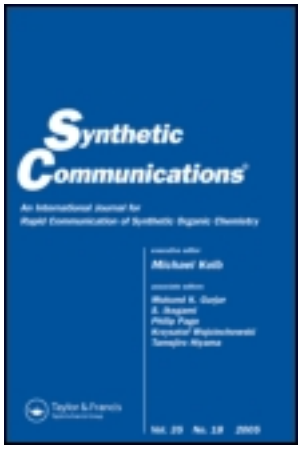

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Synthesis and in Vitro Antimicrobial Activity of 3-Aryl-4-S-benzyl-6-phenylimino-2-hepta-O-acetyl-β-D-lactosylimino-2,3-dihydro-1,3,5-thiadiazine (Hydrochloride)

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SYNTHESIS AND IN VITRO ANTIMICROBIAL ACTIVITY OF 3-ARYL-4-*S*-BENZYL-6-PHENYLIMINO-2-HEPTA-*O*-ACETYL-β-D-LACTOSYLIMINO-2,3-DIHYDRO-1,3,5-THIADIAZINE (HYDROCHLORIDE)

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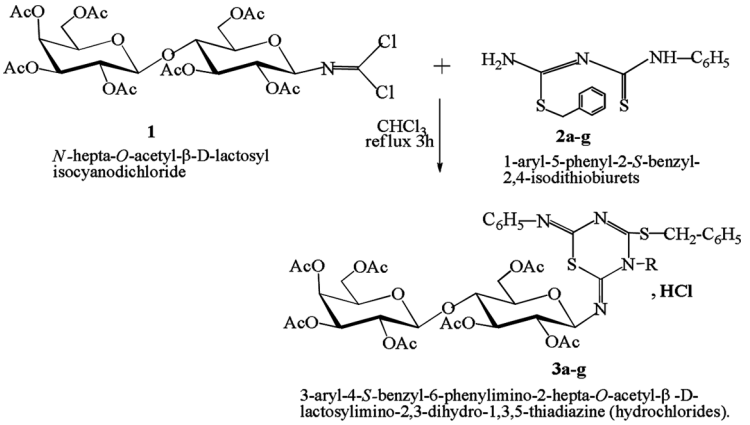
GRAPHICAL ABSTRACT



Abstract *The present work includes synthesis of several 3-aryl-4-*S*-benzyl-6-phenylimino-2-hepta-*O*-acetyl-β-D-lactosylimino-2,3-dihydro-1,3,5-thiadiazines (hydrochloride) by the interaction of* N*-hepta-*O*-acetyl-β-D-lactosyl isocyanodichloride and 1-aryl-5-phenyl-2-S-benzyl-2,4-isodithiobiurets. All these products have been characterized through the usual chemical transformations and infrared,* ^1H *NMR, and mass spectral analysis. The compounds were also screened for their antimicrobial activities.*

Keywords Isodithiobiurets; lactosyl isocyanodichloride; thiadiazines

INTRODUCTION

Nitrogen-containing heterocycles with sulfur atoms are widely utilized compounds in both pharmaceutical and agricultural fields. Azoles, triazoles, substituted thiazoles, and thiadiazoles have been known to possess wide spectra of activities such as anti-HIV,[1] antimicrobial,[2,3] and selective PDE7 inhibitory[4]

