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# Synthesis and Antimicrobial Studies of Some New Perbenzoylated *N*-Glucosyl Benzothiazolyl Carbamides and Carbamates

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## ABSTRACT

As part of ongoing studies in developing new antimicrobials, a class of structurally novel perbenzolylated glucosyl benzothiazolyl carbamides and carbamates were synthesized by the interaction of tetra-*O*-benzoyl-β-D-glucosyl isocyanate with substituted benzothiazoles and various alcohols. The identities of these newly synthesized compounds were established on the basis of usual chemical transformations and IR, $^1$H NMR, and Mass spectral studies and evaluated for their in vitro antimicrobial activities using standard cup plate method against bacteria *E. coli, P. aeruginosa, P. vulgaris, B. cereus, S. aureus* and fungi *A. niger, C. albicans.*

**Keywords:** Benzothiazolyl Carbamides, Carbamates, Antimicrobial activities.

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# INTRODUCTION

Certain sugars express important biological function[1]. Glucosyl isocyanates have been widely used as valuable intermediates in the synthesis of glucosyl derivatives. Glucosyl isocyanates have been focus of synthetic attention during recent years because of their potential pharmacological properties. Many biologically important products have a sugar unit joined by an atom (O, S, N or C) or a group of atom. Glucosyl carbamates have been posses marked biological activity such as useful in treatment of hypertension, as appetite suppersant[2] and as potential antioxidant cardio protective agent[3]. Benzothiazoles are bicyclic ring system with multiples applications. They have diverse chemical reactivity and broad spectrum of biological activity including antibacterial and antifungal properties[4]. 2-aminobenzothiazoles show wide applications in medicinal chemistry such as antitumor activity[5], antimalerial activity[6]. Bis-substituted amidino benzothiazoles act as potential anti HIV agents[7]. Also shift-base benzothiazoles possess antitubercular, anticancer, antitumor, antipyretic and sterase inhibitory activity[8]. Herein we report the synthesis of new 1-tetra-*O*-benzoyl-β-D-glucosyl-3-(2)-substituted benzothiazolyl carbamides ($II_{a-g}$) and *N*-tetra–*O*-benzoyl-β-D-glucosyl-*O*-alkyl carbamates ($III_{a-e}$). The products have been tested for their in vitro antimicrobial activities against various strains of bacteria and fungi.

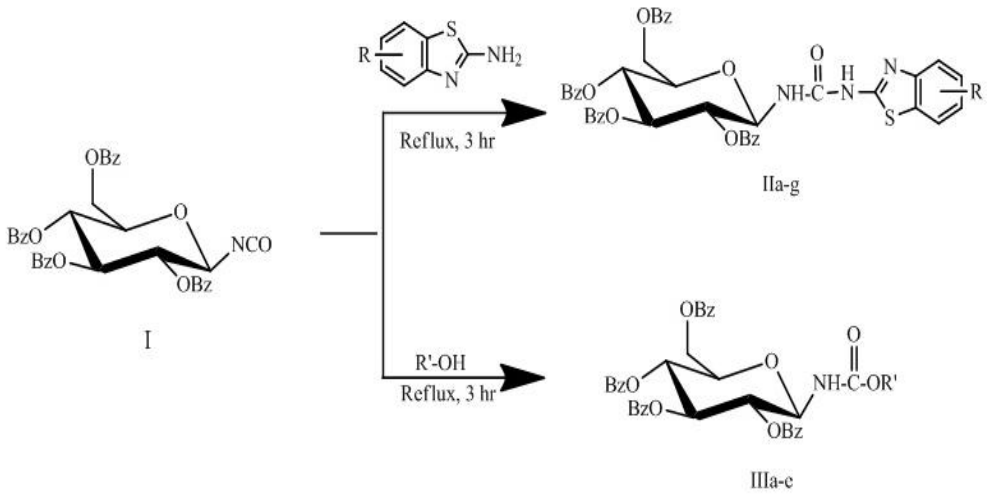
# MATERIALS AND METHODS:

## 1. Experimental

Melting points were taken in open capillary tube on Mac digital melting point apparatus and are uncorrected. Specific rotations $[\alpha]_D^{32}$ were measured on Equip-Tronics Digital Polarimeter model no. EQ 800 at $32^0$C in $CHCl_3$. IR spectrum was recorded on Perkin-Elmer Spectrum RXI-FTIR Spectrometer in solid phase KBr. $^1$H NMR spectrum were obtained on a Bruker DRX300 (300MHz FT NMR) NMR spectrometer in $CDCl_3$ solution with TMS as an internal standard. The mass spectra were recorded on a Jeol SX-102 FAB mass spectrometer. Thin Layer Chromatography [TLC] was performed on E. Merck per coated silica gel plates and detected by exposure under short UV light. The compounds reported in this paper were first time synthesized by the multistep reaction protocol. The tetra-*O*-benzoyl-β-D-glucosyl isocyanate (I) was synthesized by interaction of tetra-*O*-benzoyl-α-D-glucosyl bromide with Lead cyanate in refluxing xylene[9]. The tetra-*O*-benzoyl-α-D-glucosyl bromide was prepared according to the literature[10].

The required 2-aminobenzothiazole/2substituted benzothiazoles were prepared by the oxidative cyclization of 1-aryl thiocarbamides with the help of molecular bromine[11].

All the new compounds $II_{a-g}$, $III_{a-e}$ were characterized by m.p., elemental analysis and spectral data (IR, $^1H$ NMR, and MS), the spectral data and elemental analysis of new compounds reported in this correlated with the proposed structure.




**Scheme-I**

**Scheme-I :Chemical reaction diagram**

Where, R= a)H, b)4-$CH_3$, c)5-$CH_3$, d)6-$CH_3$, e)4-Cl, f)5-Cl, g)6-Cl, and R'= a) methyl b) Ethyl, c) propyl, d) n-butyl, e) iso-amyl Bz =$COC_6H_5$,

**2. General experimental procedure:**

**2.1 Synthesis of Tetra-*O*-benzoyl-β-D-glucosyl isocyanate[9]. (I)**

To a solution of tetra-O-benzoyl-α-D-glucosyl bromide (0.004M, 2.64g) in xylene (30ml) and lead cyanate (0.004M, 1.16g) was added and the resulting mixture was refluxed for 3hr with constant stirring. After the removal of lead bromide the xylene filtrate was evaporated under reduced pressure then triturated with petroleum ether (60-80$^0$C) to afford pale yellow solid. It was purified by dissolving it in chloroform and reprecipitating with petroleum ether (60-80$^0$C) to afford a white solid product **(1)** Yield 83.33% m.p. 110-115$^0$C.

**2.2 Synthesis of 1-tetra-*O*-benzoyl-β-D-glucosyl-3-(2)-aryl substituted benzothiazolyl carbamides ($II_{a-g}$)**

Condensation of tetra-*O*-benzoyl-β-D-glucosyl isocyanate (I) (0.004*M*, 2.48 g) and 2-amino benzothiazoles / substituted benzothiazoles (0.004*M*) in benzene (30 ml) was carried out on boiling water bath for 4h. The solvent was distilled off and the sticky residue was obtained which

was triturated with petroleum ether (60-80$^{o}$C) to afford the title compounds ($II_{a-g}$). They were purified by dissolving it in chloroform and reprecipitating with petroleum ether (60-80$^{0}$C) to afford a white solid product. The products were crystallized from ethanol-water system (3:1). The % yield, m.p., optical rotation and $R_f$ values which are shown in Table-1.

**2.3] Synthesis of *N*-tetra-*O*-benzoyl-β-D-glucosyl-*O*-alkyl carbamates ($III_{a-e}$)**

A (0.004*M*, 2.48 g) tetra-*O*-benzoyl-β-D-glucosyl isocyanate (I) was added to various alcohols (a-e) (30 ml) and the reaction mixture was refluxed for 3hr. After the refluxing it was allowed to cool and poured in water with vigorous shaking. A white granular solid separated out ($III_{a-e}$), products were crystallized from aqueous ethanol. The % yield, m.p., optical rotation and $R_f$ values which are shown in Table-1.

