Biological Evaluation of Some Newly Synthesized Thiadiazines

KAVITA M. HEDA[1], RUPALI S. MANTRI[2] AND SHIRISH P. DESHMUKH[3]

[1] Department of Chemistry, Shri R. L. T. College of Science, Akola-444001, (M. S.), India
[2] Department of Microbiology, Government medical college, Akola-444001, (M. S.), India
[3] P. G. Department of Chemistry, Shri Shivaji College, Akola-444001, (M.S.), India
Corresponding author: kavitaheda25@gmail.com

Abstract

A series of novel 2-tert butylimino-3-hepta-O-benzoyl-β-D-lactosyl-4-S-benzyl-6-arylimino-2, 3-dihydro-1, 3, 5-thiadiazines (hydrochlorides) were synthesized by the interaction of N- tert butyl isocyanodichloride with 1-aryl-5-hepta-O-benzoyl-β-D-lactosyl-2-S-benzyl-2, 4-isodithiobiurets. The identities of these newly synthesized N-lactosides have been established on the basis of usual chemical transformations and IR, ^{1}H NMR and Mass spectral analysis. The compounds synthesized were investigated for their antimicrobial activities against Escherichia coli, Proteus vulgaris, Staphylococcus aureus, Salmonella typhimurium, Klebsiella pneumonie, Psudomonas aeruginosa, and fungal strains such as Aspergillus niger and Candida albicans. Some of these compounds exhibit strongest to moderate activity against the tested strains of bacteria and fungi.

Key words: 2, 4 isodithiobiurets, *N*- tert butyl isocyanodichloride, 1, 3, 5 thiadiazines, Antimicrobial activity.

Introduction

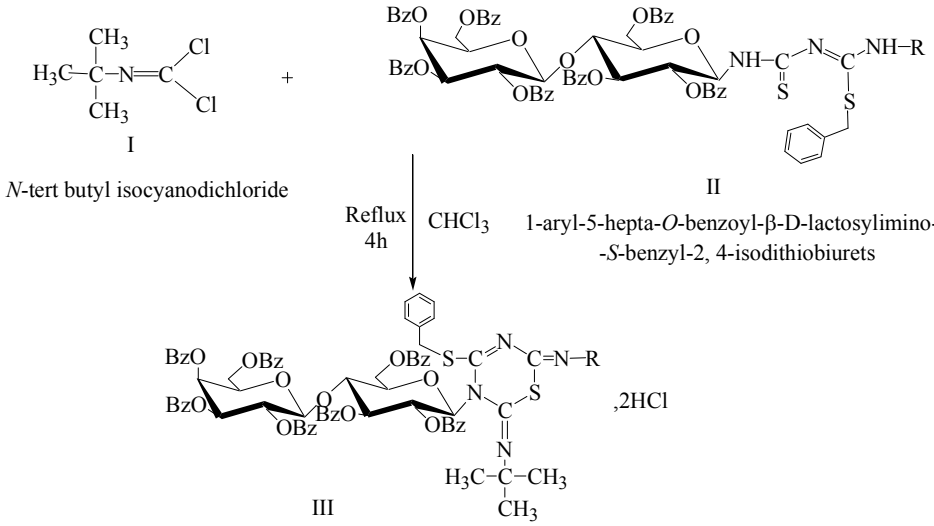
N-lactosides are those compounds in which lactosyl group or its derivatives are attached to the nitrogen of the nitrogen containing compounds. This class of compounds has several applications in industries, medicinal chemistry and in many other ways. The chemistry of heterocyclic compounds continues to explore the field of carbohydrate chemistry. Literature survey also revealed that the heterocyclic derivatives of sugar possess antimicrobial[1-3], and antitumor activity[4-6]. Thiadiazines and their derivativs acts as antifibrinolytic[7], cardiotonic[8], anesthetic, cardiovascular and hypometabolic agents[9].