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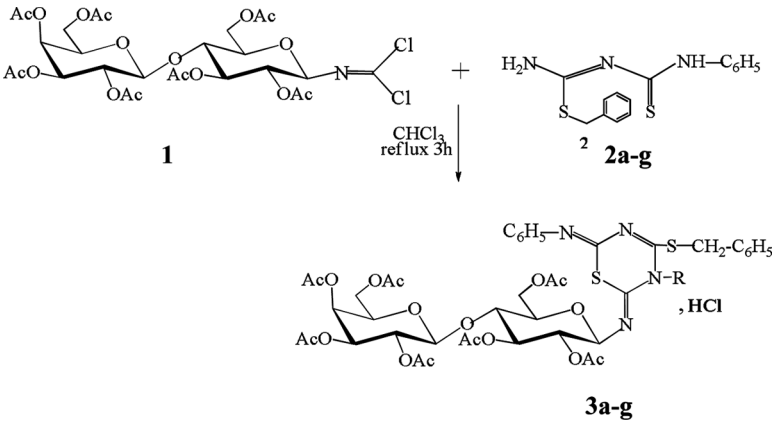
activities in the pharmaceutical industry. Similar studies have been reported on the synthesis of *N*- and *S*-linked heterocycles attached to different carbohydrate templates.[5–7] To expand these views and application profiles, efforts have been developed for the synthesis of a new class of *N*-lactosylated 1,3,5 thiadiazine (hydrochlorides). These were synthesized by the reaction of *N*-hepta-*O*-acetyl-β-D-lactosyl isocyanodichloride with 1-aryl-5-phenyl-2-*S*-benzyl-2-4-isodithiobiurets.

N-Hepta-*O*-acetyl-β-D-lactosyl isocyanodichloride[8] (1) was prepared by the extension of an earlier method by passing excess gaseous chlorine into a chloroformic solution of hepta-*O*-acetyl-β-D-lactosyl isothiocyanate. The required 1-aryl-5-phenyl-2-*S*-benzyl-2-4-isodithiobiurets (**2**) were prepared by the interaction of 1-aryl-2-*S*-benzyl isothiocarbamides and phenyl isothiocyanate in benzene medium.

RESULTS AND DISCUSSION

3-Aryl-4-*S*-benzyl-6-phenylimino-2-hepta-*O*-acetyl-β-D-lactosylimino-2,3-dihydro-1,3,5 thiadiazine (hydrochlorides) (**3a–g**, Scheme 1) were prepared by the condensation of *N*-hepta-*O*-acetyl-β-D-lactosyl isocyanodichloride (1) with 1-aryl-5-phenyl-2-*S*-benzyl-2,4-isodithiobiurets (**2a–g**) in chloroform. After condensation, the solvent was distilled off to obtain a sticky residue, which when triturated with petroleum ether (60–80 °C) afforded a pale yellow solid (**3a–g**). The product was found to be nondesulfurizable when boiled with alkaline plumbite solution. Infrared (IR) spectrum of the product shows characteristic absorption of lactose unit in the ranges of 900–910, 1000–1100, and 1200–1300 cm^{-1}. Mass spectrum showed the characteristic of lactose unit.[9]

All the compounds have been screened for both antibacterial and antifungal activity using cup plate agar diffusion method.[10] The compounds were taken at a concentration of 10 $\mu g mL^{-1}$ using dimethylsulfoxide (DMSO) as solvent. Cotrimazine was used as a standard for antibacterial activity, and griseofulvine was used as standard for antifungal activity. The compounds were screened for antibacterial



Scheme 1. Ac = $COCH_3$. R = (a) phenyl, (b) *o*-Cl-phenyl, (c) *m*-Cl-phenyl, (d) *p*-Cl-phenyl, (e) *o*-tolyl, (f) *m*-tolyl, and (g) *p*-tolyl.

Table 1. Antimicrobial activities of compounds

	Antimicrobial[a]					Antifungal[a]	
Compounds	*E. coli*	*S. aureus*	*S. typhi*	*P. vulraris*	*Pseudomonas*	*A. niger*	*F. riazoctomia*
3a	09	10	—	11	—	15	13
3b	08	18	09	10	—	11	14
3c	09	16	10	11	—	11	14
3d	08	16	09	10	—	13	18
3e	09	13	11	11	—	12	11
3f	10	14	12	12	—	12	15
3g	09	15	12	12	—	12	18
Co-trimazine	15	20	18	17	17	—	—
Griseofulvin	—	—	—	—	—	18	22

[a]Including the well diameter of 5 mm.
Note: Zone of inhibition in mm.

activity against *Escherichia coli, Staphylococcus aureus, Salmonella typhi, Proteus vulgaris*, and *Pseudomonas* in nutrient agar medium and for antifungal activity against *Aspergillus niger* and *Fusarium riazoctomia* in potato dextrose agar medium. The zone of inhibition observed around the cups after respective incubation was measured, and the results are presented in Table 1.

