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Research Article

ANTIMICROBIAL ACTIVITIES OF NOVEL N-GALACTOPYRANOSIDES

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ABSTRACT

A series of N – galactopyranosyl - 2, 4 – isodithiobiurets have been synthesized by the interaction of tetra – O – acetyl - β – D – galactopyranosyl – S – benzyl isothiocarbamide with different aryl isothiocyanates. All these products have been characterized by usual chemical transformations and IR, NMR and Mass spectral studies. All the compounds were screened for their antimicrobial activities by cup-plate agar diffusion method , against various pathogenic bacteria like E. *coli*, S. *aureus*, P. v*ulgaris* and P. *aregenosa* and fungi like A. *niger* and C. *albicans* at a concentration of 100 µg/ml (MIC) in DMSO against standards Amikacin and fluconazole for antibacterial and antifungal activities respectively at same concentration.

Keywords: Isothiocarbamide, Isothiocyanates, Isodithiobiurets, Antimicrobial activities

INTRODUCTION

S-alkyl/aryl isothiocarbamides due to their basic nature are known to react with alkyl/aryl isothiocyanates to produce corresponding 2, 4 isodithiobiurets. Literature survey reveals that non-glycosidic isodithiobiurets are known to show anticonvulsant and hypnotic activities[1], while some sugar isodithiobiurets shows potential antimicrobial activities [2]. Recently, we have reported the synthesis of 1-aryl-5-tetra-O-acetyl- β -D- galactopyranosyl -2-S-benzyl-2,4-isodithiobiurets by the interaction of tetra-O-acetyl- β -D-galactopyranosyl isothiocyanate and aryl-S-benzyl isothiocarbamides[3]. On the basis of above biological importance of isodithiobiurets and work done on sugar isodithiobiurts[4, 5]. It was of sufficient interest to work out for some novel N-galactopyranosyl isodithiobiurets, which were prepared for the first time by the interaction of tetra-O-acetyl-β-D-galactopyranosyl isothiocyanate and 1-aryl-S-benzyl isothiocarbamides. With this end in view the synthesis of 1-tetra-O-acetyl- β -D- galactopyranosyl-5-aryl-2-S-benzyl-2,4-isodithiobiurets (IVa-f) have been carried out by the interaction of tetra-O- acetyl- β -D-galactopyranosyl-S-benzyl isothiocarbamide with aryl isothiocyanates and the corresponding 2,4 isodithiobiurets having N- galactopyranosyl substituent are prepared for the first time. The structural evaluation of the newly synthesized compounds have made on the basis of the spectral interpretation of some typical cases. The new products were also screened for their antimicrobial potential.

MATERIALS AND METHODS

General Methods

Melting points are found to be uncorrected. The IR [6] spectra were recorded on a Perkin –Elmer spectrum RXI (4000-450 cm^{-1}) FT IR spectrometer. ^1H NMR[7] were obtained on a Bruker DRX-300 (300MHz FT NMR) NMR spectrometer for a sample in $CDCl_3$ solution with TMS as an internal reference. The mass[8] spectra were recorded on Joel SX-102 mass spectrometer. Optical rotations $[\alpha]_D$ were measure on a Equiptronics digital polarimeter Model No. EQ 800 in $CHCl_3$ at 36° C.

Tetra-O-acetyl- β -D-galactopyranosyl thiocarbamide(I)

It was prepared by the method described earlier which involves the interaction of tetra-O-acetyl- β -D-galactopyranosyl isothiocyanate and ammonia in benzene medium[9].

1-Tetra-O-acetyl- β -D-galactopyranosyl-S-benzyl isothiocarbamide(II)