Experimental

All chemicals were research grade. Melting points were taken in open capillary tubes and are uncorrected. IR spectra were recorded in Nujol, KBr on a FT-IR Perkin-Elmer RXI (4000-450cm-1) spectrophotometer. 1H NMR measurement were performed on a Bruker DRX-300 (300 MHz FT NMR) NMR spectrometer in CDCl3 solution with TMS as an internal reference. The Mass spectra were recorded on a THERMO Finnigan LCQ Advantage max ion trap Mass spectrometer. Optical rotation $[\alpha]_D^{31}$ measured on a Equip-Tonics Digital Polarimeter EQ-800 at 31° c in $CHCl_3$. Thin layer chromatography (TLC) was performed on silica gel G for TLC (Merck) and spots were visualized by iodine vapor.

Synthesis of 2-tert butylimino-3-hepta-*O*-benzoyl-β-D-lactosyl-4-*S*-benzyl-6-phenylimino-2, 3-dihydro-1, 3, 5-thiadiazines (hydrochlorides)[10].

In a typical preparation of 2-tert butylimino-3-hepta-*O*-benzoyl-β-D-lactosyl-4-*S*-benzyl-6-phenylimino-2, 3-dihydro-1, 3, 5-thiadiazines (hydrochlorides) (IIIa) (where aryl = phenyl) the reaction of *N*-tert butyl isocyanodichloride (I) and 1-phenyl-5-hepta-*O*-benzoyl-β-D-lactosyl-2-*S*-benzyl-2, 4-isodithiobiuret (IIa) has been carried out in boiling chloroform medium for 4 hr. Afterwards, solvent was distilled off and syrupy mass was left. The mass on repeated trituration with petroleum ether (60-80°C) gave a solid (IIIa). The product (IIIa) was purified from chloroform-Petroleum ether, purity was checkeded by TLC. m.p. 145°C. The elemental analysis of this new product indicated molecular formula as $C_{81}H_{70}O_{17}N_4S_2.2HCl$.



Where, OBz=$OCOC_6H_5$

R = a) Phenyl b) *o*-Cl-phenyl c) *m*-Cl-phenyl d) *p*-Cl-phenyl e) *o*-tolyl f) *p*-tolyl g) *o*-hydroxy-phenyl h) *m*-hydroxy-phenyl i) *p*-hydroxy-phenyl j) *o*-methoxy phenyl k) *m*-methoxy-phenyl l) *p*-methoxy-phenyl

Antimicrobial Activity

All the compounds have been screened for both antimicrobial and antifungal activity by using disc diffusion assay[11-12]. For this sterile filter paper disc (6mm) impregnated with fixed doses of compounds were placed on pre-inoculated Mullar-Hilton plate. The disc bearing plates were incubated at 37°C for 24 hrs. Inhibition zones read after incubation at 37°C for 24 hrs. for bacterial strains and for fungal strains inhibition zones read after incubation at 35°C for 48 hrs.

Table 1:- Characterization of 2-tert butylimino-3-hepta-*O*-benzoyl-β-D-lactosyl-4-*S*-benzyl-6-arylimino-2, 3-dihydro-1, 3, 5-thiadiazines (hydrochlorides) (IIIa-l)

