INTERNATIONAL JOURNAL OF PURE AND APPLIED RESEARCH IN ENGINEERING AND TECHNOLOGY

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SPECIAL ISSUE FOR INTERNATIONAL LEVEL CONFERENCE "ADVANCES IN SCIENCE, TECHNOLOGY & MANAGEMENT" (IC-ASTM)

SYNTHESIS AND ANTIMICROBIAL STUDIES OF PERACETYLATED *N*-MALTOSYLATED CARBAMIDES

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Accepted Date: 05/09/2017; Published Date: 10/10/2017

Abstract: The area of sugar urea derivatives has received considerable attention in recent years because of the unique structural properties and activities that these compounds display. Thiourea and urea are important functional groups in various natural products and drug intermediates. They are used as neutral receptor for various anions (anion complexation) and building blocks for various heterocycles and show remarkable biological activity. Here we have synthesized certain 1-hepta -*O*-acetyl-ß-D-maltosyl carbamides by the interaction of various aminophenols and aminopyridines with maltosyl isocyanate. The structure of title compounds were confirmed by IR, NMR spectral data and elemental analysis. The compounds were screened for their antibacterial and antifungal activity against various pathogenic bacteria and fungi. The title compounds exhibited promising antibacterial and antifungal activity.

Keywords: Maltosyl carbamides, Maltosyl isocyanate, Aminophenols, Aminopyridines antimicrobial activities.

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How to Cite This Article:

S. M. Thorat, IJPRET, 2017; Volume 6 (2): 185-192

INTRODUCTION

The structural diversity and biological importance of heterocycles containing N-linked sugar derivatives have made them attractive synthetic targets over many years. N-glycoside**s** have several applications in industries as carbohydrate based detergents[1] and in medicines as antitumor[2] and antitubercular[3] activities. Urea and thiourea derivatives possess many promising biological activities such as herbicidal, antioxidant[4], antiviral, antiHIV[5], antitumor activity and also have been used as purification agents for organic and inorganic effluents, industrial, agricultural and mining wastes and in paper and paints. Urea derivatives exhibit antimalarial[6] and antidiabetic[7] activities. In view of these observations we have synthesized new compounds incorporating the above pharmacophores together in order to prepare molecules having enhanced antimicrobial activity.

We report the synthesis of 1-hepta -*O*-acetyl-ß-D-maltosyl carbamides by the interaction of maltosyl isocyanate[8, 9] with various aminophenols and aminopyridines and study their utility as antibacterial and antifungal compounds. The reactivity of glycosyl isocyanates and isothiocyanates permits them as adaptable intermediates in the synthesis of molecules which have versatile medicinal applications.[10-12]

EXPERIMENTAL

Melting points were taken in open capillary tubes on Mac digital melting point apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer spectrum RXI FTIR spectrometer 4000-450 cm^{-1}. The ^1H NMR spectra were recorded in $CDCl_3$ at 300 MHz on a Bruker DRX-300 NMR spectrometer. The FAB Mass spectra were recorded on a Jeol SX-102/Da-600 mass spectrometer/data system using argon/xenon (6 KV, 10mA) as the FAB gas. The accelerating voltage was 10 KV, and the spectra were recorded at room temperature, Optical rotations $[\alpha]_D^{31}$ were measured on Equip-Tronics EQ-800 Digital Polarimeter at 31° in Chloroform. Thin layer chromatography (TLC) was performed on E. Merck pre-coated silica gel plates.

The required 1-hepta-*O*-acetyl-ß-D-maltosyl isocyanate **(I)** was prepared by the interaction of hepta-*O*-acetyl-α-D-lactosyl bromide with lead cyanate in boiling xylene medium. In spectral analysis, IR spectrum of maltosyl isocyanate shows absorption bands such as N=C=O stretching band at 2121 cm^{-1}, C=O stretching band at 1751cm^{-1}, C-O stretching band at 1233 cm^{-1}, and characteristic of maltose at 1053 & 905cm^{-1}. ^1H NMR spectra displayed signals due to acetyl protons at δ 2.16-1.97 & lactose ring protons at δ 5.36-3.77ppm.

Synthesis of 1-hepta -*O*-acetyl-ß-D-maltosyl carbamides of hydroxyaniline.(IIIa-c)

A benzene solution of hepta-*O*-acetyl-ß-D-maltosyl isocyanate **(I)** (0.001M, 0.661g) and aminophenol (IIa-c) (0.001M, 0.109 g in 15 ml) was refluxed in water bath for 5 hr. The reaction was monitored by TLC. After the completion of reaction, the solvent was distilled off and sticky residue obtained was triturated with petroleum ether to afford yellow solid (IIIa-c). It was crystallized by ethanol- petroleum ether. Molecular formula was found to be $C_{33}H_{42}O_{19}N_2$.

