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Synthesis of Benzimidazolyl-6-amino-β-D-glucopyranoses

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Benzimidazolyl-6-amino-β-D-glucopyranoses (**5a-j**) has been rapidly, selectively and efficiently synthesized by condensation of 2-substituted-6-amino-1*H*-benzimidazoles with acetobromoglucose. The structures were assigned with elemental analysis, melting point and spectral analysis.

Key Words: Benzimidazole, Carbohydrate, N-Glucoside.

INTRODUCTION

Benzimidazole is an important heterocyclic nucleus in medicinal chemistry due to broad range of biological activity such as antivirus, antiulcer and antitumour activity[1-7]. Certain halogenobenzimidazole shows considerable potential for inhibiting growth of diverse microbial and protozoal species. Beside this many showed marked activity against human breast cancer and prostate cancer cell lines. It is also found that many are potent inhibitor of casein kinase CK2 present in numerous eukaryotic organisms[8-14]. Recently, carbohydrate, a diverse class of biomolecules plays a significant role in many physiological responses like immunology, virology and cancer, antibiotic activity. Further they contain many chiral centers and functional groups suitable for the synthesis of complex molecule exhibiting diverse biological activity[15-19]. Owing to broad-spectrum activity of benzimidazoles and importance of carbohydrate, we wish to report a new approach toward the synthesis of benzimidazolyl-6-amino-β-D-glucopyranose.

EXPERIMENTAL

All melting points are uncorrected and were obtained in open capillary. FT-IR spectra were recorded using KBr disc on Perkins Elmer IR spectrophotometer and ^{1}H NMR on a Bruker AC-300 Hz NMR spectrophotometer using DMSO as a solvent and TMS as an internal standard. Mass spectra were recorded by the direct insertion technique with a Hitachi Perkin-Elmer RMU 6D mass spectrophotometer. Purity of compounds was checked on silica gel G plate using iodine as a visualizing agent. Elemental analyses were determined using flash EA 1112 C, H, N analyzer (Thermofining Italy).

2-Chloromethyl-6-nitro-1*H*-benzimdazole (2a): The mixture of 4-nitro-O-phenylenediamine (3.06 g, 0.02 mol), chloroacetic acid (1.3 mL, 0.03 mol) and HCl acid (5.5 N, 50 mL) was boiled for 3 h in round bottom flask under reflux. The reaction mixture was then cooled to room temperature, diluted with water and neutralized with dil NaOH. The separated solid **2a** was filtered, washed with water, dried and crystallized from alcohol.

2-Chloromethyl-6-amino-1*H*-benzimidazole (3a): To a solution of 2-chloromethyl-6-nitro-1*H*-benzimidazole (**2a**) (4.22 g, 0.01 mol) in super dried alcohol (50 mL), Raney nickel (1.2 g, 0.02 mol) was added in three-necked hydrogenation flask. The hydrogen gas was bubbled with constant stirring at room temperature for 3 h. Filtered and washed the metal residue twice with alcohol. Washing was collected and concentrate under reduced pressure.

Likewise, other 2-haloalkyl and aryl-6-amino-1*H*-benzimidazoles (**3b-j**) were synthesized.

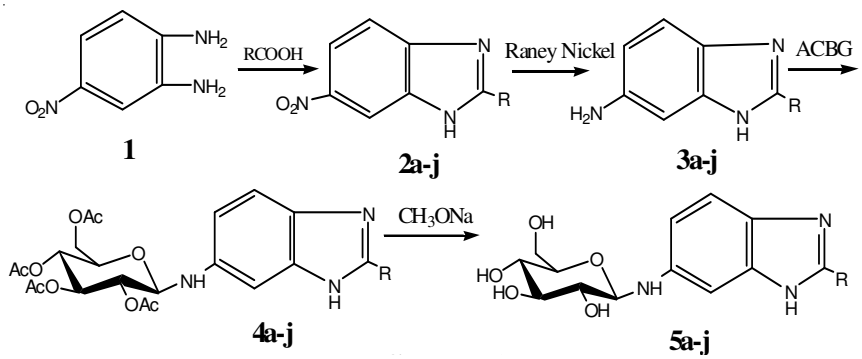
2-Chloromethyl benzimidazolyl-6-amino-β-D-2,3,4,6-tetra-O-acetyl glucopyranose (4a): A mixture of 2-chloromethyl-6-amino-1*H*-benzimidazole (**3a**) (1.80 g, 0.01 mol) and α-D-2,3,4,6-tetra-O-acetyl glucopyranosyl bromide[21] (4.1 g, 0.01 mol) was refluxed in dried ethyl alcohol (80 mL) for 2 h. Cool the reaction mixture, filter and concentrated filtrate under vacuum.

