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Synthesis, Characterization And Biological Evaluation Of N-Glucosylated 1,2,4-Dithiazolidines

Snehal A. Chavan[1]*, Baliram N. Berad[1] and Avinash G. Ulhe[1]

1 P.G. Department of Chemistry, Mahatma Jyotiba Phule Educational Campus, Rashtrasant Tukadoji Maharaj Nagpur University, Nagpur-440 033, Maharashtra (India).

ABSTRACT

An efficient synthesis of N-glucosylated 1, 2, 4-dithiazolidines from 1-arylidene-4-arylthiosemicarbazides and N-tetra-O-acetyl-β-D-glucopyranosylimino chloromethane sulphenyl chloride has been worked out. 1-Arylidene-4-arylthiosemicarbazides were synthesized by reacting different aryl/hetero aryl aldehydes/ketones with 4-arylthiosemicarbazides. The identities of new glucosylated heterocycles have been established on the basis of usual chemical transformation, IR, NMR and mass spectral studies. The final compounds were screened for biological activity against different bacterial strains.

Keywords: N-glucosylated 1,2,4-dithiazolidines, 1-arylidene-4-arylthiosemicarbazides, 4-arylthiosemicarbazides

*Corresponding Author Email: i_snehal123@yahoo.com
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INTRODUCTION

The present report describes the use of carbohydrate derivatives in the synthesis of N-glucosylated 1,2,4-dithiazolidines. 1,2,4-Dithiazolidines have been found to possess potent anti-tumor, antituberculosis[1], anti-diabetic and anti-cancer properties[2]. 1,2,4-Dithiazolidine-3,5-dione has been used in orthogonal protection strategies in peptide[3] and amino-glycoside[4] synthesis. This has also proved useful as a masked isocyanate[3,5-6] and (inversely) sulfurization reagent for trivalent phosphorus, particularly for synthesis of phosphorothioate DNA[5].

Carbohydrate derivatives are structurally important component of numerous biologically active natural products and these can be used for the synthesis of drugs. Such type of drugs shows low toxicity and immunogenicity. Presence of glucosyl moiety may result in increased pharmacological properties and bio-adaptability of compound as glycosylation converts water insoluble and unstable organic compounds into the corresponding water soluble and stable compounds. On the other hand, precursor used for the synthesis of N-glucosylated 1,2,4-dithiazolidines i.e. thiosemicarbazone (1-arylidene-4-arylthiosemicarbazide) is a class of biochemically important compounds possessing a wide range of biological activities, and is very promising in the treatment of many diseases.[7-10] Thus heterocyclic derivatives of thiosemicarbazone expected to be biologically active. As 3-(tetra-O-acetyl-β-D-glucopyranosylimino)-4-(arylideneamino)-5-(arylimino)-1,2,4-dithiazolidines possess imine group as one of the substituent; its further reaction with ketene gives β-lactam which is a pharmacophoric moiety in various drugs.

We report herein the synthesis of N-glucosylated 1,2,4-dithiazolidine using straightforward procedure. N-tetra-O-acetyl-β-D-glucopyranosylimino chloromethane sulphenyl chloride is a very useful reagent for the preparation of glucosylated compounds by virtue of their ability to undergo cyclization reactions which was synthesized by the extension of earlier known procedure[11].

MATERIALS AND METHODS:

Experimental:

All melting points were uncorrected and obtained in capillary using paraffin bath. FT-IR spectra were recorded using KBr disk on Perkin Elmer FT-IR KBr spectrophotometer recorded as thin films on KBr pellets with ν_{max} in inverse centimeter. ^{1}H and ^{13}C NMR spectra were taken on Brucker Avance II 400 NMR spectrometer using $CDCl_3$ as solvent and tetramethylsilane (TMS) as internal standard and chemical shifts being reported in parts per million (δ) relative to TMS.

The mass spectra were obtained using electron impact (EI) at an ionizing potential of 70eV. Purity of the compounds was checked on E. Merck TLC aluminium sheet Silica Gel 60 F_{254} using UV light and iodine vapours as a visualizing agent.

Synthesis of N-tetra-O-acetyl-β-D-glucopyranosylimino chloromethane sulphenyl chloride(4):

Through chloroform solution of N-tetra-O-acetyl-β-D-glucopyranosyl isothiocyanate (3.89g in 15 mL chloroform), chlorine gas (0.71g) was passed maintaining temperature 0-5 ^{o}C. The pale yellow reaction mixture was then subjected to the vacuum distillation to give sticky mass which was dissolved in hot benzene and finally petroleum ether was added to benzene solution to precipitate out N-tetra-O-acetyl-β-D-glucopyranosylimino chloromethane sulphenyl chloride as white solid.

