Int. J. Chem. Sci.: 10(1), 2012, 137-142
ISSN 0972-768X
www.sadgurupublications.com

ANTIBACTERIAL AND ANTIFUNGAL ACTIVITIES OF SOME NOVEL N-LACTOSYL ISOTHIOBIURETS

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ABSTRACT

Several 1-aryl-5-hepta-O-benzoyl-β-D-lactosyl-2-S-benzyl-2-isothiobiurets have been synthesized by the interaction of hepta-O-benzoyl-β-D-lactosyl isocyanate with several 1-aryl-S-benzyl isothiocarbamides. All the synthesized compounds were characterized on the basis of elemental analysis, IR, ^{1}H NMR and Mass spectral analysis. The polarimetric studies of total compounds were carried out. In the present investigation, activities of these N-lactosides against pathogenic bacteria and fungi such as *E. coli*, *S. aureus*, *P. vulgaris*, *S. typhi*, *K. Pneumoniae*, *P. auriginosa*, *B. subtilis*, *C. albicancs* and *A. niger* are discussed.

Key words: Synthesis, 1-Aryl-S-benzyl isothiocarbamides, Isothiobiuretes, Antimicrobial activity.

INTRODUCTION

Carbohydrates play an important role in the number of biological events and play a crucible role in their synthetic strategy as well. Similarly the amino sugars are an important class of glycosidase inhibitors and are arousing great interest as potential therapeutic agents such as antimicrobial, antifluenza activity, antitumor, antileukemic activity, antiviral and therapeutic agents for some genetic disorders[1-9].

The synthesis and pharmacological evaluation of the varieties of glycosyl isodithiobiurets have been reported[10-15]. On the basis of biological importance of isothiobiurets and work done on sugar mono and dithiobiurets, it was of sufficient interest to work out for N-lactosylated isothiobiurets, we have synthesized a series of such N-lactoside compounds. In the present investigation, activities of these N-lactosides against pathogenic bacteria and fungi such as *E. coli*, *S. aureus*, *P. vulgaris*, *S. typhi*, *K. Pneumoniae*, *P. auriginosa*, *B. subtilis*, *C. albicancs* and *A. niger* are reported.

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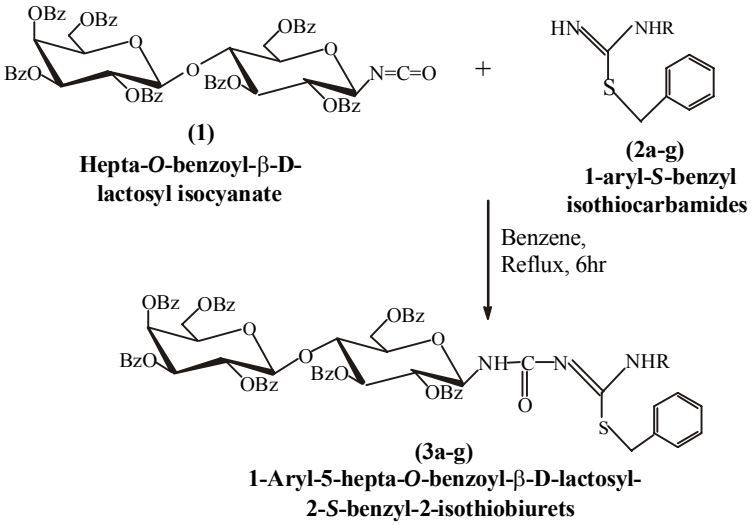
EXPERIMENTAL

Melting points were determined on an electro thermal melting point apparatus and were uncorrected. The structures of the synthesized compounds were elucidated on the basis of elemental analysis, IR, ^{1}H NMR and Mass spectral studies. Optical rotations $[\alpha]_D^{31}$ were measured on the Equip-Tronics EQ-800 Digital Polarimeter at 31°C in $CHCl_3$. IR spectra were recorded on Perkin-Elmer spectrum RXI FTIR (4000-450 cm^{-1}) spectrometer. ^{1}H NMR was obtained on Bruker DRX-300 NMR spectrometer. Samples were prepared in $CDCl_3$ with TMS as an internal reference. The mass spectra were obtained on Jeol-102 mass spectrometer.

