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Synthesis of Bis-(*N*-glucosylated triazolodithiadiazinyl) alkanes using N-Glucosylated Sulfenyl Chloride Reagent

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Methodology is reported for the synthesis of a six-membered heterocyclic ring involving cyclocondensation reaction through sulfur-sulfur bond formation. This method of synthesis allows for developing a new class of dithiadiazines. A series of bis-[6-tetra-*O*-acetyl-β-D-glucopyranosylimino-1,2,4-triazolo[3,4-b]-1,2,4,5-dithiadiazin-4-yl] alkanes have been synthesized by using a reagent, tetra-*O*-acetyl-β-D-glucopyranosylimino chloromethane sulfenyl chloride and bis-(4-amino-5-mercapto-1,2,4-triazol-3-yl) alkanes. These newly formulated N-glycosylated molecules could serve as a potential biological entity.

1. Introduction

Organic heterocycles with three or more heteroatoms are indeed a fascinating area of study. They exhibit a broad spectrum of chemical and physical properties that make them highly valuable in various fields.[1-4] The dithiadiazine core is a six membered heterocycle containing two sulfur atoms and two nitrogen atoms whereas triazole is a five membered heterocycle with three nitrogen atoms. Despite the fact that the triazolodithiadiazine is not present in nature, it may have biological activities. 'Aza' analogues of 1,2-dithianes have not received much attention. The dithiadiazine heterocycle is an uncommon system with limited reports on its chemistry. To the extent of our knowledge, a handful of reports on the synthesis of dithiazines[5] and biological applications of dithiazoles are available.[6]

The method of formation of 1,2,4,5-dithiadiazines has been disclosed in earlier communications.[7,8] The formation of a 1,4,2,3-dithiadiazine and its single crystal X-ray determination has been reported.[9] The preparation of 1,4,2,5-dithiadiazine and dioxides of some fused [1,4,2,6] dithiadiazine has also been reported.[10-12]

Interestingly, some dithiadiazines and 1,2,4-triazolo-[3,4-c]-1,2-dithia-4,5-diazines have been demonstrated to have fungicidal activity. [13-15] Direct condensation method for the synthesis of 1,2,4,5-dithiadiazine along with their antimicrobial activity has been previously reported.[16-19] There have been only a handful of reports on the formation of glycosyl derivatives of 1,2,4,5-dithiadiazine.[20] The method of preparation & chemical properties of some triazole derivatives have been recently reported.[21-23] The synthesis of 1,2,4,5-dithiadiazine containing triazole nucleus and a carbohydrate moiety is not well documented. We primarily focused on combining three moieties viz. triazole, dithiadiazine and glucosyl derivative. Moreover, with the thought that this new heterocyclic compound could serve as a good medicinal scaffold, we tested this molecule for antifungal activity. Our design strategy is based on the use of glucosylated chloromethane sulfenyl chloride for the synthesis of six membered rings involving formation of the sulfur-sulfur bond. Looking at the significance of heterocycles with glucosyl modifications, herein we are detailing the synthesis of bis-(*N*-glucosylated triazolo 1,2,4,5-

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dithiadiazinyl) alkanes by the cyclocondensation reaction of bis-1,2,4-triazole with *N*-glucosylimino chloromethane sulfenyl chloride.

2. Results and Discussion

The methodology detailed in **Fig. 1** represents a clean stepwise synthesis of the target compound bis-(N-glucosylated triazolodithiadiazinyl) alkanes **(6a-i).** The formation of the product can be reconciled with the mechanism shown in **Fig. 2.** A range of bis-(4-amino-5-mercapto-1,2,4-triazol-3-yl)alkanes **(3a-i)** have been synthesized through the combination of thiocarbohydrazide **(2)** and aliphatic dicarboxylic acids **(1a-i).**[24-26]

N-Tetra-O-acetyl-β-D-glucopyranosylimino chloromethane sulfenyl chloride **(4)** has been synthesized by the known route.[27,28] It was engaged in reaction with bis-(4-amino-5-mercapto-1,2,4-triazol-3-yl) methane **(3a)** using $CHCl_3$-DMF (1:1) as a refluxing medium to obtain a salt variant of the product as illustrated in **Fig. 1.** The occurrence of the cyclocondensation reaction was confirmed by testing with litmus paper for the evolution of hydrogen chloride gas. The target compound **(6a)** was identified as a salt form which then subjected to saturated solution of base i.e. $NaHCO_3$ to yield a free base with mp.71°C.

