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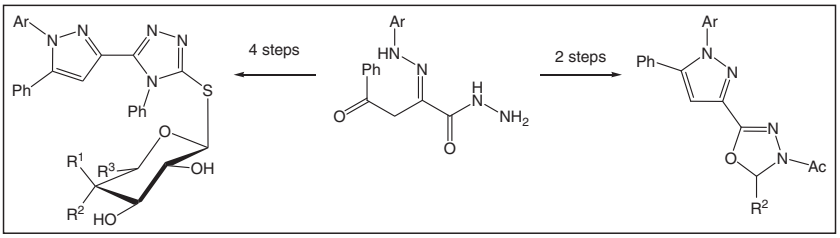

New substituted pyrazole, thiazole, and 1,2,4-triazole derivatives were synthesized. The sugar hydrazones, their acetylated derivatives as well as their derived acyclic *C*-nucleoside analogs, and the thioglycosides of the 1,2,4-traizole derivatives were also prepared. The antitumor activity of some of the synthesized compounds were studied, and a number of the tested compounds showed significant activities.

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INTRODUCTION

The chemistry of pyrazole-containing compounds is particularly interesting because of their potential application in medicinal chemistry as analgesic [2], anti-inflammatory [3], antitumor [4,5], antimicrobial [6], and therapeutic agents [7]. Because of many promising pharmacological, agrochemical, and analytical applications, a number of substituted pyrazoles are being used as inhibitors of heat-shock protein 90 and as therapeutics of cancer, and therefore, they have been the focus of many synthetic targets [8]. Pyrazole-based heterocyclic structures have also attracted synthetic interest for being essential moieties in many chemotherapeutic agents with potential antiparasitic [9], antimalarial [10], and antiviral activities [11]. As far as the anticancer activity is concerned, literature citation revealed that a wide range of pyrazole derivatives were reported to contribute to a variety of antineoplastic potentials against a wide range of cancer cell lines [12–14]. On the other hand, 1,2,4-triazole derivatives are known to exhibit antimicrobial [15], antitubercular [16], anticancer [17,18], anticonvulsant [19], anti-inflammatory, and analgesic [20] properties. The arrangement of three basic nitrogen atoms in triazole ring induces the antiviral activities in the compounds containing triazole ring [21]. 1,2,4-Triazole nucleus has been incorporated in a wide variety of therapeutically interesting drug candidates including H_1/H_2 histamine receptor blockers, cholinesterase active agents, anti-anxiety, and sedatives [22]. There are some known drugs containing 1,2,4-triazole moiety, for example, Triazolam [23], Alprazalam [24], Etizolam [25], Furacylin [26], Ribavirin [27], and Propiconazole [28]. The glycosylthio heterocycles [29–31] and the acyclic nucleoside analogs (with modification of both the glycon part and the heterocyclic base) have stimulated extensive research as biological inhibitors [32–34]. In view of the aforementioned facts and as continuation of interest in identification of new valuable candidates in synthesizing new potent and less toxic active agents [35–40], we here report the synthesis and anticancer activity of new substituted pyrazole derivatives linked to 1,3,4-oxadiazoline and 1,2,4-triazole rings. Furthermore, the derived acyclic *C*-nucleoside analogs and the 1,2,4-triazole thioglycoside derivatives were synthesized.

RESULTS AND DISCUSSION

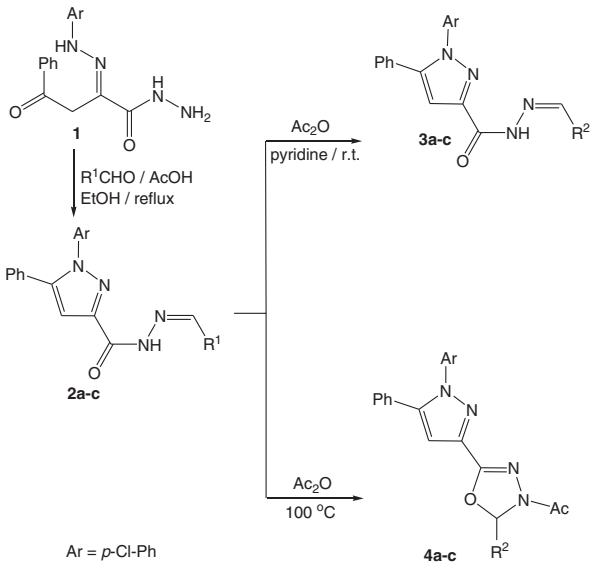
The starting acid hydrazide **1** [41] was allowed to react with a number of monosaccharides, namely, D-glucose, D-galactose, and D-mannose in presence of glacial acetic acid to afford the corresponding sugar hydrazones **2a–c**. The IR spectra of the latter products revealed characteristic absorption bands for the hydroxyl, NH, and C═N groups, and their ^{1}H NMR spectra confirmed the presence of sugar protons, NH, and aromatic proton signals. The H-1 methine proton signal appeared as doublet at δ 7.46–7.55 ppm.

The reaction of sugar aroylhydrazones with acetic anhydride is well known to give the respective per-*O*-acetyl derivatives. However, it has been found that different products can be obtained depending on the applied reaction conditions. Thus, acetylation of the sugar hydrazones **2a–c** with acetic anhydride in pyridine at room temperature afforded *O*-acetylated sugar derivatives **3a–c**. The structures

of compounds **3a–c** were established on the basis of their spectral and analytical data, which agreed with the assigned structures (experimental part).

It has been reported [42–45] that when the reaction was carried out at high temperature, acetic anhydride at high temperatures, cyclization usually takes place in addition to per-*O*-acetylation to afford acyclic *C*-nucleoside analogs. We reported previously [42,45] the synthesis of 1,2,4-triazolo[1,3,4]oxadiazole and *N*-acetyl-1,3,4-oxadiazoline acyclic nucleoside analogs by the reaction of hydrazinyl sugars with boiling acetic anhydride. Thus, when the hydrazones **2a–c** were heated in acetic anhydride at 100 °C, they gave the 1,3,4-oxadiazoline acyclic nucleoside analogs **4a–c**, respectively. Their IR spectra showed absorption bands in the carbonyl frequency region at 1660–1665 cm^{-1} and 1748–1752 cm^{-1} corresponding to the carbonyl amide and the carbonyl ester groups, respectively, indicating the presence of *N*-acetyl group in addition to the *O*-acetyl groups. The ^1H NMR spectra showed signals corresponding to the *O*-acetyl-methyl protons in addition to the *N*-acetyl-methyl protons each as singlet and signals corresponding to the rest of the alditolyl chain protons. The ^{13}C NMR spectra of **2a–c** showed the resonances of the acetyl-methyl carbons at δ 20.80–24.08 ppm. The value of the chemical shift of the *C*-N-Ac (C-1 in the original sugar chain moiety and C-2 in the oxadiazoline ring) appeared at δ 89.79–90.18 ppm, which indicated its *N,N*-acetal nature rather than being a C═N. The signals at δ 169.05–172.10 ppm correspond to the carbonyl groups (Scheme 1).