Synthesis of 1-aryl-5-hepta-O-benzoyl-β-D-lactosyl-2-S-benzyl-2-isothiobiurets **(1a-g)**.

An equimolar benzene solution of hepta-O-benzoyl-β-D-lactosyl isocyanate (0.001 M in 10 mL) and 1-aryl-S-benzyl thiocarbamides (0.001 M in 5 mL) was allowed to reflux over boiling water bath for 6 hr. Afterwards, benzene solvent was distilled off and resultant syrupy mass was triturated with petroleum ether (60-80°C), a solid was obtained **(3a-g)** (Table 2). It was crystallized from ethanol-water.



Scheme

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.

Spectral analysis

(3a): 1-Phenyl-5-hepta-O-benzoyl-β-D-lactosyl-2-S-benzyl-2-isothiobiuret

IR (KBr): ν 2966 (Ali. C-H), 1729 (C = O), 3431 (N-H), 1269 (C-N), 767 (C-S), 1101 & 1026 cm^{-1} (Characteristic of lactose); **^{1}H NMR ($CDCl_3$):** δ 8.0-7.1 (m, 47H, Ar-H), δ 5.63-3.60 (m, 14H, lactosyl protons), δ 6.11-6.19 (m, 2N-H, Ar), δ 5.75 ppm (s, 1N-H, Ali); **Mass (m/z):** 1338 (M^+), 1053, 932, 579; Anal. Calcd. for $C_{76}H_{64}O_{18}N_3S$, Requires: C, 68.16; H, 4.78; N, 3.13; S, 2.39; Found: C, 66.09; H, 4.72; N, 3.07; S, 2.32%.

(3d): 1-p-Tolyl-5-hepta-O-benzoyl-β-D-lactosyl-2-S-benzyl-2-isothiobiuret

IR (KBr): ν 2965 (Ali. C-H), 1728 (C = O), 3652 (N-H), 1270 (C-N), 760 (C-S), 1098 & 1025 cm^{-1} (Characteristic of lactose); **^{1}H NMR ($CDCl_3$):** δ 8.01-7.14 (m, 44 H, Ar-H), δ 5.60-3.60 (m, 14 H, lactosyl protons), δ 6.11-6.19 (m, 2N-H, Ar), δ 4.43 (s, 1 H, Ali); δ 5.75-3.90 (s, 2H, S-CH_2); δ 2.30 ppm (s, 3H, -CH_3); **Mass (m/z):** 1352 (M^+), 1053, 976, 948, 932, 579, 135; Anal. Calcd. for $C_{77}H_{66}O_{18}N_3S$, Requires: C, 66.34; H, 4.88; N, 3.10; S, 2.36; Found: C, 66.28; H, 4.81; N, 3.04; S, 2.32%.

(3g): 1-o-Cl-Phenyl-5-hepta-O-benzoyl-β-D-lactosyl-2-S-benzyl-2-isothiobiuret

IR (KBr): ν 2965 (Ali. C-H), 1728 (C = O), 3441 (N-H), 1271 (C-N), 770 (C-S), 1099 & 1025 cm^{-1} (Characteristic of lactose); **^{1}H NMR ($CDCl_3$):** δ 8.01-5.53 (m, 49 H, Ar-H), δ 5.75-4.38 ppm (m, 14 H, lactosyl protons); **Mass (m/z):** 1372 (M^+), 1053, 976, 948, 932, 579, 135; Anal. Calcd. for $C_{76}H_{63}O_{18}N_3SCl$, Requires: C, 66.47; H, 4.59; N, 3.06; S, 2.33; Found: C, 66.40; H, 4.55; N, 3.02; S, 2.30%.

