Synthesis and Anticancer Activity of Some New Fused Pyrazoles and Their Glycoside Derivatives

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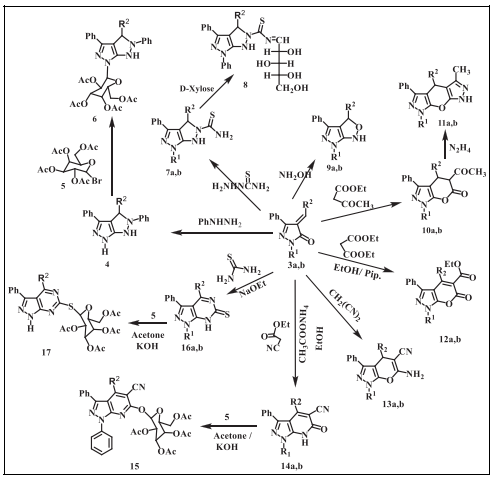


4-(4-Chlorobenzylidene)-2,5-diphenyl-2,3-dihydro-3*H*-pyrazol-3-one **3a** and 4-(3,4-dimethoxybenzylidene)-5-phenyl-2,3-dihydro-3*H*-pyrazol-3-one **3b** were prepared and were reacted with phenylhydrazine, thiosemicarbazide, hydroxylamine hydrochloride, ethyl acetoacetate, diethylmalonate, malononitrile, ethyl cyanoacetate, and thiourea yielding fused pyrazole derivatives. Some of the new compounds were reacted with cyclic and acyclic sugars to produce new *S*-, *O*-, and *N*-glycoside derivatives. The antitumor activity against the human breast cancer cells (MCF-7) was assessed. Four of the new compounds showed IC_{50} values less than those of the positive control, indicating that these four compounds are better anticancer agents than doxorubicin.

INTRODUCTION

Pyrazole derivatives represent an important class of heterocycles owing to their prominent biological and pharmacological activities. Several pyrazole compounds have been reported to be potential therapeutic agents for the treatment of inflammation [1–4] including the marketed selective COX-2 drug, celecoxib, that have been shown to be well tolerated with reduced gastrointestinal side effects [5]. Moreover, various substituted pyrazoles were reported to possess antitumor activities [6,7]; others were used for treating Alzheimer's disease [8] and acquired immunodeficiency syndrome [9]. Some pyrazole derivatives were also found to have antimicrobial [10,11], antiviral [12], and antimalarial activities [13]. Many pyrazole derivatives are known to exhibit a wide range of biological properties such as cannabinoid hCB1 and hCB2 receptors, anti-inflammatory agents, inhibitors of p38 kinase, and CB1 receptor antagonists [14–17]. The incorporation of heterocyclic rings into prospective pharmaceutical candidates is a major strategy to obtain activity and safety advantages. As a consequence, much attention has been paid to the design and synthesis of fused pyrazole derivatives [18–22]. Pyrazolopyrimidines derivatives are known to have potent pharmacological activities that enabled using them as anticancer agents [23], GSK-3 inhibitors [24], and antiviral agents [25]. They also manifest potential cytotoxicity activity against *human laryngeal epidermoid carcinoma cells* (Hep2) [26]. Furthermore, some pyrazolo[3,4-*d*]pyrimidine derivatives manifested significant activity as anti-inflammatory agents [27]. We have been aiming in this work to synthesize some new substituted heterocyclic systems on the basis of pyrazole moiety of expected biological interest and to test them as biodegradable agrochemicals [28–41].

RESULTS AND DISCUSSION

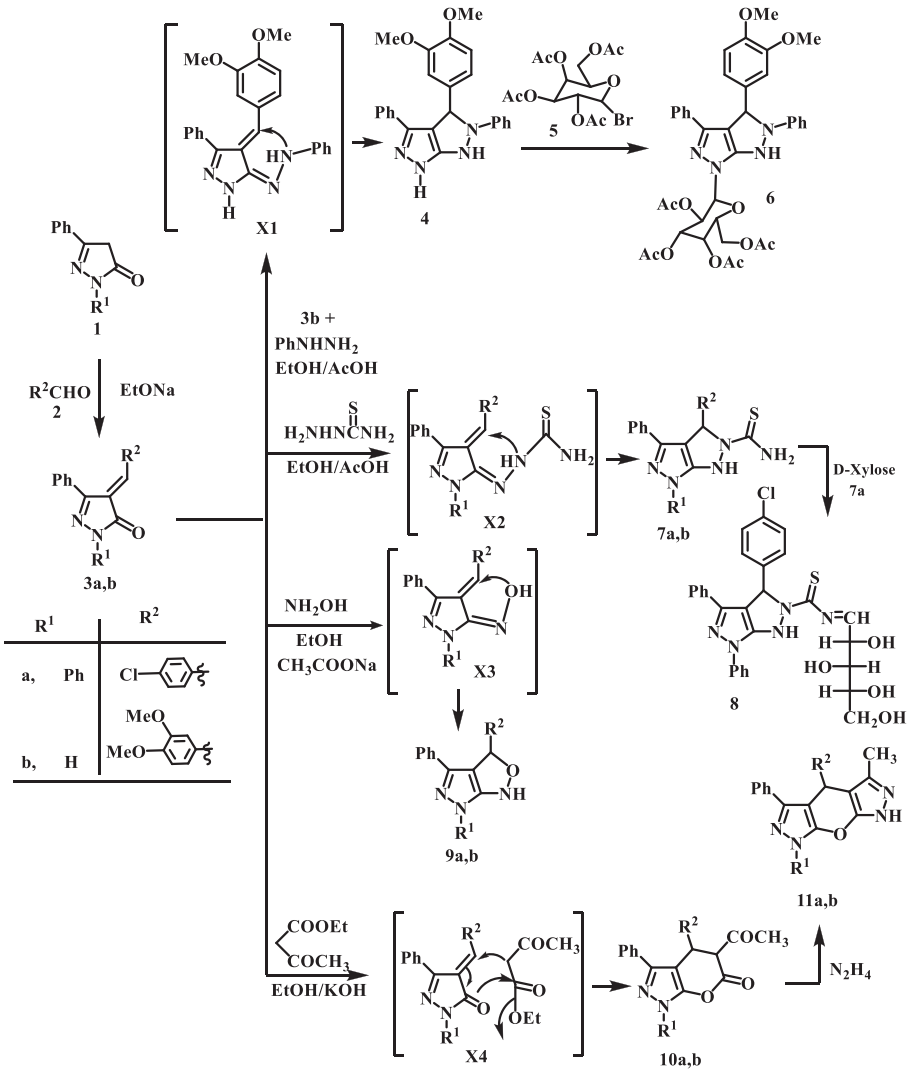
Chemistry. 4-(4-Chlorobenzylidene)-2,5-diphenyl-2,3-dihydro-3*H*-pyrazol-3-one **3a** [42] and 4-(3,4-dimethoxybenzylidene)-5-phenyl-2,3-dihydro-3*H*-pyrazol-

3-one **3b** were synthesized by Claisen–Schmidt condensation reaction of the pyrazolonone derivatives **1a** with 4-chlorobenzaldehyde **2a** or **1b** with 3,4-dimethoxybenzaldehyde **2b** in sodium ethoxide solution, respectively. The IR spectrum of **3b** showed strong absorption bands assigning the aromatic (C–H) and carbonyl group at ν_{max} 3045 and 1665 cm^{-1}, respectively. On the other hand, ^1H NMR spectrum revealed signals at 9.6, 3.86, and 3.84 ppm assignable for exchangeable NH and two methoxy groups beside the aromatic and (═C*H*) signals at their specific regions. The ^{13}C NMR spectrum of **3b** showed signals at δ 56.1 and 56.2 assignable for two methoxy groups of the phenyl ring (Ar–C, C-4, ═CH, and C-3) around 112.0–154.0 ppm and at 170 ppm for C═O of the pyrazolone moiety.