Synthesis of 1-hepta -*O*-acetyl-ß-D-maltosyl carbamides of amino pyridine. (IIId-f)

A benzene solution of hepta-*O*-acetyl-ß-D-maltosyl isocyanate **(I)** (0.001M, 0.661g) and amino pyridine (IId-f) (0.001M, 0.0941 g in 15 ml) was refluxed in water bath for 5 hr. The reaction was monitored by TLC. After the completion of reaction, the solvent was distilled off and sticky residue obtained was triturated with petroleum

ether to afford pale yellow solid (IIId-f). It was crystallized by ethanol- petroleum ether. Molecular formula was found to be $C_{32}H_{41}O_{18}N_3$. The physical characterization of compounds **IIIa-f** is exhibited in **Table1.**

Table 1 : Physical characterization and analytical data of compounds (IIIa-f)

Product	Yield (%)	m.p. (°C)	R_f	$[\alpha]_D^{32}$ (*c*,1.013 in $CHCl_3$)	%Found (Calculated) N
(IIIa)	51.00	193-195	0.58	+42.10	**3.56 (3.62)**
(IIIb)	55.27	178-180	0.51	+22.09	**3.53(3.62)**
(IIIc)	60.00	170-172	0.43	+32.08	**3.55 (3.62)**
(IIId)	48.33	143-145	0.59	+53.14	**5.50 (5.56)**
(IIIe)	50.44	155-157	0.48	+61.05	**5.52 (5.56)**
(IIIf)	**51.63**	**108-110**	**0.65**	**+23.07**	**5.51 (5.56)**

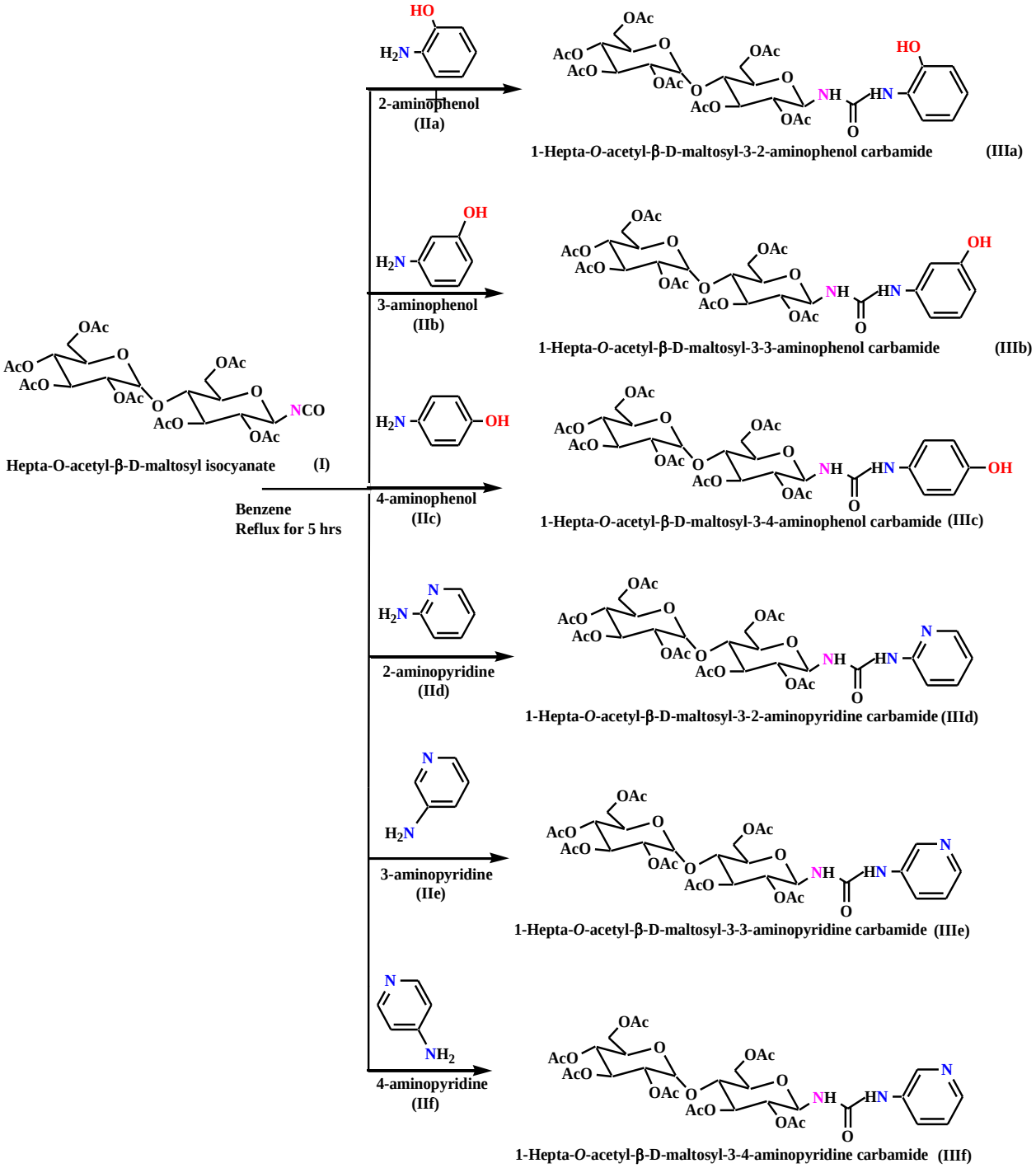
Hepta-O-acetyl-β-D-maltosyl isocyanate (I)
Benzene
Reflux for 5 hrs
2-aminophenol
(IIa)
3-aminophenol
(IIb)
4-aminophenol
(IIc)
2-aminopyridine
(IId)
3-aminopyridine
(IIe)
4-aminopyridine
(IIf)
1-Hepta-O-acetyl-β-D-maltosyl-3-2-aminophenol carbamide (IIIa)
1-Hepta-O-acetyl-β-D-maltosyl-3-3-aminophenol carbamide (IIIb)
1-Hepta-O-acetyl-β-D-maltosyl-3-4-aminophenol carbamide (IIIc)
1-Hepta-O-acetyl-β-D-maltosyl-3-2-aminopyridine carbamide (IIId)
1-Hepta-O-acetyl-β-D-maltosyl-3-3-aminopyridine carbamide (IIIe)
1-Hepta-O-acetyl-β-D-maltosyl-3-4-aminopyridine carbamide (IIIf)

