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Antimicrobial activities of some newly synthesized N-lactosylated dithiazolidines and thiadiazines

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Abstract

A newly synthesized 4-Aryl-5-hepta-*O*-benzoyl-β-D-lactosylimino -3-thio-1,2,4-dithiazolidines (hydrochloride)(1a-f) have been prepared by the interaction of 1– hepta - *O* –benzoyl - β –D–lactosyl-S–chloro–isothiocarbamoyl chloride and ammonium aryl dithiocarbamates. Similarly, the compounds 2-hepta-*O*-benzoyl-β-D-lactosylimino-3-aryl-4-S-benzyl-6-phenylimino-2, 3 dihydro-1, 3, 5-thiadiazines (hydrochlorides) (2a-f) have been prepared by the interaction of 1-aryl-5-phenyl-2-S-benzyl-2, 4 isodithiobiurets and hepta-*O*-benzoyl-β-D-lactosyl-isocyanodichloride. 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) (3a-f) have been synthesized by the interaction of several 1-hepta-*O*-benzoyl-β-D-lactosyl-3-aryl benzothiozolyl-thiocarbamides with *N*-phenyl isocyanodi-chloride. In the present investigation activities of these *N*-lactosides against bacteria and fungi such as *Escherichia coli, Proteus vulgaris, Staphylococcus aureus, Salmonella typhi, Klebsiella pneumoniae, Pseudomonas aeruginosa, Aspergillus niger* and *Candida albicans* are discussed.

Keywords: Synthesis, 1, 2, 4-dithiazolidines, 1, 3, 5-thiadiazin-es, triazino, benzothiozolyl-thiocarbamides, isocyanodichlori-de, 2, 4 isodithiobiurets, ammonium aryl dithiocarbamates.

1. Introduction

A series of new *N*-lactosides have been found to be use as diuretic, analgesics, antidiabetic, bacteriostatic, antifungal, antimicrobial and antithyroid drugs. *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 reveled that the heterocyclic derivatives of sugar posses antibacterial and antitumor activity [3]. Benzothiazole derivatives found to exhibit anticancer, anti HIV, and antimalarial activity [4-8]. In the present investigation, activities *of* these N-lactosides against pathogenic bacteria and fungi such as *Escherichia coli, Proteus vulgaris, Staphylococcus aureus, Salmonella typhi, Klebsiella pneumoniae, Pseudomonas aeruginosa , Aspergillus niger* and *Candida albicans* are reported.

2. Methodology

Experimental

Melting points determined are uncorrected. IR spectra were recorded in KBr on a FT-IR Perkin-Elmer RXI(4000-450cm^{-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[16] were recorded on a THERMO Finnigan LCQ Advantage max ion trap Mass spectrometer. The identities of these new *N*-lactosides have been established on the basis of usual chemical transformations and also IR, ^{1}HNMR and Mass spectral studies[9-11]. Optical rotation $[\alpha]_D^{31}$ measured on a Equip-Tronics Digital Polarimeter EQ-800 at 31^{0}C in $CHCl_3$. Thin layer chromatography (TLC) was performed on silica jel G and spots were visualized by iodine vapour.

2.1 Synthesis of 4-Aryl-5-hepta-*O*-benzoyl-β-D-lactosylimino-3-thio-1,2,4-dithiazolidines (hydrochloride) (Scheme 1: 1a-f)

The mixture of *N* – hepta -*O*-benzoyl -β – D –lactosyl -S –chloro – isothiocarbamoyl chloride and Ammonium -aryl- dithiocarbamate was reflux in chloroform over a boiling water bath for 3 hr monitoring reaction by TLC. The reaction proceed with evolution of HCl. The escess of $CHCl_3$ was distilled off and the resultant syrupy mass was triturated several times with petroleum ether (60-80^{0}c) to afforded pale yellow solid (1a-f) The solid was recrystallised by chloroform – petroleum ether.

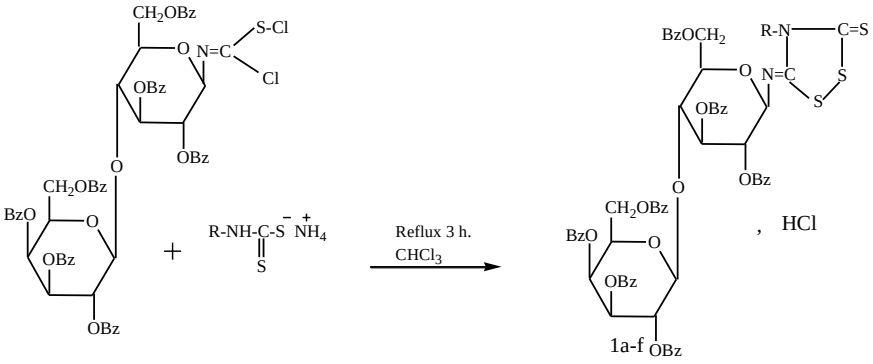
2.2 Synthesis of 2-hepta-*O*-benzoyl-β-D-lactosylimino-3-aryl-4-S-benzyl-6-phenylimino-2, 3 dihydro-1, 3, 5-thiadiazines (hydrochlorides) (Scheme 2: 2a-f)

