Synthesis of disubstituted- and deoxydisubstituted- derivatives of α-D-xylofuranose as anticancer agents

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Abstract
Several disubstituted- and deoxydisubstituted- derivatives of α-D-xylofuranose have been synthesized and evaluated on various *in vitro* human cancer cell lines. In primary *in vitro* screening, seven derivatives expressed anticancer activity.

Keywords: Synthesis, aminoalkyl derivatives, xylofuranose, anticancer activity

Introduction

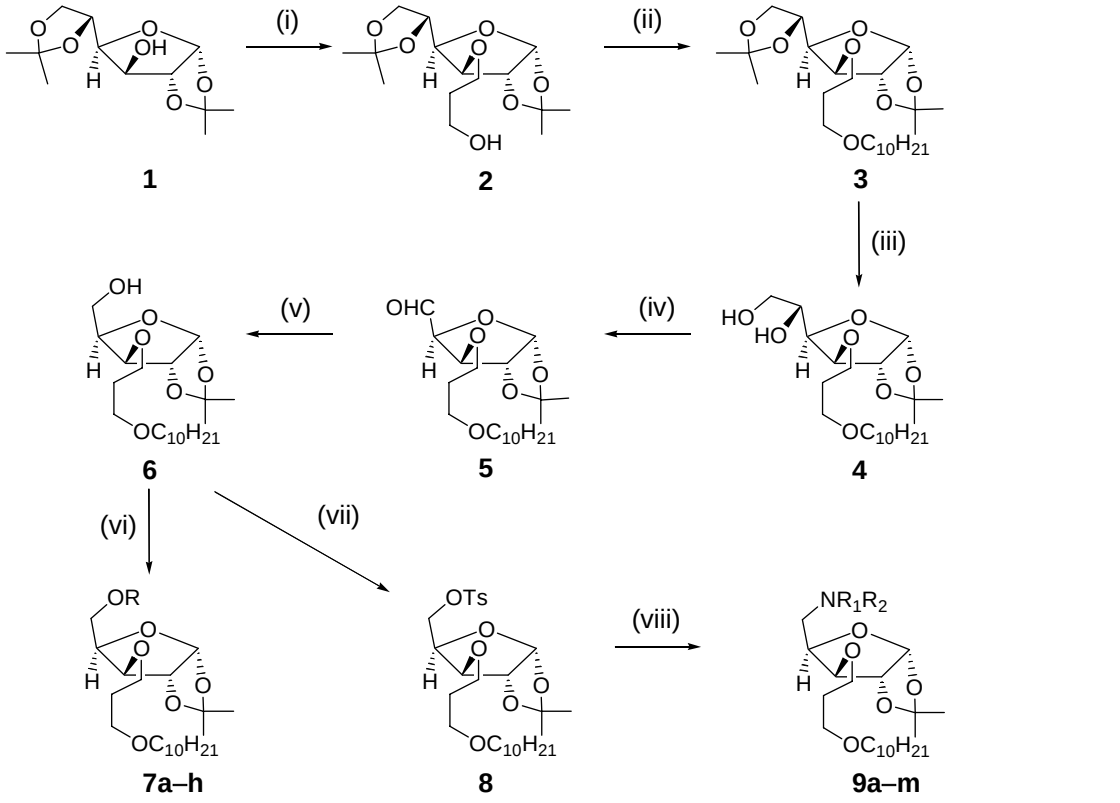
A large number of compounds with diverse chemical structure and molecular weight are reported to be effective anticancer agents.[1-15] Among them, several branched-chain sugar derivatives,[11-15] as well as some low molecular weight sugar derivatives with aminoalkyl appendages,[1-4] have shown potent anticancer activity. In continuation of our efforts to find potent anticancer agents and on the basis of the correlation of anticancer activity *in vitro*, *in vivo*, and lipophilicity of the compounds of our previous work on aminoalkyl derivatives of sugars,[4,16] we have synthesized disubstituted- and deoxydisubstituted- derivatives of α-D-xylofuranose and evaluated them for anticancer activity.

Results and Discussion

Chemistry

Scheme 1 indicates the synthetic route to 3-*O*-{3′-(decyloxy)propyl}-1,2-*O*-isopropylidene-5-*O*-(substituted)-α-D-xylofuranose (**7a–h**) from 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (**1**)[17]. Compound **1** was *O*-alkylated at the C-3 position with 3-chloro-1-propanol in the presence

of NaOH at 110 °C to afford compound **2** in 74% yield, which was further *O*-alkylated at C-3′ position with 1-bromodecane to give 3-*O*-{3′-(decyloxy)propyl}-1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (**3**) in good yield.



