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Synthesis and Antimicrobial Activity of 1,3,4-Oxadiazoline, 1,3-Thiazolidine, and 1,2,4-Triazoline Double-Tailed Acyclo C-Nucleosides

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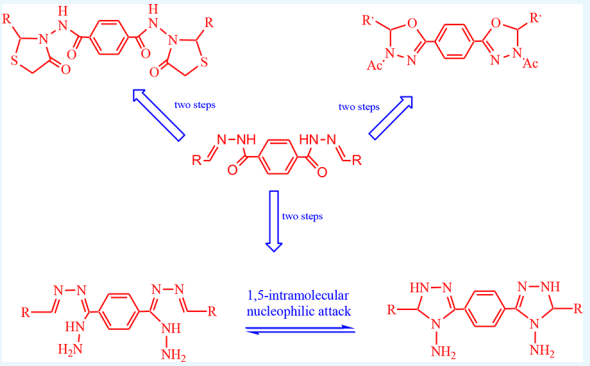
ABSTRACT: The condensation products of terphthaloyl bishydrazide with two equivalents of various monosaccharide aldoses were found to have a bis(sugarhydrazone) form or bis-glycosylhydrazide structure or coexist in tautomeric equilibrium depending on the sugar configuration. The condensation products were substantially utilized as 3-acetyl-1,3,4-oxadiazoline, 1,3-thiazolidine, and 4-amino-1,2,4-triazoline double-tailed acyclo C-nucleosides synthons. The preliminary antimicrobial activities of representative examples of the prepared compounds were evaluated.



1. INTRODUCTION

In the past few decades, synthesis of sulfur, oxygen, and nitrogen containing five-membered heterocyclic arrangements became the main research line of many investigators not only for their importance in scientific research as being available building units for further larger heterocycles but also for their value as biologically active molecules. Therefore, synthesis of 1,3,4-oxadiazoles, 1,3-thiazoles, and 1,2,4-triazoles occupied a vast area in the research fields of many chemists and medicinal chemists. It has been reported that 1,3,4-oxadiazoline derivatives displayed an efficient antibacterial activity against some Gram-positive and Gram-negative bacteria which was rational to the presence of a toxophoric (−N═C−O−) moiety in the structural skeleton of 1,3,4-oxadiazole ring which may attack the nucleophilic centers of bacterial cells.[1] It is also worthy to underline that among 1,3,4-oxadiazole derivatives, 3-acetyl-1,3,4-oxadiazolines showed higher antibacterial activity compared to nonacetylated congeners due to the presence of an extra toxophoric function in their molecular rearrangement.[2,3] Also, belonging to the field of five-membered heterocycles, extensive efforts have been directed toward alternative routes for the synthesis of new 1,3-thiazolines especially following the export of amido-1,3-thiazolidinone as a structural backbone of a potent anticonvulsant drug Ralitoline.[4] In addition, numerous publications are known to be associated with synthesis of 1,2,4-triazoles to evaluate their promising multifarious biological activities. Enormous 1,2,3-triazoles scaffold have been recommended as antibacterial agents, and many studies demonstrated that introducing the free amino group at the *N*-4 position of the 1,2,4-triazole nucleus results in the more favorable antibacterial effect.[5] On the other hand, in the recent 2 decades, significant growth in scientific publications dealing with the synthesis of numerous acyclo C-nucleosides analogues, especially after many the members showed diverse biological activities. Furthermore, several modifications have been made at the molecular structural level of acyclo C-nucleosides including a number of nucleobase[6−10] (head) and alditolyl chains[11,12] (tail). Among the structurally modified acyclo C-nucleosides, there are double-tailed acyclo C-nucleosides and a unique structural feature is the presence of two carbon-linked alditolyl chains of one or two of identical nucleobases or more of different nucleobase. Based on the above-mentioned data, in this article we model a hybridization between 3-acetyl-1,3,4-oxadiazolines, 1,3-thiazolidines, or 1,2,4-triazolines and double sugar residues to generate new double-tailed C-nucleosides.

2. RESULTS AND DISCUSSION

2.1. Chemistry. The outcome of coupling of acylhydrazines or thioacylhydrazines with various reducing saccharides has been reported to exist in solution as sugar hydrazones (acyclic forms)[12−21] or glycosylhydrazides (cyclic forms)[22−26]

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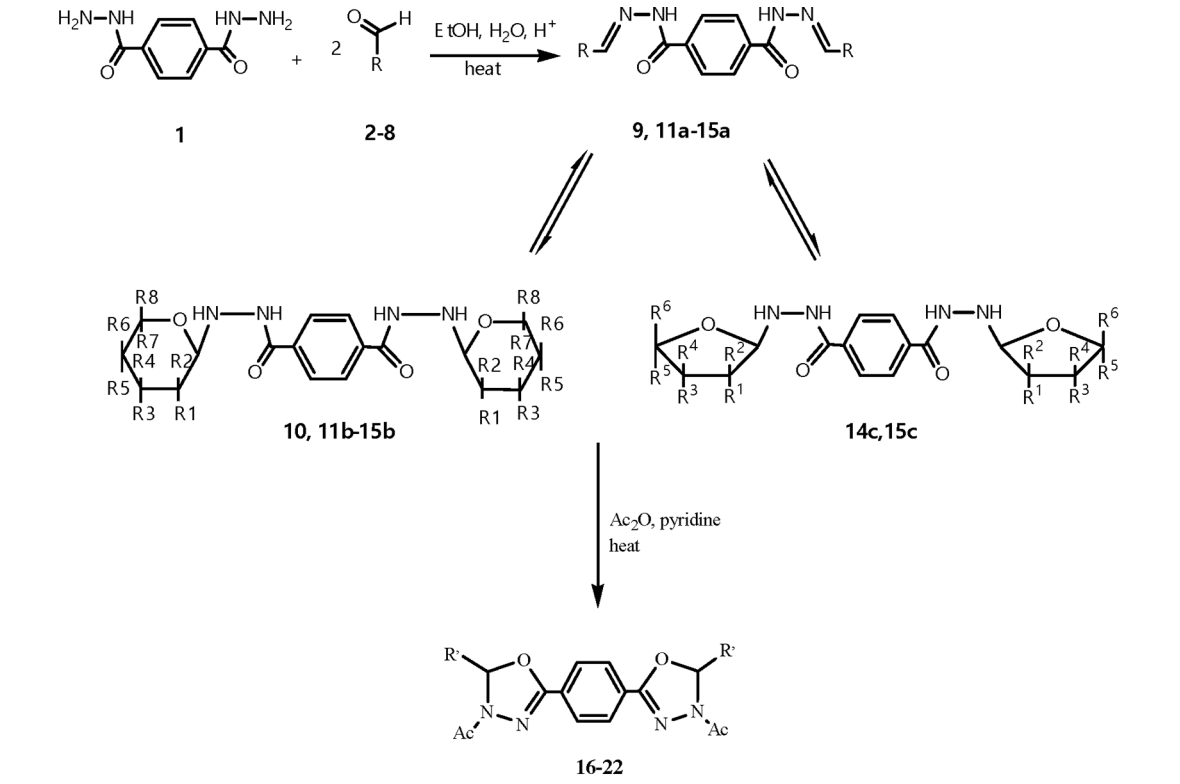
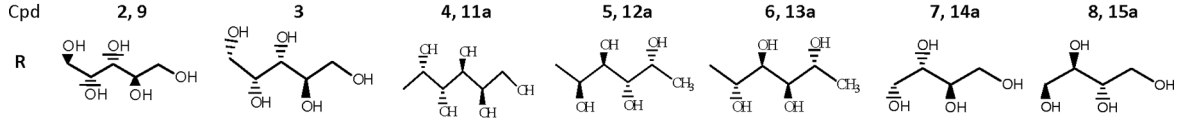
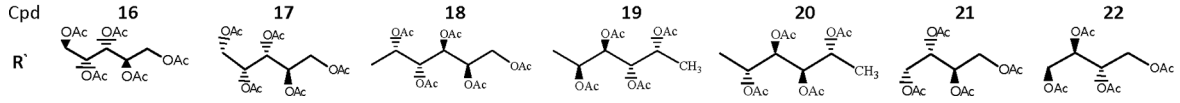
Scheme 1. Synthesis of Terephthaloyl Bis(sugar hydrazones) and 1,4-Bis-[3-acetyl-2-(poly-O-acetyl-alditol-1-yl)-2,3-dihydro-1,3,4-oxadiazol-5-yl]benzenes





Cpd	R1	R2	R3	R4	R5	R6	R7	R8
10	OH	H	H	OH	OH	H	H	CH_2OH
11b	OH	H	H	OH	H	OH	H	CH_2OH
12b	H	OH	OH	H	OH	H	CH_3	H
13b	OH	H	OH	H	H	OH	CH_3	H
14b	H	OH	OH	H	OH	H	-	-
14c	H	OH	OH	H	H	CH_2OH	-	-
15b	OH	H	H	OH	H	OH	-	-
15c	OH	H	H	OH	CH_2OH	H	-	-



and often coexist in tautomeric equilibrium mixtures.[24,25,27,28] The preference of adopting the open chain, cyclic structures, or an interconvertable equilibrated mixture of them has been synergistically effected by the basicity of hydrazines, reaction conditions, pH of the reaction mixture, solvent used in ^{1}H NMR spectra, as well as sugar configuration.[29]

