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SYNTHESIS AND ANTIMICROBIAL EVALUATION OF *S*-HEPTA-*O*-ACETYL MALTOSYL-1 ARYLISOTHIOCARBAMIDES

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ABSTRACT

A novel series of several *S*-hepta-*O*-acetyl maltosyl-1-arylisothiocarbamides (III) have been synthesized by the interaction of hepta-*O*-acetyl maltosyl bromide (I) with aryl thiocarbamides (II) in isopropanolic medium. The identities of these newly synthesized *S*-maltosides have been established on the basis of usual chemical transformations and IR, ^{1}H NMR and Mass spectral studies. The polarimetric study of the compounds has been carried out. Antibacterial and antifungal activities of these compounds were determined on *E. coli, S. aureus, Ps. aeruginosa, S. typhi, R. oligosporus* and *A. niger.* These compounds show appreciable activity towards these micro-organisms.

Keywords: Hepta-*O*-acetyl maltosyl bromide, aryl thiocarbamides, arylisothiocarbamides, antimicrobial evaluation.

INTRODUCTION

Thiourea and its derivatives are a group of compounds possessing a wide spectrum of biological activities such as anticonvulsant[1], herbicidal[2] and it is versatile reagent in organic synthesis. Also thiomaltosides are an important constitute of carbohydrate chemistry. The glycosyl thioureide derivatives have *S*-linked or *N*-linked function and have several applications in medicinal chemistry such as antifungal[3], anticancer[4], antiviral[5] and antimalerial activities[6]. The synthesis and pharmacological evaluation of various thioglycosides have been well documented[7-8].

In view of applications of *S*-maltosylated compounds, we report the synthesis of *S*-hepta-*O*-acetyl maltosyl-1-arylisothiocarbamides **(IIIa-f)** by the interaction of hepta-*O*-acetyl maltosyl bromide **(I)** and aryl thiocarbamides **(IIa-f)**.

EXPERIMENTAL

All the melting points recorded using open capillary tube on Mac digital melting point apparatus and were found to be uncorrected. The structures of newly synthesized compounds were confirmed on the basis of elemental and spectral analysis. The IR spectra of the compounds were recorded in KBr Disks on SHIMADZU IR affinity-1-FTIR spectrometer. ^{1}H NMR spectra are run on Brucker DRX-300 instrument operating at 300 MHz using $CDCl_3$ solution with TMS at internal standard. The mass spectrum was recorded on an Agilent 6520-QTOF LCMS having an ESI source in positive mode Mass Spectrometer. Specific rotations were measured on Equip-Tronics EQ-801 Digital Polarimeter in $CHCl_3$. To check purity thin layer chromatography was performed on E. Merck pre-coated silica gel plates and spot were visualized by iodine vapours.

Materials and methods

The reagents required for the synthesis of *S*-maltosides are as follows:

