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SYNTHESIS AND BIOLOGICAL EVALUATION OF SOME NOVEL PER-*O*-ACETYLATED GLUCOSYL -2-ISOTHIOBIURETS

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ABSTRACT

Carbohydrates play an important role in vast array of biological processes and particularly there are many advantages, for example carbohydrate based drugs show low toxicity and immunogenicity, thus the interest in their preparation is very high. They play a pivotal role in the preparation of a broad series of functional group such as amide, isonitrile, carbodimide. The chemistry of *N*-glucosylated isothiobiurets showed many applications in medicinal chemistry and in many other ways. So it was interesting to study the synthesis and antimicrobial activity of newly prepared various *N*-glucosylated isothiobiurets. In the present investigation, a series of 2-*S*-tetra-*O*-acetyl-β-D-galactosyl-1-aryl-5-tetra-*O*-acetyl-β-D-glucosyl-2-isothiobiurets have been synthesized with the interaction of *S*-tetra-*O*-acetyl-β-D-galactosyl-1-arylisothiocarbamides and tetra-*O*-acetyl-β-D-glucosyl isocyanate. The required *S*-tetra-*O*-acetyl-β-D-galactosyl-1-arylisothiocarbamides have been prepared by the reaction of tetra-*O*-acetyl-α-D-galactosyl bromide and various aryl thiocarbamides. All these newly synthesized compounds were screened for their antibacterial and antifungal activity against various pathogenic strains like *E. coli , P. vulgaris, S. aureus, P. aeruginosa, A. niger and Penicillium.* Result showed that most of compounds possess promising activity. The identities of these newly synthesized compounds have been established on the basis of usual chemical transformations and IR, ^{1}H NMR and Mass spectral analysis.

Key word:Synthesis, glucosyl isocyanate, galactosyl isothiocarbamides, isothiobiurets.

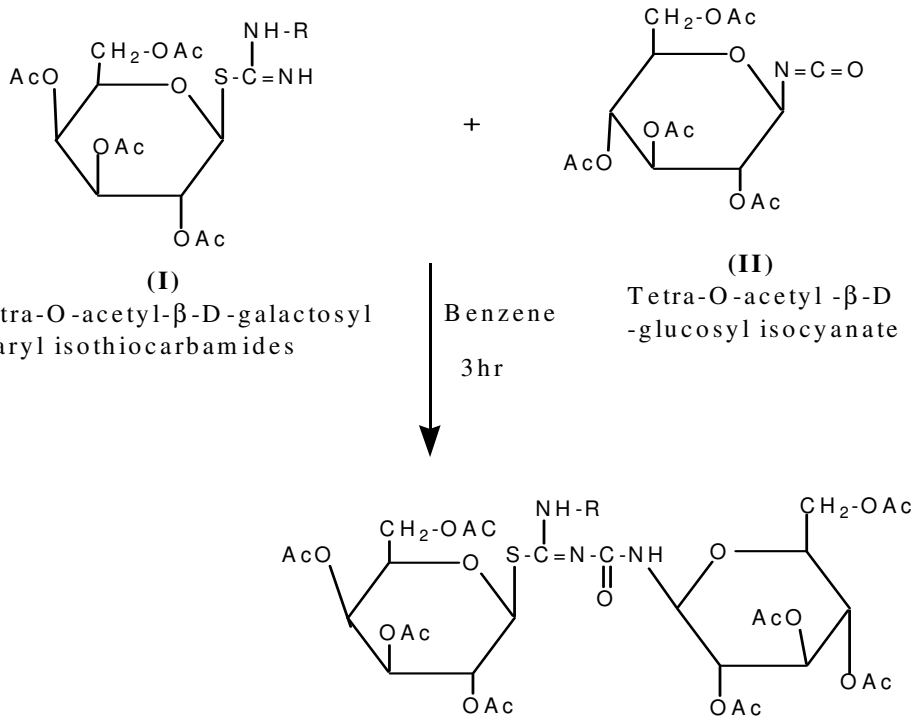
INTRODUCTION

The chemistry and biology of carbohydrates is an emerging field of interest, especially in this postgenomic era. The mechanisms of these events are, however, not well understood and most recent efforts in the field are to develop new tools for use to understand the molecular-level carbohydrate recognition and to enable the carbohydrate-based drug discovery process. The emergence of antibiotic resistance is a growing problem in the treatment of infectious diseases. Some other gram-positive bacteria has encountered resistance and this new public health crisis has renewed the interest in antibacterial development.