Thus, condensation of terphthaloyl bishydrazine[30] (**1**) with two equivalents of an aqueous solution of D-mannose (**2**) in ethanol, gave a bishydrazone structure **9** on the basis of ^{1}H NMR in DMSO-d_6 that revealed the two azomethine protons (−CH═N−) at δ 7.95−7.71, two exchangeable hydrazono-amide NH protons (−CH═N−NH−CO−) at δ 11.66 ppm plus ^{13}C NMR sp^2 azomethine carbons at 154.3 ppm. On the contrary, the ^{1}H NMR spectrum of the coupling product of D-glucose (**3**) in DMSO-d_6 lacked the presence of hydrazono-azomethine protons and revealed two sets of signals at δ 10.09 and 5.92 ppm for two exchangeable hydrazido-amide protons (−CONH−) and two exchangeable glycosyl-amino protons (glycosyl−NH), respectively. These spectroscopic data were in agreement with the structure of *bis*-glucosylhydrazide **10** (Scheme 1). The pyranoside form of the assigned cyclic structure rather than the furanoside form is readily identified by the presence of an anomeric carbon at δ 91.57 ppm in the ^{13}C NMR spectrum. The higher coupling constant ($J_{1',2'}$) of 9.25 Hz indicated that the β-form of anomeric configuration of pyranosyl structure **10** is more abundant. This finding is in

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harmony with previously reported results[24−27] which supports the β-configuration form at the anomeric centers of the products in the reactions of sugars with various hydrazides.

Unlike ^{1}H NMR spectra of D-mannose hydrazone **9** or D-glucosylhydrazide **10**, the condensation product derived from the interaction of *bis*-hydrazide **1** and the double equivalents of D-galactose (**4**) exhibited azomethine and hydrazono-amide protons ^{1}H NMR signals characteristic of sugar hydrazone, in addition to the hydrazido-amide, glycosyl-hydrazide features. Therefore, the condensation product of D-galactose exists in DMSO-d_6 as an equilibrium mixture of the open chain sugar hydrazone **11a** and the pyranose form **11b** (Scheme 1) in 10:12.5 ratio. The $J_{1',2'}$ value of 8.98 Hz established anomerization of the more favorable β-configuration of the cyclic form **11b**. On the other hand, the presence of a deoxy substitution at the end of the alditolyl chain and the outcome of the products is explored. Therefore, the condensation of *bis*-hydrazide **1** with two molar equivalents of 6-deoxy-L-hexoses, namely: 6-deoxy-L-galactose (L-fucose) **5** or 6-deoxy-L-mannose (L-rhamnose) **6**. It was interesting to find out that L-fucose behaved differently compared to the parent D-galactose in giving the *bis*-acyclic sugar hydrazone **12a** as a major component and the *bis*-cyclic sugar **12b** as a minor product in an ∼10:1.3 ratio. Moreover, while D-mannose adduct was exclusively adapted the acyclic form **9a** (Scheme 1), the L-rhamnose adduct was obtained as acyclic **13a** and cyclic **13b** structures in an equilibrium mixture in a 10:2 ratio.

In addition, an attempt to investigate the influence of the enantiomerization of sugar chains on the ratio of the acyclic/cyclic ratios of condensation products, we choose D-arabinose (**7**) and L-arabinose (**8**) as models for enantiomeric aldopentose, and we can account for the hydrazone/hydrazide ratios which is found to be 10:13 compared to 10:6.8 in the condensation product of D-arabinose and L-arabinose, respectively. Each ^{13}C NMR spectrum of the two adducts showed azomethine-carbons for acyclic forms **14a** and **15a**, two sets of anomeric carbons signals for pyranosyl **14b**, **15b** and furanosyl **14c**, **15c** carbons with ^{1}H NMR large coupling-constant for $J_{1',2'}$ establish the β-pyranosyl and β-furanosyl (Scheme 1).

Numerous publications that adopt the reaction of several sugar acyl hydrazones with hot acetic anhydride to proceed through the condensed cyclic hydrazide-hydrazone structure and the concomitant acetylation of the aldetolyl hydroxyl chain to provide 3-acetyl-1,3,4-oxadiazolin. Each O-acetyl acyclo-C nucleosides reaction of various sugar acylhydrazones with hot acetic anhydride proceeds through condensative-cyclization hydrazide-hydrazone structure and concomitant O-acetylation of the alditolyl chain hydroxyls to afford 3-acetyl-1,3,4-oxadiazoline per O-acetyl acyclo C-nucleosides.[31−35] On the other hand, it should be noted that limited reports[36,37] support dehydrogenative-cyclization/O-acetylation to give 1,3,4-oxadiazole acyclo C-nucleoside or only led to aldehydeo-sugar acyclohydrazones poly-O-acetate or its N-acetyl derivatives without ring closure. Therefore, subjecting terephthaloyl *bis*-(hydrazide D-mannose hydrazone) **9** to react with boiling acetic anhydride gave a product that showed IR absorptions at 1753 (*O*Ac), 1664 (*N*ac), and 1625 cm^{-1} (C═N) and was analyzed correctly for $C_{44}H_{54}N_4O_{24}$, indicating the introduction of 12 acetyl groups: 10 as O-acetyl blocking the double pentitolyl chain 4ydroxyl groups and the other two groups having to replace either the oxadiazolinyl 2NH protons of structure **16** or the hydrazonyl 2NHCO protons of the hydrazone structure. These data overruled the probability of formation of both 1,3,4-oxadiazole per O-acetate and hydrazone polyacetates. Examination of two types of resonance spectra of the product revealed ^{1}H NMR at δ 6.25 ppm which was attributed to oxadiazolinyl C5−H and showed ^{13}C NMR signal for sp^3-hybridized oxadiazoline C5 at δ 89.7 ppm. Had the product been the alternative uncyclized *N*-acetylhydrazone polyacetate, its proton azomethine ^{1}H NMR would be located in the downfield region of nearly δ 7−8 ppm and would show the ^{13}C NMR of azomethine carbon at about δ 150.0−160.0 ppm as in the ^{1}H and ^{13}C resonance of the parent *bis*-hydrazone **9**. There is no doubt that the structure of the acetylation product is 1,4-*bis*-[3-acetyl-2-(2,3,4,5,6-penta-*O*-acetyl-D-*manno*-pentitol-1-yl)-2,3-dihydro-1,3,4-oxadiazol-5-yl]benzene (**16**) (Scheme 1).

In this context, it seems interesting to investigate whether acetylation of the cyclic tautomer, namely, terephthaloyl *bis*-(β-D-glucosylhydrazide) (**10**) with hot acetic anhydride behaved similarly to acyclic tautomer **9** to give 3-acetyl-1,3,4-oxadiazoline structure or behaved differently to afford the proposed *N*-acetyl-D-glucohydrazide (Scheme 1). Corroboration of the obtained product assigned the structure of 1,3,4-oxadiazoline acyclo *C*-nucleoside **17** was made on the basis of its microanalytical data agreeing with the molecular formula $C_{44}H_{54}N_4O_{24}$. In addition, the ^{1}H NMR spectrum provides firm evidence for the assigned structure **17**, thus, beside the 2*N*ac, 10 *O*ac, 12 alditolyl proton signals, it showed 2 oxadiazolinyl protons as well as acetyl, oxadiazoline C5 and C3, aromatic carbons, alditolyl carbons, and acetyl methyl carbons in ^{13}C NMR spectrum. The disappearance of anomeric proton ^{1}H NMR at δ 3.85−3.84 ppm as well as an anomeric carbon ^{13}C NMR at δ 91.6 ppm in the resonance spectra of assigned structure **17** instead new signals characteristic of ^{1}H NMR oxadiazolinyl protons at δ 6.66−6.42 ppm and ^{13}C NMR oxadiazolinyl C5 at δ 89.4, 89.3 ppm led to safe conclusion that the *bis*-glucopyranosyl hydrazide **10** underwent pyranose ring opening and double condensation cyclization to build up the two oxadiazoline rings when reacted with boiling acetic anhydride. Such pyranose ring opening associated with the acetylation process has been reported in the literature.[38,39] An additional proof for the assigned structure **16** and **17** originated from the examination of its MS spectrum which revealed its molecular ion peak at *m*/*z* 1022 in low relative intensity (0.31%) (see the Experimental Section). Moreover, it is well-known a fragment of a base carrying a protonated formyl group (B−CHO$^+$H) is indicative of the carbon−carbon linkage between the alditolyl chain and the base moiety of the C-nucleoside having a mono sugar tail.[40] It is not unusual, therefore, to find out the presence of two fragments characteristic of a double tail acylo C-nucleoside at *m*/*z* 691 and at *m*/*z* 243.

