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SYNTHESIS AND ANTIMICROBIAL ACTIVITY OF 4 - HEPTA-*O*-ACETYL-β-D-LACTOSYL-1-ARYLIDINE THIOSEMICARBAZONES

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ABSTRACT

Certain 4-hepta-*O*-acetyl–β–D-lactosyl-1-arylidine thiosemicarbazones have been reported synthesized by the interaction of hepta-*O*-acetyl-β-D-lactosyl thiosemicarbazide and aryl aldehydes. The identities of these new compounds have been established on the basis of usual chemical transformations and IR, ^{1}H NMR and Mass spectral analysis. The products were assayed for their antimicrobial activity against some selected organism. Some of the products displayed promising activity.

Key words: Lactosyl thiosemicarbazide, Aryl aldehydes, Lactosyl arylidine thiosemicarbazones and Antimicrobial activity.

INTRODUCTION

Various glycosyl derivatives of 1,2,4-triazole, 1,3,4-thiadiazole, 1,2,4-dithiazolidines and thiadiazines exhibit broad spectrum of pharmacological properties[1-4]. Thiosemicarbazones are a class of small molecules that have been evaluated over the last 50 years as antivirals and as anticancer therapeutics, as well as for their parasiticidal action. Thiosemicarbazones can be used for making electrodes, or formation of complexes of metallic ions. Thiosemicarbazones exhibit various biological activities such as antituberculosis[5], antimicrobial[6], anti-inflammatory, antiviral, anticonvulsant, antihypertensive, local anesthetic[7], anticancer[8], hypoglycemic, cytotoxic activities and antitrypanosomal activity, etc. There has been evidences about inhibitory mechanisms of heterocyclic thiosemicarbazones for human ribonucleotide reductase. Moreover, the chemistry of thiosemicarbazide derivatives of saccharides is of interest.[9,10]

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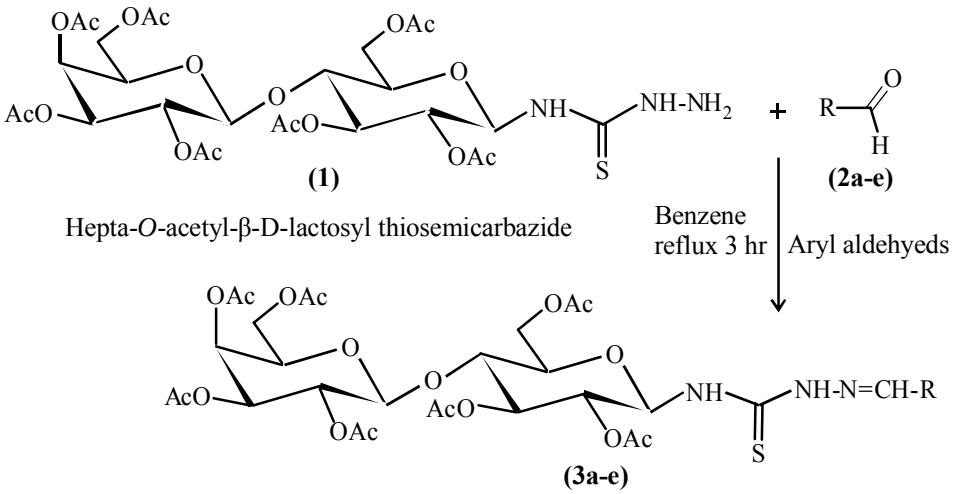
Such noteworthy and diversified pharmaceutical values of thiosemicarbazones have prompted us to synthesize 4-hepta-*O*-acetyl-β-D-lactosyl-1-arylidine thiosemicarbazones (**3a-e**) by the interaction of hepta-*O*-acetyl-β-D-lactosyl thiosemicarbazide (**1**) and aryl aldehydes (**2a-e**).