Current strategies for tackling the problem of antibiotic resistance generally involve chemical modification of existing antibiotics to resist these mechanisms or development of new types of antibiotics. Our interest in the field is to develop new antibiotics that target unique carbohydrates or carbohydrate-utilizing compounds in bacteria and resist the resistance development.

Several *S*-glucosylated isothiobiurets with potential microbial activities have been reported[1]. Glucosyl isocynate and isothiocyanate[2], likewise other glycosyl isocyanates has a significant role in synthetic Carbohydrate Chemistry. Many compounds have been synthesized by the use of glycosyl isocyanate, for example, galactosyl isocyanide[3], galactosyl amino derivatives[4] and other heterocycles[5].But there is no report on the synthesis of isothiobiurets having a β - glucosyl substituent. On the basis of knowledge gained on the work done on *N*- glucosylated isomonothio and dithiobiurets[6-7], it was quite interesting to synthesize some new *N*- glucosylated isothiobiurets. In the present investigation, a series of 2-*S*-tetra-*O*-acetyl-β-D-galactosyl-1-aryl-5-tetra-*O*-acetyl-β-D-glucosyl-2-isothiobiurets have been synthesized with the interaction of *S*-tetra-*O*-acetyl-β-D-galactosyl-1-arylisothiocarbamides and tetra-*O*-

acetyl-β-D-glucosyl isocyanate. All the products obtained have been crystallized form alcohol .IR spectra of the products show characteristic absorption of prominent peaks,[1]H NMR spectra shows characteristics peaks due to N-H, acetyl and glycosidic protons, while the ESI Mass spectra shows peaks due to acetoglucose unit[8-11].



(I)
S-tetra-O-acetyl-β-D-galactosyl -1-aryl isothiocarbamides

(II)
Tetra-O-acetyl -β-D -glucosyl isocyanate

(III)
2-S-tetra-O-aceryl-β-D-galactosyl -1aryl-5-tetra-O-acetyl-β-D-glucosyl -2-isothiobiurets

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. Ac = -$COCH_3$

EXPERIMENTAL

General methods

Melting points are uncorrected. Optical rotations $[\square]_D$ were measured on a Equip-Tronics digital polarimeter model no. EQ 800 in $CHCl_3$ at 39^0C. IR spectra were recorded on a Perkin-Elmer spectrum RXI (4000-450cm^{-1}) FTIR spectrometer. ^{1}HNMR 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. The mass spectra were recorded on a Micromass Quattro II triple quadruple mass spectrometer.

Preparation of S-tetra-*O*-acetyl-β-D-galactosyl-1-aryl-isothiocarbamides (1a-g)

The isopropanolic suspension of tetra-O-acetyl-α-D-galactosyl bromide (0.014 M 6.0g in 20 ml) was mixed with the isoproponalic suspension of Phenyl thiocarbamide (0.014 M, 2.22 g in 10 ml). This mixture was warmed at 70°C until the clear solution was obtained. This clear solution was then kept at room temperature for 18 hr. Then it was mixed with distilled water (100 ml). Some semisolid mass was separated. It was identified as unreacted phenyl thiocarbamide, m.p 152°C.

The aqueous filtrate was acidic to litmus and gave brisk effervescences with sodium bicarbonate solution. It was non-desulphurisable when boiled with alkaline plumbite.

