A VERSATILE SYNTHESIS AND ANTIMICROBIAL ACTIVITY OF 5-TETRA-*O*-BENZOYL-β-D-GLUCOPYRANOSYLIMINO-3-OXO-2-ARYL-4- *m*-TOLYL -1, 2, 4,-THIDIAZOLIDINES

K.N. Puri[*] and U.W. Karhe

[*]Department of Chemistry, Shri Shivaji Science College, Amravati (M.S.) India
Department of Chemistry, Anuradha Engineering College, Chikhli (M.S.) India
[*]knpuri2008@rediffmail.com

ABSTRACT

5-Tetra-O-benzoyl-β-D-glucopyranosylimino-3-oxo-2-aryl-4-m-tolyl-1,2,4 thidiazolidines have been prepared by the interaction of Tetra-O-benzoyl-β-D-glucopyranosyl-S-chloro-isothiocarbamoyl chloride and 1-aryl-3-m-tolyl carbamides. This converted high isolated yields which find applications in the area of medicinal chemistry. The identities of these newly synthesized compounds are established on the basis of elemental analysis IR, ^{1}HNMR, and Mass spectral analysis. These compounds were assayed for their antibacterial and antifungal activity against some selected pathogenic organisms like E. coli, P. vulgaris, S. aureus, Ps. aeruginosa,B.cereus and A. niger, C. albicans to get potent bioactive molecule.

Keywords: *Carbamides, 1,2,4 thidiazolidines, antibacterial and antifungal activity, spectral studies*

Introduction

Glucose derivatives are known to be selective and efficient catalytic inhibitors of human liver glycogen phosphorylase, a target for the design of type 2 diabetes therapeutics[1]. Isothiocyanates are precursors of a wide range of N-thiocarbamoyl derivatives; their tendency to undergo nucleophilic additions and cycloadditions make them highly important intermediates in organic synthesis[2] for the preparation of heterocyclic compounds[3,4]. Thus heterocyclic compounds have been used as anti-tumoral[5, 6] or antiviral agents, including AIDS[7, 8] and hepatitis B[9, 10] treatments.

To expand these views and application profiles, efforts have been developed for the synthesis of a new class of 5-Tetra-*O*-benzoyl-β-D-glucopyranosylimino-3-oxo-2-aryl-4-*m*-tolyl-1, 2, 4 thidiazolidines **(5a-g)**. These were synthesized by the reaction of benzylic solution of Tetra-*O*-benzoyl-β-D-glucopyranosyl-*S*-chloro-isothiocarbamoyl chloride and 1-aryl-3-*m*-tolyl carbamides.

Antimicrobial activity

Newly synthesized 1, 2, 4, thidiazolidines were tested against following pathogenic microbes for their antibacterial and antifungal activities using cup plate agar diffusion method[11-13]. *Escherichia coli*, *Proteus vulgaris*, *Staphalococcus aureus*, *Psudomonas aeruginosa*, *Bacillus cereus* in nutrient agar medium and for antifungal activity against *Aspergillus niger and Candida albicancs* in potato dextrose agar medium. The compounds were taken at a concentration of 1mg/ml using dimethyl sulphoxide as solvent. Gentamycine (100µg/ml) was used as a standard for antibacterial and Nystatin (100µg/ml) as a standard for antifungal activity. Most of the synthesized compounds exhibited mild to moderate anti-microbial activity against the tested microorganisms. Compounds were found to possess significant antibacterial and antifungal activity when compared to standard drug (*Gentamycine and Nystatin* for antibacterial and antifungal respectively).

It has been observed that the compounds **5a, 5b, 5c** and **5d** showed moderate activity against *Escherichia coli*, *Staphalococcus aureus*, *Proteus vulgaris*, *Psudomonas aeruginosa*, *Bacillus cereus.*

Experimental

Melting points were recorded on electro thermal melting point apparatus are uncorrected. Specific rotations were

measured on Equip-Tronic digital polarimeter model no. Eq 800 at 30^0c in $CHCl_3$. IR spectra were recorded on a Perkin Elmer spectrometer. ^1H NMR were obtained on a Bruker DRX-300 (300 MHz FT NMR) NMR spectrometer in $CDCl_3$ solution with TMS as an internal reference. The mass spectra were recorded on a DART mass spectrometer. Purity of the compounds was checked by thin layer chromatography using Merck silica gel coated aluminum plates and petroleum ether: ethyl acetate as eluent.

Synthesis of 1-phenyl-3-*m*-tolyl carbamide (3)

When *m*-tolyl isocyanate **1** (0.0025M, 0.66ml) was added to the benzylic solution of aniline **2** (0.0025M, 0.63ml, 20ml benzene), stirred it and kept for 24h at room temp. The solvent benzene was distilled off and the resultant solid mass was triturated several times with petroleum ether (60-80^0C) to afford a white granular solid.

The *m*-tolyl isocyanate was purchased from Sigma-Aldrich (U.S.A.)