To a suspension of tetra-O-acetyl – β -D-galactopyranosyl thiocarbamide (0.01mol, 4g) in ethanol (15ml) was added a solution of benzyl chloride (0.01mol, 1.2 g) in ethanol (10ml).The resultant mixture was refluxed for 90 min. This acidic solution was then rendered basic with dilute ammonium hydroxide, when a syrupy mass was obtained. It was triturated with petroleum ether, but it failed to solidify. So this residual mass was purified on a silica gel column prepacked in chloroform. Eluent was then evaporated to dryness when syrup was isolated (2.2g, 45%). The product was found non desulphurisable when boiled with alkaline plumbite solution. Its $[\alpha]^{36}_D$ -60.2° (c, 0.9 in $CHCl_3$). The elemental analysis of this syrupy mass indicates its molecular formula as $C_{22}H_{28}O_9N_2S$. (found: C,53.29; H,5.72; N,5.69; S,6.5 requires C,53.22, H,5.68; N,5.64; S 6.46%). The above observations have clearly indicated that the product with molecular formula $C_{22}H_{28}O_9N_2S$ as tetra-O- acetyl- β -D-galactopyranosyl-S- benzyl isothiocarbamide (II).

Aryl isothiocyanates (III a-f)

The required aryl isothiocyanates were prepared as usual, by the oxidative decomposition of ammonium aryl dithiocarbamates with the help of lead nitrate[10].

1-tetra – O – acetyl – β – D – galactopyranosyl – 5 – aryl – 2 – S - benzyl- 2-,4-isodithiobiurets (IV a-f)

To the benzene solution of 1-tetra-O-acetyl- β -D galactopyranosyl-S-benzyl isothiocarbamide (0.005mol, 2.5 g in 20ml) was added a benzene solution of aryl isothiocyanate (0.005 mol, in 10ml) and the mixture was refluxed for 8hr. Afterwards, the solvent benzene was distilled off and the resultant syrupy mass was triturated with petroleum ether to afford a solid (IV a-f). It was crystallized from alcohol.

RESULT AND DISCUSSION

Interaction of tetra-O-acetyl- β -D-galactopyranosyl thiocarbamide **(I)** was carried out with benzyl chloride in boiling ethanol for 1 ½ hr. After cooling, it was rendered basic with dilute ammonium hydroxide. A syrupy mass of expected tetra-O- acetyl- β -D-galactopyranosyl-S-benzyl isothiocarbamide **(II)** was obtained. Attempts, made to solidify the product were unsuccessful. This intermediate was then directly used for further reaction.

In a typical reaction, condensation of tetra-O-acetyl- β -D-galactopyranosyl-S-benzyl-isothiocarbamide (II) and aryl isothiocyanate (III a-f) has been carried out in refluxing dry benzene medium for 6hr. After refluxing, benzene was distilled off and the sticky mass was obtained as residue. When it was triturated with petroleum ether, a solid was obtained. It was crystallized from alcohol. The elemental analysis and spectral interpretation confirms the formation of the products (IV a-f) (Scheme – 1). The products after complete analysis were screened for their antimicrobial activities against some pathogenic bacteria like S. *aureus*, E. *coli*, P. *vulgaris* and P. *aregenosa*, and fungi like A. *niger*, and C. *albicans* (Table – 1).

1-tetra-O-acetyl-β -D- galactopyranosyl-5-phenyl-2-S-benzyl-2, 4 isodithiobiuret (IVa)

Yield (1.8g, 58%), R_f 0.78 ($CC1_4$: n-hexane, 1:3), m.p. 112-114°C, $[\alpha]^{36}_D$ -84.2° (c, 0.95 in $CHCl_3$), IR (KBr, cm^{-1}): ν 3327(N-H), 1752(C =O), 1581(C=N), 1370(C-N), 1229(C-O), 1049(C=S), 914(β –D-galactopyranosyl ring deformation)[11]. ^1H NMR ($CDCl_3$): δ 7.50-7.05

(m, 12H, NH, Ar-H); 5.41-3.96(m, 9H, galactopyranosyl ring protons, $2CH_2$); 2.15-1.93(m, 12H, 4 $COCH_3$). m/s (m/z): 631(M^+), 632(M^++1, 100%), 540(M^+- $CH_2C_6H_5$), 331(characteristic of glycopyranose)[12], 91($C_7H_7^+$). [found: C, 55.10; H, 5.17; N, 6.56; S, 10.00, $C_{29}H_{33}O_9N_3S_2$ requires C, 55.15; H, 5.22; N, 6.65; S, 10.14 %].