In spite of condensation products **11a−15a** ⇌ **11b−15b** existing in an equilibrated mixture of the acyclic and cyclic forms, they gave a single product in each reaction with boiling acetic anhydride. The obtained products were also assigned the double-tailed 1,3,4-oxadiazoline acyclo C-nucleoside. In their ^{1}H NMR spectra, there is a noticeable change from the location of the azomethine proton at δ 7.76−7.95 ppm or anomeric protons at δ 3.59−4.10 ppm in the starting equilibrated mixture (sugar hydrazones ⇌ glycosylhydraides) to oxadiazolines C5−H at 6.22−6.66 ppm. In addition to acetylation of the double alditolyl chain hydroxyl groups, the formation of the 1,3,4-oxadiazoline ring of **18−22** most

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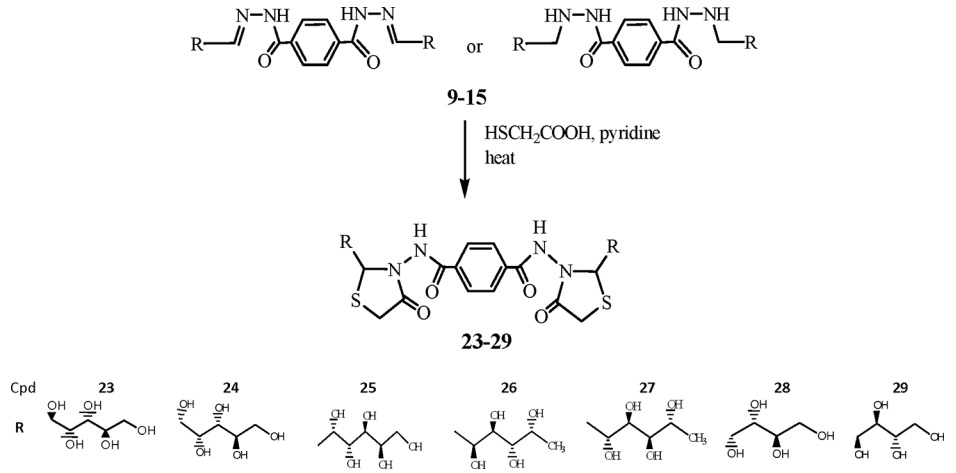
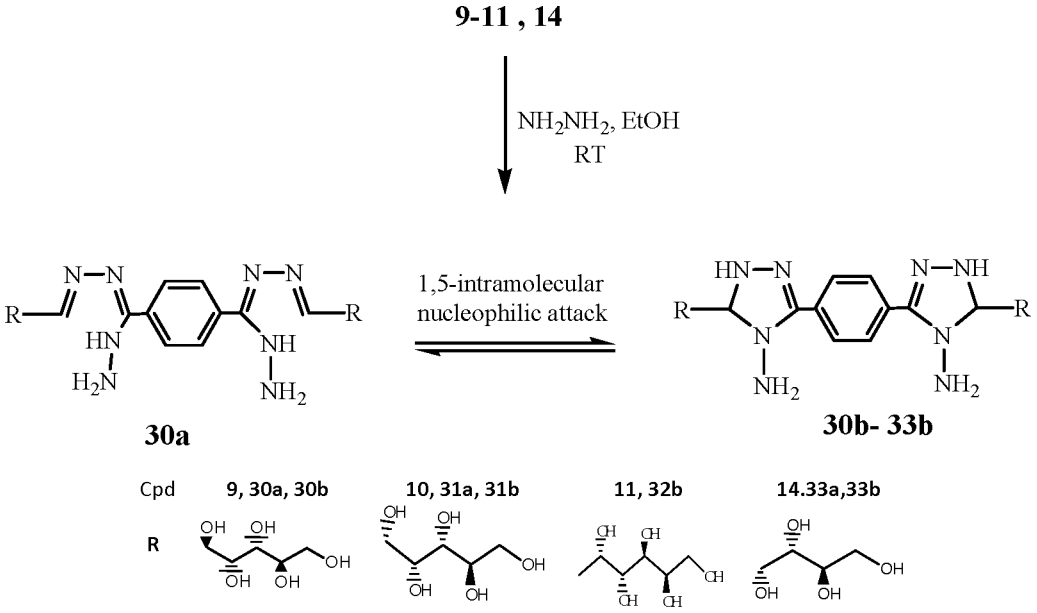
Scheme 2. Synthesis of *N,N′*-Bis(2-alditol-1-yl-4-oxo-1,3-thiazolin-3-yl)ter-phthalamides



Scheme 3. Synthesis of 1,4-Bis(3-alditol-1-yl-4-amino-1,2,4-triazolin-5-yl)benzenes



probably takes place by generation of the N-acyliuminum ion due to nucleophilic attack of azomethine nitrogen atom with acetic anhydride and tautomerization into a carbocation which enhanced the 1,5-intramolecular nucleophilic attack of oxygen atom leading to the final products.

Akin to the same strategy to utilize the bis(sugar hydrazide-hydrazones) as new double tailed acyclo C-nucleoside synthones, heating the hydrazones **9**−**15** with an excess amount of thioglycolic in the presence of pyridine afforded products assigned the structure *N,N,*-bis(2-alditol-1-yl-4-oxo-1,3- thiazolidin-3-yl)terphthalamides **23**−**29** (Scheme 2). Corroboration of the later structures has been made on the basis of the appearance of OH, NH, CON IR absorptions and lacking the C═N in IR absorptions of the parents. ^{1}H NMR examination of each product showed beside the expected 2 exchangeable amido-NH, 4 protons signal for the aromatic and double sugar chain proton signals and the new 2 thiazolidinyl CH and CH_2 proton signals at δ 6.29−8.58 and δ 3.36−3.93 ppm, respectively. It is worth mentioning that like their reactions with acetic anhydride, cyclic sugar moieties in the tautomeric forms undergo pyranose ring opening under acidic conditions of thioglycolic acids. In the literature,[41] such acidic media promote pyranose ring opening. Additional proof for the assigned 1,3-thiazolidine acyclo *C*-nucleoside comes from MS of **23**, which showed its molecular ion peak at *m*/*z* 666 (M + 1) beside the a fragments ($C_4H_7^+$) at *m*/*z* 545 and *m*/*z* 423 diagnostic of double tailed acyclo *C*-nucleoside.

In the same line, the exploitation of the *bis*(sugar hydrazide-hydrazones) as building units for *bis* acyclo *C*-nucleoside analogues and treatment of terphthaloyl *bis*-(D-mannose hydrazone) **9** with ethanolic hydrazine hydrate at ambient temperature afforded a product which showed NH_2, OH, NH, and C═N and lacked CON absorption in the IR region (Scheme 3). On the other hand, the appearance of both signals attributed to 2 HC═N overlapping aromatic protons at δ 7.89−7.83 and 2 triazolinyl protons at δ 6.97−6.95 ppm in the ^{1}H NMR spectrum of the product is an evident for the presence of both acyclic **30a** and cyclic **30b** in an equilibrated chain-ring tautomerization. An additional proof for the coexistence of both tautomers in DMSO-d_6 came from the location of sp^2 azomethine carbons of the acyclic structure and the sp^3 triazolinyl carbons of the cyclic structure at δ 154.3 and

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Table 1. Antibacterial and Antifungal Activity of the Investigated Compounds against Some Reference Strains[a]

	inhibition zones (mm)				
cmpd no.	*Staphylococcus aureus*	*Bacillus subtilis*	*Pseudomonas aeruginosa*	*Escherichia coli*	*Candida albicans*
9	10	12	12	10	8
10	16	12	12	14	12
14	16	12	12	16	14
16	9	6	6	5	
17	10	7	6	6	
21	12	8	6	8	
23	18	16	16	12	18
24	14	16	12	10	16
28	20	16	14	12	18
30	12	14	10	12	12
31	12	12	14	12	10
33	16	14	14	12	12
ampicillin	17	21	21	17	17
streptomycin	22	35	32	30	20
DMF		6.5		6.5	

[a]The microorganisms is considered insensitive if the diameter of the zone is less than 10 mm, weakly sensitive if the diameter is 11−15 mm, sensitive for diameters 15−25 mm, and highly sensitive for diameters more than 25 mm.

71.6 ppm, respectively, in the ^{13}C NMR spectrum of the product.

Taking into consideration, it is well-known that the glyscosylhydrazides in hydrazine solutions undergo tautomerization to give the saccharide hydrazones,[42,43] and it is interesting to explore the reaction of terphthaloyl *bis*(*β*-D-glucopyranosylhydrazide) **10** with hydrazine hydrate proceeding to undergo two pyranose rings opening to form dipentitol residue or the sugar part enabling it to remain in the pyranose form. An equilibrium mixture of tautomeric forms evidently presents in the ^{1}H NMR spectrum of the product in DMSO. It showed azomethaine protons of **31a** in addition to CH of 1,2,4-triazoline ring **30b**. The ^{13}C NMR spectrum is in harmony with the presence of the two tautomeric isomers, and it revealed carbon signals for the hydrogen of **31b**, the azomethine hydrazone carbon structure at 165.3 ppm and triazolinyl C3 at 78.5 ppm of the structure of **31b**. In contradiction, the sugar-chain or ring−chain tautomerism were not obviously noticeable in the ^{1}H and ^{13}C NMR signals of the product resulting from the treatment of bis(D-galactose hydrazone) **11a** ⇌ bis(*β*-D-galactopyranosylhydrazide **11b**. The ^{1}H NMR showed two deuterated NH as one singlet signal at 9.85, two triazolinyl protons as a doublet signal at (7.05−7.04), two deuterated NH_2 as one singlet signal at 6.04 ppm, and lacked azomethine and anomeric proton signals. In support of the bis(4-amino-1,2,4-triazoline) double-tailed acyclo C-nucleoside, the ^{13}C NMR revealed triazolinyl C3 and C5 at 74.8 and 165.6 ppm, respectively. Examination of the ^{1}H and ^{13}C NMR in DMSO-d_6 of the resulting product of reaction of D-arabinohydrzone **14a** ⇌ D-arabinosylhydrzide **14b** with ethanolic hydrazine showed the existence of two tautomers of the acyclic hydrazone structure **33a** and the 1,2,4-triazoline form **33b**.

