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Synthesis and Antimicrobial Activity of 4*H*, 4-Thio-2-hepta-*O*-benzoyl-β-D-lactosylimino-3-phenyl-2,3-dihydro-(1,3,5)-triazino-(2,1b) 6, 7 or 8-Aryl benzothiozoles (hydrochlorides)

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A series of novel 4H, 4-thio-2-hepta-*O*-benzoyl-β-D-lactosylimino-3-phenyl-2,3-dihydro-(1,3,5)-triazino-(2,1b) 6,7 or 8 aryl benzothiozoles (hydrochlorides) have been synthesized by the interaction of several 1-hepta-*O*-benzoyl-β-D-lactosyl-3-aryl benzothiozolyl thiocarbamides with *N*-phenyl isocyanodichloride. These compounds were screened for their antibacterial and antifungal activities against-*Escherichia coli, Proteus vulgaris, Staphylococcus aureus, Salmonella typhimurium, Klebsiella pneumonie, Psudomonas aeruginosa*, *Aspergillus niger and Candida albicance*. The newly synthesized compounds have been characterized by analytical and IR, ^{1}H NMR and mass spectral studies.

Key Words: Benzothiazoles, *N*-phenyl isocyanodichloride, 1,3,5-Triazino compounds.

INTRODUCTION

Benzoylated lactosyl nucleosides having aryl benzothiazoles are an important class of heterocyclic compounds in organic chemistry. Benzothiozoles are bicyclic ring system with multiple applications. They have diverse chemical reactivity and broad spectrum of biological activity including antibacterial and antifungal properties[1-3], 2-aminobenzothiozoles shows antitumor[4] and antimalerial activity[5]. *Bis*-substituted amidino benzothiozole act as potential anti HIV agents[6]. The Schiff-base of benzothiozoles also possesses antitubercular, anticancer, antitumor, antipyretic and sterase inhibitory activity[7,8]. Nitrogen containing heterocycles with sulphur are an important class of existing drugs. Azoles, triazoles, substituted thiazoles, thiadiazoles have been known to possess wide spectrum of activity. In our laboratory, 1-hepta-*O*-benzoyl-β-D-lactosyl-3-aryl-benzothiazolyl thiocarbamides have been prepared for the first time by the interaction of 1-hepta-*O*-benzoyl-β-D-lactosyl-isothiocyanate-with 2-amino-aryl benzothiozoles[9-11]. In view of our interest in *N*-lactosylated heterocyclic compounds, now we report the synthesis of 4*H*-4-thio-2-hepta-*O*-benzoyl-β-D-lactosylimino-3-phenyl-2,3-dihydro-1,3,5-triazino-6,7 or 8-aryl benzothiozoles (hydrochlorides).

EXPERIMENTAL

Melting points determined are uncorrected. IR spectra were recorded in KBr on a FT-IR Perkin-Elmer RXI (4000-450 cm^{-1}) spectrophotometer. ^{1}H NMR measurements were performed on a Bruker DRX-300 (300 MHz FT NMR) NMR spectrometer in $CDCl_3$ solution with TMS as internal reference. The Mass spectra were recorded on a THERMO Finnigan LCQ Advantage max ion trap Mass spectrometer. Optical rotation[12] $[\alpha]_D^{31}$ measured on a equip-tronics digital polarimeter EQ-800 at 31 ºC in $CHCl_3$. Thin layer chromatography[13] was performed on silica gel G and spots were visualized by iodine vapour.

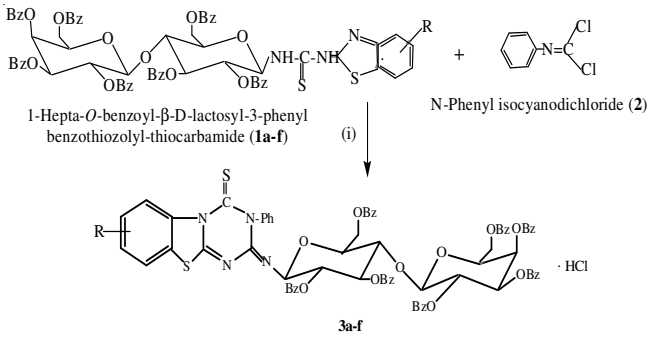
Synthesis of 4*H*,4-thio-2-hepta-*O*-benzoyl-β-D-lactosylimino-3-phenyl-2,3-dihydro-(1,3,5)-triazino-(2,1b)6,7 or 8 phenyl benzothiozoles (3a) (hydrochlorides): A mixture of 1-hepta-*O*-benzoyl-β-D-lactosyl-3-phenyl benzothiozolyl-thiocarbamide (**1a-f**) (1.261 g, 0.001 M, in 15 mL $CHCl_3$) with *N*-phenyl isocynodichloride (**2**) (0.173 g, 0.001 M, in 5 mL $CHCl_3$) was gently refluxed for 3 h. The progress of reaction was monitored by TLC. After completion of the reaction, the reaction mixture was brought to room temperature and the solvent removed under reduced pressure to obtain residue. This residue was triturated with petroleum ether (60-80 ºC) to afford a pale yellow solid (**3a**). The crude product was purified by chloroform-petroleum ether (0.927 g, 83.43 %), m.p. 160 ºC. The physical characterization results are summarized in Table-1 (**3a-f**). The compounds **3b-f** were also prepared by similar methods (**Scheme-I**).