The reaction of **3b** with phenylhydrazine in ethanol and acetic acid solution yielded *N*-phenylpyrazolo[3,4-*c*] pyrazole derivative **4**. The structure of **4** was elucidated by different spectral and elemental analyses (cf. section). The IR spectrum of **4** revealed a characteristic band at 3150 cm^{-1} for NH groups. On the other hand, ^1H NMR spectrum of **4** showed three singlet signals at 5.1, 8.5, and 9.50 ppm for CH and two exchangeable NH groups of pyrazole ring. The ^{13}C NMR spectrum of **4** showed signals at δ 56.1 and 56.2 for two methoxy groups, 76 (C4) and 101 (C-8), and at 112–154 ppm assignable for (Ar–C, C-3, and C-7).

The *N*-glucoside derivative **6** was formed by the reaction of compound **4** with 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide **5** in acetone and aqueous KOH solution. The IR spectrum of **6** revealed two characteristic bands at 3157 and 1735 cm^{-1} attributed to NH and C═O groups. On the other hand, ^1H NMR spectrum of **6** shows four singlet signals (12 H) around δ 1.96–2.10 ppm assignable for four methyl groups of the

Scheme 1. Synthesis of compounds 4–11.



acetylated sugar beside the signals corresponding to the sugar protons in the region δ 3.67–5.72 ppm. The coupling constants of the anomeric protons $J_{1',2'}$ equal 9.6 Hz, indicating the *N*-glycosidic *β*-configuration, which agrees with the assigned structure. The ^{13}C NMR spectrum of the same compound revealed new signals assignable for (4 CH_3) and (4 C═O) groups in addition to signals for the sugar moiety and the aromatic systems (cf. Experimental part and Scheme 1).

Refluxing of **3a**,**b** with thiosemicarbazide in the presence of absolute EtOH and glacial AcOH afforded pyrazolo[3,4-*c*]pyrazole-2(1*H*)-carbothioamide derivatives **7a**,**b**, respectively. The IR spectra of **7a**,**b** showed bands for NH_2 and NH groups. The ^{1}H NMR spectra of the same compounds showed new signals of exchangeable NH_2 and NH groups at 6.25 and 9.8 ppm, respectively, beside signals of the aromatic protons at their specific regions. The ^{13}C NMR spectra of the same compounds revealed new signals assignable for C═S at 180 ppm in addition to signals of the aromatic and bis-pyrazolyl rings. Compound **7a** was reacted with D-xylose in ethanol and acetic acid solution to afford the sugar carbothioamide derivative **8**. The IR spectrum of **8** showed characteristic bands at 3350–3200 cm^{-1} for the OH groups of the xylose moiety and at 3152 cm^{-1} for NH group of the pyrazole ring. The ^{1}H NMR spectrum of **8** showed signals of exchangeable NH group at 9.90 ppm and one singlet signal at 7.52 ppm for (N═*CH*) of the condensed sugar beside the signals concerning the sugar moiety. The ^{13}C NMR spectrum revealed new signals assignable for the sugar moiety in addition to signal for C═S, aromatic, and bis-pyrazolyl rings (cf. Experimental section).

Refluxing **3a**,**b** with hydroxylamine hydrochloride in absolute EtOH and anhydrous sodium acetate afforded pyrazolo[3,4-*c*]isoxazole derivatives **9a**,**b**, respectively. The IR spectra of **9a**,**b** revealed strong bands of NH groups of oxazole rings at 3180 and 3170 cm^{-1}. ^{1}H NMR spectra of compound **9a** showed one singlet signal of exchangeable NH group at 11.20 ppm of the oxazole ring beside the other signals in their expected positions, while the ^{1}H NMR spectrum of **9b** showed two NH signals at 6.59 and 11.20 ppm. The ^{13}C NMR spectra of **9a**,**b** showed new signals assignable for the new isoxazole moiety beside the other signals for aromatic and pyrazole rings (cf. Experimental section).

The reactions of **3a**,**b** with phenylhydrazine, thiosemicarbazide, or hydroxylamine presumably take place via the attack of the –NH_2 on the carbonyl carbon in pyrazolones followed by elimination of water to afford the condensation intermediates X1–X3 (shown in Scheme 1), which then undergo cyclization by addition of the NH or OH to the C═C of the chalcone moiety.

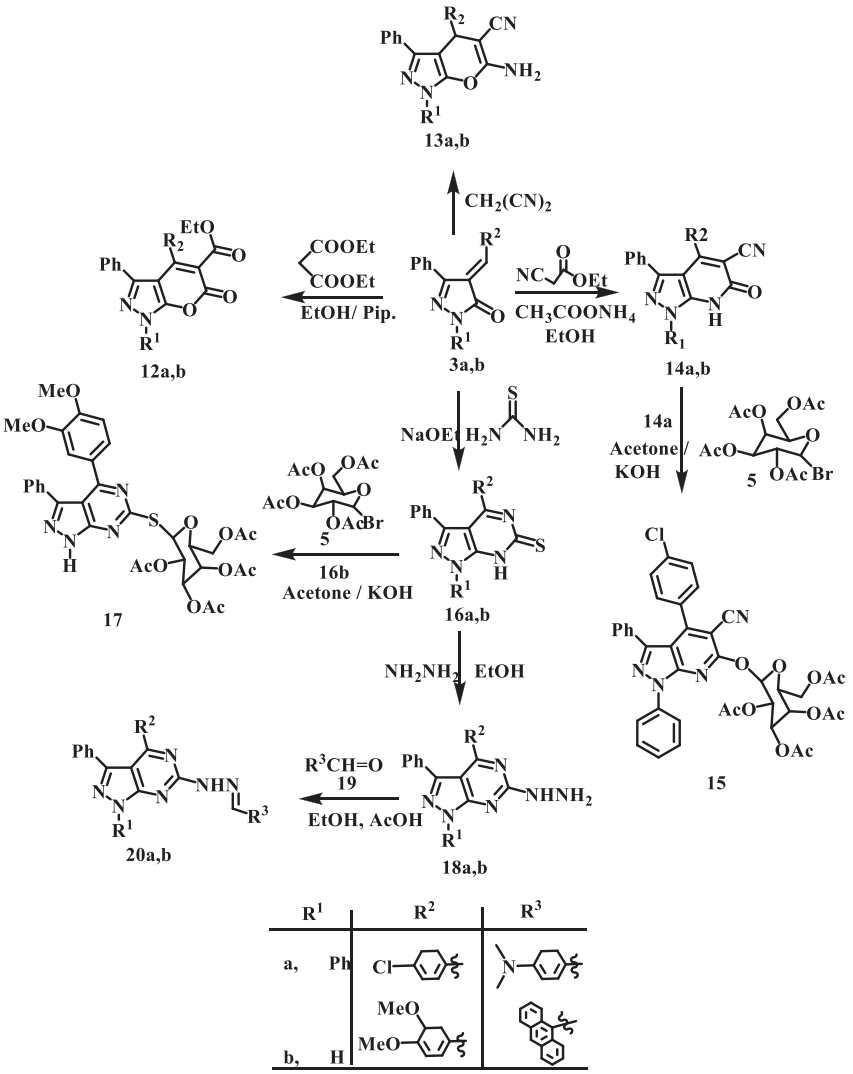
Furthermore, refluxing **3a**,**b** with ethyl acetoacetate in the presence of KOH and ethanol gave 3-acetylpyrano[2,3-*c*]pyrazolone derivatives **10a**,**b**, respectively. IR spectra of **10a**,**b** revealed two strong bands at 1670 and 1600 cm^{-1} of the two carbonyl groups of the acetylpyranone rings. On the other hand, the ^{1}H NMR spectra of compounds **10a**,**b** showed one singlet signal of the acetyl methyl group at 2.31 ppm and two doublets at 3.4 and 4.4 ppm for two CH groups concerning the pyranone ring moiety. The ^{13}C NMR spectrum of **10a** revealed signals of one CH_3, 2 (CH), and 2 (C═O) groups at 28.1, 40.5, 62.5, 165.6, and 200.2 ppm in addition to signals for pyrano-pyrazole moiety in their specific positions.

3-Methyl pyrazolo[4,3-*f*]indazole derivatives **11a**,**b** were prepared by the reaction of **10a**,**b** with hydrazine hydrate in absolute EtOH. The IR spectra of **11a**,**b** revealed the NH band of new pyrazole ring at 3160 cm^{-1}. On the other hand, ^{1}H NMR spectra of compounds **11a**,**b** showed two singlet signals of exchangeable NH of the pyrazole and CH of the pyranone rings at 10.0 and 4.7 ppm in **11a**, while in **11b**, ^{1}H NMR spectrum showed two NH signals at 10 and 12.57 ppm beside the CH of the pyranone ring at 4.7 ppm. The ^{13}C NMR spectrum of **11a** revealed signals of one CH_3 and CH groups at 28.1 and 40.0 ppm in addition to signals for bis-pyrazolopyran moiety in their specific positions (cf. Experimental section and Scheme 1).

