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Synthesis of 2-Substituted-6-Nitro-N-1-β-D-Glucopyranosyl Benzimidazoles

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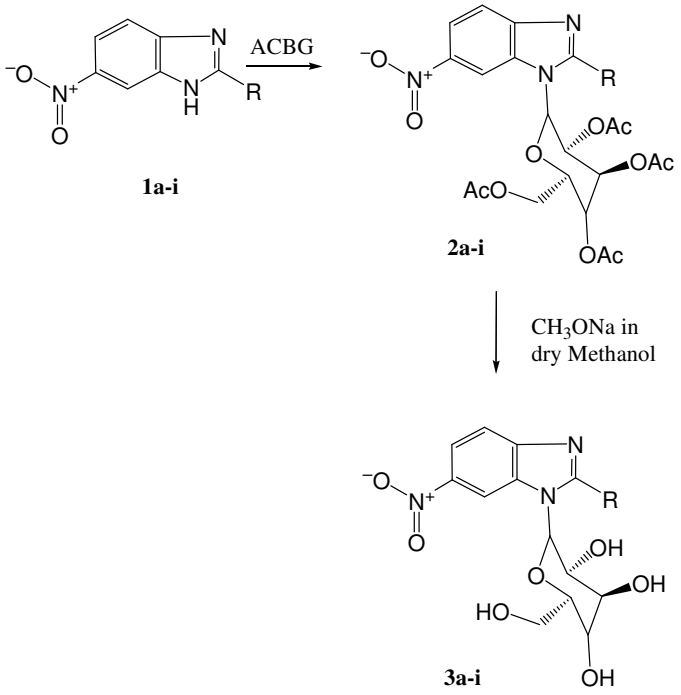
Abstract : The 2-substituted-6-nitro-*N*-1-β-D-glucopyranosyl benzimidazoles have been synthesized in high yields by condensation of 2, 3, 4, 6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide with appropriate 2-substituted 6-nitro-1*H*-benzimdazoles. Their structures were assigned with elemental analysis, melting point and spectral analysis like IR, ^{1}H NMR and EI MS.

Key word: Benzimidazole, Carbohydrate, *N*-glucoside.

Graphical Abstract



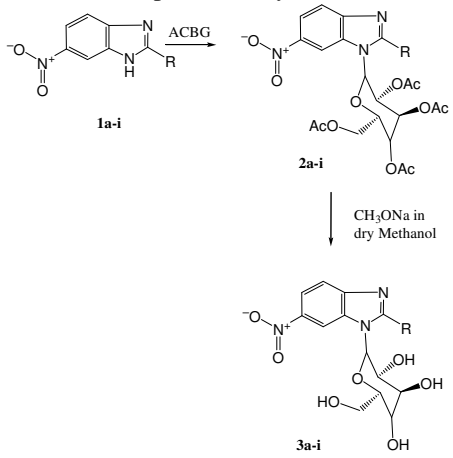
Scheme 1

Introduction

Benzimidazoles represent one of the largest groups of heterocyclic compound and have attracted a great deal of interest over the decades due to their wide potent biological activities[1-6] .The wide range of biological activities of benzimidazoles and glucosides[7-16] and in continuous to earlier work herein promoted us to prepare new class of benzimidazoles with simple and efficient method.

Results and discussion

In continuation of our earlier work[17] , in this article, we report a convenient synthesis of 2-substituted-6-nitro-N-1-β-D-glucopyranosyl benzimidazoles **(3a-i)** outlined in **Scheme 1.** In order to make **(2a-i)**, we carry out glucosylation 2-substituted-6-nitro-1*H*-benzimidazoles (**1a-i**) with ACBG[18] in dioxane. The precursor molecules for glucosylation (**1a-i**) were stable and characterized by usual techniques. The synthesis of target compounds was generated in two steps, beginning with condensation of ACBG with 2-substituted-6-nitro-1*H*-benzimidazoles and deacetylation in subsequent step. Displacement of the imino proton by ACBG followed by loss of HBr generates 2-substituted-6-nitro-*N*-1-β-D-tetra-*O*-acetyl glucopyranosyl benzimidazoles **(2a-i)**. Their structure was assigned with elemental analysis and IR, ^{1}H NMR spectral analysis.