3a) IR (KBr, ν_{max}, cm^{-1}): 1727.5 (C=O), 1631.1 (C=N), 1175 (C=S), 1269 (C-O), 1098 (lactosyl ring deformation), 770 (1,2- disubstituted ring), 710 (monosubstituted ring) cm^{-1};

TABLE-1
PHYSICAL DATA FOR CHARACTERIZATION OF COMPOUNDS (3a-f) REACTANT: *N*-PHENYL ISOCYANODICHLORIDE (2) (0.173 g, 0.001 M)

1-Hepta-*O*-benzoyl-β-D-lactosyl-3-aryl benzothiozolyl-thiocarbamides (1a-f)	g	Product	Yield (%)	m.p. (ºC)	R_f value (Petroleum ether : EtOAc 6:4)	$[\alpha]_D^{31}$ $CHCl_3$ (c, $CHCl_3$)	Analysis (%): found (required)	
							N	S
3-phenyl	1.26	3a	66.18	160	0.80	+142.8 (c, 0.7)	3.93 (3.90)	4.42 (4.45)
3-*o*-Cl-phenyl	1.29	3b	62.58	150	0.64	+128.5 (c,0.7)	3.76 (3.80)	4.32 (4.35)
3-*m*-Cl-phenyl	1.29	3c	69.23	164	0.54	+57.14 (c, 0.7)	3.77 (3.80)	4.36 (4.35)
3-*p*-Cl-phenyl	1.29	3d	61.18	180	0.72	-155 (c, 0.7)	3.78 (3.80)	4.33 (4.35)
3-*o*-tolyl	1.27	3e	77.14	154	0.69	+114.2 (c, 0.7)	3.83 (3.86)	4.43 (4.41)
3-*p*-tolyl	1.27	3f	70	167	0.60	+28.57 (c, 0.7)	3.84 (3.86)	4.38 (4.41)

C and H analysis was found satisfactory in all cases



Scheme-I: i) $CHCl_3$, refluxed, 3h; where, Bz = COC_6H_5 (Benzoyl); R = (a) Phenyl, (b) *o*-Cl-phenyl, (c) *m*-Cl-phenyl, (d) *p*-Cl-phenyl, (e) *o*-tolyl, (f) *p*-tolyl

^{1}H NMR (δ in ppm, $CDCl_3$): δ 8.01-7.16 (44H, m, $7COC_6H_5$, C_6H_5, C_6H_4), 6.29-3.71 (14 H, m, lactose ring protons); Mass (*m/z*): 1435 (M^+), 1330 (M^+-C_7H_5O), 1300 (M^+-$C_8H_7O_2$), 1053 (HBL^+), 976 (HBL^+-C_6H_5), 948 (HBL^+-C_7H_5O), 932 (HBL^+-$C_7H_5O_2$), 918 (HBL^+-$C_8H_7O_2$) 579 (TBG^+), (found : C, 63.52; H, 4.06; N, 3.93; S, 4.42, calculated for $C_{76}H_{58}N_4O_{17}S_2$, 2HCl required C, 63.55; H, 4.04; N, 3.90; S, 4.45; %).

3b) IR (KBr, ν_{max}, cm^{-1}): 2963 (ali C-H), 1727.4 (C=O), 1597.0 (C=N), 1268.4 (C-O), 1101 (lactosyl ring deformation), 771.2 (monosubstituted ring) 710.3 (C-S), 558.6 (C-Cl); ^{1}H NMR (δ in ppm, $CDCl_3$): δ 8.13-7.16 (43H, m, $7COC_6H_5$, C_6H_5, C_6H_3), 6.75-3.71 (14 H, m, lactose ring protons) mass (*m/z*): 1470 (M^+), 1435 (M^+-Cl), 1365 (M^+-C_7H_5O), 1349 (M^+-$C_7H_5O_2$), 1337 (M^+-$C_8H_7O_2$), 1053 (HBL^+), 976 (HBL^+-C_6H_5), 948 (HBL^+-C_7H_5O), 932 (HBL^+-$C_7H_5O_2$), 579 (TBG^+), (found :C, 62.03; H, 3.85; N, 3.76; S, 4.32, calculated for $C_{76}H_{57}N_4O_{17}S_2$, 2HCl required C, 62.02; H, 3.87; N, 3.80; S, 4.35; %).