7	OR
a	-O(H$_2$C)$_2$-N
b	-O(H$_2$C)$_2$-N
c	-O(H$_2$C)$_2$-N
d	-O(H$_2$C)$_3$-N NH
e	-O(H$_2$C)$_3$-N
f	-O(H$_2$C)$_3$-
g	-O(H$_2$C)$_2$-N O
h	-O(CH$_2$)$_3$NMe$_2$

9	NR$_1$R$_2$
a	—N
b	—N
c	—N O
d	—HN(H$_2$C)$_2$-N
e	—HN(CH$_2$)$_3$NMe$_2$
f	—NHC$_7$H$_{15}$
g	—HN(CH$_2$)$_3$OH

9	NR$_1$R$_2$
h	—HN(H$_2$C)$_2$-N O
i	—HN(H$_2$C)$_2$- N H$_3$C
j	—HN(H$_2$C)$_2$-N
k	—HN(H$_2$C)$_3$-N
l	—HN(H$_2$C)$_2$-N
m	—HN(H$_2$C)$_3$-N N

Scheme 1. Synthesis of compounds **7** and **9**. (i) Cl(CH$_2$)$_3$OH, NaOH, 110 °C, 8 h. (ii) C$_{10}$H$_{21}$Br, NaOH, 110 °C, 10 h. (iii) 30% HClO$_4$, THF, 0→5 °C, 6–8 h. (iv) NaIO$_4$, H$_2$O, 0→5 °C, 6–7 h; (v) NaBH$_4$, MeOH, 0→5 °C, 6–8 h. (vi) RCl, NaOH, 100 °C, 7–8 h. (vii) Tosyl chloride, pyridine, 0→5 °C, 6–7 h. (viii) R$_1$R$_2$NH, 70 °C, 6–8 h.

The selective deprotection of the 5,6-*O*-isopropylidene group in compound **3** led to the formation of diol **4** in excellent yield. In the ^{1}H NMR of compound **4**, both the O*H* protons resonated at δ 4.70 as a broad singlet. The oxidative cleavage of vicinal diol **4** gave the aldehyde **5** in excellent yield. The signal for the aldehydic proton in compound **5** appeared at δ 9.61 as a broad singlet in the ^{1}H NMR spectrum. Compound **5** gave the key intermediate 3-*O*-{3′-(decyloxy)propyl}-1,2-*O*-isopropylidene-α-D-xylofuranose (**6**) in 89% yield on $NaBH_4$ reduction. The condensation of key intermediate **6** with various 1-(ω-haloalkyl)-amines in the presence of a base gave the required compounds **7a–h** in good yields. The structures of compounds **7a–h** were assigned on the basis of spectral and analytical data. Thus, the ^{1}H NMR spectra of these compounds, in general, showed a triplet for the terminal C*H*$_3$ protons between δ 0.90–0.96, a multiplet between δ 1.60–1.79 for –OCH$_2$C*H*$_2$CH$_2$O– protons, signals for NC*H*$_2$ and OC*H*$_2$ protons appeared between δ 2.28–2.82 and 3.24–3.80 respectively, all other methylene protons appeared together between δ 1.18–1.68, and 1-C*H* proton showed a doublet between δ 5.88–6.00. The mass spectra of compounds **7a–h** also gave their correct molecular ion peaks as M+1.

The key intermediate **6** was further used to synthesize different 3-*O*-{3′-(decyloxy)propyl}-5-deoxy-5-(substituted)-α-D-xylofuranoses (**9a–m**) *via* tosylation of the primary alcohol (5–OH) by *p*-toluenesulphonyl chloride in pyridine at 0 ^{o}C followed by displacement of the tosylate group with various primary and secondary amines as shown in Scheme 1. The structures of all these compounds were determined on the basis of complementary spectroscopic (^{1}H NMR and MS) and analytical data (cf. experimental section).

Pharmacological Evaluation

Several compounds were submitted to the National Cancer Institute (Bethesda, MD) for screening. For primary *in vitro* screening, compounds **7a–h** and **9a–m** were evaluated for their cytotoxic potency on three human cell lines (NCI-H460 lung cancer, MCF7 breast cancer and SF-268 CNS cancer). A compound is considered to be active when it reduces the growth of any of the cell lines to 32% or less. Among them, seven compounds (**7a**, **7b**, **7c**, **7f**, **7g**, **9c** and **9h**) were found active (concentration 10^{-4} M) in primary screening. Details of this *in vitro* test method and the information, encoded by the activity pattern over all cell lines, have been previously reported.[18] Further investigation is in progress.

In summary, a series of disubstituted- and deoxydisubstituted- derivatives of α-D-xylofuranose was synthesized and evaluated for anticancer activity. The first results confirm the validity of our approach providing practical access to α-D-xylofuranose based derivatives possessing *in vitro* antiproliferative activity against human tumor cells. Evaluation of compounds **7a**, **7b**, **7c**, **7f**, **7g**, **9c** and **9h** on a full panel of 60 human cancer cell lines is underway and the results will be disclosed in due course.

Experimental Section

General Procedures. Melting points were determined in open capillaries on a Büchi B-545 melting point apparatus. Compounds were routinely checked for their purity on silica gel 60 F_{254} TLC plates and their spots were visualized by exposing them to iodine vapors or by charring the plates with 5% H_2SO_4–EtOH reagent or by spraying the plates with Dragendorff's reagent. IR spectra were recorded on a Perkin-Elmer spectrum RX series FT-IR spectrophotometer. ^{1}H NMR spectra were recorded on a Bruker Advance DRX 200 MHz instrument as solutions (in $CDCl_3$) using TMS as internal reference, and chemical shifts values are expressed in δ units. Mass spectra were run on an Applied Biosystems API 3000 instrument using direct inlet system under positive ion electrospray ionization source. Elemental analyses were carried out with a Perkin Elmer 2400 analyzer and the values found were within ±0.4% of theoretical values.

