obtain a yield (96 - 98%) of the title compound as a solid.

2.4a *Synthesis of N-hexanoyl-L-tyrosine (**7**)*: The crude mixture was purified by silica-gel chromatography by using solvent mixture (chloroform/methanol 95:5, v/v), with 98% yield of the title compound which was obtained as a solid. ^{1}H-NMR ($CDCl_3$ + CD_3OD, 300 MHz): δ 7.00 (d, J = 8.25 Hz, 2H), 6.74 (d, J = 8.25 Hz, 2H), 4.72 (t, J = 6.05 Hz, 1H), 2.94–3.14 (m, 2H), 2.16 (t, J = 7.42 Hz, 2H), 1.51–1.60 (m, 2H), 1.21–1.33 (m, 4H), 0.86 (t, J = 6.60 Hz, 3H); ^{13}C-NMR ($CDCl_3$ + CD_3OD, 75 MHz): δ 173.8(C=O), 173.7(C=O), 155.5(Ar-C-OH), 130.1(Ar-C), 126.9(Ar-CH), 115.1(Ar-CH), 53.1(NH-CH), 36.4(Ar-CH_2), 36.1(O = C-CH_2), 31.1(CH_2), 25.1(CH_2), 22.1(CH_2), 13.5(CH_3); IR (KBr): 3350, 2958, 2928, 1690, 1656, 1538, 1462, 1278, 1223, 829 cm^{-1}; *ESI* m/z at 278 [M - H].

2.4b *Synthesis of N-undec-10-enoyl-L-tyrosine (**8**)*: The crude mixture was purified by using by silica-gel chromatography by using solvent mixture (chloroform/methanol 95:5, v/v), with 98% yield of the title compound which was obtained as a solid. ^{1}H-NMR ($CDCl_3$ + CD_3OD, 500 MHz): δ 7.02 (d, J = 8.54 Hz, 2H), 6.74 (d, J = 8.54 Hz, 2H), 5.76–5.84 (m, 1H), 4.90–4.99 (m, 2H), 4.69 (t, J = 7.17 Hz, 1H), 2.93–3.12 (m, 2H), 2.17 (t, J = 7.32 Hz, 2H), 2.01–2.05 (m, 2H), 1.55 (m, 2H), 1.27–1.37 (m, 10H); ^{13}C-NMR ($CDCl_3$ + CD_3OD, 75 MHz): δ 173.7(C=O),

173.6(C=O), 155.5(Ar-C-OH), 138.9(H_2C-$\underline{CH}$ = CH_2), 130.1(Ar-C), 126.8(Ar-CH), 115.1(Ar-CH), 113.8(CH = $\underline{CH_2}$), 53.1(NH-CH), 36.4(Ar-CH_2), 36.1(O = C-CH_2), 33.5(O = C-CH_2-$\underline{CH_2}$, $\underline{H_2C}$-CH = CH_2), 29(CH_2), 28.9(CH_2), 28.8(CH_2), 28.6(CH_2), 25.3(CH_2); IR(KBr): 3452, 2958, 2922, 1692, 1654, 1278, 1234, 816 cm^{-1}; ESI m/z at 346 [M - H].

2.4c *Synthesis of N-tetradecanoyl-L-tyrosine (**9**)*: The crude mixture was purified by silica-gel chromatography by using solvent mixture (chloroform/methanol 95:5, v/v), with 96% yield of the title compound which was obtained as a solid. ^{1}H-NMR ($CDCl_3$ + CD_3OD, 500 MHz): δ 6.99 (d, J = 8.54 Hz, 2H), 6.74 (d, J = 8.54 Hz, 2H), 4.71 (t, J = 6.25 Hz, 1H), 2.96–3.11 (m, 2H), 2.16 (t, J = 7.47 Hz, 2H), 1.55 (m, 2H), 1.25 (m, 20H), 0.88 (t, J = 6.86 Hz, 3H); ^{13}C-NMR ($CDCl_3$ + CD_3OD, 75 MHz): δ 173.7(C=O), 173.5(C=O), 155.5(Ar-C-OH), 130(Ar-C), 126.8(Ar-CH), 115(Ar-CH), 53(NH-CH), 36.3(Ar-CH_2), 36(O = C-CH_2), 31.6(O = C-CH_2-CH_2), 29.3(CH_2), 29.2(CH_2), 29(CH_2), 28.9(CH_2), 25.3(CH_2), 22.3(CH_2), 13.7(CH_3); IR(KBr): 3250, 2942, 2926, 1678, 1662, 1278, 1245, 736 cm^{-1}; *ESI* m/z at 390 [M - H].

2.4d *Synthesis of N-oleoyl-L-tyrosine (**10**)*: The crude mixture was purified by silica-gel chromatography by using solvent mixture (chloroform/methanol 95:5, v/v), with 98% yield of the title compound which was obtained as a solid. ^{1}H-NMR ($CDCl_3$, 500 MHz): δ 6.93 (d, J = 7.62 Hz, 2H), 6.68 (d, J = 7.62 Hz, 2H), 6.34 (s, 1H),5.29–5.37 (m, 2H), 4.82 (m, 1H), 3.04 (m, 2H), 2.17 (t, J = 7.62 Hz, 2H), 1.98–2.00 (m, 4H), 1.54 (m, 2H), 1.25 (m, 20H), 0.87 (t, J = 6.71 Hz, 3H); ^{13}C-NMR ($CDCl_3$, 100 MHz): δ 174.8(C=O), 174.5(C=O), 155.2(Ar-C-OH), 130.3(HC=CH), 130(HC=CH), 129.6(Ar-C), 126.9(Ar-CH), 115.6(Ar-CH), 53.4(NH-CH), 36.7(HC = CH-$\underline{CH_2}$), 36.3 (O = C-CH_2), 31.8(O = C-CH_2-CH_2), 29.7(CH_2), 29.5(CH_2), 29.2(CH_2), 29.1(CH_2), 27.2(CH_2), 25.5(CH_2), 22.6(CH_2), 14.1(CH_3); IR(KBr): 3342, 2947, 2929, 1692, 1670, 1278, 1236, 832 cm^{-1}; ESI m/z at 444 [M - H].

2.4e *Synthesis of N-(5-(1, 2-dithiolan-3-yl) pentanoyl)-L-tyrosine (**11**)*: The crude mixture was purified by silica-gel chromatography by using solvent mixture (chloroform/methanol 92:8, v/v), with 96% yield of the title compound which was obtained as a solid. ^{1}H-NMR ($CDCl_3$ + CD_3OD, 300 MHz): δ 7.02 (d, J = 8.25 Hz, 2H), 6.74 (d, J = 8.25 Hz, 2H), 4.69 (t, J = 5.77 Hz, 1H), 2.91–3.19 (m, 3H), 2.79 (m, 1H), 2.19 (t, J = 7.42 Hz, 2H), 1.87–2.05 (m, 2H), 1.56–1.68 (m, 4H), 1.40 (m, 2H); ^{13}C-NMR ($CDCl_3$ + CD_3OD, 75 MHz): δ 173.5(C=O), 155.3(Ar-C-OH), 129.9(Ar-C), 127(Ar-CH), 114.9(Ar-CH), 56(S-CH), 53.1(NH-CH), 39.8(S-$\underline{CH}$-CH_2), 38(Ar-CH_2), 36.2(S-CH_2), 35.5(S-CH-$\underline{CH_2}$), 34.1(O = C-$\underline{CH_2}$), 29.2(CH_2), 24.9(CH_2); IR(KBr): 3332, 3022, 2945, 2884, 1695, 1647, 1615, 1515, 1441, 1368, 1220, 754 cm^{-1}; ESI m/z at 368 [M - H].

2.5 *General procedure for synthesis of β-D-glucose and β-D-galactose penta acetates*[26]

A mixture of dextrose/galactose (6.0 g, 33.32 mmol) and sodium acetate (8.196 g, 99.99 mmol) were dissolved in acetic anhydride (51.6 mL, 549.6 mmol). The reaction mixture was refluxed for 2.5 h at 90°C. After the reaction time, the reaction mixture was cooled to room temperature and poured into a beaker containing crushed ice (250 mL) under stirring conditions. The penta-acetate was precipitated. The precipitation was filtered and washed with ice-cold water until the odor of the acetic acid disappeared. The crude product was purified by recrystallization from MeOH to afford the title compound (11.95 g, 92%) as a white crystalline solid.

2.5a *Synthesis of 1,2,3,4,6 penta-O-acetyl-β-D-glucopyranose*[26] *(**a**)*: M.p. 130−135°C, lit. 132−133.5°C. ^{1}H-NMR (500 MHz, $CDCl_3$) δ 5.72 (d, J = 8.3 Hz, 1H), 5.26 (t, J = 9.3 Hz, 1H), 5.11−5.16 (m, 2H), 4.29 (dd, J = 4.5, 12.5 Hz, 1H), 4.11 (dd, J = 2.1, 12.5 Hz, 1H), 3.83–3.86 (m, 1H), 2.11 (s, 3H), 2.09 (s, 3H), 2.03 (s, 6H), 2.01 (s, 3H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 170.4(C=O),169.9(C=O), 169.2(C=O), 169(C=O), 168.7(C=O), 91.5(C1), 72.6(C3), 72.5(C5), 70(C2), 67.5(C4), 61.3(C6), 20.6(CH_3), 20.5(CH_3), 20.4(CH_3). IR ($CHCl_3$) 3027, 2969, 2951, 2907,1756, 1743, 1422, 1371, 1322, 1225, 1067,1048, 912, 756, 704, 641, 599 cm^{-1}. HRMS (ESI) m/z [M + Na]-calc for $C_{16}H_{22}O_{11}Na$ 413.10543 Found: 413.10449.

2.5b *Synthesis of 1, 2, 3, 4, 6 penta-O-acetyl-β-D-galactopyranose (**b**)*: M.p. 142−145°C, lit. 143−144°C. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 5.71 (d, J = 8.31 Hz, 1H), 5.42–5.43 (m, 1H), 5.31–5.36 (m, 1H), 5.1 (dd, J = 3.42, 10.39 Hz, 1H), 4.1–4.19 (m, 2H), 4.05–4.06 (m, 1H), 2.17 (s, 3H), 2.12 (s, 3H), 2.05 (s, 6H), 2.0 (s, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 170(C=O), 169.8(C=O), 169.6(C=O), 169.1(C=O), 168.7(C=O), 91.9(C1), 71.4(C3), 70.5(C5), 67.6(C2), 66.6(C4), 60.8(C6), 20.5(CH_3), 20.4(CH_3), 20.3(CH_3); IR ($CHCl_3$) 3029, 2969, 2946, 2852,1752, 1748, 1424, 1368, 1322, 1228, 1060,1048, 912, 756, 704, 641, 599 cm^{-1}. ESI-MS: m/z at 413 [M + Na].