Synthesis of Tetra-*O*-benzoyl-β-D-glucopyranosyl-*S*-chloro-isothiocarbamoylchloride (4)

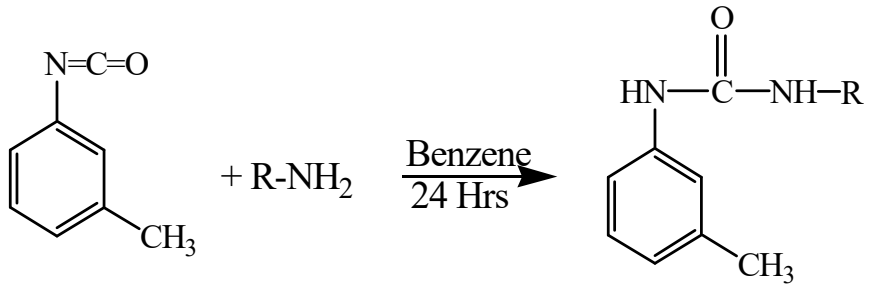
The required Tetra-*O*-benzoyl-β-D-glucopyranosyl-*S*-chloro-isothiocarbamoyl chloride was prepared by earlier known method.

Synthesis of 5- Tetra-*O* -benzoyl-β-D-glucopyranosylimino-3-oxo-2-phenyl-4-*m*-tolyl-1, 2, 4-thidiazolidines (5a-g)

1-Tetra-*O*-benzoyl-β-D-glucopyranosyl-*S*-chloro-isothiocarbamoyl chloride **(4)** (0.005M, 2.3gm in 20 ml $CHCl_3$) when reflux with1-phenyl-3-*m*-tolyl carbamide **(3)** (0.005M, 1.25gm, 20ml $CHCl_3$) for 3 hrs. Evolution of hydrochloride gas was noticed. After condensation benzene was distilled off and the resultant syrupy mass was triturated several times with petroleum ether ($60\text{-}80^0$), to afford white granular solid **(5a-g)**. Crystallized from chloroform-petroleum ether. The product was found to be nondesulphurizable when boiled with alkaline plumbite solution.

When the reaction of Tetra-*O*-benzoyl-β-D-glucopyranosyl-*S*-chloroisothiocarbamoyl chloride extended to several other 1-aryl-3-*m*-tolyl carbamides, corresponding 5-Tetra-*O*-benzoyl-β-D-glucopyranosylimino-3-oxo-2-aryl-4-*m*-tolyl--1,2,4-thidiazolidines **(5b-g)** have been isolated.

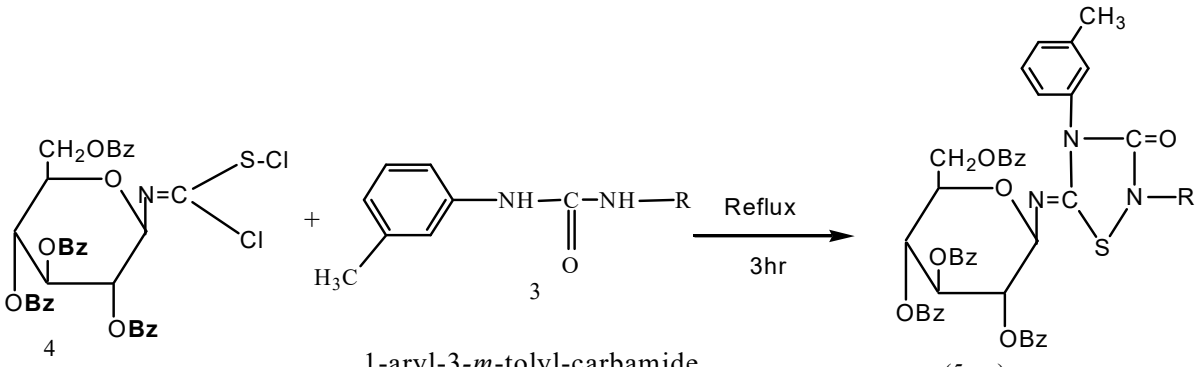
Scheme



1 *m*-tolyl isocyanate

2 Aryl amine

3 1-aryl-3-*m*-tolyl carbamide



Tetra-*O*-benzoyl-β-D-glucopyranosyl-isothiocarbamoyl chloride

1-aryl-3-*m*-tolyl-carbamide

(5a-g)

5-Tetra-*O*-benzoyl-β-D-glucosylimino-3-oxo-2-aryl-4-*m*-tolyl-1,2,4,thidiazolidines

Where, Bz – COC_6H_5

R = a) *Phenyl* , b) *o-Cl-Phenyl*, , c) *m-Cl-Phenyl* ,d) *p-Cl-Phenyl*, e) *o-Tolyl,* f) *m-Tolyl*, g*) p-Tolyl.*

5a: 5-Tetra-*O*-benzoyl-β-D-glucopyranosylimino-3-oxo-2-phenyl-4-*m*-tolyl-1,2,4-thidiazolidines

IR (KBr) cm-1: ν 3062 (Ar-H) str , 2962 (aliphatic C-H) str,1741 (C=O) str, 1602(C=C)str,1178(C-N)str,1282(C-O)str,1492 (C=N) str, 1029 (C-S) str,852 (char. of glucopyranosyl ring). **^{1}HNMR ($CDCl_3$) ppm:** 8.05-7.04 (m,29H, Ar-H), 5.89-4.47 (m, 7H, glucosyl-H), 2.39 (s, 3H, CH_3). **MS** (m/z) : 861 (M+), 579, 457, 335, 105 (Anal. Calcd. For $C_{49}H_{39}O_{10}N_3S$: C 68.29, H 4.52, O 18.58, N 4.87, S 3.71 Found C 68.21, H 4.48, O 18.52, N 4.75, S 3.60 %).

