SYNTHESIS, CHARACTERIZATION AND BIOLOGICAL EVALUATION OF 1-HEPTA-*O*-BENZOYL-B-D-MALTOSYL-3-SUBSTITUTED BENZOTHIAZOLYL CARBAMIDES

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Abstract:
Synthesis of 1-hepta-*O*-benzoyl-β-D-maltosyl-3-substituted benzothiazolyl carbamides by the interaction of 1-hepta-*O*-benzoyl-β-D-maltosyl Isocyanate with various substituted benzothiazoles. The synthesized compoundshave been characterized by spectral technique such as FTIR,NMR and Mass and usual chemical transformations. The newly synthesized compounds were screened for their microbial activities.

Keywords: Isocyanate, Maltosylated, Benzothiazolyl, Carbamides, Antimicrobial Activity.

1)Introduction:-

Benzothiazoles are bicyclic ring system having multiple applications. Substituted benzothiazoles have found applications in several areas of chemistry.2-aminobenzothiazoles are broadly found in bioinorganic medicinal chemistry with applications in drug discovery and development for the treatment of diabetes[1],epilepsy[2],inflammation[3],amyotropic lateral sclerosis[4],analgesia[5],tuberculosis[6] and viral infections[7].It is also a novel mechanistic class of antitumor agents[8-9].Moreover, they were studied extensively for their activities like antiglutamate,immunosupressive[10],amyloid imaging agents[11] and thrombin inhibitors[12].Furthermore, the importance of substituted benzothiazoles is well established in the protection of paper against forgery[13] and agricultural chemistry. Apart from this several methodologies have been reported for the preparation of benzothiazoles[14].As isocyanates are the most powerful starting materials for the synthesis of various *N*-linked sugar derivatives. Taking in to account previous knowledge in this field, we have synthesized series of maltosyl benzothiazolyl carbamides by the addition of maltosyl Isocyanate to the substituted benzothiazoles.The reaction of molecular bromine with aryl thiocarnamides is known to produce 2-aminobenzothiazoles.herein we reportthe Synthesis of new 1-hepta-*O*-benzoyl-β-D-maltosyl-3-substituted benzothiazolyl carbamides (III_{a-f}) by the interaction of 1-hepta-*O*-benzoyl-β-D-maltosyl Isocyanate with various substituted benzothiazoles.

2)Materials and method

2.1 Materials

The melting point of compounds were determined with the help of Thermionic melting point apparatus and were found uncorrected. The structures of newly synthesized compounds were confirmed on the basis of elemental and spectral analysis. IR Spectra were recorded on KBr disks on SHIMADZU IR affinity-1 FTIR spectrometer. ^{1}H NMR was obtained on Bruker DRX-300 NMR Spectrometer. Samples were prepared in $CDCl_3$ with TMS as an internal reference. The mass spectra were obtained on JEOL-AccuTof JMS-T100LC and Thermo Fennigan LCQ Advantage max ion trap mass spectrometer. Thin layer chromatography (TLC) was performed on silica gel G for TLC (Merck) and spot were visualized by iodine vapour.

2.2 Method:The reagents required for the given synthesis are obtained as follows-

2.2.1:Preparation ofhepta-*O*-Benzoyl-β-D-Maltosyl Isocyanates (I):

Hepta-*O*-Benzoyl-β-D-Maltosyl Isocyanateswas prepared by the condensation of Hepta-*O*-Benzoyl-α-D-Maltosyl bromide (0.005 mol 3.4g) and lead cyanate (0.005 mol, 1.4g) in

boiling xylene (25 ml) medium for3 hrs. with frequent shaking. After the removal of lead bromide the xylene filtrate was triturated with petroleum ether (60-80^{o}C) when Hepta-*O*-Benzoyl-β-D-Maltosyl Isocyanates was precipitated out. It was purified by dissolving it in a minimum quantity of chloroform and reprecipitating with petroleum ether (60-80^{o}C) to afford a pale yellow solid.The homogeneity of the product was checked by TLC. m.p. 112 ^{o}C,(Fig:1)

2.2.2: Preparation of substituted benzothiazolyl carbamides (II):

The reaction of molecular bromine with aryl thiocarbamides is known to produce 2-aminobenzothiazole so the requisitesubstituted benzothiazoles were prepared by oxidative cyclization of substituted aryl thiocarbamides with molecular bromine in chloroform.(Fig:2)

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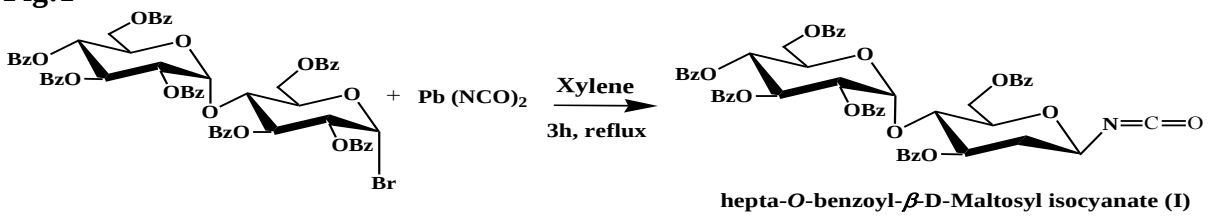
Fig:1