1,2:5,6-Di-*O*-isopropylidene-α-D-glucofuranose (1). This was prepared according to the literature method[17] in 41% yield; mp 108–109 °C (lit.[17] mp 109–110 °C). ^{1}H NMR ($CDCl_3$): δ 1.38 (s, 6H), 1.42 (s, 6H), 2.59 (br s, 1H), 3.80–4.62 (m, 6H), 5.94 (d, *J* = 4.0Hz, 1H). MS: *m/z* (%) 261 (100) [M+1].

1,2:5,6-Di-*O*-isopropylidene-3-*O*-{3'-(hydroxy)propyl}-α-D-glucofuranose (2). A mixture of compound **1** (49.9 g, 192 mmol), 3-chloro-1-propanol (19.9 g, 211 mmol) and NaOH (23.0 g, 576 mmol) was stirred at 110 °C for 8 h. After cooling to 25–30 °C, the reaction mixture was extracted with EtOAc (2×200 mL). The combined organic layers were washed with water (2×100 mL), brine (1×100 mL), dried (Na_2SO_4) and filtered. The filtrate was concentrated under reduced pressure to yield the crude product, which was purified by column chromatography over silica gel (100–200 mesh) using EtOAc–hexane (5:95) as eluent to give **2** as a colorless, thick oil, yield 52.1 g (85%). ^{1}H NMR ($CDCl_3$): δ 1.39 (s, 6H), 1.42 (s, 6H), 1.80–1.92 (m, 2H), 2.05 (br s, 1H), 3.48–3.61 (m, 4H), 3.80–4.62 (m, 6H), 5.84 (d, *J* = 4.0Hz, 1H). MS: *m/z* (%) 319 (100) [M+1]. Anal. Calcd for $C_{15}H_{26}O_7$ (318.36): C, 56.59; H, 8.23%. Found: C, 56.91; H, 7.96%.

1,2:5,6-Di-*O*-isopropylidene-3-*O*-{3′-(decyloxy)propyl}-α-D-glucofuranose (3). A mixture of compound **2** (50.0 g, 157.2 mmol), 1-bromodecane (38.2 g, 172.9 mmol) and NaOH (18.9 g, 471.6 mmol) was stirred at 110 °C for 8 h. After cooling to 25–30 °C, the reaction mixture was extracted with EtOAc (2×200 mL). The combined organic layers were washed with water (2×100 mL), brine (1×100 mL), dried (Na_2SO_4) and filtered. The filtrate was concentrated under reduced pressure to yield the crude product, which was purified by column chromatography over silica gel (100–200 mesh) using EtOAc–hexane (5:95) as eluent to give **3** as a colorless, thick oil, yield 62.1 g (86%). ^{1}H NMR ($CDCl_3$): δ 0.95 (t, *J* = 6.5Hz, 3H), 1.24–1.60 (m, 30H), 3.28–3.57 (m, 6H), 3.80–4.65 (m, 6H), 5.90 (d, *J* = 4.0Hz, 1H). MS: *m/z* (%) 459 (100) [M+1]. Anal. Calcd for $C_{25}H_{46}O_7$ (458.63): C, 65.47; H, 10.11%. Found: C, 65.76; H, 10.32%.

3-*O*-{3′-(Decyloxy)propyl}-1,2-*O*-isopropylidene-α-D-glucofuranose (4). To a stirred solution of compound **3** (62.0 g, 135.4 mmol) in THF (310 mL) was added 30% $HClO_4$ (62 mL) at 0 °C. After completion of the addition, stirring was continued at the same temperature for 6 h. The

reaction mixture was neutralized with a saturated solution of Na_2CO_3 (pH 9.0) and the compound was extracted with EtOAc (2×150 mL). The combined EtOAc extracts were washed with water (2×100 mL), brine (1×100 mL), dried (Na_2SO_4) and filtered. The filtrate was concentrated under reduced pressure to give a crude product, which was purified by column chromatography over silica gel (100–200 mesh) using EtOAc–hexane (1:1) as eluent to give **4**, yield 50.15 g (89%). ^{1}H NMR ($CDCl_3$): δ 0.98 (t, *J* = 6.5Hz, 3H), 1.20–1.71 (m, 24H), 3.30–3.60 (m, 6H), 3.65–4.65 (m, 6H), 4.70 (br s, 2H), 5.90 (d, *J* = 4.0Hz, 1H). MS: *m/z* (%) 419 (100) [M+1]. Anal. Calcd for $C_{22}H_{42}O_7$ (418.56): C, 63.13; H, 10.11%. Found: C, 62.89; H, 9.99%.