**3. Antimicrobial activity:**

The antimicrobial activity of newly synthesized compounds were tested in *vitro* against a selected gram positive, gram negative bacteria and fungi are presented in table-2 in comparison with those of the reference drugs Gentamicin (100µg/ml) and Fluconazole (100µg/ml) respectively. The antimicrobial activity was evaluated against different bacterial and fungal strains such as *E.coli, P. aeruginosa, P.vulgaris, S.aureus* and fungal strains *A.niger C. albicans* by using cup plate agar diffusion method[12]. The compounds investigated were dissolved in DMSO [1 mg/ml] and filled in 8mm wells in agar media. Inhibition zones read after incubation at 30$^{0}$C 24 hr for bacterial strains and for fungal strains inhibition zones read after incubation at 35$^{0}$C for 48 hr.

## RESULTS AND DISCUSSION:

Most of the synthesized compounds exhibited mild to moderate anti-microbial activity against the tested microorganisms. Compounds **IIb, IIc, IIe** and **IIg** were found to possess significant antibacterial and antifungal activity when compared to standard drug (Gentamicin and Fluconazole for antibacterial and antifungal respectively). The entire synthesized compounds exhibited mild to moderate activity are shown in Table -2. In general, the inhibitory activities against the bacteria were higher than that of the fungi.

The IR spectra[13-16, 19] of the compounds showed strong characteristic absorption of β-D-Glucopyranosyl ring deformation in the range of ν 860-848 cm$^{-1}$. The absorption bands for (N-H), (C=O) (C-N) (C-O) and (C-S) stretch have appeared in the region ν 3500-3100 cm$^{-1}$, ν 1750-1715 cm$^{-1}$ , ν 350-1210 cm$^{-1}$, ν 1200-1050 cm$^{-1}$, ν 800-600 cm$^{-1}$ respectively.

$^{1}$HNMR spectrum[13e,15-17,22-24] of the products shows signals due to glucosyl protons at δ 6.4-4.3 ppm, resonance signals for aromatic protons at δ 8.42-7.01 ppm and N-H protons δ 8.5-5.01 ppm. Mass spectra[17, 20-21] exhibited molecular ion peak along with characteristic fragments of tetra-*O*-benzoyl-β-D-glucosyl at *m/z*, 579, 351, 322, 245, 153, 138, and 105.

**Table-1: Physical characterization data of 1-tetra-*O*-benzoyl β-D-glucosyl-3-(2)-aryl substituted benzothiazolyl carbamides ($II_{a-g}$) and *N*-tetra-*O*-benzoyl-α-D-glucosyl-*O*-alkyl carbamates ($III_{a-e}$).**

| Compounds | M.P.($^{O}$C) | Yield (%) | $[\alpha]_D^{32}$(in$CHCl_3$) | $R_f$ (Hexane:EtOAc) (1:1) |
|---|---|---|---|---|
| 2a | 159-163 | 83.23 | +117.11 (c,1.10) | 0.82 |
| 2b | 137-141 | 73.80 | +114.28 (c,1.07) | 0.80 |
| 2c | 135-139 | 65.23 | +96.36 (c,1.04) | 0.76 |
| 2d | 144-149 | 78.55 | +78.43 (c,1.06) | 0.86 |
| 2e | 154-157 | 73.22 | -76.85 (c,1.05) | 0.83 |
| 2f | 140-143 | 76.12 | +62.69 (c,1.08) | 0.69 |
| 2g | 153-158 | 80.32 | -69.10 (c,1.05) | 0.88 |
| 3a | 128-131 | 79.74 | +138.15(c,1.01) | 0.67 |
| 3b | 136-139 | 63.14 | +102.23(c,1.13) | 0.61 |
| 3c | 141-145 | 66.21 | +110.07(c,1.17) | 0.68 |
| 3d | 164-168 | 59.30 | -90.01 (c,1.02) | 0.62 |
| 3e | 158-161 | 57.10 | +81.19 (c,1.12) | 0.58 |

