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Design, Synthesis and Antimicrobial Assay of 1-glycosyl -3-(5-phenylimino)-1, 2, 4-thiadiazolidine carbamides

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ABSTRACT

1-glycosyl-3-(5-phenylimino-1,2,4-thidiazolidine) carbamides have been synthesized by the interaction of various glycosyl isocyanates with 3-amino-5-phenylimino-1, 2, 4- thiadiazolidine. Furthermore, 3-amino-5-phenylimino-1, 2, 4-thiadiazolidine have been synthesized by the oxidative cyclization of 1-amidino-3-aryl thiocarbamide. This 1-amidino 3-aryl thiocarbamide was prepared by the interaction of guanidine nitrate and phenyl isothiocyanate. The identities of these newly synthesized compounds have been established on the basis of usual chemical transformations, elemental analysis and IR, ^{1}H NMR and Mass spectral studies. The titled compounds were screened for their antibacterial assay against human pathogenic bacteria like E. coli, S. aureus, P. vulgaris, P. aeruginosa and K. pneumonia; for antifungal assay against plant pathogenic fungi like A. flavous, S. rolfisi, F. oxysporum and R. bataticola, to get potent bioactive molecule.

Keywords: Glycosyl isocyanates, 3-amino-5-phenylimino-1, 2, 4- thiadiazolidine, 1-amidino-3-aryl thiocarbamide, antibacterial and antifungal assay.

INTRODUCTION

Thiadiazole especially considered ‘‘privileged’’ structures for the many bioactive products which are of significance for human and animal health[1] and synthesis and development of new drugs [2-3]. Likewise saccharide with its *N*-linked heterocyclic derivatives are known for having variety of biological[4-7], pharmacological[8-9] properties and many of them function as therapeutic agents[10-11].

It is known that the biological activity of molecule is related to their structure and physicochemical properties. Hence, there is need to design the new compounds with further modification of 1,2,4-thiadiazolidine. In present investigation we reported the synthesis and antibacterial assay of *N*-linked glycosyl 1,2,4-thiadiazolidine carbamides.

MATERIALS AND METHODS

The melting point of newly synthesized compounds were recorded using open capillary tube on Mac Digital melting point apparatus and are uncorrected. IR spectra were recorded in KBr disks on SHIMADZU IR Affinity-1 FTIR spectrometer. ^{1}H NMR spectra were run on BRUKER AVANCE II 400 NMR spectrometer instrument using $CDCl_3$ solution with TMS as internal standard. The MASS spectra were recorded on WATER, Q-TOF Micromass (LC-MS) spectrometer. Optical rotation $[\alpha]^{41}_D$ were measured on the Equip-Tronics Digital Polarimeter EQ-800 at 41°C in $CHCl_3$. The purity of the synthesized compounds have been checked by the Thin layer chromatography (TLC) was performed on E-Merk pre-coated silica gel plates and spot were visualized by iodine vapor.

STARTING MATERIAL

1. Synthesis of Tetra-*O*-acetyl-β-D-glucosyl isocyanate (1a)

The Tetra-*O*-acetyl-β-D-glucosyl isocyanate **(1a)** was synthesized by the condensation of tetra-*O*-acetyl- α-D-glucosyl bromide and lead cyanate.

Similarly, Hepta-*O*-acetyl- β -D-lactosyl isocyanate (1b), Hepta-*O*-acetyl-β-D-maltosyl isocyanate (1c), Tetra-*O*-benzoyl-β-D-glucosyl isocyanate (1d), Hepta-*O*- benzoyl-β-D-lactosyl isocyanate (1e), Hepta-*O*- benzoyl-β-D-maltosyl isocyanate (1f) were synthesized.

2. Synthesis of Aryl isothiocyanate [12]

Aryl isothiocyanate was prepared by oxidative decomposition of ammonium aryl dithiocarbamate by lead nitrate.

3. Synthesis of 1- amidino-3-phenyl thiocarbamide (2)[13]

1- amidino-3-phenyl thiocarbamides was synthesized by the interaction of guanidine nitrate and phenyl isothicyanate.

