SYNTHESIS AND ANTIMICROBIAL STUDIES OF NEW 2-*S*-TETRA-*O*-ACETYL-β-D-GLUCOPYRANOSYL-1-ARYL-5-HEPTA-*O*-ACETYL-β-D-MALTOSYL-2-ISOTHIOBIURETS

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ABSTRACT:-
2-*S*-tetra-*O*-acetyl-β-D-glucopyranosyl-1-aryl-5-hepta-*O*-acetyl-β-D-maltosyl-2-isothiobiurets have been synthesized for the first time by the interaction of *S*-tetra-*O*-acetyl-β-D-glucosyl-1-aryl-isothiocarbamides and hepta-*O*-acetyl-β-D-maltosyl isocyanate. All the synthesized compounds were characterized on the basis of elemental analysis and IR, ^{1}HNMR and Mass spectral studies. The polarimetric study of the title compounds have been carried out and evaluated for their in vitro antimicrobial activities using standard cup plate method against bacteria *E.coli, P. aeruginosa*, *P.vulgaris, S.aureus* and fungi *A.niger, C. albicans.*
Key words: Isothiobiurets, Maltosyl Isocyanate, Isothiocarbamides, Antimicrobial.

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Introduction:

Several *S*-glucosylated isothiobiurets with potential microbial activities have been reported [1]. These isothiobiurets were prepared by the interaction of *S*-tetra-*O*-benzoyl-D-glucopyranosyl-1-aryl isothiocarbamides and phenyl isocyanate [2]. Also recently in our laboratory work has been done on the synthesis of *N* and *S*-linked bis lactosyl isothiobiurets involving the interaction of *S*-hepta-O-acetyl-β-D-lactosyl-1-aryl-isothiocarbamides and hepta-*O*-acetyl-β-D-lactosyl isocyanate[3]. Recently several lactosyl isothiocarbamides and lactosyl isocyanate are also reported to form corresponding lactosyl monothio and dithiobiurets [4-5].

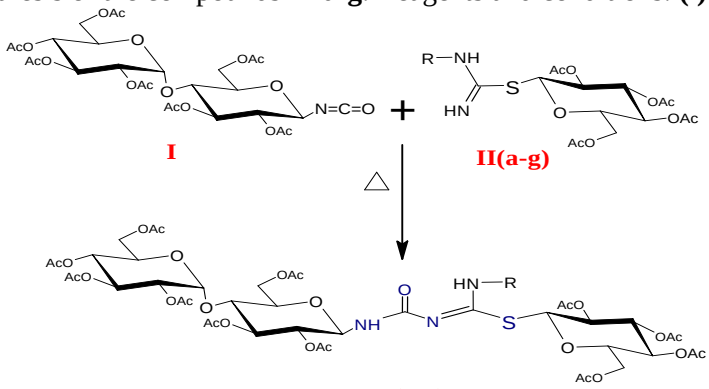
The aryl thiocarbamides because of their basic nature are known to react with alkyl / aryl isocyanate and produce corresponding-2-isothiobiurets [6-7]. It was interesting to study the chemistry of these glucosyl aryl isothiocarbamides with special reference to their reaction with hepta-*O*-acetyl-β-D-maltosyl isocyanate.

EXPERIMENTAL

Chemistry

Melting points were recorded on electrothermal melting point apparatus and are uncorrected. Specific rotations $[\alpha]_D$ were measured on Equip-Tronics digital polarimeter model no. EQ 800 at 30°c in chloroform. IR spectra were recorded on a Perkin-Elmer spectrum RXI (4000-450 cm^{-1}) FTIR spectrometer. ^1H NMR spectrum was obtained on a Bruker DRX-300 (300 MHz) NMR spectrometer using $CDCl_3$ solution with TMS as an internal reference. The Mass spectra were recorded on Jeol SX-102 mass spectrometer. Thin layer chromatography (TLC) was performed in E. Merck precoated Silica Gel G60 aluminum sheets. The elemental analyses (N, S) of all compounds were performed in laboratory.

Scheme 1. Synthesis of the compounds **IIIa-g**. Reagents and conditions: **(i)** Benzene, reflux, 4-5hrs.