2.6 *General procedure for synthesis of D-mannose, L-rhamnose penta and tetra acetates*[27]

L-rhamnose monohydrate/mannose (22 mmol) was dissolved in pyridine (30 mL) and followed by acetic anhydride (30 mL) was added slowly to the reaction mixture. The reaction mixture was stirred for 12 h at RT. After completion of the consumption of the starting material, the reaction mixture was quenched with 1 M HCl. Then, the reaction mixture was dissolved in EtOAc and the organic layer was extracted with 1 M HCl and water. The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by silica gel chromatography using solvent mixture hexane: EtOAc (60: 40, v/v) to semi-solid.

2.6a *Synthesis of 1, 2, 3, 4, 6 penta-O-acetate-D-mannopyranose (**c**)*: ^{1}H-NMR (500 MHz, $CDCl_3$) δ 6.09 (m, 1H), 5.14–5.34 (m, 3H), 3.82–4.29 (m, 3H), 2.2 (s, 3H), 2.18 (s, 3H), 2.1 (s. 3H), 2.06 (s, 3H), 2.0 (s, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 170.3(C=O), 169.7(C=O), 169.4(C=O), 169.2(C=O), 167.8(C=O), 90.3(C1), 90.1(C1), 72.9(C3), 70.3(C5), 68.5(C2), 68(C2), 65.2(C4), 65.1(C4), 61.8(C6), 20.6(CH_3), 20.5(CH_3), 20.4(CH_3), 20.2(CH_3); IR ($CHCl_3$) 3018, 2932, 2872, 1752, 1734, 1456, 1376, 1321, 1225, 1074,1052, 916, 756, 704, 641, 599 cm^{-1}; ESI-MS: m/z at 413 [M + Na].

2.6b *Synthesis of 1, 2, 3, 4 tetra-O-acetate-L-rhamnopyranose*[27] *(d)*: ^{1}H-NMR (300 MHz, $CDCl_3$) δ 6.01 (d, J = 1.7 Hz, 1H), 5.84 (d, J = 0.94 Hz, 1H), 5.24–5.33 (m, 1H), 5.07–5.15 (m, 1H), 3.64–4.15 (m, 1H), 2.23 (s, 3H), 2.16 (s, 3H), 2.07 (s, 3H), 2.01 (s, 3H), 1.22–1.28 (m, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 170.1(C=O), 169.9(C=O), 169.6(C=O), 168.3(C=O), 90.5(C1), 90.2(C1), 71.3(C3), 70.5(C4), 70.3(C4), 68.7(C5), 68.6(C5), 68.5(C2), 68.4(C2), 20.7(CH_3), 20.6(CH_3), 20.5(CH_3), 20.4(CH_3), 17.2(C6); IR(Neat) 1752.3, 1433.8, 1371.6, 1222, 1150.1, 1087.8, 1055.5, 973.6 cm^{-1}; HRMS (ESI) m/z [M + Na]-calc for $C_{14}H_{20}O_9Na$ = 355.0999; Found: 355.0994.

2.7 *General procedure for synthesis of methyl N-(5-(1,2-dithiolan-3-yl) pentanoyl)-O-α/β-D/L-glycopyranosyl-(S)-tyrosinates*

To a solution of hexose penta acetate (2.56 mmol) in dichloromethane (10 mL) was added methyl lipoyl tyrosinate (3.704 mmol) and borontrifloride etherate (3.84 mmol) at 0°C and the reaction mixture was stirred at room temperature for overnight. The reaction mixture was dissolved in $CHCl_3$ and washed with $NaHCO_3$ solution and water (2 × 150 mL). The organic phase was dried over sodium sulphate and concentrated to a yield a liquid. The crude compound was directly used for the next step. This crude mixture was dissolved in dry methanol that contained a catalytic amount of sodium methoxide. The reaction mixture was allowed to stir at ambient temperature for 30 min under nitrogen. After total consumption of the starting material, the reaction mixture was neutralized by the addition of Amberlite IR-120 (H^+) resin. Then, the reaction mixture was filtered and concentrated under reduced pressure to obtain a crude product. This crude product was purified by silica gel chromatography using a gradient of chloroform: methanol (92:8, v/v) to give title compounds (**6a–6d**) as yellow solids with 70–75% yields.

2.7a *Synthesis of methyl N-(5-(1,2-dithiolan-3-yl) pentanoyl)-O-β-D-glucopyranosyl-(S)-tyrosinate (**6a**)*: This solid was purified by silica gel chromatography using a gradient of chloroform/methanol (92:8, v/v) to obtain a yield of 71%, as a yellow solid. ^{1}H-NMR (CD_3OD, 300MHz): δ 7.10 (d, J = 8.49 Hz, 2H), 6.99 (d, J = 8.49 Hz, 2H), 4.84 (d, J = 7.36 Hz, 1H), 4.60–4.65 (m, 1H), 3.85–3.89 (m, 1H), 3.71 (m, 1H), 3.67 (s, 3H), 3.51 (m, 1H), 3.40–3.45 (m, 3H), 3.04–3.19 (m, 3H), 2.85–2.92 (m, 1H), 2.37–2.48 (m, 1H), 2.16 (t, J = 7.17 Hz, 2H), 1.80–1.88 (m, 1H), 1.50–1.67 (m, 4H), 1.31–1.38 (m, 2H), 1.25 (m, 1H); ^{13}C-NMR ($CDCl_3$+CD_3OD, 75 MHz): δ 175.6(C=O), 173.4(C=O), 157.7(Ar-C-OH), 131.7(Ar-C), 130.9(Ar-CH), 117.6(Ar-CH), 102.1(C1), 77.7(C3), 77.6 (C5), 74.6(C2), 71.1(C4), 62.3(C6), 57.3(S-CH), 54.9(NH-CH), 52.7(CH_3), 41.1(S-CH-$\underline{CH_2}$), 39.2(Ar-CH_2), 37.4(S-CH_2), 36.3(S-CH-$\underline{CH_2}$), 35.5(O = C-$\underline{CH_2}$), 29.5(CH_2), 26.3(CH_2); IR(KBr): 3404, 2924, 2855, 1742, 1647, 1512, 1233, 1077, 830 cm^{-1}; HRMS (ESI) m/z [M+Na]-calc. for $C_{24}H_{35}O_9NS_2$ = 568.1645; Found: 568.1659.

2.7b *Synthesis of methyl N-(5-(1, 2-dithiolan-3-yl) pentanoyl)-O-β-D-galactopyranosyl-(S)-tyrosinate (**6b**)*: This solid was purified by silica gel chromatography using a gradient of chloroform/methanol (92:8, v/v) to obtain a yield of 72%, as a yellow solid. ^{1}H-NMR (CD_3OD, 300MHz): δ 7.12 (d, J = 8.49 Hz, 2H), 7.03 (d, J = 8.68 Hz, 2H), 6.70 (d, J = 7.93 Hz, 1H), 4.82 (d, J = 7.74, 1H), 4.60–4.64 (m, 1H), 3.88–3.96 (m, 2H), 3.74–3.80 (m, 2H), 3.67 (s, 3H), 3.49–3.59 (m, 2H), 3.04–3.20 (m, 2H), 2.84–2.92 (m, 2H), 2.38–2.48 (m, 1H), 2.16 (t, J = 6.98 Hz, 2H), 1.80–1.91 (m, 1H), 1.49–1.67 (m, 4H), 1.30–1.38 (m, 2H), 1.27 (m, 1H); ^{13}C-NMR (CD_3OD, 75 MHz): δ 175.8(C=O), 173.6(C=O), 158(Ar-C-OH), 131.8(Ar-C), 131.1(Ar-CH), 117.7(Ar-CH), 102.9(C1), 76.7(C3), 74.7(C5), 72.2(C2), 70.1(C4), 62.3(C6), 57.5(S-CH), 55.1(NH-CH), 52.7(CH_3), 41.2(S-CH-$\underline{CH_2}$), 39.3(Ar-CH_2), 37.5(S-CH_2), 36.7 (S-CH-$\underline{CH_2}$), 35.6(O = C-$\underline{CH_2}$), 29.6(CH_2), 26.5(CH_2); IR(KBr): 3402, 2928, 2848, 1748, 1632, 1522, 1223, 1072, 830 cm^{-1}; HRMS (ESI) m/z [M+Na]-calc. for $C_{24}H_{35}O_9NS_2$ = 568.1645; Found: 568.1659.

2.7c *Synthesis of methyl N-(5-(1, 2-dithiolan-3-yl) pentanoyl)-O-α-D-mannopyranosyl-(S)-tyrosinate (**6c**)*: This solid was purified by silica gel chromatography using a gradient of chloroform/methanol (92:8, v/v) to obtain a yield of 70%, as a yellow solid. ^{1}H-NMR (CD_3OD, 300MHz): δ 8.29 (d, J = 7.74 Hz, 1H), 7.13 (d, J = 8.49 Hz, 2H), 7.03 (d, J = 7.93 Hz, 2H), 5.43 (br s, 1H), 4.62 (m, 1H), 3.98 (m, 1H), 3.85–3.89 (m, 1H), 3.71–3.75 (m, 3H), 3.68 (s, 3H), 3.50–3.58 (m, 1H), 3.06–3.17 (m, 2H), 2.83–2.91 (m, 2H), 2.39–2.48 (m, 1H), 2.16 (t, J = 6.98 Hz, 2H), 1.81–1.90 (m, 1H), 1.48–1.63 (m, 4H), 1.27–1.36 (m, 3H); ^{13}C-NMR (CD_3OD, 75 MHz): δ 175.9(C=O), 173.6(C=O), 156.9(Ar-C-OH), 132(Ar-C), 131.2(Ar-CH), 117.8(Ar-CH), 100.2(C1), 75.3(C3), 72.4(C5), 72(C2), 68.3(C4), 62.6(C6), 57.5(S-CH), 55.2(NH-CH), 52.7(CH_3), 41.3(S-CH-$\underline{CH_2}$), 39.3(Ar-CH_2), 37.6(S-CH_2), 36.4(S-CH-$\underline{CH_2}$), 35.7(O = C-$\underline{CH_2}$), 29.6(CH_2), 26.5(CH_2); IR(KBr): 3398, 2964, 2854, 1740, 1642, 1532, 1233, 1072, 830 cm^{-1}; HRMS (ESI) m/z [M+Na]-calc. for $C_{24}H_{35}O_9NS_2$ = 568.1645; Found: 568.1657.