A few target compounds have been tested for antifungal activity against *A.niger* and *C. oxysporum* antifungal strains and found to be highly active.

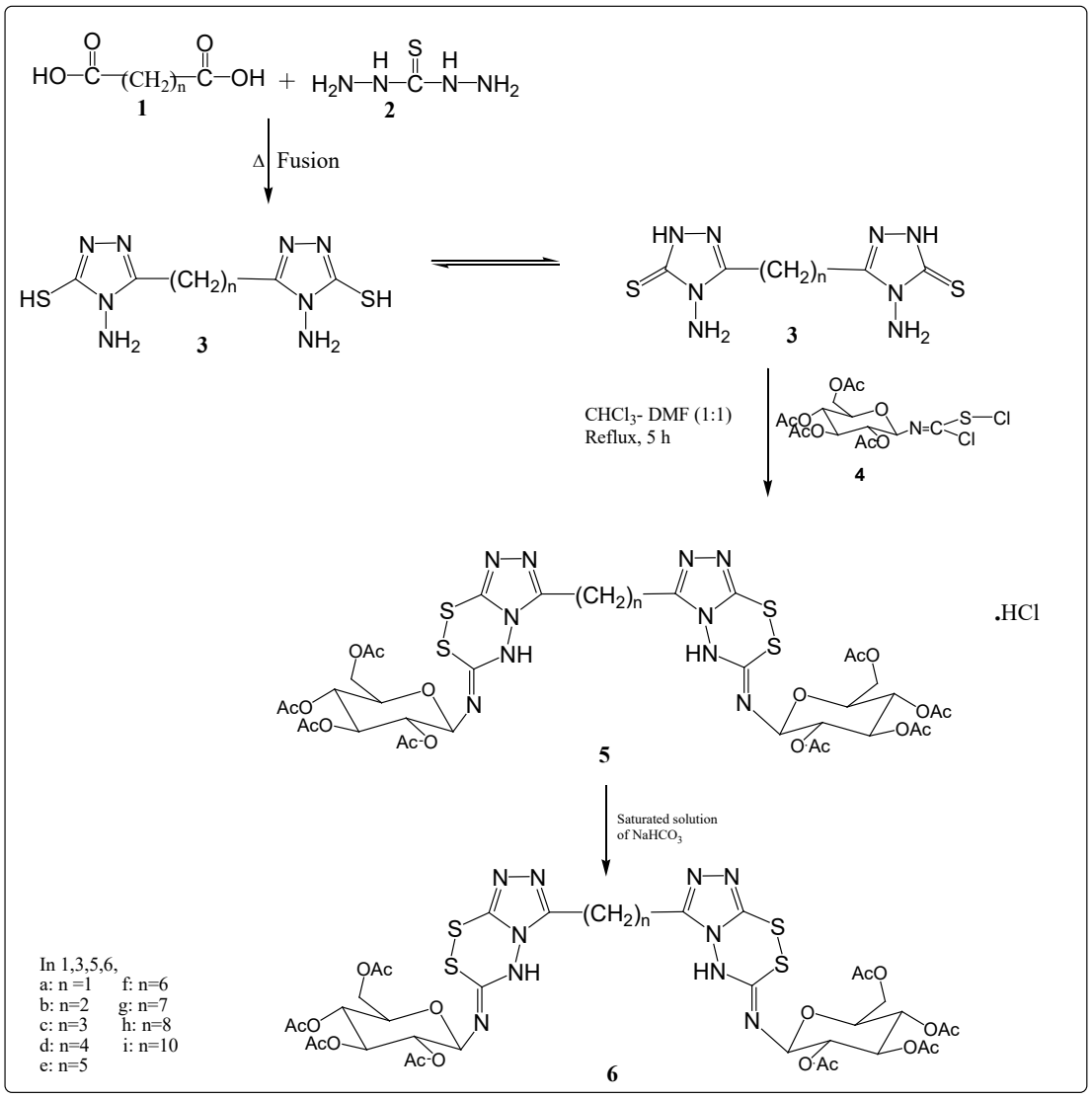

Fig. 1. Synthesis Pathway for the synthesis of *N*-glucosylated triazolodithiadiazinyl alkanes **(6a-i)**