Figure: 1

ANTIMICROBIAL ACTIVITY

The antibacterial and antifungal activities of synthesized compounds **(IIIa-f)** were tested *in vitro* against bacteria *Escherichia coli, Staphylococcus aureus, Proteus vulgaris, Pseudomonas aeruginosa*, *Salmonella typhimurium* and fungi *Aspergillus niger* and *Rhizoctonia* by cup plate agar diffusion method.[13,14] Amikacin (100µg/ml) was used as a standard drug for antibacterial activity and Fluconazole(100µg/ml) as a standard drug for antifungal activity. The antibacterial activity was carried out in nutrient agar medium and antifungal in 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 triangular loop. A stainless steel cylinder of 8 mm diameter (pre-sterilized**)** was used to bore the cavities. All the synthesized compounds (100 µg/ml) were placed serially in the cavities with the help of micropipette and allowed to diffuse for 1.0 hr. DMSO was used as a solvent for all the compounds and as a control. These plates were incubated at 37ºC for 24 hr and 28ºC for 48 hr, for antibacterial and antifungal activities respectively. The zone of inhibition observed around the cups after respective incubation was measured in mm. The results are presented in **Table 2**.

RESULTS AND DISCUSSION

We have synthesized novel 1-hepta -*O*-acetyl-ß-D-maltosyl carbamides (**IIIa-f) Fig.1** from hepta-*O*-acetyl-ß-D-maltosyl isocyanate **(I)** with various aminophenols and amino pyridines. The synthesized compounds were soluble in common organic solvents and insoluble in water. The structural elucidation was confirmed by elemental and spectral analysis.[15-17]

Spectral analysis:

1-hepta -*O*-acetyl-ß-D-maltosyl-3-2-hydroxyaniline carbamide. **(IIIa)**

IR (v/cm^{-1}): 3483.44(NH), 3026.31 (C-H aromatic), 2958.80 C-H (CH_2), 1745.58 (C=O), 1155.36 (C-N), 1240.23 (C-O), 1047.35 & 941.10 (lactose) ; ^{1}H NMR ($CDCl_3$) (δ ppm): 9.10(s,1H, hydroxyl proton),8.64(s,1H,NH proton), 7.11 – 7.09 (m, 4H, Ar-H), 5.34 – 3.71 (m, 14H, maltose unit), 2.39 -1.25 (m, 21H, 7$COCH_3$), 5.08-4.44(d,1H,NH protons).

1-hepta -*O*-acetyl-ß-D-maltosyl-3-3-hydroxyaniline carbamide. **(IIIb)**

IR (v/cm^{-1}): 3489.64(NH), 3020.21 (C-H aromatic), 2963.80 C-H (CH_2), 1741.38 (C=O), 1151.26 (C-N), 1220.33 (C-O), 1057.32& 921.10 (lactose) ; ^{1}H NMR ($CDCl_3$) (δ ppm): 9.11 (s,1H, hydroxyl proton),8.65(s,1H,NH proton), 7.12 – 7.10 (m, 4H, Ar-H), 5.35 – 3.72 (m, 14H, maltose unit), 2.41 -1.29 (m, 21H, 7$COCH_3$), 5.10-4.46(d,1H,NH protons).