3-*O*-{3′-(Decyloxy)propyl}-1,2-*O*-isopropylidene-5-carboxaldehyde-α-D-xylofuranose (5). To a stirred solution of diol **4** (50.0 g, 119.6 mmol) in water (100 mL), was added a solution of $NaIO_4$ (50.9 g, 239.2 mmol) in water (100 mL) at 0 °C. After completion of the addition, stirring was continued at the same temperature for 6 h. Ethanol (500 mL) was added to the reaction mixture and the precipitated salts were filtered off and washed with ethanol (1×50 mL). The filtrate was concentrated under reduced pressure and the residue was dissolved in EtOAc (100 mL), dried (Na_2SO_4) and filtered. The filtrate was concentrated under reduced pressure to give **5** as a colorless, thick oil, yield 40.2 g (87%). ^{1}H NMR ($CDCl_3$): δ 0.90 (t, *J* = 6.5Hz, 3H), 1.20–1.69 (m, 24H), 3.33–3.65 (m, 6H), 4.05–4.66 (m, 3H), 6.05 (d, *J* = 4.0Hz, 1H), 9.61 (br s, 1H). MS: *m/z* (%) 387 (100) [M+1]. Anal. Calcd for $C_{21}H_{38}O_6$ (386.52): C, 65.25; H, 9.91%. Found: C, 65.31; H, 10.05%.

3-*O*-{3′-(Decyloxy)propyl}-1,2-*O*-isopropylidene-α-D-xylofuranose (6). To a stirred solution of aldehyde **5** (38.0 g, 98.4 mmol) in absolute MeOH (150 mL) was added $NaBH_4$ (5.5 g, 147.6 mmol) in portions at 0 °C. After completion of the addition, the reaction mixture was stirred at the same temperature for 6 h. The excess $NaBH_4$ was then decomposed by addition of acetone (20 mL) and the resulting solution was concentrated under reduced pressure. The residue was dissolved in EtOAc (200 mL) and washed with brine (1×50 mL). The organic layer was dried (Na_2SO_4), filtered and the filtrate was concentrated under reduced pressure to give **6** as a colorless thick oil, yield 34.1 g (89%). ^{1}H NMR ($CDCl_3$): δ 0.92 (t, *J* = 6.5Hz, 3H), 1.20–1.64 (m, 24H), 3.25–3.61 (m, 6H), 4.25–4.55 (m, 5H), 4.69 (br s, 1H), 5.90 (d, *J* = 4.0Hz, 1H). MS: *m/z* (%) 389 (100) [M+1]. Anal. Calcd for $C_{21}H_{40}O_6$ (388.54): C, 64.92; H, 10.38%. Found: C, 65.12; H, 10.59%.

3-*O*-{3′-(Decyloxy)propyl}-1,2-*O*-isopropylidene-5-*O*-{2′-(pyrrolidin-1-yl)ethyl}-α-D-xylofuranose (7a). General procedure for the preparation of 7. A mixture of compound **6** (0.78 g, 2.0 mmol), 1-(2-chloroethyl)pyrrolidine hydrochloride (0.37 g, 2.2 mmol) and NaOH (0.32 g, 8.0 mmol) was stirred at 110 °C for 6 h. The reaction mixture was cooled to 25–30 °C and then extracted with EtOAc (2×25 mL). The combined EtOAc layers were washed with water (1×25 mL), brine (1×25 mL), dried (Na_2SO_4) and filtered. The filtrate was concentrated under reduced pressure to give **7a** as a colorless, thick oil, which was purified by column chromatography over silica gel (100–200 mesh) using EtOAc–hexane (7:3) as eluent, yield 0.64 g (66%). IR (neat): 3100, 2900, 2800, 1440, 1390, 1150 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 0.92 (t, *J* = 6.5Hz, 3H), 1.22–1.60 (m, 24H), 1.72–1.79 (m, 4H), 2.57–2.82 (m, 6H), 3.34–3.65 (m, 10H),

4.19–4.65 (m, 3H), 6.00 (d, *J* = 4.0Hz, 1H). ^{13}C NMR ($CDCl_3$): δ 99.1, 97.9, 79.7, 72.2, 70.2, 69.4, 66.5, 64.9, 54.3, 51.8, 32.5, 32.0, 31.0, 30.3, 30.0, 28.6, 26.6, 23.5, 23.1, 14.0. MS: *m/z* (%) 486 (100) [M+1]. Anal. Calcd for $C_{27}H_{51}NO_6$ (485.70): C, 66.77; H, 10.58; N, 2.88%. Found: C, 66.98; H, 10.69; N, 3.07%.

3-*O*-{3′-(Decyloxy)propyl}-1,2-*O*-isopropylidene-5-*O*-{2′-(1-hexamethyleneimino)ethyl}-α-D-xylofuranose (7b). Colorless, thick oil (119 mg, 58%). IR (neat): 3120, 2850, 2700, 1410, 1370, 1130 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 0.95 (t, *J* = 6.5Hz, 3H), 1.18–1.52 (m, 22H), 1.66–1.77 (m, 10H), 2.60–2.66 (m, 2H), 2.73–2.80 (m, 4H), 3.33–3.70 (m, 10H), 4.20–4.62 (m, 3H), 5.89 (d, *J* = 4.0Hz, 1H). MS: *m/z* (%) 514 (100) [M+1]. Anal. Calcd for $C_{29}H_{55}NO_6$ (513.75): C, 67.80; H, 10.79; N, 2.73%. Found: C, 68.02; H, 10.93; N, 2.88%.