Satisfactory C H analysis were obtained for all the compounds

**Table-2:Antimicrobial activities of synthesized compounds (IIa-g, IIIa-e)**

| Compounds | (Inhibition zone diameter in mm) | | | | | | |
|---|---|---|---|---|---|---|---|
| | Bacteria | | | | | Fungi | |
| | *E. coli* | *P.vulgaris* | *P.aeruginosa* | *S.aureus* | *B.cereus* | *A.niger* | *C.albicans* |
| 2a | 17 | 20 | 18 | 19 | 18 | 15 | -- |
| 2b | 21 | 18 | 20 | 19 | 19 | 17 | 14 |
| 2c | 20 | 17 | 19 | 18 | 17 | 19 | 12 |
| 2d | 19 | 19 | 15 | 17 | 18 | 14 | 13 |
| 2e | 20 | 20 | 21 | 18 | 18 | 18 | 16 |
| 2f | 17 | 15 | 14 | 15 | 15 | 18 | -- |
| 2g | 22 | 21 | 21 | 20 | 19 | 20 | 16 |
| 3a | 18 | -- | 17 | 19 | 17 | 15 | 12 |
| 3b | 17 | 18 | 19 | 18 | 15 | 19 | 15 |
| 3c | 20 | 16 | 16 | 16 | 11 | 16 | 14 |
| 3d | 16 | 14 | 19 | 16 | 13 | 15 | 13 |
| 3e | 16 | 14 | 15 | 17 | 14 | 18 | 12 |
| Gentamicin | 20 | 19 | 19 | 21 | 19 | - | - |
| Fluconazole | - | - | - | - | - | 21 | 20 |

--- No activity was observed.,
a, Values are the average of three readings.
Including well diameter of 8 mm

**1-tetra-*O*-benzoyl β-D-glucosyl-3-(2) benzothiazolyl carbamide. ($II_a$)**

IR (KBr, $cm^{-1}$): ν 3426 (N-H); 3064 (Ar-C-H); 2962 (Ali-C-H); 1726 (C=O); 1601 (Ar-C=C); 1450 (C=N); 1269.9 (C-N); 1102 (C-O); 858 (D-glucosyl ring deformation); and 771 (C-S). $^1$HNMR ($CDCl_3$, 300MHz, δ ppm) 7.26-7.55 (m, 4H, Ar-H), 7.09-8.23(m, 20H, $4COC_6H_5$), 7.01 and 5.86 (s, 2H, N-H), 4.2-5.86 (m, 7H, glucose unit). Mass m/z: M+: 771, 637, 623, 579, 351, 322, 245, 153, 138, 105. Anal. Calcd for $C_{42}H_{33}N_3O_{10}S$: C, 65.36; H, 4.28; N, 5.44; S, 4.15%; Require; C, 65.34; H, 4.27; N, 5.43; S, 4.14% Found.

**1-tetra-*O*-benzoyl-β-D-glucosyl-3-(2)-*p*-tolyl benzothiazolyl carbamide. ($II_d$)**

IR (KBr, $cm^{-1}$): ν 3463 (N-H); 3064 (Ar-C-H); 2958 (Ali-C-H); 1728 (C=O); 1601 (Ar-C=C); 1451 (C=N); 1270 (C-N); 1100 (C-O); 854 (D-, 300MHz, δ ppm) 7.16-7.23 (m, 4H, Ar-H); 7.48-8.13 (m, 20H, $4COC_6H_5$); 6.86 and 5.85 (s, 2H, N-H); 4.2-5.97 (m, 7H, glucose unit); 1.68 (s, 3H, Ar-$CH_3$). Mass m/z: M+: 785, 771, 637, 623,579,351, 322, 245, 153, 138, 105. Anal. Calcd for $C_{43}H_{35}N_3O_{10}S$: C, 65.73; H, 4.45; N, 5.35; S, 4.07% glucosyl ring deformation); 802 (1-4 sub. Benzene ring) and 771 (C-S). $^1$HNMR ($CDCl_3$Required; C, 65.72; H, 4.44; N, 5.34; S, 4.05% Found.

