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Synthesis of novel glycosyl thiadiazole triazines and screening for antimicrobial activity

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In continuation to our search for a new bioactive potent molecule, we have synthesized several new 1-glycosyl-3-(5-phenyl-[1,3,4]thiadiazolyl)-carbamides by the interaction of various glycosyl isocyanates with 2-amino-5-phenyl-[1,3,4]-thiadiazole in acetone medium. Furthermore, several novel 6-glycosyl-2-phenyl-5-phenylimino-5,6-dihydro-[1,3,4]thiadiazolo [3,2-a][1,3,5]triazin-7-one have been synthesized by the interaction of phenyl isocyanodichloride and 1-glycosyl-3-(5-phenyl-[1,3,4]thiadiazolyl)-carbamides. The identities of these newly synthesized glycosyl carbamides and glycosyl thiadiazolo triazine have been established based on usual chemical transformations and IR, ^{1}H and ^{13}C NMR and mass spectral studies and these will be assayed for their antibacterial activity against common pathogens like *E. coli*, *S. aureus*, *P. vulgaris*, *S. typhi*, *K. pneumoniae*, *Pseudomonas aeruginosa* and for antifungal activity against *Aspergillus niger* and *Candida albican* to get potent bioactive molecule.

Keywords: Glycosylisocyanates, Thiadiazole, Glycosyl Carbamides, Glycosyl Thiadiazolotriazine, Antimicrobial Activity

O-Glycosides have been the subject of considerable interest in carbohydrate chemistry as many carbohydrate derivatives exhibit very interesting biological activities. Glycosyl isocyanate is a good precursor and versatile intermediate for the synthesis of *S*- and *N*-glycosides. Heterocyclic compounds offer a high degree of structural diversity and have proven to be broadly useful as therapeutic agents. Owing to the biological activities of glycosides, carbamides, and thiadiazolo triazines, we have designed and synthesized compounds through the combination of different pharmacophores in one structure to prepare molecules with enhanced antimicrobial activity.

The chemistry and diverse applications of heterocyclic glycosyl derivatives have received much attention due to their pronounced biological activity. Recently some condensed derivatives of 1,3,4-thiadiazole were reported to possess a broad spectrum of biological activity, including antibacterial, antitumor, fungicidal, and herbicidal properties. However, thiadiazoles and their condensed analogs are still insufficiently studied. In continuation to the search for substances possessing the increased ability to permeate through biological membranes of various infectious species[1], we have attempted to prepare thiadiazolotriazine derivatives. The diverse and interesting biological activity of thiadiazoles has been reported[2,3]. It is well known that these heterocycles are valuable building blocks. Many methods for the preparation of these heterocyclic ring systems and their fused analogs have been described in the literature. Heterocycles represent the class of compounds that contains the majority of biologically or pharmacologically active substances. A vast number of 1,3,5-triazines[4,5] with antifungal, herbicidal, antibacterial, and tubercolo-static activities have also been described. Similarly, 1,3,5-traizines were also reported as potential fungicdes[6]. In the present investigation, we have fused 1,3,4-thiadiazole nucleus with 1,3,5-triazine ring to prove how far this combination could enhance the antimicrobial activity. The reaction sequence leading to the formation of the title compounds has been outlined in the reaction scheme.

In the last few years, the intensive use of antibiotic has led to an increase in the emergence of resistant bacteria. Hence, there is a growing need for a new class of antibacterial compounds, that have different mechanisms of action compared to existing drugs. Carbohydrate is the key element in the number of biological events[7,8] and plays a crucial role in their synthetic strategy as well. Its *N*-linked glycosyl

derivatives also exhibit a wide range of medicinal activities[9-11]. Isocyanates of sugars are one of the versatile reagents in the field of synthetic carbohydrate chemistry. *S* and *N*-glycosylated derivatives and their utilities in medicinal chemistry have been extensively studied[12-14]. Thiadiazole and its derivatives also show noticeable pharmaceutical and biological values. Not only the glycosyl carbamides but also the heterocyclic compounds containing thiadiazolotriazine fused rings gain immense importance in human life due to their various applications in pharmaceutical, industrial, and medicinal chemistry. When one biologically active molecule is linked to another, the resultant molecule generally has an increase in potency[15-19]. Keeping in view these observations, in search for a new bioactive potent molecule, it was thought worthwhile to synthesize and examine for antimicrobial activity of different *N*-linked glycosyl carbamides[20] and thiadiazolotriazine.

Results and Discussion

Herein, we report the synthesis of various 1-glycosyl-3-(5-phenyl-[1,3,4]thiadiazolyl) carbamides-(3a-f) and 6-glycosyl-2-phenyl-5-phenylimino-5,6-dihydro-[1,3,4]thiadiazolo [3,2-a][1,3,5]triazin-7-one(5a-f). All products were crystallized from ethanol before recording the physical data (Table 1). The reactions are monitored by TLC. The structure of the newly synthesized compounds was elucidated by their IR, ^{1}H NMR, ^{13}C NMR, and Mass spectral analysis[21-23]. The optical rotation of the product was also recorded. In the IR spectra, the band due to C=N and C=O group, which is present in all studies compounds were observed at about 1610 cm^{-1} and 1730 cm^{-1} respectively. The bands at about 1100-1000 cm^{-1} and 910-900 cm^{-1} were characteristic of the glycosyl ring. In ^{1}H NMR spectra, the aromatic protons were observed at about δ 8.2 to 7.1 ppm. In all the synthesized compounds, the glycosyl protons appeared at about δ 6.0 to 3.5 ppm. The acetyl protons were observed at about δ 2.1 to 2.01 ppm in acetylated derivatives. In ^{13}C NMR spectra of synthesized compounds, carbonyl carbon, and aromatic carbon peaks were observed at about δ 170 to 166 and δ 133 to 128 ppm respectively. Glycosyl carbons were observed at about δ 77 to 62 ppm. The acetyl carbons were observed at about δ 29 to 20 ppm in acetylated derivatives. In Mass spectra, molecular ion peak (M^+) and confirmative fragment peaks were obtained from ESI-MS.

