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ANTIBACTERIAL AND ANTIFUNGAL ACTIVITIES OF SOME NOVEL *N*-LACTOSIDES

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ABSTRACT

A series of *N*-lactosides like 1-hepta-*O*-benzoyl-β-D-lactosyl-3-aryl thiocarbamides, thiocarbamates and benzothiazolyl thiocarbamides were synthesized by the interaction of 1-hepta-*O*-benzoyl-β-D-lactosyl isothiocyanate with aryl amines, alcohols and 2-amino benzothiazole / substituted benzothiazoles, respectively. 1-Aryl-5-hepta-*O*-benzoyl-β-D-lactosyl-2-*S*-benzyl-2, 4-isoditiobiurets were synthesized by the interaction of 1-hepta-*O*-benzoyl-β-D-lactosyl isothiocyanate with *S*-benzyl-aryl isothiocarbamides. 3 – Hepta – *O* - benzoyl – β - D - lactosylimino - 5- arylimino - 1, 2, 4 - dithiazolidines (hydrobromide) were synthesized by oxidative debenzylation and cyclization of 1-aryl-5-hepta-*O*-benzoyl-β-D-lactosyl-2-*S*-benzyl-2, 4-isodithiobiurets with molecular bromine in chloroform medium. These newly synthesized compounds were characterized on the basis of usual chemical transformations, IR, NMR and mass spectral analysis. In the present investigation, activities of these *N*-lactosides against pathogenic baceteria and fungi such as *E. Coli, S. aureus, P. vulgaris, S. typhi*, *Candida guilliermondii* and *A. niger* are discussed.

Key words: Synthesis, Thiocarbamides, Thiocarbamates, Benzothiazolyl thiocarbamides, Isodithiobiurets, Dithiazolidines, Antibacterial, Antifungal.

INTRODUCTION

N-lactosides are those compounds in which lactosyl group or its derivatives are attached to the nitrogen of the nitrogen containing compounds. This class of compounds has several applications in industries, medicinal chemistry and in many other ways[1, 2]. Literature survey revealed that the heterocyclic derivatives of sugars posses antibacterial and antitumor activity [3]. Benzthiazole derivatives found to exhibit anticancer, anti HIV and antimalerial activity[4-8]. We have synthesized a series of such N-lactoside compounds. In the present investigation, activities of these N-lactosides against pathogenic baceteria and fungi such as *E. Coli, S. aureus, P. vulgaris, S. typhi*, *Candida guilliermondii* and *A. niger*

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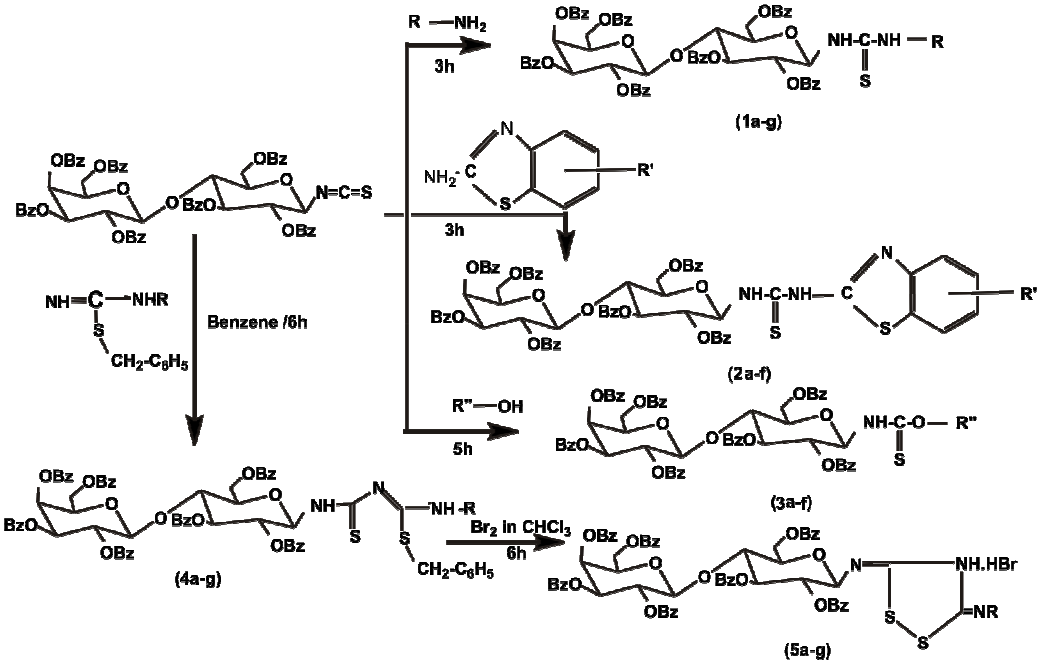
are reported.