2.7d *Synthesis of methyl N-(5-(1, 2-dithiolan-3-yl) pentanoyl)-O-α-L-rhamnopyranosyl-(S)-tyrosinate (**6d**)*: This solid was purified by silica gel chromatography using a gradient of chloroform/methanol (92:8, v/v) to obtain a yield of 74%, as a yellow solid. ^{1}H-NMR (CD_3OD, 300MHz): δ 7.13 (d, J = 8.49 Hz, 2H), 6.98 (d, J = 8.30 Hz, 2H), 6.69 (d, J = 8.30 Hz, 1H), 5.38 (br s, 1H), 4.61–4.66 (m, 1H), 3.98 (m, 1H), 3.79–3.84 (m, 1H), 3.69 (s, 3H), 3.34–3.64 (m, 4H), 3.03–3.19 (m, 3H), 2.83–2.91 (m, 2H), 2.37–2.47 (m, 1H), 2.16 (t, J = 6.98 Hz, 2H), 1.79–1.90 (m, 1H), 1.48–1.63 (m, 4H), 1.27–1.36 (m, 3H), 1.2 (s, 3H); ^{13}C-NMR (CD_3OD + $CDCl_3$, 75 MHz): δ 175.6(C=O), 173.5(C=O), 156.5(Ar-C-OH), 131.6(Ar-C), 131.1(Ar-CH), 117.4(Ar-CH), 99.6(C1), 73.6(C3), 72(C4), 71.8(C5), 70.4(C2), 57.3(S-CH), 54.9(NH-CH), 52.7(CH_3), 41.1(S-CH-$\underline{CH_2}$), 39.2(Ar-CH_2), 37.5(S-CH_2), 36.3(S-CH-$\underline{CH_2}$), 35.5(O = C-$\underline{CH_2}$), 29.5(CH_2), 26.4(CH_2), 18(C6); IR(KBr): 3379, 2927, 1736, 1647, 1512, 1229, 1016, 831 cm^{-1}; HRMS (ESI) m/z [M+Na]-calc. for $C_{24}H_{35}O_8NS_2$ = 552.1696; Found: 552.1707.

2.8 *General procedure for synthesis of N-(fatty acyl)-O-α/β-D/L-glycopyranosyl-(S)-tyrosines*

To a solution of hexose penta acetate (2.56 mmol) in dichloromethane (10 mL) was added methyl N-acyl tyrosinate (3.704 mmol) and boron trifloride etherate (3.84 mmol) at 0°C and the reaction mixture was stirred at room temperature for overnight. The reaction mixture was dissolved in $CHCl_3$ and washed with $NaHCO_3$ solution and water (2 × 150 mL). The organic phase was dried over sodium sulphate and concentrated to yield a liquid. The crude compound was directly used for the next step. Methyl ester (1 eq.) was dissolved in THF: H_2O (7:3) and added (3 eq.) of LiOH, stirred the reaction mixture at RT for 16 h. After completion of reaction, the mixture was concentrated under vaccum to obtain a white precipitate. This white precipitate was neutralized with 2 N HCl and the reaction mixture was extracted with ethyl acetate. The organic layer was dried over sodium sulphate. This organic layer was concentrated to yield a white solid. This solid was purified by silica gel chromatography using a gradient of chloroform/methanol (75:25, v/v) to obtain a yield (65–77%) of the title compound as a solid.

2.8a *Synthesis of N-(hexanoyl)-O-β-D-glucopyrano syl-(S)-tyrosine (**7a**)*: This solid was purified by silica gel chromatography using a gradient of chloroform/methanol (75:25, v/v) to obtain a yield of 65%, as a white solid. ^{1}H-NMR (CD_3OD, 300MHz): δ 7.15 (d, J = 8.49 Hz, 2H), 7.01 (d, J = 8.68 Hz, 2H), 4.84 (d, J = 7.36 Hz, 1H), 4.58–4.62 (m, 1H), 3.85–3.89 (m, 1H), 3.66–3.71 (m, 1H), 3.39–3.45 (m, 4H), 3.11–3.17 (m, 1H), 2.85–2.92 (m, 1H), 2.14 (t, J = 7.36 Hz, 2H), 1.46–1.56 (m, 2H), 1.21–1.33 (m, 4H), 0.87 (t, J = 6.79 Hz, 3H); ^{13}C-NMR (CD_3OD, 125 MHz): δ 175.6(C=O), 174.7(C=O), 157.5(Ar-C-OH), 131.9(Ar-C), 131(Ar-CH), 117.4(Ar-CH), 102.1(C1), 77.6(C3), 77.5(C5), 74.4(C2), 71(C4), 62.3(C6), 54.7(NH-CH), 37.4(Ar-CH_2), 36.6(O = C-CH_2), 32.1(CH_2), 26.2(CH_2), 23.1(CH_2), 14.2(CH_3); IR(KBr): 3399, 3303, 2928, 1735, 1647, 1538, 1232, 1082, 830 cm^{-1}; HRMS (ESI) m/z [M - H]-calc. for $C_{21}H_{30}O_9N$ = 440.1915; Found: 440.1924.

2.8b *Synthesis of N-(hexanoyl)-O-β-D-galactopyran osyl-(S)-tyrosine (**7b**)*: This solid had a little impurity which was purified by silica gel chromatography using a gradient of chloroform/methanol (75:25, v/v) to obtain a yield of 65%,as a white solid. ^{1}H-NMR (CD_3OD, 300MHz): δ 7.14 (d, J = 8.52 Hz, 2H), 7.01 (d, J = 8.52 Hz, 2H), 4.84 (d, J = 7.42 Hz, 1H), 4.58–4.62 (m, 1H), 3.85–3.89 (m, 1H), 3.69 (dd, J = 4.67, 11.82 Hz, 1H), 3.39–3.45 (m, 4H), 3.11–3.17 (m, 1H), 2.84–2.92 (m, 1H), 2.14 (t, J = 7.42 Hz, 2H), 1.46–1.56 (m, 2H), 1.16–1.37 (m, 4H), 0.88 (t, J = 6.87 Hz, 3H); ^{13}C-NMR (CD_3OD, 75 MHz): δ 176.1(C=O), 175.0(C=O), 158.0(Ar-C-OH), 132.4(Ar-C), 131.2(Ar-CH), 117.7(Ar-CH), 102.5(C1), 78.1(C3), 77.9(C5), 74.9(C2), 71.4(C4), 62.5(C6), 55.1(NH-CH), 37.6(Ar-CH_2), 36.7(O = C-CH_2), 32.4(CH_2), 30.7(CH_2), 26.5(CH_2), 23.4(CH_2), 14.3(CH_3); IR(KBr): 3418, 3301, 2929, 1732, 1647, 1542, 1262, 1082, 830 cm^{-1}; HRMS (ESI) m/z [M - H]-calc. for $C_{21}H_{30}O_9N$ = 440.1915; Found: 440.1923.

2.8c *Synthesis of N-(hexanoyl)-O-α-D-mannopyrano syl-(S)-tyrosine (**7c**)*: This solid was purified by silica gel chromatography using a gradient of chloroform/methanol (75:25, v/v) to obtain a yield of 66%, as a white solid. ^{1}H-NMR (CD_3OD, 300MHz): δ 7.17 (d, J = 8.52 Hz, 2H), 6.99 (d, J = 8.80 Hz, 2H), 5.38 (d, J = 1.65 Hz, 1H), 4.62–4.67 (m, 1H), 3.97–3.99 (m, 1H), 3.84 (dd, J = 3.30, 9.35 Hz, 1H), 3.59–3.66 (m, 3H), 3.45 (t, J = 9.62 Hz, 1H), 3.14–3.21 (m, 1H), 2.85–2.92 (m, 1H), 2.15 (t, J = 7.70 Hz, 2H), 1.45–1.55 (m, 2H), 1.8–1.29 (m, 4H), 0.87 (t, J = 7.42 Hz, 3H); ^{13}C-NMR (CD_3OD, 75 MHz): δ 176.1(C=O), 174.8(C=O), 156.7(Ar-C-OH), 132.1(Ar-C), 131.3(Ar-CH), 117.4(Ar-CH), 99.9(C1), 73.8(C3), 72.2(C5), 72.1(C2), 70.5(C4), 62.5(C6), 54.9(NH-CH), 37.6(Ar-CH_2), 36.7(O = C-CH_2), 32.3(CH_2), 26.5(CH_2), 23.4(CH_2), 14.3(CH_2); IR(KBr): 3372, 3318, 2918, 1738, 1652, 1530, 1231, 1081, 830 cm^{-1}; HRMS (ESI) m/z [M - H]-calc. for $C_{21}H_{30}O_9N$ = 440.1915; Found: 440.1924.

2.8d *Synthesis of N-(hexanoyl)-O-α-L-rhamnopyran osyl-(S)-tyrosine (**7d**)*: This solid was purified by silica gel chromatography using a gradient of chloroform/methanol (75:25, v/v) to obtain a yield of 65%, as a white solid. ^{1}H-NMR (CD_3OD, 300MHz): δ 7.17 (d, J = 8.49 Hz, 2H), 6.99 (d, J = 8.30 Hz, 2H), 6.7 (d, J = 8.3 Hz, 1H), 5.38 (br s, 1H), 4.63–4.67 (m, 1H), 3.98 (m, 1H), 3.85 (dd, J = 3.02, 9.25 Hz, 1H), 3.59–3.66 (m, 1H), 3.46 (t, J = 9.44 Hz, 1H), 3.15–3.2 (m, 1H), 2.85–2.93 (m, 1H), 2.16 (t, J = 7.36 Hz, 2H), 1.46–1.56 (m, 2H), 1.8–1.3 (m, 4H), 0.87 (t, J = 6.79 Hz, 3H); ^{13}C-NMR (CD_3OD, 75 MHz): δ 176.1(C=O), 156.7(Ar-C-OH), 132.1(Ar-C), 131.3(Ar-CH), 117.4(Ar-CH), 99.9(C1), 73.8(C3), 72.2(C4), 72.1(C5), 70.5(C2), 54.9(NH-CH), 37.6(Ar-CH_2), 36.7(O = C-CH_2),

32.3(CH_2), 26.5(CH_2), 23.3(CH_2), 18(C6), 14.3(CH_2); IR(KBr): 3383, 2926, 2856, 1735, 1640, 1536, 1514, 1236, 1025, 817 cm^{-1}; HRMS (ESI) m/z [M - H]-calc. for $C_{21}H_{30}O_8N$ = 424.1965; Found: 424.1978.