Scheme 1

R= a;H b;CH_3 c;CH_2CH_3 d; $CH_2CH_2CH_3$ e; $(CH_2)_3CH_3$ f; $C(CH_3)_3$ g;$CH_2C_6H_5$ h; $(CH_2)_2COOH$ i;C_6H_5

The formation of (**2a-i**) is proved by positive molisch test of carbohydrate. The disappearance of (NH) peak, but appearance of peak at 1789 (C=O of $OCOCH_3$), 1374 (C=O), 1039 (C-O) in IR spectrum and no signal in ^{1}H NMR due to (NH) proton but appearance of signal at 2.06-2.19 (s, 3H, $OCOCH_3$), 4.42-4.81 (d, 1H, β-anomeric proton) confirms formation of (**2a-i**). To synthesized target molecules (**3a-i**), all 2-substituted-6-nitro-*N*-1-β-D-tetraacetyl glucopyranosyl benzimidazoles were deprotected with sodium methoxide. Formations of **(3a-i)** were ascertained by elemental analysis and IR, ^{1}H NMR and EI MS spectral analysis. IR exhibited characteristic band at 3411-3578 (OH peak of carbohydrate residue) and no two characteristic absorption band of (C=O) 1740 and (C-O) 1200. ^{1}H NMR showed signals 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 proton and EI-MS of (3a) showed molecular ion peak at m/z, 326 (MH^+) indicating formation of 2-substituted-6-nitro-*N*-1-β-D-glucopyranosyl benzimidazoles. The splitting of the sugar-nitrogen showed peak at 163 m/z. The base peak observed at 162 m/z due to the C-N bond cleavage.

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 glucoside showed moderate to excellent antibacterial activity against both organisms as compared to aglycon (Table 1).

Table 1. Antibacterial activities (zone of inhibition) (in mm)

products	*E.coli*	*S. aureus*
1a (3a)	11 (14)	10 (12)
1b (3b)	-- (11)	15 (17)
1c (3c)	14 (13)	11 (--)
1d (3d)	11 (16)	13 (14)
1e (3e)	10 (13)	-- (16)
1f (3f)	08 (12)	10 (18)
1g (3g)	10 (12)	09 (11)
1h (3h)	11 (--)	11 (12)
1i (3i)	10 (13)	12 (14)

= no inhibition of growth and diameter of zone of inhibition 13-18 and 9-12 shows excellent and moderate activity for bacterial strains respectively.

Experimental

General methods 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 vapour and UV chamber as a visualizing agent. Elemental analyses were determined using flash EA 1112 C, H, N analyzer, thermofining Italy.

6-Nitro-*N*-1β-D-2, 3, 4, 6-tetra-*O*-acetyl glucopyranosyl benzimidazole: 6-Nitro-1*H*-benzimidazole (3.26 g, 0.02 mole) and ACBG (8.5 g, 0.02 mole) were dissolved in dioxane (80 mL) at 100^{0}C and kept at this temperature for 4 hrs. The progress of reaction is monitored by TLC. The solvent was removed under reduced pressure. The resulting syrup was dissolved in MeOH-$CHCl_3$, (1:4) and chromatographed on 60-120 mesh silica gels eluting with 10% methanol in chloroform. The brown syrup of *N*-1-β-D-2, 3, 4, 6-tetra acetyl glucopyranosyl-6-nitro-benzimidazole was obtained. **2a** Elemental analysis: C, 51. 12, H, 4.82, and N, 8.54; $[\alpha]_{25}^D$ 26.23 (c, 0.1%, EtOH); R_f 0.42, IR: 2929 (CH), 1500 (NO_2), 1572 (C=C Ar); ^{1}H NMR: δ 6.78-8.41 (m, 4H,CH), 2.19 (s, 3H, OAc), 3.73 m, 1H``, 4.11 m, 1H```, 3.79 m, 1H````, 4.21 m, 1H`````, 4.81-5.01 (d, 1H). **2b**: Elemental analysis: C, 52.54, H, 5.15, N, 8.43; $[\alpha]_{25}^D$ 32.12 (c, 0.1%, EtOH) R_f 0.35, IR: 2964 (CH), 1531 (N-C=N), 1545 (C=C Ar) and ^{1}H NMR: 7.02-8.41 (m, 3H, CH), 2.46 (s, 3H, CH_3), 2.23 (s, 3H, OAc), 3.64 m, 1H``, 4.11 m, 1H```, 3.84 m, 1H````, 4.21 m, 1H`````, 4.81-4.87 (d, 1H`). **2g** Elemental analysis: C, 57.89, H, 5.21, and N, 7.32; $[\alpha]_{25}^D$ 37.22 (c, 0.1%, EtOH); R_f 0.73, IR: 2939 (CH), 3045 (Ph CH), 1549 (N-C=N), 1576 (C=C Ar) and ^{1}H NMR: 7.14-8.31 (m, 3H, CH), 2.46 (s, 2H, $PhCH_2$), 2.19 (s, 3H, OAc), 3.81 m, 1H``, 4.27 m, 1H```, 3.89 m, 1H````, 4.32 m, 1H`````, 4.78-4.97 (d, 1H`). **2i**: Elemental analysis: C, 56.82, H, 4.84 N, 7.52; $[\alpha]_{25}^D$ 28.29 (c, 0.1%, EtOH); R_f 0.28, IR: 3068 (Ph CH), 1549 (N-C=N), 1565 (C=C Ar); ^{1}H NMR: 7.23-8.32 (m, 3H, CH), 2.33 (s, 3H, OAc), 3.75 m, 1H``, 4.33 m, 1H```, 4.21 m, 1H````, 4.56 m, 1H``````, 4.81-5.17 (d, 1H`).

