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Synthesis of 2-Haloalkyl Benzimidazolyl-6-oxy-*O*- -D-Glucopyranoses

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Abstract :A simple and efficient method for the preparation of several 2-haloalkyl-1*H*-benzimidazolyl-6-oxy-*O*- -D-glucopyranose derivatives is reported. Compounds were synthesized via condensation, starting from 2-haloalkyl-*1H*-benzimidazolyl-6-ol and 2, 3, 4, 6-tetra-*O*-acetyl- -D-glucopyranosyl bromide. Their structures were assigned with elemental analysis, melting point and spectral analysis like IR, ^1H NMR and EI MS and optical activity. The antibacterial activity of these compounds was recorded using cup plate method. Some compounds of the series were found to active.

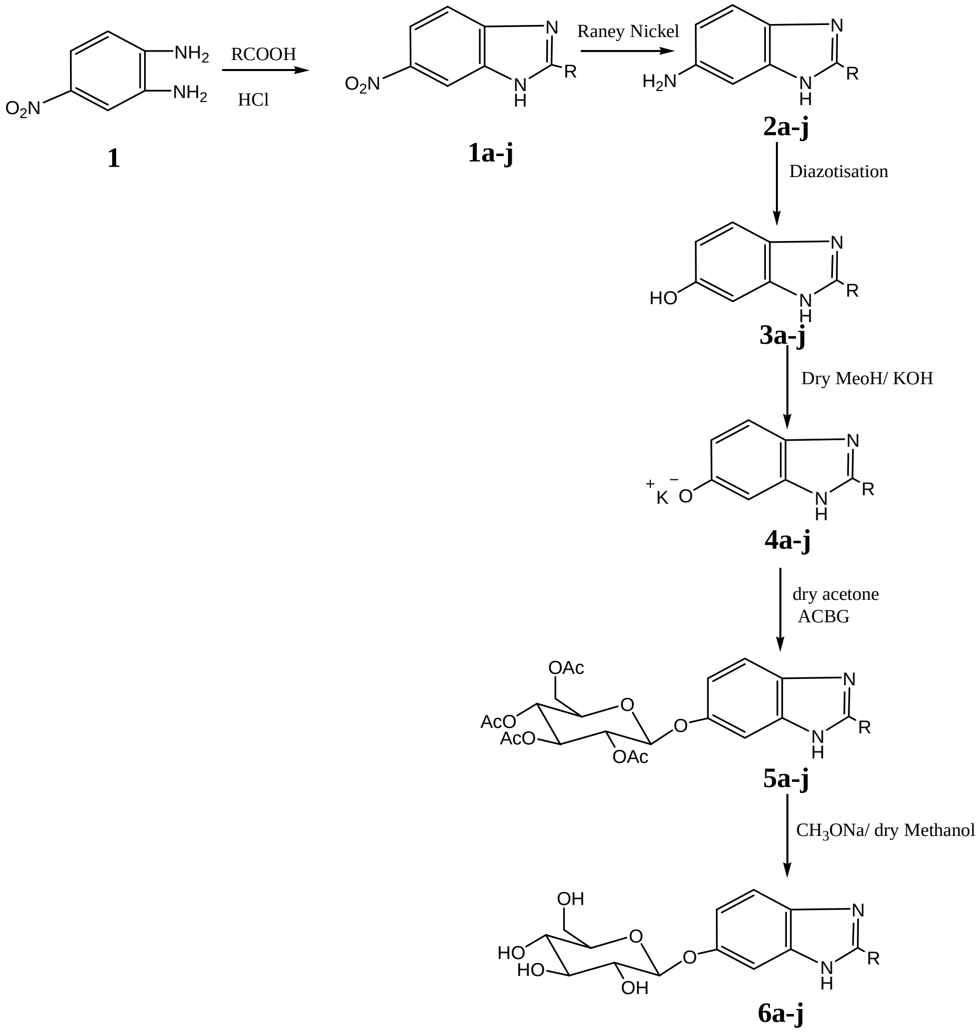
Keyword: Benzimidazole, Carbohydrate, *O*-glucoside