General Method for the Synthesis of 1-arylidene-4-arylthiosemicarbazides (3a-h):

Aldehyde/ketone (2) (0.01mol) was added dropwise to a solution of 4-arylthiosemicarbazide (1) (0.01mol) in ethanol. Catalytic amount of AcOH was added to the reaction mixture and refluxed for 4h. The solution was kept overnight to form a precipitate. It was filtered to obtain crystalline solid. (3a)Yield: 70%, mp: 190^{o}C.

General Method for the Synthesis of 3-(tetra-O-acetyl-β-D-glucopyranosylimino)-4-(arylideneamino)-5-(arylimino)-1,2,4-dithiazolidines (5a-h):

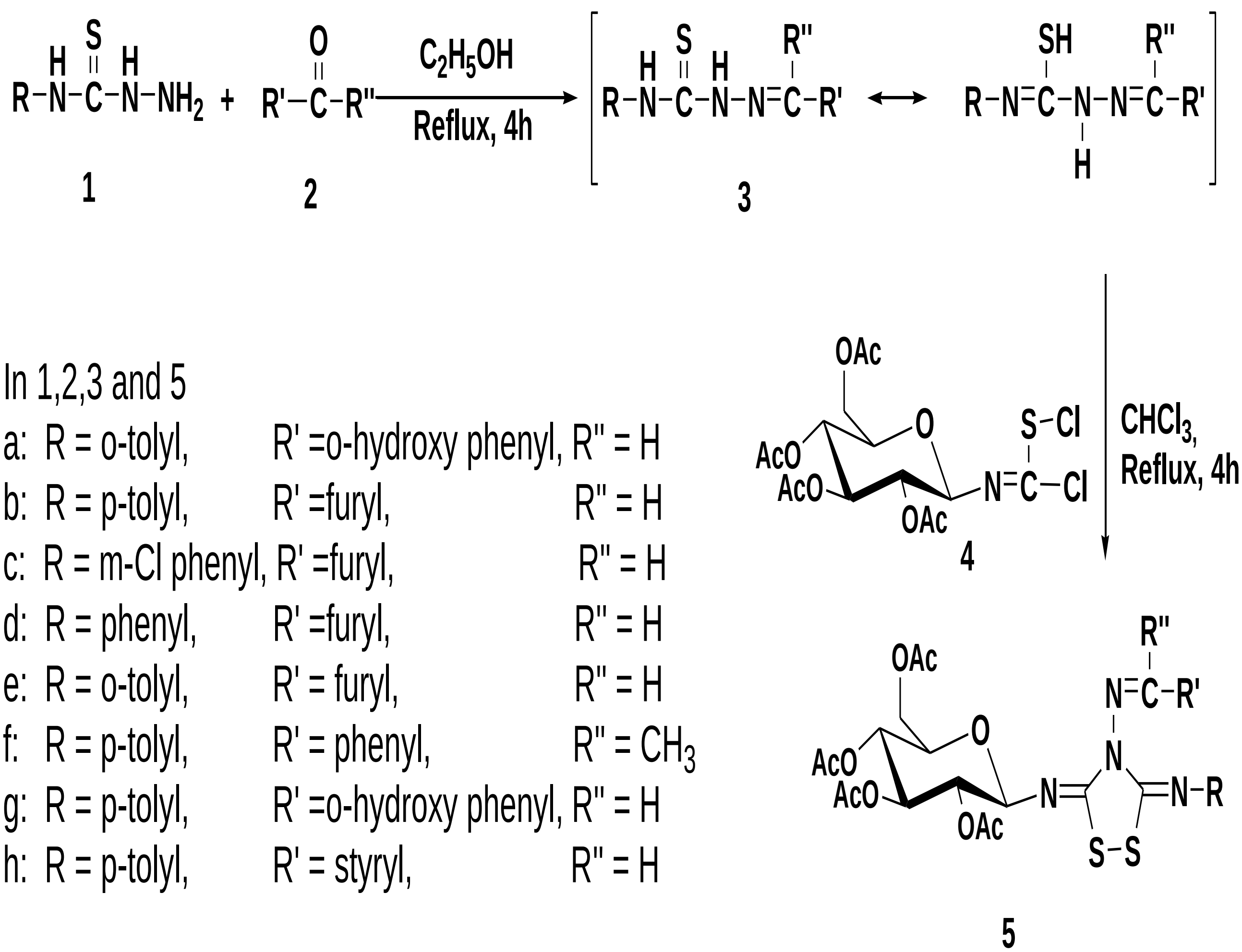
3-(Tetra-O-acetyl-β-D-glucopyranosylimino)-4-(arylideneamino)-5-(arylimino)-1,2,4-dithiazolidines (5a-h) was synthesized by adding N-tetra-O-acetyl-β-D-glucopyranosylimino chloromethane sulphenyl chloride (4) (2.0 mmol) to the stirred solution of 1-arylidene-4-arylthiosemicarbazide (3) (2.0 mmol) in chloroform medium. Reaction mass was allowed to reflux for 4h during which evolution of hydrogen chloride gas was observed. Progress of the reaction was monitored with TLC. After completion of the reaction, the solvent was evaporated under reduced pressure. Crude product thus obtained was recrystallized from 95% ethanol.