Scheme 1



2	R^1
a	D-glucopentitolyl
b	D-galactopentitolyl
c	D-mannopentitolyl

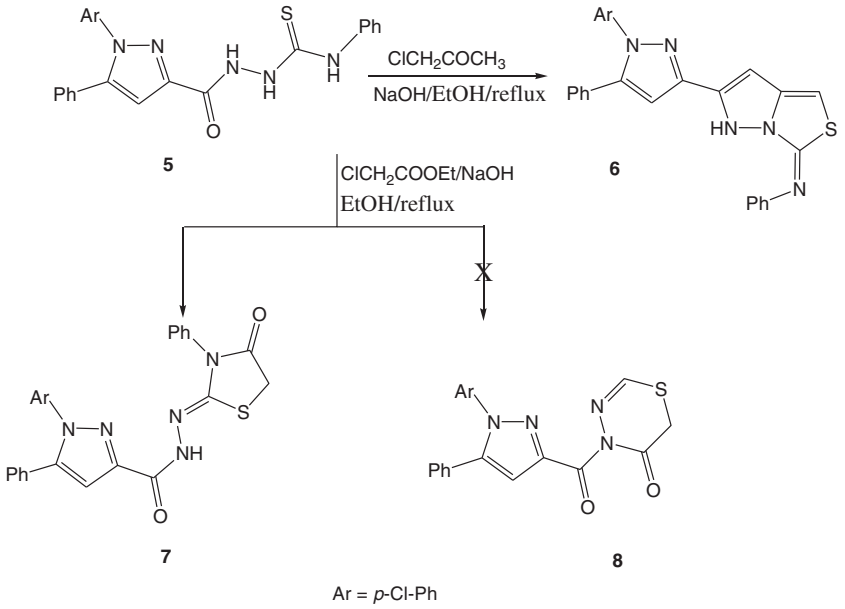
3,4	R^2
a	Penta-*O*-acetyl-D-glucopentitolyl
b	Penta-*O*-acetyl-D-galactopentitolyl
c	Penta-*O*-acetyl-D-mannopentitolyl

The thiosemicarbazide **5** [41], produced by reaction of hydrazide **1** with phenyl isothiocyanate, underwent cyclization with chloroacetone to give the corresponding pyrazolothiazolidine derivative **6**. Inspection of the IR and ^{13}C NMR spectra of the latter product **6** revealed the absence of C═O and C═S signals, and ^1H NMR spectrum showed signals at δ 5.40 and 6.98 for H-3 and H-4, respectively. In addition, the MS spectrum gave the molecular ion peak at *m/z* 468 corresponding to the assigned formula. Reaction of the thiosemicarbazide **5** with ethyl chloroacetate in the presence of alcoholic sodium hydroxide afforded thiazolidine derivative **7**, not compound **8**, as indicated by its spectral and analytical data. Its ^1H NMR spectrum showed signals corresponding to CH_2, pyrazole H-4, and NH groups. The ^1H NMR spectrum showed also signals corresponding to three phenyl groups, which were confirmed by the mass spectrum agreeing with the assigned structure (Scheme 2).

The 1,2,4-triazole **9** [41], obtained by cyclization of the thiosemicaribazide **5** by using sodium hydroxide solution, was alkylated with methyl iodide to give the corresponding *S*-methyl derivative **10**. The ^1H NMR spectrum showed methyl group signal at δ 2.44 ppm. Compound **9** was reacted with α-halogenated sugars **11a–c** for the synthesis of functionalized 1,2,4-triazole-β-D-glycosides **12a–c**, respectively. The structures assigned for compounds **12a–c** were based on spectroscopic and analytical data. The IR spectra of the thioglycosides **12a–c** showed characteristic absorption bands in the carbonyl frequency region at 1746–1750 cm^{-1} corresponding to the acetyl-carbonyl groups. The ^1H NMR spectra showed signals corresponding to the acetyl-methyl signals and the sugar protons in addition to the aromatic protons. The anomeric proton signal appeared at δ 5.78–5.80 ppm with a coupling constant 9.8–10.2 Hz indicating the β-orientation of the thioglycosidic bond. It was reported [46–48] that the anomeric proton in β-*N*-glycosides having an adjacent C═S appears at higher chemical shift because of the anisotropic deshielding effect of the C═S. The ^{13}C NMR spectrum of **12a** and **12c** showed signals at δ 91.71 and 91.05 ppm, respectively, corresponding to the anomeric C-1, which also confirmed the β-configuration. The absence of a peak corresponding to the C═S group indicates that the attachment of the sugar has taken place at the sulfur atom and not on the nitrogen atom. Also, as indicated earlier, methylation of compound **9** with methyl iodide was conducted to give 3-methylthio derivative **10**, which confirms the assigned structure of compounds **12a–c**.

Treatment of the acetylated thioglycoside **12a–c** with methanolic ammonia gave the deacetylated thioglycoside derivatives **13a–c**, respectively. Their IR spectra showed absorption band corresponding to the hydroxyl groups in addition to the absence of the carbonyl absorption bands. The ^1H NMR spectra showed the disappearance of the

Scheme 2



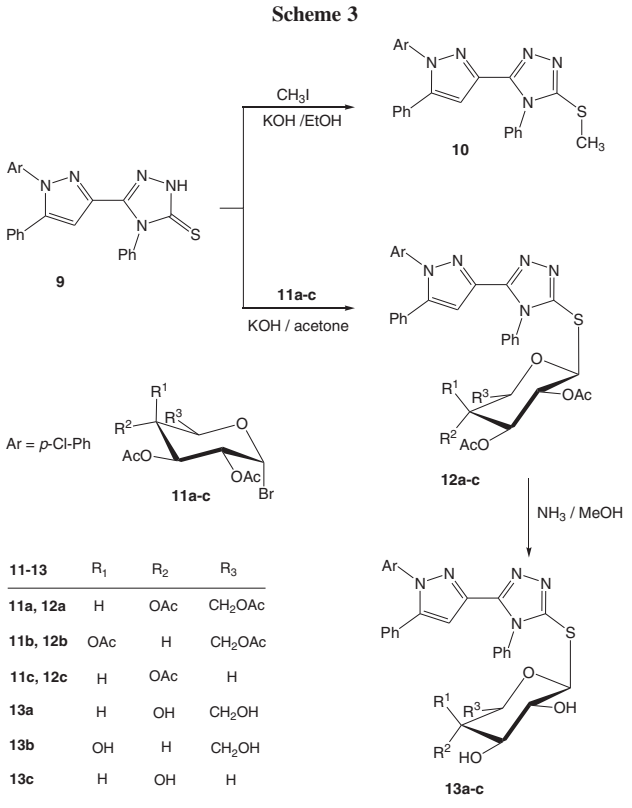
acetyl-methyl signals and the presence of hydroxyl signals (Scheme 3).