Similarly, different acetylated glucopyranoses (**4b-J**) were prepared.

2-Chloromethyl benzimidazolyl-6-amino-β-D-glucopyranose (5a): To a solution of 2-chloromethyl benzimidazolyl-6-amino-β-D-2,3,4,6-tetra-O-acetyl glucopyranose (**4a**) (0.5 g) in 25 mL of dry methanol was added freshly prepared 5 % sodium methoxide (1.5 mL) solution and mixture was kept at 25 ºC for 24 h. The reaction mixture was neutralized with ion-exchange resin (Amberlite IR120, SD Fine H^+ form), filtered and concentrated in vacuum. Following same procedure, other 6-amino-β-D-glucopyranoses (**5b-j**) were prepared.

RESULTS AND DISCUSSION

The method used to synthesize the 2-substituted benzimidazolyl-6-amino-β-D-glucopyranoses is illustrated in **Scheme-I**. The condensation of 4-nitro-O-phenylene diamine with halocarboxylic acids[20] affords benzimidazoles (**2a-j**). Their structure was assigned with elemental and spectral analysis. Chemically, **2a-j** showed positive nitro and negative amino group test. The **2a** showed peak at 3172 ν(NH), 2814 ν(CH), 1408 ν(C=C Ar), 1590 ν(C-NO_2), 1514 ν(N-C=N), 770 cm^{-1} ν(CCl) and ^{1}H NMR δ_H at 4.19 (s, CH_2), 6.13 (s, 1H, NH), 7.5-8.20 (m, 3H, CH). The 2-substituted-6-amino-1*H*-benzimidazoles (**3a-j**) were synthesized by reduction using Raney nickel in dried ethanol at room temperature. The **3a-j** gave positive



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)FC_6H_5; **j**; (4)ClC_6H_5

Scheme-I

dye test and negative nitro group test. IR spectrum of **3a** showed peak at 3460 ν(NH_2), 3013 ν(NH), 2921 ν(CH), 1517 ν(N-C=N), 1570 ν(C=C Ar), 777 cm^{-1} ν(CCl) and ^1H NMR signals at δ_H 4.24 (s, 2H, CH_2), 6.19 (s, 1H, NH), 8.68-9.89 (s, 2H, NH_2), 6.87-8.43 (m, 3H, CH). All **3a-j** were subjected to glucosylation to produce glucopyranoses (**4a-j**) that gives negative test of amino group and positive ester group and Molisch test. The IR spectrum of **4a** showed peak at 3013 ν(NH), 2921 ν(CH), 1519 ν(N-C=N), 1578 ν(C=C Ar), 760 ν(CCl) and ^1H NMR signals at δ_H 4.29 (s, 2H, CH_2), 6.26 (s, 1H, NH), 6.81-8.34 (m, 3H CH), 2.13 (s, 3H, OAc), 3.77 m, 1H``, 4.16 m, 1H```, 3.89 m, 1H````, 4.32 m, 1H`````, 4.85-5.13 (d, 1H`). The deacetylation of **4a-j** using sodium methoxide affords 2-substituted benzimidazolyl-6-amino-β-D-glucopyranose (**5a-j**) that showed negative ester group test and positive Molisch test. IR spectrum of **5a** showed peak at 3063 ν(NH), 2956 ν(CH), 1534 ν(N-C=N), 1579 ν(C=C Ar), 790 cm^{-1} ν(CCl) and ^1H NMR signals at δ 4.33 (s, 2H, CH_2), 6.31 (s, 1H, NH), 6.94-8.43 (m, 3H, CH), 3.84 m, 1H``, 4.11 m, 1H```, 4.15 m, 1H````, 4.44 m, 1H`````, 4.95-5.13 (d, 1H`). EI MS: Molecular ion peak at m/z, 344 (MH^+) and base peak at 181 (100 %) is produced due to loss of glucose. The analytical and spectral data of the deacetyled **4a-j** and amino-β-D-glucopyranose (**5a-j**) are given in Table-1.

Antibacterial activity: The synthesized compound **3a-j** and **5a-j** were tested for their antibacterial activity by cup plate method using *S. aureous* and *E. coli* at 150 μg/mL concentration. The screening results showed moderate to excellent activity against both organisms (Table-2).