EXPERIMENTAL

Melting points were determined on an electrothermal melting point apparatus and were uncorrected. The structures of the synthesized compounds were elucidated on the basis of elemental analysis and IR [9-12], NMR [13-15] and Mass [16] spectral studies (Table 1). IR spectra were recorded in KBr on a FT IR Perkin–Elmer (4000-450 cm^{-1}) spectrophotometer. NMR spectra are run on Brucker DRX 300 instrument operating at 300 MHz using $CDCl_3$ solution with TMS as internal standard and mass spectra on Jeol SX 102 FAB instrument.

Synthesis of 1-hepta-*O*-benzoyl-β-D-lactosyl 3-aryl thiocarbamides (1a-g)

A mixture of hepta-*O*-benzoyl-β-D-lactosyl isothiocyanate and aryl amines in benzene was refluxed at 90^0C for 3 h while monitoring by TLC. After completion of the reaction, the solvent was triturated with petroleum ether ($60\text{-}80^0$) to afford a white solid (**1a-g).** The products were purified from chloroform- petroleum ether.

Synthesis of 1-hepta-*O*-benzoyl-β-D- lactosyl-3-[2- substituted benzothiazolyl] thiocarbamides (2a-f)

A mixture of hepta -*O*-benzoyl-β-D- lactosyl isothiocyanate and 2-aminobenzothiazole/substituted benzothiazoles in 30 mL of benzene was refluxed at 90^0C for 3 h while monitoring by TLC. After completion of the reaction, the solvent was triturated with petroleum ether (60-80º) to afford a white solid **(2a-f).** The products were purified from chloroform- petroleum ether.

Synthesis of 1-hepta-*O*-benzoyl-β-D-lactosyl –*O*-alkyl thiocarbamates (3a-f)

A mixture of hepta -*O*-benzoyl-β-D- lactosyl isothiocyanate in alcohol and the reaction was carried out over boiling water bath for 5 h. Then the reaction mixture was poured into ice cold water when 1-hepta-*O*-benzoyl-β-D-lactosyl –*O*-alkyl thiocarbamates **(3a-f)** separate out.

Synthesis of 1-hepta-*O*- benzoyl -β-D- lactosyl-5-aryl-2-*S*-benzyl-2, 4 - isodithiobiurets (4a-g)

1- Hepta- *O* - benzoyl -β-D- lactosyl isothiocyanate was added to a benzene solution of phenyl *S*-benzyl-isothiocarbamide and the reaction mixture was refluxed over a boiling water bath for 6 h. Then benzene was distilled off and the resulting syrupy mass was triturated several times with petroleum ether (60-80ºC) to afford a white solid **(4a-g).** It was purified by chloroform – petroleum ether.

Synthesis of 3- hepta- *O* - benzoyl -β-D- lactosylimino--5-arylimino-1, 2, 4-dithiazolidines(hydrobromide). (5a-g)

1- Aryl- 5-hepta *O* - benzoyl -β-D- lactosyl- 2-*S*-benzyl-2, 4- isodithiobiuret was made into a paste with chloroform and bromine solution was added to it in chloroform drop by drop with stirring. The bromine solution in chloroform was added till the evolution of lachrymatory fumes of benzyl bromide ceased. An orange red sticky mass was obtained. It was then allowed to stand for 5-6 h. The sticky mass was washed several times with small quantity of ethanol to remove excess of bromine. Some quantity of product went into ethanol and after sometimes, it was separated out **(5a-g).**

Table 1. Characterization data of N-lactosides (1-5)(a-g)

