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SYNTHESIS, CHARACTERIZATION AND BIOLOGICAL STUDY OF BENZOYL PROTECTED S- GLYCOSYL-1-ARYL-3-AMIDINO ISOTHIOCARBAMIDES

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ABSTRACT

Certain benzoyl protected S-glycosyl-1-aryl-3-amidino isothiocarbamides were prepared by interaction of benzoyl protected glycosyl bromides and 1-amidino-3-aryl thiocarbamides in isopropanol medium. The required benzoyl protected glycosyl bromides were prepared by interaction of various glycosyl benzoates with brominating reagent while 1- amidino-3-aryl thiocarbamides were prepared by reaction of aryl isothiocyanates and guanidine nitrate. The identities of these newly synthesized compounds have been established on the basis of usual chemical transformations, elemental analysis, IR, ^{1}H NMR and Mass spectral studies. These compounds were undergone the biological study of antibacterial and antifungal activity against some selected organisms like *Escherichia coli, Staphylococcus aureus, Salmonella typhi, Proteus vulgaris*, *Candida albicans* and *Aspergillus niger*. Some of the compounds displayed promising activity.

Keywords: Benzoyl protected glycosyl bromides, 1-amidino-3-aryl thiocarbamides, 3-amidino isothiocarbamides, and biological activity.

INTRODUCTION

Glycosyl sulfide or thioglycosides have found versatile applications in carbohydrate chemistry as very effective and stable glycosyl donar[1-3]. There are number of reports in the literature for the preparation of thioglycosides viz as antifungal[4], anticancer[5],antiviral[6] and antimalerial activities[7]. In the relevance of above, there is a constant need to develop a suitable alternative reaction methodology in which the guanidium moiety interacts with aryl isothiocyanates which provide a structurally complex molecule with biological and pharmacological activities from a relatively simple starting material as a convergent approach[8]. From these finding we here reported the synthesis of benzoyl protected *S*-glycosyl-1-aryl-3-amidino thiocarbamides **(3a-d)** (Scheme-2 and 3) by the interaction of Hepta-*O*-benzoyl glycosyl bromides **(1a, b)** with various 1-amidino-3- aryl thiocarbamides **(1a, b)** (Scheme-1).

EXPERIMENTAL

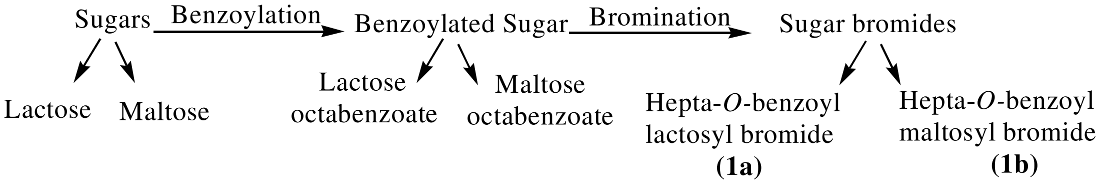
All the chemicals used were of research grade. The melting points of synthesized compounds were determined with the help of thermonic melting point apparatus and uncorrected. The structures of newly synthesized compounds were elucidated on the basis of elemental and IR, ^{1}H NMR and MASS spectral analysis[9-12]. IR spectra were recorded in KBr disks on SHIMADZU IR Affinity-1 FTIR spectrometer. ^{1}H NMR spectra were obtained on BRUKER AVANCE II 400 NMR spectrometer, sample were prepared in $CDCl_3$ with TMS as an internal reference. The MASS spectra were obtained on WATER, Q-T FO Micromass (LC-MS) spectrometer. Optical rotation $[\alpha]^{31}_D$ were measured on the Equip-Tronics EQ-800 Digital polarimeter at 31°C in $CHCl_3$. Thin layer chromatography (TLC) was performed on silica gel G for TLC (Merk) and spot were visualized by iodine vapor.

General preocedure

The reagents required for the given synthesis were prepared as follows-

Preparation of benzoyl protected glycosyl bromides (1a-c)

Hepta-*O*-benzoyl-α-D-lactosyl bromide **(1a)**, Hepta-*O*-benzoyl-α-D-maltosyl bromide **(1b)** was prepared by the interaction of lactose octabenzoate, maltose octabenzoate and brominating agent respectively.