The reaction of **3a**,**b** with diethylmalonate in ethanol/piperidine solution yielded 6-oxo-pyrano[2,3-*c*] pyrazole-5-carboxylate derivatives **12a**,**b**, respectively. The IR spectra of **12a**,**b** revealed two strong bands of two carbonyl groups, one for the ester group and the other for the carbonyl of the pyranone ring at 1735 and 1550 cm^{-1}, respectively. The ^{1}H NMR spectra of compounds **12a**,**b** showed signals at δ 1.26 (t) for one CH_3 group and at 4.20 (q) for CH_2 group. The ^{13}C NMR spectra of **12a**,**b** revealed signals of CH_3 group and one CH_2 at 15.0 and 61 ppm beside the signals for pyrano-pyrazole moiety in their specific positions (cf. Experimental section and Scheme 2).

Refluxing **3a**,**b** with malononitrile in absolute ethanol and few drops of piperidine gave the 6-aminopyrano[2,3-*c*]pyrazole-5-carbonitrile derivatives **13a**,**b**, respectively. The structures of compounds **13a**,**b** were inferred by their analytical and spectral data, which are in full agreement with their proposed structures. The IR spectra of **13a**,**b** revealed two bands at ν_{max} 3310 and 2230 cm^{-1} assignable for NH_2 and CN groups. On the other hand, ^{1}H NMR spectra of the same compounds showed a signal at δ 6.74 attributed to exchangeable NH_2. The ^{13}C NMR spectra of **13a** and **13b** revealed a signal of CN group at 115 ppm beside signals of the pyrano-pyrazole moiety in their specific positions.

Scheme 2. Synthesis of compounds 12–20.



The chalcone derivatives **3a**,**b** were also reacted with ethyl cyanoacetate in ethanol in presence of ammonium acetate to afford the pyrazolo[3,4-*b*]pyridine-5-carbonitrile derivatives **14a**,**b**, respectively. The IR spectra of **14a**,**b** revealed bands at ν_{max} 3170, 2220, and 1660 cm^{-1} for NH, CN, and C═O groups, respectively. ^1H NMR spectra of **14a**,**b** showed a signal at 11.10 for exchangeable NH proton of the pyridone ring in **14a** and two singlet signals at 11.50 and 13.10 ppm for two NH groups in **14b**. The ^{13}C NMR spectrum of **14a**,**b** revealed signals of CN and C═O groups at 115.0 and 163.0 ppm beside the other signals of aromatic and pyrazolopyrimidinyl moieties.

The reaction of the chalcones **3a**,**b** with the active methylene esters or malononitrile (Scheme 2) presumably takes place via the same mechanism shown in Scheme 1 (X4), involving a Michael addition of the active methylene to the C═C of the chalcone, enolization of the carbonyl group to –OH followed by elimination of ethanol from the esters, or addition of the –OH to a cyano group of malononitrile to afford pyrano-pyrazoles. The presence of ammonium acetate transforms the pyran ring into a pyridine ring.

The reaction of **14a** with 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide **5** gave the acetylated *O*-glucoside derivative **15**. The ^1H NMR spectrum of **15** showed the appearance of four singlet signals (12 H) at δ 1.94–2.16 ppm assignable for the four methyl groups beside the signals corresponding to the sugar protons in the region δ 3.48–5.20 ppm. The coupling constants of the anomeric protons $J_{1',2'}$ equal 10.0 Hz, indicating the *O*-glycosidic *β*-configuration, which agreed with the assigned structure. The ^{13}C NMR spectrum of **15** revealed signals at δ 19.32–23.05 ppm for 4 CH_3 and at

167.0–170.0 ppm assignable for (4 C═O) in addition to the signals for the sugar and the aromatic systems (cf. Experimental part and Scheme 2).

Compounds **3a**,**b** were reacted with thiourea in KOH solution, affording the pyrazolopyrimidine derivatives **16a**,**b**, respectively. The IR spectrum of **16b** revealed characteristic bands at ν_{max} 3200 and 3183 cm^{-1} attributed to two NH groups. The ^1H NMR spectrum of **16b** showed two singlet signals for NH protons at 7.0 and 12.66 ppm, respectively. The ^{13}C NMR spectra of **16b** showed the presence of C═S group at 180.7 ppm.

The acetylated thioglycoside derivative **17** was obtained by the reaction of **16b** with 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide **5** in acetone and aqueous KOH solution. The ^1H NMR spectrum of **17** showed the appearance of four singlet signals (12 H) at δ 2.01–2.06 ppm assignable for four methyl groups beside the signals corresponding to the sugar protons in the region δ 3.67–5.75 ppm. The coupling constant of the anomeric proton $J_{1',2'}$ equals 9.2 Hz, indicating the *S*-glycosidic *β*-configuration, which agreed well with the assigned structure. The ^{13}C NMR spectrum of **17** provided also a confirmation of *S*-glycosidic *β*-configuration of the cyclic sugar.

On the other hand, refluxing **16a**,**b** with hydrazine hydrate in absolute EtOH yielded the hydrazinyl derivatives **18a**,**b**, respectively. The IR spectra of **18a**,**b** showed two bands at ν_{max} 3304–3162 cm^{-1} for NH_2 and NH groups. The ^1H NMR spectra of **18a** exhibited two D_2O exchangeable singlet signals at δ 5.91 and 9.1 ppm assigned to the NH_2 and NH groups, while **18b** has two NH signals at 8.10 and 11.10 ppm beside the NH_2 signal. The ^{13}C NMR spectrum of **18a** revealed the signals of pyrazolopyrimidine at 105.1–164.6 ppm (cf. Experimental section and Scheme 2).

When compounds **18a** and **18b** were refluxed with 4-*N*,*N*-dimethylamino benzaldehyde **19a** and/or anthracene-9-aldehyde **19b**, they afforded the Schiff bases **20a**,**b**, respectively. The IR spectra of **20a**,**b** revealed bands around ν_{max} 3180–3150 cm^{-1} attributed to NH. The ^1H NMR spectra of **20a** showed the disappearance of the NH_2 singlet signal and the presence of the NH singlet at 9.10 ppm (exchangeable), and N═C*H* groups are enveloped in the aromatic region, while those of **20b** revealed two singlet signals (exchangeable) at 8.50 and 10.10 ppm assignable for the two NH protons, beside the other signals of the N═C*H* hidden in the aromatic multiplet. The ^{13}C NMR spectra of the two compounds provided a further confirmation of the structure (cf. Experimental section).

Antitumor activity. Nine of the synthesized compounds were examined *in vitro* for their antitumor activities against MCF-7 human breast carcinoma cell line using 3-(4,5-dimethyl-2-thiazolyl)-2,5-diphenyl-2*H*-tetrazolium bromide (MTT) assay. The percentage of the intact cells was measured and compared with that of the control and positive control doxorubicin.

The obtained results showed that all compounds showed dose-dependent anticancer activities.

The IC_{50} values are shown in Table 1.

From the results obtained in Table 1, we concluded that four compounds (**7a**, **8**, **18a**, and **20a**) showed anticancer IC_{50} values less than those of the positive control; this means that these four compounds, compared with doxorubicin, are good anticancer agents. Two compounds (**17**, **20b**) showed comparable anticancer activities to those of the positive control. The rest of the compounds (**9b**, **13a**, and **13b**) showed less anticancer activities than those of the positive control.

