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ANTIMICROBIAL ACTIVITIES OF SOME N-GALACTOSYLATED THIOCARBAMIDES

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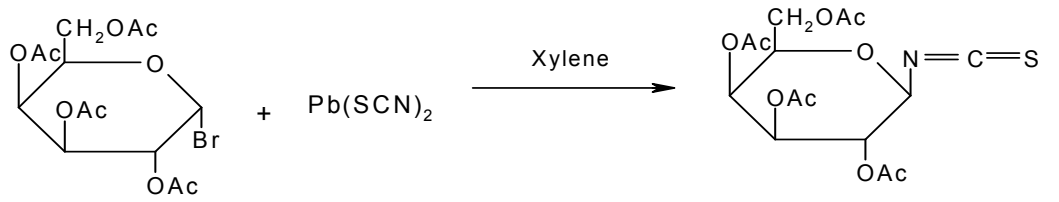
ABSTRACT

Several 1 – tetra – O – acetyl – β – D – galactosyl – 3 – aryl/H thiocarbamides **(III)** have been prepared by the interaction of tetra – O – acetyl – β – D – galactosyl isothiocyanate **(I)** and aryl amines/ ammonia **(II)**. All the products formed were well characterized by the spectral analysis and usual chemical transformations. These compounds were screened for their antimicrobial activities against various pathogenic bacteria like *E. coli*, *S. aureus*, *P. vulgaris* and *P. aregenosa* and fungi like *A. niger* and *C. albicans*. These compounds exhibit interesting activity as compared with standard drug at the same concentration.

Key words : N-Galactosides, Amines, Ammonia, Thiocarbamides, Antimicrobial activities.

INTRODUCTION

Peracetylated derivatives of sugar isothiocyanates are important class of organic compounds in the field of carbohydrate chemistry. In the last few years, hundreds of compounds have been synthesized from glycosyl isothiocyanates[1-3]. Galactosyl isothicyanate is one of the versatile intermediate in carbohydrate chemistry[4, 5].



Tetra - O - acetyl - α - D - galactosyl bromide

(I)

Tetra - O - acetyl - β - D - galactosyl isothiocyanate

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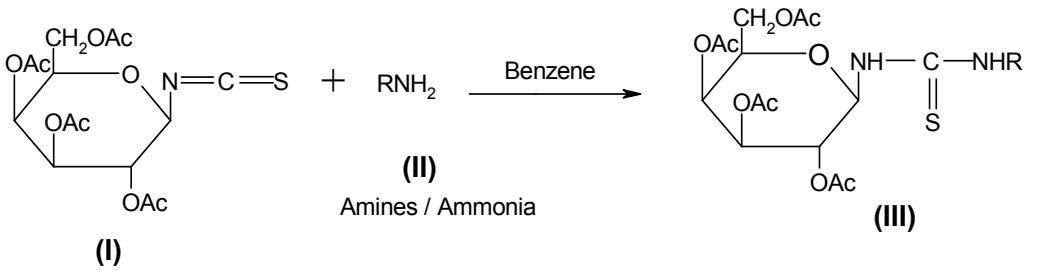

Tetra – O – acetyl –β- D - galactosyl isothiocyanate

1 – tetra – O – acetyl – β – D - galactosyl - 3- aryl/H thiocarbamides

Where, R = (a) phenyl, (b) o-Cl – phenyl, (c) m-Cl – phenyl, (d) p – Cl –phenyl, (e) o – tolyl, (f) m – tolyl, (g) p – tolyl and (h) H.

Scheme 1

Recently, we have reported the synthesis of some novel 1 – tetra – O – acetyl – β – D – galactosyl – 3 – aryl/H thiocarbamides by the interaction of tetra – O – acetyl – β – D – galactosyl isothiocyanate and aryl amines /ammonia[6]. Due to the facile reaction with ammonia/amines to form the corresponding thiocarbamides which have biological significance, it was interesting to investigate the antimicrobial activities of newly synthesized N- galactosylated thiocarbamides **(Scheme 1)**.

EXPERIMENTAL

Melting points are uncorrected. Optical rotations $[\alpha]_D$ were measured on a Equiptronics digital polarimeter Model No. EQ 800 in $CHCl_3$. IR spectra were recorded on a Perkin-Elmer spectrum RXI (4000-450 cm^{-1}) FTIR spectrometer[7,8]. ^1H NMR were obtained on a Bruker DRX-300 (300 MHz FT NMR) NMR spectrometer for a sample in $CDCl_3$ solution with TMS as an internal reference[9]. The mass spectra were recorded on a Joel SX-102 FAB mass spectrometer[10].

RESULTS AND DISCUSSION

Tetra-O-acetyl – β – D - galactosyl isothiocyanate (I)

Tetra – O – acetyl – β – D – galactosyl isothiocyanate **(I)** was prepared by employing the classical Fischer's method[11] by the interaction of tetra-O-acetyl- α –D-galactosyl bromide and lead thiocyanate instead of silver thiocyanate in anhydrous xylene medium. The product was isolated from petroleum ether and crystallized form chloroform

– petroleum ether mixture, m. p. 92 ^{o}C.

