Synthesis and Antimicrobial Activity of Substituted [(Pyrazol-4-yl)methylene]hydrazono-2,3-dihydrothiazoles and Their Sugar Derivatives

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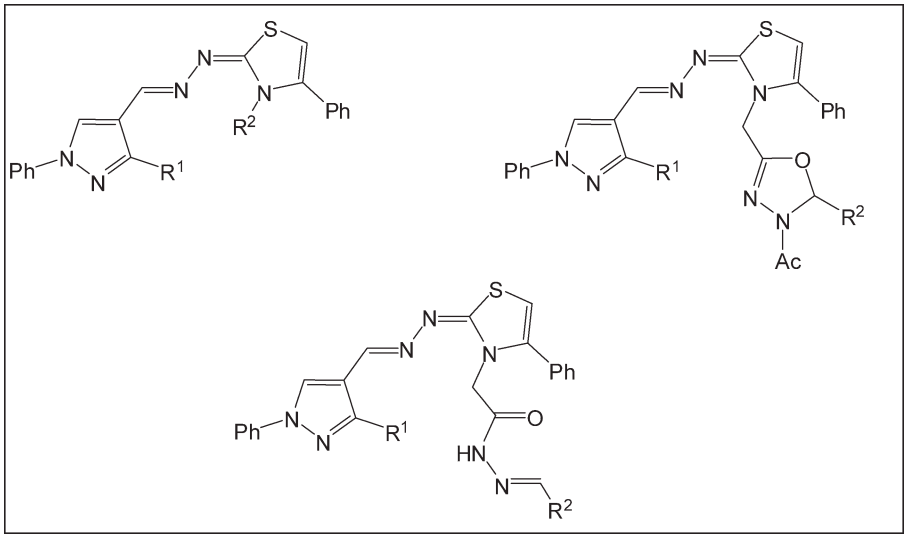

A number of new [(pyrazol-4-yl)methylene]hydrazono-2,3-dihydrothiazole derivatives, their sugar hydrazones and *N*-glycosides were synthesized. Furthermore, *N*-substituted oxygenated alkyl and hydroxyl derivatives and 1,3,4,-oxadiazoline acyclic nucleoside analogs were prepared. The newly synthesized compounds were tested for their antimicrobial activities and showed moderate to high inhibition activities.

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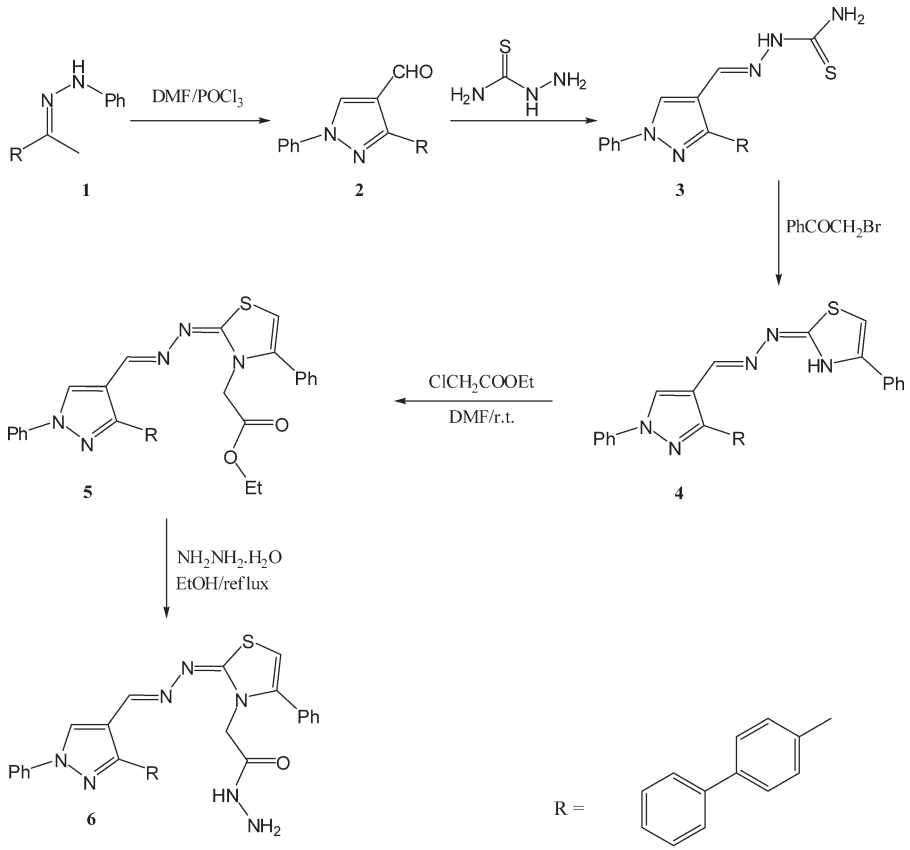
INTRODUCTION

The chemistry of 1*H*-pyrazole containing compounds is particularly interesting because of their potential application in medicinal chemistry as analgesic [1,2], anti-inflammatory [3], antitumor [4,5], antimicrobial [6–9] and therapeutic agents [10], as well as based on their wide applications in agriculture as potent insecticides [11] and herbicides [12], although scarcely found in nature [13]. Due to many promising pharmacological, agrochemical, and analytical applications, a number of substituted pyrazoles are being used as inhibitors of heat-shock protein 90 (HSP90) and as therapeutics of cancer and therefore they have been the focus of many synthetic targets over the past decades [14]. 1*H*-Pyrazole based heterocyclic structures have also attracted synthetic interest for being an essential moieties in many chemotherapeutic agents with potential antiparasitic [15], antimalarial [16] and antiviral activities [17,18]. 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 [19,20]. On the other hand, thiazole derivatives are considered as one of the most important classes of heterocyclic compounds; their derivatives are characterized with high biological activity in pharmaceutical fields and have showed antibacterial [21], antifungal [22], antitumer [23], antiviral [23,24], anti-inflammatory [25], and antineoplastic [26] activities as well as inhibitory activity of growth of gastrointestinal [27,28], biliary and pancreatic adenocarcinoma cells [29].

The thioglycosyl heterocycles [30–33] and the acyclic nucleoside analogs with modified glycon part and the heterocyclic base have stimulated extensive research as

Scheme 1



biological inhibitors [34–36]. In view of the above findings and our interest in the attachment of sugar moieties to newly synthesized heterocycles [37–39], we report in the present work the synthesis of new substituted [(pyrazol-4-yl)methylene]hydrazono-2,3-dihydrothiazole derivatives and their substituted sugar derivatives.

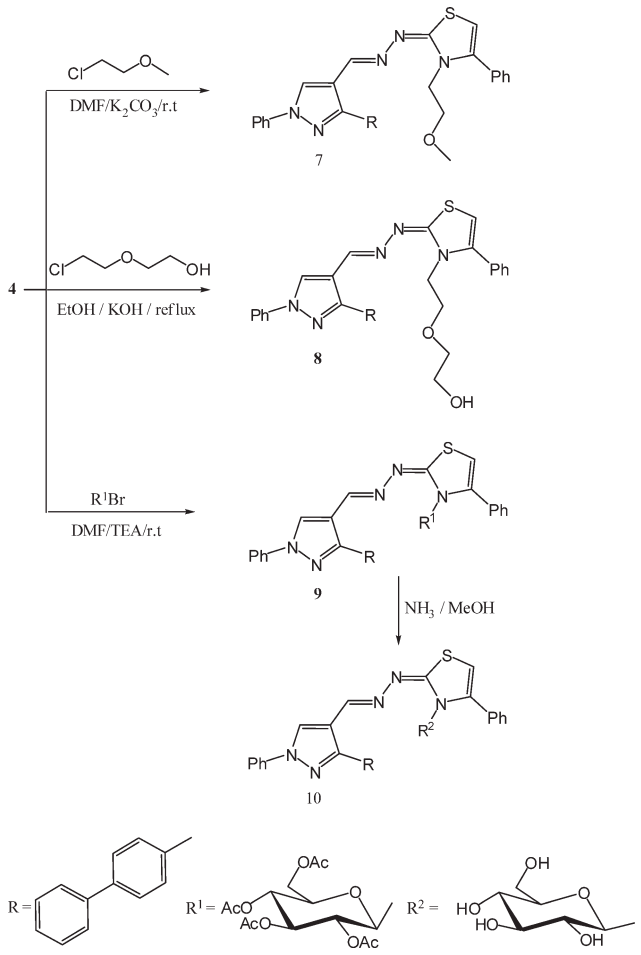
RESULTS AND DISCUSSION

Chemistry. In this investigation, reaction of biphenyl methyl ketone phenyl hydazone (**1**) with phosphorus oxychloride in dimethylformamide (DMF) at 0°C afforded 3-(biphenyl-4-yl)-1-phenyl-1*H*-pyrazole-4-carbaldehyde (**2**) in 90% yield. The synthesis of the pyrazole-4-carbaldehyde derivative **2** was carried out according to reported methods [40,41] by applying the Vilsmeier-Haack reaction. The formylating agent, also known as the Vilsmeyer-Haack Reagent, is formed *in situ* from DMF and phosphorus oxychlorid. An electrophilic substitution leads to α-chloro amines, which are rapidly hydrolyzed during work up to give the aldehyde. The IR spectrum of **2** showed the bands at 1719 and 1605 cm^{-1} corresponding to C=O and C=N. The ^1H NMR spectrum showed signals at 7.20–7.95 ppm corresponding to aryl and pyrazole H-3 protons in addition to the signal at 9.75 for the C*H*O.