Antitumor activity. In the present work, nine of the newly synthesized compounds **2a–c**, **3a**,**b**, **6**, **7**, **12a**, and **13a** were selected to evaluate their *in vitro* growth inhibitory activities against two human cultured cell lines, which are breast carcinoma cell line (MCF7) and cervix carcinoma cell line (HELA), in comparison with the known anticancer drug, cisplatin, as a reference drug.

The results presented in Table 1 revealed that compounds **2a–c**, **6**, and **7** showed potential antitumor activities against both types of carcinoma cell lines in comparison with cisplatin IC50 values, which are 3.6 and 2.8 μg/mL, against MCF7 and HELA, respectively. The thioglycoside derivatives **12a** and **13a** revealed lower inhibition activities.

The anticancer activity results and structure activity relationship indicated that the sugar hydrazones with acyclic sugar moieties attached to the pyrazole ring system revealed higher activities than the cyclic thioglycosides attached to triazole ring. Additionally, the free hydroxyl sugar hydrazones were highly active than the corresponding acetylated derivatives indicating the importance of the deprotected hydroxyl groups. The slight differences in activities between the hydrazones **2a–c** reflect the influence of the configuration of the hydroxyl groups in the acyclic sugar moiety. Furthermore, the pyrazolothiazole **6** with pyrazole ring condensed to thiazole moiety and incorporating free NH group revealed higher activity than the thiazolidinone derivative **7**. Fortunately, the best results obtained for the sugar hydrazones with acyclic D-glucopentitoly (**2a**) and D-galactopentitolyl (**2b**) moieties showed good antitumor activity against cervix carcinoma cell line (HELA) (IC50: 2.52–2.55 μg/mL) than that obtained for cisplatin (IC50: 2.80 μg/mL).

Scheme 3



11-13	R_1	R_2	R_3
11a, 12a	H	OAc	CH_2OAc
11b, 12b	OAc	H	CH_2OAc
11c, 12c	H	OAc	H
13a	H	OH	CH_2OH
13b	OH	H	CH_2OH
13c	H	OH	H

Table 1

Effect of some selected derivatives on MCF7 and HELA tumor cell lines.

	IC50 (μg/mL)	
Compound	MCF7	HELA
Cisplatin	3.60	2.80
2a	3.60	2.52
2b	3.65	2.55
2c	3.73	3.02
3a	12.40	10.70
3b	13.00	10.90
6	3.75	2.92
7	4.48	4.12
12a	14.90	12.5
13a	8.50	7.30

The new compounds tested for anticancer activity in Cairo University, National Cancer Institute, Cancer Biology Department, Cairo, Egypt.

EXPERIMENTAL

Melting points were measured using Electrothermal IA 9100 apparatus (Shimadzu, Tokyo, Japan). IR spectra were recorded as potassium bromide pellets on a Perkin-Elmer 1650 spectrophotometer (Perkin-Elmer, Norwalk, CT, USA). ^{1}H NMR was determined on a varian Gemini 300 NMR spectrometer at 300 MHz for ^{1}H and 75 MHz for ^{13}C or on a brucker Ac-250 FT spectrometer at 250 MHz for ^{1}H and at 62.9 MHz for ^{13}C with TMS as a standard. Mass spectra were recorded on VG 2AM-3F mass spectrometer (Thermo electron corporation, USA) Microanalyses were operated using Mario El Mentar apparatus, Organic Microanalysis Unit, and the results were within the accepted range (±0.40) of the calculated values. Follow-up of the reactions and checking the purity of the compounds were made by TLC on silica gel-precoated aluminum sheets (Type 60 F254, Merck, Darmstadt, Germany).

General procedure for the synthesis of the sugar hydrazone derivatives 2a–c. ***General procedure.*** A mixture of compound **1** (0.005 mol), the respective monosaccharide (0.005 mol), ethanol (25 mL), and catalytic amount of glacial acetic acid (0.3 mL) was heated at reflux temperature for 3 h. The precipitate formed on cooling was filtered off, dried, and crystallized from ethanol to give compound **2a–c**.

1-(4-Chlorophenyl)-N'-(D-glucopentitolylidene)-5-phenyl-1H-pyrazole-3-carbohydrazide (2a). Pale yellow solid, 1.82 g (77%); mp 172–173 °C; IR (KBr, υ, cm^{-1}): 3210–3380 (OH and NH), 1680 (C=O), 1608 (C=N); ^{1}H NMR (DMSO-d_6, 300 MHz): δ 3.10–3.21 (m, 2H, H-6,6′), 3.35 (m, 1H, H-5), 3.79–3.86 (m, 2H, H-4, H-3), 4.30 (dd, 1H, J = 6.4 Hz, J = 8.2 Hz, H-2), 4.42 (m, 1H, OH, D_2O exchangeable), 5.10–5.18 (m, 2H, 2OH, D_2O exchangeable), 5.60–5.75 (m, 2H, 2OH, D_2O exchangeable), 7.00 (s, 1H, pyrazole H-4), 7.12 (d, 2H, J = 7.8 Hz, Ar-H), 7.17–7.21 (m, 3H, Ar-H), 7.30 (m, 2H, Ar-H), 7.46 (d, 1H, J = 8.2 Hz, H-1), 7.52 (d, 2H, J = 7.8 Hz, Ar-H), 9.70 (s, 1H, NH, D_2O exchangeable); ^{13}C NMR (DMSO-d_6, 75 MHz): δ 61.61 (C-6), 63.05 (C-5), 69.21 (C-4), 74.44 (C-3), 75.71 (C-2), 114.26-158.8 (15 Ar-C and C-1), 171.02 (C=O). *Anal*. calcd. for $C_{22}H_{23}ClN_4O_6$ (474.89): C, 55.64; H, 4.88; N, 11.80. Found: C, 55.49; H, 4.69; N, 11.71.