Introduction

It is well known that benzimidazole is an important structural core in medicinal chemistry that shows a broad spectrum of pharmacological activities like antimicrobial[1], antitumor[2], antihistaminic[3], antifungal[4], and anthelmentic[5] and antiviral agents[6]. Halogenated benzimidazole are effective agents used as antimicrobial and antiprotozoal agent[7] Benzimidazoles, both with or without a sugar moiety, exhibit antifungal and antibacterial properties[8]. Recently, carbohydrates are recognized for playing a significant role in many physiological activity like immunology, virology, cancer and antibiotic activity. Further they contain many chiral centers and functional groups suitable for the synthesis of complex molecule exhibiting diverse biological activity[9-17]. Benzimidazoles substituted with a sugar residue at C-2 are potent inhibitors of glycogen phosphorylase and have become the targets for new drug development for treatment of diabetes mellitus[18]. Owing to broad spectrum activity of benzimidazoles and importance of carbohydrate and in continue to early work[19] we wish to explore a new approach of synthesis of O-glucopyranoses.

Result and discussion: The 2-haloalkyl-*1H*-benzoimidazolyl-6-ol described in this paper was prepared by following a general synthetic route represented in **scheme 1**. The 4-nitro-o-phenylendiamine (**1**) is commercially available or prepared according to different literature methods. It was cyclized to 6-nitro-2-substituted benzimidazoles (**1a-j**) in 4N HCl acid. The compounds (**2a-j**) were prepared by reduction of the nitro derivatives (**1a-j)** respectively. 2-Haloalkyl-*1H*-benzoimidazolyl-6-ols (**3a-j**) in next step were synthesized, according to Sandmeyer reaction. Formations of (**3a-j**) were confirmed by violet coloration with neutral ferric chloride solution and no dye with -napthol. Further they were proved by their FT-IR and ^1H NMR spectra. The IR spectrum, with strong absorption at (3500-3600) shows the unmistakable presence of hydroxyl group and at the same time presence of amine group is ruled out by absence of absorption at (3460) in IR spectrum. Moreover, the ^1H NMR spectra don't show any signal due to NH_2 is consistent with their structure. Finally to synthesis target compounds (**6a-j**), all the 2-haloalkyl-*1H*-benzoimidazolyl-6-ol first converted to their potassium salt (**4a-j**) and condensed with ACBG and later deacetylated with sodium methoxide. The targeted compound (**6a-j**) is proved by negative phenolic hydroxyl group test and positive molisch test of carbohydrate. They were again ascertained by their FT-IR and ^1H NMR spectra. The FT-IR of (**6a-j**) exhibited characteristic band at 3411-3578 (OH peak of carbohydrate residue) and the two characteristic absorption arising from 1740 (C=O) and 1200 (C-O) for ester stretching vibration are absent. ^1H NMR showed signal at 4.41-4.61 (d 1H, 4`H and m, 1H 2`H), 4.52 (d, 1H, anomeric proton), 3.53 (1H, d, 5`H, 4.19 (m, 1H, 6` 1H) and no signal of acetyl protons; EI-MS of (**6a**) showed molecular ion peak at m/z, 344 (MH^+). The splitting of the sugar-oxygen bond accompanied by the transfer of hydrogen and further loss of water showed peak at 163 m/z. The base peak observed at 181 m/z due to the C-O bond cleavage.