Reaction of **2** with thiosemicarbazide in ethanol at reflux temperature gave the corresponding hydrazinecarbothioamide derivative **3** in 88% yield. Treatment of **3** with equivalent amount of phenacyl bromide and anhydrous sodium acetate in absolute ethanol under reflux gave the corresponding substituted 2,3-dihydrothiazole derivative **4** in 78% yield. The structure of the substituted dihydrothiazole derivative was confirmed by IR, ^1H and ^{13}C NMR and mass spectra which agreed with the assigned structure. The ^1H NMR spectrum showed the singlet signal at 5.86 ppm for the thiazole H-5 in addition to the aromatic protons at 7.19–7.96 ppm and the NH at 9.82 ppm. The ^{13}C NMR spectrum revealed the presence of the signals at 107.71, 155.11, and 158.29 corresponding to thiazole C-5, C-4, and C-2, respectively. Treatment of **4** with ethyl chloroacetate in the presence of anhydrous potassium carbonate in DMF at room temperature afforded the ethyl ester derivative **5** in 90% yield. Its ^1H NMR spectrum showed the methyl group as triplet at 1.48 ppm and the CH_2 as quartet at 4.11 ppm in addition to the signal corresponding to aryl protons. The acid hydrazide **6** was obtained in 87% yield by treating of **5** with hydrazine hydrate in ethanol under reflux (Scheme 1).

Alkylation of the substituted thiazole **4** with chloroethylmethyl ether, 2-(2-chloroethoxy)ethanol, and α-

Scheme 2



acetobromoglucose gave the corresponding alkylated derivatives **7–9** in 75–90% yields. Deprotection of the acetylated sugar of unnatural nucleoside derivative **9** using a methanolic ammonia solution afforded the free hydroxyl nucleoside **10** in 91% yield (Scheme 2). The structures of these alkylated products were proved by IR, ^{1}H NMR, and mass spectra which agreed with the assigned structure.

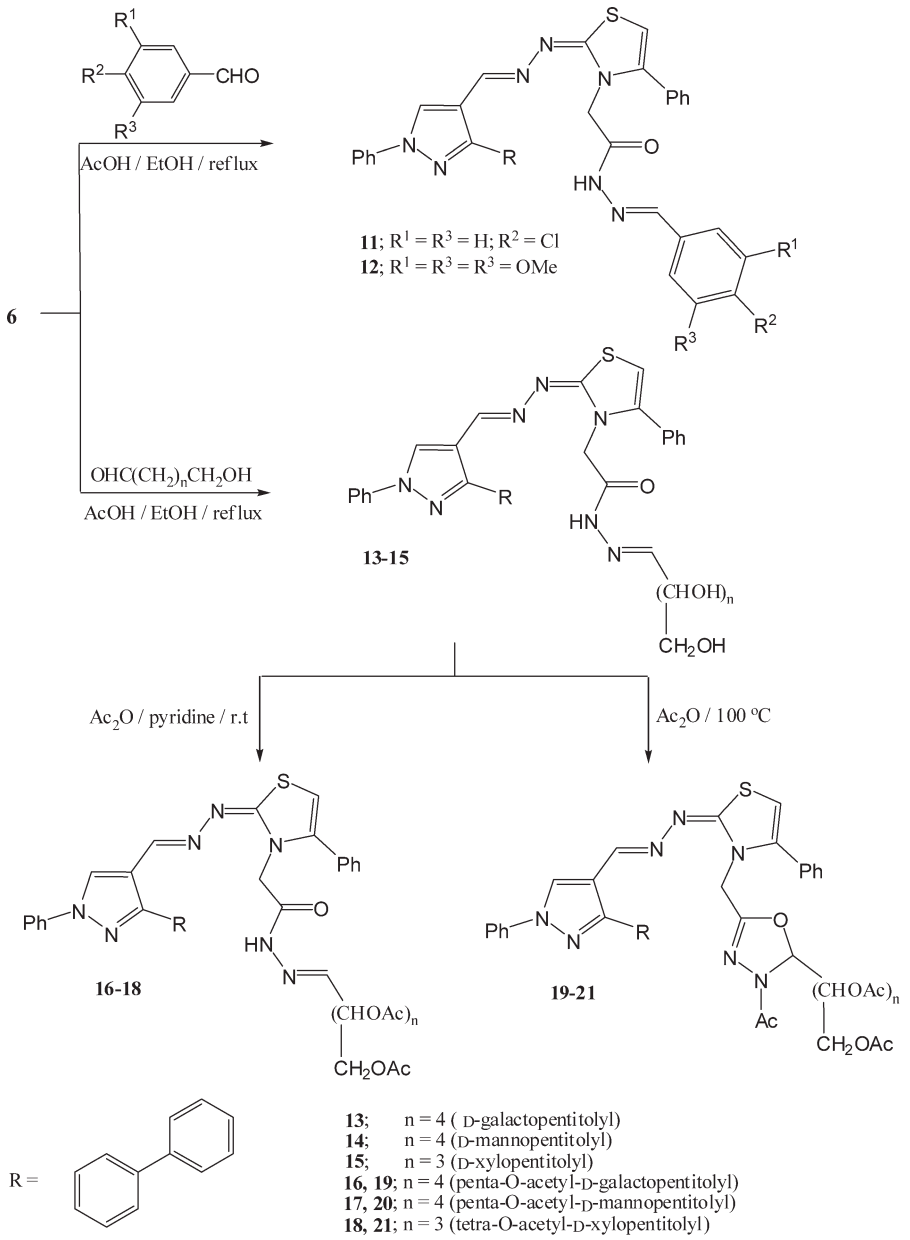
Treatment of the acid hydrazide **6** with the substituted aromatic aldehydes; *p*-chlorobenzaldehyde and 3,4,5-trimethoxybenzaldehyde afforded the corresponding *N*-arylideneacetohydrazides **11** and **12** in 89–91% yields. Furthermore when the hydrazide **6** was allowed to react with the monosaccharides; D-galactose, D -mannose or D -xylose the corresponding sugar hydrazones **13–15** were obtained in 82–92% yields. The ^{1}H NMR spectra of **13–15** showed the signals corresponding to the alditolyl chain protons and sugar hydroxyl groups. The C-1 methine proton appeared as doublet at 7.51–7.55 ppm. Acetylation of **13–15** either with acetic anhydride in pyridine at room temperature afforded the corresponding per-*O*-acetyacetylated sugar hydrazones **16–18** in 88–92% yields. It has been reported [42–-45] that when the acetylation of sugar hydrazones was carried out at high temperature in boiling acetic anhydride, cyclization usually takes place in addition to per-*O*-acetylation to afford *C*-nucleoside analogs. We reported previously [42] the synthesis of *N*-acetyl 1,3,4-oxadiazoline acyclic nucleoside analogs by the reaction of sugar hydrazones with boiling acetic anhydride. However, when the hydrazinyl sugars **13–15** were heated in acetic anhydride at 100°C they gave the corresponding *N*-acetyl 1,3,4-oxadiazoline acyclic nucleoside analogs **19–21** in 73–78% yields, respectively (Scheme 3). The IR spectra of **19–21** showed characteristic absorption bands in the carbonyl frequency region at 1665–1666 and 1741–1745 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. Their ^{1}H NMR spectra showed the signals of the *O*-acetyl-methyl protons each as singlet in the range δ 1.90–2.05 ppm and the *N*-acetyl-methyl protons in the range δ 2.20–2.22 ppm. The ^{13}C NMR spectrum of **19–21** showed the resonances of the acetyl-methyl carbons at δ 20.12–29.75 ppm. The value of the chemical shift of the *C*-N-Ac (C-1 in the original sugar chain moiety) appeared at δ 90.12 and 90.49 ppm whose value indicated its *N,N*-acetal nature rather than being a C=N group.

Antimicrobial activity. The target compounds were screened *in vitro* for their antimicrobial activities against *Escherichia coli* NRRL B-210 (Gram -ve bacteria), *Bacillus subtilis* NRRL B-543 and *Staphylococcus aureus* (Gram +ve bacteria), *Aspergillus niger*, and *Candida albicans* NRRL Y-477 (Fungi).

