Int. J. Chem. Sci.: 13(3), 2015, 1529-1534
ISSN 0972-768X
www.sadgurupublications.com

BIOLOGICAL EVALUATION AND OPTICAL ACTIVITY OF SOME 1-ARYLISOTHIOCARBAMIDES

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ABSTRACT

Several *S*-hepta-*O*-benzoyl maltosyl-1-arylisothiocarbamides have been synthesized by the interaction of hepta-*O*-benzoyl maltosyl bromide and various aryl thiocarbamides. The identities of these newly synthesized compounds have been established on the basis of usual chemical transformation and IR, ^{1}H NMR and Mass spectral studies.

Carbohydrate derivatives bearing *N*- and *S*-linked functionalities at anomeric position are known for their various biological activities and in medicinal chemistry. This class of compounds has several applications such as antifungal, antitumor, anticancer, antiviral and antimalerial activity. In view of applications in industry and also in medicinal chemistry it appeared interesting to carry out synthesis for some novel thiomaltosides and to perform their biological evaluation.

Key words: Maltosyl bromide, Aryl thiocarbamides, Arylisothiocarbamides, Biological activity.

INTRODUCTION

Carbohydrates derivatives have been extensively investigated including synthesis, characterization and biological activity. Partly due to the facts that many natural occurring saccharides and synthesized analogues exhibit various and potent biological activities and they have been widely employed as agrochemicals and pharmaceuticals.

Carbohydrate derivatives bearing *N*- and *S*-linked functionalities at anomeric position are known for their various biological activities and in medicinal chemistry. This class of compounds has several applications such as antifungal[1], antitumor[2], anticancer[3], antiviral[4] and antimalerial activity[5]. Such significant values of Glycosides have focused our interest on the studies towards the *S*-Maltosylated compounds.

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In this communication, several *S*-hepta-*O*-benzoyl maltosyl-1-arylisothiocarbamides (III) have been reported and were prepared by the interaction of hepta-*O*-benzoyl maltosyl bromide[6] (I) and aryl thiocarbamides[7] (IIa-i).

EXPERIMENTAL

All the melting points recorded were found to be uncorrected. The structures of newly synthesized compound were confirmed on the basis of elemental and spectral analysis. IR spectra were recorded in KBr on a FTIR Perkin-Elmer (4000-450 cm^{-1}) spectrophotometer. ^1H NMR spectra are run on Brucker DRX-300 instrument operating at 300 MHz using $CDCl_3$ solution with TMS at internal standard and mass spectra on JEOL-AccuT of JMS-T100 LC mass spectrometer. Specific rotations were measured on Equip-Tronics EQ-800 Digital Polarimeter. Thin layer chromatography (TLC) was performed on silica gel G for TLC (Merck) and spot were visualized by iodine vapour.

IIIa: IR (KBr cm^{-1}): 3456 (N-H), 3067 (Aromatic C-H), 2966 (Aliphatic C-H), 1725 (C=O), 1603 (C=N), 1452 (C-N), 1273 (C-O), 1102 and 1032 (Characteristics of maltose), 710 (C-S); ^1H NMR ($CDCl_3$, ppm): δ 6.207-5.699 (2H, s, 2N-H), 8.047-7.028 (40H, m, Aromatic proton), 5.699-3.708 (14H, m, maltosyl proton); Mass (m/z):1249 ($M^+ + 1$), 1157 (M^+-C_3H_7O), 1115 (M^+-C_3H_3N), 1053 (HBM^+), 1026 (HBM^+-CO), 931 (HBM^+-C_6H_5COOH), 579 (TBG^+). (Found: C, 66.29; H, 4.46; N, 2.23; S, 2.55. $C_{69}H_{58}O_{18}N_2S$ Required: C, 67.77; H, 4.68; N, 2.32; S, 2.56 %)