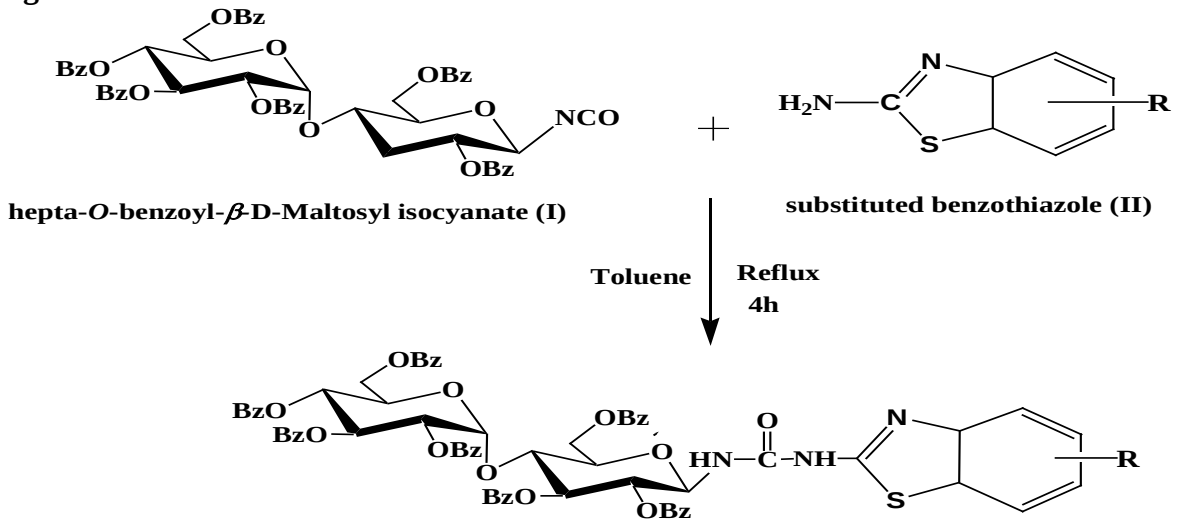


hepta-*O*-benzoyl-*β*-D-Maltosyl isocyanate (I)

Fig:2

Aryl thiocarbamide **2-amino benzothiazole (II)**

fig3:Scheme:



hepta-*O*-benzoyl-*β*-D-Maltosyl isocyanate (I) **substituted benzothiazole (II)**

hepta-*O*-benzoyl-*β*-D-Maltosyl 3-Substituted benzothiazolyl carbamides.(IIIa-f)

Where, Bz-COC_6H_5,R'= a) H, b)CH_3,c) chloro

Synthesisof1-hepta-*O*-benzoyl-β-D-maltosyl-3-substituted benzothiazolyl carbamides(III$_{a-f}$)

When a mixture of hepta-*O*-benzoyl-β-D-maltosyl isocyanate(I) and 2-aminobezothiazole (II) was refluxed in toluene medium for 4 hr. After completion of the reaction,the solvent get distilled off and sticky residue obtained was triturated with petroleum ether gives a light yellow colour solid.It was crystallized by ethanol-water. The purity of compound was checked by TLC. The spectral analysis IR, NMR, Mass spectra of the product were observed. Optical rotation of the product were also recorded in table-1. All the compounds have been screen for microbial activity were recorded in table-2

2.3:Spectral and Elemental analysis[15-17]:-

1-hepta*O*-benzoyl- β -D-Maltosyl -3-(2)-benzothiazolyl carbamide. (IIIa)

IR (KBr cm-1): 3034 (ArC-H), 2850 (Ali C-H), 1732(C=O),1651 (C=N), 1271 (C-N), 1070 (Characte-ristic maltose), 709 (C-S).

1H NMR (CDCl3) δ: 8.09-7.26 (39 H, m,Aromatic protons), 7.61 (1H, s, NH proton), 6.72 (1.3H, s, NH proton), 6.20 (14H, m, maltosyl protons)
Mass *m/z*: 1245(M+), 1217, 1175, 1007, 975, 133, 105.

1-hepta -*O*-benzoyl- β -D-Maltosyl -3-(2)-4-methyl benzothiazolyl carbamides. (IIIb)
IR(KBr cm-1): 2956 (Ar C-H), 2858 (Ali C-H), 1732 (C=O),1651 (C=N), 1256 (C-N), 1070 (Characteristic maltose), 709 (C-S).)
1H NMR (CDCl3) δ: 8.06-7.23 (38 H, m, Aromatic protons), 6.72 (1H, s, NH proton), 5.73 (1H, s, NH proton), 2.49(3H, s, methyl protons), 4.56-4.45 (14H, m, maltosyl protons)
Mass *m/z*: 1259(M+), 1245, 1217, 769, 651, 163, 191.