The results of antimicrobial activity (Table 1) indicated that compounds **1–4**, **6**, **7**, **10–14**, **16**, and **22** (13 out of 22 tested compounds) displayed high activity against the five micro-organisms. Other compounds have been shown to possess little activity or totally inactive. These results revealed the importance pyrazolyl and 1,3-thiazolidinyl ring systems as basic structural constituents in the synthesized compounds.

From the results of antimicrobial activity and structure-activity relationship it was interesting to notice that the attachment of certain acetylated open sugar moieties or glycosyl moiety to substituted 1,3-thiazolidinyl ring system resulted in marked loss of antimicrobial activity. Furthermore, no significant differences in inhibition activities were remarked as a result of changing the substituent in the para position in the aromatic ring in the synthesized substituted arylideneacetohydrazides. Moreover, the ribotetritolyl acyclonucleoside analogous of the 1,3,4-oxadiazolinyl base showed higher inhibition activity then the corresponding galacto- or mannopentitolyl sugar moieties and the corresponding acetylated sugar hydrazones.

Scheme 3



In conclusion, a number of new [(pyrazol-4-yl)methylene]hydrazono-2,3-dihydrothiazoles, sugar hydrazones, and their *N*-glycoside derivatives were synthesized and most of them displayed high inhibition activities. Compounds incorporating free hydroxyl sugar moieties displayed higher activities than the corresponding acetylated analogs.

EXPERIMENTAL

General. Melting points were determined using a Büchi apparatus. IR spectra (KBr) were recorded with a Bruker-Vector22 instrument (Bruker, Bremen, Germany). ^{1}H NMR spectra were recorded with a Varian Gemini spectrometer at 300 MHz and 200 MHz with TMS as internal standard. Chemical shifts were reported in δ scale (ppm) relative to TMS as a standard, and the coupling constants (*J* values) are given in Hz. The progress of the reactions was monitored by TLC using aluminum silica gel plates 60 F_{245}. EI-mass spectra were recorded with a HP D5988 A 1000 MHz instrument (Hewlett-Packard, Palo Alto, CA).

3-(Biphenyl-4-yl)-1-phenyl-1H-pyrazole-4-carbaldehyde (2). To an ice cold dimethylformamide (10 mL) was added dropwise with stirring phosphorus oxychloride (1.53 g, 10 mmol) over a period of 30 min, stirring was continued for further 45 min. keeping the reaction mixture at 0°C, biphenyl methyl ketone phenyl hydrazone (2.86 g, 10 mmol) was then added and the reaction mixture was allowed to attain room temperature. The mixture was heated under reflux for 2 h, allowed to cool, and

Table 1

In vitro antimicrobial activity by agar diffusion method of tested compounds.

Tested compounds	Sample wt.	Microorganisms				
		Escherichia coli	*Bacillus subtilis*	*Staph. aureus*	*Aspergillus niger*	*Candida albicans*
1	0.33 g	++ ve	++ ve	++ ve	++ ve	++ ve
2	0.34 g	++ ve	++ ve	++ ve	++ ve	++ ve
3	0.42 g	++ ve	++ ve	++ ve	++ ve	++ ve
4	0.33 g	++ ve	++ ve	++ ve	++ ve	++ ve
5	0.29 g	− ve	− ve	+ ve	+ ve	+ ve
6	0.20 g	++ ve	++ ve	++ ve	++ ve	++ ve
7	0.06 g	++ ve	++ ve	++ ve	++ ve	++ ve
8	0.20 g	+ ve	+ ve	+ ve	+ ve	+ ve
9	0.22 g	− ve	− ve	+ ve	+ ve	+ ve
10	0.06 g	++ ve	++ ve	++ ve	++ ve	++ ve
11	0.31 g	++ ve	++ ve	++ ve	++ ve	++ ve
12	0.55 g	++ ve	++ ve	++ ve	++ ve	++ ve
13	0.48 g	++ ve	++ ve	++ ve	++ ve	++ ve
14	0.05 g	++ ve	++ ve	++ ve	++ ve	++ ve
15	0.31 g	+ ve	+ ve	+ ve	− ve	− ve
16	0.05 g	++ ve	++ ve	++ ve	++ ve	++ ve
17	0.31 g	+ ve	+ ve	− ve	− ve	− ve
18	0.33 g	− ve	− ve	− ve	− ve	− ve
19	0.30 g	− ve	− ve	− ve	− ve	− ve
20	0.22 g	+ ve	+ ve	+ ve	+ ve	+ ve
21	0.18 g	+ ve	+ ve	+ ve	− ve	+ ve
22	0.14 g	++ ve	++ ve	++ ve	++ve	++ ve

+ve, zone of inhibition 10 mm or less.
++ve, zone of inhibition 20 mm or less.
−ve, no inhibition.

then poured onto ice cold water (100 mL). The mixture was boiled and the copious white precipitate obtained after cooling was filtered off, dried, and recrystallized from methanol. Yellow solid 2.916 g (90%), m.p. 225–226°C; ir (KBr) ν: 1719 (C=O), 1605 (C=N) cm^{-1}; ^{1}H NMR (DMSO-d_6, 300 MHz): δ 7.20 (d, J = 8.5 Hz, 2H, Ar—H), 7.55 (d, J = 8.2 Hz, 2H, Ar—H), 7.62 (m, 4H, Ar—H, pyrazole H-3), 7.69 (d, J = 8.5 Hz, 2H, Ar—H), 7.82 (m, 3H, Ar—H), 7.95 (d, J = 8.2 Hz, 2H, Ar—H), 9.75 (s,1H, C*H*O); ms m/z (%): 324 (M^+, 8). *Anal*. Calcd. for $C_{22}H_{16}N_2O$: C, 81.46; H, 4.97; N, 8.64. Found: C, 81.30; H, 4.89; N, 8.49%.

2-{[3-(Biphenyl-4-yl)-1-phenyl-1H-pyrazol-4-yl]methylene}-hydra-zinecarbothioamide (3). To a solution of the aldehyde derivative **2** (3.24 g, 10 mmol) in ethanol (25 mL) was added an equivalent amount of thiosemicarbazide. The mixture was heated under reflux for 5 h, filtered off, dried, and recrystallized from ethanol. Yellow solid 3.49 g (88%), m.p. 246–247°C; ir (KBr) ν: 3387 (NH_2), 3321 (NH), 1608 (C=N) cm^{-1}; ^{1}H NMR (DMSO-d_6, 300 MHz): δ 5.71 (bs, 2H, NH_2), 7.18 (d, 2H, J = 8.5 Hz, Ar—H), 7.52 (d, 2H, J = 8.2 Hz, Ar—H), 7.57 (s, 1H, C*H*=N), 7.63 (m, 4H, Ar—H, pyrazole H-3), 7.72 (d, 2H, J = 8.5 Hz, Ar—H), 7.86 (m, 3H, Ar—H), 7.98 (d, 2H, J = 8.2 Hz, Ar—H), 9.12 (s, 1H, NH); ms m/z (%): 397 (M^+, 12). *Anal*. Calcd. for $C_{23}H_{19}N_5S$: C, 69.50; H, 4.82; N, 17.62. Found: C, 69.31; H, 4.77; N, 17.50%.

2-{[[3-(Biphenyl-4-yl)-1-phenyl-1H-pyrazol-4-yl]methylene]-hydra-zono}-4-phenyl-2,3-dihydrothiazole (4). To a solution of **3** (3.97 g, 10 mmol) in absolute ethanol (20 mL) was added the equivalent amount of phenyl bromide and anhydrous sodium acetate. The reaction mixture was heated under reflux for 5 h, partially concentrated and left to cool overnight. The separated solid product was filtered off and recrystallized from aqueous ethanol. Yellow solid (3.87 g, 78%), m.p. 197–198°C; ir (KBr) ν: 3316 (NH), 1610 cm^{-1} (C=N); ^{1}H NMR (DMSO-d_6, 300 MHz): δ 5.86 (s, 1H, thiazole H-5), 7.19 (d, 2H, J = 8.5 Hz, Ar—H), 7.51 (m, 4H, Ar—H), 7.58 (s, 1H, C*H*=N), 7.64 (m, 4H, Ar—H, pyrazole H-3), 7.70 (d, 2H, J = 8.5 Hz, Ar—H), 7.79 (m, 2H, Ar—H), 7.86 (m, 4H, Ar—H), 7.96 (d, 2H, J = 8.2 Hz, Ar—H), 9.82 (s, 1H, NH); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 107.71 (thiazole C-5), 123.80–142.48 (Ar—C, pyrazole C-4,5), 153.51 (C=N), 154.14 (pyrazole C-3), 155.11 (thiazole C-4), 158.29 (thiazole C-2). ms m/z (%): 497 (M^+, 12). *Anal*. Calcd. for $C_{31}H_{23}N_5S$: C, 74.82; H, 4.66; N, 14.07. Found: C, 74.63; H, 4.49; N, 13.85%.