Antibacterial activity

The newly synthesized derivatives were investigated for antibacterial activity against six pathogenic bacterial strains namely *Escherichia coli*, *Staphylococcus aureus*, *Proteus vulgaris*, *Salmonella typhi*, *Pseudomonas aeruginosa,* and *Klebsiella pneumoniae* using cup plate agar diffusion method[24]. It was determined by measuring the inhibition zone in mm. The results of these studies are given in Fig. 1, Fig. 2, and Table 2 and compared with standard Tetracycline(100 μg/mL) drug. Interestingly, it is observed that out of twelve compounds, seven compounds were found to have efficient antibacterial activity. The zone of inhibition observed around the cups after respective incubation was measured. Antibacterial studies of synthesized compounds

Table 1 — Physical characterisation of 1-glycosyl-3-(5-phenyl-[1,3,4]thiadiazolyl)-carbamides **3a-f** and 6-glycosyl-2-phenyl-5-phenylimino-5,6-dihydro-[1,3,4]thiadiazolo [3,2a][1,3,5]triazin-7-one **5a-f**

Sr. No.	Compd	m.p. (°C)	Yield (%)	Elemental Analysis Found (Required)		$[\alpha]_D^{28}$ (c, $CHCl_3$)	R_f(3:2, Acetone: Pet.ether)
				N	S		
1	$C_{23}H_{26}O_{10}N_4S$	129-130	91	10.11 (10.18)	5.78 (5.81)	–112°(0.91)	0.61
2	$C_{43}H_{34}O_{10}N_4S$	133-135	89	6.98 (7.02)	3.97 (4.01)	–131°(0.97)	0.66
3	$C_{35}H_{42}O_{18}N_4S$	142-144	87	6.65 (6.68)	3.72 (3.81)	+109°(0.92)	0.58
4	$C_{70}H_{56}O_{18}N_4S$	137-139	88	4.37 (4.40)	2.49 (2.51)	+116°(0.97)	0.62
5	$C_{35}H_{42}O_{18}N_4S$	149-152	90	6.62 (6.68)	3.78 (3.81)	+98°(0.94)	0.64
6	$C_{70}H_{56}O_{18}N_4S$	153-155	92	4.31 (4.40)	2.45 (2.51)	+105°(0.98)	0.58
7	$C_{30}H_{29}O_{10}N_5S$	115-117	82	10.71 (10.75)	4.88 (4.91)	–124°(0.95)	0.42
8	$C_{50}H_{37}O_{10}N_5S$	122-123	74	7.73 (7.78)	3.52 (3.55)	–106°(0.99)	0.39
9	$C_{42}H_{45}O_{18}N_4S$	127-129	78	7.42 (7.45)	3.35 (3.40)	+128°(0.96)	0.37
10	$C_{77}H_{59}O_{18}N_5S$	119-121	87	5.04 (5.09)	2.31 (2.33)	+110°(0.97)	0.45
11	$C_{42}H_{45}O_{18}N_4S$	111-113	76	7.43 (7.45)	3.38 (3.40)	+122°(0.99)	0.36
12	$C_{77}H_{59}O_{18}N_5S$	124-125	84	5.02 (5.09)	2.28 (2.33)	+136°(0.99)	0.31

Satisfactory C, H analysis was obtained for all compounds.

indicated that compounds **5a** and **5e** were found to be active against *E. coli* and the rest were found to be moderately active. Compound **5e** exhibited the most significant activity against *S. aureus*, compound **5c** active towards *P. vulgaris*, compounds**3e** and **5a** towards *S. typhi*, compounds **5c** and **5e** towards *Ps. aeruginosa* and compounds **3a** and **5a** towards *K. pneumoniae.* All the other compounds exhibited low to moderate activity.

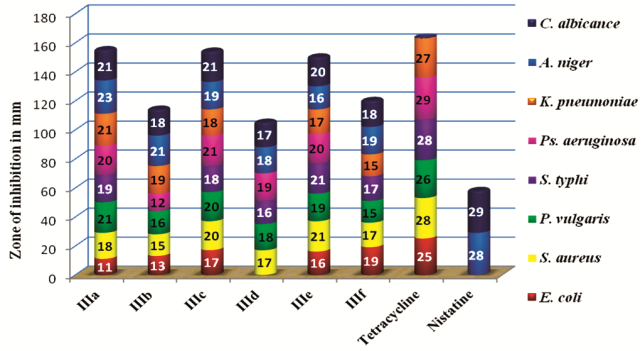


Fig. 1 — Antimicrobial activity of compounds **3a-f**

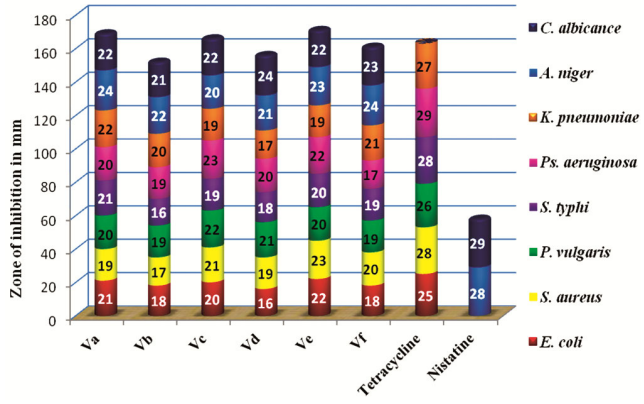


Fig. 2 — Antimicrobial activity of compounds **5a-f**

Antifungal activity

We have also investigated newly synthesized compounds for their antifungal activity against two pathogenic fungal strains namely, *Aspergillus niger* and *Candida albican* by using Potato Dextrose Agar medium. Antifungal activity was determined by measuring the diameter of the inhibition zone[25,26]. The results of these studies are given in Fig. 1, Fig. 2, and Table 2 and they are compared with the standard Nistatine (100 µg/mL) drug. It was observed that most of the compounds exhibited potent antifungal activity. The results of antifungal activities showed that compounds 3a, 5a, 5e, and 5f are most effectively active against *Aspergillus niger* and compounds 5d and 5f actively inhibited *Candida albican*. While other compounds inhibited moderate activity.

