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Synthesis and Antimicrobial Activity of Some Novel *N*-Lactosyl Thiobiurets.

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Abstract: Several 1-hepta-*O*-benzoyl-β-D-lactosyl-5-aryl-4-thiobiurets were synthesized by the interaction of hepta-*O*-benzoyl-β-D-lactosyl isocyanate and 1-aryl thiocarbamides.1-aryl thiocarbamides can be prepared by known procedure. The identities of these new *N*-lactosides have been established on the basis of elemental analysis, IR, ^{1}H NMR and Mass spectral studies. The compounds were also screened for antibacterial and antifungal activities.
Key words: Synthesis, lactosyl isocyanate, 1-aryl thiocarbamides, *N*-lactosyl thiobiurets, antibacterial, antifungal.

Introduction:

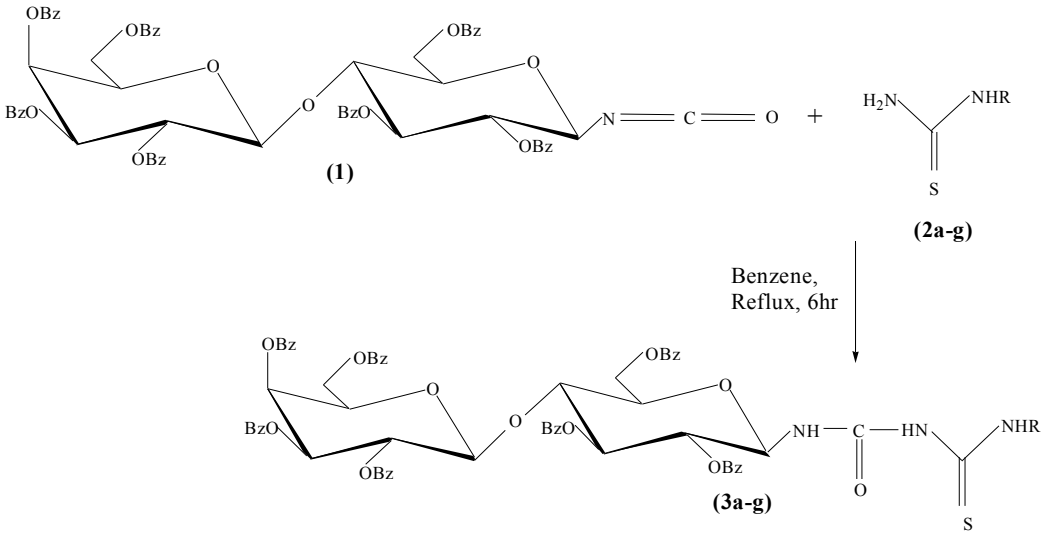
Glycobiology[1] has gain much attention because the oligosaccharide part and other glycoconjugates are responsible for their function in various biological processes viz. cell growth regulation, immunological responses, inflammation and bacterial and viral infections[2-4]. Literature survey reveals that synthesis of amino, diamino derivatives which exhibit biological and pharmaceutical activities such antimalerial effect[5, 6]. Glycosyl thioureas have been widely used as important intermediate in the synthesis of nuclieoside anologs[8-10].Thiobiurets, imidazoles and thiazolines also shows anti inflammatory, antitumor, hypnotic activities[11, 12]

In recent years, steadily increasing research effort has centered on the production of glycosyl biurets because these compounds have been shown to possess many different biological activities. Some carbohydrate base urea exhibit relevant biological properties such as the antibiotic SF-1993, CV-1. N-nitroso urea have shown to be alpha-glycosidase inhibitors, possesses antitumor activity.

In the last years the intensive use of antibiotic has lead to an increase of the emergence of resistant bacteria.[13, 15]. There is a growing need for new class of antibacterial compounds having different mechanism of action compared to existing drugs.

Result and Discussion:

In present communication we report the synthesis of 1-hepta-*O*-benzoyl-β-D-lactosyl-5-aryl-4-thiobiurets by the interaction of hepta-*O*-benzoyl-β-D-lactosyl isocyanate (**1**) and various 1-aryl thiocarbamides **(2a-g)**. The required hepta-*O*-benzoyl-β-D-lactosyl isocyanate (**1**) was prepared by the interaction of hepta-*O*-benzoyl-α-D-lactosyl bromide and lead cyanate in boiling xylene medium.