1-hepta -*O*-acetyl-ß-D-maltosyl-3-4-hydroxyaniline carbamide. **(IIIc)**

IR (v/cm^{-1}): 3498.87(NH), 3026.31 (C-H aromatic), 2958.80 C-H (CH_2), 1745.58 (C=O), 1153.36 (C-N), 1240.23 (C-O), 1049.26& 941.26 (lactose) ; ^{1}H NMR ($CDCl_3$) (δ ppm): 9.09 (s,1H, hydroxyl proton),8.61(s,1H,NH proton), 7.09 – 7.07 (m, 4H, Ar-H), 5.33 – 3.71 (m, 14H, maltose unit), 2.39 -1.26 (m, 21H, 7$COCH_3$), 5.09-4.45(d,1H,NH protons).

1-hepta -*O*-acetyl-ß-D-maltosyl-3-2-amino pyridine carbamide. **(IIId)**

IR (v/cm^{-1}): 3478.73(NH), 3026.40 (C-H aromatic), 2948.90 C-H (CH_2), 1741.55 (C=O), 1163.20 (C-N), 1239.23 (C-O), 1048.36& 931.26 (lactose) ; ^{1}H NMR ($CDCl_3$) (δ ppm): 7.28 – 7.10 (m,4H,Ar-H), 5.38 – 3.80 (m,14H,maltose unit),5.13-5.10(d,1H,NH proton), 4.45(s,1H,NH proton), 2.18 -1.27 (m, 21H, 7$COCH_3$).

1-hepta -*O*-acetyl-ß-D-maltosyl-3-3-amino pyridine carbamide. **(IIIe)**

IR (v/cm^{-1}): 3475.73(NH), 3024.38 (C-H aromatic), 2958.80 C-H (CH_2), 1743.65 (C=O), 1155.36 (C-N), 1240.23 (C-O), 1047.35 & 930.46 (lactose) ; ^{1}H NMR ($CDCl_3$) (δ ppm): 7.27 –7.09(m,4H,Ar-H), 5.36–3.77(m,14H,maltose unit), 5.12-5.10(d,1H,NH proton), 4.46(s,1H,NH proton), 2.17 -1.25 (m, 21H, 7$COCH_3$).

1-hepta -*O*-acetyl-ß-D-maltosyl-3-4-amino pyridine carbamide. **(IIIf)**

IR (v/cm^{-1}): 3375.63(NH), 3014.28 (C-H aromatic), 2932.80 C-H (CH_2), 1749.60 (C=O), 1135.30 (C-N), 1242.22 (C-O), 1042.35 & 939.48 (lactose) ; ^{1}H NMR ($CDCl_3$) (δ ppm): 7.26 – 7.08 (m,4H,Ar-H), 5.38–3.81 (m,14H,maltose unit),5.15-5.12(d,1H,NH proton), 4.43(s,1H,NH proton), 2.19 -1.30 (m, 21H, 7$COCH_3$).

Antimicrobial studies:

Antibacterial activity

The results of the title compounds for preliminary antimicrobial testing are shown in **Table 2.** The compounds **(IIIa-f)** exhibit strong inhibition against *S. aureus* and *P. vulgaris*, moderate activity against *Ps. aeruginosa, S. typhi,* while weak activity against *E. coli.*

Antifungal activity

The compound **IIIe** exhibited low activity against *A. niger* and *Rhizoctonia* whereas the rest compounds exhibited moderate to strong activity against *A. niger* and *Rhizoctonia* .

Table 2: Antimicrobial activities of IIIa-f

Compounds	Antimicrobial activity						
	Antibacterial activity					Antifungal activity	
	P.vulgaris	*Ps.Aeruginosa*	*S.aureus*	*E.coli*	*S. typhi*	*A. niger*	*Rhizoctonia*
IIIa	20	18	20	12	18	19	20
IIIb	14	14	19	13	16	21	19
IIIc	18	18	21	11	15	18	21
IIId	20	17	20	12	18	18	19
IIIe	19	18	17	14	18	14	15

IIIf	17	16	18	13	17	15	18
Amikacin	25	24	25	23	24	----	----
Fluconazole	--	--	--	--	--	23	22

Zone of inhibition in mm, (12-14) weak activity, (15-18) moderate, and above 18mm, strong activity.

Conclusion:

The present study reports the synthesis of 1-hepta -*O*-acetyl-ß-D-maltosyl carbamides of amino phenols and amino pyridine. The method adapted for synthesis is efficient and inexpensive and is useful in synthesizing pharmacologically important molecules.

Acknowledgement

Author is grateful to SAIF, CDRI, Lucknow for providing the spectral data. Author also thank Dr. S. G. Bhadange, Principal, Shri Shivaji College, Akola for providing necessary facilities to carry out the work.

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