3-*O*-{3′-(Decyloxy)propyl}-1,2-*O*-isopropylidene-5-*O*-{2′-(piperidin-1-yl)ethyl}-α-D xylofuranose (7c). Colorless, thick oil (139 mg, 70%). IR (neat): 3150, 2900, 2750, 1450, 1350, 1100 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 0.90 (t, *J* = 6.5Hz, 3H), 1.21–1.58 (m, 28H), 1.66–1.70 (m, 2H), 2.23–2.31 (m, 4H), 2.59–2.62 (m, 2H), 3.35–3.68 (m, 10H), 4.21–4.60 (m, 3H), 5.90 (d, *J* = 4.0Hz, 1H). MS: *m/z* (%) 500 (100) [M+1]. Anal. Calcd for $C_{28}H_{53}NO_6$ (499.72): C, 67.30; H, 10.69; N, 2.80%. Found: C, 67.11; H, 10.37; N, 2.62%.

3-*O*-{3′-(Decyloxy)propyl}-1,2-*O*-isopropylidene-5-*O*-{3′-(piperazin-1-yl)propyl}-α-D-xylofuranose (7d). Colorless, thick oil (121 mg, 59%). IR (neat): 3200, 2950, 2800, 1440, 1390, 1150 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 0.92 (t, *J* = 6.5Hz, 3H), 1.02–1.65 (m, 26H), 2.33–2.50 (m, 10H), 3.37–3.62 (m, 11H), 4.29–4.56 (m, 3H), 5.89 (d, *J* = 4.0Hz, 1H). MS: *m/z* (%) 515 (100) [M+1]. Anal. Calcd for $C_{28}H_{54}N_2O_6$ (514.74): C, 65.33; H, 10.57; N, 5.44%. Found: C, 65.13; H, 10.25; N, 5.30%.

3-*O*-{3′-(Decyloxy)propyl}-1,2-*O*-isopropylidene-5-*O*-{3′-(piperidin-1-yl)propyl}-α-D xylofuranose (7e). Colorless, thick oil (123 mg, 60%). IR (neat): 3150, 2910, 2805, 1430, 1390, 1160 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 0.92 (t, *J* = 6.5Hz, 3H), 1.19–1.68 (m, 32H), 2.16–2.23 (m, 4H), 2.51–2.56 (m, 2H), 3.38–3.60 (m, 10H), 4.19–4.60 (m, 3H), 5.85 (d, *J* = 4.0Hz, 1H). MS: *m/z* (%) 514 (100) [M+1]. Anal. Calcd for $C_{29}H_{55}NO_6$ (513.75): C, 67.80; H, 10.79; N, 2.73%. Found: C, 67.99; H, 10.86; N, 2.78%.

3-*O*-{3′-(Decyloxy)propyl}-1,2-*O*-isopropylidene-5-*O*-{3′-(1-phenyl)propyl}-α-D-xylofuranose (7f). Colorless, thick oil (109 mg, 54%). IR (neat): 3200, 2960, 2830, 1410, 1360, 1140 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 0.93 (t, *J* = 6.5Hz, 3H), 1.20–1.55 (m, 24H), 1.62–1.70 (m, 2H), 2.84–2.92 (m, 2H), 3.36–3.80 (m, 10H), 4.31–4.58 (m, 3H), 5.90 (d, *J* = 4.0Hz, 1H), 7.00–7.20 (m, 5H). MS: *m/z* (%) 507 (100) [M+1]. Anal. Calcd for $C_{30}H_{50}O_6$ (506.71): C, 71.11; H, 9.95%. Found: C, 70.78; H, 9.69%.

33-*O*-{3′-(Decyloxy)propyl}-1,2-*O*-isopropylidene-5-*O*-{2′-(morpholin-1-yl)ethyl}-α- D-xylofuranose (7g). Colorless, thick oil (125 mg, 63%). IR (neat): 3100, 2905, 2810, 1450, 1380, 1150 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 0.94 (t, *J* = 6.5Hz, 3H), 1.20–1.65 (m, 24H), 2.28–2.60 (m, 6H), 3.24–3.64 (m, 14H), 4.19–4.65 (m, 3H), 5.92 (d, *J* = 4.0Hz, 1H). MS: *m/z* (%) 502 (100) [M+1]. Anal. Calcd for $C_{27}H_{51}NO_7$ (501.70): C, 64.64; H, 10.25; N, 2.79%. Found: C, 64.39; H, 10.01; N, 2.54%.

3-*O*-{3′-(Decyloxy)propyl}-1,2-*O*-isopropylidene-5-*O*-{3′-(*N*′,*N*′-dimethylamino)propyl}-α-D-xylofuranose (7h). Colorless, thick oil (110 mg, 58%). IR (neat): 3200, 2950, 2830, 1440, 1390, 1120 cm^{-1}. ^1H NMR ($CDCl_3$): δ 0.96 (t, *J* = 6.5Hz, 3H), 1.19–1.59 (m, 22H), 1.67–1.70 (m, 4H), 2.00–2.39 (m, 8H), 3.40–3.60 (m, 10H), 4.19–4.59 (m, 3H), 5.88 (d, *J* = 4.0Hz, 1H). MS: *m/z* (%) 474 (100) [M+1]. Anal. Calcd for $C_{26}H_{51}NO_6$ (473.69): C, 65.93; H, 10.85; N, 2.96%. Found: C, 66.22; H, 10.97; N, 3.23%.