Ethyl 2-{2-[[(3-(biphenyl-3-yl)-1-phenyl-1H-pyrazol-4-yl] methyl-ene]hydrazono}-4-phenylthiazol-3(2H)-yl)acetate (5). To a solution of the substituted thiazole **4** (2.46 g, 5 mmol) and anhydrous potassium carbonate (0.69 g, 5 mmol) in DMF (25 mL), was added ethyl chlorocetate (0.61 g, 5 mmol). The solution was stirred at room temperature for 12 h and then poured on ice-cold water. The resulting precipitate was filtered off and recrystallized from ethanol. White solid 2.62 g (90%), m.p. 155–156°C; ir (KBr) ν: 1739 (C=O), 1610 (C=N) cm^{-1}; ^{1}H NMR (DMSO-d_6, 300 MHz): δ 1.48 (t, 3H, J = 5.4 Hz, CH_3), 4.11 (q, 2H, J = 5.4 Hz, CH_2), 4.88 (s, 2H, CH_2), 5.89 (s, 1H, thiazole H-5), 7.21 (d, 2H, J = 8.5 Hz, Ar—H), 7.50 (m, 4H, Ar—H), 7.57 (s, 1H, C*H*=N), 7.64 (m, 4H, Ar—H, pyrazole H-3), 7.71 (d, 2H, J = 8.5 Hz, Ar—H), 7.79 (m, 2H,

Ar—H), 7.88 (m, 4H, Ar—H), 7.97 (d, 2H, J = 8.2 Hz, Ar—H); MS m/z (%): 583 (M^+, 9). *Anal*. Calcd. for $C_{35}H_{29}N_5O_2S$: C, 72.02; H, 5.01; N, 12.00. Found: C, 71.89; H, 4.98; N, 11.90%.

2-{2-[[(3-(Biphenyl-3-yl)-1-phenyl-1H-pyrazol-4-yl]methylene)-hydrazono]-4-phenylthiazol-3(2H)-yl}acetohydrazide (6). A solution of the ethyl ester derivative **5** (5.83 g, 10 mmol) and hydrazine hydrate (0.5 g, 10 mmol) in ethanol was heated under reflux for 6 h. The solution was cooled and the resulting precipitate was filtered off and recrystallized from ethanol. White solid 4.82 g (87%), m.p. 205–206°C; ir (KBr) ν: 3279 (NH_2), 3227 (NH), 1668 (C=O), 1610 (C=N) cm^{-1}; ^{1}H NMR (DMSO-d_6, 300 MHz): δ 5.08 (s, 2H, CH_2), 5.41 (s, 2H, NH_2), 5.88 (s, 1H, thiazole H-5), 7.20 (d, 2H, J = 8.5 Hz, Ar—H), 7.51 (m, 4H, Ar—H), 7.58 (s, 1H, C*H*=N), 7.65 (m, 4H, Ar=H, pyrazole H-3), 7.73 (d, 2H, J = 8.5 Hz, Ar—H), 7.78 (m, 2H, Ar—H), 7.86 (m, 4H, Ar—H), 7.96 (d, 2H, J = 8.2 Hz, Ar—H), 10.02 (s, 1H, NH); ms m/z (%): 569 (M^+, 9). *Anal*. Calcd. for $C_{33}H_{27}N_7OS$: C, 69.57; H, 4.78; N, 17.21. Found: C, 69.38; H, 4.45; N, 17.38%.

2-{[[3-(Biphenyl-3-yl)-1-phenyl-1H-pyrazol-4-yl]methylene]-hydrazono}-3-(2-methoxyethyl)-4-phenyl-2,3-dihydrothiazole (7). To a solution of the substituted thiazole **4**, (4.97 g, 10 mmol) and anhydrous potassium carbonate (1.38 g, 10 mmol) in DMF (25 mL), was added chloroethylmethyl ether (0.94 g, 10 mmol). The solution was stirred at room temperature for 12 h and then poured on ice-cold water. The resulting precipitate was filtered off and recrystallized from ethanol. Yellow solid 4.16 g (75%), m.p. 171–172°C; ir (KBr) ν: 1612 (C=N) cm^{-1}; ^{1}H NMR (DMSO-d_6, 300 MHz): δ 3.84 (s, 3H, OCH_3), 4.25 (t, 2H, J = 6.2 Hz, CH_2), 4.74 (t, 2H, J = 6.2 Hz, CH_2), 5.87 (s, 1H, thiazole H-5), 7.22 (d, 2H, J = 8.5 Hz, Ar—H), 7.53 (m, 4H, Ar—H), 7.58 (s, 1H, C*H*=N), 7.64 (m, 4H, Ar—H, pyrazole H-3), 7.72 (d, 2H, J = 8.5 Hz, Ar—H), 7.79 (m, 2H, Ar—H), 7.86 (m, 4H, Ar—H), 7.96 (d, 2H, J = 8.2 Hz, Ar—H); ms m/z (%): 555 (M^+, 9). *Anal*. Calcd. for $C_{34}H_{29}N_5OS$: C, 73.49; H, 5.26; N, 12.60. Found: C, 73.31; H, 5.18; N, 12.39%.

2-{2-[2-[[[3-(Biphenyl-3-yl)-1-phenyl-1H-pyrazol-4-yl]methylene]-hydrazono]-4-phenylthiazol-3(2H)-yl]ethoxy}ethanol (8). To a solution of the substituted thiazole **4** (4.97 g, 10 mmol) and potassium hydroxide (0.56 g, 10 mmol) in absolute ethanol (20 mL) was added 2-(2-chlorethoxy)ethanol (1.24 g, 10 mmol). The reaction mixture was heated under reflux for 6 h and the precipitated solid material was filtered. The solvent was concentrated under reduced pressure and after cooling the precipitated solid material was filtered off and dried. White foam 4.62 g (79%); ir (KBr) ν: 3426 (OH), 1612 (C=N) cm^{-1}; ^{1}H NMR (DMSO-d_6, 300 MHz): δ 3.96 (t, 2H, J = 6.2 Hz, CH_2), 4.12 (t, 2H, J = 6.6 Hz, CH_2), 4.25 (m, 2H, CH_2), 4.74 (t, 2H, J = 6.6 Hz, CH_2), 5.89 (s, 1H, thiazole H-5), 7.20 (d, 2H, J = 8.5 Hz, Ar—H), 7.51 (m, 4H, Ar—H), 7.57 (s, 1H, C*H*=N), 7.65 (m, 4H, Ar—H, pyrazole H-3), 7.70 (d, 2H, J = 8.5 Hz, Ar—H), 7.83 (m, 2H, Ar—H), 7.86 (m, 4H, Ar—H), 7.99 (d, 2H, J = 8.2 Hz, Ar—H); ms m/z (%): 585 (M^+, 10). *Anal*. Calcd. for $C_{35}H_{31}N_5O_2S$: C, 71.77; H, 5.33; N, 11.96. Found: C, 71.50; H, 5.19; N, 11.74%.

2-{[[3-(Biphenyl-3-yl)-1-phenyl-1H-pyrazol-4-yl]methylene]-hydrazono}-3-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-4-phenyl-2,3-dihydrothiazole (9). To a solution of the substituted thiazole **4** (2.48 g, 5 mmol) in aqueous potassium hydroxide [(0.28 g, 5 mmol) in distilled water (3 mL)] was added a solution of 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide (2.06 g, 5 mmol) in acetone (20 mL). The reaction mixture was stirred at room temperature for 7 h (TLC). The solvent was evaporated under reduced pressure at 40°C and the residue was washed with distilled water to remove the formed potassium bromide. The product was dried, and recrystallized from ethanol. Yellow solid 3.72 g (90%), m.p. 151–152°C; ir (KBr) ν: 1744 (C=O), 1612 (C=N) cm^{-1}; ^{1}H NMR (DMSO-d_6, 300 MHz): δ 1.87, 1.88, 2.05, 2.09 (4s, 12H, $4CH_3$), 3.88 (m, 1H, H-5), 4.18 (dd, 1H, J = 11.4 Hz, J = 2.8 Hz, H-6′), 4.18 (m, 1H, H-6″), 4.52 (s, 2H, CH_2), 4.75 (t, 1H, J = 9.3 Hz, H-4′), 4.88 (dd, 1H, J = 9.6 Hz, $J_{3',4'}$ = 9.3 Hz, H-3′), 5.14 (t, 1H, J = 9.6 Hz, H-2′), 5.72 (d, 1H, J = 9.8 Hz, H-1′), 5.81 (s, 1H, thiazole H-5), 7.21 (d, 2H, J = 8.5 Hz, Ar—H), 7.51 (m, 4H, Ar—H), 7.58 (s, 1H, C*H*=N), 7.62 (m, 4H, Ar—H, pyrazole H-3), 7.72 (d, 2H, J = 8.5 Hz, Ar—H), 7.78 (m, 2H, Ar—H), 7.86 (m, 4H, Ar—H), 7.98 (d, 2H, J = 8.2 Hz, Ar—H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 19.30, 19.54, 20.18, 20.25 ($4CH_3$), 62.88 (C-6′), 64.20 (C-4′), 68.65 (C-3′), 70.37 (C-2′), 71.84 (C-5′), 88.96 (C-1′), 107.72 (thiazole C-5), 122.80–142.47 (Ar-C, thiazole C-4, pyrazole C-4,5), 153.51, 154.14, 156.29 (3C=N), 169.78, 170.14, 170.56, 170.84 (4C=O). ms m/z (%): 827 (M^+, 7). *Anal*. Calcd. for $C_{45}H_{41}N_5O_9S$: C, 65.28; H, 4.99; N, 8.46. Found: C, 65.02; H, 4.81; N, 8.30%.