Graphical Abstract (Scheme 1)



Where **R**=

a;CH_2Cl
b;$CHCl_2$
c; CCl_3
d; CH_2I
e; CF_3
f; $(CH_2)_2Br$
g; $(2)ClC_6H_5$
h; $(3)ClC_6H_5$
i; $(4)ClC_6H_5$
j; $(4)\ FC_6H_5$

Biological activity: For antibacterial bioassays, the compounds were dissolved in MeOH of concentration 150 µg/ml. Standard norfloxacin was used for the comparison of the results. In order to ensure that the solvent had no effect on bacterial activity, negative control tests were performed using MeOH at the same concentrations. In this assay, the bacterial strain used for screening are *Staphylococcus aureus* and *Escherichia coli.* The sterilized Mullier-Hinton agar medium (50 mL) was inoculated with test organism and poured into petri-plates under aseptic condition. Four holes of 6 mm diameter were made carefully with the help of sterile cork-borer and these were completely filled with test solution. The plates were incubated for 24 hours at 37 ^{0}C and zone of inhibition were measured. The screening results indicate that *O*-glucoside showed moderate to excellent antibacterial activity against both organisms as compared to aglycon (Table 1).

Table 1. Data for in vitro antibacterial activity

products	*E.coli*	*S aureus*
3a (4a)	*09 (11)*	*10 (13)*
3b (4b)	*13 (19)*	*15 (16)*
3c (4c)	*14 (- -)*	*11 (09)*
3d (4e)	*11 (16)*	*- - (11)*
3f (4f)	*08 (12)*	*- - (12)*
3g (4g)	*09 (12)*	*09 (11)*
3h (4h)	*12 (18)*	*13 (14)*
3h (4i)	*10 (16)*	*12 (16)*
3j (4j)	*13 (14)*	*11 (15)*

- - = no inhibition of growth.

Diameter of zone of inhibition 13-18 and 9-12 shows excellent and moderate activity for bacterial strains respectively. Norfloxacine 100 g/mL used as standard against E. *coli*, and S. aureous, zone of inhibition is 20.

Experimental

General methods All melting points are uncorrected and were obtained in capillary using paraffin bath or sulfuric acid. FT-IR spectra were recorded using KBr disc on Perkins Elmer FT-IR (KBr) spectrophotometer and ^{1}H NMR on a Bucker AC-3OOMHz NMR spectrophotometer using DMSO as a solvent and tetramethylsilane as an internal standard. Mass spectra were recorded by the direct insertion technique with a Hitachi perking Elmer RMU 6D mass spectrophotometer. Purity of compounds was checked on silica gel G plate using iodine vapor and UV chamber as a visualizing agent. Elemental analyses were determined using flash EA 1112 C, H, and N analyzer, thermofining Italy.