**1-tetra-*O*-benzoyl-β-D-glucosyl-3-(2)-*p*-Cl-phenyl benzothiazolyl carbamide (IIg)**

IR (KBr, $cm^{-1}$): ν 3429 (N-H); 3067 (Ar-C-H); 2961 (Ali-C-H); 1728.8 (C=O);1602 (Ar-C=C); 1452 (C=N); 1269 (C-N); 1096 (C-O); 854 (D-glucosyl ring deformation); 826 (1-4 di sub. Benzene ring) and 771 (C-S). $^1$HNMR ($CDCl_3$, 300MHz, δ ppm) 7.45-7.30 (m, 4H, Ar-H); 7.4-8.14 (m, 20H, $4COC_6H_5$); 7.04 and 6.30 (s, 2H, N-H); 4.42-5.73 (m, 7H, glucose unit). Mass m/z: M+: 805, 770, 637, 623, 579, 351, 322, 245, 153, 138, 105.Anal.Calcd for $C_{42}H_{32}N_3O_{10}SCl$: C, 62.60; H, 3.97; N, 5.21; S, 3.97% Required; C, 62.59; H, 3.96; N, 5.20; S, 3.95% Found.

***N*-tetra–*O*-benzoyl-β-D-glucosyl-*O*-ethyl carbamate. ($III_b$)**

IR (KBr, $cm^{-1}$): ν 3451 (N-H); 2964 (Ali-C-H); 1728.3 (C=O); 1602 (Ar-C=C); 1272 (C-N), 1165 (C-O) and 858 (D-glucosyl ring deformation). $^1$HNMR ($CDCl_3$, 300 MHz,δ ppm); 8.15-7.29 (m, 20H, $4COC_6H_5$); 7.31 (s, 1H, N-H); 5.96-4.1 (m, 7H, glucose unit); 3.1 (m, 2H, $CH_2$); 1.07 (t, 3H, $CH_3$). Mass: m/z $M^+$ 681, 653, 621, 593, 579, 307, 289, 138, 105. Anal Calcd $C_{37}H_{33}NO_{11}$ C, 66.56; H, 4.94; N, 2.09% Required; C, 66.55; H, 4.94; N, 2.08% Found.

***N*-tetra–*O*-benzoyl-β-D-glucosyl-*O*-butyl carbamate($III_e$)**

IR (KBr, $cm^{-1}$): ν 3469.2 (N-H); 3068.2 (Ar-C-H); 2970.2 (Ali-C-H); 1728.5 (C=O); 1601.8 (Ar-C=C); 1271 (C-N); 1103.7 (C-O) and 856 (D-glucosyl ring deformation). $^1$HNMR ($CDCl_3$, 300 MHz, δ ppm) 7.29 (s, 1H ,N-H); 7.4-8.04 (m, 20H ,$COC_6H_5$); 4.6-6.3 (m, 7H, glucose unit); 4.8-

4.2 (m, 2H, $CH_2$); 1.8 (m, 2H, $CH_2$); 1.3-1.2 (m, 2H, $CH_2$); 0.9 (q, 3H, $CH_3$). Mass: m/z $M^+$ 695,622,594,579,307,289,138 105. Anal Calcd $C_{37}H_{33}NO_{11}$ C, 67.33; H, 5.32; N, 2.01% Required; C, 67.33; H, 5.31; N, 2.00% Found**.**

## CONCLUSION:

Here we describe a new, convenient and cheaper method for the synthesis of some new perbenzoylated *N*-glucosyl benzothiazolyl carbamides and a series of new *N*-glucosyl carbamates. We studies in developing new Antimicrobials Agents. Synthesis compounds exhibits comparable antibacterial and antifungal activities against the organisms tested. Synthesis compounds shows inhibitory activities against the bacteria were higher than that of the fungi. The method adopted in this investigation is simple, efficient, inexpensive, and is useful in synthesizing pharmacologically important molecules.

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