2-{[[3-(Biphenyl-3-yl)-1-phenyl-1H-pyrazol-4-yl]methylene]-hydrazono}-3-(β-D-glucopyranosyl)-4-phenyl-2,3-dihydrothiazole (10). A solution of the thiazole glycoside **9** (8.27 g, 10 mmol) in methanolic ammonia solution (150 mL) was stirred at room temperature for 7 h. The solvent was evaporated under reduced pressure and the residue was dissolved in absolute ethanol (10 mL) and left over night to give the free glycoside **10** as a yellow solid. Yellow solid 5.93 g (91%), m.p. 196–197°C; ir (KBr) ν: 3398 (OH), 1612 (C=N) cm^{-1}; ^{1}H NMR (DMSO-d_6, 300 MHz): δ 3.88 (m, 2H, H-6′,6″), 4.15 (m, 2H, H-4′,5′), 4.47 (s, 2H, CH_2), 4.24 (m, 2H, H-2′,3′), 5.74 (d, 1H, J = 9.8 Hz, H-1′), 5.88 (s, 1H, thiazole H-5), 7.19 (d, 2H, J = 8.5 Hz, Ar—H), 7.51 (m, 4H, Ar—H), 7.59 (s, 1H, C*H*=N), 7.65 (m, 4H, Ar—H, pyrazole H-3), 7.71 (d, 2H, J = 8.5 Hz, Ar—H), 7.80 (2H, m, Ar—H), 7.87 (m, 4H, Ar—H), 7.98 (d, 2H, J = 8.2 Hz, Ar—H); ms m/z (%) 659 (M^+, 12). *Anal*. Calcd. for $C_{37}H_{33}N_5O_5S$: C, 67.36; H, 5.04; N, 10.62. Found: C, 67.05; H, 4.91; N, 10.31%.

N'-Arylidene-2-{2-[[[3-(biphenyl-3-yl)-1-phenyl-1H-pyrazol-4-yl]methylene]hydrazono]-4-phenylthiazol-3(2H)-yl}acetohydrazide (11 and 12). General procedure. To a well stirred solution of the respective aldehyde (100 mmol) and glacial acetic acid (0.2 mL) in ethanol (25 mL) was added the acid hydrazide **6**, (100 mmol). The mixture was heated under reflux for 5–6 h. and the resulting solution was concentrated and left to cool. The formed precipitate was filtered off, washed with water and ethanol and then dried.

2-{2-[[[3-(biphenyl-3-yl)-1-phenyl-1H-pyrazol-4-yl]methylene] hydra-zono]-4-phenylthiazol-3(2H)-yl}-N'-(4-chlorobenzylidene) aceto-hydrazide (11). White solid 0.62 g (89%), m.p. 200–201°C; ir (KBr) ν: 1681 (C=O), 1612 cm^{-1} (C=N); ^{1}H NMR (DMSO-d_6, 300 MHz): δ 5.11 (s, 2H, CH_2), 5.89 (s, 1H, thiazole H-5), 7.26 (d, 2H, J = 8.5 Hz, Ar—H), 7.54 (m, 4H, Ar—H), 7.59 (m, H, C*H*=N), 7.64 (m, 4H, Ar—H, pyrazole H-3), 7.73 (d, 2H, J = 8.5 Hz, Ar—H), 7.82 (m, 4H, Ar—H), 7.88 (m, 4H, Ar—H), 7.97 (m, 3H, Ar—H), 10.17 (s, 1H, NH);

ms m/z (%): 692 (M^+, 10). *Anal*. Calcd. for $C_{40}H_{30}ClN_7OS$: C, 69.40; H, 4.37; N, 14.16. Found: C, 69.12; H, 4.29; N, 14.30%.

2-{2-[[[3-(Biphenyl-3-yl)-1-phenyl-1H-pyrazol-4-yl]methylene]-hydrazono]-4-phenylthiazol-3(2H)-yl}-N'-(3,4,5-trimethoxybenzyl-idene)acetohydrazide (12). White solid 0.68 g (91%), m.p. 208–209°C; ir (KBr) ν: 1680 (C=O), 1610 (C=N) cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz): δ 3.82 (s, 3H, OCH_3), 3.93 (s, 6H, $2OCH_3$), 5.14 (s, 2H, CH_2), 5.88 (s, 1H, thiazole H-5), 7.23 (d, 2H, J = 8.5 Hz, Ar—H), 7.55 (m, 4H, Ar—H), 7.59 (s, 1H, C*H*=N), 7.69 (m, 4H, Ar—H, pyrazole H-3), 7.73 (d, 2H, J = 8.5 Hz, Ar—H), 7.84 (m, 4H, Ar—H), 7.88 (m, 4H, Ar—H), 7.98 (d, 2H, J = 8.2 Hz, Ar—H), 10.21 (s, 1H, NH); ms m/z (%): 747 (M^+, 10). *Anal*. Calcd. for $C_{43}H_{37}N_7O_4S$: C, 69.06; H, 4.99; N, 13.11. Found: C, 69.16; H, 4.84; N, 13.05%.

Sugar 2-{2-[[(3-(biphenyl-3-yl)-1-phenyl-1H-pyrazol-4-yl]methylene)hydrazono]-4-phenylthiazol-3(2H)-yl}acetohydrazones (13-15). General procedure. To a well stirred solution of the respective monosaccharide (10 mmol) in water (2 mL), and glacial acetic acid (0.2 mL) was added **6** (10 mmol) in ethanol (10 mL). The mixture was heated under reflux for 6 h, and the resulting solution was concentrated and left to cool. The formed precipitate was filtered off, washed with water and ethanol, then dried and recrystallized from ethanol.

D-Galactose 2-{2-[[(3-(biphenyl-3-yl)-1-phenyl-1H-pyrazol-4-yl]methyl-ene)hydrazono]-4-phenylthiazol-3(2H)-yl}acetohydrazone (13). Yellow solid 6.72 g, (92%), m.p. 198–199°C; ir (KBr) ν: 3372–3351 (OH), 1668 (C=O), 1610 (C=N) cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz): δ 3.64 (m, 2H, H-6′,6″), 4.18 (m, 2H, H-4′,5′), 4.29 (m, 2H, H-2′,3′), 5.14 (s, 2H, CH_2), 5.88 (s, 1H, thiazole H-5), 7.18 (d, 2H, J = 8.5 Hz, Ar—H), 7.52 (m, 4H, Ar—H), 7.55 (d, 1H, J = 7.8 Hz, H-1′), 7.59 (s, 1H, C*H*=N), 7.64 (m, 4H, Ar—H, pyrazole H-3), 7.75 (d, 2H, J = 8.5 Hz, Ar—H), 7.81 (m, 2H, Ar—H), 7.86 (m, 4H, Ar—H), 7.97 (d, 2H, J = 8.2 Hz, Ar—H), 10.18 (s, 1H, NH); ms m/z (%): 731 (M^+, 7). *Anal*. Calcd. for $C_{39}H_{37}N_7O_6S$: C, 64.01; H, 5.10; N, 13.40. Found: C, 63.95; H, 5.02; N, 13.32%.