5b: 5-Tetra-*O*-benzoyl-β-D-glucopyranosylimino 3-oxo-2-*o*-chlorophenyl-4-*m*-tolyl-1, 2, 4-thidiazolidines

IR (KBr) cm- 1 : ν 3061 (Ar-H) str , 2902 (aliphatic C-H)str,1730(C=O),1529(C=C)str, 1178 (C-N), 1269(C-O)str, 1452(C=N)str,1026 (C-S) str, 852 (char. of glucopyranosyl ring). **^{1}HNMR ($CDCl_3$) ppm:** 8.22-6.78 (m,28H, Ar-H), 6.14- 4.39 (m, 7H, glucosyl-H), 2.30 (s, 3H, CH_3).

MS: 895 (M+), m/z 579,457, 335, 105. (Anal. Calcd. For $C_{49}H_{38}O_{10}ClN_3S$: C 65.69, H 4.24, O 17.87, N 4.69, S 3.57 Found C 65.66, H 4.26, O 17.81, N 4.65, S 3.48 %).

5e: 5-Tetra-*O*-benzoyl-β-D-glucopyranosylimino 3-oxo-2-*o*-tolyl-4-*m*-tolyl-1, 2, 4-thidiazolidines

IR (KBr) cm- 1: ν 3061 (Ar-H) str , 2910 (aliphatic C-H) str, 1735 (C=O) str,1529(C=C), 1178 (C-N), 1280 (C-O), 1492(C=N)str, 1028 (C-S)str,854 (char. of glucopyranosyl ring).**^{1}HNMR ($CDCl_3$) ppm :** 8.17-6.75 (m,28H, Ar-H), 5.67-4.40 (m, 7H, glucosyl-H), 2.29 (s, 3H, CH3), 2.26(s,3H,CH_3). **MS**: 875 (M+), m/z 579, 457, 335, 263,105. (Anal. Calcd. For $C_{50}H_{41}O_{10}N_3S$: C 68.57, H 4.68, O 18.28, N 4.8, S 3.65 Found C 68.52, H 4.60, O 18.27, N 4.78, S 3.59 %).

Table 1: Physical data of characterization of compounds (5a-g):

Sr. No.	Product (5a-g)	Reactants (2a-g)	Yield (%)	M.P. (^oC)	$[\alpha]_D^{30}$ (0.1, in $CHCl_3$)	Found (Required)		Rf (Pet.Ether:EtOAC) (1:1)
						N	S	
1	5a	-phenyl..	87	118	168	4.75 (4.87)	3.60 (3.71)	0.51
2	5b	-*o*-Cl-Phenyl..	98	121	+181	4.65 (4.69)	3.48 (3.57)	0.62
3	5c	-*m*-Cl-Phenyl..	82	125	-138	4.62 (4.69)	3.50 (3.57)	0.74
4	5d	-*p*-Cl-Phenyl..	85	149	+187	4.61 (4.69)	3.51 (3.57)	0.80
5	5e	-*o*-Tolyl..	86	138	-224	4.78 (4.80)	3.59 (3.65)	0.43
6	5f	-*m*-Tolyl..	91	152	+107	4.69 (4.80)	3.61 (3.65)	0.73
7	5g	-*p*-Tolyl..	93	128	+179	4.72 (4.80)	3.59 (3.65)	0.61

Table-2: Antimicrobial activity of 5-Tetra-*O*-benzoyl-β-D-glucopyranosylimino-3-oxo-2-aryl-4-*m*- tolyl-1, 2, 4 thidiazolidines.(5a-g)
Inhibition zone diameter in mm*

Compound	Bacteria					Fungi	
	E. coli	*P. vulgaris*	*S. aureus*	*P.aeruginosa*	*B. cereus*	*A. niger*	C. albicans
5a	*18*	*19*	*17*	*17*	*16*	*18*	17
5b	*19*	*14*	*14*	*16*	*18*	*20*	19
5c	*17*	*16*	*16*	*17*	*12*	*19*	17
5d	*19*	*16*	*14*	*12*	*19*	*18*	20
5e	*18*	*16*	*16*	*12*	*16*	*17*	16
5f	*14*	*12*	*12*	*14*	*13*	*20*	18
5g	*15*	*14*	*14*	*14*	*19*	*18*	20
Gentamycine	*20*	*20*	*20*	*20*	*20*	---	---
Nystatin	---	---	----	---	---	*22*	22

** Values are the average of three readings / --- No activity was observed.*

Conclusion

A series of new glucosides were synthesized and characterized by IR, ^{1}H NMR and Mass Spectral and Elemental analysis. The titled compounds exhibits promising 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.

Acknowledgement

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