3. BIOLOGICAL ACTIVITY

3.1. Antimicrobial Activity Discussion. The preliminary antimicrobial activities of representative examples of the prepared compounds were evaluated in vitro against the two Gram positive bacteria, *Staphylococcus aureus* (ATCC6538P) and *Bacillus subtilis* (ATCC19659), and the two Gram negative bacteria, *Pseudomonas aeruginosa* (ATCC9027) and *Escherichia coli* (ATCC8739), as well as for antifungal activity against *Candida albicans* (ATCC2091) using the agar diffusion method.[44] In general, their antimicrobial activity ranged from weak to moderate activity (Table 1). Among the tested compounds, 1,4-*bis*-(4-oxo-2-D-*arabino*-pentitol-1-yl-1,3-thiazolidin-3-yl)-terephthalamide (**28**) showed the highest antimicrobial activity. The antibacterial results indicated that the *bis*-(thiazolidine acyclo C-nucleosides) **23** and **28** showed the highest effect on the used microbes. In the term of the structure activity relationship (SAR), the importance of the heterocyclic ring containing sulfur and nitrogen atoms has to be pointed out to demonstrate the antibacterial activity. In general, the tested compounds linked to D-arabino configuration reveal a higher antibacterial activity when compared to those carrying the D-manno or D-gluco configuration.

3.2. Antimicrobial Screening. Sterile nutrient agar plates (100 mL) were separately inoculated with a 24 h of broth culture (1 mL) of *Escherichia coli*, *Bacillus subtilis*, *Staphylococcus aureus*, *Candida albicans*, and *Pseudomonas aeruginosa*. Solutions (60 mL) of the tested compounds (0.34 mg) in DMF (1 mL) were placed in wells (6 mm diameter) cut in the agar media, and the plates were incubated at 37 °C in the case of bacteria and 25 °C in the case of yeast. The diameter of the resulting inhibition zones were measured after 28 h for bacteria and 96 h for yeast. Zones ≤10, 11−15, 15−22, and >25 mm in diameter were taken to indicate insensitivity, weak, sensitivity, reasonable sensitivity, and high sensitivity of the microorganism to the screened compound, respectively.

4. CONCLUSION

The new coupling terphthaloyl *bis*(hydrazide-hydrazones) containing double-sugar moieties resulting from the reaction of terphthaloyl bishydrazide with two equivalents of an aqueous solution of aldehydosugars (e.g., D-mannose, D-glucose, D-galactose, L-rhamnose, D-arabinose, and L-arabinose) were shown to exist in DMSO-d_6 in acyclic, cyclic forms, or equilibrated in the two forms of sugar chains. The reaction of the compounds **9**, **10**, **11a-15a** ⇌ **11b-15b** with boiling acetic anhydride gave the corresponding 1,4-bis-[3-acetyl-2-(poly-O-acetyl-alditol-1-yl)-2,3-dihydro-1,3,4-oxadiazol-5-yl]benzenes **16−22**. The obtained products were also assigned the double-

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tailed 1,3,4-oxadiazoline acyclo C-nucleoside. In order to utilize new double tailed acyclo C-nucleoside synthones, heating of the hydrazones **9**−**15** with an excess amount of thioglycolic in the presence of pyridine afforded the corresponding *N,N*-bis(2-alditol-1-yl-4-oxo-1,3- thiazolidin-3-yl)terphthalamides **23**−**29**. Also the reaction of hydrazone (**9**), glucosylhydrazide (**10**), or their tautomeric mixtures (**11a** ⇌ **11b**), (**14a** ⇌ **14b** ⇌ **14c**) with hydrazine hydrate afforded 1,4-bis(3-alditol-1-yl-4-amino-1,2,4-triazolin-5-yl)benzenes **30**−**33**. The preliminary antimicrobial activities of the new 1,3,4-oxadiazoline, 1,3-thiazolidine, and 1,2,4-triazoline double-tailed acyclo C-nucleosides showed promising results

5. EXPERIMENTAL SECTION

5.1. Materials and Methods. Melting points were determined on a MEL-TEMP II melting point apparatus in open glass capillaries. The homogeneity of the products and follow up of the reactions were checked by thin layer chromatography (TLC) on plates precoated with silica gel G (Merck; layer thickness 0.25 mm), used without pretreatment. All ratios of the used solvent systems were volume to volume (V/V); the distance of the solvent travel was 5 cm, and the spots were visualized by exposure to iodine vapor for a few minutes. The infrared spectra (IR) were recorded for potassium bromide (KBr) discs on a PerkinElmer USA spectrophotometer, model 1430, covering the frequency range of 200−4000 cm^{-1}. Proton magnetic resonance (^{1}H NMR) spectra were carried out at ambient temperature (~25 °C) with Joule JNM ECA 500 MHz or with Bruker 400 MHz spectrometers using tetramethylsilane (TMS) as an internal standard; the chemical shifts are reported in parts per million on the δ scale. Mass spectra (MS) were performed on a GCMS solution DI Analysis Shimadzu Qp-2010 Plus. Elemental microanalyses were performed at the Microanalytical Unit, Cairo University, Cairo, Egypt. Antimicrobial activity of the screened samples was carried out at the Faculty of Pharmacy, Pharmaceutical Microbiology Lab, Alexandria University.

5.2. Chemistry. *5.2.1. General Method for Synthesis of Terephthaloyl Bis(sugar hydrazones) and Their Tautomeric Forms.* A solution of terephthaloyl *bis*-hydrazide (**1**) (1 mmol) in ethanol (20 mL) was added to solution of respective monosaccharide (2 mmol) in water (5 mL) containing two drops of acetic acid then heated under reflux for 6 h. The product formed during heating was left at room temperature and then filtered and crystallized from water−ethanol (1:1).

*5.2.1.1. Terephthaloyl Bis(D-mannose hydrazone) (**9**).* Color: white, yield (98.5%); mp 242 °C; IR (KBr) ν_{max}: 3392 (OH), 3325 (NH), 1650 (CON), 1558 cm^{-1} (C═N); ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.66 (s, 2H, NH, D_2O exchangeable), 7.95 (s, 2H, Ar H), 7.91−7.85 (m, 2H, Ar H), 7.72−7.71 (d, 2H, azomethine CH═N), 5.26−5.25 (d, 2H, OH, D_2O exchangeable), 4.46−4.45 (d, 2H, D_2O exchangeable, 1OH and alditolyl H), 4.33 (t, 2H, D_2O exchangeable, OH), 4.30−4.27 (m, 4H, D_2O exchangeable, OH), 4.09−4.05 (m, 2H, D_2O exchangeable H, 1OH and alditolyl H), 3.67 (t, 2H, alditolyl H), 3.63−3.58 (m, 2H, alditolyl H), 3.54 (t, 2H, alditolyl H), 3.46−3.43, and 3.40−3.36 ppm (2m, 2H each, alditolyl H). ^{13}C NMR (125 MHz, DMSO-d_6): δ 162.8 (C═O), 154.3 (C═N), 136.5, 136.0, 128.1, 128.0, 127.7, and 127.5 (Ar C), 71.8, 71.6, 71.3, 71.0, 70.4, 69.9, 69.6, 67.9, 64.3, and 62.2 ppm (alditolyl C). (*m/z*): 518 and 148 (M^+ $C_8H_8N_2O$, 100%). Anal. Calcd for $C_{20}H_{30}N_4O_{12}$: C, 46.33; H, 5.79; N, 10.81. Found: C, 46.37; H, 5.60; N, 11.01.

*5.2.1.2. Terephthaloyl Bis(β-D-glucopyranosylhydrazide) (**10**).* Color: white, yield (85%); mp 207−209 °C; IR (KBr) ν_{max}: 3401 (OH), 3295 (NH), 1644 cm^{-1} (CON); ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.09 (s, 2H, D_2O exchangeable, CONH), 7.94−7.86 (m, 4H, Ar H), 5.92 (s, 2H, D_2O exchangeable, HN−N), 5.17 (s, 1H, D_2O exchangeable, OH), 4.96−4.86 (m, 3H, D_2O exchangeable, OH), 4.51−4.09 (m, 5H, D_2O exchangeable 3H, 3OH and 2 glucosyl H), 3.85−3.84 (d, 2H, anomeric H), 3.66−3.42 (m, 5H, D_2O exchangeable 1H, 1OH and 4 glucosyl H) and 3.18−2.96 ppm (m, 6H, glucosyl H). ^{13}C NMR (125 MHz, DMSO-d_6): δ166.2, 165.2 (C═O), 137.5, 132.4, 129.6, 128.3, 127.8 (Ar C), 91.6 (anomeric C), 78.5, 77.2, 71.9, 70.9, and 61.9 ppm (glucosyl C). (*m/z*): 518 and 148 (M^+ $C_8H_8N_2O$, 100%). Anal. Calcd for $C_{20}H_{30}N_4O_{12}$: C, 46.33; H, 5.79; N, 10.81. Found: C, 46.12; H, 5.62; N, 10.54.