EXPERIMENTAL

Chemistry. All melting points were measured using a Reichert Thermovar apparatus (Reichert Technologies, Depew, NY) and are uncorrected. Yields listed are of isolated compounds. The IR spectra were recorded on a PerkinElmer model 1720 FTIR spectrometer (Perkin-Elmer, Waltham, MA) for KBr disc. Routine NMR measurements were made on a Bruker AC-300 or DPX-300 (Brucker, Elk Grove Village, IL) spectrometer at 300 and 75 MHz respectively. Chemical shifts were reported in δ scale (ppm) relative to tetramethylsilane as a reference standard, and the coupling constants *J* values are given in Hz. The progress of the reactions was monitored by thin-layer chromatography using aluminum silica gel plates 60 F245. Spectral measurements and elemental analyses were performed at the Micro Analytical Center at the Faculty of Science, Cairo University, Cairo, Egypt. Compounds **3a** and **16a** were prepared according to literature method [33]: Compound **3a**: mp 212–213°C (Lit. mp 215–217°C); **16a**: mp 130–132°C (Lit. mp 136–138°C) [42]. Antitumor activity was

Table 1

The anticancer IC_{50} values of the eight compounds using MTT assay against the human breast cancer cells.

Compound	MCF-7, IC_{50} (μ*M*)
7a	10.7
8	15.4
9b	27.9
13a	23.8
13b	24.3
17	19.2
18a	14.4
20a	18.5
20b	21.5
DOXO	18.6

evaluated at the Laboratory of Microbiology and Biotechnology at the National Research Center, Giza, Egypt.

4-(3,4-Dimethoxybenzylidene)-5-phenyl-2,4-dihydro-3H-pyrazol-3-one 3b. A mixture of compound **1b** (0.01 mol) and 3,4-dimethoxybenzaldehyde (0.01 mol) in sodium ethoxide solution [prepared from sodium metal (0.23 g, 10 mmol) and 50 mL of absolute ethanol] was refluxed for 10 h, left to cool, poured on crushed ice, and then neutralized with diluted HCl. The precipitate that formed was dried and recrystallized from ethyl acetate to give compound **3b** as a brown powder; yield (75%), mp 175–176°C; IR (KBr cm^{-1}) ν_{max}: 3045 (CH), 1665 (C═O); ^{1}H NMR (DMSO-d_6): 3.84 (s, 3H, CH_3), 3.86 (s, 3H, CH_3), 6.6–6.72 (m, 5H, Ar–H), 7.12 (d, J = 7.2 Hz, 1H, Ar–H), 7.36 (d, J = 7.2 Hz, 1H, Ar–H), 7.39–8.04 (m, 2H, Ar–H, and ═C*H*), 9.6 (s, 1H, NH exchangeable) ppm; ^{13}C NMR (DMSO-d_6): δ 56.1, 56.2 ($2CH_3$), [112.0–154.0 (Ar–C, C-4, ═CH, C-3)], 170 (C═O). *Anal*. Calcd. for $C_{18}H_{16}N_2O_3$ (308.34): C, 70.12; H, 5.23; N, 9.09. Found: C, 70.05; H, 5.27; N, 9.0.

3-(3,4-Dimethoxyphenyl)-2,4-diphenyl-1,2,3,6-tetrahydropyrazolo[3,4-c]pyrazole 4. Compound **3b** (0.01 mol) was refluxed with phenylhydrazine (0.01 mol) in dry ethanol (20 mL) and glacial acetic acid at 80°C for 8 h. The solvent was evaporated under reduced pressure. The formed precipitate was recrystallized from ethanol to produce compound **4** as a black powder; yield (55%), mp 134–136°C; IR (KBr cm^{-1}) ν_{max}: 3150 (NH), 1590 (C═N); ^{1}H NMR (DMSO-d_6): 3.84, 3.86 (2s, 6H, $2CH_3$), 5.10 (s, 1H, CH pyrazole), 6.6–6.72 (m, 5H, Ar–H), 7.12 (d, J = 7.2 Hz, 1H, Ar–H), 7.36 (d, J = 7.2 Hz, 1H, Ar–H), 7.39–7.6 (m, 6H, Ar–H), 8.50 (s, 1H, NH exchangeable), 9.50 (s, 1H, NH exchangeable) ppm; ^{13}C NMR (DMSO-d_6): δ 56.1, 56.2 ($2CH_3$), 76 (C4), 101 (C-8), [112–154 (Ar–C, C-3, C-7)]. *Anal*. Calcd. for $C_{24}H_{22}N_4O$ (398.47): C, 72.34; H, 5.57; N, 14.06. Found: C, 72.22; H, 5.60; N, 14.04.

2-[(2′,3′,4′,6′-Tetra-O-acetyl-β-D-glucopyranosyl)-6-(4-(3,4-dimethoxyphenyl)-3,5-diphenyl-5,6-dihydropyrazolo[3,4-c]pyrazole 6. 2,3,4,6-Tetra-*O*-acetyl-α-D-glucopyranosyl bromide **5** (5 mmol) was dissolved in acetone (20 mL) and added to thione **4** (5 mmol) in aqueous KOH solution (0.28 g, 5 mmol, 2 mL). The mixture was stirred at room temperature for 8 h. Then, the solvent was evaporated under reduced pressure at 40°C, and the residue was washed with water to remove the formed potassium bromide. The precipitate formed was dried and recrystallized from ethanol to yield compound **6** as dark brown powder; yield (60%), mp 104–106°C; IR (KBr cm^{-1}) ν_{max}: 3157 (NH), 1735 (C═O), 1593 (C═N); ^{1}H NMR (DMSO-d_6): δ 1.96–2.1 (4s, 12H, 4 CH_3CO), 3.60 (m, 2H, 6′,6″-H), 3.84, 3.86 (2s, 6H, $2CH_3$), 4.10–4.35 (m, 2H, 5′-H, 4′H), 5.10 (s, 1H, CH pyrazole), 5.0–5.13 (m, 2H, 2′-H, 3′H), 5.72 (d, $J_{1',2'}$ = 9.6 Hz, 1H, H-1′), 6.6–6.72 (m, 5H, Ar–H), 7.12 (d, J = 7.2 Hz, 1H, Ar–H), 7.36 (d, J = 7.2 Hz, 1H, Ar–H), 7.39–7.6 (m, 6H, Ar–H), 8.50 (s, 1H, NH exchangeable) ppm; ^{13}C NMR (DMSO-d_6): δ 19.32, 19.50, 20.18, 23.05, 56.1, 56.2 (6 CH_3), 62.88 (C-6′), 64.37 (C-4′), 68.65 (C-3′), 70.39 (C-2′), 72.82 (C-5′), 76 (C4), 95.0 (C-1′), 101.6 (C-8), [111.9–154.6 (Ar–C, C-3 and C-7)], 168.0–170.0 (4 C═O) ppm. *Anal*. Calcd. for $C_{38}H_{40}N_4O_{11}$ (728.76): C, 62.63; H, 5.53; N, 7.69. Found: C, 62.52; H, 5.60; N, 7.74.

General procedure for synthesis of compounds 7a,b. A solution of the chalcone **3a** or **b** (0.01 mol) and thiosemicarbazide (0.01 mol) in ethanol (10 mL) and glacial acetic acid (2 mL) was refluxed for 5 h, the reaction mixture was poured on crushed ice and was kept overnight at room temperature, and the solid that formed was filtered off, washed with water and dried, and then recrystallized from methanol to form compounds **7a**,**b**.

3-(4-Chlorophenyl)-4,6-diphenyl-3,6-dihydropyrazolo[3,4-c]pyrazole-2(1H)-carbothioamide 7a. Yellow powder; mp 165–167°C; IR (KBr cm^{-1}) ν_{max}: 3304–3162 (NH_2 and NH), 1619 (C═N); ^{1}H NMR (DMSO-d_6): δ 5.2 (s, 1H, CH pyrazole), 6.20 (s, 1H, NH exchangeable), 7.25 (m, 1H, Ar–H), 7.44–7.86 (m, 9H, Ar–H), 7.89 (d, J = 6.8 Hz, 2H, Ar–H), 7.99 (d, J = 6.8 Hz, 2H, Ar–H), 9.9 (s, 2H, NH_2 exchangeable) ppm; ^{13}C NMR (DMSO-d_6): δ 76 (C4), 101 (C-8), [123–148 (Ar–C, C-3, C-7)], 180 (C═S). *Anal*. Calcd. for $C_{23}H_{18}ClN_5S$ (431.94): C, 63.96, H, 4.20, N, 16.21. Found: C, 64.0; H, 4.30; N, 16.30.