D-Mannose 2-{2-[[(3-(biphenyl-3-yl)-1-phenyl-1H-pyrazol-4-yl]methyl-ene)hydrazono]-4-phenylthiazol-3(2H)-yl}acetohydrazone (14). Yellow solid 6.58 g, (90%), m.p. 211–212°C; ir (KBr) ν: 3387–3341 (OH), 1667 (C=O), 1610 (C=N) cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz): δ 3.66 (m, 2H, H-6′,6″), 4.19 (m, 2H, H-4′,5′), 4.29 (m, 2H, H-2′,3′), 5.16 (s, 2H, CH_2), 5.18 (s, 2H, CH_2), 5.89 (s, 1H, thiazole H-5′), 7.21 (d, 2H, J = 8.5 Hz, Ar—H), 7.51 (m, 4H, Ar—H), 7.54 (d, 1H, J = 7.8 Hz, H-1′), 7.59 (s, 1H, C*H*=N), 7.64 (m, 4H, Ar—H, pyrazole H-3), 7.59 (s, 1H, C*H*=N), 7.65 (m, 4H, Ar—H, pyrazole H-3), 7.72 (d, 2H, J = 8.5 Hz, Ar—H), 7.80 (m, 2H, Ar—H), 7.86 (m, 4H, Ar—H), 7.96 (d, 2H, J = 8.2 Hz, Ar—H), 10.17 (s, 1H, NH); ms m/z (%): 731 (M^+, 7). *Anal*. Calcd. for $C_{39}H_{37}N_7O_6S$: C, 64.01; H, 5.10; N, 13.40. Found: C, 63.90; H, 5.14; N, 13.31%.

D-Xylose 2-{2-[[(3-(biphenyl-3-yl)-1-phenyl-1H-pyrazol-4-yl]methylene)-hydrazono]-4-phenylthiazol-3(2H)-yl}acetohydrazone (15). Yellow solid 5.74 g (82%), m.p. 203–200°C; ir (KBr) ν: 3412–3367 (OH), 1664 (C=O), 1614 (C=N) cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz): δ 3.64 (m, 2H, H-5′,5″), 4.18 (m, 2H, H-4′), 4.23 (m, 2H, H-2′,3′), 5.16 (s, 2H, CH_2), 5.88 (s, 1H, thiazole H-5), 7.25 (d, 2H, J = 8.5 Hz, Ar—H), 7.51 (d, 1H, J = 7.8 Hz, H-1′), 7.55 (m, 4H, Ar—H), 7.59 (s, 1H, C*H*=N), 7.69 (m, 4H, Ar—H, pyrazole H-3), 7.75 (d, 2H, J = 8.5 Hz, Ar—H), 7.79 (m, 2H, Ar—H), 7.86 (m, 4H, Ar—H), 7.98 (d, 2H, J = 8.2 Hz, Ar—H), 10.22 (s, 1H, NH); ms m/z (%): 701 (M^+, 10). *Anal*. Calcd. for $C_{38}H_{35}N_7O_5S$: C, 65.03; H, 5.03; N, 13.97. Found: C, 64.96; H, 4.94; N, 13.72%.

O-Acetyl-sugar 2-{2-[[(3-(biphenyl-3-yl)-1-phenyl-1H-pyrazol-4-yl]methylene)hydrazono]-4-phenylthiazol-3(2H)-yl}acetohydrazones (16-18). General procedure. To a solution of the sugar hydrazones **13–15**, (1 mmol) in pyridine (7 mL) was added acetic anhydride (10 mmol) and stirred at room temperature for 6–8 h. The resulting solution was poured onto crushed ice, and the product that separated out was filtered off, washed with a saturated solution of sodium hydrogen carbonate followed by water and then dried.

2,3,4,5,6-Penta-O-acetyl-D-galactose-2-{2-[[(3-(biphenyl-3-yl)-1-phenyl-1H-pyrazol-4-yl]methylene)-hydrazono]-4-phenylthiazol-3(2H)-yl}acetohydrazone (16). White solid 0.87 g (92%), m.p. 147–148°C; ir (KBr) ν 1740 (C=O), 1668 (C=O), 1610 (C=N) cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz): δ 1.91, 1.94, 1,98, 2.02, 2.04 (5s, 15H, $5CH_3$), 3.88 (dd, 1H, J = 11.4 Hz, J = 2.8 Hz, H-6′), 4.18 (m, 1H, H-6″), 4.24 (m, 1H, H-5′), 4.75 (t, 1H, J = 9.3 Hz, H-4′), 4.88 (dd, 1H, J = 9.6 Hz, J = 9.3 Hz, H-3′), 5.14 (t, 1H, J = 9.6 Hz, H-2′), 5.18 (s, 2H, CH_2), 5.87 (s, 1H, thiazole H-5), 7.19 (d, 2H, J = 8.5 Hz, Ar-H), 7.50 (m, 4H, Ar—H), 7.54 (d, 1H, J = 7.8 Hz, H-1′), 7.59 (s, 1H, C*H*=N), 7.66 (m, 4H, Ar—H, pyrazole H-3), 7.70 (d, 2H, J = 8.5 Hz, Ar—H), 7.80 (m, 2H, Ar—H), 7.86 (m, 4H, Ar—H), 7.97 (d, 2H, J = 8.2 Hz, Ar—H), 10.26 (s, 1H, NH); ms m/z (%): 941 (M^+, 12). *Anal*. Calcd. for $C_{49}H_{47}N_7O_{11}S$: C, 62.48; H, 5.03; N, 10.41. Found: C, 61.37; H, 4.94; N, 10.18%.

2,3,4,5,6-Penta-O-acetyl-D-mannose-2-{2-[[(3-(biphenyl-3-yl)-1-phenyl-1H-pyrazol-4-yl]methylene)-hydrazono]-4-phenylthiazol-3(2H)-yl}acetohydrazone (17). White solid 0.85 g (90%), m.p. 149-150 °C; ir (KBr) ν: 1742 (C=O), 1661 (C=O), 1610 cm^{-1} (C=N); ^1H NMR (DMSO-d_6, 300 MHz): δ 1.92, 1.94, 1,97, 2.02, 2.05 (5s, 15H, $5CH_3$), 3.89 (dd, 1H, J = 11.4 Hz, J = 2.8 Hz, H-6′), 4.21 (m, 1H, H-6″), 4.25 (m, 1H, H-5′), 4.75 (t, 1H, J = 9.3 Hz, H-4′), 4.88 (dd, 1H, J = 9.6 Hz, J = 9.3 Hz, H-3′), 5.15 (t, 1H, J = 9.6 Hz, H-2′), 5.24 (s, 2H, CH_2), 5.87 (s, 1H, thiazole H-5), 7.21 (d, 2H, J = 8.5 Hz, Ar—H), 7.51 (m, 4H, Ar—H), 7.55 (d, 1H, J = 7.8 Hz, H-1′), 7.60 (s, 1H, C*H*=N), 7.68 (m, 4H, Ar—H, pyrazole H-3), 7.70 (d, 2H, J = 8.5 Hz, Ar—H), 7.82 (m, 2H, Ar—H), 7.88 (m, 4H, Ar—H), 7.99 (d, 2H, J = 8.2 Hz, Ar—H), 10.29 (s, 1H, NH); ms m/z (%): 941 (M^+, 11). ms m/z (%) 941 (M^+, 12). *Anal*. Calcd. for $C_{49}H_{47}N_7O_{11}S$: C, 62.48; H, 5.03; N, 10.41. Found: C, 61.38; H, 4.90; N, 10.17%.

2,3,4,5-Tetra-O-acetyl-D-xylose-2-{2-[[(3-(biphenyl-3-yl)-1-phenyl-1H-pyrazol-4-yl]methylene)-hydrazono]-4-phenylthiazol-3(2H)-yl}acetohydrazone (18). Yellow solid 0.76 g (88%), m.p. 152-153 °C; ir (KBr) ν: 1739 (C=O), 1663 (C=O), 1610 (C=N) cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz): δ 1.90, 1.93, 1.98, 2.05 (4s, 12H, $4CH_3$), 3.88 (dd, 1H, J = 11.4 Hz, J = 2.8 Hz, H-5′), 4.18 (m, 1H, H-5″), 4.75 (t, 1H, J = 9.3 Hz, H-4′), 5.18 (s, 2H, CH_2), 4.89 (dd, 1H, J = 9.6 Hz, J = 9.3 Hz, H-3′), 5.15 (t, 1H, J = 9.6 Hz, H-2′), 5.86 (s, 1H, thiazole H-5), 7.21 (d, 2H, J = 8.5 Hz, Ar—H), 7.52 (d, 1H, J = 7.8 Hz, H-1′), 7.56 (m, 4H, Ar—H), 7.60 (s, 1H, C*H*=N), 7.64 (4H, m, Ar—H, pyrazole H-3), 7.73 (d, 2H, J = 8.5 Hz, Ar—H), 7.79 (m, 2H, Ar—H), 7.88 (m, 4H, Ar—H), 8.02 (d, 2H, J = 8.2 Hz, Ar—H), 10.25 (s, 1H, NH); ms m/z (%): 869 (M^+,

12). *Anal*. Calcd. for $C_{46}H_{43}N_7O_9S$: C, 63.51; H, 4.98; N, 11.27. Found: C, 63.36; H, 4.88; N, 11.14%.