2.8e *Synthesis of N-(10-undecenoyl)-O-β-D-gluco pyranosyl-(S)-tyrosine (**8a**)*: This solid was purified by silica gel chromatography using solvent mixture of chloroform/methanol (75:25, v/v) to obtain a yield of 72%, as a white solid. ^{1}H-NMR ($CDCl_3$+CD_3OD, 300MHz): δ 7.13 (d, J = 8.12 Hz, 2H), 7.0 (d, J = 7.55 Hz, 2H), 6.73 (d, J = 8.3 Hz, 1H), 5.72–5.86 (m, 1H), 4.92–5.0 (m, 2H), 4.89 (m, 1H), 4.52 (d, J = 7.55 Hz, 1H), 3.67–3.92 (m, 4H), 3.45–3.5 (m, 2H), 2.93–3.21 (m, 2H), 2.18 (t, J = 6.8 Hz, 2H), 2.0 – 2.06 (m, 2H), 1.56 (m, 2H), 1.29 (m, 10H); ^{13}C-NMR ($CDCl_3$ + CD_3OD, 75 MHz): δ 174(C=O), 171.9(C=O), 155.8(Ar-C-OH), 138.3(H_2C-$\underline{CH}$ = CH_2), 129.4(Ar-C), 115.9(Ar-CH), 113.2(CH = $\underline{CH_2}$, Ar-CH), 100.3(C1), 76.2(C3), 75.7(C5), 72.7(C2), 69.3(C4), 60.8(C6), 52.9(NH-CH), 36(Ar-CH_2), 35.9(O = C-CH_2), 35.333.5($\underline{H_2C}$-CH = CH_2), 33(O = C-CH_2-$\underline{CH_2}$), 28.5(CH_2), 28.4(CH_2), 28.3(CH_2), 28.2(CH_2), 24.9(CH_2); IR(KBr): 3414, 2924, 2854, 1730, 1600, 1459, 1220, 1089, 765 cm^{-1}; HRMS (ESI) m/z [M - H]-calc. for $C_{26}H_{38}O_9N$ = 508.2541; Found: 508.2553.

2.8f *Synthesis of N-(10-undecenoyl)-O-β-D-galacto pyranosyl-(S)-tyrosine (**8b**)*: This solid was purified by silica gel chromatography using a gradient of chloroform/methanol (75:25, v/v) to obtain a yield of 70%, as a white solid. ^{1}H-NMR ($CDCl_3$ + CD_3OD, 300MHz): δ 7.09 (d, J = 8.49 Hz, 2H), 7.04 (d, J = 8.87 Hz, 1H), 6.99 (d, J = 8.68 Hz, 2H), 5.73–5.87 (m, 1H), 4.90–5.01 (m, 2H), 4.84 (d, J = 7.74 Hz, 1H), 4.71 (t, J = 5.85, 1H), 3.90–3.96 (m, 2H), 3.78–3.84 (m, 2H), 3.57–3.66 (m, 2H), 2.98–3.15 (m, 2H), 2.18 (t, J = 7.17 Hz, 2H), 2.0–2.06 (m, 2H), 1.57 (m, 2H), 1.28 (m, 10H); ^{13}C-NMR ($CDCl_3$ + DMSO-d_6, 125 MHz): δ 172.9(C=O), 172.5(C=O), 155.8(Ar-C-OH), 138.6(H_2C-$\underline{CH}$ = CH_2), 129.9(Ar-C), 116.05(Ar-CH), 113.7(CH = $\underline{CH_2}$, Ar-CH), 100.7(C1), 74.5(C3), 73.2(C5), 70.6(C2), 68.2(C4), 60.8(C6), 52.7(NH-CH), 36.2(Ar-CH_2), 35.8(O = C-CH_2), 33.2($\underline{H_2C}$-CH = CH_2), 33(O = C-CH_2-$\underline{CH_2}$), 28.7(CH_2), 28.5(CH_2), 28.3(CH_2), 25.08 (CH_2); IR(KBr): 3398, 2934, 2862, 1728, 1618, 1438, 1230, 1081, 765 cm^{-1}; HRMS (ESI) m/z [M - H]-calc. for $C_{26}H_{38}O_9N$ = 508.2541; Found: 508.2550.

2.8g *Synthesis of N-(10-undecenoyl)-O-α-D-mannopy ranosyl-(S)-tyrosine (**8c**)*: This solid was purified by silica gel chromatography using a gradient of chloroform/methanol (75:25, v/v) to obtain a yield of 70%, as a white solid. ^{1}H-NMR ($CDCl_3$ + CD_3OD, 300MHz): δ 7.13 (d, J = 7.74 Hz, 2H), 6.98 (d, J = 7.74 Hz, 2H), 5.73–5.86 (m, 1H), 5.46 (br s, 1H), 4.89–5.0 (m, 2H), 4.57 (m, 1H), 4.03 (m, 1H), 3.93–3.97 (m, 1H), 3.71–3.86 (m, 4H), 3.59–3.63 (m, 1H), 2.94–3.16 (m, 2H), 2.16 (t, J = 6.98 Hz, 2H), 2.02 – 2.04 (m, 2H), 1.54 (m, 2H), 1.27 (m, 10H); ^{13}C-NMR ($CDCl_3$ + DMSO-d_6, 75 MHz): δ 172.7(C=O), 170.5(C=O), 153.3(Ar-C-OH), 137.1(H_2C-$\underline{CH}$ = CH_2), 128.6(Ar-C), 114.6(Ar-CH), 112.6(CH = $\underline{CH_2}$, Ar-CH), 97.4(C1), 72.5(C3), 69.2(C5), 68.6(C2), 65.3(C4), 59.5(C6), 52.9(NH-CH), 34.8(Ar-CH_2), 34.1(O = C-CH_2), 31.733.2 ($\underline{H_2C}$-CH = CH_2), 27.5(O = C-CH_2-$\underline{CH_2}$), 27.3(CH_2), 27.03(CH_2), 26.8(CH_2), 23.7(CH_2); IR(KBr): 3356, 2928, 2858, 1728, 1622, 1462, 1228, 1078, 765 cm^{-1}; HRMS (ESI) m/z [M - H]-calc. for $C_{26}H_{38}O_9N$ = 508.2541; Found: 508.2551.

2.8h *Synthesis of N-(10-undecenoyl)-O-α-L−rhamno pyranosyl-(S)-tyrosine (**8d**)*: This solid was purified by silica gel chromatography using a gradient of chloroform/methanol (75:25, v/v) to obtain a yield of 70%, as a white solid. ^{1}H-NMR ($CDCl_3$ + CD_3OD, 300MHz): δ 7.13 (d, J = 8.49 Hz, 2H), 6.98 (d, J = 8.68 Hz, 2H), 6.73 (d, J = 6.49 Hz, 1H), 5.73–5.86 (m, 1H), 5.40 (br s, 1H), 4.89–5.0 (m, 2H), 4.69 (m, 1H), 4.02 (m, 1H), 3.88 (dd, J = 3.39, 9.44 Hz, 1H), 3.63–3.73 (m, 1H), 3.47 (t, J = 9.44 Hz, 1H), 2.93–3.19 (m, 2H), 2.18 (t, J = 7.36 Hz, 2H), 2.0–2.07 (m, 2H), 1.55 (m, 2H), 1.24 - 1.28 (m, 13H); ^{13}C-NMR ($CDCl_3$+CD_3OD, 75 MHz): δ 175.1(C=O), 174.2(C=O), 150.6(Ar-C-OH), 139.5(H_2C-$\underline{CH}$ = CH_2), 130.8(Ar-C), 116.9(Ar-CH), 114.4(CH = $\underline{CH_2}$, Ar-CH), 99(C1), 73.2(C3), 71.7(C4), 71.2(C5), 69.7(C2), 54.08(NH-CH), 37.1(Ar-CH_2), 36.6(O = C-CH_2), 34.3($\underline{H_2C}$-CH = CH_2), 29.8(O = C-CH_2 − $\underline{CH_2}$), 29.6(CH_2), 29.5(CH_2), 29.4(CH_2), 26.2(CH_2), 17.8(C6); IR(KBr): 3514, 3334, 2920, 2850, 1735, 1645, 1514, 1235, 1068, 1015, 663 cm^{-1}; HRMS (ESI) m/z [M - H]-calc. for $C_{26}H_{38}O_8N$ = 492.2591; Found: 492.2603.

2.8i *Synthesis of N-(tetradecanoyl)-O-β-D-glucopy ranosyl-(S)-tyrosine (**9a**)*: This solid had a little impurity which was purified by silica gel chromatography using a gradient of chloroform/methanol (75:25, v/v) to obtain a yield of 75%, as a white solid. ^{1}H-NMR (CD_3OD, 300MHz): δ 7.12 (d, J = 8.49 Hz, 2H), 7.01 (d, J = 8.49 Hz, 2H), 5.39 (d, J = 3.55 Hz, 1H), 4.82 (d, J = 7.36 Hz, 1H), 4.46–4.50 (m, 1H), 3.79–3.88 (m, 1H), 3.60–3.69 (m, 2H), 3.49–3.54 (m, 1H), 3.38–3.44 (m, 2H), 3.1–3.6 (m, 1H), 2.85–2.92 (m, 1H), 2.12 (t, J = 7.35 Hz, 2H), 1.49 (m, 2H), 1.26 (m, 20H), 0.88 (t, J = 6.23 Hz, 3H); ^{13}C-NMR (CD_3OD, 75 MHz): δ 177.8(C=O), 175.6(C=O), 157.8(Ar-C-OH), 131.4(Ar-C), 117.9(Ar-CH),, 102.5(Ar-CH), 99.5(C1), 78(C3), 74.9(C5), 73.3(C2), 71.4(C4), 62.5(C6), 56.8(NH-CH), 38.2(O = C-CH_2), 37.1(O = C-CH_2-CH_2), 33(CH_2), 31.8(CH_2), 30.7(CH_2), 30.3(CH_2), 30.4(CH_2), 26.9(CH_2), 23.7(CH_2), 21.1(CH_2), 14.5(CH_3); IR(KBr): 3421, 2921, 2850, 1728, 1650, 1511, 1228, 1064, 839 cm^{-1}; HRMS (ESI) m/z [M - H]-calc. for $C_{29}H_{46}O_9N$ = 552.3167; Found: 552.3180.