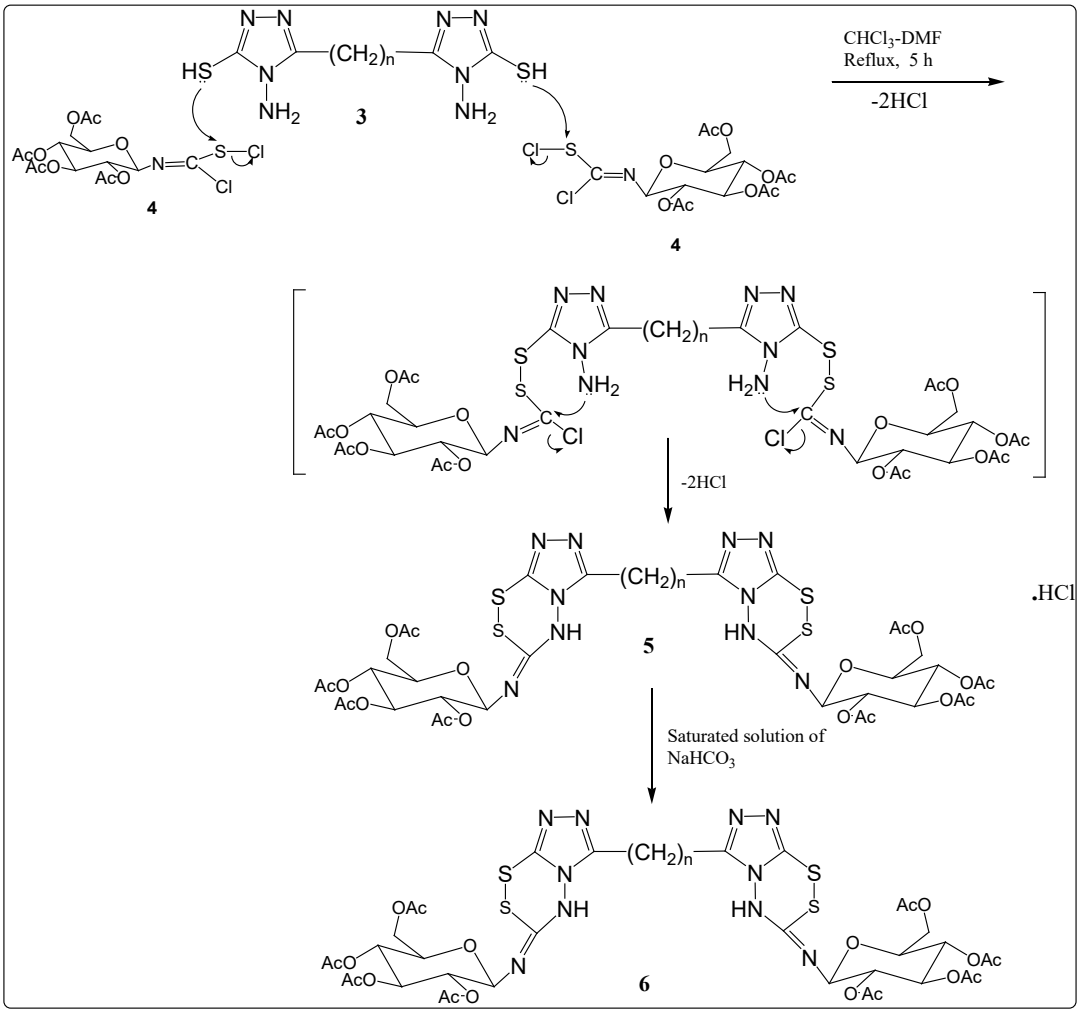

Fig. 2. Viable mechanism for the formation of target compounds **(6a-i).**

The product **6a** was examined for the preliminary tests. It was found that the melting point was71ºC. It was soluble in absolute ethanol, chloroform, dichloromethane and dimethyl sulfoxide whereas insoluble in water, and partially soluble in acetone. It was observed that on warming with concentrated sulfuric acid, the product charred indicating the presence of glucosyl moiety. On boiling with an alkaline plumbite solution the product was found non-desulfurizable. This has indicated that sulfur is the part of a stable heterocyclic ring. The specific rotation of the product was also measured, $[\alpha]_D^{25} = +60°$ (c = 0.5, EtOH). The purity of the product was assessed using TLC and determined R_f value as 0.50 (50% EtOAc-hexane). The molecular formula of the product was established as $C_{35}H_{42}N_{10}O_{18}S_4$. Spectral analyses of **6a** were carried out. The infrared spectral analysis of the product prominently displayed absorption bands attributable to $\nu_{C=O}$, $\nu_{C=N}$, ν_{C-N}, ν_{N-N}, ν_{S-S}, ν_{C-S}. The ^{1}H NMR spectrum revealed signals corresponding to the acetyl, glucosyl and methylene protons. The ^{13}C NMR spectrum revealed characteristic signals attributed to the presence of glucosyl carbons. It also displayed signals for triazole and dithiadiazine ring carbons. Mass spectrum showed $[M+1]^+$ and $[M+Na]^+$ peaks along with the characteristic fragment ion peaks.

Based on all the aforementioned evidence, the compound **(6a)** has been identified as having the structure as *b*is-[6-tetra-*O*-acetyl-β-D-glucopyranosylimino-1,2,4-triazolo[3,4-b]-1,2,4,5-dithiadiazin-4-yl] methane. The reaction of glucosyl chloromethane sulfenyl chloride **(4)** has been extended to other bis-(4-amino-5-mercapto-1,2,4-triazol-3-yl) alkanes **(3b-i)** to afford the corresponding bis-(*N*-glucosylated triazolodithiadiazinyl alkanes **(6b-i)** in good yields as depicted in **Table 1**.

Table. 1. Physical Characterization of Target Molecules **6a-i**