1-(4-Chlorophenyl)-N'-(D-galactopentitolylidene)-5-phenyl-1H-pyrazole-3-carbohydrazide (2b). Pale yellow solid, 1.78 g (75%); mp 175–176 °C; IR (KBr, υ, cm^{-1}): 3230–3400 (OH and NH), 1681 (C=O), 1606 (C=N); ^{1}H NMR (DMSO-d_6, 300 MHz): δ 3.09–3.21 (m, 2H, H-6,6′), 3.36 (m, 1H, H-5), 3.77–3.91 (m, 2H, H-4, H-3), 4.32 (m, 1H, H-2), 4.44 (m, 1H, OH, D_2O exchangeable), 5.13–5.18 (m, 2H, 2OH, D_2O exchangeable), 5.59–5.78 (m, 2H, 2OH, D_2O exchangeable), 7.10 (s, 1H, pyrazole H-4), 7.12 (d, 2H, J = 7.8 Hz, Ar-H), 7.16–7.22 (m, 3H, Ar-H), 7.32 (m, 2H, Ar-H), 7.48 (d, 2H, J = 7.8 Hz, Ar-H), 7.52 (d, 1H, J = 8.0 Hz, H-1), 9.77 (s, 1 H, NH, D_2O exchangeable); ^{13}C NMR (DMSO-d_6, 75 MHz): δ 61.74 (C-6), 63.09 (C-5), 69.22 (C-4), 74.47 (C-3), 76.31 (C-2), 112.28–159.02 (15 Ar-C and C-1), 171.10 (C=O). *Anal*. calcd. for $C_{22}H_{23}ClN_4O_6$ (474.89): C, 55.64; H, 4.88; N, 11.80. Found: C, 55.52; H, 4.73; N, 11.66.

1-(4-Chlorophenyl)-N'-(D-mannopentitolylidene)-5-phenyl-1H-pyrazole-3-carbohydrazide (2c). Yellow solid, 1.82 g (77%); mp 182–183 °C; IR (KBr, υ, cm^{-1}): 3200–3390 (OH and NH), 1669 (C=O), 1606 (C=N); ^{1}H NMR (DMSO-d_6, 300 MHz): δ 3.10–3.21 (m, 2H, H-6,6′), 3.35 (m, 1H, H-5), 3.77–3.91 (m, 2H, H-4, H-3), 4.36 (m, 1H, H-2), 4.43 (m, 1H, OH, D_2O exchangeable), 5.14–5.18 (m, 2H, 2OH, D_2O exchangeable), 5.56–5.74 (m, 2H, 2OH, D_2O exchangeable), 7.08 (s, 1H, pyrazole H-4), 7.12 (d, 2H, J = 8.4 Hz, Ar-H), 7.15–7.21 (m, 3H, Ar-H), 7.34 (m, 2H, Ar-H), 7.49 (d, 2H, J = 8.4 Hz, Ar-H), 7.55 (d, 1H, J = 8.2 Hz, H-1), 9.90 (s, 1 H, NH, D_2O exchangeable); ^{13}C NMR (DMSO-d_6, 75 MHz): δ 63.15 (C-6), 63.09 (C-5), 69.22 (C-4), 74.47 (C-3), 76.31 (C-2), 119.68–158.73 (15 Ar-C and C-1), 172.19 (C=O). *Anal*. calcd. for $C_{22}H_{23}ClN_4O_6$ (474.89): C, 55.64; H, 4.88; N, 11.80. Found: C, 55.50; H, 4.72; N, 11.71.

General procedure for the synthesis of the per-*O*-acetylsugar hydrazone derivatives 3a–c. ***General procedure.*** A mixture of compounds **2a–c** (0.002 mol) was stirred in a mixture of dry pyridine (15 mL)/acetic anhydride (5 mL) at room temperature for 3–4 h. The reaction mixture was left overnight with occasional shaking. It was poured onto crushed ice, and the separated product was filtered off, washed with potassium hydrogen carbonate and water, dried, and then crystallized from ethanol.

1-(4-Chlorophenyl)-N'-(penta-O-acetyl-D-glucopentitolylidene)-5-phenyl-1H-pyrazole-3-carbohydrazide (3a). White solid, 1.04 g (76%); mp 117–118 °C; IR (KBr, υ, cm^{-1}): 3650 (NH), 1750 (C=O), 1670 (C=O), 1610 (C=N). ^{1}H NMR (DMSO-d_6, 300 MHz): δ 1.90, 1.95, 1.99, 2.03, 2.06 (5s, 15H, 5CH_3CO), 3.88 (dd, 1H, J = 11.8 Hz, J = 2.8 Hz, H-6), 4.10 (m, 1H, H-6′), 4.26 (m, 1H, H-5), 4.35 (dd, 1H, J = 7.2 Hz, J = 7.8 Hz, H-4), 4.90 (dd, 1H, J = 7.2 Hz, J = 7.8 Hz, H-3), 5.39 (t, 1H, J = 7.8 Hz, H-2), 6.98 (s, 1H, pyrazole H-4), 7.20 (d, 2H, J = 7.8 Hz, Ar-H), 7.17–7.21 (m, 3H, Ar-H), 7.30 (m, 2H, Ar-H), 7.52 (d, 1H, J = 7.8 Hz, H-1), 7.90 (d, 2H, J = 7.8 Hz, Ar-H), 9.81 (s, 1H, NH, D_2O exchangeable); ^{13}C NMR (DMSO-d_6, 75 MHz): δ 20.45, 20.55, 20.59, 20.92, 21.08 (5 CH_3), 61.20 (C-6), 65.38 (C-5), 68.41 (C-4), 69.7 (C-3), 70.95 (C-2), 108–142.85 (15 Ar-C and C-1), 169.50, 169.64, 170.15, 170.86, 172.15, 172.25 (6 C=O). *Anal*. calcd. for $C_{32}H_{33}ClN_4O_{11}$ (685.08): C, 56.10; H, 4.86; N, 8.18. Found: C, 56.02; H, 4.74; N, 8.05.

1-(4-Chlorophenyl)-N'-(penta-O-acetyl-D-galactopentitolylidene)-5-phenyl-1H-pyrazole-3-carbohydrazide (3b). White solid, 1.07 g (78%); mp 114–115 °C; IR (KBr, υ, cm^{-1}): 3650 (NH), 1750 (C=O), 1676 (C=O). ^{1}H NMR (DMSO-d_6, 300 MHz): δ 1.91, 1.95, 1.98, 2.03, 2.07 (5s, 15H, 5CH_3CO), 3.89 (dd, 1H, J = 11.8 Hz, J = 2.8 Hz, H-6), 4.12 (m, 1H, H-6′), 4.26 (m, 1H, H-5), 4.36 (t, 1H, J = 7.2 Hz, H-4), 4.95 (dd, 1H, J = 7.2 Hz,

J = 7.8 Hz, H-3), 5.37 (t, 1H, J = 7.8 Hz, H-2), 6.97 (s, 1H, pyrazole H-4), 7.20 (d, 2H, J = 7.8 Hz, Ar-H), 7.27–7.31 (m, 3H, Ar-H), 7.38 (m, 2H, Ar-H), 7.49 (d, 1H, J = 7.8 Hz, H-1), 7.88 (d, 2H, J = 7.8 Hz, Ar-H), 9.80 (s, 1H, NH, D_2O exchangeable); ^{13}C NMR (DMSO-d_6, 75 MHz): δ 20.42, 20.55, 20.50, 20.79, 21.06 (5 CH_3), 61.20 (C-6), 65.38 (C-5), 68.41 (C-4), 69.7 (C-3), 70.95 (C-2), 127.09-145.85 (15 Ar-C and C-1), 169.36, 169.42, 170.11, 170.75, 171.11, 172.22 (6 C═O). *Anal*. calcd. for $C_{32}H_{33}ClN_4O_{11}$ (685.08): C, 56.10; H, 4.86; N, 8.18. Found: C, 55.94; H, 4.80; N, 8.09.