3-(3,4-Dimethoxyphenyl)-4-phenyl-3,6-dihydropyrazolo[3,4-c]pyrazole-2(1H)-carbothioamide 7b. Brown powder; yield (50%), mp 190–192°C; IR (KBr cm^{-1}) ν_{max}: 3310–3152 (NH_2 and NH), 1610 (C═N); ^{1}H NMR (DMSO-d_6): 3.84, 3.86 (2s, 6H, $2CH_3$), 5.30 (s, 1H, CH pyrazole), 6.25 (bs, 1H, NH), 7.05 (d, J = 7.2 Hz, 1H, Ar–H), 7.36 (d, J = 7.2 Hz, 1H, Ar–H), 7.39–8.04 (m, 6H, Ar–H), 9.56 (s, 2H, NH_2 exchangeable), 12.57 (s, 1H, NH exchangeable); ^{13}C NMR (DMSO-d_6): δ 56.1, 56.2 ($2CH_3$), 76 (C4), 101 (C-8), [112–154 (Ar–C, C-3, C-7)], 180 (C═S). *Anal*. Calcd. for $C_{19}H_{19}N_5O_2S$ (381.45): C, 59.83; H, 5.02; N, 18.36. Found: C, 59.90; H, 5.10; N, 18.34.

3-(4-Chlorophenyl)-4,6-diphenyl-N-(D-xylotetritolylidene)-3,6-dihydropyrazolo[3,4-c]pyrazole-2(1H)-carbothioamide 8. Compound **7a** (5 mmol) in ethanol (15 mL) was added to a well-stirred solution of D-xylose (5 mmol) in water (5 mL) and glacial acetic acid (1 mL). The mixture was heated under reflux for 3 h. The solvent was concentrated and left to cool. The formed precipitate was filtered off, washed with water, dried, and recrystallized from ethanol to afford compound **8** as a dark brown powder; yield (49%), mp 135–1137°C; IR (KBr cm^{-1}) ν_{max}: 3350–3200 (OH), 3152 (NH); ^{1}H NMR (DMSO-d_6): δ 3.39–3.59 (m, 2H, H-5′,5″), 3.60 (m, 1H, H-4′), 4.20 (m, 1H, H-3′), 4.40 (dd, J = 7.4 Hz, J = 7.8 Hz, 1H, H-2′), 4.56 (m, 1H,

OH), 4.84 (d, J = 6.4 Hz, 1H, OH), 5.2 (s, 1H, CH pyrazole), 5.60 (t, J = 4.6 Hz, 1H, OH), 5.72 (t, J = 4.6 Hz, 1H, OH), 7.25 (m, 1H, Ar–H), 7.52 (s, 1H, N=C*H*), 7.60–7.86 (m, 9H, Ar–H), 7.89 (d, J = 6.8 Hz, 2H, Ar–H), 7.99 (d, J = 6.8 Hz, 2H, Ar–H), 7.52 (d, 1H, $J_{1',2'}$ = 7.8 Hz, H-1′), 9.9 (s, 1H, NH exchangeable) ppm; ^{13}C NMR (DMSO-d_6): δ 62.22 (C-5′), 63.15 (C-4′), 69.32 (C-3′), 73.0 (CH), 74.56 (C-2′), 121.4–150.03 (pyrazole-C and Ar–C), 150.44 (C-1′), 178.0 (C=S) ppm. *Anal*. Calcd. for $C_{28}H_{26}ClN_5O_4S$ (564.06): C, 59.62; H, 4.65; N, 12.42. Found: C, 59.65; H, 4.50; N, 12.58.

General procedure for synthesis of compounds 9a,**b**. A mixture of **3a**,**b** (0.01 mol) and hydroxylamine hydrochloride (0.01 mol) in absolute ethanol (30 mL) and anhydrous sodium acetate (0.01 mol) was refluxed for 10 h, the mixture was poured on crushed ice, and the solid formed was filtered off, washed with water and dried, and then recrystallized from methanol to form compounds **9a**,**b**.

3-(4-Chlorophenyl)-4,6-diphenyl-3,6-dihydro-1H-pyrazolo[3,4-c]isoxazole 9a. Yellow powder; mp 165–167°C; IR (KBr cm^{-1}) ν_{max}: 3180 (NH); ^{1}H NMR (DMSO-d_6): δ 7.38 (m, 1H, Ar–H), 7.49–7.68 (m, 9H, Ar–H), 7.92 (d, J = 6.8 Hz, 2H, Ar–H), 7.95 (d, J = 6.8 Hz, 2H, Ar–H), 11.20 (s, 1H, NH exchangeable) ppm; ^{13}C NMR (DMSO-d_6): δ 87 (C4), 101 (C-8), [123–148 (Ar–C, C-3, C-7)]. *Anal*. Calcd. for $C_{22}H_{16}ClN_3O$ (373.84): C, 70.68; H, 4.31; N, 11.24. Found: C, 70.70; H, 4.30; N, 11.15.

3-(3,4-Dimethoxyphenyl)-4-phenyl-3,6-dihydro-1H-pyrazolo[3,4-c]isoxazole 9b. Bale brown powder; yield (60%), mp 185–187°C; IR (KBr cm^{-1}) ν_{max}: 3170 (NH); ^{1}H NMR (DMSO-d_6): 3.84, 3.86 (2s, 6H, 2CH$_3$), 5.90 (s, 1H, CH pyrazole), 7.05 (d, J = 7.2 Hz, 1H, Ar–H), 7.36 (d, J = 7.2 Hz, 1H, Ar–H), 7.39–8.04 (m, 6H, Ar–H), 6.59 (s, 1H, NH exchangeable), 11.20 (s, 1H, NH exchangeable); ^{13}C NMR (DMSO-d_6): δ 56.1, 56.2 (2CH$_3$), 87 (C4), 101 (C-8), [112–154 (Ar–C, C-3, C-7)]. *Anal*. Calcd. for $C_{18}H_{17}N_3O_3$ (323.35): C, 66.86; H, 5.30; N, 13.00. Found: C, 66.90; H, 5.40; N, 13.04.

General procedure for synthesis of compounds 10a,**b**. A solution of **3a**,**b** (0.01 mol), ethyl acetoacetate (0.01 mol), and ammonium acetate (0.01 mol) in absolute ethanol (15 mL) containing aqueous KOH solution (1 mL, 10%) was refluxed for 2 h and left overnight at room temperature. The precipitate formed was filtered off and recrystallized from ethyl acetate to produce compounds **10a**,**b**.

5-Acetyl-4-(4-chlorophenyl)-1,3-diphenyl-4,5-dihydropyrano[2,3-c]pyrazol-6(1H)-one 10a. Yellow powder; mp 120–122°C; ^{1}H NMR (DMSO-d_6): IR (KBr cm^{-1}) ν_{max}: 1670, 1600 (2C=O); δ 2.31 (s, 3H, CH$_3$), 3.4, 4.4 (2d, 2H, 2CH), 7.38 (m, 1H, Ar–H), 7.49–7.68 (m, 9H, Ar–H), 7.89 (d, J = 6.8 Hz, 2H, Ar–H), 7.99 (d, J = 6.8 Hz, 2H, Ar–H) ppm; ^{13}C NMR (DMSO-d_6): δ 28.1, 56.1, 56.2 (3CH$_3$), 40.5, 62.5 (2CH), 112.7–156.5 (pyrazolopyranyl-C and Ar–C), 165.6, 200.2 (2C=O) ppm. *Anal*. Calcd. for $C_{26}H_{19}ClN_2O_3$ (442.90): C, 70.51; H, 4.32; N, 6.33. Found: C, 70.60; H, 4.30; N, 6.25.

5-Acetyl-4-(3,4-dimethoxyphenyl)-3-phenyl-4,5-dihydropyrano[2,3-c]pyrazol-6(1H)-one 10b. Black powder; yield (65%), mp 138–140°C; IR (KBr cm^{-1}) ν_{max}: 3154 (NH), 1670, 1600 (2C=O); ^{1}H NMR (DMSO-d_6): δ 2.08 (s, 3H, CH$_3$), 3.52, 4.1 (2d, 2H, 2CH pyranone), 3.84, 3.86 (2s, 6H, 2CH$_3$), 7.05 (d, J = 7.2 Hz, 1H, Ar–H), 7.36 (d, J = 7.2 Hz, 1H, Ar–H), 7.39–8.04 (m, 6H, Ar–H), 12.50 (s, 1H, NH exchangeable); ^{13}C NMR (DMSO-d_6): δ 28.1 (CH$_3$), 40.5, 62.5 (2CH), 112.7–145.5 (pyrazolopyranyl-C and Ar–C), 165.6, 200.2 (2C=O) ppm. *Anal*. Calcd. for $C_{22}H_{20}N_2O_5$ (392.41): C, 67.34; H, 5.14; N, 7.14. Found: C, 67.40; H, 5.20; N, 7.10.