Where, **Bz-** COC_6H_5
R- a) phenyl, b) *o*-tolyl, c) *m*-tolyl, d) *p*-tolyl, e) *o*-Cl-phenyl, f) *m*-Cl-phenyl, g) *p*-Cl-phenyl.

Experimental

Optical rotations $[\alpha]_D^{31}$ were measured on the Equip-Tronics EQ-800 Digital Polarimeter at 31^0C in $CHCl_3$. IR Spectra were recorded on Perkin-Elmer spectrum RXI FTIR Spectrometer 4000-450cm^{-1}. ^{1}H NMR was obtained on Bruker DRX-300(300 MHz NMR) Spectrometer. Samples were prepared in $CDCl_3$ with TMS as an internal reference. The mass spectra were obtained on Thermo Finnegan LCQ Advantage max ion trap mass spectrometer.

General Procedure

A 0.005 M of 1-aryl thiocarbamides in a 5ml of benzene was added to 0.005 M solution of hepta-*O*-benzoyl-β-D-lactosyl isocyanate (**1**) in 15ml of benzene the reaction mixture was reflux over boiling water bath for 6hr. After refluxing the solvent was distilled off and the sticky residue obtained was triturated with petroleum ether (60-80 ^{0}C) to afford a white solid (**3a-g**). The product was purified by chloroform-petroleum ether.

(1) Yield 80.52%, m. p. 97^0C, $[\alpha]_D^{31}$ = +62 ^{0}(c, 0.91mol, chloroform),
IR (KBr):- ν 2967 (Ali. C-H), 2105 (N=C=O), 1730 (C=O), 1453 (C-N), 1100 (C-O),1025 & 936 cm^{-1}(Characteristic of Lactose); ^{1}H NMR ($CDCl_3$):- δ 8.35-6.68 (m, 35H, Ar-H), δ 5.31-3.71 (m, 14H, lactosyl protons); Mass: - m/z 1095(M^+) 1053, 595, Anal. Calcd

For $C_{62}H_{49}NO_{18}$ C, 67.94; H, 4.47; N, 1.27; Found C, 67.93; H, 4.45; N, 1.23 %.

(3a) IR (KBr):- ν 2967 (Ali. C-H), 1729 (C=O), 3452 (N-H), 1269 (C-O), 1101 & 1026 cm^{-1}
(Characteristic of Lactose); ^{1}H NMR ($CDCl_3$):- δ 8.01-7.14(m, 42H, Ar-H), 6.14-3.75 (m, 14H, lactosyl protons); Mass: - m/z 1247 (M^+), 1204, 1126, 1053, 932,579; Anal. Calcd for $C_{69}H_{58}O_{18}N_3S$; C, 66.34; H, 4.64; N, 3.36; S, 2.80; Found C, 66.33; H, 4.62;N, 3.35; S, 2.78%.

(3d) IR (KBr):- ν 2972 (Ali. C-H), 1728 (C=O), 3443 (N-H), 1270 (C-O), 1101 & 1027cm^{-1}
(Characteristic of Lactose); ^{1}H NMR ($CDCl_3$):- δ 8.01-7.10 (m, 41H, Ar-H), δ 2.37 (s, 3H, CH_3), δ 6-3.82 (m, 14H, lactosyl protons); Mass: - m/z 1261 (M^+), 1218, 1140,1053, 932, 579; Anal. Calcd for $C_{70}H_{60}N_3O_{18}S$; C, 66.56; H, 4.75; N, 3.32; S, 2.77; Found C, 66.53; H, 4.72; N, 3.31; S, 2.73%.

(3g) IR (KBr):- ν 3067 (Ali. C-H), 1728 (C=O), 3345 (N-H), 1175 (C-O), 1096 & 1026 cm^{-1}
(Characteristic of Lactose); ^{1}H NMR ($CDCl_3$):- δ 8.04-7.12 (m, 41H, Ar-H), δ 5.88-3.76 (m, 14H, lactosyl protons); Mass: - m/z 1281(M^+), 1238, 1160, 1053,932,579; Anal. Calcd for $C_{69}H_{57}N_3O_{18}Cl$ C, 65.61; H, 4.51; N, 3.27; S, 2.73%; Found C, 65.59; H, 4.50; N, 3.25; S, 2.70 %.