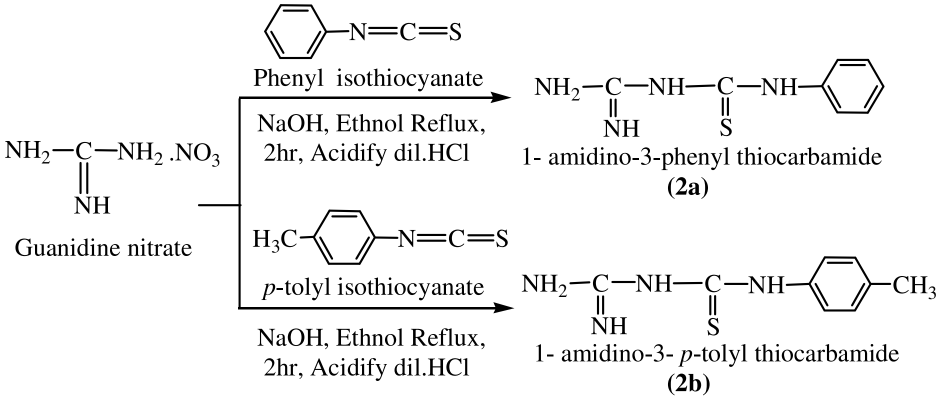


Scheme-1

Synthesis of 1- amidino-3-phenyl thiocarbamides (2a)

A typical synthesis of 1- amidino-3-phenyl thiocarbamide **(2a)** was prepared by refluxing the mixture of guanidine nitrate (0.01 M) and phenyl isothiocyanate (0.01 M) and sodium hydroxide in ethanolic medium (20 mL) for 2 hr. The reaction mixture was cooled to ambient temperature and acidified with dil. HCl on a little crushed ice when solid was isolated. The product wash several times with petroleum ether (60-80^0) white solid was obtained. The solid was expected of 1- amidino-3-phenyl thiocarbamides **(2a)**. It was crystallized by ethanol-water system. Similarly, 1- amidino-3-*p*-tolyl thiocarbamide (**2b**) was synthesized by the interaction of guanidine nitrate and *p*-tolyl isothiocyanate in ethanol medium.

It was soluble in ethanol, acetone, chloroform, carbon tetrachloride, benzene while insoluble in water and petroleum ether. The compound was desulfurisable when boiled with alkaline plumbite solution. The purity of compound was check by TLC.