*5.2.1.3. Terephthaloyl Bis(D-galactose hydrazone) (**11a**) ⇌ Terephthalolyl Bis(β-D-galacto- pyranosylhydrazide) (**11b**).* Color: white, yield (98%); mp 224−228 °C; IR (KBr) ν_{max}: 3399 (OH), 3215 (NH), 1655 cm^{-1} (CON), 1557 cm^{-1} (C═N); ^{1}H NMR (500 MHz, DMSO-d_6) δ11.66−11.64 (d, 2H, D_2O exchangeable, CONH acyclic form), 10.19−10.14 (m, 2H, D_2O exchangeable, CONH cyclic form), 7.94−7.84 (m, 6H, 4Ar H and 2 azomethine CH═N), 5.84, 5.50 (2d, 2H, D_2O exchangeable, NH cyclic form), 5.25, 5.01 (2s, broad, 2H, D_2O exchangeable, OH), 4.57−4.52 (m, 3H, D_2O exchangeable, OH), 4.45−4.43 (m, 2H, D_2O exchangeable H, OH, and glucosyl H), 4.35 (m, 2H, D_2O exchangeable H, OH, and glucosyl H), 4.21−4.17 (m, 3H, D_2O exchangeable, OH), 3.90−3.87 (m, 3H, 2 anomeric H and alditolyl H), 3.69−3.68 (d, 2H, alditolyl H), 3.61 (m, 1H, alditolyl H), 3.51(s, 3H, alditolyl H), and 3.46−3.45 ppm (m, 3H, alditolyl H). Anal. Calcd for $C_{20}H_{30}N_4O_{12}$: C, 46.33; H, 5.79; N, 10.81. Found: C, 46.37; H, 5.80; N, 11.10.

*5.2.1.4. Terephthaloyl Bis(L-fucose hydrazone) (**12a**) ⇌ Terephthalolyl Bis(β-L-fucopyranosyl-hydrazide) (**12b**).* Color: white, yield (92%); mp 247−251 °C; IR (KBr) ν_{max}: 3400 (OH), 3222 (NH), 1656 cm^{-1} (CON), 1560 cm^{-1} (C═N); ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.74 (s, 2H, D_2O exchangeable, CONH acyclic form), 8.04−7.95 (m, 6H, 4Ar H and 2 azomethine CH═N), 5.31−5.09 (m, 2H, D_2O exchangeable, OH), 4.43 (t, 6H, D_2O exchangeable 3H, 3OH, and 3 glucosyl H), 3.97 (s, 2H, D_2O exchangeable, OH), 3.59−3.39 (m, 8H, D_2O exchangeable 1H, 1OH, 2 anomeric H, and 5 glucosyl H), 1.18 ppm (s, 6H, $2CH_3$). Minor signals may be due to the cyclic structure in a minor amount at 10.27−10.26 (m, 2H, D_2O exchangeable, CONH cyclic form) and 5.93 ppm (s, 2H, D_2O exchangeable, NH cyclic form). Anal. Calcd for $C_{20}H_{30}N_4O_{10}$: C, 49.38; H, 6.17; N, 11.52. Found: C, 49.09; H, 6.31; N, 11.27.

*5.2.1.5. Terephthaloyl Bis(L-rhamnose hydrazone) (**13a**) ⇌ Terephthalolyl Bis(β-L-rhamno-pyranosylhydrazide) (**13b**).* Color: white, yield (95%); mp 244−247 °C; IR (KBr) ν_{max}: 3407 (OH), 3323(NH), 1724, 1647 (CON), 1622, 1559 cm^{-1} (C═N); ^{1}H NMR (500 MHz, DMSO-d_6) δ11.70 (s, 2H, D_2O exchangeable, CONH acyclic form), 8.05−7.88 (m, 6H, 4Ar H and 2 azomethine CH═N), 5.30−5.29 (d, 2H, D_2O exchangeable, OH), 4.88−4.71 (m, 1H, D_2O exchangeable, OH), 4.49−4.48 (d, 2H, D_2O exchangeable, OH), 4.32−4.10 (m, 6H, D_2O exchangeable 3H, 3OH, and 3 glucosyl H), 3.89−3.60 (m, 5H, glucosyl H), 1.16−1.14 (d, 6H, $2CH_3$). Weak signals which characterized the cyclic structure at δ 10.34−10.23 (m, 2H, D_2O exchangeable,

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CONH acyclic form) and 5.74 ppm (s, 2H, D_2O exchangeable, NH cyclic form). Anal. Calcd for $C_{20}H_{30}N_4O_{10}$: C, 49.38; H, 6.17; N, 11.52. Found: C, 49.34; H, 6.32; N, 11.22.

*5.2.1.6. Terephthaloyl Bis(D-arabinose hydrazone) (**14a**) ⇌ Terephthalolyl ⇌ Bis(β-D-arabinopyrano-sylhydrazide) (**14b**) and Terephthalolyl Bis(β-D-arabinofuranosyl hydrazide) (**14c**).* Color: white, yield (98%); mp 224−228 °C; IR (KBr) ν_{max}: 3407 (OH), 3271 (NH), 1655 cm^{-1} (CON), 1567 cm^{-1} (C═N); ^1H NMR (500 MHz, DMSO-d_6) δ11.63 (t, 2H, D_2O exchangeable, CONH acyclic form), 10.24−10.14 (m, 2H, D_2O exchangeable, CONH cyclic form), 7.94−7.84 (m, 4H, Ar H), 7.79−7.78 (d, 2H, azomethine CH═N), 6.08−6.07 (d, 2H, D_2O exchangeable, NH cyclic form), 5.06−5.05 (m, 2H, D_2O exchangeable, OH), 4.85 (s, 1H, D_2O exchangeable, OH), 4.62−4.50 (m, 4H, D_2O exchangeable, OH), 4.35−4.32 (m, 2H, D_2O exchangeable H, OH and alditolyl H), 4.10−4.07 (m, 3H, 2 anomeric H and alditolyl H), 3.14−3.13 ppm (d, 7H, alditolyl H), and 2.05 ppm (s, 1H, alditolyl H). ^{13}C NMR (125 MHz, DMSO-d_6): δ 165.5, 164.9, 162.8 (C═O), 154.7 (C═N), 136.2, 136.0, 135.5, 128.0, 127.8, and 127.5 (Ar C), 96.1 (anomeric C, furanose form), 91.4 (anomeric C, pyranose form), 84.9, 79.4, 77.2, 74.0, 72.7, 71,5 70.8 and 69.3 (alditolyl C cyclic 63.9, and 62.1 ppm (alditolyl C acyclic form). Anal. Calcd for $C_{18}H_{26}N_4O_{10}$: C, 47.16; H, 5.67; N, 12.22. Found: C, 46.81; H, 5.63; N, 11.94.

*5.2.1.7. Terephthaloyl Bis(L-arabinose hydrazone) (**15a**) ⇌ Terephthalolyl Bis(β-L-arabinopyranos-ylhydrazide) (**15b**) ⇌Terephthalolyl Bis(β-L-arabinofuranosylhydrazide) (**15c**).* Color: white, yield (90%); mp 202−205 °C; IR (KBr) ν_{max}: 3397 (OH), 3227 (NH), 1656 (CON), 1557 cm^{-1} (C═N); ^1H NMR (500 MHz, DMSO-d_6) δ11.68−11.66 (d, 2H, D_2O exchangeable, CONH acyclic form), 10.24−10.19 (d, 2H, D_2O exchangeable, CONH cyclic form), 7.90 (t, 4H, Ar H), 7.78−7.77 (d, 2H, azomethine CH═N), 5.32 (s, 2H, exchangeable, NH cyclic form), 5.10−5.09 (d, 2H, D_2O exchangeable, OH), 4.76 (t, 1H, D_2O exchangeable, OH), 4.64 (t, 3H, D_2O exchangeable, OH), 4.55 (s, 1H, alditolyl H), 4.39 (s, 2H, D_2O exchangeable H, OH, and alditolyl H), 4.32 (s, 1H, D_2O exchangeable, OH), 3.84, 3.74 (2s, 1H each, alditolyl H), 3.59−3.56 (m, 2H, anomeric CH), 3.49 (s, 2H, alditolyl H), and 3.42−3.35 ppm (s, 4H, alditolyl H). ^{13}C NMR (125 MHz, DMSO-d_6): δ 165.2, 164.9, 164.3, 164.1, 162.8, and 162.7 (C═O), 155.0, 154.7 (C═N), 138.0, 136.2, 135.9, 135.5, 132.6, 132.2, 129.7, 129.6, 128.5, 128.1, 128.0, 128.0, 127.9, 127,8, 127.7, and 127.6 (Ar C), 96.1 (anomeric C, furanose form), 96.07 (anomeric C, pyranose form), 91.4, 84.9, 79.3, 77.2, 74.0, 72.7, 71.4, 70.8, and 70.6 (alditolyl C cyclic form), 69.8, 69.3, 68.2, 67.6, 65.6, 64.1, 63.9, and 62.1 ppm (alditolyl C acyclic form). Anal. Calcd for $C_{18}H_{26}N_4O_{10}$: C, 47.16; H, 5.67; N, 12.22. Found: C, 46.93; H, 5.50; N, 12.20.