A mixture of 1-aryl-5-phenyl-2-S-benzyl-2, 4 isodithio-biurets and hepta-O-benzoyl-β-D-lactosyl-iso-cynodi-chloride was reflux in chloroform over a boiling water bath for 4 hr.The progress of the reaction was monitored by TLC.After condensation, the solvent was distilled off to obtain sticky residue. This residue was triturated several times with petroleum ether (60-80^0) to afford a pale yellow solid (2a-f). The solid was recrystallised by chloroform – petroleum ether.

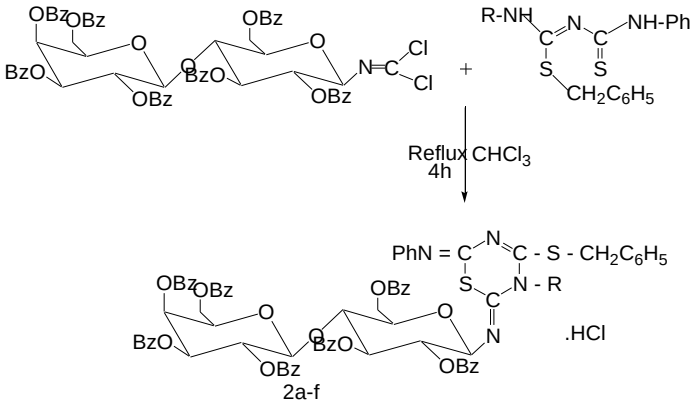
2.3 Synthesis of 4H, 4-thio-2-hepta-*O*-benzoyl-β-D-lactosylimino-3-phenyl-2, 3-dihydro-(1, 3, 5)-triazino-(2, 1b) 6, 7 or 8 aryl benzothiozoles (hydrochlorides) (Scheme 3: 3a-f)

Several 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) (3a-f) have been prepa-red by the interaction of several 1-hepta-*O*-benzoyl-β-D-lactosyl-3aryl benzothiozolyl-thiocarbamides with *N*-phenyl isocyanodichloride in $CHCl_3$. After condensa-tion, the solvent was distilled off to obtain a sticky resi-due. This residue was triturated with petroleum ether (60-80^{0}C) to afford a pale yellow solid (3a-f). The solid was recrystallised by chloroform – petroleum ether.

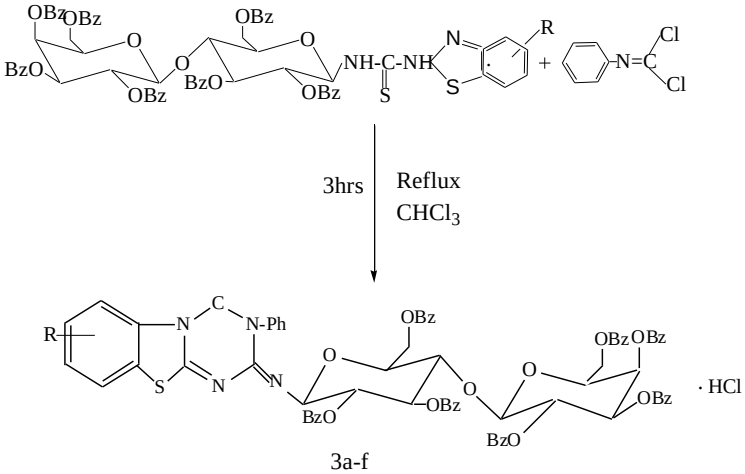
General Procedure



Scheme 1



Scheme 2



Scheme 3

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

3. Results & Discussions

Table 1: Characterisation data of *N* lactosides (Scheme 1-3)(a-f)