Procedure for antimicrobial screening:

Media Used (Nutrient broth): Peptone-10 g, NaCl-10g and Yeast extract 5g, Agar 20g in 1000 ml of distilled water. Initially, the stock cultures of bacteria were revived by inoculating in broth media and grown at 37ºC for 18 hrs. The agar plates of the above media were prepared and wells were made in the plate. Each plate was inoculated with 18 h old cultures (100 µl, 10^4 cfu) and spread evenly on the plate. After 20 minutes, the wells were filled with sample solution (15mg/ml). The control wells were filled with Gentamycin. All the plates were incubated at 37 ºC for 24 h and the diameter of inhibition zones were noted in mm.

RESULTS AND DISCUSSION

The reaction of 1-arylidine -4-arylthiosemicarbazide was carried out with N-tetra-O-acetyl-β-D-glucopyranosylimino chloromethane sulphenyl chloride in refluxing chloroform for 4h as shown in **scheme 1**. The evolution of hydrogen chloride gas was clearly noticed as tested with moist blue litmus paper. The solvent was distilled off to yield 3-(tetra-O-acetyl-β-D-glucopyranosylimino)-4-arylideneamino-5-arylimino-1,2,4-dithiazolidine (5) as a solid mass which was recrystallized from ethanol. The final compound (5) was charred on treatment with concentrated sulphuric acid which indicates the presence of glucosyl moiety. In the IR spectra, the characteristic band at 1742cm^{-1} due to the C=O stretching vibration of the acetyl groups indicates that the glucosides are acetylated. The bands corresponding to C=N, C-N, C-S and S-S stretching vibration are observed at 1579-1622, 1316-1382, 733-753 and 593-613 cm^{-1} respectively confirms the formation of dithiazolidine ring. The coupling constant $J_{1\text{-}H,2\text{-}H}$ (8.16–9.6 Hz) is an evidence which confirms the β configuration in all the compounds (5a-h).



Scheme 1: Synthetic route for compound 5a-h

Table-1: Physical characterization data of 3-(tetra-O-acetyl-β-D-glucopyranosylimino)-4-(arylideneamino)-5-(arylimino)-1,2,4-dithiazolidines (5a-h)

Sr. No.	Compound	Molecular Formula	Melting Point °C	%Yield	R_f (30% EtOAc:Hexane)
1.	5a	$C_{30}H_{32}N_4O_{10}S_2$	150	99.0	0.45
2.	5b	$C_{28}H_{30}N_4O_{10}S_2$	138	92.91	0.60
3.	5c	$C_{27}H_{27}ClN_4O_{10}S_2$	130	97.90	0.60
4.	5d	$C_{27}H_{28}N_4O_{10}S_2$	100	86.82	0.60
5.	5e	$C_{28}H_{30}N_4O_{10}S_2$	148	93.58	0.60
6.	5f	$C_{31}H_{34}N_4O_9S_2$	150	91.95	0.60
7.	5g	$C_{30}H_{32}N_4O_{10}S_2$	169	97.87	0.45
8.	5h	$C_{32}H_{34}N_4O_9S_2$	138	93.16	0.60

Characterization of N-tetra-O-acetyl-β-D-glucopyranosylimino chloromethane sulphenyl chloride(4):

Yield-3.7g, 80.43 %, mp - 122 °C. Molecular formula: $C_{15}H_{19}Cl_2NO_9S$; IR (KBr)ν_{max} cm^{-1}: 1654 (C=N), 746 (C-S), 1037(C-O), 1742 (O=C-O), 845 (D-glucosyl ring deformation); ^{1}H NMR δ ppm ($CDCl_3$): 5.32-5.27(1H, t, J=9.4Hz, H_1), 5.21-3.81(6H, m, glucosyl proton), 2.12-2.01(m, 12H, acetyl protons). Mass analysis: Molecular ion peak M^+ (m/z) ($Cl^{35, 37}$): 463.