The aqueous solution when basified with aqueous ammonia a sticky mass was separated out which was not solidified on standing for several hours. The sticky mass was failed to afford a solid when triturated several times with petroleum ether. The sticky mass was purified by ethanol-water and solid was obtained.

Tetra-*O*-acetyl –β-D- glucosyl isocyanate[12] (2)

Tetra-*O*-acetyl- β –D- glucosyl isocyanate (**2**) was prepared by interaction of Tetra-O-acetyl-α-D-glucosyl bromide and lead cyanate in anhydrous xylene medium[11].

Table-1: Synthesis of 2-S-tetra-O-acetyl- β -D-galactosyl-1-aryl-5-tetra-O-acetyl- β -D-glucosyl-2-isothiobiurets (III).

S. No.	S-tetra-O-acetyl- β -D-galactosyl-1-aryl isothiocarbamides (I)	2-S-tetra-O-acetyl- β -D-galactosyl-1-aryl-5-tetra-O-acetyl- β -D-glucosyl-2-isothiobiurets (III)	Yield (%)	M.P. (°C)
1	…1-phenyl…. (Ia)	…1-phenyl… (IIIa)	92.20	90-95
2	…1-o-Cl-phenyl… (Ib)	…1-o-Cl-phenyl… (IIIb)	88.51	140-145
3	…1-m-Cl-phenyl…(Ic)	…1-m-Cl-phenyl…(IIIc)	91.40	131-135
4	…1-p-Cl-phenyl… (Id)	…1-p-Cl-phenyl… (IIId)	82.20	122-124
5	…1-o-tolyl…. (Ie)	…1-o-tolyl… (IIIe)	86.51	125-130
6	…1-m-tolyl …. (If)	…1-m-tolyl… (IIIf)	81.30	140
7	…1-p-tolyl …. (Ig)	…1-p-tolyl… (IIIg)	74.20	110-112

Table -2: Antimicrobial activities of 2-S-tetra-O-acetyl- β -D-galactosyl-1-aryl-5-tetra-O-acetyl- β -D-glucosyl-2-isothiobiurets

Compounds	*E.coli*	*P.vulgaris*	*S.aureus*	*P.aeruginosa*	*A.niger*	*Penicillium*
III –a	+++	+++	++	+++	++	++
III –b	+++	++++	++++	++++	+++	++
III –c	+++	++++	++++	++++	+++	++
III –d	+++	++++	++++	++++	+++	++
III –e	++	++++	++++	++++	++	--
III –f	++	+++	+++	+++	++	--
III –g	++	++++	++++	++++	--	--

Synthesis of 2-S-tetra-O-acetyl- β -D-galactosyl-1-aryl-5-tetra-O-acetyl- β -D-glucosyl-2-isothiobiurets (IIIa-g)

Benzene solution of Tetra-O-acetyl- β -D-glucosyl isocyanate (0.005 M, 1.9 g in 20 ml) was added to benzene solution of S-tetra-O-acetyl- β -D-galactosyl-1-phenyl isothiocarbamide (0.005 M, 2.2 g in 10 ml) and the reaction was refluxed over boiling water bath for 4 hr. Afterwards, solvent benzene was removed by distillation and resultant syrupy mass was triturated several times with petroleum ether, a granular solid was obtained, crystallized from ethanol-water, m.p. 90-95°C.

2-S-tetra-O-acetyl- β -D-galactosyl-1-phenyl-5-tetra-O-acetyl- β -D- glucosyl-2- isothiobiuret(3a).

IR (KBr) : υ 3354 (N-H); 2966 (Ar-H); 1746 (C=O); 1597 (C = N) 1375 (C-N); 1232 (C-O);941 (D-glucose ring deformation). ^{1}HNMR ($CDCl_3$) : δ 8.3- 7.3 (Ar-H); 6.26 (N-H); 5.5-4.2 (m, 7H, glucosyl ring); 2.5-1.6 (m, 12H, $4COCH_3$).ESI Mass (M/z) : 855.4 (M^+.+1), 331, 271, 169, 109. Anal. Calcd. for $C_{36}H_{44}O_{19}N_3S$: C, 50.58, H, 5.15; N, 4.91, S, 3.74 Found: C, 50.42; H, 5.22; N, 4.82; S, 3.65, %].