1. ***Synthesis of Hepta-O-acetyl maltosyl bromide***[9] **(I)**

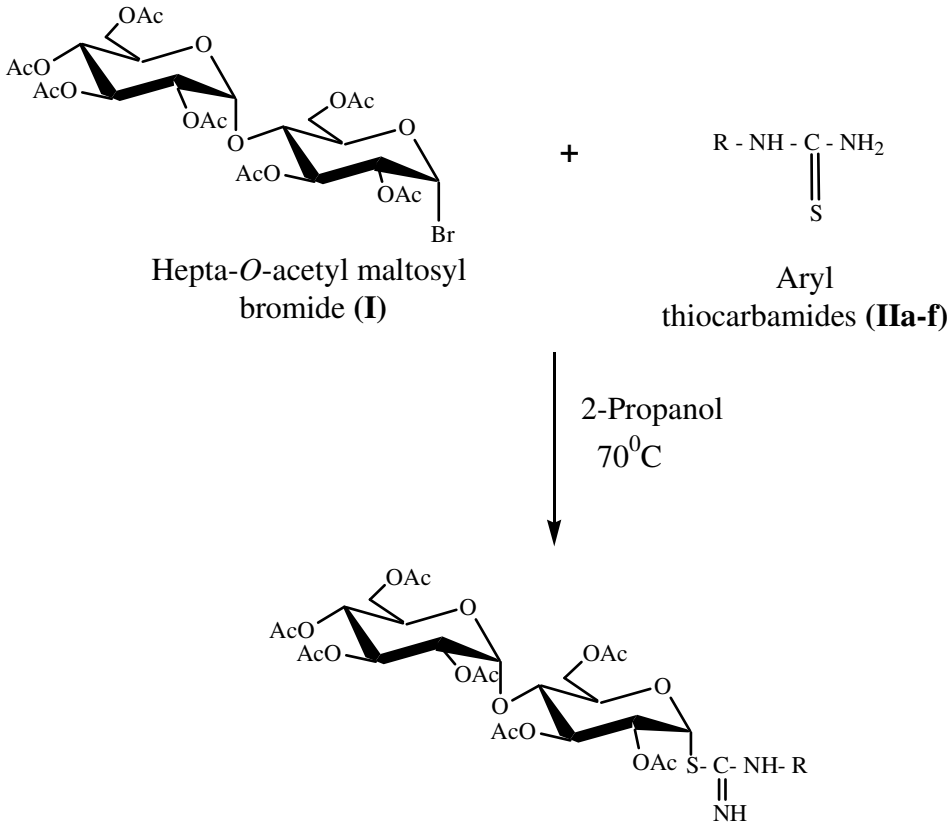
Hepta-*O*-acetyl maltosyl bromide was prepared by the interaction of maltose octaacetate with brominating reagent.

2. ***Synthesis of Aryl thiocarbamides***[10] **(IIa-f)**

Aryl thiocarbamides were prepared by the interaction of aryl amines, conc. HCl and ammonium thiocyanate.

3. ***Synthesis of Hepta-O-acetyl maltosyl-1-aryl-isothiocarbamides*** **(IIIa-f)**

Isopropanolic suspension of hepta-*O*-acetyl maltosyl bromide and aryl thiocarbamides was heated on water bath at about 70°C until the suspension gets cleared. The clear solution was then kept at room temperature for 18 hours. The aqueous solution was basified with ammonium hydroxide afforded a sticky mass which was not solidified on standing for several hours. The sticky mass was purified by ethanol-water and solid was obtained.



Hepta-*O*-acetyl maltosyl bromide **(I)**

Aryl thiocarbamides **(IIa-f)**

S-hepta-*O*-acetyl maltosyl-1-aryl isothiocarbamides **(IIIa-f)**

Where, R = (a) Phenyl, (b) *o*-tolyl, (c) *p*-totyl, (d) *o*-Cl-phenyl, (e) *m*-Cl-phenyl, (f) *p*-Cl-phenyl
Ac = $-COCH_3$

Scheme-1

RESULTS AND DISCUSSION

Isopropanolic suspensions of hepta-*O*-acetyl maltosyl bromide (0.005M, 3.5 gm, 20 ml) **(I)** was mixed with an isopropanolic suspension of phenyl thiocarbamide (0.005M, 0.76 gm, 10 ml) **(IIa)**. This mixture was heated on water bath at 70°C, until the suspension gets cleared. The clear solution was then kept at room temperature for 18 hours. It was then mixed with 100 ml distilled water. This aqueous solution was acidic and non-desulphurisable when boiled with alkaline plumbite solution.

The aqueous solution was basified with NH_4OH afforded sticky mass which was not solidified on standing for several hours. This sticky mass was failed to afford solid when triturated several times with petroleum ether. The sticky mass was purified by ethanol-water and solid was obtained, m.p. = 142-145°C. The solid gave charring test and non-desulphurisable .The purity of compounds was checked by TLC and its R_f value was found to be 0.82 (6:4 EtOAc: Pet. Ether). Optical rotation of the product was also recorded. Its specific rotation was found $[\alpha]^{31}_D = -122.44^o$(c, 0.098 gm in $CHCl_3$).