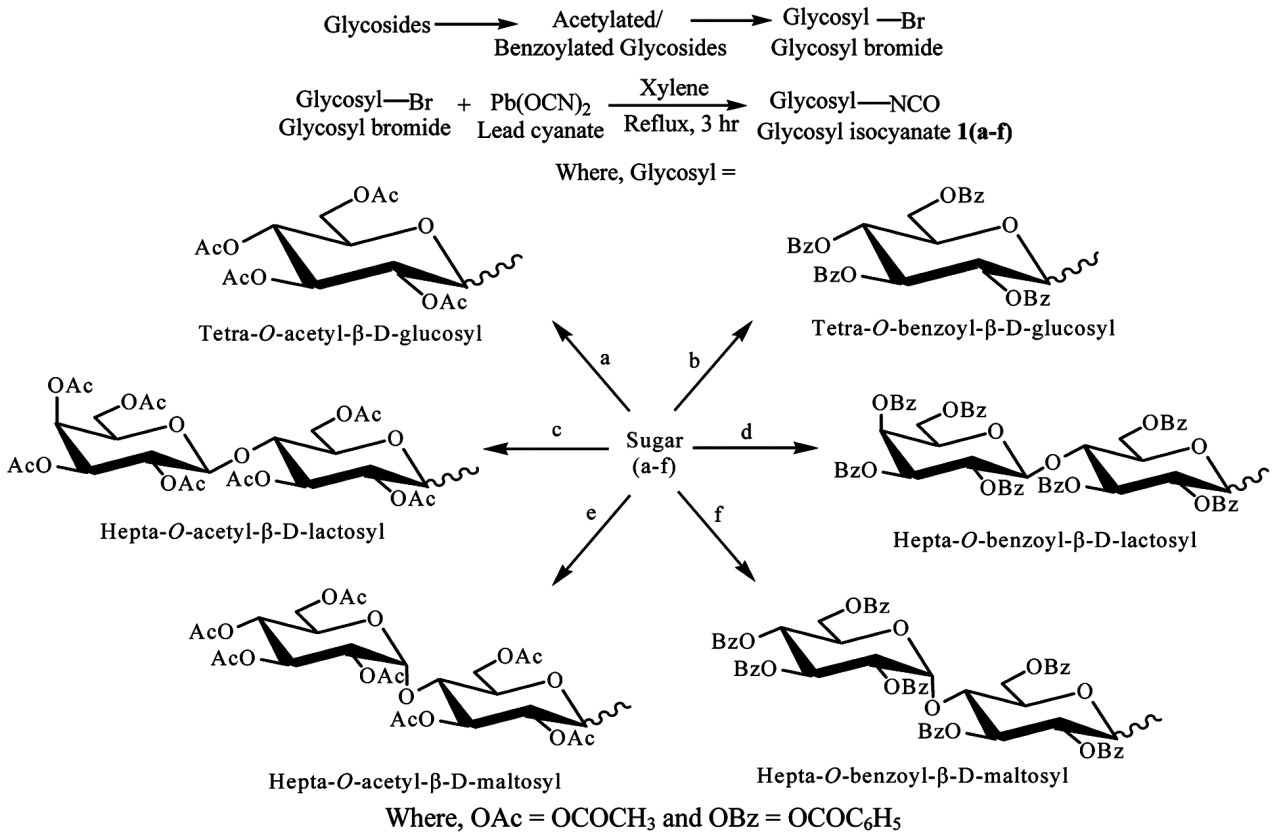
Experimental Section

The reagent-grade chemicals were obtained from commercial sources and purified by either distillation or recrystallization before use. Chemical yields refer to pure isolated substances. Melting points of all synthesized compounds were determined using an open capillary tube on Mac digital melting point apparatus and were uncorrected. IR spectra were recorded in solid phase KBr disks on Shimadzu IR affinity-1 FTIR spectrometer and ^{1}H NMR spectra in

Table 2 — Antimicrobial activities of newly synthesized 1-glycosyl-3-(5-phenyl-[1,3,4]thiadiazolyl)-carbamides **3a-f** and6-glycosyl-2-phenyl-5-phenylimino-5,6-dihydro-[1,3,4]thiadiazolo[3,2a][1,3,5]triazin-7-one **5a-f**

Sr. No.	Compd	Antibacterial**						Antifungal**	
		E. coli	*S. aureus*	*P. vulgaris*	*S. typhi*	*Ps. aeruginosa*	*K. pneumoniae*	*A. niger*	*C. albican*
1	$C_{23}H_{26}O_{10}N_4S$	11	18	21	19	20	21	23	21
2	$C_{43}H_{34}O_{10}N_4S$	13	15	16	–	12	19	21	18
3	$C_{35}H_{42}O_{18}N_4S$	17	20	20	18	21	18	19	21
4	$C_{70}H_{56}O_{18}N_4S$	–	17	18	16	19	–	18	17
5	$C_{35}H_{42}O_{18}N_4S$	16	21	19	21	20	17	16	20
6	$C_{70}H_{56}O_{18}N_4S$	19	17	15	17	–	15	19	18
7	$C_{30}H_{29}O_{10}N_5S$	21	19	20	21	20	22	24	22
8	$C_{50}H_{37}O_{10}N_5S$	18	17	19	16	19	20	22	21
9	$C_{42}H_{45}O_{18}N_4S$	20	21	22	19	23	19	20	22
10	$C_{77}H_{59}O_{18}N_5S$	16	19	21	18	20	17	21	24
11	$C_{42}H_{45}O_{18}N_4S$	22	23	20	20	22	19	23	22
12	$C_{77}H_{59}O_{18}N_5S$	18	20	19	19	17	21	24	23
	Tetracycline	25	28	26	28	29	27	–	–
	Nistatine	–	–	–	–	–	–	28	29

**Including the well diameter of 6 mm. Zone of inhibition in mm (15 or less) resistant, (16-20 mm) moderate, (more than 20 mm) sensitive, and (more than 25 mm) highly sensitive.

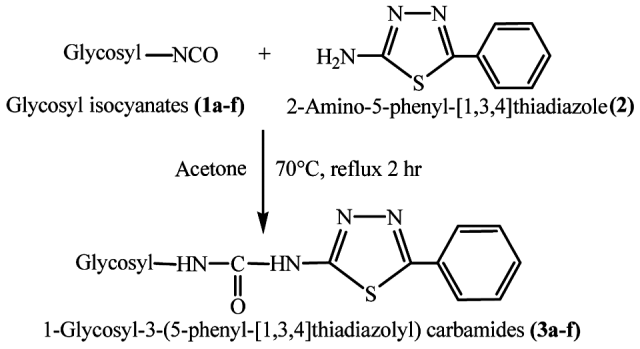


Scheme 1

$CDCl_3$ on Bruker DRX-300 NMR spectrometer at 300 MHz for ^1H and at 100 MHz for ^{13}C. All chemical shifts are reported in δ (ppm) downfield from TMS. Coupling constants (J) are reported in Hertz. Multiplicity in ^1H NMR is reported as singlet (s), doublet (d), doublet of doublets (dd), triplet (t), and multiplet (m). The mass spectra were recorded on Waters UPLC-TQD Mass Spectrometer. Optical rotations were measured on Equip-Tronics EQ 800 Digital Polarimeter in $CHCl_3$. The homogeneity of synthesized compounds has been checked by thin-layer chromatography. TLC was performed on E. Merck pre-coated silica gel plates.