1. 2-Chloromethyl-*1H*-benzimidazolyl-6-ol: The 2-chloromethyl-1*H*-benzimidazole-6-amine (1.33 g, 0.01mole) was dissolved in mixture of conc. H2SO4 (4 mL) and water (4 mL). The solution was kept at 0 ^{0}C. To this, an aqueous solution of sodium nitrite (0.70 g, 0.01 mole) in water (5.0 mL) was added dropwise with continuous stirring keeping the temperature of reaction mixture at 0-5 ^{0}C. The reaction mixture was kept for further 30 min for completion of reaction that was checked by starch iodide paper. After completion of reaction, it was added into sulfuric acid solution (2.0 mL in 10 mL water) and refluxed it for 2 h, cool it and pour into water, separated 2-chloromethyl-1*H*-benzimidazole-6-ol was washed with cold water, dried and crystallized from alcohol. Yield 66 %, C, 52.72, H, 3.92, N, 15.78 and Cl, 19.49; mp 190^{0}C; FT-IR (KBr): 3500 (OH), 3341 (NH), 2945 (CH), 1416 (C=C Ar), 1515 (N-C=N). ^{1}H NMR: 4.28 (s, 2H, CH$_2$), 6.32 (s, 1H, NH), 7.0-8.0 (m, 4H, CH), 8.18-9.34 (s, 1H, OH). Likewise, different 2-haloalkyl-6-hydroxy-1*H*-benzimidazoles (**1b-i**) were synthesized. **1b:** Yield 61%, Cryst aq. EtOH, C, 44.65, H, 3.12, N, 13.43 and Cl, 32.76; mp 155^{0}C, FT-IR: 3500 (OH), 3341 (NH), 3016 (CH), 1528 (N-C=N), 752 (CCl). ^{1}H NMR: 8.28-8.34 (s, 1H, OH), 7.0-8.23 (m, 4H, CH), 6.31 (s, 1H, NH), 4.39 (s, 1H, CH). **1c**: Yield 69%, Cryst aq. EtOH, C, 38.67, H, 2.45, N, 14.59 and Cl, 42.65; mp 110^{0}C, FT-IR: 3500 (OH), 3341 (NH), 2993 (CH), 1514 (N-C=N), 759 (CCl). ^{1}H NMR: 8.19-8.24 (s, 1H, OH), 7.0-8.16 (m, 4H, CH), 6.33 (s, 1H, NH). **1d:** Yield 51%, Cryst aq. EtOH, C, 35.69, H, 2.42, N, 10.16 and I, 46.46; mp 197 ^{0}C, FT-IR: 3500 (OH), 3341 (NH), 3015 (CH), 1512 (N-C=N), 625 (CI). ^{1}H NMR: 8.21-8.26 (s, 1H, OH), 7.0-8.17 (m, 4H, CH), 6.33 (s, 1H, NH), 4.37 (s, 2H, CH$_2$). **1e**: Yield 68%, Cryst aq. EtOH; C, 47.80, H, 2.90, N, 13.90 and F, 28.43, mp 118^{0}C; FT-IR: 3512 (OH), 3023 (NH), 1529 (N-C=N) and ^{1}H NMR: 8.34-8.37 (s, 1H, OH), 6.11 (1H, NH), 6.81-8.41 (m, 3H, CH). **1f**: Yield 45%, cryst aq. EtOH, C, 45.10, H, 3.87, N, 11.69 and Br, 33.58; mp 113^{0}C, FT-IR: 3512 (OH), 3044 (NH), 1559 (N-C=N), 649 (CBr) and ^{1}H NMR: 8.37-8.65 (s, 1H, OH), 6.26 (s, 1H, NH), 6.8-8.41 (m, 3H, CH), 3.51-3.62 (t, 4H, CH$_2$), **1g**: Yield 63%, Cryst aq. EtOH; C, 64.13, H, 3.83, N, 11.76 and Cl, 14.67; mp 262^{0}C FT-IR: 3515 (OH), 3039 (NH), 1522 (N-C=N), 752 (C-Cl) and ^{1}H NMR : 8.79-8.85 (s, 1H, OH), 7.0-8.96 (m, 7H, m), 6.24 (s, 1H, NH), **1j**: Yield 59%, Cryst aq. EtOH; C, 68.69, H, 4.13, N, 12.48 and F, 8.49; mp 196^{0}C FT-IR: 3509 (OH), 3036 (NH), 1531 (N-C=N), 1070 (C-F) and ^{1}H NMR : 8.65-8.81 (s, 1H, OH), 7.09-8.87 (m, 7H, CH), 6.34 (s, 1H, NH).