The IR, ^{1}H NMR, Mass spectral analysis[11-15] and elemental analysis (Table-1) clearly indicated the product and assign the structure as *S*-hepta-*O*-acetyl maltosyl-1-phenyl isothiocarbamide **(IIIa)**
When the reaction of hepta-*O*-acetyl maltosyl bromide **(I)** was extended to other aryl thiocarbamides **(IIb-f)** the related *S*-hepta-*O*-acetyl maltosyl-1-arylisothiocarbamides **(IIIb-f)** were obtained.

Antimicrobial studies

All the compounds have been screen for both antimicrobial and antifungal activity using cup plate agar diffusion method[16-17] by measuring the inhibition zone in mm. The compounds were taken at a concentration of 1 mg/ml using Dimethyl Sulphoxide (DMSO) as solvent. Amikacin (100 µg/ml) was used as standard for antibacterial activity and Fluconazole (100 µg/ml) as standard for antifungal activity. The compounds were screen for antibacterial activity against *Escherichia coli, Staphylococcus aureus, Pseudomonas aeruginosa* and *Salmonella typhi species* by using Nutrient Agar medium and antifungal activity against *Rhizopus oligosporus* and *Aspergillus niger species* was determined by using Potato Dextrose Agar medium. These sterilized agar media were poured into Petri dishes and allowed to solidify. On the surface of the media microbial suspensions were spread with the help of sterilized cotton swab.

Table-1: Characterization of *S*-hepta-*O*-acetyl maltosyl-1-arylisothiocarbamides (IIIa-f)

S. No.	*S*-hepta-*O*-acetyl maltosyl-1-aryl-isothiocarbamides	Yield (%)	M.P. (^{o}C)	R_f Value 6:4 EtOAc : Pet. Ether	$[\alpha]_D^{31}$ (c, in $CHCl_3$)	Elemental analysis (%) Found(Required)	
						N	S
1.	IIIa	38.01	142-145	0.82	-122.44^o (c, 0.098)	3.59 (3.63)	4.11 (4.15)
2.	IIIb	33.93	162-165	0.80	-97.82^o (c, 0.092)	3.52 (3.57)	4.00 (4.08)
3.	IIIc	41.08	160-162	0.81	-212.12^o (c, 0.099)	3.54 (3.57)	4.03 (4.08)
4.	IIId	35.71	173-175	0.78	+210.52^o (c, 0.095)	3.40 (3.48)	3.92 (3.98)
5.	IIIe	32.88	148-150	0.77	-195.87^o (c, 0.097)	3.42 (3.48)	3.95 (3.98)
6.	IIIf	39.68	153-157	0.74	+173.46^o (c, 0.098)	3.44 (3.48)	3.94 (3.98)

C and H analysis were found satisfactory in all cases.

Table-2: Antimicrobial activity of *S*-hepta-*O*-acetyl maltosyl-1-arylisothiocarbamides (IIIa-f)

Compounds	Antibacterial**				Antifungal**	
	E. coli	*S. aureus*	*S.typhi*	*Ps. aeruginosa*	*R. oligosporus*	*A. niger*
IIIa	16	22	14	12	22	14
IIIb	15	24	13	18	20	13
IIIc	15	25	12	15	16	12
IIId	14	28	14	13	21	14
IIIe	16	21	16	15	23	16
IIIf	17	22	15	14	24	15
Amikacin	20	29	20	24	-	-
Fluconazole	-	-	-	-	26	24

**zone of inhibition in mm (15 or less) resistance, (16-20mm) moderate and (more than 20mm) sensitive. *Escherichia coli* (*E.* coli), *Staphalococcus aureus* (*S.* aureus), *Salmonella typhi* (*S. typhi*), *Psudomonas auriginosa* (*Ps. auriginosa*), *Rhizopus oligosporus (R. oligosporus)* and Aspergillus *niger* (*A. niger*).