Biological Screening: Antimicrobial Activity Tests.

All the compounds have been screened for both antibacterial and antifungal activities using cup plate agar diffusion method by measuring the

inhibition zone in mm. The compounds were taken at a concentration of 1mg/mL using dimethyl sulphoxide as solvent. Amikacin (100µg/ml) was used as a standard for antibacterial and antifungal activity and fluconazole (100µg/ml) as a standard for antifungal activity. The compounds were screened for antibacterial activity against *Escherichia coli*, *Staphylococcus aureus*, *Proteus vulgaris*, *Salmonella typhi*, *Klebsiella Pneumoniae*, *Pseudomonas aeruginosa*, *Bacillus subtilis* in nutrient agar medium and for antifungal activity against *Candida albicancs* and *Aspergillus niger* in potato dextrose agar medium. These sterilized agar media were poured into Petri dishes and allowed to solidify on the surface of the media, microbial suspensions were spread with the help of sterilized triangular loop. A stainless steel cylinder of 8mm diameter (pre-sterilized) was used to bore the cavities. 0.1mL portions of the test compounds in solvent were added into these wells. The drug solution was allowed to diffuse for about an hour into the medium. The plates were incubated at 37°c for 24h and 30°c for 48h for antibacterial and antifungal activities respectively. The zone of inhibition observed around the cups after respective incubation was measured. The results are presented in **(Table 1)**.

Table1.Results of antimicrobial activity tests of the synthetic 1-hepta-*O*-benzoyl-β-D-lactosyl-5-aryl-4-thiobiurets (3a-3g).

Compd.	Antibacterial**							Antifungal**	
	E. Coli	***S. aureus***	***P. vulgaris***	***S. typhi***	***K. Pneumoniae***	***P. aeruginosa***	***B. subtilis***	***C. albicance***	***A. niger***
3a	14	10	20	16	12	15	10	06	07
3b	19	11	-	10	15	-	10	08	08
3c	19	15	20	-	16	-	-	09	10
3d	12	-	-	-	-	12	-	06	08
3e	-	20	10	-	-	15	12	07	-
3f	17	12	14	10	20	10	13	06	08
3g	11	15	-	13	13	-	-	09	-
Amikacin	25	22	25	28	22	25	22	-	27
Fluconazole	-	-	-	-	-	-	-	18	-

**zone of inhibition in mm (15 or less) resistance, (16-20mm) moderate and (more than 20mm) sensitive. *Escherichia coli (E. coli), Staphalococcus aureus (S. aureus), Proteus vulgaris (P. vulgaris), Salmonella typhi (S. typhi), Klebsialla Pneumoniae (K. Pneumoniae), Psudomonas auriginosa (P. auriginosa), Bacillus subtlis (B. subtlis), Candida albicancs (C. albicancs) and Aspergillus niger (A. niger).*

Table 2: Characterization data of 1-hepta-*O*-benzoyl-β-D-lactosyl-5-aryl--4-thiobiurets (3a-g).
Reactants: - 1) Hepta-*O*-benzoyl-β-D-lactosyl isocyanate **(1) [0.005M, 2g].**
2) 1-Aryl thiocarbamides **(2a-g) [0.005M].**

Sr. No.	Compd.	Yield (%)	m.p. (°C)	$[\alpha]_D^{31}$ ($CHCl_3$)	Analysis Required (Found)(%)		R_f
					N	S	
1	**3a**	70	141	78°(c,1.00)	3.36(3.35)	2.80(2.78)	0.80
2	**3b**	80	155	110°(c, 1.00)	3.32(3.30)	2.77(2.76)	0.71
3	**3c**	85	126	-86°(c, 0.98)	3.32(3.30)	2.77(2.76)	0.77
4	**3d**	68	139	58°(c, 0.98)	3.32(3.31)	2.77(2.73)	0.89
5	**3e**	72	130	102°(c, 1.00)	3.27(3.24)	2.73(2.72)	0.85
6	**3f**	78	147	72°(c, 1.00)	3.27(3.23)	2.73(2.72)	0.73
7	**3g**	75	129	-62°(c, 1.00)	3.27(3.25)	2.73(2.70)	0.56

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