Comp.	Mol. formula	IR (KBr) cm^{-1}	^1H NMR (ppm)	Mass (m/z)
1a	$C_{68}H_{56}O_{17}N_2S$	3458, 3066, 1729, 1271, 1176, 1096, 1068, 909	δ8.0 δ δ8.04 (1H, s, NH), 7.60-6.80 (4H, m Ar-H) 7.40-3.67 (10H, m, lactosyl Protons)	1204, 1145, 1100, 1052, 579, 391, 335, 105
1b	$C_{69}H_{58}O_{17}N_2S$	3446, 3068, 1728, 1271, 1176, 1097, 1026, 909	δ8.04 (1H, s, NH), 7.60-6.91 (4H, m, Ar-H) 7.45-3.78 (10 lactosyl protons)	1218, 1145, 1100, 1052, 579, 391, 335, 105
1e	$C_{68}H_{55}O_{17}N_2SCl$	3444, 2949, 1728, 1272, 1176, 1097, 1026, 907	δ8.01 (1H, s, NH), 7.61-6.99 (5H, m, Ar-H) 7.49-3.91 (lactosyl protons)	1238, 1145, 1100, 1052, 579, 391, 335, 105
2a	$C_{69}H_{55}O_{17}N_3S_2$	3331, 1758, 1527, 1237, 1049, 609	δ 8.34-6.69 (35H, m, Ar-H), 5.71- 4.55 (14H, m, lactosylringprotons)	1252, 1145, 1100, 1052, 579, 391, 335, 105
2b	$C_{69}H_{54}O_{17}N_3S_2Cl$	3331, 1758, 1527, 1237, 1049, 609	δ8.05 (1H, s, NH), 7.61-7.05 (5H, m, Ar-H) 7.49-4.21 (lactosyl protons)	1280, 1145, 1100, 1052, 579, 391, 335, 105
2e	$C_{70}H_{57}O_{17}N_3S_2$	3331, 1758, 1527, 1237, 1049, 609	δ8.05 (1H, s, NH), 7.61-7.05 (5H, m, Ar-H) 7.49-4.21 (lactosyl protons) ;	1259, 1145, 1100, 1052, 579, 391, 335, 105
3a	$C_{64}H_{55}O_{18}NS$	3427, 1730, 1272, 1237, 1028, 709	δ 8.34-6.69 (35H, m, Ar-H), 5.71- 3.82 (14H, m, lactosylringprotons)	1157, 1145, 1100, 1052, 579, 391, 335, 105

Cont…

Comp.	Mol. formula	IR (KBr) cm^{-1}	^1H NMR (ppm)	Mass (m/z)
3d	$C_{65}H_{57}O_{18}NS$	3445, 1729.8, 1175, 1097, 609	δ8.04 (1H, s, NH) , 7.51-7.21 (5H, m, Ar-H) 5.7-3.8 (lactosyl protons)	1172, 1145, 1100, 1052, 579, 391, 335, 105
3f	$C_{64}H_{54}O_{18}NSCl$:	3458, 1729.6, 115272, 1097, 609	δ8.04 (1H, s, NH) , 7.53-7.33 (5H, m, Ar-H) 5.7-3.65 (lactosyl protons)	1186, 1145, 1100, 1052, 579, 391, 335, 105
4a	$C_{76}H_{63}O_{17}N_3S_2$	3427, 1729, 1492, 1096, 854	δ8.05 (1H, s, NH) , 7.12-7.07 (10H, m, Ar-H) 7.14-5.73 (10H, m, lactosyl protons) δ5.94 (1H, s, NH) , , 4.57-4.21 (4H, d, $-OCH_2$)	1354, 1262, 1218, 1052, 579, 391, 335, 105
4c	$C_{76}H_{62}O_{17}N_3S_2Cl$	3448, 1728, 1509, 1070, 852	δ8.04 (1H, s, NH) , 7.09-7.03 (9H, m, Ar-H) 7.14-5.73 (10H, m, lactosyl protons) δ5.44 (1H, s, NH) , , 4.57-4.21 (4H, d, $-OCH_2$)	1388, 1277, 1233, 1052, 579, 391, 335, 105
4f	$C_{77}H_{65}O_{17}N_3S_2$	3467, 1728, 1602, 1097, 834	δ8.02 (1H, s, NH) , 7.34-7.07 (9H, m, Ar-H) 7.14-5.73 (10H, m, lactosyl protons) δ5.65 (1H, s, NH) , , 4.57-4.21 (4H, d, $-OCH_2$) , 5.91-5.73 (35H, m, 7-$COCH_3$)	1368, 1297, 1252, 1052, 579, 391, 335, 105
5a	$C_{69}H_{55}O_{17}N_3S_2$	3414, 1728.7, 1492, 1270, 1068, 756, 854	δ8.02 (1H, s, NH) , 7.34-7.07 (5H, m, Ar-H) 7.14-5.73 (10H, m, lactosyl protons) , 4.57-4.21 (4H, d, $-OCH_2$) , 5.91-5.73 (35H, m, 7-$COCH_3$	1341, 1261, 1158, 1053, 579, 391, 335, 105
5b	$C_{70}H_{57}O_{17}N_3S_2$,	3415, 1726.7, 1451, 1272, 1068, 756, 854	δ8.02 (1H, s, NH) , 7.14-6.97 (4H, m, Ar-H) 7.11-5.74 (10H, m, lactosyl protons) , 4.49-4.21 (4H, d, $-OCH_2$)	1355, 1275, 1175, 1060, 579, 391, 335, 105
5e	$C_{69}H_{54}O_{17}N_3S_2Cl$	3414, 1728.7, 1492, 1270, 1068, 804	δ8.02 (1H, s, NH) , 7.34-7.07 (4H, m, Ar-H) 7.145.73 (4H, d)	1375, 1295, 1193, 1088, 579, 391, 335, 105