3-*O*-{3′-(Decyloxy)propyl}-1,2-*O*-isopropylidene-5-*O*-*p*-tosyl-α-D-xylofuranose (8). To a solution of alcohol **6** (17.0 g, 43.8 mmol) in pyridine (50 mL), was added a solution of *p*-toluenesulphonyl chloride (8.42 g, 44.2 mmol) in pyridine (25 mL) dropwise at 0 °C with stirring. After complete addition, the reaction mixture was stirred for 6 h at the same temperature. After completion of the reaction (TLC evidence), the solvent was removed under reduced pressure and the residue was dissolved in EtOAc (100 mL), washed with water (2×20 mL) and a saturated solution of $NaHCO_3$ (2×20 mL), dried (Na_2SO_4) and filtered. The filtrate was concentrated under reduced pressure to give **8** as a viscous oil, yield 20.1 g (85%). ^{1}HNMR ($CDCl_3$): δ 0.93 (t, *J* = 6.5Hz, 3H), 1.21–1.60 (m, 22H), 1.66–1.70 (m, 2H), 2.35 (s, 3H), 3.36–3.72 (m, 8H), 4.21–4.61 (m, 3H), 5.95 (d, *J* = 4.0Hz, 1H), 7.24–7.60 (m, 4H). MS: *m/z* (%) 543 (100) [M+1]. Anal. Calcd for $C_{28}H_{46}O_8S$ (542.73): C, 61.96; H, 8.54%. Found: C, 61.88; H, 8.61%.

3-*O*-{3′-(Decyloxy)propyl}-1,2-*O*-isopropylidene-5-deoxy-5-(pyrrolidin-1-yl)-α-D-xylofuranose (9a). General procedure for the preparation of 9. A mixture of compound **8** (1.0 g, 1.85 mmol) and pyrrolidine (1.0 mL) was heated at 70 °C for 6 h. The excess of pyrrolidine was removed under reduced pressure and the residue was dissolved in EtOAc (25 mL). The EtOAc layer was washed with a saturated solution of $NaHCO_3$ (1×20 mL), brine (2×10mL), dried (Na_2SO_4) and filtered. The filtrate was concentrated under reduced pressure to give a crude product, which was purified by column chromatography over silica gel (100–200 mesh) using EtOAc–hexane (7:3) as eluent to give **9a** as a colorless, thick oil, yield 0.60 g (74%). IR (neat): 3300, 3100, 2900, 2800, 1650, 1440, 1390, 1350, 1150 cm^{-1}. ^1H NMR ($CDCl_3$): δ 0.95 (t, *J* = 6.5Hz, 3H), 1.26–1.61 (m, 24H), 1.73–1.81 (m, 4H), 2.49–2.61 (m, 6H), 3.40–3.60 (m, 6H), 4.16–4.76 (m, 3H), 5.95 (d, *J* = 4.0Hz, 1H). ^{13}C NMR ($CDCl_3$): δ 98.8, 97.9, 79.4, 73.6, 70.2, 69.2, 66.5, 64.9, 53.1, 52.1, 32.5, 32.0, 31.0, 30.3, 28.6, 26.6, 23.5, 23.1, 14.0. MS: *m/z* (%) 442 (100) [M+1]. Anal. Calcd for $C_{25}H_{47}NO_5$ (441.64): C, 67.99; H, 10.73; N, 3.17%. Found: C, 68.12; H, 10.94; N, 3.41%.

3-*O*-{3′-(Decyloxy)propyl}-1,2-*O*-isopropylidene-5-deoxy-5-(piperidin-1-yl)-α-D-xylofuranose (9b). Colorless, thick oil (136 mg, 81%). IR (neat): 3360, 3150, 2920, 2840, 1595, 1420, 1380, 1290, 1110 cm^{-1}. ^1H NMR ($CDCl_3$): δ 0.95 (t, *J* = 6.5Hz, 3H), 1.24–1.70 (m, 30H), 2.28–2.60 (m, 6H), 3.40–3.64 (m, 6H), 4.11–4.67 (m, 3H), 5.95 (d, *J* = 4.0Hz, 1H). MS: *m/z* (%) 456 (100) [M+1]. Anal. Calcd for $C_{26}H_{49}NO_5$ (455.67): C, 68.53; H, 10.84; N, 3.07%. Found: C, 68.19; H, 10.63; N, 2.82%.

3-*O*-{3′-(Decyloxy)propyl}-1,2-*O*-isopropylidene-5-deoxy-5-(morpholin-1-yl)-α-D-xylofuranose (9c). Colorless, thick oil (138 mg, 81%). IR (neat): 3320, 3105, 2900, 2850, 1620, 1410, 1350,

1290, 1140 cm^{-1}. ^1H NMR ($CDCl_3$): δ 0.96 (t, *J* = 6.5Hz, 3H), 1.24–1.62 (m, 24H), 2.34–2.63 (m, 6H), 3.40–3.75 (m, 10H), 4.19–4.70 (m, 3H), 5.90 (d, *J* = 4.0Hz, 1H). MS: *m/z* (%) 458 (100) [M+1]. Anal. Calcd for $C_{25}H_{47}NO_6$ (457.64): C, 65.61; H, 10.35; N, 3.06%. Found: C, 65.89; H, 10.41; N, 3.17%.