EXPERIMENTAL

Melting points were taken in open capillary tubes on Mac digital melting point apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer spectrum RXI FTIR spectrometer 4000-450 cm^{-1}. The ^1H NMR spectra were recorded in $CDCl_3$ at 300 MHz on a Bruker DRX-300 NMR spectrometer. The FAB Mass spectra were recorded on a Jeol SX-102/Da-600 mass spectrometer/data system using argon/xenon (6 KV, 10mA) as the FAB gas. The accelerating voltage was 10KV, and the spectra were recorded at room temperature. Optical rotations $[\alpha]_D^{31}$ were measured on Equip-Tronics EQ-800 Digital Polarimeter at 31° in Chloroform. Thin layer chromatography (TLC) was performed on E. Merck pre-coated silica gel plates.

Reaction scheme is :



4-Hepta-*O*-acetyl-β-D-lactosyl-1-arylidine thiosemicarbazones

Where, Ac = $COCH_3$

R = (a) Phenyl, (b) (4-Hydroxy-3methoxy) phenyl (c) (4-Methoxy) phenyl, (d) 4-Cl-phenyl, (e) (4-Hydroxy-3,5-dimethoxy) phenyl.

Scheme 1

RESULTS AND DISCUSSION

Synthesis of hepta-*O*-acetyl-β-D-lactosyl thiosemicarbazide

This has been synthesized by the interaction of hepta-*O*-acetyl-β-D-lactosyl isothiocyanate and hydrazine hydrate. The reaction has been carried out with stirring in benzene medium for 15-20 min. The clear solution was then kept for 15 min at room temperature. The solvent benzene was distilled off and the sticky mass was isolated as residue. This on trituration several times with petroleum ether (60-80°C) was converted to a granular solid (**1**)

Spectral analysis[11-14] of hepta-*O*-acetyl-β-D-lactosyl thiosemicarbazide 1

IR (KBr): ν (cm^{-1}) 3332.4 (N-H), 2960.6 (C-H aliphatic), 1752.1 (C=O), 1374.5 (C-N), 1228.2 (C-O), 1048.8 and 906.3 (characteristic of lactose); ^{1}H NMR δ 7.43 (1H, *s*, N-H protons), δ 6.26-3.57 (14H,m, lactose ring protons), δ 2.57-1.42 ppm (21H, m, acetyl protons), δ δ 2.57-1.42 ppm (3H, *m*, N-H protons); Mass spectrum (m/z) 709 (M^+), 693, 634, 619, 559, 331.

Preparation of 4–hepta-*O*-acetyl-β-D-lactosyl-1-benzylidine thiosemicarbazone (3a)

To a benzene solution of hepta-*O*-acetyl-β-D-lactosyl thiosemicarbazide **(1)** (0.0028 M) a solution of benzaldehyde **(2a)** (0.0028 M) was added and the reaction mixture was refluxed over a boiling water bath for 3 hr. After refluxing, benzene was distilled off and the sticky mass obtained as residue was triturated several times with petroleum ether (60-80°C). A granular colourless solid was obtained (1.7 g, 75.89%) crystallized from ethanol, m.p. 98-100°C.

Similarly, the reaction of hepta-*O*-acetyl-β-D-lactosyl thiosemicarbazide **(1)** was extended to several aryl aldehydes **(2)** and the related 4-hepta-*O*–acetyl-β-D-lactosyl-1-arylidine thiosemicarbazone **(3b-e)** were obtained.

(3a): IR (KBr): ν (cm^{-1}) 3342.1 (N-H), 2957.5 (C-H aliphatic), 1751.3 (C=O), 1655.7 (C=N), 1374.8 (C-N), 1228.2 (C-O), 1049.2 and 905.7 (characteristic of lactose), 768.2 (Monosubstituted ring); ^{1}H NMR δ 9.41 (1H, *s*, N-H protons), δ 7.26 (1H, *s*, N-H protons), δ 7.76-7.12 (5H, *s*, Ar-H), δ 5.75-3.77 (14 H, *m*, lactose ring protons), δ 2.38-2.35 (1H, *s*, methylene protons), δ 2.27-1.87 ppm (21H, *m*, acetyl protons); Mass spectrum (m/z) 798 (M^+ + 1), 720, 707, 619, 559, 331, 211. (Found: C, 51.14; H, 5.35; N, 5.20; S, 4.06 Calcd for $C_{34}H_{43}O_{17}N_3S$: Required: C, 51.19; H, 5.39; N, 5.26; S, 4.01%).