Entry	Target Molecule	n	Molecular Formula	Yield (%)	Melting Point (°C)
1	6a	1	$C_{35}H_{42}N_{10}O_{18}S_4$	60	71
2	6b	2	$C_{36}H_{44}N_{10}O_{18}S_4$	58	103
3	6c	3	$C_{37}H_{46}N_{10}O_{18}S_4$	61	109
4	6d	4	$C_{38}H_{48}N_{10}O_{18}S_4$	65	98
5	6e	5	$C_{39}H_{50}N_{10}O_{18}S_4$	71	95
6	6f	6	$C_{40}H_{52}N_{10}O_{18}S_4$	67	90
7	6g	7	$C_{41}H_{54}N_{10}O_{18}S_4$	79	122
8	6h	8	$C_{42}H_{56}N_{10}O_{18}S_4$	85	75
9	6i	10	$C_{44}H_{60}N_{10}O_{18}S_4$	73	117

n is the number of methylene groups

Various Spectroscopic techniques were employed for confirming the structure of the target molecules **6a-i** like Infrared spectroscopy (IR), proton and carbon-13 nuclear magnetic resonance and mass spectrometry. The IR spectra of target molecules **6a-i** exhibited an absorption band between 1739–1755 cm^{-1} which signified the presence of O-C=O functional group. The absorption features spanning from 1529–1584 cm^{-1} and 597-601 cm^{-1}attributed to C=N and S-S signified the formation of dithiadiazine ring. An absorption band at 3100–3200 and 2360 or 1233 cm^{-1} due to the NH_2 and SH or C=S functional groups respectively, were absent. The absence of these signals confirmed the participation of NH_2 and SH groups of the reactant bis-triazoles in the process of cyclization. The proton NMR spectra of the target molecules **6a-i**, the protons of the methylene group resonated as multiplets between δ 3.35–31.29 ppm. The glucosyl moiety showed two multiplets in the range of δ 5.97–3.74 ppm and δ 2.24-1.92 ppm due to the glucosyl ring and acetyl protons. The absence of the peak at δ 5.42 ppm for NH_2 provided further definitive confirmation for the cyclization.

The ^{13}C NMR spectra displayed peaks for glucosyl carbons in the range of δ 82.72–61.76 ppm. Mass spectral analysis of the target molecules **6a-i** revealed the presence of molecular ion peaks $[M+1]^+$, $[M+Na]^+$. Distinctive fragment ion peaks at 413, 331, 169 and corresponding to the glucosyl residue were also detected. The target molecules **6a-i** were screened for antibacterial activity against different fungal strains.