3-*O*-{3′-(Decyloxy)propyl}-1,2-*O*-isopropylidene-5-deoxy-5-{2′-(1-hexamethyleneimino)-ethylamino}-α-D-xylofuranose (9d). Colorless, thick oil (155 mg, 82%). IR (neat): 3350, 3110, 2900, 2805, 1610, 1420, 1390, 1310, 1130 cm^{-1}. ^1H NMR ($CDCl_3$): δ 0.96 (t, *J* = 6.5Hz, 3H), 1.30–1.45 (m, 22H), 1.61–1.89 (m, 11H), 2.50–2.89 (m, 10H), 3.41–3.60 (m, 6H), 4.19–4.70 (m, 3H), 5.80 (d, *J* = 4.0Hz, 1H). MS: *m/z* (%) 513 (100) [M+1]. Anal. Calcd for $C_{29}H_{56}N_2O_5$ (512.77): C, 67.93; H, 11.01; N, 5.46%. Found: C, 68.28; H, 10.84; N, 5.71%.

3-*O*-{3′-(Decyloxy)propyl}-1,2-*O*-isopropylidene-5-deoxy-5-{3′-(*N*′,*N*′-dimethylamino)-propylamino}-α-D-xylofuranose (9e). Colorless, thick oil (136 mg, 78%). IR (neat): 3330, 3110, 2900, 2850, 1650, 1430, 1400, 1330, 1150 cm^{-1}. ^1H NMR ($CDCl_3$): δ 0.95 (t, *J* = 6.5Hz, 3H), 1.32–1.64 (m, 26H), 2.10 (s, 6H), 2.20–2.88 (m, 7H), 3.39–3.70 (m, 6H), 4.21–4.68 (m, 3H), 5.95 (d, *J* = 4.0Hz, 1H). MS: *m/z* (%) 473 (100) [M+1]. Anal. Calcd for $C_{26}H_{52}N_2O_5$ (472.70): C, 66.06; H, 11.09; N, 5.93%. Found: C, 66.33; H, 10.91; N, 5.75%.

3-*O*-{3′-(Decyloxy)propyl}-1,2-*O*-isopropylidene-5-deoxy-5-(heptylamino)-α-D-xylofuranose (9f). Colorless, thick oil (120 mg, 67%). IR (neat): 3300, 3105, 2900, 2850, 1600, 1430, 1385, 1350, 1130 cm^{-1}. ^1H NMR ($CDCl_3$): δ 0.90–1.20 (m, 6H), 1.39–1.78 (m, 35H), 2.48–2.82 (m, 4H), 3.53–3.75 (m, 6H), 3.85–4.60 (m, 3H), 5.74 (d, *J* = 4.0Hz, 1H). MS: *m/z* (%) 486 (100) [M+1]. Anal. Calcd for $C_{28}H_{55}NO_5$ (485.74): C, 69.23; H, 11.41; N, 2.88%. Found: C, 68.96; H, 11.09; N, 2.57%.

3-*O*-{3′-(Decyloxy)propyl}-1,2-*O*-isopropylidene-5-deoxy-5-{3′-(hydroxy)propylamino}-α-D-xylofuranose (9g). Colorless, thick oil (106 mg, 64%). IR (neat): 3360, 3120, 2910, 2800, 1620, 1440, 1390, 1310, 1100 cm^{-1}. ^1H NMR ($CDCl_3$): δ 0.96 (t, *J* = 6.5Hz, 3H), 1.33–1.77 (m, 26H), 1.97 (br s, 2H) 2.68–2.90 (m, 4H), 3.38–3.70 (m, 8H), 3.80–4.58 (m, 3H), 5.76 (d, *J* = 4.0Hz, 1H). MS: *m/z* (%) 446 (100) [M+1]. Anal. Calcd for $C_{24}H_{47}NO_6$ (445.63): C, 64.68; H, 10.63; N, 3.14%. Found: C, 64.89; H, 10.47; N, 3.01%.

3-*O*-{3′-(Decyloxy)propyl}-1,2-*O*-isopropylidene-5-deoxy-5-{2′-(1-morpholinyl) ethylamino}-α-D-xylofuranose (9h). Colorless, thick oil (138 mg, 74%). IR (neat): 3330, 3150, 2900, 2830, 1600, 1410, 1385, 1350, 1150 cm^{-1}. ^1H NMR ($CDCl_3$): δ 0.94 (t, *J* = 6.5Hz, 3H), 1.24–1.63 (m, 24H), 1.88 (br s, 1H), 2.52–2.86 (m, 10H), 3.41–3.71 (m, 10H), 4.19–4.61 (m, 3H), 5.95 (d, *J* = 4.0Hz, 1H). MS: *m/z* (%) 501 (100) [M+1]. Anal. Calcd for $C_{27}H_{52}N_2O_6$ (500.71): C, 64.77; H, 10.47; N, 5.59%. Found: C, 64.48; H, 10.34; N, 5.30%.

