# SYNTHESIS, CHARACTERIZATION AND ANTIMICROBIAL ACTIVITY OF BENZOYL PROTECTED GLUCOPYRANOSYL 1, 2, 4,-THIDIAZOLIDINES

**K.N. Puri**
Department of Chemistry, Shri Shivaji Science College, Amravati (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 new compounds have been established on the basis of chemical transformations and IR, $^1$H NMR and Mass spectral studies. The antimicrobial activity of these compounds have been evaluated against some selected pathogenic organisms like E. coli, P. vulgaris, S. aureus, P. aeruginosa, B.cereus and A. niger, C. albicans to get potent bioactive molecule. The study reveals that most of the compounds show satisfactory antimicrobial activities.*

***Keywords:*** *Synthesis, spectral studies, carbamides, 1, 2, 4-thiadiazolines, Antimicrobial study*

## Introduction

In organic chemistry a series of heterocyclic compounds containing an unsaturated five member ring which contains two Carbons, two Nitrogens and one Sulphur atom are termed as thiadiazolines. Derivatives of thiadiazolines played a crucial role in history of heterocyclic compounds because of their wide variety of important biological properties such as antimicrobial, antioxidant, radio protective, and anti-leishmanial. The synthesis and pharmacological evaluation of variety of glycosyl thiadiazolines have been reported.

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-f). 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.

## 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 $30^0$C in $CHCl_3$. IR spectra were recorded on a Perkin Elmer spectrometer. $^1$H 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.

## General Procedure

### Synthesis of 1-*o*-hydroxy phenyl-3-*m*-tolyl carbamide (3):

When benzene solution of *m*-tolyl isocyanate **1** (0.0025M, 0.66ml) was added to *o*- amino phenol **2** (0.0025M, 0.63 g, 20ml benzene), stirred it and kept for 24h at

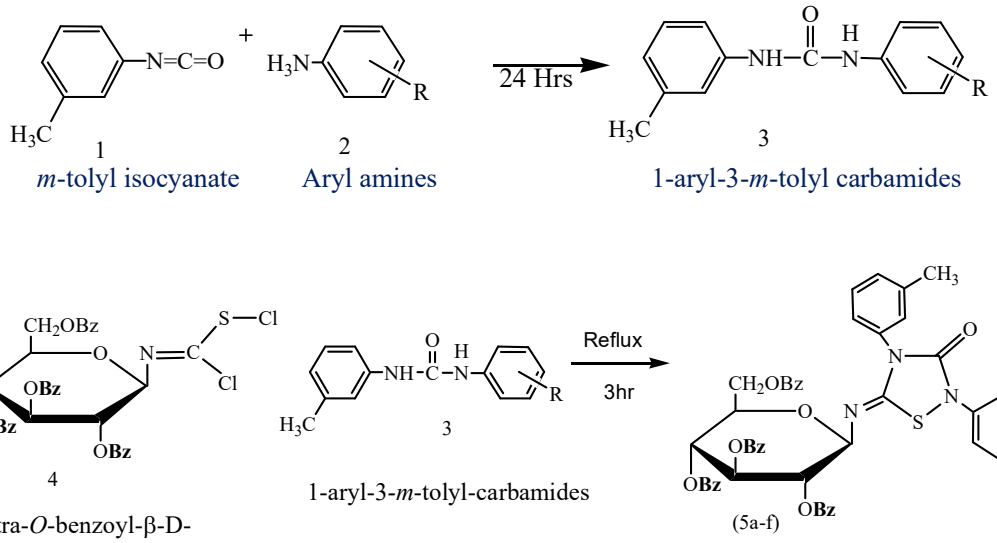
room temp. The solvent benzene was distilled off and the resultant solid mass was triturated several times with petroleum ether (60-80$^0$C) to afford a white granular solid.

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

### Synthesis of Tetra-*O*-benzoyl-β-D-glucopyranosyl-*S*-chloro-isothiocarbamoyl chloride(4):

The required Tetra-*O*-benzoyl-β-D-glucopyranosyl-*S*-chloro-isothiocarbamoyl chloride was prepared by earlier known method[17].

**Scheme:**




Where, Bz – $COC_6H_5$

R = a) *o*-Hydroxy, b) *m*- Hydroxy, c) *p*- Hydroxy, d) *o*-nitro, e) *m*- nitro, f) *p*- nitro.

## Result and Discussion

### Synthesis of 5- Tetra-*O* -benzoyl-β-D-glucopyranosylimino-3-oxo-2-*o*-hydroxy phenyl-4-*m*-tolyl-1, 2, 4-thidiazolidine (5a)

1-Tetra-*O*-benzoyl-β-D-glucopyranosyl-*S*-chloro-isothiocarbamoyl chloride **(4)** (0.005M, 2.3gm in 20 ml $CHCl_3$) when reflux with1-*o*-hydroxy-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 (60-80$^0$), to afford white granular solid **(5a)**. Crystallized from chloroform-petroleum ether. The product was found to be nondesulphurizable when boiled with alkaline plumbite solution.