TABLE-1
ANALYTICAL AND SPECTRAL ANALYSIS

Compd. (m.f.)	Analytical and spectral analysis
4a ($C_{22}H_{26}N_3O_9Cl$)	C, 51.92, H, 5.48, N, 6.93, Cl, 7.10; IR: 3013 (NH), 1517 (N-C=N), 760 (CCl); ^{1}H NMR δ_H 4.29 (s, 2H, CH_2), 6.26 (br, s, 1H, NH), 6.81-8.34 (m, 3H, CH), 2.13 (s, 3H, OAc), 3.77 m, 1H``, 4.16 m, 1H```, 3.89 m, 1H````, 4.32 m, 1H`````, 4.85-5.13 (d, 1H`).
4b ($C_{22}H_{25}N_3O_9Cl_2$)	C, 48.56, H, 4.81, N, 7.69 and Cl, 12.96; IR: 3032 (NH), 1532 (N-C=N), ^{1}H NMR δ_H 4.52 (s, 1H, CH), 6.16 (br s, 1H, NH), 6.84 -8.43 (m, 3H, CH), 2.11 (s, 3H, OAc), 3.76 m, 1H``, 4.16 m, 1H```, 3.89 m, 1H````, 4.35 m, 1H`````, 4.85-5.05 (d, 1H`)
4d ($C_{22}H_{26}N_3O_9I$)	C, 43.88, H, 4.64, N, 7.12, I, 21.42; IR: 3034 (NH), 2942 (CH), 1524 (N-C=N), 645 (CH_2I) and ^{1}H NMR δ_H 4.40 (s, 2H, CH_2), 6.19 (br s, 1H, NH), 6.79-8.38 (m, 3H, CH), 2.11 (s, 3H, OAc), 3.77 m, 1H``, 4.19 m, 1H```, 3.89 m, 1H````, 4.33 m, 1H`````, 4.85-5.11 (d, 1H`)
4e ($C_{22}H_{24}N_3O_9F_3$)	C, 49.92, H, 4.49, N, 8.11, F, 10.87; IR: 3041 (NH), 2928 (CH), 1528 (N-C=N); ^{1}H NMR δ_H 6.18 (br s, 1H, NH), 6.79-8.35 (m, 3H, CH), 2.12 (s, 3H, OAc), 3.79 m, 1H``, 4.23 m, 1H```, 3.92 m, 1H````, 4.34 m, 1H`````, 4.85-5.11 (d, 1H`)
4f ($C_{23}H_{28}N_3O_9Br$)	C, 48.63, H, 5.32, N, 7.61, Br, 25.88; IR: 3033 (NH), 2936 (CH), 1531 (N-C=N), 660 (CBr); ^{1}H NMR δ_H 3.48-3.61 (t, 2H, CH_2), 6.19 (br s, 1H, NH), 6.72-8.41 (m, 3H, CH), 2.12 (s, 3H, OAc), 3.79 m, 1H``, 4.21 m, 1H```, 3.94 m, 1H````, 4.30 m, 1H`````, 4.87-5.21 (d, 1H`)
4g ($C_{27}H_{28}N_3O_9Cl$)	C, 56.61, H, 5.13, N, 6.18, Cl, 5.83; IR: 3013 (NH), 2921 (CH), 1527 (N-C=N), 741 (CCl); ^{1}H NMR δ_H 6.21 (br s, 1H, NH), 7.12-8.86 (m, 3H, CH, m, 4H, Ph CH)), 2.12 (s, 3H, OAc), 3.76 m, 1H``, 4.22 m, 1H```, 3.91 m, 1H````, 4.32 m, 1H`````, 4.86-5.22 (d, 1H`)
4j ($C_{27}H_{28}N_3O_9F$)	C, 63.26, H, 5.52 and N, 31.81 F, 4.92; IR: 3054 (NH), 1532 (N-C=N), 1059(CF); ^{1}H NMR δ_H 6.34 (br, s, 1H, NH), 7.21-8.67 (m, 3H, CH, m, 4H, Ph CH), 2.12 (s, 3H, OAc), 3.78 m, 1H``, 4.24 m, 1H```, 3.95 m, 1H````, 4.36 m, 1H`````, 4.88-5.21 (d, 1H`)
5a ($C_{14}H_{18}N_3O_5Cl$)	C, 48.92, H, 5.48, N, 12.36, Cl, 12.50; IR: 3063 (NH), 790 (CCl); ^{1}H NMR δ 4.33 (s, 2H, CH_2), 6.31 (br s, 1H, NH), 6.94-8.43 (m, 3H, CH), 4.95-5.13 (d, 1H`), 3.84 m, 1H``, 4.11 m, 1H```, 4.15 m, 1H````, 4.44 m, 1H`````; EI MS: m/z 344 (MH^+), 181(100%), 163, 145, 117(M^+)
5b ($C_{14}H_{17}N_3O_5Cl_2$)	C, 44.56, H, 4.31, N, 11.42, Cl, 18.96; IR: 3063 (NH); ^{1}H NMR: δ_H 4.48 (s, 1H, CH), 6.38 (br s, 1H, NH), 6.94-8.41 (m, 3H, CH), 4.95-5.16 (d, 1H`), 3.85 m, 1H``, 4.13 m, 1H```, 4.19 m, 1H````, 4.43 m, 1H`````; EI MS: m/z, 378 (MH^+), 213 (100%), 163, 198, 117 (M^+)
5d ($C_{14}H_{18}N_3O_5I$)	C, 38.88, H, 4.34, N, 9.90, I, 29.42; IR: 3063 (NH), 656 (CH_2I). ^{1}H NMR: δ_H 4.46 (s, 2H, CH_2), 6.31 (br s, 1H, NH), 6.89-8.44 (m, 3H, CH), 4.95-5.19 (d, 1H`), 3.81 m, 1H``, 4.11 m, 1H```, 4.21 m, 1H````, 4.44 m, 1H`````; EI MS: m/z 436(MH^+), 271 (100%), 163, 117 (M^+)
5e ($C_{14}H_{16}N_3O_5F_3$)	C, 46.42, H, 4.49, N, 11.57, F, 15.87; IR: 3063 (NH), 2956 (CH), 1534 (N-C=N), 1579 (C=C Ar); ^{1}H NMR δ_H 6.28 (br s, 1H, NH), 6.79-8.42 (m, 3H CH), 3.83 m, 1H``, 4.11 m, 1H```, 4.19 m, 1H````, 4.41 m, 1H`````, 4.87-5.17 (d, 1H`); EI MS: m/z, 364 (MH^+), 201 (100%), 163, 185, 117, 68 (M^+)