General procedure for synthesis of compounds 11a,**b**. A mixture of compounds **10a**,**b** (0.01 mol) and hydrazine hydrate (0.015 mol) in ethanol (20 mL) was heated for 6 h. The product was allowed to cool at room temperature. The solvent was evaporated under vacuum. The formed precipitate was recrystallized from ethyl alcohol to produce compounds **11a**,**b**.

4-(4-Chlorophenyl)-5-methyl-1,3-diphenyl-1,4,7,8-tetrahydropyrazolo[4,3-f]indazole 11a. Grey powder; mp 163–165°C; IR (KBr cm^{-1}) ν_{max}: 3160 (NH); ^{1}H NMR (DMSO-d_6): δ 1.9 (s, 3H, CH$_3$), 4.46 (s, 1H, CH pyran), 7.2 (m, 1H, Ar–H), 7.49–7.88 (m, 9H, Ar–H), 7.92 (d, J = 6.8 Hz, 2H, Ar–H), 7.96 (d, J = 6.8 Hz, 2H, Ar–H), 10.0 (s, 1H, NH exchangeable) ppm; ^{13}C NMR (DMSO-d_6): δ 28.1 (CH$_3$), 41.0 (CH), [112.7–145.5 (bis-pyrazolo-pyran-C and Ar–C)] ppm. *Anal*. Calcd. for $C_{26}H_{19}ClN_4O$ (438.92): C, 71.15; H, 4.36; N, 12.77. Found: C, 71.0; H, 4.35; N, 12.80.

4-(3,4-Dimethoxyphenyl)-3-methyl-5-phenyl-4,7-dihydro-1H-pyrano[2,3-c:6,5-c′]dipyrazole 11b. Brown powder; yield (45%), mp 120–122°C; IR (KBr cm^{-1}) ν_{max}: 3200, 3160 (2NH); ^{1}H NMR (DMSO-d_6): δ 1.9 (s, 3H, CH$_3$), 4.7 (s, 1H, CH pyranone), 3.84, 3.86 (2s, 6H, 2CH$_3$), 7.05 (d, J = 7.2 Hz, 1H, Ar–H), 7.36 (d, J = 7.2 Hz, 1H, Ar–H), 7.39–8.04 (m, 6H, Ar–H), 10.0 (s, 1H, NH exchangeable), 12.57 (s, 1H, NH exchangeable); ^{13}C NMR (DMSO-d_6): δ 28.1, 56.1, 56.2 (3CH$_3$), 41.0 (CH), [112.7–156.5 (bis-pyrazolo-pyran-C and Ar–C)] ppm. *Anal*. Calcd. for $C_{22}H_{20}N_4O_3$ (388.43): C, 68.03; H, 5.19; N, 14.42. Found: C, 68.10; H, 5.20; N, 14.34.

General procedure for synthesis of compounds 12a,**b**. A solution of compounds **3a**,**b** (0.01 mol) and diethylmalonate (0.01 mol) in absolute ethanol (30 mL) and few drops of piperidine was refluxed for 6 h. The product was cooled at room temperature. Excess solvent was evaporated under vacuum. The precipitate was recrystallized from methanol to produce compounds **12a**,**b**.

Ethyl 4-(4-chlorophenyl)-6-oxo-1,3-diphenyl-1,6-dihydropyrano [2,3-c]pyrazole-5-carboxylate 12a. Brown powder; mp 120–122°C; IR (KBr cm^{-1}) ν_{max}: 1735, 1550 (2C═O); ^1H NMR (DMSO-d_6): δ 1.26 (t, J = 13.2 Hz, 3H, CH_3), 4.20 (q, J = 13.2 Hz, 2H, CH_2), δ 7.22–7.26 (m, 1H, Ar–H), 7.28–7.61 (m, 9H, Ar–H), 7.9 (d, J = 6.8 Hz, 2H, Ar–H), 8.10 (d, J = 6.8 Hz, 2H, Ar–H); ^{13}C NMR (DMSO-d_6): δ 15.0 (CH_3), 61.0 (CH_2), 112.0 (C-9), [118.5–153.0 (Ar–C, C-3, C-8, C-4, C-5)], 159, 163 (2C═O) ppm. *Anal*. Calcd. for $C_{27}H_{19}ClN_2O_4$ (470.91): C, 68.87; H, 4.07; N, 5.95. Found: C, 70.0; H, 4.05; N, 6.05.

Ethyl 4-(3,4-dimethoxyphenyl)-6-oxo-3-phenyl-1,6-dihydro pyrano[2,3-c]pyrazole-5-carboxylate 12b. Brown powder; yield (56%), mp 123–125°C; IR (KBr cm^{-1}) ν_{max}: 3170 (NH), 1730, 1665 (2C═O); ^1H NMR (DMSO-d_6): δ 1.26 (t, J = 13.2 Hz, 3H, CH_3), 3.84, 3.86 (2s, 6H, $2CH_3$), 4.20 (q, J = 13.2 Hz, 2H, CH_2), 7.05 (d, J = 7.2 Hz, 1H, Ar–H), 7.36 (d, J = 7.2 Hz, 1H, Ar–H), 7.39–8.04 (m, 6H, Ar–H), 13.10 (s, 1H, NH exchangeable) ppm; ^{13}C NMR (DMSO-d_6): δ 15.0, 56.1, 56.2 ($3CH_3$), 61.0 (CH_2), 105.0 (C-9), [108.5–153.0 (Ar–C, C-3, C-8, C-4, C-5)], 160, 163 (2C═O) ppm. *Anal*. Calcd. for $C_{23}H_{20}N_2O_6$ (362.39): C, 65.71; H, 4.80; N, 6.66. Found: C, 65.70; H, 4.92; N, 6.45.

General procedure for synthesis of compounds 13a,**b**. A mixture of **3a**,**b** (0.01 mol) and malononitrile (0.01 mol) in absolute ethanol (30 mL) was refluxed for 4 h. The product was allowed to cool at room temperature. Excess ethanol was evaporated under vacuum. The precipitate was recrystallized from ethyl acetate to produce compounds **13a**,**b**.

6-Amino-4-(4-chlorophenyl)-6-oxo-1,3-diphenyl-1,6-dihydro pyrano[2,3-c]pyrazole-5-carbonitrile 13a. Black powder; mp 175–177°C; IR (KBr cm^{-1}) ν_{max}: 3310 (NH_2), 2300 (CN); ^1H NMR (DMSO-d_6): δ 6.74 (bs, 2H, NH_2 exchangeable), 7.24–7.26 (m, 1H, Ar–H), 7.28–7.61 (m, 9H, Ar–H), 7.9 (d, J = 6.8 Hz, 2H, Ar–H), 8.10 (d, J = 6.8 Hz, 2H, Ar–H); ^{13}C NMR (DMSO-d_6): δ 25 (pyran-CH), 59, 115.0 (CN), [119.5–173.0 (Ar–C, C-3, C-8, C-4, C-6)]. *Anal*. Calcd. for $C_{25}H_{17}ClN_4O$ (424.89): C, 70.67; H, 4.03; N, 13.19. Found: C, 70.70; H, 4.05; N, 13.25.

6-Amino-4-(3,4-dimethoxyphenyl)-6-oxo-1,3-diphenyl-1,6-dihydropyrano[2,3-c]pyrazole-5-carbonitrile 13b. Black powder; yield (66%), mp 135–137°C; IR (KBr cm^{-1}) ν_{max}: 3310–3150 (NH_2 and NH), 2300 (CN); ^1H NMR (DMSO-d_6): δ 3.84, 3.86 (2s, 6H, $2CH_3$), 6.74 (bs, 2H, NH_2 exchangeable), 7.05 (d, J = 7.2 Hz, 1H, Ar–H), 7.36 (d, J = 7.3 Hz, 1H, Ar–H), 7.39–8.04 (m, 6H, Ar–H), 13.10 (s, 1H, NH exchangeable) ppm; ^{13}C NMR (DMSO-d_6): δ 25 (pyran-CH), 56.1, 56.2 ($2CH_3$), 63, 115.0 (CN), [119.5–173.0 (Ar–C, C-3, C-8, C-4, C-6)]. *Anal*. Calcd. for $C_{21}H_{18}N_4O_3$ (374.40): C, 67.37; H, 4.85; N, 14.96. Found: C, 67.10; H, 4.95; N, 15.0.