The IR, $^1$H NMR and mass spectral analysis (Experimental) and elemental analysis (Table 1) clearly indicated the product and assign the structure as **5- Tetra-*O* -benzoyl-β-D-glucopyranosylimino-3-oxo-2-*o*-hydroxy phenyl-4-*m*-tolyl- 1,2,4-thidiazolidine (5a).**

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-f)** have been isolated.

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

**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**: 877 (M+), m/z 579,457, 335, 105. (Anal. Calcd. For $C_{49}H_{39}O_{11}N_3S$: C 67.07, H 4.45, O 20.07, N 4.79, S 3.65 Found C 66.66, H 4.36, O 19.81, N 4.75, S 3.58 %).

**5d: 5-Tetra-*O*-benzoyl-β-D-glucopyranosylimino 3-oxo-2-*o*-nitrophenyl-4-*m*-tolyl-1, 2, 4-thidiazolidine:**

**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, 28H, Ar-H), 5.89-4.47 (m, 7H, glucosyl-H), 2.39 (s, 3H, $CH_3$). **MS** (m/z): 906 (M+), 579, 457, 335, 105 (Anal. Calcd. For $C_{49}H_{38}O_{12}N_4S$: C 64.90, H 4.19, O 21.69, N 6.18, S 3.53Found C 64.71, H 4.18, O 21.52, N 6.15, S 3.50 %).

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

| Sr. No. | Reactants (2a-g) | Product (5a-g) | Yield (%) | M.P (°C) | $[\alpha]_D^{30}$ (0.1, in $CHCl_3$) | Found (Required) | | R*f* (Pet.Ether: EtOAC) (1:1) |
|---|---|---|---|---|---|---|---|---|
| | | | | | | N | S | |
| 1 | -*o*- hydroxy- | 5a | 81 | 128 | +116 | 4.75 (4.79) | 3.58 (3.65) | 0.49 |
| 2 | -*m*- hydroxy- | 5b | 91 | 125 | +110 | 4.65 (4.79) | 3.58 (3.65) | 0.72 |
| 3 | -*p*-hydroxy- | 5c | 78 | 115 | +122 | 4.72 (4.79) | 3.50 (3.65) | 0.74 |
| 4 | -*o*-nitro- | 5d | 86 | 135 | +145 | 6.15 (6.18) | 3.50 (3.53) | 0.75 |
| 5 | -*m*-nitro- | 5e | 80 | 142 | +145 | 6.15 (6.18) | 3.52 (3.53) | 0.85 |
| 6 | -*p*-nitro- | 5f | 75 | 149 | +117 | 6.09 (6.18) | 3.51 (3.53) | 0.73 |

## 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 some of these compound exhibited interesting microbial activities. 5d exhibited most significant activity against *Escherichia coli,* 5a exhibited most significant activity against

*Proteus vulgaris* ,5f and 5b exhibited most significant activity against *Staphylococcus aureus,* 5c exhibited most significant activity against *Psudomonas aeruginosa,* 5a, 5d and 5f exhibited most significant activity against *Bacillus cereus,* 5b and 5f exhibited most significant activity against *A. niger,* 5b and 5d exhibited most significant activity against *C. albicans* respectively. All the other compounds exhibited low to moderate activity.

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

| Compound | Bacteria | | | | | Fungi | |
|---|---|---|---|---|---|---|---|
| | *E. coli* | *P. vulgaris* | *S. aureus* | *P. aeruginosa* | *B. cereus* | *A. niger* | C. albicans |
| **5a** | *17* | *19* | *17* | *12* | *19* | *18* | 17 |
| **5b** | *15* | *14* | *18* | *16* | *18* | *22* | 23 |
| **5c** | *17* | *15* | *16* | *19* | *12* | *19* | 17 |
| **5d** | *19* | *16* | *14* | *12* | *19* | *18* | 20 |
| **5e** | *18* | *15* | *16* | *12* | *16* | *17* | 16 |
| **5f** | *13* | *12* | *19* | *14* | *20* | *20* | 18 |
| ***Gentamycine*** | *20* | *20* | *20* | *20* | *20* | --- | --- |
| ***Nystatin*** | --- | --- | ---- | --- | --- | *22* | 22 |

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

## Conclusion

Based on the foregoing data, it may conclude that chemical transformation and spectral data supports the structure of the synthesized compounds. Thus, the newly synthesized heterocyclic compounds, exhibits comparable bacterial activity 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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