6-Nitro *N*-1-β-D-glucopyranosyl benzimidazole: To a solution of 6-nitro-*N*-1-β-D-2, 3, 4, 6-tetra-*O*-acetyl glucopyranosyl benzimidazole (1.0 g, 0.002 mole) in 25 mL of dry methanol was added freshly prepared 5% sodium methoxide (1.5 mL) solution and the mixture was kept at room temperature for 24 hour. The reaction mixture was neutralized with ion-exchange resin (Amberlite IR120, Sdfine H^+ form), filtered and concentrated in vacuo to afford viscous, strongly hygroscopic brown syrup. **3a** Elemental analysis: C, 48.12, H, 4.52, and N, 13.09; $[\alpha]_{25}^D$ 25.1 (c, 0.1%, EtOH) IR: 2978 (CH), 1588 (N-C=N), 1566 (C=C Ar); ^{1}H NMR: 6.89-8.31 (m, 4H CH), 3.84 m, 1H``, 4.17 m, 1H```, 3.82 m, 1H````, 4.49 m, 1H`````, 4.85-4.92 (d, 1H`). EI MS: m/z 326 (MH^+), 162 (100%), 116 (M^+). **3b** Elemental analysis: C, 49.54, H, 5.15, and N, 12.86; $[\alpha]_{25}^D$ 33.2 (c, 0.1%, EtOH); R_f 0.23, IR: 2949 (CH), 1555 (N-C=N), 1561 (C=C Ar); ^{1}H NMR: 6.72-8.43 (m, 3H CH), 2.59 (s, 3H, CH_3), 3.83 m, 1H``, 4.18 m, 1H```, 3.81 m, 1H````, 4.42 m, 1H`````,4.88-5.01 (d, 1H`). EI MS: m/z 340 (MH^+), 176 (100%), 130, 116, 91 (M^+). **3g** Elemental analysis: C, 57.89, H, 5.21, and N, 10.32; $[\alpha]_{25}^D$ 43.11 (c, 0.1%, EtOH); R_f 0.31, IR: 2965 (CH), 3089 (Ph CH), 1546 (N-C=N); ^{1}H NMR: δ 7.14-8.31 (m, 3H, CH), 2.46 (s, 2H, $PhCH_2$), 3.82 m, 1H``, 4.35 m, 1H```, 3.88 m, 1H````, 4.33 m, 1H`````, 4.87-4.98 (d, 1H`). EI MS: m/z 415 (MH^+), 252 (100%), 2.06, 163, 117, 130, 91, 77 (M^+). **3i**: Elemental analysis: C, 56.82, H, 4.84 and N, 10.52; $[\alpha]_{25}^D$ 28.25 (c, 0.1%, EtOH) IR: 3089 (Ph CH), 1545 (N-C=N), 1569 (C=C Ar); ^{1}H NMR: 7.11-8.33 (m, 3H CH), 3.79 m, 1H``, 4.11 m, 1H```, 4.18 m, 1H````, 4.33 m, 1H`````, 4.79-5.11 (d, 1H`). EI Mass: m/z 402 (MH^+), 238 (100%), 163, 192, 116 (M^+).

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