Compd. (m.f.)	Analytical and spectral analysis
5f ($C_{15}H_{20}N_3O_5Br$)	C, 44.63, H, 5.42, N, 10.61, Br, 19.88. IR: 3063 (NH), 2956 (CH), 1534 (N-C=N), 667 (C-Br); ^{1}H NMR δ_H 3.41-3.66 (t, 2H, CH_2), 6.34 (br s, 1H, NH), 6.87-8.47 (m, 3H,CH), 3.79 m, 1H``, 4.12 m, 1H```, 4.23 m, 1H````, 4.41 m, 1H`````, 4.89-5.10 (d, 1H`); EI MS: m/z, 402(MH^+), 237 (100%), 163, 131, 106, 117 (M^+)
5g ($C_{19}H_{20}N_3O_5Cl$)	C, 56.98, H, 5.13, N, 10.76, Cl, 8.83. IR: 3063 (NH), 2956 (CH), 1534 (N-C=N), 732 (C-Cl); ^{1}H NMR δ_H 6.36 (br s, 1H, NH), 6.71-8.41 (m, 3H, CH), 3.81 m, 1H``, 4.13 m, 1H```, 4.23 m, 1H````, 4.46 m, 1H`````, 4.91-5.17 (d, 1H`); EI MS: m/z, 407 (MH^+), 242 (100%), 163, 111, 131, 117 (M^+)
5j ($C_{19}H_{20}N_3O_5F$)	C, 58.74, H, 5.23, N, 10.58 and F, 4.92. IR: 3021(NH), 2928 (CH), 1543 (N-C=N), 1565 (C=C Ar), 1050 (C-F); ^{1}H NMR δ_H 6.35 (br s, 1H, NH), 7.29-8.66 (m, 3H, CH, m, 4H, Ph CH)), 3.79 m, 1H``, 4.16 m, 1H```, 4.23 m, 1H````, 4.41 m, 1H`````, 4.95-5.19 (d, 1H`). EI MS: m/z, 390 (MH^+), 226 (100%), 163, 132, 95 (M^+)

TABLE-2
ANTIBACTERIAL ACTIVITIES OF **3a-j** AND **5a-j**
(ZONE OF INHIBITION (mm) AGAINST BACTERIAL STRAINS)

Products	*E. coli*	*S. aureus*
4a (5a)	09 (11)	10 (13)
4b (5b)	13 (19)	15 (16)
4c (5c)	14 (13)	11 (09)
4d (5d)	11 (16)	13 (11)
4e (5e)	10 (13)	13 (14)
4f (5f)	08 (12)	10 (12)
4g (5g)	09 (12)	09 (11)
4h (5h)	12 (18)	13 (14)
4i (5i)	10 (16)	12 (16)
4j (5j)	13 (14)	11 (15)

Norfloxacine 100 µg/mL used as standard against *E. coli* and *S. aureous*.

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