Table 1: Characterization of 4-hepta-*O*-acetyl-β-D-lactosyl-1-arylidine thiosemicarbazone

S. No.	Reactant	Product	Yield (%)	m.p. (^oC)	R_f	$[\alpha]_D^{31}$ (*c*, 1.013 in $CHCl_3$)
1	(2a)	(3a)	75.89	98-100	0.68	-140.6
2	(2b)	(3b)	80.33	118-120	0.77	+9.4
3	(2c)	(3c)	80.68	124-126	0.75	+19.02
4	(2d)	(3d)	83.76	164-166	0.80	+30.07
5	(2e)	(3e)	84.55	160-162	0.65	+25.10

(3c) IR (KBr): ν (cm^{-1}) 3357.8 (N-H), 2945.5 (C-H aliphatic), 1750.6 (C=O), 1675.4 (C=N), 1373.9 (C-N), 1228.1 (C-O), 1110.0 (C=S), 1045.5 and 907.6 (characteristic of lactose), 838.9 (1,4-disubstituted ring); ^{1}H NMR δ 9.98 (1H, *s*, N-H protons), δ 7.26 (1H, *s*, N-H protons), δ 7.86-6.78 (4H, *m*, Ar-H), δ 5.66-3.75 (14 H, *m*, lactose ring protons), δ 3.89 (3H, *s*, methoxy protons), δ 2.36 (1H, *s*, methylene protons), δ 2.26-1.75 ppm (21H, *m*, acetyl protons); Mass spectrum (m/z) 827 (M^+), 796, 720, 693, 619, 331, 169. (Found: C, 50.71; H, 5.40; N, 5.00; S, 3.90 Calcd for $C_{35}H_{45}O_{18}N_3S$: Required: C, 50.78; H, 5.44; N, 5.07; S, 3.86%).

(3e) IR (KBr): ν (cm^{-1}) 2976.8 (C-H aliphatic), 1750.0 (C=O), 1608.1 (C=N), 1376.2 (C-N), 1226.7 (C-O), 1048.8 and 906.4 (characteristic of lactose), 836.2 (1,4-disubstituted ring); ^{1}H NMR δ 9.28 (1H, *s*, N-H protons), δ 7.27 (1H, *s*, N-H protons), δ 7.15 (2H, *m*, Ar-H), δ 6.16-6.13 (1H, *s*, hydroxy proton), δ 5.53-3.56 (14 H, *m*, lactose ring protons), δ3.97 (6H, *s*, methoxy protons), δ 2.38 (1H, *s*, methylene protons), δ 2.15-1.74 ppm (21 H, *m*, acetyl protons); Mass spectrum (m/z) 873 (M^+), 842, 720, 693, 619, 559, 339, 239. (Found: C, 49.42; H, 5.31; N, 4.74; S, 3.59 Calcd for $C_{36}H_{47}O_{20}N_3S$: Required: C, 49.48; H, 5.38; N 4.81; S, 3.66%).

Antibacterial activity

The compounds were screened for their antibacterial activity against various pathogenic bacteria such as *Escherichia coli*; *Staphylococcus aureus*, *Proteus vulgaris*, *Pseudomonas aeruginosa* and *Salmonella typhimurium*, using cup plate agar diffusion method[15] at a conc. 10 µg/mL in DMSO by using amikacin as a standard. All the compounds showed moderate activity against *S.aureus, P.vulgaris* and *Ps.aeruginosa*, while they were resistant against *E. coli.*

Antifungal activity

All the compounds were also screened for their antifungal activity by cup plate agar diffusion method at a conc. 10 µg/mL in DMSO by using fluconazole as a standard against *Aspergillus niger* and *Rhizoctonia*. All the compounds showed good activity against both the fungi.

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