2-*S*-tetra-*O*-acetyl-β-D-glucopyranosyl-1-aryl-5-hepta-*O*-acetyl-β-D-maltosyl-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 = $COCH_3$

General procedure for synthesis of *S*-tetra-*O*-acetyl-β-D-glucosyl-1-aryl isothiocarbamides were prepared in the isopropanolic solution of tetra-*O*-acetyl-α-D-glucosyl bromide (0.01M, 4.10g in 30ml) was added Phenyl thiocarbamides (0.01M, 1.52g). This mixture was warmed over water bath at 70°C until the clear solution was obtained. The clear solution was kept at room temperature for 18 hr. It was then mixed with cold water (100 ml), when small quantity of semisolid mass was separated. The semisolid mass was then triturated with petroleum ether was converted into solid.

General procedure for synthesis of 2-S-tetra-*O*-acetyl-β-D-glucopyranosyl-1-aryl-5-hepta-*O*-acetyl β-D-maltosyl-2-isothiobiurets.

2-S-tetra-*O*-acetyl-β-D-glucopyranosyl-1-aryl-5-hepta-*O*-acetyl β-D-maltosyl-2-isothiobiurets were synthesized in benzene solution of hepta-*O*-acetyl-β-D-maltosyl isocyanate (0.005M, 3.3g in 25ml) was added to *S*-tetra-*O*-acetyl-β-D-glucosyl-1-phenyl isothiocarbamide (0.005M, 2.41g) and reaction mixture was refluxed over boiling water bath for 4-5 hrs. Afterwards, solvent benzene was removed by distillation and resultant syrupy mass was triturated several times with petroleum ether, a granular solid was obtained. It was crystallized from ethanol-water.

2-*S*-tetra-*O*-acetyl-β-D-glucosyl-1-phenyl-5-hepta-*O*-acetyl-β-D-maltosyl-2-isothiobiuret (IIIa): IR (KBr, cm^{-1}): 3483 (N-H), 3068 (Ar-H), 1732 (C=O), 1603 (C = N), 1373 (C-N), 711 (C-S), 1032 & 907 (maltose unit), 803 (glucose unit) . ^1H NMR ($CDCl_3$) δ: 7.26 (m, 5H, Ar-H), 6.89 (s, 1H, NHCO), 5.37–3.17 (m, 14H, maltose unit), 2.14–2.02 (m, 33H, $11COCH_3$), 4.6–3.8 (m, 7H,

glucosyl protons). Mass m/z: 1144 (M+1), 1053, 812, 620, 560, 524, 331, 169, 109. (Anal. Calcd for $C_{48}H_{61}O_{27}N_3S$).

2-*S*-tetra-*O*-acetyl-β-D-glucosyl-1-*m*-Cl-phenyl-5-hepta-*O*-acetyl-β-D-maltosyl-2-isothiobiuret (IIIc): IR (KBr, cm^{-1}): 3468 (N-H), 3010 (Ar-H), 1748 (C=O), 1651 (C = N), 1376 (C-N), 689 (C-S), 1030 & 944 (maltose unit), 901 (glucose unit) . ^{1}H NMR ($CDCl_3$) δ: 7.36-7.29 (m, 4H, Ar-H), 5.59 (s, 1H, NH), 5.54–3.39 (m, 21H, glucosyl unit), 2.15–2.02 (m, 33H, $11COCH_3$). Mass m/z: 1178 (M+1), 1053, 847, 620, 560, 559, 331, 169, 109. (Anal. Calcd for $C_{48}H_{60}O_{27}N_3SCl$).

2-*S*-tetra-*O*-acetyl-β-D-glucosyl-1-*p*-tolyl-5-hepta-*O*-acetyl-β-D-maltosyl-2-isothiobiuret (IIIg): IR (KBr, cm^{-1}): 3497 (N-H), 3048 (Ar-H), 1749 (C=O), 1654 (C = N), 1379 (C-N), 764 (C-S), 1041 & 899 (maltose unit), 809 (glucose unit). ^{1}H NMR ($CDCl_3$) δ: 7.45–7.26 (m, 4H, Ar-H), 6.98 (s, 1H, NH), 4.5–3.17 (m, 21H, glucosyl unit), 2.61–2.02 (m, 33H, $11COCH_3$), 2.26 (s, 3H, CH_3 protons). Mass m/z: 1158 (M+1), 1053, 827, 620, 560, 331, 109. (Anal. Calcd for $C_{49}H_{63}O_{27}N_3S$).