1-hepta-*O*-benzoyl β -D-Maltosyl -3-(2)-4-chloro benzothiazolyl carbamides (IIId)
IR (KBr cm-1):3034 (Ar C-H), 2898 (Ali C-H), 1728 (C=O),1647(C=N), 1271 (C-N), 1070 (Characteristic maltose), 709 (C-S).
1H NMR (CDCl3) δ: 8.05-7.26 (38 H, m, Aromatic protons), 6.72 (1H, s, NH proton), 6.17 (1H, s, NH proton), 7.3-4.28 (14H, m, maltosyl protons)
proton),7.3-4.28 (14H, m, maltosyl protons)
Mass *m/z*: 1279(M+), 1247, 1217, 1177, 581, 185.

2.4: Microbial Assay:

The microbial assay of synthesized compounds have been studied using cup plate agar diffusion method[18-19] by measuring the inhibition zone in mm. the compounds were taken at a concentration of 1 mg/ml using dimethyl sulphoxide (DMSO) as solvent.

The **bacterial assay** of compounds wasstudied against *Escherichia coli, P. vulgaris Staphylococcus aureus and Pseudomonas aeruginosa* in nutrient agar medium. Amikacin (100 µg/ml) was used as standard for antibacterial activity.The results are presented in Table 2.The compounds were screen for **antifungal activity** against *Aspergillusnigar* and *Candida albicance* in potato dextrose agar medium *flucanzole* (100µg/ml) as standard for antifungal activity.Result were recorded in Table 2.

3.Result and discussion:

All products were crystallized from ethanol-water before recording the physical data (table-1).The purity of compounds was checked by TLC The spectral analysis IR,^{1}HNMR,Massspectra of the product were observed. Optical rotation of the product was also recorded.Yeild and M.P.of compound were obtained satisfactory.Antimicrobial activity of newly synthesised compound were discussed in table-2 as below.

Table1:Characterization of 1-hepta-*O*-benzoyl-β-D-maltosyl-3-substituted benzothiazolyl carbamides.

Sr. No.	Synthesized Compounds	M.P. (^{O}C)	Yield (%)	Elemental Analysis (%) Found (Required)		Rf Values	$[\alpha]^{28}_D$ [c, in $CHCl_3$]
				N	S		
1.	IIIa	160 ^{O}C	71 %	3.80(3.37)	2.48(2.57)	0.61	+105^O
2.	IIIb	180^{O}C	67%	3.30(3.33)	2.47(2.54)	0.58	+60.32^O
3.	IIIc	185^{O}C	60 %	3.31(3.33)	2.49(2.54)	0.57	+40.0^O
4.	IIId	210^{O}C	67 %	3.10 (3.28)	2.32(2.50)	0.66	+104.06^O
5.	IIIe	190^{O}C	63%	3.00(3.28)	2.1(2.50)	0.62	+64.56^O
6.	IIIf	195^{O}C	69%	3.18(3.28)	2.31(2.50)	0.63	+85.33^O

C and H analysis were found satisfactory in all cases.

Table 2: Antimicrobial study of 1-hepta-*O*-benzoyl-β-D-maltosyl-3-substituted benzothiazolyl carbamides

Sr. No.	Compounds	Antibacterial**				Antifungal**	
		E. coli	*P.vulgaris*	*S. aureus*	*Ps. Aeruginosa*	*C. albicance*	*A. Niger*
1.	IIIa	21	13	22	12	23	15
2.	IIIb	15	12	24	18	25	13
3.	IIIc	20	12	25	16	21	13
4.	IIId	13	21	10	13	22	14
5.	IIIe	15	10	14	15	20	16
6.	IIIf	17	15	13	14	20	19
7.	Amikacin	21	23	28	24	-	-
8.	Fluconazole	-	-	-	-	26	24

**zone of inhibition in mm (15 or less) resistance, (16-20mm) moderate and (more than 20mm) sensitive. *Escherichia coli* (*E*. coli), *Proteus vulgaris (P.Vulgaris), Staphalococcusaureus*(*S.* aureus), *Psudomonasauriginosa* (*Ps. auriginosa*), *Candida albicance (C.albicance) and Aspergillusniger (A.niger).*

Antibacterial study of these compound indicated that IIIa and IIIc were found to be active against *E. coli* and rest of were found to be moderately active.CompoundIIId exhibited more significant activity against*P.Vulgaris and* IIIa,IIIb,IIIc against *S. aureus.*CompoundIIIb,IIIc shows moderate against *Ps.Aeruginosa.* All other compounds exhibited low to moderate activity.

The results of **antifungal** activities are also tabulated in Table-2.Almost all compounds shows promising activity against *C.albicance*and compound IIIe and IIIf exhibited moderate activity against *A.niger and all* other compounds are resistant.

Conclusion:

A series of new benzothiazolyl carbamides were successfully synthesized and characterized by IR, ^{1}H NMR and Mass Spectral and Elemental analysis. The synthesized compounds were evaluated for their antibacterial activities. Thus, the newly synthesized benzothiazolyl carbamides derivatives, exhibits comparable antibacterial activities against the organisms tested. The method adopted in this investigation is simple, efficient and inexpensive and is useful in synthesizing pharmacologically important molecules.

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