After inoculation the well was punched by using sterile stainless steel cork borer of 6mm diameter. In to these wells were added 0.1 ml portion of the test compounds in solvent. The drug solution was allowed to diffuse for an hour into the medium. The plate was incubated at 37°C for 24 hours and 30°C for 48 hours for antibacterial and for antifungal activities respectively. The zone of inhibition observed around the cups after respective incubation was measured. The results are presented in Table-2.

Antibacterial studies of these compounds indicated that all compounds exhibited most significant activity against *S. aureus*. IIIa, IIIe and IIIf show appreciable activity towards *E. coli*. IIIb is effective towards *Ps. aeruginosa* and IIIe show good activity against *S. typhi*. All the other compounds exhibited low to moderate activity.

The results of antifungal activities are also tabulated in Table-2. All compounds displayed promising activity against *R.oligosporus*. IIIe is effective towards *A. niger*. While other compounds inhibited moderate to low activity.

Spectral Analysis

IIIa: IR(KBr, cm^{-1}): ν 3427 (N-H)**,** 3020 (Aromatic C-H), 2958 (Aliphatic C-H), 1745 (C=O), 1514 (C=N), 1371 (C-N), 1238 (C-O), 1047, 943 (Characteristics of maltose), 713 (C-S); ^{1}H NMR ($CDCl_3$, ppm): δ 7.6-6.8 (5H, m, aromatic protons), δ 6.25-6.23 (2H, s, NH), δ 5.3-3.9 (14H, m, maltosyl protons), δ 2.2-2.0 (21H,m, acetyl protons); Mass (*m/z*): 771 ($M^{+\cdot}$ protonated), 712, 619, 559, 331, 271, 227 , 127. Anal. Calcd. for $C_{33}H_{42}O_{17}N_2S$: C, 51.42; H, 5.45; N, 3.63; S, 4.15%. Found: C, 51.39; H, 5.41; N, 3.59; S, 4.11%.

IIIc: IR(KBr, cm^{-1}): ν 3437 (N-H)**,** 3061 (Aromatic C-H), 2964 (Aliphatic C-H), 1745 (C=O), 1651 (C=N), 1371 (C-N), 1236 (C-O), 1043, 948, 875 (Characteristics of maltose), 711 (C-S); ^{1}H NMR ($CDCl_3$, ppm): δ7.2-6.9 (4H, m, aromatic protons), δ 6.104 (2H,s,NH), δ 5.5-3.7 (14H, m, maltosyl protons), δ 2.103-2.0 (21H, m, acetyl protons), δ1.254 (3H, s, methyl protons); Mass (*m/z*): 785 ($M^{+\cdot}$ protonated), 726, 619, 559, 331, 167, 124, 108. Anal. Calcd. for $C_{34}H_{44}O_{17}N_2S$: C, 52.04; H, 5.61; N, 3.57; S, 4.08%. Found: C, 52.01; H, 5.57; N, 3.54; S, 4.03%.

IIIf: IR(KBr cm^{-1}): ν 3415 (N-H)**,** 3188 (Aromatic C-H), 2972 (Aliphatic C-H), 1745 (C=O), 1620 (C=N), 1402 (C-N), 1236 (C-O), 1058, 1014, 948 (Characteristics of maltose), 688 (C-S);); ^{1}H NMR ($CDCl_3$, ppm): δ7.4-6.9 (4H, m, aromatic protons), δ6.15-6.0 (2H, s, NH), δ 5.3-3.9 (14H, m, maltosyl protons), δ 2.1-2.0 (21H, m,7-acetyl protons); Mass (*m/z*): 805 ($M^{+\cdot}$ protonated), 619, 559, 331, 271,187, 170, 128, 102. Anal. Calcd. for $C_{33}H_{41}O_{17}N_2SCl$: C, 49.25; H, 5.09; N, 3.48; S, 3.98%. Found: C, 49.21; H, 5.05; N, 3.44; S, 3.94%.

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