IIIe: IR (KBr cm^{-1}): 3465 (N-H str.), 3067 (Aromatic C-H str.), 2968 (Aliphatic C-H str.), 1727 (C=O str..), 1602 (C=N str.), 1453 (C-N str.), 1272 (C-O str.), 1100, 1068 and 1029 (Characteristics of maltose), 710 (C-S str.); ^1H NMR ($CDCl_3$, ppm): δ 5.648-3.9 (2H, s, 2N-H), 8.123-7.232 (39H, m, Aromatic proton), 5.648-3.9 (14H, m, maltosylated proton); Mass (m/z): 1240 ($M^+ + 1$), 1157 (M^+-C_2H_5OCl), 1179 (M^+-$C_3H_3O_2$), 1088 (M^+-$C_7H_7N_2S$) 1053 (HBM^+), 1026 (HBM^+-CO), 931 (HBM^+-C_6H_5COOH), 579 (TBG^+). (Found: C, 65.75; H, 4.31; N, 2.18; S, 2.31. $C_{69}H_{58}O_{18}N_2S$ Required: C, 66.29; H, 4.46; N, 2.25; S, 2.55 %)

IIIh: IR (KBr cm^{-1}): 3448 (N-H str.), 3067 (Aromatic C-H str.), 2965 (Aliphatic C-H str.), 1727 (C=O str..), 1601 (C=N str.), 1452 (C-N str.), 1271 (C-O str.), 1098 and 1030 (Characteristics of maltose), 710 (C-S str.); ^1H NMR ($CDCl_3$, ppm): δ 6.082-6.244 (2H, s, 2N-H), 8.17-7.138 (39H, m, Aromatic proton), 5.921-4.24 (14 H, m, maltosylated proton), 1.88 (3H, s, CH_3); Mass (m/z):1254 ($M^+ + 1$), 1159 (M^+-$C_2H_4O_2$), 1117 (M^+-$C_2H_2O_2$), 1053 (HBM^+), 1026 (HBM^+-CO), 931 (HBM^+-C_6H_5COOH), 579 (TBG^+). (Found: C, 67.75; H, 4.61; N, 2.21; S, 2.51. $C_{69}H_{56}O_{19}N_2S$ Required: C, 66.02; H, 4.42; N, 2.23; S, 2.55 %)

Table 1: *S*-hepta-*O*-benzoyl maltosyl-1-arylisothiocarbamides (IIIa-i) (Scheme 1). Reactants-(i) Hepta-*O*-benzoyl maltosyl bromide (ii) Aryl thiocarbamides (IIa-i)

Product	m.p. (°C)	Yield (%)	Analysis (%) Found (Cal.)		R_f Value	$[\alpha]_D^{31}$ (c, in $CHCl_3$]
			N	S		
IIIa	110	78	2.11 (2.23)	2.55 (2.55)	0.67	+160° (0.5 in $CHCl_3$)
IIIb	145	76	2.18 (2.23)	2.31 (2.55)	0.72	150° (0.5 in $CHCl_3$)
IIIc	125	81	2.2 (2.23)	2.35 (2.55)	0.77	+85° (0.5 in $CHCl_3$)
IIId	130	69	2.16 (2.25)	2.38 (2.58)	0.82	270° (0.5 in $CHCl_3$)
IIIe	111	71	2.21 (2.22)	2.51 (2.58)	0.75	+40° (0.5 in $CHCl_3$)
IIIf	130	69	2.16 (2.25)	2.38 (2.58)	0.82	270° (0.5 in $CHCl_3$)
IIIg	111	71	2.21 (2.23)	2.51 (2.55)	0.75	+140° (0.5 in $CHCl_3$)
IIIh	129	77	2.15 (2.23)	2.49 (2.55)	0.69	+140° (0.5 in $CHCl_3$)
IIIi	129	77	2.15 (2.23)	2.49 (2.55)	0.69	+30° (0.5 in $CHCl_3$)

Antimicrobial activities

All the compounds have been screened for both antibacterial and antifungal activity using cup plate agar diffusion method by measuring the inhibition zone in mm. The compounds were taken at a concentration of 1 mg/mL using dimethyl sulphoxide as solvent. Amikacin (100 ůg/mL) was used as a standard for antibacterial and antifungal activity and fluconazole (100 ůg/mL) as a standard for antifungal activity. The compounds were

screened for antibacterial activity against *Escherichia coli*, *Staphylococcus aureus*, *Proteus vulgaris*, and *Salmonella typhi* in nutrient agar medium and for antifungal activity against *Candida guilliermondii* and *Microsporum* in potato dextrose agar medium.