Characterization of final Compounds (5a-h):

3-(Tetra-O-acetyl-β-D-glucopyranosylimino)-4-(o-hydroxyphenylideneamino)-5-(o-tolylimino)- 1,2,4-dithiazolidine (5a):

IR (KBr)ν_{max} cm^{-1}: 1614 (C=N), 1380 (C-N), 739 (C-S), 609 (S-S), 1240 (N-N), 1743 (O=C-O), 849 (D-glucosyl ring deformation), 3461 (-OH); ^{1}H NMR ($CDCl_3$) δ ppm: 7.26 (1H, s, =CH), 7.58-6.99 (7H, m, aromatic protons), 6.75 (1H, bs, phenolic OH) 5.23-5.18 (1H, t, J=9.32Hz, H_1), 5.13-3.81 (6H, m, glucosyl protons), 2.38 (3H, s, -CH_3), 2.18-1.92 (12H, m, acetyl protons); ^{13}C NMR ($CDCl_3$) δ ppm: 169.67- 168.81(4 C=O), 168.48 (2 ring C=N), 140.65(C=N), 158.84-125.63 (12 aromatic carbons), 88.18-61.10 (glucosyl carbons), 20.50-20.11 (5 -CH3); Mass m/z: 169(TAG-2CH_3COOH and –CH_2=C=O)$^+$, 413(TAGNCS + Na)$^+$ (where TAG= Tetra-O-acetyl-β-D-glucopyranosyl), 609(M-S_2+1)$^+$

3-(Tetra-O-acetyl-β-D-glucopyranosylimino)-4-(furfurylideneamino)-5-(p-tolylimino)-1,2,4-dithiazolidine (5b):

IR (KBr)ν_{max} cm^{-1}: 1621 (C=N), 1316 (C-N), 753 (C-S), 593 (S-S), 1200 (N-N), 1742 (O=C-O), 885 (D-glucosyl ring deformation); ^{1}H NMR ($CDCl_3$) δ ppm: 7.03 (1H, s, =CH), 7.85-6.50 (7H, m, aromatic protons), 5.34-5.32 (1H, t, J=9.24Hz, H_1), 5.15-3.92 (6H, m, glucosyl protons), 2.20-2.01 (12H, m, acetyl protons); ^{13}C NMR ($CDCl_3$) δ ppm: 170.64- 169.41(4 C=O), 168.79 (2 ring C=N), 148.70(C=N), 144.89-114.58 (10 aromatic carbons), 89.03-61.45 (glucosyl carbons), 20.88-20.45 (5 -CH3); Mass m/z: 169 (TAG-2CH_3COOH and –CH_2=C=O)$^+$, 271(TAG-CH_3COOH)$^+$, 331(TAG)$^+$, 413(TAGNCS + Na)$^+$, 489(M-tolyl and furyl +1)$^+$, 475(M-furyl and C_7H_7N)$^+$

3-(Tetra-O-acetyl-β-D-glucopyranosylimino)-4-(furfurylideneamino)-5-(m-Cl phenylimino)-1,2,4-dithiazolidine (5c):

IR (KBr)ν_{max} cm^{-1}: 1579 (C=N), 1379 (C-N), 742 (C-S), 607 (S-S), 1235 (N-N), 1742 (O=C-O); ^{1}H NMR ($CDCl_3$) δ ppm: 7.26 (1H, s, =CH), 7.97-6.77 (7H, m, aromatic protons), 5.37-4.11 (7H, m, glucosyl protons), 2.15-2.01 (12H, m, acetyl protons); ^{13}C NMR ($CDCl_3$) δ ppm: 169.73- 168.77(4 C=O), 168.25 (2 ring C=N), 148.94(C=N), 144.25-111.83 (10 aromatic carbons), 88.24-60.97 (glucosyl carbons), 20.41-20.10 (4 -CH3); Mass m/z:169(TAG-2CH_3COOH and –CH_2=C=O)$^+$, 413(TAGNCS + Na)$^+$, 599(M-furyl)$^+$, 602(M-S_2)$^+$, 629(M-Cl^{37})$^+$

3-(Tetra-O-acetyl-β-D-glucopyranosylimino)-4-(furfurylideneamino)-5-(phenylimino)-1,2,4-dithiazolidine (5d):