5.2.2. General Method for Synthesis of 1,4-Bis-[3-acetyl-2-(poly-O-acetyl-alditol-1-yl)-2,3-dihydro-1,3,4-oxadiazol-5-yl]benzenes. A mixture of hydrazone (**9a**), glucosylhydrazide (**10b**), or their tautomeric mixtures (**11a** ⇌ **11b**), (**12a** ⇌ **12b**), (**13a** ⇌ **13b**), (**14a** ⇌ **14b** ⇌ **14c**), (**15a** ⇌ **15b** ⇌ **15c**) (1 mmol), acetic anhydride (15 mL), and pyridine (3 mL) was heated under reflux with stirring for 4 h after dissolution. After attaining room temperature, the resulting solution was poured onto crushed ice, the product that separated was washed with water then filtered and crystallization from ethanol.

*5.2.2.1. 1,4-Bis-[3-acetyl-2-(2,3,4,5,6-penta-O-acetyl-D-manno-pentitol-1-yl)-2,3-dihydro-1,3,4-oxa- diazol-5-yl]-benzene (**16**).* Color: white, yield (80%); mp 189 °C; IR (KBr) ν_{max}: 1753 (*O*Ac), 1664, 1625 cm^{-1} (*N*Ac, C═N). ^1H NMR (500 MHz, $CDCl_3$) δ7.93 (s, 4H, Ar H), 6.25 (s, 2H, oxadiazolinyl H), 5.65−5.63 (m, 2H, alditolyl H), 5.52−5.50 (d, 2H, alditolyl H), 5.43−5.41, 5.21−5.11, 4.22−4.18 and 4.06−4.02 (4m, 2H each, alditolyl H), 2.24 (s, 6H, 2 *N*Ac), 2.18, 2.11, 2.08, 2.03, and 1.92 ppm (5s, 6H each, 10 *O*Ac). ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.5, 170.0, 169.9, 169.8, 169.2, and 167.9 (C═O), 155.6 (C═N), 127.1, 126.9 (Ar C), 89.7 (oxadiazolinyl C), 67.9, 67.5, 67.1, and 61.9 (alditolyl C), 21.0 20.9, 20.8, 20.7, and 20.4 ppm (CH_3). Anal. Calcd for $C_{44}H_{54}N_4O_{24}$: C, 51.66; H, 5.28; N, 5.47. Found: C, 51.99; H, 5.50; N, 5.82.

*5.2.2.2. 1,4-Bis-[3-acetyl-2-(2,3,4,5,6-penta-O-acetyl-D-gluco-pentitol-1-yl)-2,3-dihydro-1,3,4-oxadi- azol-5-yl]-benzene (**17**).* Color: white, yield (85%); mp 122 °C; IR (KBr) ν_{max}: 1754 (*O*Ac), 1675 cm^{-1} (*N*Ac, C═N). ^1H NMR (500 MHz, $CDCl_3$) δ 8.19−7.88 (m, 4H, Ar H), 6.66, 6.42 (2s, 2H, oxadiazolinyl H), 5.79−5.72 (m, 1H, alditolyl H), 5.70−5.37, 5.16−5.11 (2m, 3H each, alditolyl H), 4.28−3.89 (m, 5H, alditolyl H), 2.26, 2.22 (2s, 3H each, 2 *N*Ac), and 2.11−1.88 ppm (m, 30H, 10 *O*Ac). ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.6, 170.5, 170.4, 170.2, 170.0, 169.8, 169.7, 169.5, 169.5, 169.3, 167.9, 166.1, and 166.1 (C═O), 155.7, 155.4, and 155.2 (C═N), 133.0, 132.9, 130.9, 130.2, 129.9, 129.5, 129.4, 128.3, 127.9, 127.7, 127.4, 127.2, 127.2, 126.9, 126.8, and 126.7 (Ar C), 89.4, 89.3 (oxadiazolinyl C), 74.2, 73.7, 72.3, 71.3, 69.5, 69.2, 68.6, 68.3, 68.2, 68.1, 68.0, 67.4, 61.8, 61.5, and 52.5 (alditolyl C), 21.3, 20.9, 20.8, 20.8, 20.7, 20.7, 20.6, 20.5, 20.4, 20.3, and 20.3 ppm (CH_3). (*m*/*z*): 1022 and 577 (M^+ $C_{25}H_{29}N_4O_{12}$, 100%). Anal. Calcd for $C_{44}H_{54}N_4O_{24}$: C, 51.66; H, 5.28; N, 5.47. Found: C, 51.58; H, 5.16; N, 5.18.

*5.2.2.3. 1,4-Bis-[3-acetyl-2-(2,3,4,5,6-penta-O-acetyl-D-galacto-pentitol-1-yl)-2,3-dihydro-1,3,4-oxa-diazol-5-yl]-benzene (**18**).* Color: white, yield (80%); mp 139 °C; IR (KBr) ν_{max}: 1752 (*O*Ac), 1673 cm^{-1} (*N*Ac, C═N). ^1H NMR (500 MHz, $CDCl_3$) δ δ 8.14−7.69 (m, 4H, Ar H), 6.51−6.29 (2s, 2H, oxadiazolinyl H), 5.76 (s, 1H, alditolyl H), 5.66−5.58 (m, 2H, alditolyl H), 5.40−5.32 (m, 4H, alditolyl H), 5.21 (s, 1H, alditolyl H), 4.30−4.27 (m, 2H, alditolyl H), 3.97 (s, 1H, alditolyl H), 3.87−3.85 (m, 1H, alditolyl H), 2.31, 2.26 (2s, 3H each, 2 *N*Ac), 2.15, 2.11, 2.08, 2.03, and 1.95 ppm (5s, 6H each, 10 *O*Ac). Anal. Calcd for $C_{44}H_{54}N_4O_{24}$: C, 51.66; H, 5.28; N, 5.47. Found: C, 51.47; H, 5.11; N, 5.36.

*5.2.2.4. 1,4-Bis-[3-acetyl-2-(2,3,4,5-tetra-O-acetyl-L-fuco-pentitol-1-yl)-2,3-dihydro-1,3,4-oxadiazol-5-yl]benzene (**19**).* Color: white, yield (90%); mp 133 °C; IR (KBr) ν_{max}: 1751 (*O*Ac), 1676 cm^{-1} (*N*Ac, C═N). ^1H NMR (500 MHz, $CDCl_3$) δ7.93−7.71 (m, 4H, 4Ar H), 6.43, 6.22 (2s, 2H, oxadiazolinyl H), 5.68−5.52 (m, 2H, alditolyl H), 5.32−4.88 (m, 6H, alditolyl H), 2.18, 2.14 (2s, 3H each, 2 NAc), 2.04−1.86 (m, 24H, 8 OAc), and 1.07−1.05 ppm (d, 6H, $2CH_3$). Anal. Calcd for $C_{40}H_{50}N_4O_{20}$: C, 52.98; H, 5.51; N, 6.18. Found: C, 52.72; H, 5.41; N, 5.96.

*5.2.2.5. 1,4-Bis-[3-acetyl-2-(2,3,4,5-tetra-O-acetyl-L-rhamno-pentitol-1-yl)-2,3-dihydro-1,3,4-oxadi-azol-5-yl]benzene (**20**).* Color: white, yield (87%); mp 170 °C; IR (KBr) ν_{max}: 1755 (*O*Ac), 1676 cm^{-1} (*N*Ac, C═N). ^1H NMR (500 MHz, $CDCl_3$) δ.96−7.72 (m, 4H, Ar H), 6.42, 6.30 (2s, 2H, oxadiazolinyl H), 5.70−5.45 (m, 3H, alditolyl H), 5.25, 5,13, 5.00, and 4.89 (4s, 1H each, alditolyl H), 3.97 (s, 1H, alditolyl H), 2.34, 2.27 (2s, 3H each, 2 *N*Ac), 2.20, 2.16, 2.12, 2.09, 2.05, 2.01, 2.00, and 1.95 (8s, 3H each, 8 *O*Ac), and 1.38−1.06

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ppm (m, 6H, $2CH_3$). Anal. Calcd for $C_{40}H_{50}N_4O_{20}$: C, 52.98; H, 5.51; N, 6.18. Found: C, 52.93; H, 5.74; N, 6.40.