3. Conclusions

A series of new 1,2,4-triazolo-1,2,4,5-dithiadiazinyl alkanes bearing glucosyl, triazole and dithiadiazine moieties into a single framework have been synthesized by simple methodologies. Key factor facilitating this outcome is cyclization with sulfenyl chloride reagent to form new C-N and C-S bonds. Further development of target compound **6** will need to consider different substituents on the heterocyclic ring and how it will influence biological activities. Yield and stability of the target compound **6** with different substituents need to consider

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4. Experimental

4.1. Materials and Methods

An electro-thermal apparatus was used to measure melting points and are not corrected. FT-IR spectra were acquired with KBr pellets using a Perkin Elmer FT-IR spectrophotometer. ^{1}H and ^{13}C NMR spectra were acquired using a Brucker Avance II 400 NMR spectrometer at 298K. An ionizing potential of 70eV Electron-impact was used for mass spectra. Equip-Tronics Digital Polarimeter EQ-801 was used to measure optical rotations. The purity of the compounds was assessed via TLC, made-up of aluminum sheet Silica Gel 60 F254 (Merck), the mobile phase used was 50% hexane- EtOAc and the spots were visualized by exposing the TLC plate to UV light and iodine vapor.

4.2.1. General Procedure for Biological Screening:

Few target molecules **(6a-i)** were screened for fungicidal activity. The screening was conducted using the agar diffusion method. Media Used was Czapek-Dox with Composition (g/l) Sucrose-30.0; Sodium nitrate-2.0; K_2HPO_4-1.0, $MgSO_4$. $7H_2O$-0.5; KCl-0.5; $FeSO_4$-0.01; Agar-20. At first, the stock cultures of fungi were reactivated by inoculating them into broth media and incubated at 27^0C for 48 hrs. The agar plates containing afore mentioned media were prepared, and wells were created in the plate. Each plate was seeded with 100 µl of 48 h old culture containing 10^4 CFU and spread evenly across the surface. After 20 minutes, the wells were filled with various concentrations of the samples, while the control wells were filled with an antibiotic solution. All the plates were incubated at 27^0C for 96 h and the diameter of the inhibition zone was recorded.

4.2.2 General Procedure for synthesis of bis-[6-tetra-O-acetyl-β-D-glucopyranosylimino-1,2,4-triazolo[3,4-b]-1,2,4,5-dithiadiazin-4-yl] alkanes (6a–i):

The reagent and the reactants were synthesized by the known method of synthesis. Bis-(4-amino-5-mercapto-1,2,4-triazol-3-yl) alkanes **(3a-i)** have been synthesized by following the procedure as described earlier.[24-26] Reagent glucosyl chloromethane sulfenyl chloride **(4)** has been synthesized by the extension of earlier known method. [27-28] To a 1 mmol solution of bis-(4-amino-5-mercapto-1,2,4-triazol-3-yl) methane **(3a)** in a 1:1 mixture of $CHCl_3$-DMF, solution of 2 mmol glucosyl chloromethane sulfenyl chloride **(4)** was added slowly and refluxed for 5 h. The formation of hydrogen chloride gas was clearly detected using litmus paper. The progress of the reaction was tracked using thin-layer chromatography

(TLC). Following the reaction, the mixture was allowed to cool and was subsequently treated with dichloromethane for dilution. The organic layer was washed with water and dried with anhydrous Na_2SO_4 to remove any remaining moisture. The organic layer was removed by evaporation under reduced pressure to yield a product in its salt form **(5a)**. The product was triturated with an aqueous saturated solution of $NaHCO_3$ for 10 minutes. Following this, it was extracted using ethyl acetate and then dried with anhydrous Na_2SO_4. The dried organic layer was evaporated under reduced pressure to yield the free base, which was then crystallized from a $CHCl_3$-petroleum ether mixture, resulting in the formation of **6a** as a creamish coloured solid residue.

4.3. Spectral analyses and polarimetric study of compounds 6a-i:

4.3.1. Bis-[glucopyranosylimino-1,2,4-triazolo-1,2,4,5-dithiadiazin-4-yl] methane (6a): IR (KBr) ν_{max} cm^{-1}: 3321 (NH), 1541 (C=N), 1752 (O=C–O), 736 (C-S), 600 (S-S). ^{1}H NMR ($CDCl_3$) δ ppm: 5.62-3.87 (m, 14H, H_1-H_7), 3.35 (s, 2H, CH_2), 2.20-1.92 (m, 24H, CH_3-C=O). ^{13}C NMR ($CDCl_3$) δ ppm: 170.93, 170.20, 170.00, 169.69, 82.80, 73.16, 70.15, 70.90, 69.92, 68.45, 67.42, 61.93, 61.24, 32.59, 32.88, 31.25, 30.05, 27.56. MS (*m/z*): 1018 $[M]^+$. $[\alpha]_D^{25}$ = +60° (c = 0.5%, EtOH); R_f –0.50 (50% hexane- EtOAc).