1-tetra-O-acetyl-β-D-galactopyranosyl-5-o-tolyl-2-S-benzyl-2,4-isodithiobiuret (IVb)

Yield (1.8g, 56%), R_f 0.88 ($CC1_4$: n-hexane, 1:3), m.p. 120-122°C, $[\alpha]^{36}_D$ +81.02° (c, 0.74 in $CHCl_3$), [found: C, 55.74; H, 5.35; N, 6.44; S, 9.87; $C_{30}H_{35}O_9N_3S_2$ requires, C55.81; H, 5.42; N, 6.51; S, 9.92%].

1- tetra-O-acetyl-β-D-galactopyranosyl-5-m-tolyl-2-S-benzyl-2,4-isodithiobiuret (IVc)

Yield (2g, 63%), R_f 0.81 ($CC1_4$: n-hexane, 1:3.5), m.p. 115-117°C, $[\alpha]^{36}_D$ +17.11° (c, 0.8 in $CHCl_3$), [found: C, 55.72; H, 5.47; N, 6.58; S,10.01; $C_{30}H_{35}O_9N_3S_2$ requires, C55.81; H, 5.42; N, 6.51; S, 9.92%].

1- tetra-O-acetyl-β-D-galactopyranosyl-5-p-tolyl-2-S-benzyl-2,4-isodithiobiuret (IVd)

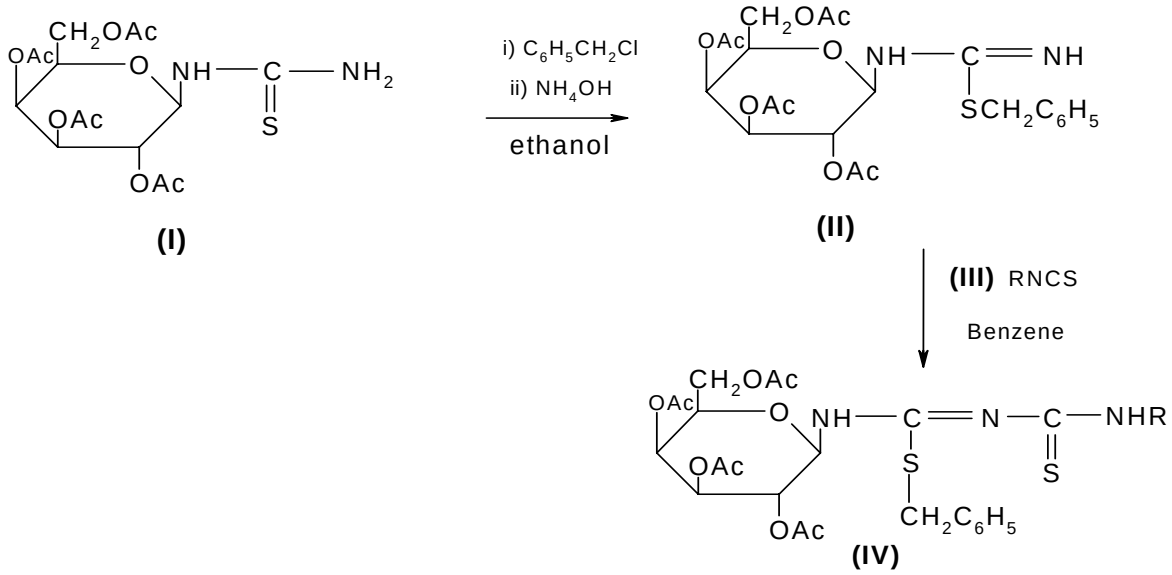
Yield (1.7g, 53%), R_f 0.79 ($CC1_4$: n-hexane, 1:3), m.p. 158-160°C, $[\alpha]^{36}_D$ +43.79° (c, 0.9 in $CHCl_3$), IR (KBr, cm^{-1}): ν 3326(N-H), 1750(C =O), 1369(C-N), 1224(C-O), 1050(C=S), 913(β –D- galactopyranosyl ring deformation). ^{1}H NMR ($CDCl_3$): δ 7.6-6.8 (m, 11H,2 NH, Ar-H); 5.7-3.9(m, 9H, galactopyranosyl ring protons, $2CH_2$); 2.49(m, 3H,Ar-CH_3), 2.13-1.91 (m,12H,4$COCH_3$). m/s(m/z): 645(M^+), 646(M^++1), 554(M^+-$CH_2C_6H_5$,100%), 331(Characteristic of glycopyranose), 91($C_7H_7^+$). [found: C, 55.72; H, 5.33; N, 6.44; S, 9.86; $C_{30}H_{35}O_9N_3S_2$ requires, C55.81; H, 5.42; N, 6.51; S, 9.92%].