General procedure for synthesis of compounds 14a,**b**. A solution of compound **3a** or **3b** (0.01 mol) and ethyl cyanoacetate (0.01 mol) and ammonium acetate (10 mmol) in ethanol (30 mL) was refluxed for 9 h and allowed to cool at room temperature. The precipitate formed after evaporation of excess solvent was recrystallized from ethanol to produce compounds **14a**,**b**.

4-(4-Chlorophenyl)-6-oxo-1,3-diphenyl-6,7-dihydro-1H-pyrazolo [3,4-d]pyridine-5-carbonitrile 14a. Yellow powder; yield (55%), mp 240–242°C; IR (KBr cm^{-1}) ν_{max}: 3170 (NH), 2320 (CN), 1660 (C═O); ^1H NMR (DMSO-d_6): δ 7.38 (m, 1H, Ar–H), 7.49–7.68 (m, 9H, Ar–H), 7.92 (d, J = 6.8 Hz, 2H, Ar–H), 7.95 (d, J = 6.8 Hz, 2H, Ar–H), 11.10 (s, 1H, NH exchangeable) ppm; ^{13}C NMR (DMSO-d_6): δ 95 (pyridine-CH), 100 (C-9), 115.0 (CN), [118.0–148.0 (Ar–C, C-3, C-8, C-4)], 163 (C═O) ppm. *Anal*. Calcd. for $C_{25}H_{15}ClN_4O$ (422.87): C, 71.01; H, 3.58; N, 13.25. Found: C, 70.90; H, 3.50; N, 13.15.

4-(3,4-Dimethoxyphenyl)-6-oxo-3-phenyl-6,7-dihydro-1H-pyrazolo[3,4-b]pyridine-5-carbonitrile 14b. Yellow powder; yield (55%), mp 138–140°C; IR (KBr cm^{-1}) ν_{max}: 3200, 3170 (2NH), 2300 (CN), 1660 (C═O); ^1H NMR (DMSO-d_6): δ 3.84, 3.86 (2s, 6H, $2CH_3$), 7.05 (d, J = 7.2 Hz, 1H, Ar–H), 7.36 (d, J = 7.2 Hz, 1H, Ar–H), 7.37–7.64 (m, 6H, Ar–H), 11.50 (s, 1H, NH exchangeable), 13.10 (s, 1H, NH exchangeable); ^{13}C NMR (DMSO-d_6): δ 56.1, 56.2 ($2CH_3$), 95 (pyridine-CH), 100 (C-9), 115.0 (CN), [118.0–148.0 (Ar–C, C-3, C-8, C-4)], 163 (C═O) ppm. *Anal*. Calcd. for $C_{21}H_{16}N_4O_3$ (372.38): C, 67.73; H, 4.33; N, 15.05. Found: C, 67.80; H, 4.20; N, 15.10.

6-(4-(4-Chlorophenyl)-5-cyano-1,3-diphenyl-6-[(2′,3′,4′,6′-tetra-O-acetyl-β-D-glucopyranosyl)-1H-pyrazolo[3,4-d]pyridine 15. 2,3,4,6-Tetra-*O*-acetyl-α-D-glucopyranosyl bromide **5** (5 mmol) dissolved in acetone (20 mL) was added to a mixture of compound **14a** (5 mmol) and aqueous potassium hydroxide (0.28 g, 5 mmol, 2 mL). The reaction mixture was stirred at room temperature for 6 h. 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 to yield a mixture of compound **15**. Dark brown powder; yield (54%), mp 126–128°C; IR (KBr cm^{-1}) ν_{max}: 1735 (C═O), 1593 (C═N); ^1H NMR (DMSO-d_6): δ 1.94–2.16 (4s, 12H, 4 CH_3CO), 3.48 (m, 2H, 6′,6″-H), 3.8–3.88 (m, 2H, 5′-H, 4′H), 4.3–4.39 (m, 2H, 2′-H, 3′H), 5.2 (d, $J_{1',2'}$ = 10.0 Hz, 1H, H-1′), δ 7.22–7.26 (m, 1H, Ar–H), 7.28–7.61 (m, 9H, Ar–H), 7.9 (d, J = 6.8 Hz, 2H, Ar–H), 8.03 (d, J = 6.8 Hz, 2H, Ar–H); ^{13}C NMR (DMSO-d_6): δ 19.32, 19.50, 20.18, 23.05 (4 CH_3), 62.88 (C-6′), 64.37 (C-4′), 68.65 (C-3′), 70.39 (C-2′), 72.82 (C-5′), 88.95 (C-1′), 101.6 (C-9), [118.9–158.6 (Ar–C, C-3, C-4 and C-8)], 167.0–170.0 (4 C═O), 172.1

(C-6) ppm. *Anal*. Calcd. for $C_{39}H_{33}ClN_4O_{10}$ (753.16): C, 62.20; H, 4.42; N, 7.44. Found: C, 62.40; H, 4.40; N, 7.50.

4-(3,4-Dimethoxyphenyl)-3-phenyl-1H-pyrazolo[3,4-d]pyrimidin-6(7H)-thione 16b. Thiourea (0.01 mmol) was added to compound **3b** (0.01 mol) and dissolved in sodium ethoxide solution [prepared from sodium metal (0.23 g, 10 mmol) in 50 mL absolute ethanol]. The reaction mixture was refluxed for 12 h. The mixture was left to cool, poured on crushed ice, and neutralized with diluted hydrochloric acid. The precipitate was collected by filtration, dried, and recrystallized from ethanol to give compound **16b**. Yellow powder; yield (65%), mp 156–158°C; IR (KBr cm^{-1}) ν_{max}: 3200, 3183 (2NH); ^{1}H NMR (DMSO-d_6): δ 3.83, 3.86 (2s, 6H, $2CH_3$), 7.05 (d, J = 7.2 Hz, 1H, Ar–H), 7.36 (d, J = 7.2 Hz, 1H, Ar–H), 7.39–8.04 (m, 5H, Ar–H), 7.48 (s, 1H, Ar–H), 7.0 (s, 1H, NH exchangeable), 12.66 (s, 1H, NH exchangeable) ppm; ^{13}C NMR (DMSO-d_6): δ 56.1, 56.2 ($2CH_3$), [105.0–164.0 (Ar–C and pyrazolopyrmidinyl-C)], 180.7 (C═S) ppm. *Anal*. Calcd. for $C_{19}H_{16}N_4O_2S$ (364.42): C, 62.62; H, 4.43; N, 15.37. Found: C, 62.55; H, 4.57; N, 15.49.

4-(3,4-Dimethoxyphenyl)-3-phenyl-1-phenyl-6-[(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)thio]-1H-pyrazolo[3,4-d]pyrimidine 17. 2,3,4,6-Tetra-*O*-acetyl-α-D-glucopyranosyl bromide **5** (5 mmol) was dissolved in acetone (20 mL) and added to thione **16b** (5 mmol) in aqueous KOH solution (0.28 g, 5 mmol, 2 mL). The reaction mixture was stirred at room temperature for 8 h. 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 obtained product was dried and recrystallized from ethanol to yield compound **17**. Dark brown powder; yield (45%), mp 115–117°C; IR (KBr cm^{-1}) ν_{max}: 3173 (NH), 1730 (CO); ^{1}H NMR (DMSO-d_6): δ 2.01–2.06 (4s, 12H, 4 CH_3CO), 3.83 and 3.86 (2s, 6H, 2OCH_3), 3.67 (m, 2H, 6′,6″-H), 4.10–4.25 (m, 2H, 5′-H, 4′H), 5.05–5.10 (m, 2H, 2′-H, 3′H), 5.75 (d, $J_{1',2'}$ = 9.2 Hz, 1H, H-1′), 7.05 (d, 1H, J = 7.2 Hz, Ar–H), 7.36 (d, 1H, J = 7.2 Hz, Ar–H), 7.39–8.04 (m, 6H, Ar–H), 11.1 (s, 1H, NH exchangeable) ppm; ^{13}C NMR (DMSO-d_6): δ 19.32, 19.50, 20.18, 20.27, 56.10, 56.20 (6 CH_3), 62.88 (C-6′), 64.37 (C-4′), 68.65 (C-3′), 70.39 (C-2′), 72.82 (C-5′), 88.95 (C-1′), 105.0 (C-9), [108.5–163 (Ar–C, C-3, C-4, C-8)], 167.0–170.0 (4 C═O), 172.2 (C-6) ppm. *Anal*. Calcd. for $C_{33}H_{34}N_4O_{11}S$ (694.71): C, 57.05; H, 4.93; N, 8.06. Found: C, 57.25; H, 4.90; N, 8.0.