3-*O*-{3′-(Decyloxy)propyl}-1,2-*O*-isopropylidene-5-deoxy-5-{2′-(1-methylpyrrol-2-yl)ethylamino}-α-D- xylofuranose (9i). Colorless, thick oil (115 mg, 63%). IR (neat): 3310, 3105, 2900, 2820, 1590, 1400, 1370, 1280, 1100 cm^{-1}. ^1H NMR ($CDCl_3$): δ 0.92 (t, *J* = 6.5Hz, 3H), 1.23–1.63 (m, 24H), 2.67–2.85 (m, 6H), 2.89 (br s, 1H) 3.40–3.71 (m, 9H), 4.19–4.68 (m, 3H), 5.95 (d, *J* = 4.0Hz, 1H), 6.10–6.52 (m, 3H). MS: *m/z* (%) 495 (100) [M+1]. Anal. Calcd for $C_{28}H_{50}N_2O_5$ (494.71): C, 67.98; H, 10.19; N, 5.66%. Found: C, 67.64; H, 9.86; N, 5.23%.

3-*O*-{3′-(Decyloxy)propyl}-1,2-*O*-isopropylidene-5-deoxy-5-{2′-(1-pyrrolidinyl)-ethylamino}-α- D-xylofuranose (9j). Colorless, thick oil (120 mg, 67%). IR (neat): 3330, 3120, 2910, 2800, 1630, 1420, 1390, 1300, 1150 cm^{-1}. ^1H NMR ($CDCl_3$): δ 0.94 (t, *J* = 6.5Hz, 3H), 1.30–1.54 (m, 24H), 1.61–1.88 (m, 7H), 2.50–2.82 (m, 8H), 3.41–3.73 (m, 6H), 4.19–4.68 (m, 3H), 5.95 (d, *J* = 4.0Hz, 1H). MS: *m/z* (%) 485 (100) [M+1]. Anal. Calcd for $C_{27}H_{52}N_2O_5$ (484.71): C, 66.90; H, 10.81; N, 5.78%. Found: C, 67.11; H, 11.08; N, 5.99%.

3-*O*-{3′-(Decyloxy)propyl}-1,2-*O*-isopropylidene-5-deoxy-5-{3′-(1-pyrrolidinyl)-propylamino}-α-D-xylofuranose (9k). Colorless, thick oil (118 mg, 64%). IR (neat): 3350, 3105, 2920, 2850, 1610, 1440, 1370, 1280, 1100 cm^{-1}. ^1H NMR ($CDCl_3$): δ 0.94 (t, *J* = 6.5Hz, 3H), 1.30–1.54 (m, 24H), 1.61–1.88 (m, 7H), 2.50–2.82 (m, 10H), 3.41–3.72 (m, 6H), 4.21–4.70 (m, 3H), 5.95 (d, *J* = 4.0Hz, 1H). MS: *m/z* (%) 499 (100) [M+1]. Anal. Calcd for $C_{28}H_{54}N_2O_5$ (498.74): C, 67.43; H, 10.91; N, 5.62%. Found: C, 67.32; H, 11.01; N, 5.77%.

3-*O*-{3′-(Decyloxy)propyl}-1,2-*O*-isopropylidene-5-deoxy-5-{2′-(1-piperidinyl)ethylamino}-α-D-xylofuranose (9l). Colorless, thick oil (137 mg, 74%). IR (neat): 3340, 2990, 2900, 2780, 1640, 1400, 1390, 1350, 1150 cm^{-1}. ^1H NMR ($CDCl_3$): δ 0.94 (t, *J* = 6.5Hz, 3H), 1.31–1.48 (m, 22H), 1.58–1.90 (m, 9H), 2.51–2.86 (m, 10H), 3.39–3.70 (m, 6H), 4.18–4.72 (m, 3H), 5.90 (d, *J* = 4.0Hz, 1H). MS: *m/z* (%) 499 (100) [M+1]. Anal. Calcd for $C_{28}H_{54}N_2O_5$ (498.74): C, 67.43; H, 10.91; N, 5.62%. Found: C, 67.61; H, 10.66; N, 5.40%.

3-*O*-{3′-(Decyloxy)propyl}-1,2-*O*-isopropylidene-5-deoxy-5-{3′-(1-imidazolyl)-propyl amino}-α-D-xylofuranose (9m). Colorless, thick oil (138 mg, 75%). IR (neat): 3310, 3105, 2910, 28005, 1610, 1450, 1390, 1320, 1110 cm^{-1}. ^1H NMR ($CDCl_3$): δ 0.96 (t, *J* = 6.5Hz, 3H), 1.35–1.76 (m, 25H), 2.05–2.45 (m, 2H), 2.80–3.85 (m, 6H), 3.90–4.15 (m, 6H), 4.20–4.59 (m, 3H), 5.65 (d, *J* = 4.0Hz, 1H), 6.92–7.45 (m, 3H). MS: *m/z* (%) 496 (100) [M+1]. Anal. Calcd for $C_{27}H_{49}N_3O_5$ (495.70): C, 65.42; H, 9.96; N, 8.48%. Found: C, 65.76; H, 10.13; N, 8.54%.

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