Preparation of glycosyl isocyanate [18]

Various isocyanate of glycosyls were synthesized by the condensation of glycosyl bromide (5.0 mmol) and lead cyanate (5.0 mmol) in boiling sodium dried xylene (25 mL) for 3 h with frequent shaking. The solution was then filtered and the filtrate was concentrated to get the syrupy mass. It was triturated with petroleum benzine (40-60°C) and purified by dissolving it in a minimum quantity of chloroform and re-precipitating with petroleum ether (**1a-f**, Scheme 1).



Scheme 2

Preparation of 1-glycosyl-3-(5-phenyl-[1,3,4]thiadiazolyl) carbamides

An acetone solution of glycosyl isocyanate **1a-f** (0.025 mmol, in 20 mL) was mixed with an acetone solution of 2-amino-5-phenyl-[1,3,4]thiadiazole **2** (0.025 mmol, in 10 mL) and mixture after stirring for some time was refluxed at 70°C for 2 h (monitored by TLC). Acetone was distilled to obtain a sticky residue. This residue was triturated several times with petroleum ether to afford a pale yellow-colored solid (**3a-f**, Scheme 2).

1-Tetra-*O*-acetyl-β-D-glucosyl-3-(5-phenyl-[1,3,4]thiadiazolyl) carbamides, 3a

White solid. m.p.129-130°C. Yield 91%. $[\alpha]_D^{28}$: –112.6° (*c*, 0.91, $CHCl_3$); R_f: 0.61; IR (KBr): 3461 (N-H stretch), 2964 (Aliphatic C-H strech), 1742 (C=O), 1600 (C=N), 1556 (N-H bend), 1430 (C-N), 1237 (C-O), 845 cm^{-1} (characteristic of glucose); ^1H NMR ($CDCl_3$): δ 7.189-6.516 (m, 5H, Ar-H),5.089 (d, 1H, *J*= 9.5Hz, glu H_1), 4.262 (s, 1H, NH), 4.257-4.205 (m, 3H, glu H_2, glu H_4, and glu H_3), 4.233 (s, 1H, NH), 4.148-4.104 (m, 2H, glu H_{6b} and glu H_{6a}), 3.850 (d, 1H, *J*= 4.2Hz, H_5), 2.063 (s, 3H, $COCH_3$), 2.040 (s, 3H, $COCH_3$), 2.036 (s, 3H, $COCH_3$), 2.021 (s, 3H, $COCH_3$); MS: *m/z* 550 ($M^{\ddagger}$), 331(100%), 211, 169,109. Anal. Calcd for $C_{23}H_{26}O_{10}N_4S$: C, 50.18; H, 4.72; N, 10.18; S, 5.81. Found: C, 50.15; H, 4.69; N, 10.11; S, 5.78%.

1-Tetra-*O*-benzoyl-β-D-glucosyl-3-(5-phenyl-[1,3,4]thiadiazolyl) carbamides, 3b

Light yellow solid. m.p.133-135°C. Yield 89%. $[\alpha]_D^{28}$: –131° (c,0.97, $CHCl_3$); R_f: 0.66; IR (KBr):3273 (N-H), 3061 (Ar C-H), 2958 (Aliphatic C-H), 1730 (C=O), 1601 (C=N), 1514 (N-H bend), 1452 (C-N), 1265 (C-O), 854 (characteristic of glucose), 711 cm^{-1} (C-S); ^1H NMR ($CDCl_3$): δ 8.221-7.324 (m, 25H, Ar-H), 7.263 (s, 1H, NH), 6.966 (s, 1H, NH),6.330 (d, 1H, *J*= 3.3Hz, glu H_1), 5.628 (d, 1H, *J*= 7.8Hz, glu H_3), 4.526-4.437 (m, 2H, glu H_2 and glu H_4), 4.437 (dd, 1H, *J*= 4.2, 4.5Hz, glu H_{6a}), 4.215 (dd, 1H, *J*= 1.5, 5.1Hz, glu H_{6b}), 4.178 (d, 1H, *J*= 3.0Hz, glu H_5); MS: *m/z* 799 ($M^{\ddagger}$+1), 774, 756 (100%), 579, 354, 281, 177. Anal. Calcd for $C_{43}H_{34}O_{10}N_4S$: C, 64.66; H, 4.26; N, 7.02; S, 4.01. Found: C, 64.61; H, 4.23; N, 6.98; S, 3.97%.

1-Hepta-*O*-acetyl-β-D-lactosyl-3-(5-phenyl-[1,3,4]thiadiazolyl) carbamides, 3c

Light grey solid. m.p.142-144°C. Yield 87%. $[\alpha]_D^{28}$: +109° (c,0.92 in $CHCl_3$); R_f: 0.58; IR (KBr):3277 (N-H), 3022 (Ar C-H), 2985 (Aliphatic C-H), 1745 (C=O), 1643 (C=N), 1514 (N-H bend), 1433 (C-N), 1236 (C-O), 1047 & 910 (characteristic of lactose), 759 cm^{-1} (C-S); ^1H NMR ($CDCl_3$): δ 7.442-6.810 (m, 5H, Ar-H),6.782 (s, 1H, NH), 5.593 (s, 1H, NH), 5.452 (d, 1H, *J*= 2.1Hz, glu H_1), 5.561-5.466 (m, 1H, glu H_3), 5.082 (dd, 1H, *J*= 3.0, 4.8Hz, gal H_4), 4.999 (d, 1H, *J*= 3.3Hz, gal H_2), 4.976 (d, 1H, *J*= 3.3Hz, gal H_3), 4.941 (d, 1H, *J*= 6.6Hz, glu H_2), 4.851 (dd, 1H, *J*= 3.6, 3.9Hz, glu H_{6a}), 4.519-4.438 (m, 1H, gal H_1), 4.192-3.729 (m, 6H, glu H_4, glu H_5, glu H_{6b}, gal H_5, gal H_{6a} and gal H_{6b}), 2.135 (s, 3H, $COCH_3$), 2.113 (s, 3H, $COCH_3$), 2.094 (s, 3H, $COCH_3$), 2.067 (s, 3H, $COCH_3$), 2.056 (s, 3H, $COCH_3$), 2.032 (s, 3H, $COCH_3$), 2.010 (s, 3H, $COCH_3$); MS: *m/z* 838 ($M^{\ddagger}$), 814, 701, 659 (100%), 434, 282. Anal. Calcd for $C_{35}H_{42}O_{18}N_4S$: C, 50.12; H, 5.01; N, 6.68; S, 3.81. Found: C, 50.10; H, 4.99; N, 6.65; S, 3.72%.