Table 1: Physical characterization and analytical data of synthesized compounds IIIa-g.

Compd.	m.p. ^{0}C	Yield %	$[\alpha]_D^{29}$ [c,0.01 in $CHCl_3$]	Rf EtOA:Hexane 1:1	Found (calcd) % N	S
IIIa	140-141	78.65	+59.57°	0.91	3.65 (3.67)	2.34 (2.79)
IIIb	119-122	81.73	+63.32^0	0.89	3.57 (3.56)	2.64 (2.71)
IIIc	135-136	67.08	+49.92°	0.87	3.55 (3.56)	2.65 (2.71)
IIId	112-118	78.26	+57.26°	0.86	3.54 (3.56)	2.68 (2.71)
IIIe	172-174	72.00	+93.08°	0.73	3.59 (3.63)	2.74 (2.93)
IIIf	180-184	70.17	+74.37°	0.79	3.64 (3.63)	2.74 (2.93)
IIIg	201-202	73.56	+64.58°	0.77	3.63	2.76

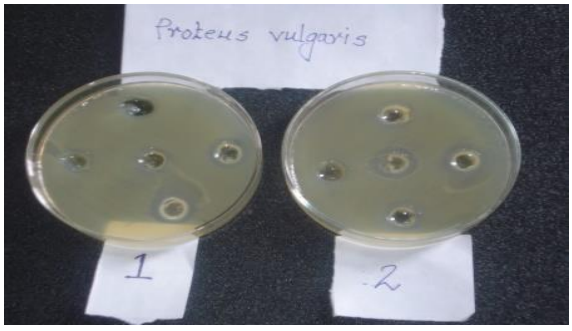
ANTIBACTERIAL /ANTIFUNGAL ACTIVITY

The antimicrobial activities of newly synthesized compounds were tested in vitro against bacteria *E.coli* (MTCC 1680), *P. aeruginosa* (MTCC 7197), *P.vulgaris* (MTCC 1771), *S.aureus* (MTCC 3160) and clinically isolated fungi *A.niger*, *C. albicans* by cup plate agar diffusion method[8]. After incubation at 35^{0}c for 24h for bacteria and for fungi the plates were incubated at 30^{0}c for 24-48h, the diameters of the inhibition zones were measured in millimeters[9]. The compounds were taken at a concentration of 1mg/mL and compared with Gentamicin and Fluconazole as a positive control for different strains of bacteria and fungi for antibacterial and antifungal activities respectively (**Table 2**). The compounds 2-S-tetra-*O*-acetyl-β-D-glucopyranosyl-1-aryl-5-hepta-*O*-acetyl-β-D-maltosyl-2-isothiobiurets **(IIIa-g)** show weak to moderate activity against used micro-organism. The compounds IIIa-d and IIIf showed good activity against *S. aureus*, *P. vulgaris* and *P. aeruginosa* while other showed moderate and weak activity against used micro-organism.

Table 2: Antibacterial and antifungal activities of synthesized compounds **IIIa-g.**

Compd.	Bacteria				Fungi	
	E.coli (MTCC 1680)	*P. aeruginosa* (MTCC 7197)	*P.vulgaris* (MTCC 1771)	*S.aureus* (MTCC 3160)	*A.niger* (clinically isolated)	*C. albicans* (clinically isolated)
IIIa	21	19	15	20	15	21
IIIb	15	20	16	21	15	22
IIIc	20	20	16	20	11	22
IIId	16	17	16	10	10	18
IIIe	15	21	---	22	---	21
IIIf	15	15	16	15	11	15
IIIg	10	16	8	16	11	---
Gentamicin	24	20	23	24	---	---
Fluconazole	---	---	---	---	20	18

(Diameter of inhibition zone, measured in mm[a])
Bore size =7mm
--- No activity was observed.
[a] values are the average of three readings.



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