It has been observed that all of these compounds showed nearly the same activity as that of the standard fluconazole and amikacin (Table 2). Similarly also it has been observed that some of these compounds exhibited interesting microbial activities. **3a**, **3b**, **3c** and **3g**, **3h** exhibited most significant activity against *Salmonella* and *E.coli* while **3d**, **3e**, **3f**, **3i**. Inhibited *S.aureus* and *P.vulgaris*. All other compounds exhibited low to moderate activity

Table 2: Antimicrobial activities of compounds (IIIa-i)

Compd. No.	Antibacterial**				Antifungal**	
	E. coli	***S. aureus***	***P. vulgaris***	***S. typhi***	***C. guilliermondii***	***A. niger***
3a	17	22	23	24	20	20
3b	23	19	18	23	23	23
3c	19	19	20	23	20	22
3d	15	19	17	19	20	22
3e	15	14	18	20	20	22
3f	15	22	23	16	22	22
3g	17	24	22	23	21	22
3h	18	19	20	16	20	21
3i	19	19	18	19	20	17
Amikacin	18	21	23	24	-	-
Fluconazole	-	-	-	-	22	21

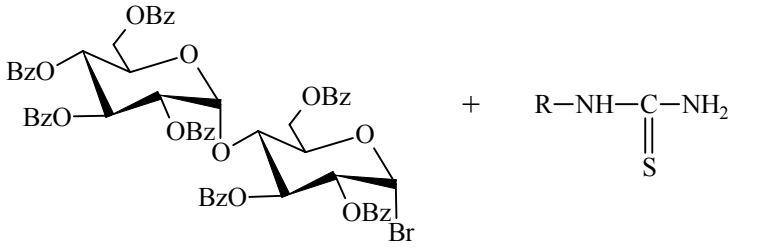
RESULTS AND DISCUSSION

Isopropanolic suspension of hepta-*O*-benzoyl maltosyl bromide (0.005 M, 5.7 g in 20 mL) was mixed with an Isopropanolic suspension of phenyl thiocarbamide (0.005 M, 0.76 g in 10 mL). This mixture was warmed at 70^{o}C, until the clear solution was obtained. The clear solution was then kept at room temperature for 18 hours. It was then mixed with

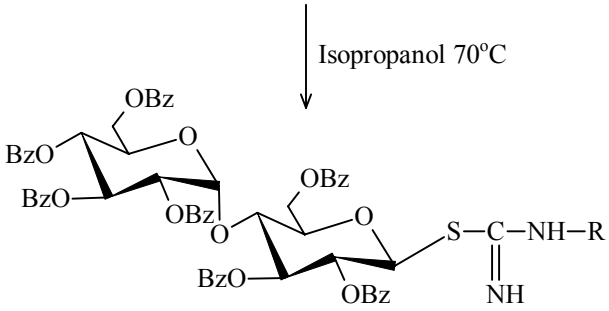
100 mL distilled water. This aqueous solution was acidic and nondesulphurisable when boiled with alkaline plumbite solution. The aqueous solution when basified with NH_4OH afforded a sticky mass, which was not solidified on standing for several hours. It was purified by ethanol and water (Yield-4.7 g). It gives charring test and was nondesulphurisable. Its specific rotation[8] was found $[\alpha]^{31}_{D}$ + 260° (c, 0.5 g in $CHCl_3$).

The IR, ^{1}H NMR and Mass[9-12] spectral analysis and elemental analysis (Table 1) indicate the product and design the structure as *S*-hepta-*O*-benzoyl maltosyl-1-phenyl isothiocarbamide (IIIa).

Similarly, when the hepta-*O*-benzoyl maltosyl bromide interacts with other arylthiocarbamides (IIb-i) the related *S*-hepta-*O*-benzoyl maltosyl-1-arylisothiocarbamides (IIIb-i) were obtained **Scheme 1**.



Hepta-O-benzoyl maltosyl bromide **(I)** Aryl thiocarbamides **(IIa-f)**



S-Hepta-O-benzoyl maltosyl-1-arylisothiocarbamides **(IIIa-i)**

Where, Bz = COC_6H_5

R = (a) o-Nitro phenyl, (b) m-Nitro phenyl (c) p-Nitro phenyl, (d) o-methoxy phenyl, (e) m-methoxy phenyl, (f) p-methoxy phenyl, (g) o-carboxylic phenyl (h) m-carboxylic phenyl, (i) p- carboxylic phenyl.

ACKNOWLEDGEMENT

Authors are thankful to SAIF, CDRI Lucknow for providing the spectral data and also to Dr. V. D. Nanoty, Principal, Shri R. L. T. College of Science, Akola, Akola for providing necessary facilities.

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Accepted : 02.09.2015