Antimicrobial activities

All the compounds have been screened for both; antibacterial and antifungal activity using cup plate agar diffusion method by measuring the inhibition zone in mm. The compounds were taken at a concentration of 1 mg/mL using dimethyl sulphoxide as solvent. Amikacin (100 μg/mL) was used as a standard for antibacterial and antifungal activity and fluconazole (100 μg/mL) as a standard for antifungal activity. The compounds were screened for antibacterial activity against *E. coli*, *S. aureus*, *P. vulgaris*, *S. typhi*, *K. Pneumoniae*, *P. auriginosa* and *B. subtilis* in nutrient agar medium and for antifungal activity against *C. albicancs* and *A. 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 8 mm diameter (pre-sterilized) was used to bore the cavities. 0.1 mL 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 24 h and 30°C for 48 h 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.

Table 1: Results of antimicrobial activity tests of the synthetic 1-aryl-5-hepta-O-benzoyl-β-D-lactosyl-2-S-benzyl-2-isothiobiurets (3a-3g)

Compd.	Antibacterial**						Antifungal**		
	E. Coli	***S. aureus***	***P. vulgaris***	***S. typhi***	***K. Pneumoniae***	***P. aeruginosa***	***B. subtilis***	***C. albicance***	***A. niger***
3a	10	12	20	15	20	12	10	06	-
3b	21	12	15	12	17	-	-	07	-
3c	20	-	22	-	15	-	14	07	10
3d	10	15	-	09	10	-	20	-	07
3e	-	19	-	17	11	12	12	09	06
3f	-	13	15	12	18	10	10	07	08
3g	9	17	20	10	15	16	-	10	-
Amikacin	25	22	25	28	22	25	22	-	27
Fluconazole	-	-	-	-	-	-	-	18	-

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

RESULTS AND DISCUSSION

It has been observed that, some of these compounds exhibited interesting microbial activities. **(3a), (3c), (3f)** and **(3g)** exhibited most significant activity against *E. coli*, *P. vulgaris* and *K. Pneumoniae* while **(3c)** and **(3e)** are effective against *C. albicancs* and *A. niger*. Some compounds shows low to moderate activity (Table 2).

Table 2: Characterization data of N-lactosyl isothiobiurets (3a-g)

Reactants: (1) Hepta-O-benzoyl-β-D-lactosyl isocyanate (1) [0.001M, 1.1 g]

(2) 1-Aryl-S-benzyl isothiocarbamides (2a-g) [0.001M]

S. No.	Compd.	Yield (%)	m.p. (^oC)	$[\alpha]_D^{31}$ ($CHCl_3$)	Analysis Found (Required) (%)		R_f
					N	S	
1	**3a**	68.65	138	40.32° (c,0.992)	3.07 (3.13)	2.32 (2.39)	0.84
2	**3b**	61.48	133	-50.24° (c, 0.916)	3.06 (3.10)	2.32 (2.36)	0.72
3	**3c**	57.03	142	+70.20° (c, 0.920)	3.07 (3.10)	2.33 (2.36)	0.63
4	**3d**	81.48	158	+50.21° (c, 0.986)	3.04 (3.10)	2.32 (2.36)	0.57
5	**3e**	64.96	140	+60.53° (c, 0.962)	3.02 (3.06)	2.30 (2.33)	0.81
6	**3f**	53.28	152	+85.36° (c, 0.980)	3.02 (3.06)	2.31 (2.33)	0.76
7	**3g**	46.71	167	+31.56° (c, 0.940)	3.03 (3.06)	2.27 (2.33)	0.79

ACKNOWLEDGEMENT

Authors are thankful to RSIC, CDRI, Lucknow for providing spectral data and also Dr. S. G. Bhadange, Principal, Shri Shivaji College, Akola for providing necessary facilities.

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Accepted : 25.08.2011