*5.2.2.6. 1,4-Bis-[3-acetyl-2-(2,3,4,5-tetra-O-acetyl-D-arabino-pentitol-1-yl)-2,3-dihydro-1,3,4-oxadi- azol-5-yl]benzene (**21**).* Color: white, yield (80%); mp 91 °C; IR (KBr) ν_{max}: 1752 (*O*Ac), 1675 cm^{-1} (*N*Ac, C═N). ^1H NMR (500 MHz, $CDCl_3$) δ 8.06−7.46 (m, 4H, Ar H), 6.47,6.27 (2s, 1H each, oxadiazolinyl H), 5.70 (s, 1H, alditolyl H), 5.55−5.38 (m, 3H, alditolyl H), 5.16−5.10 (m, 2H, alditolyl H), 4.22−4.16 (d, 2H, alditolyl H), 4.03−3.99 (m, 2H, alditolyl H), 2.24, 2.20 (2s, 3H each, 2 *N*Ac), 2.16, 2.15, 2.03, 2.01, 1.99, 1.98, 1.96, and 1.89 ppm (8s, 3H each, 8 *O*Ac). ^{13}C NMR (125 MHz, $CDCl_3$): δ170.7, 170.6, 170.1, 170.0, 169.8, 169.7, 169.5, 169.4, 169.4, 169.3, and 168.2 (C═O), 155.7, 154.9 (C═N), 127.4, 127.0, 126.9, and 126.8 (Ar C), 90.9, 88.9 (oxadiazolinyl C), 69.2, 68.3, 68.1, 68.1, 67.9, 67.6, 67.5, 61.9, 61.8, and 61.4 (alditolyl C), 21.5, 21.1, 20.9, 20.9, 20.8, 20.7, 20.7, 20.6, and 20.2 ppm (CH_3). Anal. Calcd for $C_{38}H_{46}N_4O_{20}$: C, 51.93; H, 5.23; N, 6.37. Found: C, 51.84; H, 5.55; N, 6.75.

*5.2.2.7. 1,4-Bis-[3-acetyl-2-(2,3,4,5-tetra-O-acetyl-L-arabino-pentitol-1-yl)-2,3-dihydro-1,3,4-oxadi-azol-5-yl]benzene (**22**).* Color: white, yield (85%); mp 102 °C; IR (KBr) ν_{max}: 1752 (*O*Ac), 16754 cm^{-1} (*N*Ac, C═N). ^1H NMR (500 MHz, $CDCl_3$) δ 8.14−7.87 (m, 4H, Ar H), 6.55, 6.36 (2s, 1H each, oxadiazolinyl H), 5.78, 5.63, 5.49 (3s, 3H, alditolyl H), 5.24−5.19 (d, 2H, alditolyl H), 4.27 (s, 3H, alditolyl H), 4.10, 3.96 (2s, 2H, alditolyl H), 2.32, 2.28 (2s, 3H each, 2 *N*Ac), and 2.24−1.97 ppm (m, 24 H, 8 *O*Ac). Anal. Calcd for $C_{38}H_{46}N_4O_{20}$: C, 51.93; H, 5.23; N, 6.37. Found: 51.64; H, 5.11; N, 6.45.

5.2.3. General Method for Synthesis N,N′-Bis(2-alditol-1-yl-4-oxo-1,3-thiazolin-3-yl)ter-phthalamides. A mixture of hydrazone (**9a**), glucosylhydrazide (**10b**), or their tautomeric mixtures (**11a** ⇌ **11b**), (**12a** ⇌ **12b**), (**13a** ⇌ **13b**), (**14a** ⇌ **14b** ⇌ **14c**), (**15a** ⇌ **15b** ⇌ **15c**) (1 mmol) in pyridine (5 mL) was heated under reflux for 6−8 h with thioglycolic acid (2 mL). After attaining ambient temperature, the resulting solution was poured onto crushed ice, and the separated product was filtrated and crystallized from water−ethanol (1:1).

*5.2.3.1. N,N′-bis(4-oxo2-D-manno-pentitol-1-yl-1,3-thiazolin-3-yl)ter-phthalamides (**23**).* Color: brown, yield (90%); mp 255 °C; IR (KBr) ν_{max}: 3395 (OH + NH), 1649 cm^{-1} (CON). ^1H NMR (500 MHz, DMSO-d_6) δ 11.68 (s, 2H, D_2O exchangeable, NH), 7.95−7.86 (m, 4H, 4Ar H), 7.70 (s, 2H, thiazolinyl H), 5.53, 5.28 (2s, 1H for each, D_2O exchangeable, 2OH), 4.73−4.69, 4.51−4.48 (2D, 2H each, D_2O exchangeable, OH), 4.31−4.22 (m, 4H, D_2O exchangeable, OH), 4.06 (s, 2H, alditolyl H), 3.79, 3.73. 3.67 (3s, 1H each alditolyl H), 3.62−3.59 (d, 2H alditolyl H),3.55 (s, 1H, alditolyl H), 3.53−3.36 (m, 6H, 2 thiazolinyl CH_2 + 2 alditolyl H), 3.13−2.99 ppm (m, 2H, alditolyl H). (*m*/*z*): 666 and 55 (M^+ $C_4H_7^+$, 100%). Anal. Calcd for $C_{24}H_{34}N_4O_{14}S_2$: C, 43.24; H, 5.10; N, 8.40. Found: 43.11; H, 5.03; N, 8.29.

*5.2.3.2. N,N′-bis(4-oxo2-D-gluco-pentitol-1-yl-1,3-thiazolin-3-yl)ter-phthalamides (**24**).* Color: brown, yield (85%); mp 256 °C; IR (KBr) ν_{max}: 3375 (OH + NH), 1661 cm^{-1} (CON). ^1H NMR (500 MHz, DMSO-d_6) δ 12.30−12.09 (d, 2H, D_2O exchangeable, NH), 8.58−7.40 (m, 6H, 4Ar H and 2 thiazolidinyl CH_2), the other alditolyl and hydroxyl chain protons were associated with the solvent absorption at a large signal at 3.43 ppm. ^{13}C NMR (125 MHz, DMSO): δ172.5 (C═O), 136.6 and 128.2 (Ar C), 75.1 (thiazolinyl C), 71.5, 63.1 (alditolyl C), and 21.3 ppm (thiazolinyl CH_2). Anal. Calcd for $C_{24}H_{34}N_4O_{14}S_2$: C, 43.24; H, 5.10; N, 8.40. Found: 43.46; H, 5.49; N, 8.72.

*5.2.3.3. N,N′-Bis(4-oxo2-D-galacto-pentitol-1-yl-1,3-thiazolin-3-yl)ter-phthalamides (**25**).* Color: brown, yield (80%); mp 232 °C; IR (KBr) ν_{max}: 3407 broad (OH + NH), 1665 cm^{-1} (CON). ^1H NMR (500 MHz, DMSO-d_6) δ 10.71 (s, 2H, D_2O exchangeable, NH), 8.05 (s, 6H, 4Ar H and 2 thiazolidinyl CH_2). The rest of the alditolyl and hydroxyl protons were located at a broad signal at 3.39 ppm. Anal. Calcd for $C_{24}H_{34}N_4O_{14}S_2$: C, 43.24; H, 5.10; N, 8.40. Found: 43.34; H, 4.89; N, 8.61.

*5.2.3.4. N,N′-Bis(4-oxo2-L-fuco-pentitol-1-yl-1,3-thiazolin-3-yl)ter-phthalamides (**26**).* Color: brown, yield (87%); mp 250 °C; IR (KBr) ν_{max}: 3366 broad (OH + NH), 1663 cm^{-1} (CON). ^1H NMR (500 MHz, DMSO-d_6) δ 12.17 (s, 2H, D_2O exchangeable, NH), 8.58−7.38 (m, 6H, 4Ar H and CH_2 thiazolidinyl proton) and 1.24 ppm (s, 6H, $2CH_3$. The rest of hydroxyl protons of two sugar chains were located at the broad signal of DMSO at 3.35 ppm. Anal. Calcd for $C_{24}H_{34}N_4O_{12}S_2$: C, 45.42; H, 5.36; N, 8.83. Found: 45.74; H, 4.93; N, 8.95.

*5.2.3.5. N,N′-bis(4-oxo2-L-rhamno-pentitol-1-yl-1,3-thiazolin-3-yl)ter-phthalamides (**27**).* Color: brown, yield (85%); mp 255 °C; IR (KBr) ν_{max}: 3412 broad (OH + NH), 1661 cm^{-1} (CON). ^1H NMR (500 MHz, DMSO-d_6) δ 12.26−12.16 (d, 2H, D_2O exchangeable, NH), 8.58−7.39 (m, 4H, Ar H), 6.85−6.29 (2s, 2CH thiazolidinyl proton), 5.00−4.60 (m, 1H, exchangeable, OH), 3.66 (m, 4H, $2CH_2$ thiazolidinyl proton), 1.37 (s, 6H, $2CH_3$), and the rest of the hydroxyl protons of two sugar chains were located at the broad signal of DMSO at 3.38 ppm. Anal. Calcd for $C_{24}H_{34}N_4O_{12}S_2$: C, 45.42; H, 5.36; N, 8.83. Found: 45.17; H, 5.21; N, 9.21.

*5.2.3.6. N,N′-bis(4-oxo2-D-arabiono-pentitol-1-yl-1,3-thiazolin-3-yl)ter-phthalamides (**28**).* Color: solid, yield (94%); mp 234 °C; IR (KBr) ν_{max}: 3429 broad (OH + NH), 1662 cm^{-1} (CON). ^1H NMR (500 MHz, DMSO-d_6) δ 12.25−12.11 (d, 2H, D_2O exchangeable, NH), 8.12−7.79 (m, 6H, 4Ar H, 2CH thiazolidinyl proton), 5.04−4.62 (m, 3H, exchangeable, OH), 3.88 (s, 4H, $2CH_2$ thiazolidinyl proton), 3.04−2.69 (m, 3H, alditolyl protons), and the rest of hydroxyl protons of two sugar chains were located at the broad signal of DMSO at 3.54 ppm. Anal. Calcd for $C_{22}H_{30}N_4O_{12}S_2$: C, 43.56; H, 4.95; N, 9.24. Found: 43.73; H, 4.83; N, 9.58.