It has been observed that the compounds **3a**, **3b**, **3c**, and **3f** showed moderate activity against *S. aureus, P. vulgaris, and S. typhi* while the other compounds were resistant against *Pseudomonas*. All the compounds exhibited the most significant activity against *A. niger* and *F. riazoctomia*.

EXPERIMENTAL

All the chemicals were research grade. Melting points are uncorrected. All the products were crystallized from ethanol before recording the physical data. Optical rotations were measured at 28 °C. IR spectra[11] were recorded in the range 4000–450 cm^{-1}. ^1H NMR spectra[12] were obtained at 300 MHz for solutions in $CDCl_3$ (reference to tetramethylsilane). The fast atom bombardment (FAB) mass spectra[13] were recorded on a Jeol SX-102/Da-600 mass spectrometer / data system using argon/xenon (6 kv, 10 mÅ) as the FAB gas. The accelerating voltage was 10 kV, and the spectra were recorded at room temperature. m-Nitrobenzyl alcohol (NBA) was used as the matrix unless specified otherwise. Thin-layer chromatography (TLC) was conducted on E. Merck TLC aluminium sheet silica gel 60 F_{254} using $CHCl_3$–ethyl acetate as the mobile phase.

Preparation of 3-Phenyl-4-*S*-benzyl-6-phenylimino-2-hepta-*O*-acetyl-β-D-lactosylimino-2,3-dihydro-1,3,5-thiadiazine (Hydrochloride) (3a)

A solution of *N*-hepta-*O*-acetyl-β-D-lactosyl isocyanodichloride (**1**) (0.0025 M, 1.78 g in 5 ml $CHCl_3$) was added to a solution of 1,5-diphenyl-2-*S*-benzyl-2,4-isodithiobiurets (**2a**) (0.0025 M, 0.94 g in 20 ml $CHCl_3$), and the reaction mixture was gently refluxed for 3 h. The evolution of hydrogen chloride was noticed. The

solvent chloroform was distilled off, and the resultant syrupy mass was triturated several times with petroleum ether (60–80 °C) to afford a pale yellow solid (**3a**). The product was purified by chloroform–ether and recrystallized by ethanol–water, mp 119–122 °C (2.46 g, 93.60%). On extending the reaction of *N*-hepta-*O*-acetyl-β-D-lactosyl isocyanodichloride with 1-aryl-5-phenyl-2-*S*-benzyl 2,4-isodithiobiurets, several 3-aryl-4-*S*-benzyl-6-phenylimino-2-hepta-*O*-acetyl-β-D-lactosylimino-2,3-dihydro-1,3,5-thiadiazine (hydrochlorides) have been isolated.

Analytical and Spectral Data of Prepared Compounds

Compound 3a. Mp 119–122 °C; yield 93.60% $[\alpha]_D^{28} + 20$ (*c*, 1.013 in $CHCl_3$); R_f 0.70; IR (KBr): ν 2958.41 (C-H aliphatic), 1750.0 (C=O), 1568.2 (C=N), 1371.3 (C–N), 1227.7 (C – O), 757.1 (C-S), characteristic of lactose at 1050.6 and 904.4 cm^{-1} ^1H NMR (ppm) δ 7.74–7.27 (15H, m, Ar – H), δ 5.36–3.77 (16H, m, lactosyl protons, S-CH_2), 2.18–1.97 ppm (21H, m, acetyl protons). Mass spectrum (*m/z*) 1056 (M^+), 979, 933, 620, 560, 331, 169, 109. Anal. calcd. for $C_{48}H_{52}O_{17}N_4S_2 \cdot HCl$: C, 54.54; H, 5.01; N, 5.30; S, 6.06% (found: C, 54.49; H, 4.94; N, 5.26; S, 6.17%).