General procedure for synthesis of compounds 18a,**b**. A solution of compounds **16a**,**b** (0.01 mol) and hydrazine hydrate (0.15 mol) in absolute ethanol (30 mL) was refluxed for 6 h. The mixture was allowed to cool at room temperature. The solvent was evaporated under vacuum. The formed precipitate was recrystallized from ethyl acetate to produce compounds **18a**,**b**.

4-(4-Chlorophenyl)-6-hydrazinyl-1,3-diphenyl-1H-pyrazolo[3,4-d]pyrimidine 18a. Brown powder; yield (55%), mp 126–128°C; IR (KBr cm^{-1}) ν_{max}: 3304–3162 (NH_2 and NH), 1619 (C═N); ^{1}H NMR (DMSO-d_6): δ 5.91 (bs, 2H, NH_2 exchangeable), δ 7.24–7.26 (m, 1H, Ar–H), 7.28–7.61 (m, 9H, Ar–H), 7.9 (d, J = 6.8 Hz, 2H, Ar–H), 8.10 (d, J = 6.8 Hz, 2H, Ar–H); 9.10 (s, 1H, NH exchangeable) ppm; ^{13}C NMR (DMSO-d_6): δ 105.0 (C-9), [123.9–164.6 (Ar–C, C-3, C-8, C-6, and C-4)] ppm. *Anal*. Calcd. for $C_{23}H_{17}ClN_6$ (412.88): C, 66.91; H, 4.15; N, 20.36. Found: C, 66.90; H, 4.05; N, 20.35.

4-(3,4-Dimethoxyphenyl)-6-hydrazinyl-3-phenyl-1H-pyrazolo [3,4-d]pyrimidine 18b. Brown powder; yield (70%), mp 115–116°C; IR (KBr cm^{-1}) ν_{max}: 3300–3160 (NH_2 and NH), 1619 (C═N); ^{1}H NMR (DMSO-d_6): δ 3.84, 3.86 (2s, 6H, $2CH_3$), 6.1 (bs, 2H, NH_2 exchangeable), 7.05 (d, 1H, J = 7.2 Hz, Ar–H), 7.36 (d, 1H, J = 7.2 Hz, Ar–H), 7.39–8.04 (m, 6H, Ar–H), 8.10 (s, 1H, NH exchangeable), 11.10 (s, 1H, NH exchangeable) ppm; ^{13}C NMR (DMSO-d_6): δ 56.1, 56.2 ($2CH_3$), 105.0 (C-9), [108.5–163.0 (Ar–C, C-3, C-8, C-4, C-6)]. *Anal*. Calcd. for $C_{19}H_{18}N_6O_2$ (362.39): C, 62.97; H, 5.01; N, 23.19. Found: C, 63.10; H, 5.02; N, 23.25.

General procedure for synthesis of compounds 20a,**b**. A solution of compounds **18a**,**b** (0.01 mol) and aromatic aldehydes as 4-*N*,*N*-dimethylamino benzaldehyde **19a** or anthracene-9-aldehyde **19b** in absolute ethanol (30 mL) and glacial acetic acid (one to two drops) was refluxed for 10 h. The solid product was allowed to cool at room temperature. The solvent was evaporated under vacuum. The powder was recrystallized from ethyl alcohol to produce compounds **20a**,**b**.

4-(2-(4-(4-Chlorophenyl)-1,3-diphenyl-1H-pyrazolo[3,4-d] pyrimidin-6yl)hydrazono)methyl-N,N-dimethylaniline 20a. Grey powder; mp 160–162°C; IR (KBr cm^{-1}) ν_{max}: 3180–3150 (NH), 3050 (CH); ^{1}H NMR (DMSO-d_6): δ 2.99, 3.01 (2s, 6H, $2CH_3$), 7.1 (d, J = 6.6 Hz, 2H, Ar–H), 7.23 (s, 1H, N═C*H*), 7.28–7.61 (m, 10H, Ar–H, and N═C*H*), 7.74 (d, J = 6.6 Hz, 2H, Ar–H), 7.9 (d, J = 6.8 Hz, 2H, Ar–H), 8.10 (d, J = 6.8 Hz, 2H, Ar–H); 9.10 (s, 1H, NH exchangeable) ppm; ^{13}C NMR (DMSO-d_6): δ 40.1, 40.2 ($2CH_3$), 105.0 (C-9), [112.0–164.6 (Ar–C, N═CH, C-3, C-8, C-6, and C-4)] ppm. *Anal*. Calcd. for $C_{32}H_{26}ClN_7$ (544.06): C, 70.65; H, 4.82; N, 18.02. Found: C, 70.70; H, 4.95; N, 18.05.

6-(2-Anthracene-9-ylmethylene)hydrazinyl)-4-(3,4-dimethoxy phenyl)-3-phenyl-1H-pyrazolo[3,4-d]pyrimidine 20b. Dark brown powder; yield (50%), mp 150–152°C; IR (KBr cm^{-1}) ν_{max}: 3210, 3180 (2NH), 3052 (CH); ^{1}H NMR (DMSO-d_6): δ 3.84, 3.86 (2s, 6H, $2CH_3$), 7.07 (s, 1H, Ar–H), 7.25–7.40 (d, J = 6.8 Hz, 2H, Ar–H), 7.42–7.75 (m, 12H, Ar–H + CH methine), 7.90 (d, J = 6.8 Hz, 2H, Ar–H), 8.0 (s, 1H, Ar–H), 8.50 (s, 1H, NH exchangeable), 10.10 (s, 1H, NH exchangeable) ppm; ^{13}C NMR (DMSO-d_6): δ 56.26, 56.5 ($2CH_3$), 102.66 (C-9), [120.3–172.48 (Ar–C, N═CH, C-3, C-8, C-4, C-6)]. *Anal*. Calcd. for

$C_{34}H_{26}N_6O_2$ (550.62): C, 74.17; H, 4.76; N, 15.26. Found: C, 74.10; H, 4.80; N, 15.25.

***In vitro* anticancer activity.** The antitumor activity against the human breast cancer cells was assessed using the MTT assay [43–45]. This cancer cell line was purchased from ATCC (Rockville, MD, USA).

The cells were cultured in a 96-well sterile microplate (5×10^4 cells per well) at 37°C in Roswell Park Memorial Institute medium (RPMI-1640) supplemented with 10% heat-inactivated fetal bovine serum and 100 U/mL of both penicillin and streptomycin in a 5% CO_2-humidified atmosphere. After 24 h, the media were removed and a fresh serum-free medium (90 μL/well) was added together with 10 μL of a series of compounds or doxorubicin (positive control) concentrations in DMSO for 48 h. Then, media were removed, and MTT (40 μL of 2.5 mg/mL) was added to each well and incubated for 4 h; 200 μL of DMSO was added to solubilize the formazan dye crystals (purple color). With the use of a SpectraMax® Paradigm® Multi-Mode Microplate Reader, the absorbance was measured at 590 nm. Each experiment was repeated on three different days and conducted in triplicate. The relative cell cytotoxicity was measured according to the following equation:

$$\%\text{cytotoxicity} = (1 - \text{As}/\text{Ab})^* 100,$$

where As is the absorbance of each sample and Ab the absorbance of the blank. The probit analysis using the SPSS software program (version 20, SPSS Inc., Chicago, IL, USA) was used to determine each IC_{50}.

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