2.8j *Synthesis of N-(tetradecanoyl)-O-β-D-galactopy ranosyl-(S)-tyrosine (**9b**)*: This solid was purified by silica gel chromatography using a gradient of chloroform/methanol (75:25, v/v) to obtain a yield of 75%, as a white solid. ^{1}H-NMR (CD_3OD, 300MHz): δ 7.13 (d, J = 8.49 Hz, 2H),

7.06 (d, J = 8.87 Hz, 1H), 7.0 (d, J = 8.49 Hz, 2H), 4.8 (d, J = 7.55 Hz, 1H), 4.54–4.58 (m, 1H), 3.87–3.88 (m, 1H), 3.64–3.78 (m, 4H), 3.55 (dd, J = 3.39, 9.82 Hz, 1H), 3.09–3.15 (m, 1H), 2.84–2.92 (m, 1H), 2.13 (t, J = 6.6 Hz, 2H), 1.5 (m, 2H), 1.26 (m, 20H), 0.87 (t, J = 6.23 Hz, 3H); ^{13}C-NMR (CD_3OD, 75 MHz): δ 176(C=O), 175.7(C=O), 158(Ar-C-OH), 132.4(Ar-C), 131.2(Ar-CH), 117.7(Ar-CH), 103(C1), 76.7(C3), 74.8(C5), 72.2(C2), 70.1(C4), 62.3(C6), 55.5(NH-CH), 37.7(O = C-CH_2), 36.8(O = C-CH_2-CH_2), 33(CH_2), 30.7(CH_2), 30.6(CH_2), 30.4(CH_2), 30.2(CH_2), 26.8(CH_2), 23.7(CH_2), 14.5(CH_3); IR(KBr): 3408, 2928, 2852, 1730, 1656, 1518, 1218, 1064, 839 cm^{-1}; HRMS (ESI) m/z [M - H]-calc .for $C_{29}H_{46}O_9N$ = 552.3167; Found: 552.3183.

2.8k *Synthesis of N-(tetradecanoyl)-O-α-D-mannopyranosyl-(S)-tyrosine (**9c**)*: This solid was purified by silica gel chromatography using a gradient of chloroform/methanol (75:25, v/v) (71 % yield) to obtain as a white solid. ^{1}H-NMR (CD_3OD, 300MHz): δ 7.13 (d, J = 8.49 Hz, 2H), 6.99 (d, J = 8.68 Hz, 2H), 5.41 (br s, 1H), 4.52–4.56 (m, 1H), 3.95–3.97 (m, 1H), 3.85–3.89 (m, 1H), 3.7–3.76 (m, 3H), 3.53–3.59 (m, 1H), 3.1–3.16 (m, 1H), 2.83–2.91 (m, 1H), 2.13 (t, J = 7.36 Hz, 2H), 1.48 (m, 2H), 1.26 (m, 20H), 0.87 (t, J = 6.23 Hz, 3H); ^{13}C-NMR (CD_3OD, 75 MHz): δ 176.5(C=O), 175.9(C=O), 156.7(Ar-C-OH), 132.7(Ar-C), 131.4(Ar-CH), 117.6(Ar-CH), 100.2(C1), 75.2(C3), 72.4(C5), 72(C2), 68.3(C4), 62.5(C6), 55.9(NH-CH), 37.9(O = C-CH_2), 37(O = C-CH_2-CH_2), 33(CH_2), 30.7(CH_2), 30.6(CH_2), 30.4(CH_2), 30.2(CH_2), 26.9(CH_2), 23.7(CH_2), 14.5(CH_3); IR(KBr): 3402, 2962, 2863, 1738, 1642, 1552, 1238, 1060, 839 cm^{-1}; HRMS (ESI) m/z [M - H]-calc. for $C_{29}H_{46}O_9N$ = 552.3167; Found: 552.3182.

2.8l *Synthesis of N-(tetradecanoyl)-O-α-L-rhamnopyranosyl-(S)-tyrosine (**9d**)*: This solid was purified by silica gel chromatography using a gradient of chloroform/methanol (75:25, v/v) to obtain a yield of 71% as a white solid. ^{1}H-NMR (CD_3OD, 300MHz): δ 7.14 (d, J = 8.68 Hz, 2H), 6.96 (d, J = 8.49 Hz, 2H), 6.67 (d, J = 8.3 Hz, 1H), 5.36 (br s, 1H), 4.59 – 4.64 (m, 1H), 3.95 (m, 1H), 3.81 (dd, J = 3.39, 9.44 Hz, 1H), 3.56–3.67 (m, 1H), 3.43 (t, J = 9.44 Hz, 1H), 3.11–3.17 (m, 1H), 2.83–2.91 (m, 1H), 2.13 (t, J = 7.36 Hz, 2H), 1.46–1.53 (m, 2H), 1.18 - 1.26 (m, 23H), 0.88 (t, J = 6.23 Hz, 3H); ^{13}C-NMR (CD_3OD, 75 MHz): δ 176.1(C=O), 174.8(C=O), 156.7(Ar-C-OH), 132.1(Ar-C), 131.3(Ar-CH), 117.4(Ar-CH), 99.9(C1), 73.8(C3), 72.2(C4), 72(C5), 70.5(C2), 54.9(NH-CH), 37.6(O = C-CH_2), 36.8(O = C-CH_2-CH_2), 33(CH_2), 30.7(CH_2), 30.5(CH_2), 30.4(CH_2), 30.1(CH_2), 26.8(CH_2), 23.7(CH_2), 18(C6), 14.5(CH_3); IR(KBr): 3445, 3321, 2850, 1734, 1647, 1607, 15551, 1234, 1058, 1016, 838 cm^{-1}; HRMS (ESI) m/z [M - H]-calc. for $C_{29}H_{46}O_8N$ = 536.3217; Found: 536.3229.

2.8m *Synthesis of N-(oleoyl)-O-β-D-glucopyranosyl-(S)-tyrosine (**10a**)*: This solid was purified by silica gel chromatography using a gradient of chloroform/methanol (75:25, v/v) to obtain a yield of 76%, as a white solid. ^{1}H-NMR (CD_3OD, 300MHz): δ 7.13 (d, J = 8.30 Hz, 2H), 6.98 (d, J = 8.30 Hz, 2H), 5.28–5.38 (m, 2H), 4.88 (d, J = 7.36 Hz, 1H), 4.55 (m, 1H), 3.87–3.91 (m, 1H), 3.73–3.76 (m, 1H), 3.44–3.50 (m, 4H), 3.10–3.16 (m, 1H), 2.94–3.01 (m, 1H), 2.17 (t, J = 7.36 Hz, 2H), 2.01–2.08 (m, 4H), 1.56 (m, 2H), 1.28 (m, 20H), 0.88 (t, J = 6.6 Hz, 3H); ^{13}C-NMR ($CDCl_3$ + DMSO-d_6, 75 MHz): δ 172.4(C=O), 155.8(Ar-C-OH), 131.3(Ar-C), 130.1(HC=CH), 129.9(HC=CH), 129.4(Ar-CH), 115.6(Ar-CH), 100.4(C1), 78.7(C3), 76.7(C5), 73.1(C2), 69.6(C4), 60.7(C6), 48.8(NH-CH), 36.3(HC = CH-$\underline{CH_2}$), 35.6(O = C-CH_2), 31.3(O = C-CH_2-CH_2), 29.2(CH_2), 29(CH_2), 28.9(CH_2), 28.8(CH_2), 28.7(CH_2), 26.7(CH_2), 25.3(CH_2), 22.1(CH_2), 13.9(CH_3); IR(KBr) 3323, 2925, 2853, 1722, 1644, 1512, 1238, 1080, 695 cm^{-1}; HRMS (ESI) m/z [M - H]-calc. for $C_{33}H_{52}O_9N$ = 606.3636; Found: 606.3660.

2.8n *Synthesis of N-(oleoyl)-O-β-D-galactopyranosyl-(S)-tyrosine (**10b**)*: This solid was purified by silica gel chromatography using a gradient of chloroform/methanol (75:25, v/v) to obtain a yield of 76%, as a white solid. ^{1}H-NMR (CD_3OD, 300MHz): δ 7.10 (d, J = 7.74 Hz, 2H), 7.02 (d, J = 8.87 Hz, 1H), 6.98 (d, J = 7.93 Hz, 2H), 5.29–5.38 (m, 2H), 4.83 (d, J = 7.55 Hz, 1H), 4.59 (m, 1H), 3.94–4.04 (m, 2H), 3.72–3.84 (m, 2H), 3.58–3.64 (m, 2H), 3.14–2.97 (m, 2H), 2.17 (t, J = 7.36 Hz, 2H), 2.0–2.02 (m, 4H), 1.57 (m, 2H), 1.27 (m, 20H), 0.88 (t, J = 6.42 Hz, 3H); ^{13}C-NMR ($CDCl_3$ + CD_3OD, 75 MHz): δ 175.6(C=O), 174.3(C=O), 156.4(Ar-C-OH), 131.3(Ar-C), 130.6(HC=CH), 130.1(HC=CH), 129.9(Ar-CH), 117.2(Ar-CH), 101.5(C1), 75.2(C3), 73.5(C5), 71.1(C2), 69.02(C4), 61.7(C6), 54.8(NH-CH), 37.1(HC = CH-$\underline{CH_2}$), 36.5(O = C-CH_2), 32.7(O = C-CH_2-CH_2), 29.9(CH_2), 29.8(CH_2), 29.7(CH_2), 29.5(CH_2), 29.4(CH_2), 27.4(CH_2), 25.8(CH_2), 22.8(CH_2), 14.1(CH_3); IR(KBr) 3300, 2935, 2826, 1732, 1634, 1522, 1238, 1080, 695 cm^{-1}; HRMS (ESI) m/z [M - H]-calc. for $C_{33}H_{52}O_9N$ = 606.3636; Found: 606.3655.

2.8o *Synthesis of N-(oleoyl)-O-α-D-mannopyranosyl-(S)-tyrosine (**10c**)*: This solid was purified by silica gel chromatography using a gradient of chloroform/methanol (75:25, v/v) to obtain a yield of 76%, as a white solid. ^{1}H-NMR (CD_3OD, 300MHz): δ 7.12 (d, J = 8.12 Hz, 2H), 6.98 (d, J = 8.12 Hz, 2H), 5.46 (br s, 1H), 5.28–5.38 (m, 2H), 4.58 (m, 1H), 4.02 (m, 1H), 3.92–3.96 (m, 1H), 3.71 – 3.84 (m, 3H), 3.59–3.62 (m, 1H), 2.93–3.17 (m, 2H), 2.17 (t, J = 7.36 Hz, 2H), 2.01–2.02 (m, 4H), 1.55 (m, 2H), 1.28 (m, 20H), 0.88 (t, J = 6.79 Hz, 3H); ^{13}C-NMR ($CDCl_3$ + CD_3OD + DMSO-d_6, 75 MHz): δ 174.5(C=O), 172.6(C=O), 155.2(Ar-C-OH), 131.8(Ar-C), 130.3(HC=CH), 130.1(HC=CH), 129.7(Ar-CH), 116.4(Ar-CH), 99.1(C1), 74.4(C3), 70.9(C5), 70.3(C2), 66.8(C4), 61.1(C6), 54.5(NH-CH), 36.6(HC = CH-$\underline{CH_2}$), 35.7(O = C-CH_2), 32.2(O = C-CH_2-CH_2), 31.5(CH_2), 29.4(CH_2), 29.2(CH_2), 29.1(CH_2), 28.9(CH_2), 26.9(CH_2), 25.5(CH_2), 22.3(CH_2), 14.0(CH_3); IR(KBr) 3312, 2918, 2842, 1736,

1640, 1532, 1238, 1080, 695 cm^{-1}; HRMS (ESI) *m/z* [M - H]-calc. for $C_{33}H_{52}O_9N$ = 606.3636; Found: 606.3651.