1-(4-Chlorophenyl)-N'-(penta-O-acetyl-D-mannopentitolylidene)-5-phenyl-1H-pyrazole-3-carbohydrazide (3c). White solid, 1.01 g (74%); mp 111–112 °C; IR (KBr, υ, cm^{-1}): 3628 (NH), 1742 (C═O), 1669 (C═O); ^{1}H NMR (DMSO-d_6, 300 MHz): δ 1.89, 1.94, 1.98, 2.04, 2.05 (5s, 15H, 5CH_3CO), 3.88 (dd, 1H, J = 11.8 Hz, J = 2.8 Hz, H-6), 4.09 (m, 1H, H-6′), 4.27 (m, 1H, H-5), 4.35 (dd, 1H, J = 7.2 Hz, J = 7.8 Hz, H-4), 4.92 (t, 1H, J = 7.8 Hz, H-3), 5.39 (dd, 1H, J = 7.8 Hz, J = 8.2 Hz, H-2), 6.91 (s, 1H, pyrazole H-4), 7.22 (d, 2H, J = 7.8 Hz, Ar-H), 7.27–7.32 (m, 3H, Ar-H), 7.37 (m, 2H, Ar-H), 7.50 (d, 1H, J = 8.2 Hz, H-1), 7.89 (d, 2H, J = 7.8 Hz, Ar-H), 10.14 (s, 1H, NH, D_2O exchangeable); ^{13}C NMR (DMSO-d_6, 75 MHz): δ 19.92, 20.50, 20.72, 20.93, 21.05 (5 CH_3), 61.24 (C-6), 66.30 (C-5), 69.21 (C-4), 69.79 (C-3), 71.98 (C-2), 128.09–154.80 (15 Ar-C and C-1), 169.60, 169.82, 170.15, 170.68, 171.08, 172.24 (6 C═O). *Anal*. calcd. for $C_{32}H_{33}ClN_4O_{11}$ (685.08): C, 56.10; H, 4.86; N, 8.18. Found: C, 56.05; H, 4.77; N, 8.07.

4-Acetyl-5-(*O*-acetyl alditolyl)-2-[1-(4-chlorophenyl)-5- phenyl-1*H*-pyrazole-3-yl)-2,3-dihydro-1,3,4-oxadiazoline (4a–c). ***General procedure.*** A solution of compounds **2a–c** (0.003 mol) in acetic anhydride (10 mL) was stirred in a water bath for 2–3 h at 100 °C. The resulting solution was poured onto crushed ice, and the product that separated out was filtered off, washed with sodium hydrogen carbonate followed by water, dried, and then crystallized from ethanol.

4-Acetyl-2-[1-(4-chlorophenyl)-5-phenyl-1H-pyrazole-3-yl)]-5-(1,2,3,4,5-penta-O-acetyl-D-glucopentitolyl)-2,3-dihydro-1,3,4-oxadiazoline (4a). Pale yellow solid, 1.28 g (59%); mp 101–102 °C; IR (KBr, υ, cm^{-1}): 1752 (C═O), 1665 (C═O), 1612 (C═N); ^{1}H NMR (DMSO-d_6, 300 MHz): δ 1.81, 1.90, 1.97, 2.01, 2.04, 2.21 (6s, 18H, 6CH_3CO), 3.98 (dd, 1H, J = 11.8 Hz, J = 2.8 Hz, H-5), 4.10 (m, 1H, H-5′), 4.30 (t, 1H, J = 7.2 Hz, H-4), 4.92 (dd, 1H, J = 7.2 Hz, J = 7.6 Hz, H-3), 5.30 (t, 1H, J = 7.6 Hz, H-2), 5.42 (dd, 1H, J = 7.6 Hz, J = 8.4 Hz, H-1), 5.77 (d, 1H, J = 8.4 Hz, oxadiazoline H-2), 7.02 (s, 1H, pyrazole H-4), 7.20 (d, 2H, J = 7.8 Hz, Ar-H), 7.25–7.52 (m, 3H, Ar-H), 7.61 (m, 2H, Ar-H), 7.90 (d, 2H, J = 7.8 Hz, Ar-H); ^{13}C NMR (DMSO-d_6, 75 MHz): δ 20.85, 20.75, 20.89, 20.92, 21.04, 23.05 (6 CH_3), 61.20 (C-5), 65.38 (C-4), 68.41 (C-3), 69.7 (C-2), 70.95 (C-1), 90.18 (oxadiazoline C-2), 120.09–153.72 (15 Ar-C), 161.10 (oxadiazoline C-5), 169.18, 169.62, 170.15, 170.85, 171.02, 172.10 (6 C═O). *Anal*. calcd. for $C_{34}H_{35}ClN_4O_{12}$ (727.11): C, 56.16; H, 4.85; N, 7.71. Found: C, 56.04; H, 4.79; N, 7.61.

4-Acetyl-2-[1-(4-chlorophenyl)-5-phenyl-1H-pyrazole-3-yl)]-5-(1,2,3,4,5-penta-O-acetyl-D-galactopentitolyl)-2,3-dihydro-1,3,4-oxadiazoline (4b). Yellow solid, 1.33 g (61%); mp 90–91 °C; IR (KBr, υ, cm^{-1}): 1748 (C═O), 1660 (C═O), 1611 (C═N); ^{1}H NMR (DMSO-d_6, 300 MHz): δ 1.79, 1.89, 1.96, 2.00, 2.05, 2.29 (6s, 18H, 6CH_3CO), 4.10 (dd, 1H, J = 11.8 Hz, J = 2.8 Hz, H-5), 4.19 (m, 1H, H-5′), 4.33 (t, 1H, J = 7.2 Hz, H-4), 4.95 (dd, 1H, J = 7.2 Hz, J = 7.8 Hz, H-3), 5.32 (t, 1H, J = 7.6 Hz, H-2), 5.45 (dd, 1H, J = 7.6 Hz, J = 8.2 Hz, H-1), 5.79 (d, 1H, J = 8.2 Hz, oxadiazoline H-2), 7.00 (s, 1H, pyrazole H-4), 7.24 (d, 2H, J = 7.8 Hz, Ar-H), 7.28–7.52 (m, 3H, Ar-H), 7.62 (m, 2H, Ar-H), 7.92 (d, 2H, J = 7.8 Hz, Ar-H); ^{13}C NMR (DMSO-d_6, 75 MHz): δ 20.80, 21.75, 20.89, 20.92, 21.38, 24.08 (6 CH_3), 61.80 (C-5), 65.39 (C-4), 68.49 (C-3), 69.72 (C-2), 72.93 (C-1), 89.79 (oxadiazoline C-2), 121.00–154.69 (15 Ar-C), 161.70 (oxadiazoline C-5), 169.05, 169.00, 169.65, 170.15, 170.84, 172.01 (6 C═O). *Anal*. calcd. for $C_{34}H_{35}ClN_4O_{12}$ (727.11): C, 56.16; H, 4.85; N, 7.71. Found: C, 56.10; H, 4.78; N, 7.59.