Compound 3b. Mp 140 °C (d); yield 97.30% $[\alpha]_D^{28} + 22$ (*c*, 1.013 in $CHCl_3$); R_f 0.81. Anal. calcd. for $C_{48}H_{51}O_{17}N_4S_2Cl \cdot HCl$: C, 52.84; H, 4.77; N, 5.13; S, 5.87% (found: C, 52.78; H, 4.73; N, 5.08; S, 5.94%).

Compound 3c. Mp 128–130 °C; yield 92.81% $[\alpha]_D^{28}$–60 (*c*, 1.013 in $CHCl_3$); R_f 0.69. IR (KBr): ν 2958.7 (C-H aliphatic), 1750.6 (C=O), 1571.6 (C=N), 1370.6 (C – N), 1226.5 (C – O), 770.9 (C-S), characteristic of lactose at 1051.0 and 902.9 cm^{-1}. ^1H NMR (ppm) δ 7.77–7.20 (14H, m, Ar – H), δ 5.40–3.79 (16H, m, lactosyl protons, S-CH_2), 2.21–1.85 (21H, m, acetyl protons). Mass spectrum (*m/z*) 1090 (M^+), 967, 620, 560, 413, 331, 169, 109. Anal. calcd. for $C_{48}H_{51}O_{17}N_4S_2Cl \cdot HCl$: C, 52.84; H, 4.77; N, 5.13; S, 5.87% (found: C, 52.76; H, 4.70; N, 5.09; S, 5.80%).

Compound 3d. Mp 115–117 °C; yield 85.51% $[\alpha]_D^{28} + 10$ (*c*, 1.013 in $CHCl_3$); R_f 0.72. Anal. calcd. for $C_{48}H_{51}O_{17}N_4S_2Cl \cdot HCl$: C, 52.84; H, 4.77; N, 5.13; S, 5.87% (found: C, 52.77; H, 4.72; N, 5.08; S, 5.84%).

Compound 3e. Mp 113–115 °C; yield 97.63% $[\alpha]_D^{28} + 110$ (*c*, 1.013 in $CHCl_3$); R_f 0.74. IR (KBr): ν 2939.3 (C-H aliphatic), 1747.3 (C=O), 1564.8 (C=N), 1371.2 (C – N), 1230.2 (C – O), 764.6 (C-S), 699.4 characteristic of lactose at 1049.4 and 906.1 cm^{-1}. ^1H NMR (ppm) δ 7.78–7.14 (14H, m, Ar – H), δ 5.39–3.58 (14H, m, lactosyl protons, S-CH_2), 2.46–1.84 (21H, m, acetyl protons), 1.25 (3H, s, Ar-CH_3). Mass spectrum (*m/z*) 1070 (M^+), 979, 870, 620, 560, 331, 169, 109. Anal. calcd. for $C_{49}H_{54}O_{17}N_4S_2 \cdot HCl$: C, 54.95; H, 5.14; N, 5.23; S, 5.98% (found: C, 54.90; H, 5.12; N, 5.19; S, 6.06%).

Compound 3f. Mp 118–120 °C; yield 86.36% $[\alpha]_D^{28} + 90$ (*c*, 1.013 in $CHCl_3$); R_f 0.68. Anal. calcd. for $C_{49}H_{54}O_{17}N_4S_2 \cdot HCl$: C, 54.95; H, 5.14; N, 5.23; S, 5.98% (Found: C, 54.88; H, 5.09; N, 5.17; S, 6.08%).

Compound 3g. Mp 122–125 °C; yield 90.38% $[\alpha]_D^{28} + 40$ (*c*, 1.013 in $CHCl_3$); R_f 0.77. Anal. calcd. for $C_{49}H_{54}O_{17}N_4S_2 \cdot HCl$: C, 54.95; H, 5.14; N, 5.23; S, 5.98% (found: C, 54.88; H, 5.07; N, 5.19; S, 6.10%).

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