Sr. No	M.P. (^oC)	R_f(Pet ether: EtOAc)	$[\alpha]^{29}_D$ (c, in $CHCl_3$)	IR(KBr)cm^{-1}	^{1}HNMR (ppm)	Mass(mz)
IIIa	145	0.65	-50.36^{o}C (c, 0.11 in $CHCl_3$)	3062.9, 2976.1, 1730.1, 1600.9, 1379.1, 1176.5, 1026.4, 908.4	δ8.04-7.21 (45H,m,Ar), δ6.23-3.72(16H,m), δ2.12-1.25(9H,m),	1507(M^+), 1470, 1434, 1467, 1053, 976, 948, 931, 579, 353, 135, 105
IIIb	142-144	0.71	+79.86^{o}C (c, 0.17 in $CHCl_3$)	3062.9, 2978.3, 1730.1, 1600.9, 1176.5, 1379.1, 1070.4, 910.4	δ8.32-7.22 (44H,m,Ar), δ6.23-3.90(16H,m), δ2.17-1.03(9H,m),	1547(M^+), 1468, 1501, 1365, 1053, 976, 948, 931, 579, 353, 135, 105
IIIe	150	0.57	+118.06^{o}C (c, 0.17 in $CHCl_3$)	3062.9, 2978.0, 1730.1, 1600.9, 1379.1, 1176.5, 1070.4, 908.4	δ8.21-7.02(44H,m,Ar), δ6.19-3.68(16H,m), δ2.23-1.25(9H,m),	1521(M^+), 1484, 1365, 1053, 976, 948, 931, 579, 353, 135, 105
IIIg	134	0.50	+78.30^{o}C (c, 0.15 in $CHCl_3$)	3032.1, 2956.8, 1730.1, 1600.9, 1371.3, 1273.0, 1026.1, 910.4	δ8.31-7.18 (45H,m,Ar), δ6.19-3.17(16H,m), δ2.00-1.25(9H,m),	1523(M^+), 1450, 1418, 1248, 1053, 976, 948, 931, 579, 353, 135, 105
IIIj	133-135	0.59	+113.5^{o}C (c, 0.14 in $CHCl_3$)	3030.1, 2964.5, 1730.1, 1600.9, 1315.4, 1026.1, 910.4	δ8.13-7.16 (45H,m,Ar), δ6.22-3.69(16H,m), δ2.16-1.25(12H,m),	1537(M^+), 1464, 1432, 1382, 1278, 1053, 976, 948, 931, 579, 353, 105

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. The zone of inhibition observed and interpreted by using antibiotic zone reader. The results were cited in Table 2

From Table 2:

The compounds III**a** displayed strong activity against *E. coli* and *A. niger.* It displayed moderate to weak activity against *S. typhi, S. aureus, P. vulgaris*, *A. niger* and *C. albican* .It showed no activity against *P. aeruginosa.* The compound **IIIb** showed strong activity against both fungi, no activity against *E. coli* and *P. vulgaris*. It showed moderate to weak activity against *S. aureus, P. aeruginosa, S. typhi, K. pneumonie*, *A. niger* and *C. albicans*. The III**c** showed promising activity against *S. typhi*, moderate to weak activity against all the bacteria and fungi.The compound III**d** showed no activity against *E. coli, P. vulgaris, K. pneumonie* and *C. albicans*. While it showed moderate to weak activity against *S. aureus, P. vulgaris. S. typhi,* and *A. niger.*The compounds III**e** and III**f** showed moderate to weak activity against *S. aureus, P.*

aeruginosa, S. typhi, K. pneumonie, *A. niger* and *C. albicans*.While no activity against *E. coli* and *P. vulgaris*. The compound III**k** showed promising activity against *E. coli* and *P. vulgaris*. The compound III**l** showed good activity against *C. albicans* and *S. typhi* while IIIi showed good activity against *C. albicans.*

Amikacin (100µg/mL) was used as a standard for antibacterial activity and Fluconazole (100µg/mL) was used as a standard for antifungal activity.

Table 2: Antimicribial avtivities of 2-tert butylimino-3-hepta-*O*-benzoyl-β-D-lactosyl-4-*S*-benzyl-6-arylimino-2, 3-dihydro-1, 3, 5-thiadiazines (hydrochlorides) (IIIa-l)

Comp.	*E. Coli*	*S. Aureus*	*P. vulgaris*	*P. aeruginosa*	*S. typhi*	*K. pneumonie*	*A. niger*	*C. albicance*
IIIa	++++	++	++	--	++	++	++++	++
IIIb	--	+++	--	++	+++	++	++++	++++
IIIc	++	++	++	++	++++	++	+++	++
IIId	--	++	+++	--	++	--	++	--
IIIe	--	++	--	++	+++	++	++	+++
IIIf	--	++	--	++	+++	+++	+++	+++
IIIg	+++	--	++	++	--	++	++	+++
IIIh	++	--	+++	+++	--	+++	+++	++
IIIi	--	+++	--	++	++	++	++	++++
IIIj	+++	--	--	+++	+++	--	+++	+++
IIIk	++++	--	++++	+++	++	--	+++	+++
IIIl	++	+++	+++	+++	++++	--	--	++++

++++	Strong activity (above 18mm)
+++	Moderate activity (above 14 to 18mm)
++	Weak activity (above 8-14mm)
--	Inactive (below 8mm)

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