1-tetra-O-acetyl- β -D-galactosly-5-m-cl-phenyl-2-S-benzyl-2,4-isodithiobiuret (IVe)

Yield (1.8g, 55%), R_f 0.8 ($CC1_4$: n-hexane, 1:2.5), m.p. 123-125°C, $[\alpha]^{36}_D$ +36.6° (c, 0.91 in $CHCl_3$), IR (KBr, cm^{-1}): ν 3313(N-H), 1750(C =O), 1572(C=N), 1369(C-N), 1224(C-O), 1049(C=S), 901 (β –D-galactopyranosyl ring deformation). ^{1}H NMR ($CDCl_3$): δ 7.55-7.12 (m, 11H, 2 NH, Ar – H); 5.42 – 4 .11(m , 9H, galactopyranosyl ring protons, $2CH_2$); 2.16 – 1 .93 (m, 12H, 4$COCH_3$). m/s(m/z): 665(M^+), 667(M^++2, 100%), 575(M^++1-$CH_2C_6H_5$,), 331(Characteristic of glycopyranose), 91($C_7H_7^+$). [Found: C, 52.28; H, 4.86; N, 6.22; S, 9.59; $C_{29}H_{32}O_9N_3S_2Cl$ requires, C, 52.33; H, 4.96; N, 6.31; S, 9.62%].

1 – tetra – O – acetyl – β – D – galactopyranosyl – 5 – o – methoxy phenyl – 2 – S – benzyl – 2 4 – isodithiobiuret (IVf)

Yield (1.7g, 51%), R_f 0.81 ($CC1_4$: n-hexane, 1:4), m.p. 110-112°C, $[\alpha]^{36}_D$ -96.06° (c, 0.86 in $CHCl_3$), [Found : C; 54.51; H, 5.39; N, 6.41;S, 9.59, $C_{30}H_{35}O_{10}N_3S_2$ requires, C,54.4; H, 5.29; N, 6.35; S, 9.68%].



R = a)phenyl, b) o-tolyl, c) m-tolyl, d) p-tolyl , e) m – Cl – phenyl, f) o - methoxy phenyl, Ac = $COCH_3$,

Scheme - 1

Antimicrobial Activity

All the compounds IV a-f were screened for their antimicrobial activities by cup-plate agar diffusion method [13-18], against various pathogenic bacteria like E. *coli*, S. *aureus*, P. v*ulgaris* and P. *aregenosa* and fungi like A. *niger* and C. *albicans* at a concentration of 100 µg/ml (MIC) in DMSO against standards Amikacin and fluconazole for antibacterial and antifungal activities respectively at same concentration. The zone of inhibition is measured in mm and readings are tabulated in table-1.

Table 1: Antimicrobial activities of Compounds (IV a- f)

Compound	Antibacterial activity				Antifungal activity	
	S. aureus	**E. *Coli***	**P. *vulgaris***	**P. *aregenosa***	**A. *niger***	**C. *albicans***
IVa	24	21	21	22	19	21
IV b	26	26	28	27	21	10
IV c	-	21	29	20	19	19
IV d	28	25	17	25	18	18
IV e	24	23	22	23	17	-
IV f	25	-	-	23	-	-
Amikacin	21	23	23	22	-	-
Fluconazole	-	-	-	-	15	15

From the table it was observed that, compounds IIIb, IIId,IIIe are active against the bacteria and fungi while all other compounds show low to moderate activity against the said microorganisms as compared to the standard drugs.

CONCLUSIONS

Thus a new series of N-galactopyranosyl isodithiobiurets having potential antimicrobial activities have been synthesized by using simple conventional method of S- benzylation.

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