1-Tetra-*O*-acetyl-β- D - galactosyl-3-aryl/H thiocarbamides (IIIa-h) (Scheme 1)

Condensation of tetra-O-acetyl-β- D - galactosyl isothiocyanate **(I)**, (0.005M, 2g) and aryl amines/ammonia (**IIa-h**, 0.005M) was carried out in boiling benzene on water bath for 3h. The reaction was monitored by TLC. After the reaction has been completed, the excess solvent was distilled off and sticky residue obtained was triturated with petroleum ether (60-80^{0}C) to afford a solid. All products formed were purified from $CHCl_3$ –petroleum ether.

Antimicrobial activity

All the compounds **(I and IIIa – h)** have been screened for both; antibacterial and antifungal activity by employing cup –plate agar diffusion method[12, 13], by measuring the zone inhibition in mm. Amikacin (100 µg/mL) was used as standard for antibacterial activity and fluconazole (100 µg/mL) as a standard for antifungal activity. The compounds were screened for antibacterial activity against *E. coli*, *S. aureus*, *P. vulgaris* and *P. aregenosa* in nutrient agar medium and for antifungal activity against *C. albicans* and *A. niger* in potato dextrose agar medium. The results are presented in Table 1.

It has been observed that some of these compounds exhibit interesting microbial activities. Compounds **IIIa**, **IIId** and **IIIf** exhibit interesting activity against *S. aureus*. **IIIa**, **IIIe**, **IIIh** and **I**, **IIIc**, **IIIh** exhibit significant activities against *E. coli* and *P. vulgaris* respectively. All other compounds show low to moderate activity. The results of antifungal activity are also shown in Table 1 Compounds **IIIb**, **IIIf** and **IIIh** are effective towards *A. niger* and *C. albicans*. All other compounds show low to moderate activity.

Table 1. Antimicrobial activities of compounds I and IIIa – h

Compound	Antibacterial activity				Antifungal activity	
	S. aureus	***E. coli.***	***P. aregenosa***	***P. vulgaris***	***A. niger***	***C. albicans***
I	14	19	17	20	07	08
IIIa	20	23	15	13	09	07
IIIb	13	18	-	-	11	10

Cont…

Compound	Antibacterial activity				Antifungal activity	
	S. aureus	***E. coli.***	***P. aregenosa***	***P. vulgaris***	***A. niger***	***C. albicans***
IIIc	17	-	13	22	-	07
IIId	19	12	-	12	08	07
IIIe	15	16	14	17	08	07
IIIf	19	13	-	17	09	09
IIIg	-	13	16	17	-	09
IIIh	-	22	14	21	11	10
Amikacin	23	28	25	28	-	-
Fluconazole	-	-	-	-	18	18

Yield 55%, m. p. 92^0C; $[\alpha]_D^{32} = +53.57^0$ (C, 0.373); R_f : 0.71 IR (KBr) : ν 2104 (-N=C=S); 1751 (C=O); 1239 (C-O), 1092 (C=S). ^{1}H NMR ($CDCl_3$) : δ 5.41(d, 1H, H_4), 5.33(t, 1H, $J_{1,22} = 9$ Hz, H_2), 5.04 (d, 1H, H_3), 5.00 (d, 1H, $J_{1,22} = 9$Hz, H_1), 4.13(d, 2H, $H_{6,6'}$), 3.97 (t, 1H, H_5), 2.18 – 1.99 (4s, 12H, 4$COCH_3$). Mass (M/z) : 389 (M^+), 331, 211, 169, 109. Anal. Calcd. for : $C_{15}H_{19}NO_9S$: C46.27; H, 4.88;N, 3.59; S, 8.22 found; C, 6.19; H, 4.80; N, 3.44; S, 8.34 %.

(IIIa) IR (KBr) : - ν3364 (N-H); 2954 (Ar-H); 1749 (C=O); 1373 (C-N); 1229 (C-O); 1051 (C=S). ^{1}H NMR ($CDCl_3$) : δ 8.19 (s, 1H, NH); 7.49-7.19 (m, 5H, Ar-H); 6.64-6.61 (d, 1H, J = 9Hz, NH); 5.84 (t, 1H, J = 9Hz, H_1); 5.43 (s, 1H, H_4); 5.2-5.16 (dd, 1H, H_3); 5.1 - 5.06 (t, 1H, H_2); 4.13 - 4.05 (m, 3H, $H_{5,6,6'}$); 2.17-1.89 (m, 12H, 4$COCH_3$). Mass (M/z) : 482(M^+.), 331, 211, 169, 109.Anal. Calcd. for : - $C_{21}H_{26}N_2O_9S$: C, 52.28; H, 5.39; N, 5.8; S, 6.63, found, C, 52.33; H, 5.46; N, 5.66, S, 6.76 %.