1-Hepta-*O*-benzoyl-β-D-lactosyl-3-(5-phenyl-[1,3,4]thiadiazolyl) carbamides, 3d

White solid. m.p.137-139°C. Yield 88%. $[\alpha]_D^{28}$: +116° (c,0.97 in $CHCl_3$);R_f: 0.62; IR (KBr):3375 (N-H stretch), 3062 (Ar-H stretch), 2976 (Aliphatic C-H stretch), 1730 (C=O), 1600 (C=N), 1554 (N-H bend), 1452 (C-N), 1176 (C-O), 1026 & 902 cm^{-1} (characteristic of lactose); ^1H NMR ($CDCl_3$): δ 8.051-7.135 (m, 40H, Ar-H), 6.109 (s, 1H, NH), 5.972 (s, 1H, NH), 5.842-5.687 (m, 2H, glu H_3 and glu H_1), 5.634 (d, 1H, *J*= 3.6Hz, gal H_4), 5.392 (ddd, 1H, *J*= 3.0, 3.6, 3.3Hz, gal H_2), 5.267 (dd, 1H, *J*= 3.3, 3.9Hz, gal H_3), 4.952 (dd, 1H, *J*= 8.1, 6.3Hz, glu H_2), 4.715 (d, 1H, *J*= 8.1Hz, glu H_{6a}), 4.578 (d, 1H, *J*= 11.7Hz, gal H_1), 4.492 (d, 1H, *J*= 8.4Hz, glu H_5), 4.416-4.187 (m, 3H, glu H_{6b}, gal H_{6a} and gal H_{6b}), 3.968-3.880 (m, 2H, glu H_4 and glu H_5); MS: *m/z* (M^+)-1273 ($M^{\ddagger}$), 1247, 1126, 1095, 1088 (100%), 1052, 931, 579, 531; Anal. Calcd for $C_{70}H_{56}O_{18}N_4S$: C, 66.03; H, 4.40; N, 4.40; S, 2.51. Found: C, 65.97; H, 4.36; N, 4.37; S, 2.49%.

1-Hepta-*O*-acetyl-β-D-maltosyl-3-(5-phenyl-[1,3,4]thiadiazolyl) carbamides, 3e

Light yellow solid. m.p.149-152°C. Yield 90%. $[\alpha]_D^{28}$: +98° (c,0.94 in $CHCl_3$);R_f: 0.64; IR (KBr):3429 (N-H stretch), 2965 (Aliphatic C-H strech), 1730 (C=O), 1643 (C=N), 1556 (N-H bend), 1433 (C-N), 1238 (C-O), 1043 & 929 cm^{-1} (characteristic of maltose); ^1H NMR ($CDCl_3$): δ 7.621-6.521 (m, 5H, Ar-H),δ 5.591 (t, 1H, *J*= 18.9Hz, glu H_3), 5.456 (d, 1H, *J*= 3.9Hz, glu H_1), 5.377 (d, 1H, *J*= 2.7Hz, glu $H_{3'}$), 5.346 (d, 1H, *J*= 4.8Hz, glu $H_{4'}$), 5.111-5.031 (m, 2H, glu $H_{2'}$ and glu H_2), 4.896 (dd, 1H, *J*= 3.9, 3.9Hz, glu $H_{1'}$), 4.812 (dd, 1H, *J*= 3.6, 2.7Hz, glu H_{6a}), 4.769 (s, 1H, NH), 4.613 (s, 1H, NH), 4.526 (s, 1H, glu $H_{6a'}$), 4.493 (d, 1H, *J*= 2.7Hz, glu H_{6b}), 4.072 (s, 1H, glu $H_{6b'}$), 4.031 (d, 1H, *J*= 4.2Hz, glu H_5), 3.999 (s, 1H, glu H_4), 3.969 (s, 1H, glu $H_{5'}$), 2.188 (s, 3H, $COCH_3$), 2.155 (s, 3H, $COCH_3$), 2.108 (s, 3H, $COCH_3$), 2.064 (s, 3H, $COCH_3$), 2.032 (s, 3H, $COCH_3$), 2.024 (s, 3H, $COCH_3$), 2.010 (s, 3H, $COCH_3$); MS: *m/z*838 ($M^{\ddagger}$),814, 721, 696, 654

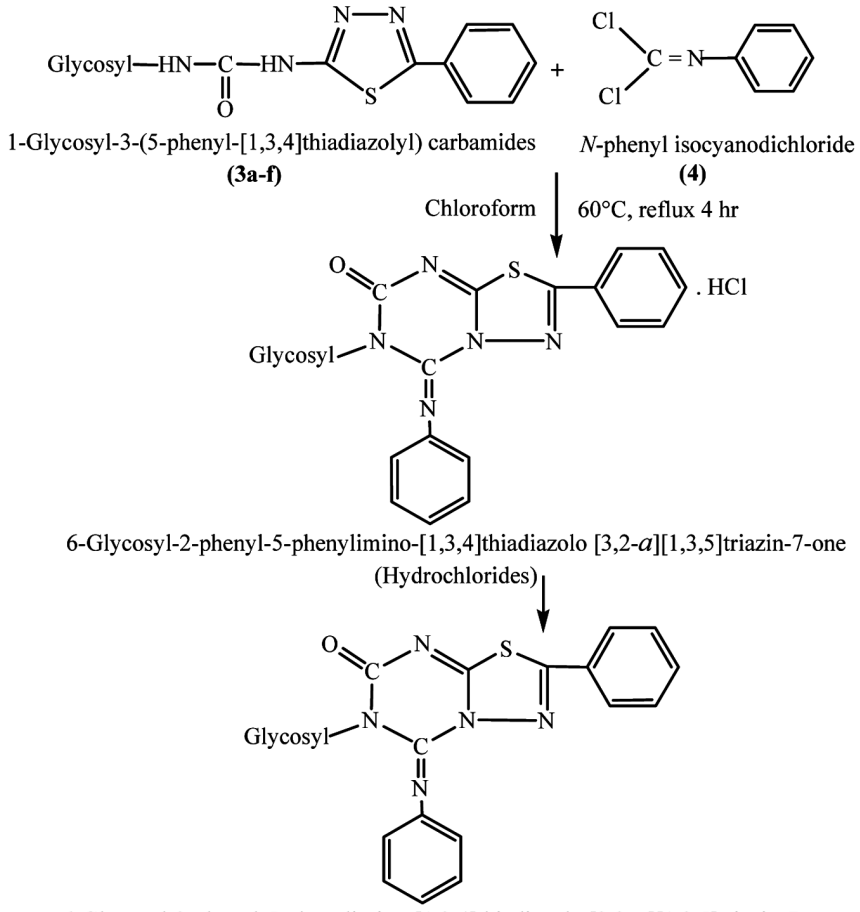
(100%), 531, 300, 288. Anal. Calcd for $C_{35}H_{42}O_{18}N_4S$: C, 50.12; H, 5.01; N, 6.68; S, 3.81. Found: C, 50.09; H, 4.97; N, 6.62; S, 3.78%.