2.8p *Synthesis of N-(oleoyl)-O-α-L-rhamnopyranosyl-(S)-tyrosine (**10d**)*: This solid was purified by silica gel chromatography using a gradient of chloroform/methanol (75:25, v/v) to obtain a yield of 76%, as a white solid. ^{1}H-NMR (CD_3OD, 300MHz): δ 7.10 (d, *J* = 8.49 Hz, 2H), 6.97 (d, *J* = 8.49 Hz, 2H), 5.42 (br s, 1H), 5.29–5.38 (m, 2H), 4.73 (m, 1H), 4.03 (m, 1H), 3.89 (dd, *J* = 3.39, 9.44 Hz, 1H), 3.65–3.74 (m, 1H), 3.47 (t, *J* = 9.44 Hz, 1H), 2.98–3.17 (m, 2H), 2.18 (t, *J* = 7.36 Hz, 2H), 2.0–2.02 (m, 4H), 1.57 (m, 2H), 1.25–1.27 (m, 23H), 0.88 (t, *J* = 6.42 Hz, 3H); ^{13}C-NMR ($CDCl_3$ + CD_3OD, 75 MHz): δ 174.3(C=O), 173.8(C=O), 155.7(Ar-C-OH), 130.6(Ar-C), 130.3(HC=CH), 130.2(HC=CH), 129.9(Ar-CH), 116.6(Ar-CH), 98.6(C1), 73(C3), 71.5(C4), 70.9(C5), 69.3(C2), 53.5(NH-CH), 36.9(HC = CH-$\underline{CH_2}$), 36.5(O = C-CH_2), 32.8(O = C-CH_2-CH_2), 30(CH_2), 29.9(CH_2), 29.7(CH_2), 29.5(CH_2), 29.4(CH_2), 27.4(CH_2), 25.9(CH_2), 22.9(CH_2), 17.6(C6), 14.2(CH_3); IR(KBr): 3416, 3322, 2923, 2852, 1725, 1650, 1229, 1011, 668 cm^{-1}; HRMS (ESI) *m/z* [M - H]-calc. for $C_{33}H_{52}O_8N$ = 590.3700; Found: 590.3687.

2.9 *In vitro cytotoxicity evaluation*

The cytotoxicity of the prepared glycosylated *N*-fatty acyl-*L*-tyrosine derivatives was evaluated 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), PC3 derived from human prostate cancer cells (ATCC No. CRL-1435), MDA-MB-231 derived from human breast adenocarcinoma cells (ATCC No. HTB-26), HepG2 derived from human liver adenocarcinoma cells (ATCC No HB-8065) and HUVEC derived from human umbilical vein endothelial cells (ATCC No. CRL-1730) using the MTT assay.[28] 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.

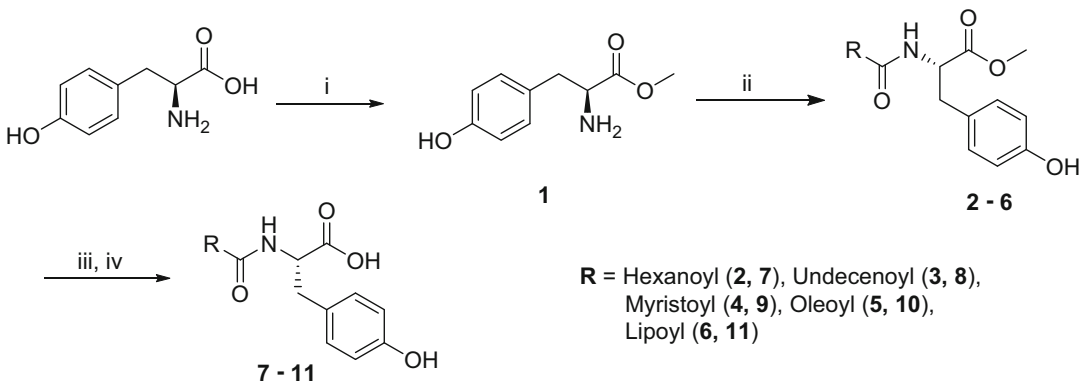
2.10 *Antimicrobial activity*

Antimicrobial activity of the prepared glycosylated *N*-fatty acyl-*L*-tyrosine derivatives was determined using well diffusion method[29] against a panel of pathogenic bacterial strains, including *Micrococcus luteus* MTCC 2470, *Staphylococcus aureus* MTCC 96, *Staphylococcus aureus* MLS16 MTCC 2940, *Bacillus subtilis* MTCC 121, *Escherichia coli* MTCC 739, *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 medium 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 standard). Wells of 6.0 mm diameter were prepared in the media plates using a cork borer and the glycosylated *N*-fatty acyl-*L*-tyrosine derivatives 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 solutions 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.

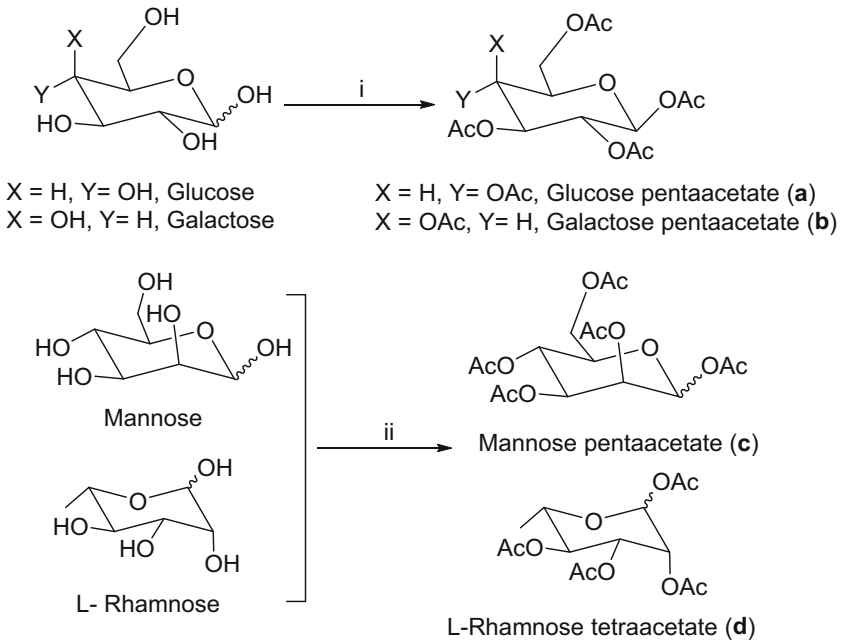
3. Results and Discussion

3.1 *Synthesis and characterization*

As per Scheme 1, the synthesis of glycosylated *N*-fatty acyl-*L*-tyrosine derivatives initiated with the preparation of methyl-*L*-tyrosinate[24,25,30] (**1**) from *L*-tyrosine



Scheme 1. Reagents and conditions: i) H_2SO_4-MeOH, 4 h, Reflux, 70%; ii) Fatty acid, EDC.HCl, HOBT, DCM, rt, 12 h, 80–89%; iii) LiOH, THF, rt, 16 h; iv) 2N HCl, 96–98%.



Scheme 2. Regents and conditions: i) NaOAc, Ac_2O, 90°C, Reflux, 2.5 h, 92%; ii) Pyridine/Ac_2O, rt, 12 h, 98%.

using methanol-sulfuric acid solution. This methyl-*L*-tyrosinate (**1**) was further derivatized to afford *N*-fatty acyl-*L*- tyrosine methyl esters (**2–6**) with different fatty acids using EDC-HCl and HOBt coupling reagents.

Further, to obtain fattyacyl-*L*-tyrosine (**7–11**), *N*-fatty acyl-*L*-tyrosine methyl esters (**2–6**) were hydrolyzed with LiOH.H_2O in THF-H_2O solvent mixture and this was followed by acidification of lithium salts with 2N HCl. The penta-*O*-acetyl-*β*-D-glucose (**a**) and penta-*O*-acetyl-*β*-D-galactose (**b**) were prepared by employing NaOAc/Ac_2O method as per our previous report[26] and penta-*O*-acetyl-*α*-D-mannose (**c**) and tetra-*O*-acetyl-α-L-rhamnose (**d**) were prepared by adopting pyridine/Ac_2O method[27] as indicated in Scheme 2.