Table 2. Antimicrobiol activities of N-lactosides (1–5)(a-g)

Comp.	M. P. (°C)	Antibacterial**				Antifungal**	
		E. c	*S. a*	*P. v*	*S. t*	*C. g*	*A. n*
1a	128-132	17	14	18	16	20	20
1b	130-135	20	20	22	23	21	20
1c	155-160	19	19	20	21	20	22
1d	145	23	19	17	22	20	22
1e	145-150	17	14	18	16	20	22
1f	130	17	14	18	16	22	22
1g	148	17	14	18	16	20	22
2a	155-160	17	19	18	23	24	22
2b	162	17	14	18	16	20	22
2c	170-174	17	19	18	24	20	22
2d	162-168	17	19	18	18	19	20
2e	160-170	19	18	16	15	17	19
2f	165-`70	18	20	21	20	19	17
3a	153-155	17	18	17	19	17	16
3b	146-148	16	18	17	20	19	18
3c	143-145	17	18	18	20	21	19
3d	142-144	16	17	16	17	18	19
3e	158-160	16	20	21	19	18	17
3f	166-170	17	23	23	20	23	20
4a	140	15	23	22	20	21	22
4b	133-135	17	20	18	16	19	20
4c	145-148	16	18	20	21	23	19
4d	150-152	22	21	21	21	21	19

Cont…

Comp.	M. P. (°C)	Antibacterial**				Antifungal**	
		E. c	*S. a*	*P. v*	*S. t*	*C. g*	*A. n*
4e	123-125	17	20	18	16	19	20
4f	135-138	18	16	19	20	21	20
4g	100-102	18	20	21	20	19	17
5a	143-145	23	21	22	21	20	19
5b	108-111	19	18	16	15	17	19
5c	110-112	17	20	18	16	19	20
5d	109-113	22	21	21	21	21	19
5e	165-168	17	21	20	19	24	22
5f	133-135	17	20	18	16	19	20
5g	135-137	18	24	21	20	22	20
DMSO	-	-	-	-	-	-	-
Amikacin		18	21	23	24	-	-
Fluconazole		-	-	-	-	24	25

*including the well diameter of 8 mm. **zone of inhibition in mm (15 or less) resistance, (16-20 mm)moderate and (more than 20 mm) sensitive. E. c (*E. coli*), S. a (*S. aureus*), P. v (*P. vulgaris*), S. t (*S, typhi*), C. s (*Candida guilliermondii*), A. n (*A. niger*)

Antimicrobial activities

All the compounds have been screened for both; antibacterial and antifungal activity using cup plate agar diffusion method[17] 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 *Escherichia coli, Staphylococcus aureus, Proteus vulgaris and Salmonella typhi* in nutrient agar medium and for antifungal activity against *Candida guilliermondii* and *Microsporum* 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 37ºC for 24 h and 30^{o}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 2).

It has been observed that some of these compounds exhibited interesting microbial activities. **1b**, **2a**, **2c**, **3d** and **5g** exhibited most significant activity against *Salmonella*. **1d**, **4d** and **5a** inhibited *E. coli* while **3f**, **4a** inhibited *S. aureus* and *P. vulgaris*, respectively. All other compounds exhibited low to moderate activity (Table 2).

The results of antifungal activity are also tabulated in Table 2. **2a**, **3f**, **4c** and **5e** are effective towards *Candida guilliermondii* while other exhibited moderate to low activity. **1e**, **3d**, **4e**, **5c** and **5f** are effective against *Microsporum* while others exhibited moderate to low activity (Table 2).

Thus, these novel N-lactosides, exhibit comparable antibacterial and antifungal activities against the organisms tested. The method adopted in this investigation is simple, efficeient, inexpensive and is useful in synthesizing pharmacologically important molecules.

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