4-Acetyl-2-[1-(4-chlorophenyl)-5-phenyl-1H-pyrazole-3-yl)]-5-(1,2,3,4,5-penta-O-acetyl-D-mannopentitolyl)-2,3-dihydro-1,3,4-oxadiazoline (4c). Pale yellow solid, 1.37 g (63%); mp 95–96 °C; IR (KBr, υ, cm^{-1}): 1750 (C═O), 1662 (C═O), 1614 (C═N); ^{1}H NMR (DMSO-d_6, 300 MHz): δ 1.84, 1.90, 1.96, 1.99, 2.05, 2.27 (6s, 18H, 6CH_3CO), 4.05 (dd, 1H, J = 11.8 Hz, J = 2.8 Hz, H-5), 4.15 (m, 1H, H-5′), 4.32 (dd, 1H, J = 7.0 Hz, J = 7.6 Hz, H-4), 4.91 (t, 1H, J = 7.0 Hz, H-3), 5.33 (dd, 1H, J = 7.2 Hz, J = 7.8 Hz, H-2), 5.46 (dd, 1H, J = 7.8 Hz, J = 8.4 Hz, H-1), 5.82 (d, 1H, J = 8.4 Hz, oxadiazoline H-2), 7.05 (s, 1H, pyrazole H-4), 7.24 (d, 2H, J = 7.8 Hz, Ar-H), 7.26–7.53 (m, 3H, Ar-H), 7.70 (m, 2H, Ar-H), 7.94 (d, 2H, J = 7.8 Hz, Ar-H); ^{13}C NMR (DMSO-d_6, 75 MHz): δ 20.83, 20.94, 20.89, 20.97, 21.38, 24.02 (6 CH_3), 61.82 (C-5), 65.52 (C-4), 68.49 (C-3), 69.75 (C-2), 72.95 (C-1), 89.92 (oxadiazoline C-2), 120.80–154.70 (15 Ar-C), 161.80 (oxadiazoline C-5), 169.70, 169.18, 169.65, 170.14, 170.88, 172.02 (6 C═O). *Anal*. calcd. for $C_{34}H_{35}ClN_4O_{12}$ (727.11): C, 56.16; H, 4.85; N, 7.71. Found: C, 55.93; H, 4.69; N, 7.58.

General procedure for the synthesis of compounds 6 and **7**. A mixture of thiosemicarbazide **5** (0.01 mol), ethylchloroacetate or chloroacetone (0.012 mol), and sodium hydroxide (0.02 mol) in ethanol (30 mL) was refluxed for 2–4 h. The solvent was concentrated under reduced pressure, and the reaction mixture was poured onto ice-cold water. The obtained precipitate was filtered off, washed with water, dried, and crystallized from ethanol.

N-{2-[1-(4-Chlorophenyl)-5-phenyl-1H-pyrazole-3-yl]pyrazolo[1,5-c]thiazole-6(1H)-ylidene}benzenamine (6). Yellow solid, 3.55 g (76%); mp 170–171 °C; IR spectrum (KBr, ν, cm^{-1}): 3280 (NH), 1608 (C═N); ^{1}H NMR (DMSO-d_6, 300 MHz): δ 5.40 (s, 1H, H-3), 6.94 (s, 1H, pyrazole H), 6.98 (s, 1H, H-4), 6.98 (m, 2H, Ar-H), 7.14 (m, 2H, Ar-H), 7.26 (d, 2H, J = 7.8 Hz, Ar-H), 7.31–7.59 (m, 4H, Ar-H), 7.71 (m, 2H, Ar-H), 7.92 (d, 2H, J = 7.8 Hz, Ar-H), 9.55 (s, 1H, NH, D_2O exchangeable); ^{13}C NMR (DMSO-d_6, 75 MHz): δ 95.05 (C-3), 102.6 (pyrazole C-4), 105.16 (C-4), 119.18–158.29 (18 Ar-C, C-2, pyrazole C-3,5, C-3a, and C-6); MS, *m/z* (%): 468 (M$^+$, 79). *Anal*. calcd. for $C_{26}H_{18}ClN_5S$ (467.97): C, 66.73; H, 3.88; N, 14.97. Found: C, 66.58; H, 3.71; N, 14.75.

1-(4-Chlorophenyl)-N-(4-oxo-3-phenylthiazolidine-2-ylidene)-5-phenyl-1H-pyrazole-3-carbohydrazide (7). Yellow solid, 3.95 g (81%); mp 178–179 °C; IR spectrum (KBr, ν, cm^{-1}): 3085 (NH), 1680 (C═O); ^{1}H NMR (DMSO-d_6, 300 MHz): δ 4.82 (s, 2H, CH_2), 6.70 (s, 1H, pyrazole H-4), 6.90 (m, 2H, Ar-H), 7.15 (m, 2H, Ar-H), 7.28 (d, 2H, J = 7.8 Hz, Ar-H), 7.33–7.60 (m, 4H, Ar-H), 7.75 (m, 2H, Ar-H), 7.95 (d, 2H, J = 7.8 Hz, Ar-H), 9.72 (s, 1H, NH, D_2O exchangeable); ^{13}C NMR (DMSO-d_6, 75 MHz): δ 48.2 (CH_2), 106.3 (pyrazole C-4), 122.18–159.94 (18 Ar-C, pyrazole C-3,5, and thiazole C-2,5), 170.39, 172.50 (2 C═O); MS, *m/z* (%): 488 (M$^+$, 90). *Anal*. calcd. for $C_{25}H_{18}ClN_5O_2S$ (487.96): C, 61.54; H, 3.72; N, 14.35. Found: C, 61.40; H, 3.61; N, 14.27.