4.3.2. Bis-[glucopyranosylimino-1,2,4-triazolo-1,2,4,5-dithiadiazin-4-yl] ethane (6b): IR (KBr) ν_{max} cm^{-1}: 3323 (N-H), 1567 (C=N), 1751 (O=C–O), 734 (C-S), 601 (S-S). ^{1}H NMR ($CDCl_3$) δ ppm: 5.80-3.75 (m, 14H, H_1-H_7), 3.21 (bs, 4H, $2CH_2$), 2.20-2.02 (m, 24H, CH_3-C=O). ^{13}C NMR ($CDCl_3$) δ ppm: 170.70, 170.13, 169.25, 169.00, 82.48, 72.79, 71.00, 70.89, 70.05, 69.98, 68.92, 62.92, 61.50, 34.06, 32.20, 31.62, 30.15, 27.08, 26.95. MS (*m/z*): 1054 $[M\text{-}1+Na]^+$. $[\alpha]_D^{25}$ = +50° (c = 0.5%, EtOH); R_f –0.51 (50% EtOAc-hexane).

4.3.3. Bis-[glucopyranosylimino-1,2,4-triazolo-1,2,4,5-dithiadiazin-4-yl] propane (6c): IR (KBr) ν_{max} cm^{-1}: 1752 (O=C–O), 3329 (N-H), 1577 (C=N), 737 (C-S), 600 (S-S). ^{1}H NMR ($CDCl_3$) δ ppm: 5.97-3.87 (m, 14H, H_1-H_7), 2.81 (bs, 4H, $2CH_2$), 2.21-2.00 (m, 24H, CH_3-C=O), 1.91 (m, 2H, CH_2). ^{13}C NMR ($CDCl_3$) δ ppm: 171.11, 170.28, 169.10, 169.01, 83.00, 72.54, 71.27, 71.00, 69.74, 69.12, 67.22, 62.43, 61.70, 34.23, 32.30, 31.78, 29.98, 26.18, 25.85, 23.34. MS (*m/z*): 1047 $[M+1]^+$. $[\alpha]_D^{25}$ = +90° (c = 0.5%, EtOH); R_f – 0.49 (50% EtOAc-hexane).

4.3.4. Bis-[glucopyranosylimino-1,2,4-triazolo-1,2,4,5-dithiadiazin-4-yl] butane (6d): IR (KBr) ν_{max} cm^{-1}: 1739 (O=C–O), 3325(N-H), 736 (C-S), 1529 (C=N), 597 (S-S).^{1}H NMR ($CDCl_3$) δ ppm: 5.80-3.74 (m, 14H, H_1-H_7), 3.20 (bs, 2H, CH_2), 2.72 (bs, 2H, CH_2), 2.24-2.03 (m, 24H, CH_3-C=O), 1.72 (bs, 4H, $2CH_2$). ^{13}C NMR ($CDCl_3$) δ ppm: 170.25, 169.95, 169.31, 168.29, 81.39, 73.09, 72.88, 71.54, 70.23, 69.69, 67.37, 61.00, 60.98, 34.11, 33.24, 31.99, 30.54, 25.45, 25.00, 21.13, 20.79. MS (*m/z*): 1060 M^+. $[\alpha]_D^{25}$ = +50° (c = 0.5%, EtOH); R_f –0.50 (50% EtOAc-hexane).

4.3.5. Bis-[glucopyranosylimino-1,2,4-triazolo-1,2,4,5-dithiadiazin-4-yl] pentane (6e): IR (KBr) ν cm^{-1}: 3315 (N-H), 1752 (O-C=O), 1536 (C=N), 737 (C-S), 600 (S-S).^{1}H NMR ($CDCl_3$) δ ppm: 5.57-3.75 (m, 14H, H_1-H_7), 2.78-2.60 (m, 4H, $2CH_2$), 2.31-1.41 (m, 30H,8 CH_3-C=O and $3CH_2$). ^{13}C NMR ($CDCl_3$) δ ppm: 170.90, 170.23, 169.90, 169.69, 82.50, 72.86, 71.15, 70.80, 69.95, 68.55, 67.42, 62.03, 61.74, 33.26, 32.30, 31.58, 30.15, 25.28, 24.55, 20.76, 20.71, 20.60. MS (*m/z*): 1075 $[M+1]^+$. $[\alpha]_D^{25}$ = +70° (c = 0.5%, EtOH); R_f –0.51 (50% EtOAc-hexane).