*5.2.3.7. N,N′-bis(4-oxo2-L-arabiono-pentitol-1-yl-1,3-thiazolin-3-yl)ter-phthalamides (**29**).* Color: solid, yield (90%); mp 230 °C; IR (KBr) ν_{max}: 3405 broad (OH + NH), 1661 cm^{-1} (CON). ^1H NMR (500 MHz, DMSO-d_6) δ 12.24−12.15 (d, 2H, D_2O exchangeable, NH), 8.58−7.39 (m, 6H, 4 Ar H, 2CH thiazolidinyl proton), 4.99−4.62 (m, 3H, exchangeable, OH), 3.91−3.61 (m, 4H, $2CH_2$ thiazolidinyl proton), and the rest of hydroxyl protons of two sugar chains were located at the broad signal of DMSO at 3.38 ppm. Anal. Calcd for $C_{22}H_{30}N_4O_{12}S_2$: C, 43.56; H, 4.95; N, 9.24. Found: 43.84; H, 4.61; N, 9.62.

5.2.4. General Method for Synthesis 1,4-Bis(3-alditol-1-yl-4-amino-1,2,4-triazolin-5-yl)benzenes. A mixture of hydrazone (**9**), glucosylhydrazide (**10**), or their tautomeric mixtures (**11a** ⇌ **11b**), (**14a** ⇌ **14b** ⇌ **14c**) (1 mmol), and hydrazine hydrate (99%, 4 mmol) in ethanol (20 mL) was stirred at ambient temperature overnight. The product formed was separated by filtration and then crystallization from ethanol.

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*5.2.4.1. 1,4-Bis-(D-mannose monocarbohydrazonohydrazide)benzene (**30a**) ⇌ 1,4-Bis-(4-amino-3-D-manno-pentitol-1-yl-1,2,4-triazolin-5-yl)-benzene (**30b**).* Color: white, yield (85%); mp 213−215 °C; IR (KBr) ν_{max}: 3322 (NH_2), 3229 (OH + NH), 1622 cm^{-1} (C═N). ^1H NMR (500 MHz, DMSO-d_6) δ 9.85 (s, 2H, D_2O exchangeable, triazolinyl NH), 7.89−7.83 (m, 6H, 4Ar H and 2 azomethine CH═N), 6.97−6.95 (d, 2H, triazolinyl H), 6.07 (s, 4H, D_2O exchangeable, $2NH_2$), 4.78, 4.68 (2s, 1H each, D_2O exchangeable, OH), 4.53 (s, broad, 4H, D_2O exchangeable, OH), 4.42 (s, 1H, D_2O exchangeable, OH), 4.35 (s, 3H, D_2O exchangeable, OH), 4.15−4.09 (m, 3H, alditolyl H), 3.89−3.65 (m, 2H, alditolyl H), 3.61−3.48 (m, 4H, alditolyl H), and 3.42 ppm (s, 3H alditolyl H). A weak D_2O exchangeable signal at 11.63 ppm is attributed to NH−NH_2 and the rest of NH_2 present under the broad signal of DMSO at δ 3.35 ppm. ^{13}C NMR (125 MHz, DMSO-d_6): δ 165.6, 162.8 (C═N), 154.3 (azomethine C), 136.5, 135.9, 128.1, 128.0, and 127.4 (Ar C), 71.6 (triazolinyl C), 71.3, 71.0, 69.9, and 64.3 ppm (alditolyl C). Anal. Calcd for $C_{20}H_{34}N_8O_{10}$: C, 43.95; H, 6.22; N, 20.51. Found: 43.47; H, 5.90; N, 20.18.

*5.2.4.2. 1,4-Bis(β-D-glucopyranosyl monocarbohydrazonohydrazide)benzene (**31a**), 1,4-Bis(D-glucose monocarbohydrazonohydrazide)benzene (**31b**), and 1,4-Bis(4-amino-3-D-gluco-pentitol-1-yl-1,2,4-triazolin-5-yl)benzene (**31c**).* According to the previous general method, a white solid was obtained. Yield (85%); mp 180−183 °C; IR (KBr) ν_{max}: 3321 broad (NH_2+ (OH + NH), 1633 cm^{-1} (C═N). ^1H NMR (500 MHz, DMSO-d_6) δ 9.86 (s, 2H, D_2O exchangeable, triazolinyl NH), 7.92−7.69 (m, 8H, 4Ar H, 2 azomethine CH═N and 2 triazolinyl H), 5.93 (s, 2H, D_2O exchangeable, N−NH pyranosyl form), 5.67−5.51 (m, 2H, D_2O exchangeable, NH_2), 5.20 (s, 2H, D_2O exchangeable, NH_2), 5.00−4.88 (m, 8H, D_2O exchangeable, $4NH_2$), 4.55−4.34 (m, 10H, D_2O exchangeable, OH), 4.17, 3.92 (2s, 1H each, alditolyl H), 3.84 (s, 2H, alditolyl H), 3.76 (s, 1H, alditolyl H), 3.67−3.55 (m, 3H, 2 anomeric CH, and 1 alditolyl H), 3.18−3.11 (m, 3H, alditolyl H), and 3.03−2.95 ppm (m, 3H, alditolyl H). A weak D_2O exchangeable signal at 11.65 and 10.16 ppm attributed to NH of open chain sugar hydrazone (**31b**) and HN−NH_2 of pyranosyl hydrazone (**31a**), respectively. ^{13}C NMR (125 MHz, DMSO-d_6): δ166.2, 165.6, and 165.5 (C═N), 165.3 (azomethine C), 137.9, 137.4, 135.9, 132.4, 132.1, 129.6, 128.3, 127.8, and 127.4 (Ar C), 91.6 (anomeric C), 78.5 (triazolinyl C), 77.2, 71.9, 70.9, and 61.9 ppm (alditolyl C). Anal. Calcd for $C_{20}H_{34}N_8O_{10}$: C, 43.95; H, 6.22; N, 20.51. Found: 44.32; H, 5.89; N, 20.43.

*5.2.4.3. 1,4-Bis(4-amino-3-D-galacto-pentitol-1-yl-1,2,4-triazolin-5-yl)benzene (**32**).* Color: white, yield (92%); mp 174 °C; IR (KBr) ν_{max}: 3325 broad (NH_2+ (OH + NH), 1625 cm^{-1} (C═N). ^1H NMR (500 MHz, DMSO-d_6) δ 85 (s, 2H, D_2O exchangeable, NH), 7.99−7.83 (m, 4H, Ar H), 7.05−7.04 (d, 2H, triazolinyl H), 6.04 (s, 4H, exchangeable, NH_2), 4.49−4.43 (d, 7H, D_2O exchangeable 4H, 4OH, and 3 alditolyl H), 4.27−4.12 (m, 7H, D_2O exchangeable 2H, 2OH, and 5 alditolyl H), 3.83−3.39 (m, 6H, D_2O exchangeable 2H, 2OH, and 4 alditolyl H), and 3.13 (s, 2H, D_2O exchangeable, OH). ^{13}C NMR (125 MHz, DMSO-d_6): δ 165.6 (C═N), 135.9, 129.6, 127.8, and 127.4 (Ar C), 74.8 (triazolinyl C), 70.5, 69.6, 63.6, and 61.0 ppm (alditolyl C). Anal. Calcd for $C_{20}H_{34}N_8O_{10}$: C, 43.95; H, 6.22; N, 20.51. Found: 44.07; H, 6.51; N, 20.74.

*5.2.4.4. 1,4-Bis(D-arabinose monocarbohydrazonohydrazide)benzene (**33a**) and 1,4-Bis(4-amino-3-D-arabino-pentitol-1-yl-1,2,4-triazolin-5-yl)-benzene (**33b**).* According to the previous general method a white solid was obtained. Yield (85%); mp 176−178 °C; IR (KBr) ν_{max}: 3321 broad (NH_2+ (OH + NH), 1624 cm^{-1} (C═N). ^1H NMR (500 MHz, DMSO-d_6) δ 9.90 (s, 2H, exchangeable, triazolinyl NH), 7.90−7.50 (m, 6H, 4 Ar H and 2 azomethine CH═N), and 4.56−4.10 ppm (m, 10H, exchangeable, $2NH_2$ and 6 OH). The weak signals at 11.70 and 7.10 ppm refer to NH−NH_2 and triazolinyl H, respectively. The rest of the sugar chain protons and exchangeable signals of NH_2 and hydroxyl protons are located at the broad signal at δ 3.39 ppm. Anal. Calcd for $C_{18}H_{30}N_8O_8$: C, 44.44; H, 6.17; N, 23.04.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.1c06339.

IR and ^1H NMR spectra of all synthesized compounds and ^{13}C NMR and mass spectra of some selected compounds (PDF)

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Notes

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