1-Hepta-*O*-benzoyl-β-D-maltosyl-3-(5-phenyl-[1,3,4]thiadiazolyl) carbamides, 3f

White solid. m.p.153-155°C. Yield 92%. $[\alpha]_D^{28}$: +105° (c,0.98 in $CHCl_3$);R_f: 0.58; IR (KBr):3329 (N-H), 3062 (Ar C-H), 2972 (Aliphatic C-H), 1730 (C=O), 1651 (C=N), 1504 (N-H bend), 1452 (C-N), 1176 (C-O), 1070 & 908 (characteristic of maltose), 708 cm^{-1} (C-S);^{1}H NMR ($CDCl_3$): δ 8.072-7.163 (m, 40H, Ar-H), 6.378 (s, 1H, NH), 6.272 (s, 1H, NH), 6.159 (dd, 1H, *J*= 3.3, 9.6Hz, glu H_1), 5.535 (t, 1H, *J*= 15.3Hz, glu H_3), 5.421 (dd, 1H, *J*= 4.2, 9.9Hz, glu $H_{3'}$), 5.355 (s, 1H, NH), 5.105 (d, 1H, *J*= 15.0Hz, glu $H_{4'}$), 4.823 (s, 1H, NH), 4.594 (d, 1H, *J*= 6.6Hz, glu H_2), 4.529 (s, 1H, glu $H_{2'}$), 4.486 (d, 1H, *J*= 6.0Hz, glu $H_{1'}$), 4.466 (s, 1H, glu H_{6a}), 4.428 (s, 1H, glu $H_{6a'}$), 4.236 (d, 1H, *J*= 6.6Hz, glu H_{6b}), 4.052 (s, 1H, glu $H_{6b'}$), 3.994-3.753 (m, 3H, glu $H_{5'}$, glu H_4 and glu H_5); MS: *m/z* 1273 ($M^{\ddagger}$+1), 1248, 1126, 989, 756, 590, 434 (100%) 354. Anal. Calcd for $C_{70}H_{56}O_{18}N_4S$: C, 66.03; H, 4.40; N, 4.40; S, 2.51. Found: C, 65.99; H, 4.37; N, 4.31; S, 2.45%.

Preparation of 6-glycosyl-2-phenyl-5-phenylimino-5,6-dihydro-[1,3,4]thiadiazolo [3,2-a][1,3,5]triazin-7-one

A chloroform solution of 1-glycosyl-3-(5-phenyl-[1,3,4]thiadiazolyl) carbamides **3a-f** (2.0 mmol in 2 mL) was mixed with a cold solution of *N*-phenyl isocyanodichloride **4** (2.0 mmol in 10 mL) chloroform. The reaction was quite brisk and exothermic with the evolution of hydrogen chloride. The mixture was refluxed at 60°C for 4 h. The chloroform was distilled off. The resultant solution was then basified to get a sticky mass. Then sticky mass obtained was triturated several times with petroleum ether (60-80°C). It furnished a granular solid (**5a-f**, Scheme 3).



Scheme 3

6-Tetra-*O*-acetyl-β-D-glucosyl-2-phenyl-5-phenylimino-5,6-dihydro-[1,3,4]thiadiazolo [3,2-a][1,3,5]triazin-7-one, 5a

Light yellow solid. m.p.115-117°C. Yield 82%. $[\alpha]_D^{28}$: –124° (c,0.95 in $CHCl_3$);R_f: 0.42; IR (KBr):3241 (N-H stretch), 2976 (Aliphatic C-H strech), 1730 (C=O), 1602 (C=N), 1555 (N-H bend), 1454 (C-N), 1187 (C-O), 846 (characteristic of glucose), 709 cm^{-1} (C-S); ^{1}H NMR ($CDCl_3$): δ 7.238-7.056 (m, 10H, Ar-H),5.089 (d, 1H, *J*= 9.5Hz, glu H_1), 4.257-4.205 (m, 3H, glu H_2, glu H_4, and glu H_3), 4.148-4.104 (m, 2H, glu H_{6b} and glu H_{6a}), 3.850 (d, 1H, *J*= 4.2Hz, H_5), 2.063 (s, 3H, $COCH_3$), 2.040 (s, 3H, $COCH_3$), 2.036 (s, 3H, $COCH_3$), 2.021 (s, 3H, $COCH_3$); ^{13}C NMR (100 MHz, $CDCl_3$): δ 134.9-133.6 (2C_6H_5),166.21 (C=O); 166.18, 166.07, 165.21 and 165.11 (4*C*OCH_3); 122.85 (C=N);121.41 (C=N); 120.20 (C=N);77.12 (glu C_1); 76.34 (glu C_5); 72.61 (glu C_3); 70.87 (glu C_4); 68.31 (glu C_2); 62.77 (glu C_6), 28.96-21.73 (4CO*C*H_3); MS: *m/z* 651($M^{+\cdot}$), 332, 219 (100%), 169, 109. Anal. Calcd for $C_{30}H_{29}O_{10}N_5S$: C, 55.29; H, 4.45; N, 10.75; S, 4.91. Found: C, 55.27; H, 4.41; N, 10.71; S, 4.88%.