4. Synthesis of 3-amino-5-phenylimino-1, 2, 4-thiadiazolidine (3)[14]

3-amino-5-phenylimino-1, 2, 4-thiadiazolidine (3) was synthesized by the oxidative cyclization of 1-amidino-3-phenyl thiocarbamide **(2)** using iodine.

5. Synthesis of 1-Glycosyl -3-(5-phenylimino-1,2,4–thidiazolidine) carbamide (4a)

In a typical preparation of 1-Glycosyl-3-(5-phenylimino-1, 2, 4-thidiazolidine) carbamide (4a) (where, Glycosyl = Tetra-*O*-acetyl-β-D-glucosyl), the benzene solution of 3-amino-5-phenylimino-1,2,4-thiadiazolidine (3) and Glycosyl isocyanate (1a) was refluxed for 2 hr 30 min. The reaction was easily monitored by the TLC (Thin Layer Chromatography) and also recorded the R_f values After completion of reaction, the solvent gets distilled off to obtained a sticky mass. The sticky mass was triturated several times with petroleum ether (60-80^o) afford off white solid (4a). It was purified by chloroform petroleum ether system. It gave a granular solid, m.p. 111^{o}C.

Similarly, when the reactions of various Glycosyl isocyanates **(1b-f**) were extended to 3-amino-5-phenylimino-1,2,4-thiadiazolidine **(3)**, the related 1-Glycosyl-3-(5-phenylimino-1,2,4–thidiazolidine) carbamides **(4b-f)** were isolated.

RESULT AND DISCUSSION

All the product were puirfied by the chloroform-petroleum ether system before recording the physical data Table 1. The purity of compounds was checked by TLC (Thin Layer Chromatography). The spectral analysis [15-17] IR, ^{1}H NMR and Mass spectra of the product were observed. Optical rotation of the products were recorded.

All the compounds have been screened for antibacterial assay using cup plate agar method[18-19] by measuring the inhibition zone in mm. Amikacin (100g/ml) was used as standard for antibacterial activity. Antibacterial assay of these synthesized compounds indicated that the compound 4e was found active towards *E. coli*, 4b and 4e were exhibit significant activities against *S. aureus*, 4d, 4e and 4f compounds show good activities against *P. vulgaris*, 4d, 4e and 4f compounds were found very active towards *P. aeruginosa* and 4d, 4e and 4f compounds were exhibit most significance activities against *K. pneumonia*. While other compounds show low to moderate activities (Table 2).

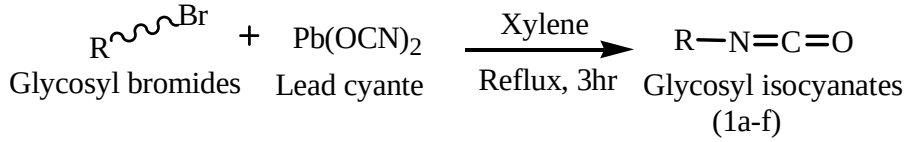
All the compounds have been screened for antifungal assay using spore suspension method[20] by measuring the inhibition zone in mm. Tropiconazol was used as standard for antibacterial activity. Antifungal assay of these synthesized compounds indicated that the compounds 4e and 4f were found active towards *A. flavous*, 4d, 4e and 4f were exhibit significant activities against *S. rolfisi*, 4e and 4f compounds show good activities against *F. oxysporum*, 4e compound show appreciable activites against *R. bataticola.* While other compounds show low to moderate activities (Table 3).

Spectral Data

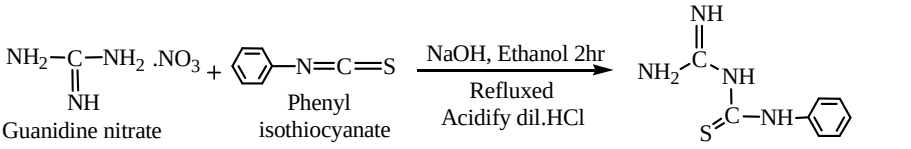
4a) IR (KBr, cm^{-1}) : υ 3497 (N-H stretch), 3022 (Aromatic C-H stretch), 2999 (Aliphatic C-H stretch), 1741 (C=O), 1666 (C=N), 1531 (C=C), 1379 (C-N), 1236 (C-O), 983 (characteristic of glucose unit), 846 (monosubstituted benzene ring), 756 (C-S). **^{1}H NMR (CDCl$_3$, ppm) :** δ 7.21 (1H, s, NH), δ 6.26-5.10 ppm (5H, m, Aromatic protons), δ 5.07-4.01 ppm (7H, m, Glucosyl protons), δ 4.21 ppm (1H, s, NH), 1.97-1.96 ppm (12H, acetyl protons), 1.95 ppm (1H, s, NH). **Mass (m/z):** 564 (M^+), 414, 413, 331, 271, 211, 169, 109. Anal. Calcd. for $C_{23}H_{26}O_{10}N_5S$, requires : C, 42.20; H, 4.60; N, 12.40; S, 11.34. Found : C, 42.18; H, 4.59; N, 12.39; S, 11.31%.