4.3.6. Bis-[glucopyranosylimino-1,2,4-triazolo-1,2,4,5-dithiadiazin-4-yl] hexane (6f): IR (KBr) ν_{max} cm^{-1}: 3315 (N-H), 1752 (O-C=O), 1536 (C=N), 737 (C-S), 600 (S-S). ^{1}H NMR ($CDCl_3$) δ ppm: 5.58-3.87 (m, 14H, H_1-H_7), 2.71 (s, 2H, CH_2), 2.31 (s, 2H, CH_2), 2.21-2.03 (m, 24H, CH_3-C=O), 1.95 (m, 8H, $4CH_2$). ^{13}C NMR ($CDCl_3$) δ ppm: 170.63, 169.56, 163.63, 158.50, 148.06, 82.72, 73.51, 72.77, 70.68, 68.56, 68.06, 61.78, 28.89, 26.40, 24.77, 22.64, 20.74, 20.58. MS (*m/z*): 1088 M^+ was not located but characteristic peaks were observed at (*m/z*) 545 $[M\text{-}C_{20}H_{26}N_5O_9S_2]^+$, 413, 169, 371. $[\alpha]_D^{25}$ = +80° (c = 0.5%, EtOH); R_f –0.52 (50% EtOAc-hexane).

4.3.7. Bis-[glucopyranosylimino-1,2,4-triazolo-1,2,4,5-dithiadiazin-4-yl] heptane (6g): IR (KBr) ν_{max} cm^{-1}: 3291 (N-H), 1752 (O-C=O), 1584 (C=N), 737 (C-S), 600 (S-S). ^{1}H NMR ($CDCl_3$) δ ppm: 5.92-3.99 (m, 14H, H_1-H_7), 2.42 (m, 4H, CH_2), 2.02-1.93 (m, 24H, CH_3-C=O), 1.60 (m, 4H, $2CH_2$). ^{13}C NMR ($CDCl_3$) δ ppm: 172.25, 171.57, 168.79, 160.87, 146.19, 81.49, 72.24, 72.19, 70.27, 68.97, 67.48, 60.48, 27.72, 25.92, 24.41, 23.46, 22.11, 20.24, 20.02s. MS (*m/z*): 1102 M^+ was not located but characteristic peaks were observed at (*m/z*) 109, 169, 413. $[\alpha]_D^{25}$ = +60° (c = 0.5%, EtOH); R_f – 0.53 (50% EtOAc-hexane).

4.3.8. Bis-[glucopyranosylimino-1,2,4-triazolo-1,2,4,5-dithiadiazin-4-yl] octane (6h): IR (KBr) ν_{max} cm^{-1}: 3278 (N-H), 1741 (O-C=O), 1535 (C=N), 734 (C-S), 597 (S-S). ^{1}H NMR ($CDCl_3$) δ ppm: 5.39-3.89 (m, 14H, H_1-H_7), 3.25-2.75 (m, 4H, $2CH_2$), 2.18-1.94 (m, 24H, CH_3-C=O), 1.76-1.21 (m, 12H, $6CH_2$). ^{13}C NMR ($CDCl_3$) δ ppm: 171.87, 170.35, 169.32, 162.56, 83.00, 71.87, 70.19, 70.00, 69.83, 68.78, 61.27, 27.72, 26.82, 24.91, 24.40, 23.87, 22.54, 20.24, 20.02. MS (*m/z*): 1116 M^+ not located but the characteristic peaks were observed at (*m/z*) 169, 331, 413. $[\alpha]_D^{25}$ = +20° (c = 0.5, EtOH); R_f – 0.51 (50% EtOAc-hexane).