2. 2-Chloromethyl benzimidazolyl-6-oxy-tetra-*O*-acetyl- -D-glucopyranose: To (**1a**) (1.34 g 0.01 mole in 25 mL of 2.5% methanolic KOH), -acetobromoglucose (4.11 g, 0.01 mole in 30 mL of dry acetone) was added drop wise. The resulting mixture was stirred at 0-5 ^{0}C for 8 hours. The progress of reaction was monitored by thin layer chromatography. After the completion of reaction mixture, the solvent was concentrated under reduced pressure. The brown sticky mass separated was dissolved in MeOH-CHCl3 (10:10) and chromatographed on 60-120 mesh silica gel eluting with 10% methanol in chloroform to afford the titled compound. It was found to be optically active and its specific rotation [ ]^{27} D in CHCl$_2$ was found to be 37.10. Yield 74%; R$_f$ 0.19 (CHCl$_3$: MeOH 95:5); 51.62, H, 4.92, N, 5.78 and Cl, 7.19; FT-IR: 3313 (NH), 2976 (CH), 1783 (C=O of OCOCH$_3$), 1370 (C=O), 1030 (C-O), 770 (C-Cl). ^{1}H NMR: 7.0-8.3 (m, 4H, CH), 6.34 (s, 1H, NH), 2.01-2.19 (s, 3H, OAc), 4.4-4.8 (d, 1H, -anomeric proton), 4.31 (s, 2H, CH$_2$). In the same way, different (**4b-j**) were synthesized. **2b:** Yield 51%; R$_f$ 0.21 (CHCl$_3$: MeOH 95:5); [ ]$_D^{25}$ (CH$_2$Cl$_2$) 40.41^0; C, 48.65, H, 4.62, N, 5.43 and Cl, 12.32; FT-IR: 3323 (NH), 2955 (CH), 1788 (C=O of OCOCH3), 1374 (C=O), 1038 (C-O) and 775 (C-Cl).

^{1}H NMR: 7.02-8.18 (m, 3H, CH), 6.38 (s, 1H, NH), 2.02-2.21 (s, 3H, OAc), 4.42-4.78 (d, 1H, -anomeric proton), 4.36 (s, 1H, CH). **2c:** Yield 59%; R$_f$ 0.17 (CHCl$_3$: MeOH 95:5); [ ]$_D^{25}$ (CH$_2$Cl$_2$) 44.32^0; C, 45.67, H, 4.15, N, 4.89 and Cl, 18.65; FT-IR: 3319 (NH), 2948 (CH), 1782 (C=O), 1374 (C-O), 1030 (C-O) and 774 (CCl). ^{1}H NMR: 7.04-8.12 (m, 3H, CH), 6.3 (s, 1H, NH), 2.01, 1.95, 1.98, 2.17 (s, 3H, OAc), 4.41-4.82 (d, 1H, -anomeric proton). **2d**: Yield 51%; R$_f$ 0.23 (CHCl$_3$: MeOH 95:5); [ ]$_D^{25}$ (CH$_2$Cl$_2$) 46.65^0; C, 44.35, H, 4.42, N, 5.16 and I, 21.23; FT-IR: 3319 (NH), 1783 (C=O), 1370 (C=O), 1030 (C-O) and 587 (CI). ^{1}H NMR: 7.10-8.07 (m, 3H, CH), 6.31 (s, 1H, NH), 2.00-2.18 (s, 3H, OAc), 4.32-4.91 (d, 1H, -anomeric proton), 4.41 (s, 2H, CH$_2$). **2e**: Yield 68%; R$_f$ 0.21 (CHCl$_3$: MeOH 95:5); [ ]$_D^{25}$ (CH$_2$Cl$_2$) 11.98^0; C, 49.80, H, 2.90, N, 5.89 and F, 10.87; FT-IR: 3323 (NH), 1312 (C-F) and ^{1}H NMR: 7.16-8.11 (m, 3H, CH), 6.31 (1H, NH), 2.01-2.19 (s, 3H, OAc), 4.33-4.97 (d, 1H, -anomeric proton). **2f**: Yield 45%; R$_f$ 0.19 (CHCl$_3$: MeOH 95:5); [ ]$_D^{25}$ (CH$_2$Cl$_2$) 21.32^0; C, 48.60, H, 4.87, N, 5.69 and Br, 14.58; FT-IR: 3344 (NH), 678 (C-Br) and ^{1}H NMR : 6.85-8.41 (m, 3H, CH), 6.26 (s, 1H, NH), 3.51-3.57 (t, 4H, CH$_2$), 2.05-2.23 (s, 3H, OAc), 4.36-5.02 (d, 1H, -anomeric proton). **2g**: Yield 63 %; R$_f$ 0.21 (CHCl$_3$: MeOH 95:5); [ ]$_D^{25}$ (CH$_2$Cl$_2$) 26.42^0; C, 56.64, H, 4.83, N, 5.69 and Cl, 14.58; FT-IR: 3339 (NH), 752 (CCl) and ^{1}H NMR: 6.95-8.36 (m, 7H, CH), 6.29 (s, 1H, NH), 2.02-2.20 (s, 3H, OAc), 4.33-4.97 (d, 1H, -anomeric proton). **2j**: Yield 59 %; R$_f$ 0.17 (CHCl$_3$: MeOH 95:5); [ ]$_D^{25}$ (CH$_2$Cl$_2$) 19.66^0; C, 68.69, H, 5.13, N, 5.12 and F, 8.49; FT-IR: 3331 (NH), 1075 (CF) and ^{1}H NMR: 7.09-8.87 (m, 7H, CH), 6.34 (s, 1H, NH), 2.03-2.28 (s, 3H, OAc), 4.35-4.94 (d, 1H, -anomeric proton).