3-[1-(4-Chlorophenyl)-5-phenyl-1*H*-pyrazole-3-yl]-5-(methylthio)-4-phenyl-4H-[1,2,4]triazole (10). To a warmed

ethanolic potassium hydroxide solution [prepared by dissolving KOH (0.01 mol) in ethanol (50 mL)], compound **9** (0.01 mol) was added. Heating was continued for 30 min at 60 °C, and the mixture was allowed to cool to room temperature. Methyl iodide (0.012 mol) was added, then the reaction mixture was stirred at 70 °C for 5 h, cooled to room temperature, and poured onto water. The resulting precipitate was filtered off andcrystallized from ethanol. White solid, 3.42 g (77%); mp 152–154 °C; IR spectrum (KBr, ν, cm^{-1}): 3088 (NH), 1614 (C═N); ^{1}H NMR (DMSO-d_6, 300 MHz): δ 2.41 (s, 3H, CH_3), 6.80 (s, 1H, pyrazole H-4), 6.94 (m, 2H, Ar-H), 7.13 (m, 2H, Ar-H), 7.24 (d, 2H, J = 7.8 Hz, Ar-H), 7.32–7.61 (m, 4H, Ar-H), 7.77 (m, 2H, Ar-H), 7.96 (d, 2H, J = 7.8 Hz, Ar-H); MS, m/z (%): 444 (M^+, 95). *Anal*. calcd. $C_{24}H_{18}ClN_5S$ (443.95): C, 64.93; H, 4.09; N, 15.78. Found: C, 64.76; H, 4.02; N, 15.65.

5-[1-(4-Chlorophenyl)-5-phenyl-1*H*-pyrazole-3-yl]]-4-phenyl-3-(*O*-acety-β-D-sugarpyranosyl)thio-[1,2,4]triazole (12a–c). ***General procedure.*** A solution of *O*-acetyl-α-D-glycopyranosyl bromide derivatives **11a–c** (0.003 mol) in acetone (30 mL) was added to a solution of compound **9** (0.003 mol) in aqueous potassium hydroxide [0.003 mol in distilled water (2 mL)]. The reaction mixture was stirred at room temperature for 4–5 h (followed by TLC). The solvent was evaporated, and the residue was washed with distilled water to remove potassium bromide, formed, and filtered. The product was dried and crystallized from ethanol.

5-[1-(4-Chlorophenyl)-5-phenyl-1H-pyrazole-3-yl]-4-phenyl-3-(O acety-β-D-glucopyranosyl)thio-[1,2,4]triazole (12a). Pale yellow solid, 1.64 g (72%); mp 120–121 °C; IR (KBr, υ, cm^{-1}): 1750 (C═O), 1615 (C═N); ^{1}H NMR (DMSO-d_6, 300 MHz): δ 1.92, 1.96, 1.99, 2.06 (4s, 12H, 4CH_3CO), 3.96 (m, 1H, H-6), 4.09 (dd, 1H, J = 8.6, J = 3.4 Hz, H-6′), 4.21 (m, 1H, H-5), 5.01 (dd, 1H, J = 7.2 Hz, J = 8.8 Hz, H-4), 5.32 (t, 1H, J = 7.2 Hz, H-3), 5.46 (dd, 1H, J = 7.4 Hz, J = 10.2 Hz, H-2), 5.79 (d, 1H, J = 10.2 Hz, H-1), 6.91 (s, 1H, pyrazole H-4), 6.97 (m, 2H, Ar-H), 7.15 (m, 2H, Ar-H), 7.25 (d, 2H, J = 7.8 Hz, Ar-H), 7.34–7.62 (m, 4H, Ar-H), 7.79 (m, 2H, Ar-H), 7.94 (d, 2H, J = 7.8 Hz, Ar-H); ^{13}C NMR (DMSO-d_6, 75 MHz): δ 18.92, 19.28, 20.08, 20.69 (4CH_3), 62.82 (C-6), 64.02 (C-4), 69.32 (C-3), 70.39 (C-2), 72.18 (C-5), 91.71 (C-1), 109.18 (pyrazole C-4), 121.51–158.50 (18 Ar-C, triazole C-3,5, pyrazole C-3,5), 169.29, 170.02, 170.84, 171.16 (4 C═O). *Anal*. calcd. for $C_{37}H_{34}ClN_5O_9S$ (760.21): C, 58.46; H, 4.51; N, 9.21. Found: C, 58.29; H, 4.31; N, 9.14.

5-[1-(4-Chlorophenyl)-5-phenyl-1H-pyrazole-3-yl]-4-phenyl-3-(O acety-β-D-galactopyranosyl)thio-[1,2,4]triazole (12b). Pale yellow solid, 1.68 g (74%); mp 112–113 °C; IR (KBr, υ, cm^{-1}): 1746 (C═O), 1612 (C═N); ^{1}H NMR (DMSO-d_6, 300 MHz): δ 1.96, 1.98, 2.02, 2.06 (4s, 12H, 4CH_3CO), 3.98 (m, 1H, H-6), 4.14 (dd, 1H, J = 8.6, J = 3.4 Hz, H-6′), 4.23 (m, 1H, H-5), 5.10 (dd, 1H, J = 7.2 Hz, J = 8.8 Hz, H-4), 5.29 (t, 1H, J = 7.2 Hz, H-3), 5.44 (dd, 1H, J = 7.2 Hz, J = 10.2 Hz, H-2), 5.80 (d, 1H, J = 10.2 Hz, H-1), 6.92 (s, 1H, pyrazole H-4), 6.99 (m, 2H, Ar-H), 7.18 (m, 2H, Ar-H), 7.27 (d, 2H, J = 7.8 Hz, Ar-H), 7.36–7.63 (m, 4H, Ar-H), 7.82 (m, 2H, Ar-H), 7.96 (d, 2H, J = 7.8 Hz, Ar-H). *Anal*. calcd. for $C_{37}H_{34}ClN_5O_9S$ (760.21): C, 58.46; H, 4.51; N, 9.21. Found: C, 58.28; H, 4.39; N, 9.14.

5-[1-(4-Chlorophenyl)-5-phenyl-1H-pyrazole-3-yl]-4-phenyl-3-(O acety-β-D-xylopyranosyl)thio-[1,2,4]triazole (12c). Yellow solid, 1.48 g (72%); mp 119–120 °C; IR (KBr, υ, cm^{-1}): 1748 (C═O), 1616 (C═N); ^{1}H NMR (DMSO-d_6, 300 MHz): δ 1.95, 2.02, 2.05 (3s, 9H, 3CH_3CO), 3.98 (m, 1H, H-5), 4.09 (dd, 1H, J = 8.6, J = 3.4 Hz, H-5′), 4.42 (m, 1H, H-4), 5.24 (t, 1H, J = 7.2 Hz, H-3), 5.42 (dd, 1H, J = 7.2 Hz, J = 9.8 Hz, H-2), 5.78 (d, 1H, J = 9.8 Hz, H-1), 6.91 (s, 1H, pyrazole H-4), 6.98 (m, 2H, Ar-H), 7.19 (m, 2H, Ar-H), 7.26 (d, 2H, J = 7.8 Hz, Ar-H), 7.37–7.62 (m, 4H, Ar-H), 7.82 (m, 2H, Ar-H), 7.94 (d, 2H, J = 7.8 Hz, Ar-H); ^{13}C NMR (DMSO-d_6, 75 MHz): δ 19.20, 20.14, 20.72 (3CH_3), 62.89 (C-5), 64.19 (C-4), 69.30 (C-3), 72.14 (C-2), 91.05 (C-1), 109.18 (pyrazole C-4), 121.51–158.50 (18 Ar-C, triazole C-3,5, pyrazole C-3,5), 169.29, 170.02, 171.16 (3 C═O). *Anal*. calcd. for $C_{34}H_{30}ClN_5O_7S$ (688.15): C, 59.34; H, 4.39; N, 10.18. Found: C, 59.18; H, 4.24; N, 10.02.