6-Tetra-*O*-benzoyl-β-D-glucosyl-2-phenyl-5-phenylimino-5,6-dihydro-[1,3,4]thiadiazolo [3,2-a][1,3,5]triazin-7-one, 5b

Light yellow solid. m.p.122-123°C. Yield 74%. $[\alpha]_D^{28}$: –106° (c,0.99 in $CHCl_3$); R_f: 0.39; IR (KBr):3062 (Ar C-H), 2957 (Aliphatic C-H), 1753 (C=O), 1653 (C=N), 1440 (C-N), 1232 (C-O), 898 (characteristic of glucose), 754 cm^{-1} (C-S);^{1}H NMR ($CDCl_3$): δ 8.048-7.256 (m, 30H, Ar-H), 6.069 (d, 1H, *J*= 3.9Hz, glu H_1), 6.012 (t, 1H, *J*= 6.6Hz, glu H_3), 5.796 (dd, 1H, *J*= 3.6, 3.6Hz, glu H_2), 5.341-5.294 (m, 1H, glu H_4), 4.708 (d, 1H, *J*= 3.3Hz, glu H_{6a}), 4.482 (dd, 1H, *J*= 4.8, 7.8Hz, glu H_{6b}), 4.278 (dd, 1H, *J*= 3.6, 3.9Hz, glu H_5); ^{13}C NMR (300 MHz, $CDCl_3$): δ 166.3 (C=O), 165.9-164.8(4*C*OC_6H_5); 134.9-133.6 (2C_6H_5), 132.11-128.27 (4COC_6H_5); 123.2 (C=N), 121.7 (C=N), 120.9 (C=N),77.62 (glu C_1); 76.58 (glu C_5); 72.50 (glu C_3); 70.80 (glu C_4); 68.32 (glu C_2); 62.37 (glu C_6); MS: *m/z* 900 ($M^{+\cdot}$), 797, 796 (100%), 712, 754, 579, 281, 253, 205. Anal. Calcd for $C_{50}H_{37}O_{10}N_5S$: C, 66.74; H, 4.11; N, 7.78; S, 3.55. Found: C, 66.72; H, 4.09; N, 7.73; S, 3.52%.

6-Hepta-*O*-acetyl-β-D-lactosyl--2-phenyl-5-phenylimino-5,6-dihydro-[1,3,4]thiadiazolo [3,2-a][1,3,5]triazin-7-one, 5c

Light Grey solid. m.p.127-129°C. Yield 78%. $[\alpha]_D^{28}$: +128° (c,0.96 in $CHCl_3$); R_f: 0.37; IR (KBr):3064 (Ar C-H), 2960 (Aliphatic C-H), 1730 (C=O), 1641 (C=N), 1453 (C-N), 1168 (C-O), 1028 & 937 (characteristic of lactose), 709 cm^{-1} (C-S). ^{1}H NMR ($CDCl_3$): δ 8.83-7.09 (m, 10H, Ar-H), δ 5.371 (d, 1H, *J*= 2.1Hz, glu H_1), 5.586-5.436 (m, 1H, glu H_3), 5.172 (dd, 1H, *J*= 3.0, 4.8Hz, gal H_4), 4.989 (d, 1H, *J*= 3.3Hz, gal H_2), 4.970 (d, 1H, *J*= 3.3Hz, gal H_3), 4.945 (d, 1H, *J*= 6.5Hz, glu H_2), 4.872 (dd, 1H, *J*= 3.6, 3.3Hz, glu H_{6a}), 4.509-4.468 (m, 1H, gal H_1), 4.219-4.060 (m, 6H, glu H_4, glu H_5, glu H_{6b}, gal H_5, gal H_{6a} and gal H_{6b}), 2.23 (3H, s, $COCH_3$), 2.11 (3H, s, $COCH_3$), 2.06 (3H, s, $COCH_3$), 2.03 (3H, s, $COCH_3$), 2.01 (3H, s, $COCH_3$), 2.00 (3H, s, $COCH_3$), 1.99 (3H, s, $COCH_3$). ^{13}C NMR (300 MHz, $CDCl_3$): δ 167.4 (C=O), 166.8-165.2 (7*C*OCH_3), 133.4-128.2 (2C_6H_5), 122.9 (C=N), 122.2 (C=N), 121.8 (C=N), 77.51 (glu $C_{1'}$), 77.20 (glu C_1), 77.05 (glu C_4 and glu C_5), 76.44 (glu C_3), 75.30 (glu $C_{3'}$), 72.37 (glu $C_{2'}$), 70.63 (glu $C_{4'}$), 69.34 (glu $C_{5'}$), 67.78 (glu C_2), 63.81 (glu C_6), 62.72 (glu $C_{6'}$), 29.11-20.03 (7CO*C*H_3); MS: *m/z* 939 ($M^{+\cdot}$), 889, 619, 559, 413, 345, 286 (100%), 226.Anal. Calcd for $C_{42}H_{45}O_{18}N_4S$: C, 53.67; H, 4.79; N, 7.45; S, 3.40. Found: C, 53.64; H, 4.75; N, 7.42; S, 3.35%.

6-Hepta-*O*-benzoyl-β-D-lactosyl--2-phenyl-5-phenylimino-5,6-dihydro-[1,3,4]thiadiazolo [3,2-a][1,3,5]triazin-7-one, 5d

Light brown solid. m.p.119-121°C. Yield 87%. $[\alpha]_D^{28}$: +110° (c,0.97 in $CHCl_3$); R_f: 0.45; IR (KBr):3062 (Ar-H stretch), 2960 (Aliphatic C-H stretch), 1730 (C=O), 1643 (C=N), 1452 (C-N), 1176 (C-O), 1026 & 937 (characteristic of lactose),709 cm^{-1} (C-S); ^{1}H NMR ($CDCl_3$): δ 8.208-7.183 (m, 45H, Ar-H), 5.929 (d, 1H, *J*= 2.1Hz, glu H_1), 5.762 (t, 1H, *J*= 3.9Hz, glu H_3), 5.588 (d, 1H, *J*= 3.3Hz, gal H_4), 5.448 (t, 1H, *J*= 3.9Hz, gal H_2), 5.398 (d, 1H, *J*= 3.3Hz, gal H_3), 5.263 (dd, 1H, *J*= 3.6, 3.9Hz, glu H_2), 4.715-4.078 (m, 6H, glu H_{6b}, glu H_{6a}, gal H_5, gal H_{6a}, gal $H_{6b}$and gal H_1), 4.004-3.676 (m, 2H, glu H_4 and glu H_5); ^{13}C NMR (300 MHz, $CDCl_3$): δ170.30 (C=O), 165.44 (7*C*OC_6H_5), 134.8-133.5 (2C_6H_5),133.39-128.30 (7COC_6H_5),122.05 (C=N), 121.47 (C=N), 120.6 (C=N),77.41 (gal C_1), 77.19 (glu C_1), 76.99 (glu C_4), 76.57-75.04 (glu C_2, glu C_3 and glu C_5), 69.95 (gal C_5), 67.32 (gal C_3), 66.74 (gal C_2), 65.61 (gal C_4), 62.10 (gal C_6), 61.0 (glu C_6); MS: *m/z* 1373 ($M^{+\cdot}$), 1291, 1094, 990, 672 (100%), 579, 515, 475. Anal. Calcd for $C_{77}H_{59}O_{18}N_5S$: C, 67.29; H, 4.29; N, 5.09; S, 2.33. Found: C, 67.26; H, 4.27; N, 5.04; S, 2.31%.