Reaction schemes

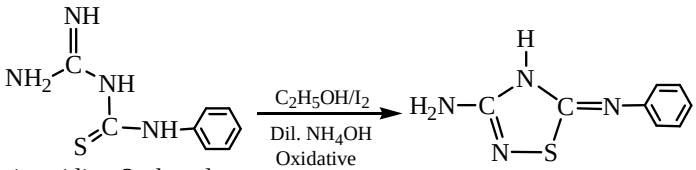
Scheme I



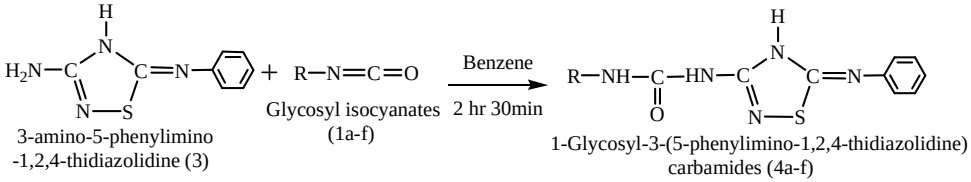
Scheme II



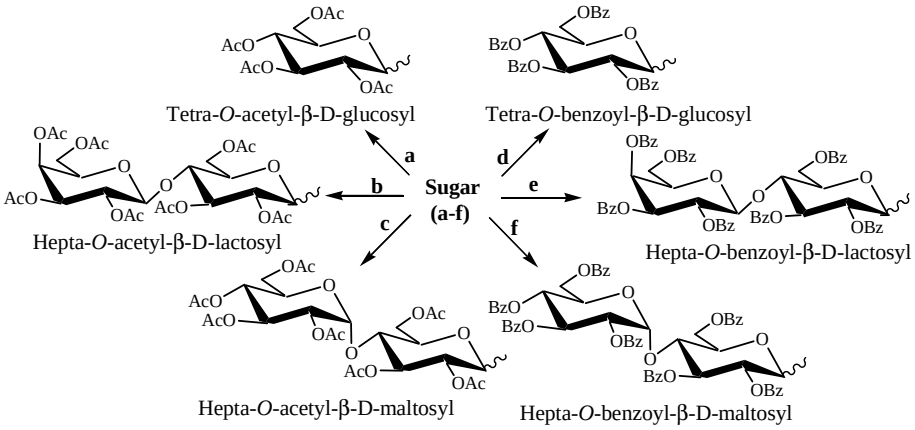
Scheme III



Scheme IV



Where, R =



Where, OAc = $OCOCH_3$ **and OBz** = $OCOC_6H_5$

Table 1: General characterization of 1-Glycosyl-3-(5-phenylimino-1,2,4–thiadiazolidine) carbamides (4a-f)

Sr. No.	Compds (4a-f)	Yield (%)	M.P. (0C)	Found (Required)		$[\alpha]_D^{41}$ (0.2, in CHCl3)	Rf value, (Ethyl acetate: Petroleum ether, 7:3)
				N	S		
1.	4a	61.22	111	12.39 (12.41)	11.31 (11.34)	+134.3	0.70
2.	4b	64.82	139	8.18 (8.20)	7.48 (7.50)	+147.9	0.79
3.	4c	65.18	145	8.19 (8.20)	7.49 (7.50)	+142.4	0.72
4.	4d	71.28	154	8.57 (8.61)	7.85(7.87)	-199.7	0.66
5.	4e	72.00	161	5.42 (5.43)	4.95 (4.97)	+225.8	0.92
6.	4f	76.89	168	5.42 (5.43)	4.96 (4.97)	+220.5	0.76

Satisfactory C and H elemental analysis found in all compounds.