5-[1-(4-Chlorophenyl)-5-phenyl-1*H*-pyrazole-3-yl]-4-phenyl-3-(β-D-sugarpyranosyl)thio-[1,2,4]triazole (13a–c) ***General procedure.*** Gaseous ammonia was passed through a solution of compounds **12a–c** (0.003 mol) in dry methanol (10 mL) for about 1 h with cooling and stirring, and then the reaction mixture was stirred at room temperature for about 5 h. The solvent was evaporated under reduced pressure at 40 °C to give a solid residue, which was crystallized from ethanol.

5-[1-(4-Chlorophenyl)-5-phenyl-1H-pyrazole-3-yl]-4-phenyl-3-(β-D-glucopyranosyl)thio-[1,2,4]triazole (13a). Yellow solid, 1.26 g (71%); mp 200–201 °C; IR (KBr, υ, cm^{-1}): 3340–3500 (OH), 1618 (C═N); ^{1}H NMR (DMSO-d_6, 300 MHz): δ 3.72 (m, 2H, H-6,6′), 3.81 (m, 1H, H-5), 4.20–4.25 (m, 2H, H-3, H-4), 4.35 (dd, 1H, J = 7.8 Hz, J = 10.2 Hz, H-2), 5.48 (m, 1H, OH), 5.24 (t, 1H, J = 4.8 Hz, OH), 5.45 (m, 1H, OH), 5.52 (m, 1H, OH), 5.86 (d, 1H, J = 10.2 Hz, H-1), 7.01 (s, 1H, pyrazole H-4), 6.96 (m, 2H, Ar-H), 7.21 (m, 2H, Ar-H), 7.27 (d, 2H, J = 7.8 Hz, Ar-H), 7.42–7.65 (m, 4H, Ar-H), 7.85 (m, 2H, Ar-H), 7.98 (d, 2H, J = 7.8 Hz, Ar-H). *Anal*. calcd. for $C_{29}H_{26}ClN_5O_5S$ (592.07): C, 58.83; H, 4.43; N, 11.83. Found: C, 58.70; H, 4.38; N, 11.68.

5-[1-(4-Chlorophenyl)-5-phenyl-1H-pyrazole-3-yl]-4-phenyl-3-(β-D-galactopyranosyl)thio-[1,2,4]triazole (13b). Yellow solid, 1.31 g (74%); mp 180–181 °C; IR (KBr, υ, cm^{-1}): 3343–3497 (OH), 1616 (C═N); ^{1}H NMR (DMSO-d_6, 300 MHz): δ 3.70 (m, 2H, H-6,6′), 3.83 (m, 1H, H-5), 4.22–4.29 (m, 2H, H-3, H-4), 4.37 (dd, 1H, J = 7.8 Hz, J = 10.2 Hz, H-2), 5.45 (m, 1H, OH), 5.20 (t, 1H, J = 4.8 Hz, OH), 5.47 (m, 1H, OH), 5.54 (m, 1H, OH), 5.85 (d, 1H, J = 10.2 Hz, H-1), 6.90 (s, 1H, pyrazole H-4), 6.98 (m, 2H, Ar-H), 7.20 (m, 2H, Ar-H), 7.25 (d, 2H, J = 7.8 Hz, Ar-H), 7.40–7.65 (m, 4H, Ar-H), 7.83 (m, 2H, Ar-H), 7.98 (d, 2H, J = 7.8 Hz, Ar-H). *Anal*. calcd. for $C_{29}H_{26}ClN_5O_5S$ (592.07): C, 58.83; H, 4.43; N, 11.83. Found: C, 58.60; H, 4.29; N, 11.66.

5-[1-(4-Chlorophenyl)-5-phenyl-1H-pyrazole-3-yl]-4-phenyl-3-(β-D-xylopyranosyl)thio-[1,2,4]triazole (13c). Yellow solid, 1.18 g (70%); mp 197–198 °C; IR (KBr, υ, cm^{-1}): 3310–3444 (OH), 1614 (C═N); ^{1}H NMR (DMSO-d_6, 300 MHz): δ 3.68 (m, 2H, H-5,5′), 3.81 (m, 1H, H-4), 4.22 (m, 2H, H-3), 4.35 (dd, 1H, J = 7.8 Hz, J = 10.2 Hz, H-2), 5.41 (m, 1H, OH), 5.25 (t, 1H, J = 4.8 Hz, OH), 5.48 (m, 1H, OH), 5.81 (d, 1H, J = 10.2 Hz, H-1), 6.90 (s, 1H, pyrazole H-4), 7.11 (m, 2H, Ar-H), 7.22 (m, 2H, Ar-H), 7.25 (d, 2H, J = 7.8 Hz, Ar-H), 7.38–7.65 (m, 4H, Ar-H), 7.86 (m, 2H, Ar-H), 7.99 (d, 2H, J = 7.8 Hz, Ar-H). *Anal*. calcd. for $C_{28}H_{24}ClN_5O_4S$ (562.04): C, 59.84; H, 4.30; N, 12.46. Found: C, 59.67; H, 4.25; N, 12.31.

Anticancer screening. Preliminary experiments were performed using the human breast carcinoma cell tumor line and cervix carcinoma cell line to identify the potential toxicity of nine

selected newly synthesized compounds **2a–c**, **3a**,**b**, **6**, **7**, **12a**, and **13a** in comparison with the known anticancer drug Cisplatin using the method of Skehan *et al*. [49] as follows. Cells were plated in 96-multiwell plates (10^4 cells/well) for 24 h before treatment with the compounds to allow attachment of cell to the wall of the plate. Different concentrations of the compounds under test (0.0, 5, 12.5, 25, and 50 μg/mL) were added to the cell monolayer triplicate wells and prepared for each individual dose. Monolayer cells were incubated with the compounds for 48 h at 37 °C and in atmosphere of 5% CO_2. After 48 h, cells were fixed, washed, and stained with Sulfo-Rhodamine-B stain. Excess stain was washed with acetic acid, and attached stain was recovered with tris EDTA buffer. Color intensity was measured in an ELISA reader at 570 nm. The relation between surviving fraction and drug concentrations is plotted to obtain the survival curve of each tumor cell line after the specified compound

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