2-S-tetra-O-acetyl- β -D-galactosyl-1-o-Cl-phenyl-5-tetra-O-acetyl- β-D- glucosyl-2-isothiobiuret(3b)

IR (KBr) : υ 3455 (N-H); 2966 (Ar-H); 1746 (C=O); 1588 (C = N) 1378 (C-N); 1234 (C-O); 941(D-glucosyl ring deformation).^{1}HNMR ($CDCl_3$) : δ 7.8-7.1 (Ar-H.) ; 6.30 (N-H); 5.5-3.8 (m, 7H, glucosyl ring); 2.2-1.4 (m,12H,$4COCH_3$). ESI Mass (M/z) : 888(not located) (M^+.), 331, 271, 169, 109, Anal. Calcd. for $C_{36}H_{43}O_{19}N_3SCl$: C, 48.64; H, 4.95; N, 4.72; S, 3.60 . Found : C, 48.16; H, 4.50; N, 4.52; S, 3.76;, %.

Synthesis 2-S-tetra-O-acetyl- β -D-galactosyl-1-o-tolyl-5-tetra-O-acetyl- β -D-glucosyl-2- isothiobiuret(3e)

IR (KBr) : υ 3381 (N-H); 2966 (Ar-H); 1745 (C=O); 1593 (C = N) 1377 (C-N); 1233 (C-O); 941(D-glucosyl ring deformation).^{1}HNMR ($CDCl_3$) : δ 8.2-7.5 (Ar-H.) ; 6.30 (N-H); 5.5-4.1 (m, 7H, glucosyl ring); 2.2-1.6

(m,12H,4COCH$_3$). ESI Mass (M/z) : 868(not located) (M^+.), 331, 271, 169, 109Anal. Calcd. for $C_{37}H_{48}O_{19}N_3S$: C, 51.30; H, 5.51; N, 4.82; S, 3.67 Found : C, 52.10; H, 5.40; N, 4.78; S, 3.60 %.

RESULTS AND DISCUSSION

A several 2-*S*-tetra-*O*-acetyl-β-D-galactosyl-1-aryl-5-tetra-*O*-acetyl-β-D-glucosyl-2-isothiobiurets (**3a-g**) have been synthesized with the interaction of *S*-tetra-*O*-acetyl-β-D-galactosyl-1-arylisothiocarbamides(**1a-g)** and tetra-*O*-acetyl-β-D-glucosyl isocyanate **(2)** in benzene for 3hr. The reaction was monitored by TLC, after complete reaction, the solvent was distilled off and the resultant sticky residue was triturated with petroleum ether (60-80^{0}C) to afford the products (**3a-g**). All the products were crystallized from alcohol. Structures of all products synthesized were established on the basis of usual Chemical transformations and IR, NMR and Mass spectral studies.

Antibacterial activity

These compounds were screened for their *in vitro* antimicrobial activities against gram positive bacteria viz. *S. aureus* and gram negative bacteria viz. *E. coli, P. vulgaris, P. aeruginosa*. Amikacin was used as a positive control for bacteria. Compounds 3a, 3d exhibited comparable inhibitory activity as compared to the control against *S. aureus* whereas others showed moderate to less activity. 3c and 3f showed inhibition as good as control drug against *P. aeruginosa* and 3a was inactive. Other compounds showed moderate to less activity while some were inactive Table 2.

Antifungal Activity

The synthesized compounds have also been evaluated for their antifungal activity against two representative fungi *viz.*, *Penicillium* and *A. niger* by cup plate agar diffusion method using Fluconazole as standard drug. Compounds 3g exhibited comparable activity against *A. niger* and others were moderately active against fungi. Although the rest of the compounds showed varying degree of inhibition, none were as effective as Fluconazole Table 2.

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