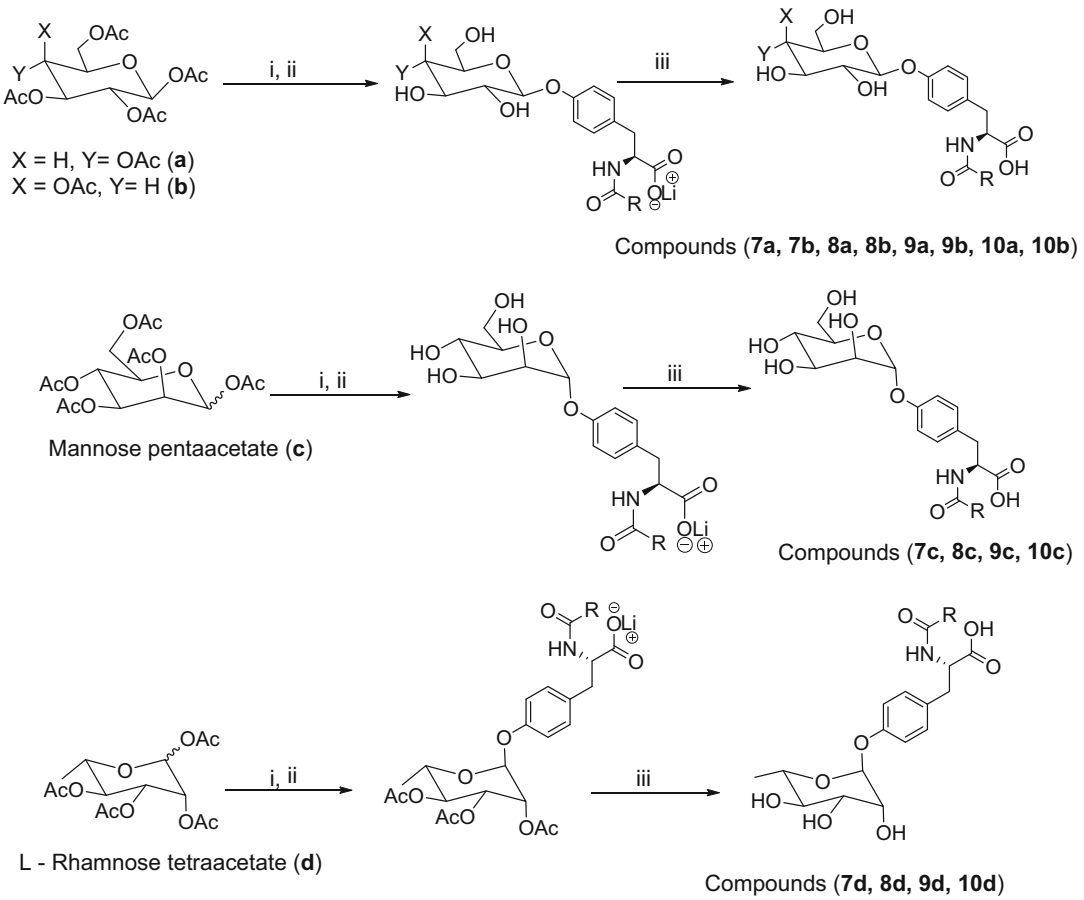
As depicted in Scheme 3, glycosylation of *N*-fatty acyl-*L*-tyrosine methyl esters (**2–5**) with sugar acetates (**a–d**) was achieved with the Lewis acid BF_3-Et_2O[31] and simultaneous deacylation and methyl ester hydrolysis was accomplished with LiOH.H_2O in THF-H_2O solvent mixture and this was followed by acidification of lithium salts with 2N HCl to obtain the final glycosylated *N*-fatty acyl-*L*-tyrosines (**7a–7d, 8a–8d, 9a–9d, 10a–10d**). Attempts were made to prepare glycosylated *N*-lipoyl-*L*-tyrosines using the same synthetic protocol as mentioned in Scheme 3.

However, we observed that the extraction of the glycosylated *N*-lipoyl-*L*-tyrosine from the reaction mixture was very difficult. The plausible reason may be attributable to the more polar nature of glycosylated *N*-lipoyl-*L*-tyrosine as compared to the other series of compounds (**7a–7d, 8a–8d, 9a–9d, 10a–10d**), which is due to the presence of sulfur-containing shorter acyl chain lipoic acid. Hence, we restricted the synthesis up to *N*-lipoyl-*L*-tyrosine methyl esters (**6a–6d**) and in the final step, only sugar acetate groups were deprotected by using NaOMe/MeOH instead of LiOH.H_2O reagent (Scheme 4).

The glucose and galactose *N*-fatty acyl-*L*-tyrosines were formed in β–configuration and the mannose and rhamnose *N*-fatty acyl-*L*-tyrosines were formed in α–configuration due to neighboring group participation of C2-acetate group of the sugar during the glycosylation. The data on the ^{1}H-NMR chemical shifts and $J_{1,2}$ coupling constants corroborate with the published reports;[32,33] for glucose and galactose derivatives the coupling constant of $J_{1,2}$ is $\geq$ 7 Hz indicating the β-configuration and for mannose and rhamnose derivatives the coupling constant of $J_{1,2}$ is $<$ 3 Hz representing α-configuration.

3.2 *Biological studies*

3.2a *Cytotoxicity*: The amino acid acylated and glycosylated with fatty acids and carbohydrates represent a separate class of lipid derivatives which demand a detailed investigation. In this context, glycosylated *N*-fatty acyl-*L*-tyrosines and *N*-lipoyl-*L*-tyrosine methyl ester derivatives were synthesized and evaluated to examine the impact of sugar and fatty acid on the biological activity of this aglycone moiety. All the synthesized

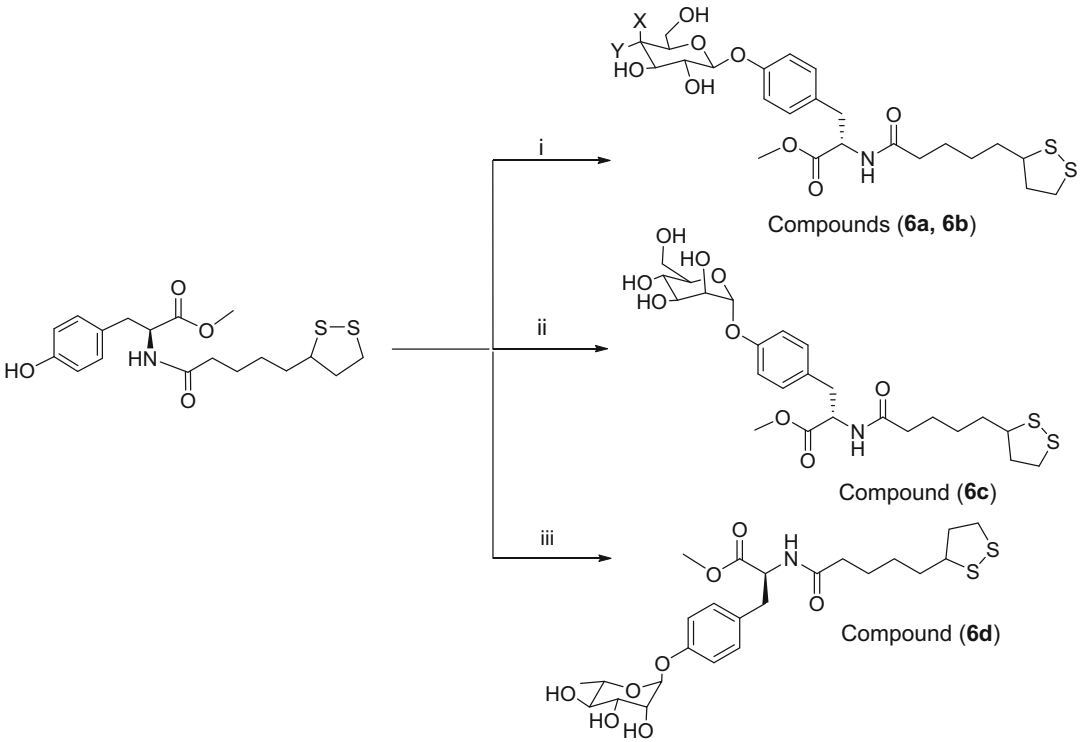


Scheme 3. Reagents and conditions: i) Compounds **2–5**, $BF_3.Et_2O$, DCM, rt, Overnight; ii) LiOH, THF, rt, 16 h; iii) 2N HCl, 65-77 %.

glycosylated *N*-fatty acyl-*L*-tyrosines (**7a–7d, 8a–8d, 9a–9d and 10a–10d**) were tested against a panel of four cancer cell lines, namely A549, PC3, MDA-MB-231, and HepG2.[28]

Based on the results depicted in Table 1, compounds **7a–7c, 8c, 9c** and **10c** exhibited moderate cytotoxicity against all the tested cancer cell lines irrespective of the carbohydrate and lipid (saturated and short to medium chain) moieties and the IC_{50} values ranged between 19.5−45.6 μM. However, in case of oleic (unsaturated) acid, the compounds **10a** (IC_{50} value of 15.6 μM) and **10d** (IC_{50} value of 17.6 μM) showed promising cytotoxicity against MDA-MB-231, and compound **10b** (IC_{50} value of 18.7 μM) showed significant activity against A549 cell line. The compounds **10a**,**10b** and **10d** also showed good to moderate cytotoxicity against all the other tested cancer cell lines. Here, the respective non-glycosylated free carboxylic acid derivative (**10**) showed poor cytotoxicity and excellent antimicrobial activity when compared to glycosylated one. In addition to that when compared to other fatty acid derivatives like saturated (**7a–7d**, **9a–9d**) and undecenoic acid (**8a–8d**) derivatives showed a poor cytotoxicity. These results demonstrate that the sugar and fatty acid both substituents enhance the activity. Further, the non-glycosylated *N*-fatty acyl-*L*-tyrosine methyl esters (**2–6**) and *N*-fatty acyl-*L*-tyrosines (**7**–**11**) showed poor cytotoxicity against all the tested cell lines as compared to the glycosylated *N*-fatty acyl derivatives (Table 1).

Similarly, glycosylated *N*-lipoyl-*L*-tyrosine methyl esters (**6a**–**6d**) were evaluated for cytotoxicity against the same panel of cancer cell lines. Based on the results shown in Table 1, the compounds (**6b**–**6d**) bearing an unusual, highly active α-lipoic acid moiety exhibited good cytotoxicity against all the cell lines and the IC_{50} values ranged between 9.4−13.8 μM. Among them, the compound **6d** exhibited promising activity with IC_{50} values of 10.5, 9.4, 10.9 and 12.1 against A549, PC3, MDA-MB-231 and HepG2, respectively. However, the compound **6a** did not exhibit any cytotoxicity. Whereas in non-glycosylated free carboxylic acid derivative (**11**) and non-glycosylated methyl ester compound **6** showed very poor cytotoxicity and good



Scheme 4. Reagents and conditions: i) A) **a** or **b**, $BF_3.Et_2O$, DCM, rt, Over night; B) NaOMe, MeOH, 70-75%; ii) A) **c**, $BF_3.Et_2O$, DCM, rt, Over night; B) NaOMe, MeOH, 70-75%; iii) A) **d**, $BF_3.Et_2O$, DCM, rt, Over night; B) NaOMe, MeOH, 70-75%.

antimicrobial activity when compared to glycosylated derivative. It is also noteworthy to mention that all the synthesized compounds (**7a–7d, 8a–8d, 9a–9d, 10a–10d** and **6b–6d**) did not exhibit any antimicrobial activity; however, they showed promising cytotoxicity. These results again proved that the fatty acid and sugar play significant role in enhancing or affecting the biological activity of these compounds. Moreover, irrespective of the lipid moiety all the mannose analogues (**7c, 8c, 9c, 10c** and **6c**) exhibited moderate cytotoxicity against all the tested cell lines. From a mechanistic perspective, it is presumed that these glycosides may be causing cell cycle arrest in the S and G2/M phases, enabling the activation of the caspase cascade and thus inducing the apoptosis in the cancerous cell lines.[17,34,35] In addition, these phenolic glycosides from natural sources have been reported to exhibit diverse biological activities and have been claimed to function as pro-drugs.[36,37]

Based on the cytotoxicity results, the cytotoxicity of aglycone moiety depends on the fatty acid nature (oleic acid and lipoic acid) and sugar moiety. These two substituents in combination enhance the cytotoxicity of aglycone as well as the sugar moiety inversely affects the antimicrobial activity of aglycone.