(IIIb) IR (KBr) : - ν 3341 (N-H); 2967 (Ar-H); 1749 (C=O); 1371 (C-N); 1228 (C-O); 1052 (C=S). ^{1}H NMR ($CDCl_3$) : δ 8.04 (s, 1H, NH); 7.55-7.28 (m, 4H, Ar-H); 6.78-6.73 (d, 1H, NH); 5.76 (bs, 1H, J = 9Hz, H_1); 5.48-5.44 (s, 1H, H_4); 5.21-5.16 (dd, 1H, H_3); 5.12-5.05 (t, 1H, J = 9Hz, H_2); 4.16-4.06 (m, 3H, $H_{5,6,6'}$); 2.17-1.81 (m, 12H, $COCH_3$). Mass (M/z) : 517 (M^+. +1), 331, 211, 169, 109. Anal. Calcd. for : - $C_{21}H_{25}N_2O_9SCl$: C, 48.83; H, 4.84; N, 5.42; S, 6.20, found, C, 48.76; H, 4.88; N, 5.46, S, 6.12 %.

(IIIg) IR (KBr) : - ν 3342 (N-H); 2966 (Ar-H); 1750 (C=O); 1371 (C-N); 1229 (C-O); 1051 (C=S). ^{1}H NMR ($CDCl_3$) : - δ 8.05 (s, 1H, NH); 7.27-7.25 (d, 2H, Ar-H); 7.08-7.06 (d, 2H, Ar-H); 6.58 (d, 1H, J = .7Hz, NH); 5.85-5.79 (t, 1H, J = .7Hz, 9.3Hz, H_1); 5.43- 5.42 (S, 1H, H_4); 5.2-5.15 (dd, 1H, H_3); 5.05 (t, 1H, J = 9.3Hz, H_2); 4.13-4.05 (m, 3H, $H_{5,\ 6,\ 6'}$); 2.39(s, 3H, Ar-CH_3); 2.16-1.69 (m, 12H, $COCH_3$). Mass (M/z) : - 496 (M^+.), 331, 211, 169, 109. Anal. Calcd. for : - $C_{22}H_{28}N_2O_9S$: C, 53.22; H, 5.64; N, 5.64; S, 6.45; found, C, 53.18; H, 5.61; N, 5.55, S, 6.51%.

(IIIh) IR (KBr) : - ν 3403 (N-H); 2965 (Ali. C-H); 1748 (C=O); 1372 (C-N); 1229 (C-O); 1021 (C=S). ^{1}H NMR ($CDCl_3$) : - d 7.36 (s, 2H, NH_2); 7.08-7.05 (d, 1H, N-H, J = 9Hz); 6.61 (bs, 1H, H_1); 5.5-5.49 (d, 1H, H_4); 5.3-5.17 (m, 2H, H_2, H_3); 4.41 (m, 1H, H_6); 4.23-4.2 (dd, 1H, H_5); 4.11-4.07 (m, 1H, $H_{6'}$); 2.28-1.84 (m, 12H, $COCH_3$). Anal. Calcd. for: - $C_{15}H_{22}N_2O_9S$: C, 44.33; H, 5.41; N, 6.89; S, 7.88. found, C, 44.28; H, 5.32; N, 6.81, S, 7.93%.

Table 2. 1-Tetra-*O*-acetyl-β-D-galactosyl-3-aryl/H-thiocarbamides (IIIa-h)

Reactant : (i) Tetra-*O*-acetyl-β-D-galactosyl isothiocyanate **(I)** (0.005 M, 2 g)
(ii) Aryl amines / Ammonia **(IIa-h)** (0.005 M)

Sr. No.	Products (IIIa-h)	Amines (g)	Yield (%)	m. p. (^{o}C)	$[\alpha]_D^{32}$ ($CHCl_3$)	R_f (CCl_4 : EtOAc)
1	**IIIa**	Aniline (0.45)	65.58	128	+133.94 ^{o}(c, 0.373)	0.69 (3 : 2)
2	**IIIb**	o-Cl-Aniline (0.64)	71.69	176	+117.64^o (c, 0.340)	0.73 (3 : 2.2)
3	**IIIc**	m-Cl-Aniline (0.64)	62.26	124	+91.85^o (c, 0.326)	0.79 (3 : 2.2)
4	**IIId**	p-Cl-Aniline (0.64)	69.81	140	+155.19^o (c, 0.386)	0.86 (3 : 2.1)
5	**IIIe**	o-Toluidine (0.54)	54.9	172	+205.88^o (c, 0.340)	0.89 (3 : 2.1)
6	**IIIf**	m-Toluidine (0.54)	66.66	160	+242.42^o (c, 0.333)	0.71 (3 : 2.1)

Cont…

Sr. No.	Products (IIIa-h)	Amines (g)	Yield (%)	m. p. (^oC)	$[\alpha]_D^{32}$ ($CHCl_3$)	R_f (CCl_4 : EtOAc)
7	**IIIg**	p-Toluidine (0.54)	68.23	110	$+187.50^o$ (c, 0.320)	0.77 (3 : 2.3)
8	**IIIh**	Ammonia (0.08)	74.51	126	$+105.26^o$ (c, 0.386)	0.57 (3 : 2.1)

Satisfactory C, H, N and S analysis was found in all cases.

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