1-{5-[[2-[[[3-(Biphenyl-4-yl)-1-phenyl-1H-pyrazol-4-yl]methylene]hydrazono]-4-phenylthiazol-3(2H)-yl]methyl]-2-(O-acetylsugar)-1,3,4-oxadiazol-3(2H)-yl}ethanones (19–21). General procedure. A solution of the sugar hydrazones **13–15**, (1 mmol) in acetic anhydride (5 mL) was boiled under reflux for 1 h. The resulting solution was poured onto crushed ice, and the product that separated out was filtered off, washed with a saturated solution of sodium hydrogen carbonate followed by water and then dried.

1-{5-[[2-[[[3-(Biphenyl-4-yl)-1-phenyl-1H-pyrazol-4-yl]methylene]-hydrazono]-4-phenylthiazol-3(2H)-yl]methyl]-2-(1,2,3,4,5-penta-O-acetyl-D-galactopentitolyl)-1,3,4-oxadiazol-3(2H)-yl} ethanone (19). White foam 0.77 g (78%); ir (KBr) ν: 1743 (C=O), 1665 (C=O), 1618 (C=N) cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz): δ 1.90, 1.93, 1.97, 2.02, 2.04, 2.22 (6s, 18H, $6CH_3$), 3.88 (dd, 1H, J = 11.4 Hz, J = 2.8 Hz, H-5′), 4.22 (m, 1H, H-5″), 4.27 (m, 1H, H-4′), 4.92 (dd, 1H, J = 9.6 Hz, J = 9.3 Hz, H-3′), 5.15 (t, 1H, J = 9.6 Hz, H-2′), 5.19 (s, 2H, CH_2), 5.25 (dd, 1H, J = 9.6 Hz, J = 7.2 Hz, H-1′), 5.72 (d, 1H, J = 9.8 Hz, oxadizoline-H), 5.90 (s, 1H, thiazole H-5), 7.25 (d, 2H, J = 8.5 Hz, Ar—H), 7.56 (m, 4H, Ar—H), 7.61 (s, 1H, C*H*=N), 7.645 (m, 4H, Ar—H, pyrazole H-3), 7.71 (d, 2H, J = 8.5 Hz, Ar—H), 7.80 (m, 2H, Ar—H), 7.88 (m, 4H, Ar—H), 7.98 (d, 2H, J = 8.2 Hz, Ar—H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 20.314, 20.51, 20.55, 20.68, 20.75, 29.65 ($6CH_3$), 46.71 (CH_2), 62.91 (C-5′), 65.35 (C-4′), 68.40 (C-3′), 69.73 (C-2′), 71.15 (C-1′), 90.12 (oxadiazoline C-2), 107.39 (thiazole C-5), 122.80-142.47 (Ar—C, pyrazole C-4,5), 152.40, 153.51, 154.14, 156.29, 157.29 (4C=N, thiazole C-4), 169.14, 169.78, 170.14, 170.42, 170.77, 171.09 (6CO). ms m/z (%) 984: (M^+, 11). ms m/z (%): 984 (M^+, 11). *Anal*. Calcd. for $C_{51}H_{49}N_7O_{12}S$: C, 62.25; H, 5.02; N, 9.96. Found: C, 62.08; H, 4.95; N, 9.71%.

1-{5-[[2-[[[3-(Biphenyl-4-yl)-1-phenyl-1H-pyrazol-4-yl]methylene]-hydrazono]-4-phenylthiazol-3(2H)-yl]methyl]-2-(1,2,3,4,5-penta-O-acetyl-D-mannopentitolyl)-1,3,4-oxadiazol-3(2H)-yl} ethanone (20). White foam 0.75 g (76%); ir (KBr) ν: 1745 (C=O), 1666 (C=O), 1615 (C=N) cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz): δ 1.91, 1.94, 1,98, 2.02, 2.05, 2.20 (6s, 18H, $6CH_3$), 3.87 (dd, 1H, J = 11.4 Hz, J = 2.8 Hz, H-5′), 4.20 (m, 1H, H-5″), 4.24 (m, 1H, H-4′), 4.92 (dd, 1H, J = 9.6 Hz, J = 9.3 Hz, H-3′), 5.15 (t, 1H, J = 9.6 Hz, H-2′), 5.19 (s, 2H, CH_2), 5.24 (dd, 1H, J = 9.6 Hz, J = 7.2 Hz, H-1′), 5.71 (d, 1H, J = 9.8 Hz, oxadizoline-H), 5.89 (s, 1H, thiazole H-5), 7.24 (d, 2H, J = 8.5 Hz, Ar—H), 7.55 (m, 4H, Ar—H), 7.59 (s, 1H, C*H*=N), 7.64 (m, 4H, Ar—H, pyrazole H-3), 7.70 (d, 2H, J = 8.5 Hz, Ar—H), 7.80 (m, 2H, Ar—H), 7.87 (m, 4H, Ar—H), 7.98 (d, 2H, J = 8.2 Hz, Ar—H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 20.14, 20.52, 20.57, 20.70, 20.75, 29.66 ($6CH_3$), 46.75 (CH_2), 62.92 (C-5′), 65.35 (C-4′), 68.40 (C-3′), 69.72 (C-2′), 71.17 (C-1′), 90.42 (oxadiazoline C-2), 106.88 (thiazole C-5), 122.81-142.49 (Ar—C, pyrazole C-4,5), 152.41, 153.53, 154.15, 156.29, 15.15 (4C=N, thiazole C-4), 169.11, 169.78, 170.15, 170.44, 170.78, 171.36 (6CO). ms m/z (%) 984: (M^+, 11). *Anal*. Calcd. for $C_{51}H_{49}N_7O_{12}S$: C, 62.25; H, 5.02; N, 9.96. Found: C, 62.10; H, 4.94; N, 9.70%.

1-{5-[[2-[[[3-(Biphenyl-4-yl)-1-phenyl-1H-pyrazol-4-yl]methylene]-hydrazono]-4-phenylthiazol-3(2H)-yl]methyl]-2-(1,2,3,4-tetra-O-acetyl-D-xylotetritolyl)-1,3,4-oxadiazol-3(2H)-yl}ethanone (21). White foam 0.66 g (73%); IR (KBr) ν 1741 (C=O), 1667 (C=O), 1612 (C=N) cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz): δ 1.91, 1,98, 2.02, 2.05, 2.21 (5s, 15H, $5CH_3$), 3.89 (dd, 1H, J = 11.4 Hz, J = 2.8 Hz, H-4′), 4.21 (m, 1H, H-4″), 5.21 (s, 2H, CH_2), 4.93 (dd, 1H, J = 9.6 Hz, J = 9.3 Hz, H-3′), 5.15 (t, 1H, J = 9.6 Hz, H-2′), 5.18 (dd, 1H, J = 9.6 Hz, J = 7.2 Hz, H-1′), 5.72 (d, 1H, J = 9.8 Hz, oxadizoline-H), 5.88 (s, 1H, thiazole H-5), 7.22 (d, 2H, J = 8.5 Hz, Ar—H), 7.56 (m, 4H, Ar—H), 7.61 (s, 1H, C*H*=N), 7.66 (m, 4H, Ar—H, pyrazole H-3), 7.72 (2H, d, J = 8.5 Hz, Ar—H), 7.80 (2H, m, Ar—H), 7.86 (4H, m, Ar—H), 7.98 (2H, d, J = 8.2 Hz, Ar—H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 20.12, 20.51, 20.59, 20.67, 29.64 ($5CH_3$), 46.72 (CH_2), 62.95 (C-4′), 69.41 (C-3′), 69.74 (C-2′), 71.21 (C-1′), 90.49 (oxadiazoline C-2), 106.69 (thiazole C-5), 123.80-144.50 (Ar—C, pyrazole C-4,5), 152.41, 153.53, 154.15, 156.29, 157.19 (4C=N, thiazole C-4), 169.18, 169.73, 170.19, 170.45, 171.37 (5CO). ms m/z (%) 984: (M^+, 11). ms m/z (%): 911 (M^+, 11). *Anal*. Calcd. for $C_{48}H_{45}N_7O_{10}S$: C, 63.22; H, 4.79; N, 10.75. Found: C, 63.10; H, 4.61; N, 10.62%.

Antimicrobial activity. The target compounds were screened *in vitro* for their antimicrobial activities against *Escherichia coli* NRRL B-210 (Gram -ve bacteria), *Bacillus subtilis* NRRL B-543 and *Staphylococcus aureus* (Gram +ve bacteria), *Aspergillus niger* and *Candida albicans* NRRL Y-477 (Fungi). These microorganisms were obtained from Northern Utilization Research and Development Division, U.S. Department of Agricultural Peoria, Illinois.