3e) IR (KBr, ν_{max}, cm^{-1}): 1727.4 (C=O), 1602.1 (C=N), 1267.1 (C-O), 1099.8 (C=S) 1028.3 (lactosyl ring deformation), 863.3 (1,3 disubstituted ring), 770.6 (monosubstituted ring) 604.5 (C-S), ^{1}H NMR (δ in ppm, $CDCl_3$): δ 8.07-7.04 (43H, m, $7COC_6H_5$, C_6H_5, C_6H_3), 6.58-3.71 (14 H, m, lactose ring protons), 2.53 (3H, s, Ar-CH_3); Mass (*m/z*): 1449 (M^+), 1345 (M^+-C_7H_5O), 1329 ((M^+-$C_7H_5O_2$), 1314 (M^+-$C_8H_7O_2$), 1053 (HBL^+), 976(HBL^+-C_6H_5), 948 (HBL^+-C_7H_5O), 932 (HBL^+-$C_7H_5O_2$) 579 (TBG^+), (Found : C, 63.73; H, 4.12; N, 3.83; S, 4.43, calculated for $C_{76}H_{57}O_{17}N_4S_2$, 2HCl required C, 63.76; H, 4.14; N, 3.86; S, 4.41; %).

HBL^+ = Hepta-*O*-benzoyl-β-D-lactosyl
TBG^+ = Tetra-*O*-benzoyl-β-D-galactosyl

RESULTS AND DISCUSSION

Several 4*H*, 4-thio-2-hepta-*O*-benzoyl-β-D-lactosylimino-3-phenyl-2,3-dihydro-(1,3,5)-triazino-(2,1b)6,7 or 8-aryl benzothiozoles (hydrochlorides) (**3a-f**) have been prepared by the interaction of several 1-hepta-*O*-benzoyl-β-D-lactosyl-3 aryl benzothiozolyl uthiocarbamides (**1a-f**) with *N*-phenyl isocyanodichloride (**2**) in $CHCl_3$. After condensation, the solvent was distilled off to obtain a sticky residue. This residue was triturated several times with petroleum ether (60-80 ºC) to afford a pale yellow solid (**3a-f**). The product was found to be non-desulphurrizable when boiled with alkaline lead acetate solution. The specific rotations were measured in chloroform. The result is summarized in Table-1. In spectral analysis of products shows bands due to Ar-H, ali. C-H, C=O, C=N, C-N, C-O, C-S, C=S stretching and ^{1}H NMR spectra of products distinctly displayed signals due to aromatic protons and lactose ring protons. The mass spectrum of products was also observed. The identities of these new *N*-lactosides have been established on the basis of usual chemical transformations and also IR, ^{1}H NMR and mass spectral studies[14-16].

Antimicrobial activity: All the compounds have been screened for both antimicrobial and antifungal activity by using disc diffusion assay. For this sterile filter paper disc (6 mm) impregnated with fixed doses of compounds was placed on pre-inoculated surface. The disc bearing plates were incubated at 37 ºC for 24 h. Inhibition zones read after incubation at 37 ºC for 24 h. for bacterial strains and for fungal strains inhibition zones read after incubation at 35 ºC for 48 h. The compounds were taken at a concentration or 1 mg/mL using dimethyl sulphoxide as a solvent. Amikacin (100 µg/mL) was used as standard for antibacterial and Fluconazole (100 µg/mL) as a standard for antifungal activity. The compound were screened for antibacterial activity against *Escherichia coli, Proteus vulgaris, Staphylococcus aureus, Salmonella typhi, Klebsiella pneumoniae, Psudomonas aeruginosa* in Mullar-Hilton medium. *Aspergillus niger* and *Candida albicans* in potato dextrose agar medium. It has been observed that all the compounds showed nearly same activity against bacteria and fungi. **3a, 3b, 3d** and **3f** exhibites most significant activity against *Salmonella typhi*. All other compounds exhibited low to moderate actlvity (Table-2).

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TABLE-2
ANTIMICROBIAL ACTIVITY OF 4H, 4-THIO-2-HEPTA-*O*-BENZOYL-β-D-LACTOSYLIMINO-3-PHENYL-2, 3-DIHYDRO-(1, 3, 5)-TRIAZINO-(2, 1B) 6, 7 OR 8 ARYL BENZOTHIOZOLES (HYDROCHLORIDES)

Compound	*E. coli*	*S. aureus*	*P. vulgaris*	*P. aeruginosa*	*S. typhi*	*K. pneumonie*	*A. niger*	*C. albicans*
3a	14	10	14	-	17	11	19	20
3b	10	16	-	12	18	13	20	21
3c	13	14	12	13	15	14	17	19
3d	14	15	13	11	16	12	20	19
3e	16	13	10	10	15	10	21	22
3f	13	14	-	17	19	13	20	20
Amikacin	18	21	23	19	20	21	-	-
Fluconazole	-	-	-	-	-	-	24	24
DMSO	-	-	-	-	-	-	-	-

Zone of inhibition in mm (15 or less) resistance, (16-20 mm) moderate and more than (20 mm) sensitive

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