Comp	Mol. Formula	IR (KBr) cm^{-1}	^{1}HNMR (ppm)	Mass (m/z)
1a	$C_{69}H_{53}O_{17}N_2S_3C$	3067.2 , 2966.7 , 1730.2 , 1655 , 1270 ,1176.1 , 1026.3 , 1098.3,905.5 , 769.2 ,709.2 , 506	δ8.2- 7.18(40H,m,Ar),δ6.33-3.59(14H,m,lactose)	1314 (M^+) , 1203 , 1053 , 931 , 948 , 579 , 105.
1b	$C_{69}H_{53}O_{17}N_2S_3Cl$	3067.8, 2965.4, 1729.2, 1654.3, 1270.4, 1176.2, 1069.7 ,906.7	δ8.18-7.09(39H,m,Ar),δ6.53-3.51(14H,m,lactose)	1349(M^+),1237,1053,931,579,
1e	$C_{70}H_{56}O_{17}N_2S_3$	3065.8, 2962.9, 1727.9 , 1601.5 , 1269.2 , 1157.8, 1026.5 , 758.4 , 709.9	δ8.19-7.0(39H,m,Ar),δ6.58-3.56(14H,m,lactose) δ2.5(3H,s,Ar-CH_3)	1328 (M^+) ,1217 , 1053 , 930 ,580
2a	$C_{84}H_{68}O_{17}N_4S_2$	3065.3, 2955, 1728.5,1603.6, 1267.8, 1175.8, 1097, 709, 482.7	δ8.19-7.12(50H,m,Ar),δ6.01-3.52(lactose,S-CH_2)	1527(M^+),1053, 976, 948, 932, 918, 579,232
2c	$C_{83}H_{65}O_{17}N_4S_2Cl$	3065.8, 2955.8,1728.4,1481.4,1599.6,1268.9,1175, 1097, 756.1,709,507.8	δ8.3-6.9(49H,m,Ar), δ6.01-3.51 (16H,m,lactose,S-CH_2)	1560(M^+),1488,1053, 976, 948, 932, 579, 232
2f	$C_{84}H_{68}O_{17}N_4S_2$	3065.2, 2957.9, 1728.711602.2, 1562.1,1269.1,1098,756	δ8.25-6.92 (49H, m, Ar),δ5.53-3.52 (16,m,lactose,S-CH_2),δ2.4(3H,s,Ar-CH_3)	1540(M^+),1468,1053,976,948, 579, 232
3a	$C_{76}H_{58}O_{17}N_4S_2$	1727.5, 1631.1, 1175.5, 1269, 1098, 769.9, 710	δ8.10-7.16 (44H, m, Ar), δ6.78-3.61(14H,m,lactose)	1435 (M^+),1330, 1300, 1053, 976, 948, 932, 918, 579
3b	$C_{76}H_{57}O_{17}N_4S_2Cl$	2963, 1747.4, 1597, 1268.4, 1101, 771, 710, 558	δ8.31-7.16 (43H,m,Ar),δ6.75-3.71(14H,m,lactose)	1470(M^+),1435, 1365, 1349, 1337, 1053, 976, 948, 932, 579
3e	$C_{77}H_{60}O_{17}N_4S_2$	1727.4, 1602.1, 1267.1, 1099.8, 1028.3, 863.3, 770.6, 604.5	δ8.07-7.13 (43H,m, Ar)δ6.75-3.71 (14H,m, lactose), δ2.53 (3H,s, Ar-CH_3)	1449 (M^+), 1345, 1329, 1314, 1053, 976, 948, 932, 579

Zone size was interpreted by

Sample	Disc content	Resistant	Intermediate	Sensitive
Amikacin	100ug/ml	≤ 15 mm	16-20 mm	≥ 21 mm
Fluconazole	100ug/ml	≤ 15 mm	16-20 mm	≥ 21 mm

Table 2: Zone size of *N* lactosides (Scheme 1-3)(a-f)

Compounds	*E. Coli*	*S. aureus*	*P. vulgaris*	*P. aeruginosa*	*S. typhi*	*K. pneumonie*	*A. niger*	*C. albicance*
1a	17	16	20	19	18	21	19	20
1b	10	15	15	12	20	19	20	21
1c	18	14	19	17	15	18	17	19
1d	14	19	18	18	19	20	20	19
1e	16	13	12	10	15	17	24	22
1f	13	14	20	16	17	20	22	20
2a	10	-	13	-	14	-	19	-
2b	16	10	12	-	13	10	17	15
2c	15	12	10	10	19	13	15	17
2d	13	19	-	14	12	12	19	19
2e	-	15	16	13	17	14	18	20
2f	17	16	19	17	12	11	17	-
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
DMSO	-	-	-	-	-	-	-	-
Amikacin	18	21	23	19	20	21	-	-
Fluconazole	-	-	-	-	-	-	24	24

3.2 Antimicrobial Activity

All the compounds have been screened for both antimicrobial and antifungal activity by using disc diffusion assay[14]. For this sterile filter paper disc (6mm) impregnated with fixed doses of compounds was placed on pre-inoculated Mullar-Hilton plate. The disc bearing plates were incubated at 37^0C for 24 hrs. Inhibition zones read after incubation at 37^0C for 24 hrs. for bacterial strains and for fungal strains inhibition zones read after incubation at 35^0C for 48 hrs. The compounds were taken at a concentration or 1mg/ml using dimethyl sulphoxide as a solvent .Amikacin (100 ug/ml) was used as standard for antibacterial and Fluconazole (100ug/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 both bacteria and fungi.**1a,1b,1d,2c, 3a,3b, 3d** and **3f** exhibites most significant activity against *Salmonella typhi*.All other compounds exhibited low to moderate activity. The results of antibacterial and antifungal activity are tabulated in table 2.

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Conflicts of interest: The authors stated that no conflicts of interest.

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