The agar diffusion method [46] was used for this purpose. The bacteria and fungi were maintained on nutrient agar and Czapek's-Dox agar media, respectively. The assay medium flasks containing 50mL of nutrient agar for bacteria and Czapek's-Dox agar medium for fungi respectively were allowed to reach 40–50°C to be inoculated with 0.5 mL of the test organism cell suspension.

The flasks were mixed well and poured each into a Petri dish (15 x 2 cm) and allowed to solidify. After solidification, holes (0.6 cm diameter) were made in the agar plate by the aid of a sterile cork poorer (diameter 6 mm). Target compounds were dissolved each in 2 mL DMSO. In these holes, 100 μL of each compound was placed using an automatic micropipette. The Petri dishes were left at 5°C for 1 h to allow diffusion of the samples through the agar medium and retard the growth of the test organism. Plates were incubated at 30°C for 24 h for bacteria and 72 h of incubation at 28°C for fungi.

DMSO showed no inhibition zones. The diameter of the resulted inhibition zone was measured in cm (Table 1).

REFERENCES AND NOTES

[1] Wise, L. D.; Butler, D. E.; Dewald, H. A.; Lustgarten, D. M.; Pattison, I. C.; Schweiss, D. N.; Coughenour, L. L.; Downs, D. A.; Heffner, T. G.; Pugsley, T. A. J Med Chem 1987, 30, 1807.

[2] Gursoy, S. A.; Demirayak, G.; Capan, K. Eur J Med Chem 2000, 35, 359.

[3] Badawey, A. M.; El-Ashmawey, I. M. Eur J Med Chem 1998, 33, 349.

[4] Daidone, G.; Maggio, B.; Plescia, S.; Raffa, D.; Musiu, C.; Milia, C.; Perra, G.; Marongiu, M. E. Eur J Med Chem 1998, 33, 375.

[5] (a) Hilgard, P.; Thornes, R. D. Eur J Cancer 1976, 12, 755; (b) Taylor, E. C.; Patel, H.; Kumar, H. Tetrahedron 1992, 48, 8089.

[6] Nauduri, D.; Reddy, G. B. Chem Pharm Bull 1998, 46, 1254.

[7] Foks, H.; Pancechowska-Ksepko, D.; Kedzia, A.; Zwolska, Z. Farmaco 2005, 60, 513.

[8] Dardari, Z.; Lemrani, M.; Sebban, A.; Bahloul, A. Arch Pharm Chem Life Sci 2006, 33, 291.

[9] Gilbert, A. M.; Failli, A.; Shumsky, J.; Yang, Y. J Med Chem 2006, 49, 6027.

[10] (a) Jiang, J. B.; Hesson, D. P.; Dusak, B. A.; Dexter, D. L.; Kang, G. J.; Hamel, E. J Med Chem 1990, 33, 1721; (b) Anzai, K.; Furuse, M.; Yoshida, A.; Matsuyama, A.; Moritake, T.; Tsuboi, K. J Radiat Res 2004, 45, 319.

[11] Parlok, J. J. J Heterocycl Chem 1998, 35, 1493.

[12] Frinkelstein, B. L.; Strok, C. J. J Pestic Sci 1997, 50, 324.

[13] Eicher, T.; Hauptmann, S. The Chemistry of Heterocycles: Structure, Reactivity, Syntheses and Applications; Thieme-Verlag: New York, 1995, p 184.

[14] Jolly, C.; Morimoto, R. I. J Natl Cancer Inst 2000, 92, 1564.

[15] Bernardino, A. M. R.; Gomes, A. O.; Charret, K. S.; Freitas, A. C. C. Eur J Med Chem 2006, 41, 80.

[16] Katiyar, S. B.; Srivastava, K.; Purib, S. K.; Chauhana, P. M. S. Bioorg Med Chem Lett 2005, 15, 4957.

[17] Moukha-Chafiq, O.; Taha, M. L.; Lazrek, H. B.; Vasseur, J.-J. Farmaco 2002, 57, 27.

[18] Allen, S. H.; Johns, B. A.; Gudmundsson, K. S.; Freeman, G. A. Bioorg Med Chem 2006, 14, 944.

[19] Gopalsamy, A.; Yang, H.; Ellingboe, J. W.; Tsou, H.; Zhang, N.; Honores, E.; Powell, D.; Miranda, M.; McGinnis, J. P.; Rabindran, S. K. Bioorg Med Chem Lett 2005, 15, 1591.

[20] Cocco, M. T.; Congiu, C.; Lilliu, V.; Onnis, V. Arch Pharm Chem Life Sci 2006, 339, 7.

[21] Tsuji, K.; Ishikawa, H. Bioorg Med Chem Lett 1994, 4, 1601.

[22] Lopez-Garcia, B.; Veyrat, A.; Perez-Paya, E.; González-Candelas, L.; Marcos, J. F. Int J Food Microbiol 2003, 89, 163.

[23] Srivastava, P. C.; Pickering, M. V.; Allen, L. B.; Streeter, D. G.; Campbell, M. T.; Witkowski, J. T.; Sidwell, R. W.; Robins, R. K. J Med Chem 1977, 20, 256.

[24] Kirsi, J. J.; North, J. A.; McKernan, P. A.; Murray, B. K.; Canonico P. G.; Huggins, J. W.; Srivastava, P. C.; Robins, R. K. Antimicrob Agents Chemother 1983, 24, 353.

[25] Geronikaki, A.; Hadjipavlou-Litina, D.; Chatziopoulos, C.; Soloupis, G. Molecules 2003, 8, 472.

[26] Milne, G. W. A. Ed. Ashgate Handbook of Antineoplastic Agents; Gower: London, UK, 2000.

[27] Sato, H.; Ishihara, S.; Kawashima, K.; Moriyama, N.; Suetsugu, H.; Kazuori, H.; Okuyama, T.; Rumi, M. A. K.; Fukuda, R.; Nagasue, N.; Kinoshita, Y. Br J Cancer 2000, 83, 1394.

[28] Takahashi, N.; Okumura, T.; Motomura, W.; Fujimoto, Y.; Kawabata, I.; Kohgo, Y. FEBS Lett 1999, 455, 135.

[29] Motomura, W.; Okumura, T.; Takahashi, N.; Obara, T.; Kohgo, Y. Cancer Res 2000, 60, 5558.

[30] Brajeswar, P. Carbohydr Res 1984, 126, 27.

[31] Kuhn, C.S.; Lehmann, J.; Steck, J. Tetrahedron 1990, 46, 3129.

[32] Blanc-Muesser, M.; Vigne, L.; Driguez, H.; Lehmann, J.; Steck, J.; Urbahns, K. Carbohydr Res 1992, 224, 59.

[33] El Ashry, E. S. H.; Awad, L. F.; Atta, I. A. Tetrahedron 2006, 62, 2943.

[34] Awad, O. M. E.; Attia, W. E.; El Ashry, E. S. H. Carbohydr Res 2004, 339, 469.

[35] El Ashry, E. S. H.; El Kilany, Y. Adv Heterocycl Chem 1997, 68, 1.

[36] El Ashry, E. S. H.; El Kilany, Y. Adv Heterocycl Chem 1998, 9, 129.

[37] Abdel-Rahman, A. A.-H.; El-Sayed, W. A.; Abdel-Bary, H. M.; Abdel-Megied, A. E.-S.; Morcy, E. M. Monatsh Chem 2008, 139, 1095.

[38] El-Sayed, W. A.; Nassar, I. F.; Abdel-Rahman, A. A.-H. Monatsh Chem 2009, 140, 365.

[39] El-Sayed, W. A.; Ramiz, M. M. M.; Abdel-Rahman, A. A.-H. Monatsh Chem 2008, 139, 1499.

[40] Bernard, M.; Hulley, E.; Molenda, H.; Stochla, K.; Wrzeciono, U. Pharmazie 1986, 41, 560.

[41] Farghalya, A. A.; Bekhit, A. A.; Park, J. Y. Arch Pharm Pharm Med Chem 2000, 333, 53.

[42] Abdel-Aal, M. T.; El-Sayed, W. A.; El-Ashry, E. S. H. Arch Pharm Chem Life Sci 2006, 339, 656.

[43] Abdel Aal, M. T.; El-Sayed, W. A.; El-Ashry, E. S. H. Arch Pharm Chem Life Sci 2006, 339, 656.

[44] Ali, O. M.; Amer, H. H.; Abdel Rahman, A. A.-H. Synthesis 2007, 2823.

[45] El-Ashry, E. S. H.; Rashed, N.; Mousaad, A. Carbohydr Res 1982, 100, C39.

[46] Cruickshank, R.; Duguid, J. P.; Marion, B. P.; Swain, R. H. A. Medicinal Microbiology, 12th ed., vol. II; Churchill Livingstone, London, 1975, pp 196.