6-Hepta-*O*-acetyl-β-D-maltosyl--2-phenyl-5-phenylimino-5,6-dihydro-[1,3,4]thiadiazolo [3,2-a][1,3,5]triazin-7-one, 5e

Light orange solid. m.p.111-113°C. Yield 76%. $[\alpha]_D^{28}$: +122° (c,0.99 in $CHCl_3$);R_f: 0.36; IR (KBr):2958

(Aliphatic C-H stretch), 1749 (C=O), 1662 (C=N), 1435 (C-N), 1141 (C-O), 1041 & 901(characteristic of maltose),709 cm^{-1} (C-S);^{1}H NMR ($CDCl_3$): δ 7.180-7.099 (m, 10H, Ar-H), 5.753 (d, 1H, *J*= 6.9Hz, glu H_1), 5.545 (t, 1H, *J*= 9.9Hz, glu H_3), 5.427 (d, 1H, *J*= 11.7Hz, glu $H_{3'}$), 5.356 (d, 1H, *J*= 9.9Hz, glu $H_{4'}$), 5.217-5.078 (m, 2H, glu $H_{2'}$ and glu H_2), 4.979 (d, 1H, *J*= 10.8Hz, glu $H_{1'}$), 4.943-4.760 (m, 2H, glu $H_{6a'}$and glu H_{6a}), 4.479-4.265(m, 2H, glu $H_{6b'}$ and glu H_{6b}), 4.076 (s, 1H, glu H_5), 3.969 (s, 1H, glu H_4), 3.660 (s, 1H, glu $H_{5'}$), 2.433 (s, 3H, $COCH_3$), 2.392 (s, 3H, $COCH_3$), 2.224 (s, 3H, $COCH_3$), 2.144 (s, 3H, $COCH_3$), 2.102 (s, 3H, $COCH_3$), 2.063 (s, 3H, $COCH_3$), 2.028 (s, 3H, $COCH_3$); ^{13}C NMR (300 MHz, $CDCl_3$): δ172.50 (C=O), 170.54 (7*C*OCH_3), 133.5-132.8 (2*C*$_6H_5$), 123.8 (C=N), 122.7 (C=N), 121.41 (C=N), 77.47 (glu $C_{1'}$), 77.25 (glu C_1), 77.04 (glu C_4 and glu C_5), 76.62 (glu C_3), 75.0 (glu $C_{3'}$), 72.35 (glu $C_{2'}$), 70.13 (glu $C_{4'}$), 69.35 (glu $C_{5'}$), 67.98 (glu C_2), 63.0 (glu C_6), 62.80 (glu $C_{6'}$), 29.72-20.62 (7CO*C*H_3); MS: *m/z* 939 ($M^{\ddagger}$), 678, 659, 549, 325, 259 (100%). Anal. Calcd for $C_{42}H_{45}O_{18}N_4S$: C, 53.67; H, 4.79; N, 7.45; S, 3.40. Found: C, 53.63; H, 4.74; N, 7.43; S, 3.38%.

6-Hepta-*O*-benzoyl-β-D-maltosyl-2-phenyl-5-phenylimino-5,6-dihydro-[1,3,4]thiadiazolo [3,2-a][1,3,5]triazin-7-one, 5f

Grey solid. m.p.136-138°C. Yield 84%. $[\alpha]_D^{28}$: +136° (c,0.99 in $CHCl_3$); R_f: 0.58; IR (KBr):3064 (Ar C-H), 2969 (Aliphatic C-H), 1730 (C=O), 1645 (C=N), 1451 (C-N), 1175 (C-O), 1026 & 935 (characteristic of maltose), 710 cm^{-1} (C-S). ^{1}H NMR ($CDCl_3$): δ 8.08-7.17 (45H, m, Ar-H), 6.209 (t, 1H, *J*= 9.9Hz, glu H_3), 5.533 (d, 1H, *J*= 3.6Hz, glu H_1), 5.454 (dd, 1H, *J*= 3.9, 3.6Hz, glu $H_{3'}$), 4.827 (d, 1H, *J*= 3.3Hz, glu $H_{4'}$), 4.794 (d, 1H, *J*= 3.6Hz, glu H_2), 4.638 (d, 1H, *J*= 3.6Hz, glu $H_{2'}$), 4.586 (s, 1H, glu $H_{1'}$), 4.531 (d, 1H, *J*=2.7Hz, glu H_{6a}), 4.463 (dd, 1H, *J*=4.2, 3.9Hz, glu $H_{6a'}$), 4.378 (s, 1H, glu H_{6b}), 4.348 (s, 1H, glu H_5), 4.317 (s, 1H, glu $H_{6b'}$), 3.956 (t, 1H, *J*= 9.9Hz, glu H_4), 3.812 (d, 1H, *J*= 3.9Hz, glu $H_{5'}$); ^{13}C NMR (300 MHz, $CDCl_3$): δ 166.3 (C=O), 165.3 (7*C*OC_6H_5), 134.7-133.9 (2*C*$_6H_5$), 133.7-128.6 (7CO*C*$_6H_5$), 121.0 (C=N), 120.9 (C=N), 120.2 (C=N), 77.32 (gal C_1), 77.28 (glu C_1), 76.92 (glu C_4), 76.67-75.24 (glu C_2, glu C_3 and glu C_5), 69.85 (gal C_5), 67.71 (gal C_3), 66.70 (gal C_2), 65.64 (gal C_4), 62.18 (gal C_6), 61.09 (glu C_6);MS: *m/z* 1373 ($M^{\ddagger}$), 1291, 1232, 1063, 913, 579, 451, 396(100%), 305.Anal. Calcd for $C_{77}H_{59}O_{18}N_5S$: C, 67.29; H, 4.29; N, 5.09; S, 2.33. Found: C, 67.26; H, 4.27; N, 5.04; S, 2.31%.

Conclusion

We have successfully presented a synthetic route for the synthesis of novel1-glycosyl-3-(5-phenyl-[1,3,4]thiadiazolyl)-carbamides (**3a-f**) and6-glycosyl-2-phenyl-5-phenylimino-5,6-dihydro-[1,3,4]thiadiazolo [3,2a][1,3,5]triazin-7-one (**5a-f**). Most of the synthesized compounds showed promising antibacterial and antifungal activities against highly pathogenic organisms. This synthesis provides a potential methodology for chemical biology.

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