4.3.9. Bis-[glucopyranosylimino-1,2,4-triazolo-1,2,4,5-dithiadiazin-4-yl] decane (6i): IR (KBr) ν_{max} cm^{-1}: 3464 (N-H), 1754 (O-C=O), 1537 (C=N), 734 (C-S), 601 (S-S). ^{1}H NMR ($CDCl_3$) δ ppm: 5.40-3.86 (m, 14H, H_1-H_7), 3.24-2.62 (m, 4H, $2CH_2$), 2.21-2.03 (m, 24H, CH_3-C=O), 1.86-1.50 (m, 8H, $4CH_2$), 1.39-1.29 (m, 8H, $4CH_2$). ^{13}C NMR ($CDCl_3$) δ ppm:

170.23, 169.75, 168.82, 163.76, 81.58, 70.23, 69.30, 68.50, 67.29, 67.18, 65.45, 63.87, 27.12, 26.34, 25.22, 24.30, 23.77, 22.85, 21.10, 20.92, 20.15. MS (*m/z*): 1144 M^+ not located but characteristic peaks were observed at (*m/z*) 169, 331, 413. $[\alpha]_D^{25}$ = +60° (c = 0.5, EtOH); R_f –0.53 (50% EtOAc-hexane).

4.4. Antifungal screening studies of target compounds (6a-h):

Some of the newly developed bis (*N*-glucosylated 1,2,4-triazolodithiadiazinyl) alkanes were screened for their fungicidal activity against two fungal species, namely, *A. niger* and *C. oxysporum* by agar diffusion method at a concentration of 800µg/mL using the standard antibiotic amphotericin (100µg/mL) for the fungi. The results are presented in **Table 2** as diameter of inhibition zones in mm. Amongst the screened compounds **6b** and **6c** were found to be highly active while others showed low to moderate activity against *A. niger* and *C. oxysporum*. Compounds **6g** and **6h** were found to be inactive against *A. niger* and *C. oxysporum* respectively. **Fig. 3** showed that the activity of the compounds tested against both the organisms decreases with the increasing number of methylene groups.

Table 2. Antifungal activity of final compounds **(6a-h)** (inhibition zones, mm).

Compound	*A. niger*	*C. oxysporum*
6a	++	++
6b	+++	++
6c	+++	+++
6d	++	++
6e	+	+
6f	+	+
6g	-	+
6h	+	-
Amphotericin	+++	+++

- = Inactive -(No inhibition zone was observed), + = Weakly active (inhibition zone 1-3 mm), ++ = Moderately active (inhibition zone 4-6 mm), +++ = Highly active (inhibition zone 7-10 mm)

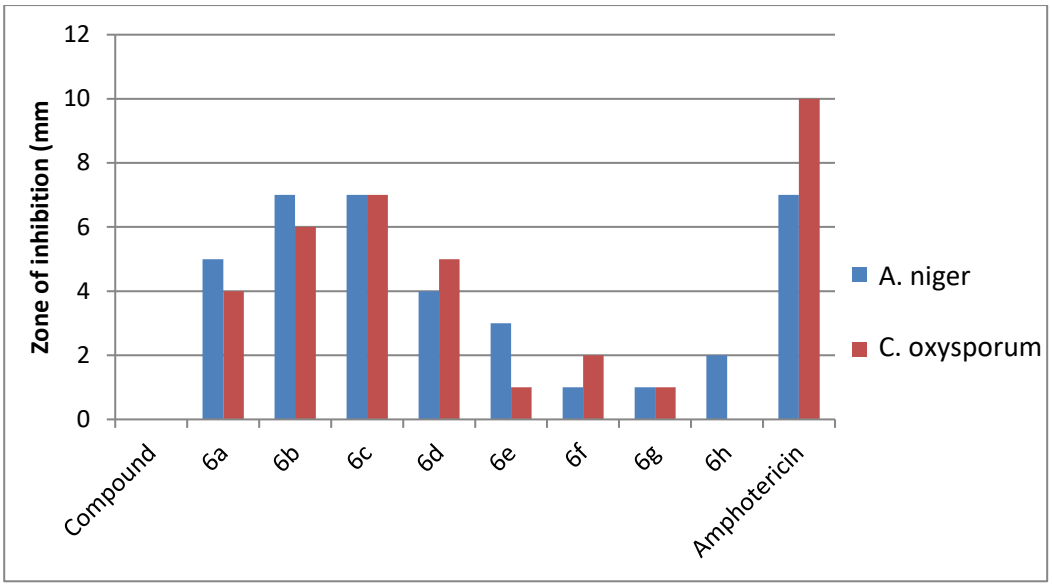

Fig. 3. Comparative Study of antifungal activity of compounds **6a-h** against two fungi

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