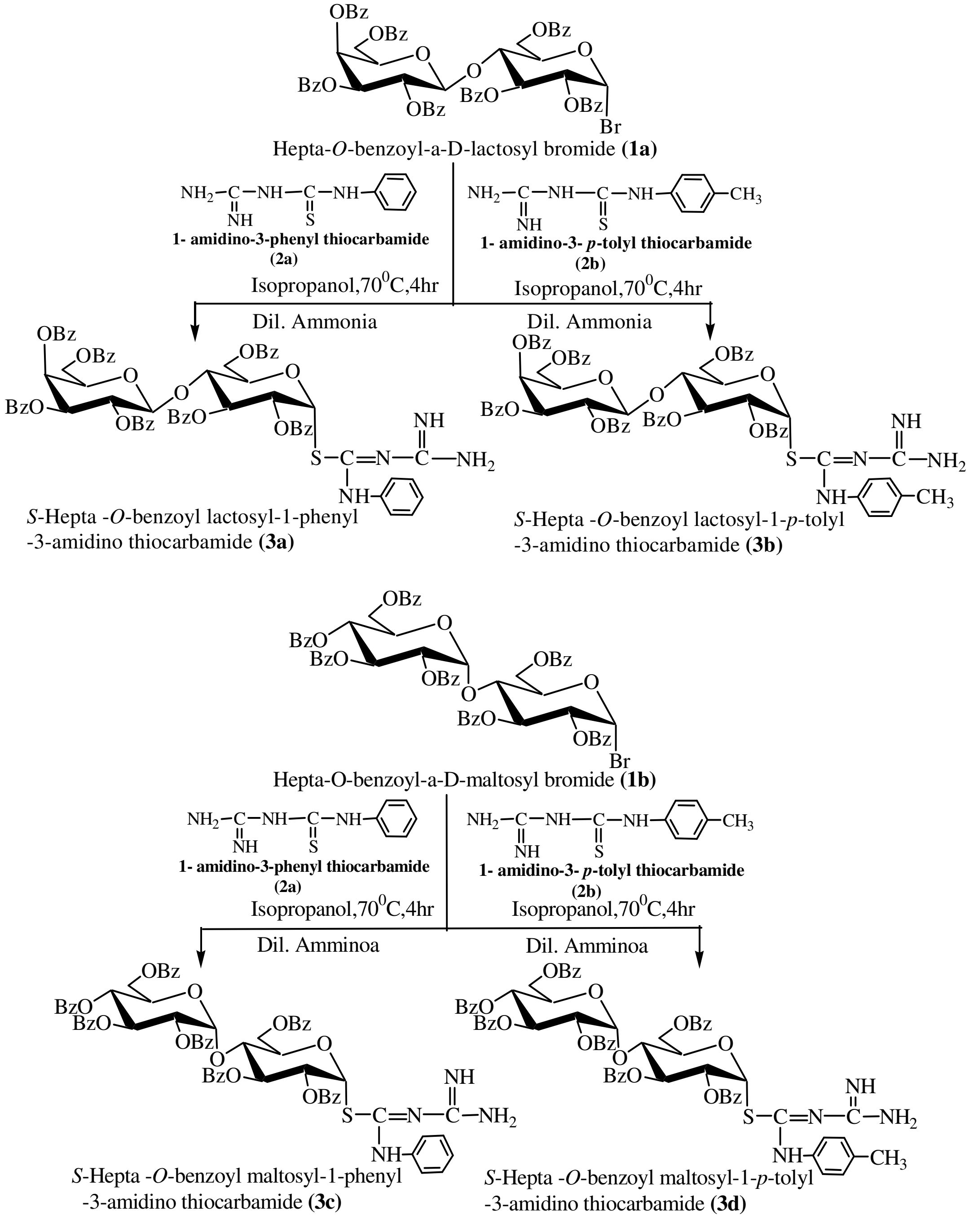
Scheme-2

Synthesis of S- hepta-O-benzoyl lactosyl-1-phenyl-3-amidino isothiocarbamide (3a)

The isopropanolic suspension of hepta-*O*-benzoyl lactosyl bromide **(1a)** (0.001M, 1.132g in 30mL) mixed with isopropanolic suspension of 1- amidino-3-phenyl thiocarbamides **(2a)** (0.001 M, 0.194 g in 30 mL). This was warmed at about 70°C, until the clear solution was obtained. The clear solution was then kept at room temperature for 18 hr. It was then mixed with 100 mL distilled water, when a small quantity of semisolid was separated. The aqueous filtrate responded following test. It was acidic to litmus and give effervescences with sodium bicarbonate solution. The aqueous solutions when basified with aqueous ammonia afforded sticky mass which was not solidified on standing for several hr. The sticky mass was failed to afford solid when triturated several time with petroleum ether (60-80^o) white solid was obtained. This solid was expected *S*- tetra-*O*-benzoyl glucosyl-1-phenyl -3-amidino isothiocarbamide **(3a)**. It was crystallized by ethanol-water system.

Similarly, when the interaction of Hepta-*O*-benzoyl-α-D-lactosyl bromide **(1a)**, Hepta-*O*-benzoyl-α-D-maltosyl bromide **(1b)** were extended to 1-amidino-3-aryl thiocarbamides **(2a,b)** the corresponding benzoyl protected *S*-glycosyl-1-aryl-3-amidino isothiocarbamides **(3a-d)** were isolated.

It was soluble in ethanol, acetone, chloroform, carbon tetrachloride, benzene while insoluble in water and petroleum ether. It charred when boil with conc. sulphiric acid. The compound was non-desulfurisable when boiled with alkaline plumbite solution. The purity of compound was check by TLC. The product was optically active and gives positive Molish's test.



Scheme-3

RESULTS AND DISCUSSION

Isopropanolic suspensions of glycosyl bromides **(1a,b)** and 1- amidino-3-phenyl thiocarbamides **(2a,b)** were heated on water bath at about 70^{o}C**,** until the clear solution was obtained. It was then mixed with 100 mL distilled water. The aqueous solutions was basified with ammonium hydroxide afforded a sticky masses. It was purified by ethanol-water system. It was non-desulphurisable and gave charring test and positive Molish's test. Optical rotation of the product was also recorded[13].

All the products were crystallized from ethanol-water system before cording the physical data (Table-1). The spectral analysis IR, ^{1}H NMR and Mass spectral analysis of the product were observed. These compounds were undergone for both antimicrobial and antifungal activity.

Table-1 : Characterization data of benzoyl Protected *S*- glycosyl-1-aryl -3-amidino isothiocarbamides (3a-d)

S.No.	Compd.	Yield(%)	m.p. (^{0}C)	$[a]_D31$ (CHCI$_3$)	Elemental Analysis*		
					Found (required) (%)		R_f
					N	S	
1	3a	80.65	142	+70.20 (c,0.920)	4.49 (4.40)	2.56 (2.49)	0.63
2	3b	81.48	158	+50.21 (c,0.986)	7.12 (7.09)	4.07 (3.91)	0.57
3	3c	64.96	140	+60.53 (c,0.962)	4.44 (4.39)	2.53 (2.45)	0.81
4	3d	78.48	152	+85.36 (c,0.980)	4.44 (4.42)	2.53 (2.51)	0.76

*Satisfactory C and H analysis are found in all cases

Antimicrobial activities

Agar well diffusion method[14,15] was employed to ascertain the antibacterial activity of newly synthesized compounds. All the compounds were tested for their antibacterial activity against *Escherichia coli, Staphalococcus aureus*, *Salmonella typhi, Proteus vulgaris* using nutrient medium. Antifungal activity was carried out against *Candida albicans* and *Aspergillus niger* using potato dextrose agar. DMSO was used as solvent control. Amikacin (100µg/ml) and Fluconazole (100µg/ml) used as a standard for antibacterial and antifungal activity respectively.