3. 2-Chloromethyl benzimidazolyl-6-oxy-*O*- -D-glucopyranose: A freshly prepared sodium methoxide (2 mL) was added to the solution of **3a** (0.45 g, 0.001 mole) in dry methanol (20 mL) and stirred at room temperature for 10 hours. The reaction mixture was neutralized with cationic ion exchanger (Amberlite IR-120, SD fine, H$^+$ form). The resin was filtered off and the filtrate was concentrated in vacuo to obtain a vigorous strongly hygroscopic brown colored mass. Yield 66%; R$_f$ 0.32 (CHCl$_3$: MeOH 98:2); [ ]$_D^{25}$ (Water) 43.09^0; C, 48.78, H, 5.12, N, 8.17 and Cl, 10.49; FT-IR: 3300 (OH), 2927 (CH), 778 (C-Cl), ^{1}H NMR: 6.31 (s, 1H, NH), 7.0-8.0 (m, 3H, CH), 4.26 (s, 2H, CH$_2$), 4.49-4.62 (d, 1H, 4\`-H and m, 1H 2\`H), 4.41 (d, 1H, anomeric proton), 3.54 (1H, d, 5\`H, 4.17 (m, 1H, 6\`H); EI MS: *m/z*, 344 (MH$^+$), 181 (100%), 163, 165, 117 (M$^+$). **3b:** Yield 61%; R$_f$ 0.12 (CHCl$_3$: MeOH 98:2); [ ]$_D^{25}$ (Water) 15.55^0; C, 44.65, H, 4.12, N, 7.43 and Cl, 10.49; FT-IR: 3319 (OH), 2948 (CH), 791 (CCl). ^{1}H NMR: 7.08-8.19 (m, 3H, CH), 6.33 (s, 1H, NH), 4.41-4.60 (d, 1H, 4\`-H and m, 1H 2\`H), 4.51 (d, 1H), 3.55 (1H, d, 5\`H, 4.11 (m, 1H, 6\`H); EI MS: *m/z*, 378 (MH$^+$), 215(100%), 163, 180, 145 (M$^+$). **3c:** Yield 69%; R$_f$ 0.39 (CHCl$_3$: MeOH 98:2); [ ]$_D^{25}$ (Water) 11.60^0; C, 40.67, H, 3.80, N, 7.14 and Cl, 25.65; FT-IR: 3323 (OH), 798 (C-Cl). ^{1}H NMR: 6.29 (s, 1H, NH), 7.21-8.02 (m, 4H, CH), 4.44-4.61 (d 1H, 4\`H and m, 1H, 2\`H), 4.49 (d, 1H, anomeric proton), 3.51 (1H, d, 5\`H, 4.21 (m, 1H, 6\`H); EI Mass: *m/z,* 413 (MH$^+$), 249 (100%), 163, 132, 117, 91(M$^+$). **3d**: Yield 51%; R$_f$ 0.18 (CHCl$_3$: MeOH 98:2); [ ]$_D^{25}$ (Water) 19.72^0; C, 38.69, H, 3.12, N, 6.60 and I, 29.46; FT-IR: 3343 (OH), 2921 (CH), 1520 (N-C=N), and 587 (CI). ^{1}H NMR: 7.12-8.21 (m, 3H, CH), 6.33 (s, 1H, NH), 4.41 (s, 2H, CH$_2$), 4.47-4.58 (d 1H, 4\`H and m, 1H, 2\`H), 4.44 (d, 1H, anomeric proton), 3.53 (1H, d, 5\`H, 4.25 (m, 1H, 6\`H); EI MS: *m/z*, 436 (MH$^+$), 273 (100%), 256, 163, 146, 132 (M$^+$). **3e**: Yield 68%; R$_f$ 0.13 (CHCl$_3$: MeOH 98:2); [ ]$_D^{25}$ (Water) 11.28^0; C, 47.80, H, 4.43, N, 7.90 and F, 15.73; FT-IR: 3319 (OH), 1534 (N-C=N), 1312 (CF) and ^{1}H NMR: 7.16-8.11 (m, 3H, CH), 6.32 (s, 1H, NH), 4.39-4.65 (d, 1H, 4\`-H and m, 1H 2\`H), 4.43 (d, 1H, anomeric proton), 3.59 (1H, d, 5\`H, 4.17 (m, 1H, 6\`H); EI MS: *m/z,* 364 (MH$^+$), 201 (100%), 185, 163, 117 (M$^+$). **3f**: Yield 45%; R$_f$ 0.16 (CHCl$_3$: MeOH 98:2); [ ]$_D^{25}$ (Water) 11.93^0; C, 44.86, H, 4.87, N, 7.11 and Br, 19.58; FT-IR: 3331 (OH), 1549 (N-C=N), 689 (CBr) and ^{1}H NMR: 6.81-8.31 (m, 3H, CH), 6.26 (s, 1H, NH), ^{1}H NMR: 6.31 (s, 1H, NH), 7.0-8.0 (m, 3H, CH), 4.51-4.65 (d, 1H, 4\`-H and m, 1H 2\`H), 4.42 (d, 1H, anomeric proton), 3.56 (1H, d, 5\`H, 4.21 (m, 1H, 6\`H); 3.48-3.51 (t, 4H, CH$_2$). EI MS: *m/z*, 402 (MH$^+$), 238 (100%), 222, 163, 107, 91 (M$^+$). **3g**: Yield 63%; R$_f$ 0.25 (CHCl$_3$: MeOH 98:2); [ ]$_D^{25}$ (Water) 26.12^0; C, 56.13, H, 4.83, N, 6.96 and Cl, 8.79; FT-IR: 3328 (OH), 1545 (N-C=N), 757 (C-Cl) and ^{1}H NMR: 6.91-8.21 (m, 7H, CH), 6.29 (s, 1H, NH), 4.49-4.58 (d, 1H, 4\`-H and m, 1H 2\`H), 4.43 (d, 1H, anomeric proton), 3.56 (1H, d, 5\`H, 4.17 (m, 1H, 6\`H); EI MS: *m/z,* 407 (MH$^+$), 243 (100%), 227, 163, 117, 111 (M$^+$). **3j**: Yield 59%; R$_f$ 0.19 (CHCl$_3$: MeOH 95:5); [ ]$_D^{25}$ (H$_2$O) 19.60^0; C, 58.69, H, 5.13, N, 7.48 and Cl, 4.16; FT-IR: 3329 (OH), 1539 (N-C=N), 1078 (C-F) and ^{1}H NMR: 7.09-8.87 (m, 7H, CH), 6.33 (s, 1H, NH), 4.49-4.61 (d, 1H, 4\`-H and m, 1H 2\`H), 4.44 (d, 1H, anomeric proton), 3.51 (1H, d, 5\`H, 4.17 (m, 1H, 6\`H). EI MS: *m/z,* 390 (MH$^+$), 227 (100%), 211, 163, 117, 95 (M$^+$).

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