IR (KBr)ν_{max} cm^{-1}: 1619 (C=N), 1379 (C-N), 738 (C-S), 611 (S-S), 1237 (N-N), 1742 (O=C-O), 846 (D-glucosyl ring deformation); ^{1}H NMR ($CDCl_3$) δ ppm : 7.05 (1H, s, =CH), 7.72-6.62 (8H, m, aromatic protons), 5.34-5.29 (1H, t, J=9.24Hz, H_1), 5.15-3.92 (6H, m, glucosyl protons), 2.15-2.01 (12H, m, acetyl protons)

3-(Tetra-O-acetyl-β-D-glucopyranosylimino)-4-(furfurylideneamino)-5-(o-tolylimino)-1,2,4-dithiazolidine (5e):

IR (KBr)ν_{max} cm^{-1}: 1618 (C=N), 1381 (C-N), 733 (C-S), 613 (S-S), 1237 (N-N), 1742 (O=C-O), 846 (D-glucosyl ring deformation); ^{1}H NMR ($CDCl_3$) δ ppm: 7.04 (1H, s, =CH), 7.82-6.33 (7H, m, aromatic protons), 5.36-5.32 (1H, t, J=8.16Hz, H_1), 5.09-3.89 (6H, m, glucosyl protons), 2.35 (3H, s, -CH_3), 2.15-2.01 (12H, m, acetyl protons); Mass m/z:169 (TAG-2CH_3COOH and –CH_2=C=O)$^+$, 413(TAGNCS + Na)$^+$, 475(M-furyl and C_7H_7N)$^+$

3-(Tetra-O-acetyl-β-D-glucopyranosylimino)-4-(phenylethylideneamino)-5-(p-tolylimino)-1,2,4-dithiazolidine (5f):

IR (KBr)ν_{max} cm^{-1}: 1585 (C=N), 1378 (C-N), 734 (C-S), 608 (S-S), 1237 (N-N), 1742 (O=C-O), 844 (D-glucosyl ring deformation); ^{13}C NMR ($CDCl_3$) δ ppm: 170.64- 169.41(4 C=O), 168.79 (2 ring C=N), 147.21(C=N), 137.30-124.54 (12 aromatic carbons), 89.03-61.44 (glucosyl carbons), 21.06-20.45 (6 -CH3); Mass m/z: 169 (TAG-2CH_3COOH and –CH_2=C=O)$^+$, 331(TAG)$^+$, 413(TAGNCS + Na)$^+$, 281(M-TAG+1)$^+$

3-(Tetra-O-acetyl-β-D-glucopyranosylimino)-4-(o-hydroxy phenylideneamino)-5-(p-

tolylimino)-1,2,4-dithiazolidine (5g):

IR (KBr)ν_{max} cm^{-1}: 1620 (C=N), 1382 (C-N), 752 (C-S), 612 (S-S), 1237 (N-N), 1742 (O=C-O), 846 (D-glucosyl ring deformation), 3460 (–OH); Mass m/z: 609$(M\text{-}S_2+1)^+$

3-(Tetra-O-acetyl-β-D-glucopyranosylimino)-4-(phenylallylideneamino)-5-(p-tolylimino)-1,2,4-dithiazolidine (5h):

IR (KBr)ν_{max} cm^{-1}: 1622 (C=N), 1382 (C-N), 738 (C-S), 606 (S-S), 1237 (N-N), 1742 (O=C-O), 845 (D-glucosyl ring deformation); Mass m/z: 169 (TAG-2CH_3COOH and –CH_2=C=O)$^+$, 271(TAG-CH_3COOH)$^+$, 413(TAGNCS + Na)$^+$, 605(M-Ph)$^+$, 475(M- C_7H_7N and styryl)$^+$, 489(M-tolyl and styryl)$^+$

Final compounds (5a-e) were screened for antibacterial activity against E.coli, S.aureus and B.subtilis micro-organisms. Amongst the screened compounds, 5b and 5c showed moderate activity while others showed less activity.

Table-2: Antibacterial activities of final compounds (5a-h)

Sr.No.	Compound	E.coli	S.aureus	B.subtilis
1.	5a	5	1	1
2.	5b	6	2	3
3.	5c	8	3	3
4.	5d	4	1	0
5.	5e	5	3	1
6.	Gentamycin	18	15	10

CONCLUSION:

Overall, we have reported one pot synthesis of 3-(tetra-O-acetyl-β-D-glucopyranosylimino)-4-(arylideneamino)-5-(arylimino)-1,2,4-dithiazolidines. The method used for the syntheses were short, simple and efficient with high percentage yield. As synthesized N-glucosylated 1,2,4-dithiazolidines possess imine group, these have significant potential to be of use in the synthesis of β-lactam which is a pharmacophoric scaffold.

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