Table-2: Antibacterial assay of 1-Glycosyl-3-(5-phenylimino-1, 2, 4–thiadiazolidine) carbamide (4a-f)

	Antibacterial assay Inhibition zone diameter in mm**				
Compounds	***E.coli***	***S. aureus***	***P.vulgaris***	***P. aeruginosa***	***K. pneumonia***
4a	09	09	09	08	09
4b	09	**12**	10	07	10
4c	10	09	10	10	08
4d	11	10	**12**	**12**	**16**
4e	**12**	**16**	**14**	**16**	**19**
4f	11	11	**13**	**18**	**21**
Amikacin	25	23	24	23	25
DMSO	--	--	--	--	--

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

Table-3: Antifungal assay of 1-Glycosyl-3-(5-phenylimino-1, 2, 4–thiadiazolidine) carbamide (4a-f)

	Antifungal assay Inhibition zone diameter in mm**			
Compounds	***A. flavous***	***S. rolfisi***	***F. oxysporum***	***R. bataticola***
4a	17	16	10	07
4b	21	22	11	08
4c	19	25	10	09
4d	20	**30**	14	10
4e	**24**	**32**	**15**	**12**
4f	**27**	**35**	**15**	11
Tropiconazol	44	45	41	40
DMSO	--	--	--	--

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

4b) IR (KBr, cm^{-1}) : υ 3487 (N-H stretch), 3062 (Aromatic C-H stretch), 2978 (Aliphatic C-H stretch), 1747 (C=O), 1651 (C=N), 1523 (C=C), 1371 (C-N), 1226 (C-O), 1056, 981 and 941 (characteristic of lactose unit), 846 (monosubstituted benzene ring), 735 (C-S). **^{1}H NMR (CDCl$_3$, ppm) :** δ 7.20 (1H, s, NH), δ 6.19-5.28 ppm (5H, m, Aromatic protons), δ 5.08-3.70 ppm (14H, m, Lactosyl protons), δ 2.11-1.94 ppm (21H acetyl protons), 1.90 ppm (2H, s, NH). **Mass (m/z) :** 853 (M^+), 701, 619, 331, 271, 211, 169, 109. Anal. Calcd. for $C_{35}H_{43}O_{18}N_5S$, requires : C, 49.23; H, 5.04; N, 8.20; S, 7.50. Found : C, 49.21; H, 5.01; N, 8.18; S, 7.48%.

4f) IR (KBr, cm^{-1}) : υ 3319 (N-H stretch), 3062 (Aromatic C-H stretch), 2960 (Aliphatic C-H stretch), 1732 (C=O), 1647 (C=N), 1525 (C=C), 1315 (C-N), 1269 (C-O), 1070, 1026, 1001 and 937 (characteristic of maltose unit), 852 (monosubstituted benzene ring), 750 (C-S). **^{1}H NMR (CDCl$_3$, ppm) :** δ 7.97-6.03 ppm (40H, m, Aromatic protons), δ 5.85-4.11 ppm (14H, m, Maltosyl protons), δ 1.90 ppm (1H, s, NH), δ 1.75 ppm (1H, s, NH), δ 1.17 ppm (1H, s, NH). **Mass (m/z) :** 1287 (M^+), 1135, 1053, 931, 457, 231, 105. Anal. Calcd. for $C_{70}H_{57}O_{18}N_5S$, requires : C, 65.26; H, 4.42; N, 5.43; S,4.97. Found : C, 65.25; H, 4.41; N, 5.42; S, 4.96%.

CONCLUSION

We synthesized sugar thiadiazolidine carbamide derivatives (4a-f). They have been isolated in good yield. The identities of these newly synthesized compounds have been established on the basis of usual chemical transformations and spectral studies. Most of the compounds showed promising antibacterial activities against the highly pathogenic organism. The method adopted is very simple, efficient and inexpensive and it is useful in synthesizing pharmacologically important molecule. Most of the synthesized compounds showed promising antibacterial and antifungal activity against the highly pathogenic organism to get more potent molecule.

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