3.2b *Antimicrobial activity*: The antimicrobial activities[29] of *N*-fatty acyl-*L*-tyrosine methyl esters (**2–6**) and *N*-fatty acyl-*L*-tyrosines (**7–11**) were examined against seven bacterial and one fungal strain and the results to this regard are shown in Table 2. It was observed that among all the synthesized compounds, *N*-fatty acyl-*L*-tyrosine methyl esters (**2–6**) showed a poor antimicrobial activity against both bacterial and fungal strains. However, *N*-fatty acyl-*L*-tyrosines (**7–11**) exhibited promising antimicrobial activity against both bacterial and fungal strains. Among these *N*-fatty acyl-*L*-tyrosines (**7–11**), specifically compound **9,** showed promising antimicrobial activity against four Gram positive bacterial strains and two Gram negative bacterial strain, such as *Staphylococcus aureus* MTCC 96, *Bacillus subtilis* MTCC 121, *S. aureus* MLS16 MTCC 2940, *Micrococcus luteus* MTCC 2470 and *Klebsiella planticola* MTCC 530, *Escherichia coli* MTCC 739 with MIC values of 1.9, 1.9, 3.9, 3.9 and 3.9, 3.9 μg/mL, respectively. Similarly compound **10** exhibited good antimicrobial activity against two Gram positive bacterial strains and three Gram negative bacterial strain, such as *Bacillus subtilis* MTCC 121, *S. aureus* MLS16 MTCC 2940 and*Klebsiella planticola* MTCC 530, *Pseudomonas aeruginosa* MTCC 2453,

Table 1. Cytotoxicity evaluation of the glycosylated *N*-fatty acyl-*L*-tyrosines (**7a–7d, 8a–8d, 9a–9d, 10a–10d**), glycosylated *N*-fatty acyl-*L*-tyrosines methyl esters (**6a–6d**), *N*-fatty acyl-*L*-tyrosine methyl esters (**2–6**) and *N*-fatty acyl-*L*-tyrosines (**7–11**).

Test compound	IC_{50} values (μM)*				
	A549	PC3	MDA-MB-231	HepG2	HUVEC
7a	40.7 ± 0.26	19.5 ± 0.11	25.9 ± 0.36	29.2 ± 0.29	89.6 ± 0.32
7b	31.2 ± 0.28	31.3 ± 0.29	32.5 ± 0.52	38.4 ± 0.48	92.3 ± 0.36
7c	45.6 ± 0.17	44.4 ± 0.36	32.6 ± 0.41	33.7 ± 0.22	100.6 ± 0.44
7d	–[a]	–	–	–	–
8a	–	–	–	–	–
8b	–	–	–	–	–
8c	25.2 ± 0.42	29.2 ± 0.35	21.6 ± 0.32	33.3 ± 0.36	121.5 ± 0.18
8d	–	–	–	–	–
9a	–	–	–	–	–
9b	–	–	–	–	–
9c	38.9 ± 0.22	25.6 ± 0.17	38.6 ± 0.44	31.9 ± 0.52	99.5 ± 0.28
9d	–	–	–	–	–
10a	23.1 ± 0.37	18.6 ± 0.35	15.6 ± 0.11	19.1 ± 0.14	112 ± 0.52
10b	18.7 ± 0.32	19.6 ± 0.26	19.2 ± 0.22	22.9 ± 0.35	125 ± 0.26
10c	25.1 ± 0.36	25.5 ± 0.24	25.1 ± 0.18	22.6 ± 0.32	98.5 ± 0.32
10d	22.8 ± 0.15	18.9 ± 0.18	17.6 ± 0.31	19.8 ± 0.22	102.3 ± 0.38
6a	–	–	–	–	–
6b	10.7 ± 0.19	11.2 ± 0.14	11.7 ± 0.22	13.2 ± 0.16	99.2 ± 0.42
6c	11.0 ± 0.26	10.6 ± 0.09	13.8 ± 0.25	12.5 ± 0.15	101.2 ± 0.36
6d	10.5 ± 0.28	9.4 ± 0.11	10.9 ± 0.22	12.1 ± 0.19	110.5 ± 0.32
2	–	215.6 ± 0.22	–	236.9 ± 0.28	–
3	–	–	–	–	–
4	152.1 ± 0.44	129.8 ± 0.38	156.3 ± 0.38	143.2 ± 0.44	201.3 ± 0.42
5	–	185.6 ± 0.55	–	–	–
6	–	201.3 ± 0.42	–	172.3 ± 0.36	210.5 ± 0.18
7	29.8 ± 0.56	30.2 ± 0.33	35.6 ± 0.19	29.6 ± 0.22	98.2 ± 0.55
8	45.6 ± 0.32	50.1 ± 0.42	51.6 ± 0.22	39.9 ± 0.28	90.4 ± 0.48
9	36.6 ± 0.28	37.5 ± 0.18	48.9 ± 0.14	40.5 ± 0.37	99.9 ± 0.42
10	40.2 ± 0.24	36.9 ± 0.22	39.2 ± 0.16	38.6 ± 0.26	101.2 ± 0.36
11	45.5 ± 0.18	50.5 ± 0.15	29.6 ± 0.38	37.2 ± 0.15	89.6 ± 0.51
Doxorubicin	0.8 ± 0.12	0.6 ± 0.11	0.9 ± 0.07	0.8 ± 0.09	68.2 ± 0.22

* Micro Molar

A549: human alveolar adenocarcinoma epithelial cells (ATCC No. CCL-185), PC3: human prostate cancer cells (ATCC No. CRL-1435), MDA-MB-231: human breast adenocarcinoma cells (ATCC No. HTB-26), HepG2: human liver adenocarcinoma cells (ATCC No. HB-8065), HUVEC: Normal human umbilical vein endothelial cells (ATCC No. CRL-1730); [a]–: No activity.

Escherichia coli MTCC 739 with MIC values of 1.9, 1.9, and 1.9, 3.9, 3.9 μg/mL, respectively.

In addition to that, compounds **9** and **10** exhibited excellent antifungal activity against *Candida albicans MTCC* 3017 fungal strain with MIC values 3.9 and 3.9 μg/mL, respectively. While all the other compounds showed moderate to poor antimicrobial activities against seven bacterial and one fungal strain with MIC values of 7.8 and > 125 μg/mL. Based on the above results, medium-chain saturated myristic acid (**9**) and unsaturated oleic acid (**10**) derivatives exhibited excellent antimicrobial activity against bacterial and fungal strains.

4. Conclusions

In conclusion, glycosylated *N*-fatty acyl-*L*-tyrosines and *N*-lipoyl-*L*-tyrosine methyl esters were synthesized and evaluated for their cytotoxicity antimicrobial activity in the present study. All the *N*-fatty acyl-*L*-tyrosines were glycosylated with four sugar moieties in presence of the Lewis acid, $BF_3.Et_2O$. All the synthesized glycosylated *N*-fatty acyl-*L*-tyrosines and esters (**7a–7d, 8a–8d, 9a–9d, 10a–10d** and **6a–6d**) were further tested for cytotoxicity against A549, PC3, MDA-MB-231 and HepG2 cell lines. Among the tested compounds, **7a–7c, 8c, 9c** and **10c** exhibited moderate activity against all the

Table 2. Antimicrobial activity of *N*-fatty acyl-*L*-tyrosine methyl esters (**2-6**) and *N*-fatty acyl-*L*- tyrosines (**7–11**).

Test compounds	Minimum inhibitory concentration (μg/mL)								
	Staphylococcus aureus MTCC 96	*Bacillus subtilis* MTCC 121	*S. aureus* MLS16 MTCC 2940	*Micrococcus luteus* MTCC 2470	*Klebsiella planticola* MTCC 530	*Escherichia coli* MTCC 739	*Pseudomonas aeruginosa* MTCC2453	*Candida albicans* MTCC 3017
2	>125	>125	>125	>125	62.5	>125	>125	–[a]
3	>125	62.5	>125	62.5	>125	31.2	>125	–
4	>125	62.5	>125	>125	62.5	>125	>125	–
5	>125	>125	>125	>125	>125	>125	>125	–
6	>125	62.5	>125	>125	>125	>125	>125	–
7	7.8	7.8	>125	7.8	>125	>125	>125	>125
8	>125	1.9	>125	>125	>125	>125	>125	>125
9	1.9	1.9	3.9	3.9	3.9	3.9	>125	3.9
10	7.8	1.9	1.9	7.8	1.9	3.9	3.9	3.9
11	>125	>125	7.8	7.8	>125	>125	>125	>125
Miconazole (Control)	–	–	–	–	–	–	–	7.8
Ciprofloxacin (Control)	0.9	0.9	0.9	0.9	0.9	0.9	0.9	–

[a]–: No activity

tested cell lines. However, in case of oleic (unsaturated) acid, the compounds **10a** and **10d** exhibited good cytotoxicity against MDA-MB-231 cell line and compound **10b** showed promising activity against A549 cell line. Whereas in case of N-lipoyl-*L*-tyrosine methyl esters (**6a–6d**), due to the presence of α-lipoic acid moiety, the compounds (**6b–6d**) exhibited good cytotoxicity against all the tested cell lines. The compound **6d** (IC_{50} value of 9.4 μM) exhibited promising cytotoxicity against PC3 cell line. All the glycosylated compounds did not show antimicrobial activity. Further, the *N*-fatty acyl-*L*-tyrosine methyl ester (**2–6**) and *N*-fatty acyl-*L*-tyrosine (**7–11**) aglycone moieties showed poor cytotoxicity, when compared to glycosylated compounds. Moreover, the *N*-fatty acyl-*L*-tyrosines (**7–11**) exhibited promising antimicrobial activity against some of the pathogenic bacterial strains. Based on the above results, it can be concluded that the carbohydrate and fatty acid moieties play a significant role in determining the cytotoxicity of aglycone and the sugar moiety inversely affects the antimicrobial activity of aglycone.

Supplementary Information (SI)

^{1}H-NMR, ^{13}C-NMR and HRMS spectral data for the synthesized compounds and HPLC results of Compounds **10a–10d** and **6a–6d** are presented in the Supplementary Information which is available at www.ias.ac.in/chemsci.

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