Antimicrobial studies

All the synthesized compounds were screened for their antimicrobial activity by agar well diffusion method. The result showed that among the tested the some of these compounds exhibited interesting antimicrobial activities. The compounds **3b** and **3c** exhibited most promising activity against *Escherichia coil*, **3c** exhibited most moderate activity against *Staphylococcus aureus*, **3a** and **3c** exhibited most promising activity against *Proteus vulgaris* and **3a**, **3c** exhibited most promising activity against *Salmonella typhi.* The compounds **3d** and **3e** are effective towards *Candida albicans* and **3a** and **3d** inhibited towards *A. niger* respectively. All other compounds exhibited low to moderate activity as tabulated in Table-2.

Spectral data

S-tetra -*O*-benzoyl lactosyl-1-phenyl-3-amidino isothiocarbamide 3a

IR (KBr, cm^{-1}): υ 3498 (N-H), 3061 (Ar C-H), 2972 (Ali C-H), 1730 (C=O), 1643 (C=N), 1454 (Ar C=C), 1313 (C-N), 1276 (C-O), 1076, 1170, 1026 and 937 (Characteristic of lactose unit), 802 (monosubstituted benzene ring), 713 (C-S). ^{1}H NMR (CDC3$_l$) ppm : δ 8.18-7.13 ppm (40H, m, Aromatic protons), δ 5.87-3.70 ppm (14H, m, lactosyl protons), and δ 1.66 ppm (1H, s, hump N-H), δ 1.25 ppm (2H, s, N-H) and δ 1.00 ppm (1H, s, N-H). Mass (m/z) : 1246 (M$^+$), 1135, 1053, 932, 931, 579, 475, 232.

S-tetra -*O*-benzoyl maltosyl-1-*p*-tolyl-3-amidino isothiocarbamide 3d

IR (KBr, cm^{-1}): υ 3522 (N-H), 3061 (Ar C-H), 2970 (Ali C-H), 1741 (C=O), 1602 (C=N), 1452 (Ar C=C), 1315 (C-N), 1284 (C-O), 1178, 1074, 937 and 823 (Characteristic of maltose unit), 719 (monosubstituted benzene ring), 713 (C-S). ^{1}H NMR (CDC3$_l$) ppm : δ 8.11-7.12 ppm (40H, m, Aromatic protons), δ 6.23-3.91 ppm (14H, m, maltosyl protons), and δ 3.18 ppm (1H, s, N-H), δ 2.32 ppm (1H, s, N-H), δ 2.16 ppm (1H, s, N-H), δ 1.03 ppm (1H, s, N-H) and 1.20 ppm (3H, s, CH_3). Mass (m/z) : 1246 (M^+), 1135, 1053, 932, 931, 579, 474, 231.

Table-2: Result of antimicrobial activity of benzoyl Protected *S*- glycosyl- 1-aryl-3-amidino isothiocarbamides (3a-d)

	Zone of inhibition in mm					
	Antibacterial activity**				Antifungal acivity**	
Compds	*E.coli*	*S.aureus*	*P.vulgaris*	*S. typhi*	*C.albicance*	*A.niger*
3c	20	17	22	17	07	10
3d	10	12	17	12	08	07
3e	17	10	12	10	09	06
3f	12	13	15	12	07	08
Amikacin	09	17	20	10	-	-
Fluconazole	-	-	-	-	09	17

** zone of inhibition in mm (15 or less) resistance, (16-20mm) moderate and (more than 20 mm) sensitive. *Escherichia coli (E. coli), Staphylococcus aureus (S. aureus), Salmonella typhi (S. typhi)* and *Proteus vulgaris(P. vulgaris)*, *Candida albicans (C.albicans)* and *Aspergillus niger (A. niger)*.

CONCLUSION

In this a series of benzoyl protected *S*-glycosyl-1-aryl-3-amidino isothiocarbamides **(3a-d)** were synthesized. The presence of functional groups were identified with the help of FTIR and ^{1}H NMR spectral analysis. The molecular weight of the compounds were estimated by Mass Spectrum. Melting points of these compounds were found and reported. These compounds were also undergone for antibacterial and antifungal activities against the organisms tested, Most of the compounds show promising activity. The method adopted in this investigation is simple, efficient and inexpesive and is useful in synthesizing pharmacologically important molecules.

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