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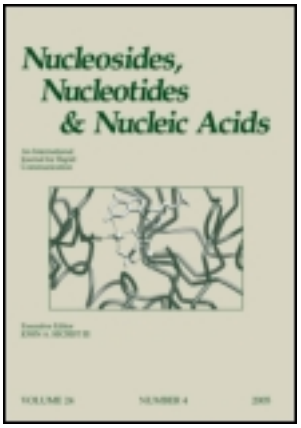

Nucleosides, Nucleotides and Nucleic Acids

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Synthesis and Antimicrobial Evaluation of Novel Pyrazolones and Pyrazolone Nucleosides

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SYNTHESIS AND ANTIMICROBIAL EVALUATION OF NOVEL PYRAZOLONES AND PYRAZOLONE NUCLEOSIDES

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□ *The synthesis of a novel series of 4-arylhydrazono-5-methyl-1,2-dihydropyrazol-3-ones* ***4a–h****, and their* N^2*-alkyl and acyclo, glucopyranosyl, and ribofuranosyl derivatives is described.* K_2CO_3 *catalyzed alkylation of* ***4a–h*** *with allyl bromide, propargyl bromide, 4-bromobutyl acetate, 2-acetoxyethoxymethyl bromide, and 2,3,4,6-tetra-*O*-acetyl-*α*-D-glucopyranosyl bromide proceeded selectively at the* N^2*-position of the pyrazolinone ring. Glycosylation of* ***4a*** *with 1,2,3,5-tetra-*O*-acetyl-*β*-D-ribofuranose under Vorbruggen glycosylation conditions gave the corresponding* N^2*-4-arylhydrazonopyrazolone ribofuranoside* ***9a*** *in good yield. Conventional deprotection of the acetyl protected nucleosides furnished the corresponding 4-arylhydrazonopyrazolone nucleosides in good yields. Selected numbers of the newly synthesized compounds were screened for antimicrobial activity. Compounds* ***4b***, ***12a***, *and* ***14d*** *showed moderate activities against* Aspergillus flavus, Penicillium sp., *and* Escherichia coli.

Keywords Pyrazolinone; pyrazolono nucleosides; acyclic nucleosides; N^2-alkyl pyrazolones; antimicrobial activity

INTRODUCTION

Structural modifications at the nucleobase moiety of nucleosides have resulted in a plethora of nucleosides with interesting chemical and biological properties.[1,2] For instance, ribavirin (**1**), a triazolyl ribonucleoside, has shown a wide range of activity against DNA and RNA viruses.[3]

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We thank Dr. Ashraf A. Sabry of the Microbiology Department, Faculty of Science, Zagazig University for determining the antimicrobial activity reported in the manuscript.
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The current standard care of hepatitis C virus (HCV) infection is based on the combination of ribavirin and pegylated interferon-α (PEG-INF)[4], or most recently, as a triple therapy (ribavirin/PEG-INF/protease inhibitor; telaprevir or boceprevir).[5] In another instance, bredinine (**2**) is an imidazolyl ribonucleoside antibiotic[6] with immunosuppressant,[7] antirheumatism,[8] and antitumor[9] activities. Pyrazolones have attracted considerable attention because of their interesting structural features and applications in diverse areas.[10] Pyrazolone derivatives are reported to have analgesic,[11] anti-inflammatory,[12] antiviral,[13] and antimicrobial activities.[14,15] Anchoring a 3-methyl-1-phenyl-2-pyrazolin-5-one moiety at the 5-position of 2′-deoxyuridine has been shown to produce anti-orthopox virus activity.[16] 4-Arylhydrazono-pyrazolones were disclosed to have inhibitory activities against glycogen synthase kinase-3 (GSK-3), Aurora-2 protein kinase, and cyclin-dependent kinase-2 (CDK-2) with the potential use for prevention and treatment of disorders such as diabetes and Alzheimer's disease.[17] 4-Hydrazonopyrazolones have an interesting structural feature, that the 4-arylhydrazino group most likely forms an internal hydrogen bond with the pyrazolone carbonyl forming a pseudobicyclic 6,5-ring system,[18] mimicking the shape-structure of a 1-substituted purine. N^1-3-fluorophenylinosine (**3**) and N^1-3-fluorophenylhypoxanthine have been reported to show interesting anti-Hantaan virus activity.[19] It is of interest to check whether nucleosides derived from 4-hydrazonopyrazolones **4a–h** would exert desirable biological properties. In continuation of our efforts to search for nucleosides with biological activities,[20] we wish to report on the synthesis of novel 4-arylhydrazono-3-methylpyrazolin-5-ones **4a–h**; their N^2–alkyl derivatives **5a–d**; **6a,c,f**; and N^2-nucleosides derivatives **8b,c,g**; **10**; **12a,b,f**; **14b,e,g,h** and the antimicrobial evaluation of selected number of newly synthesized compounds (Figure 1).

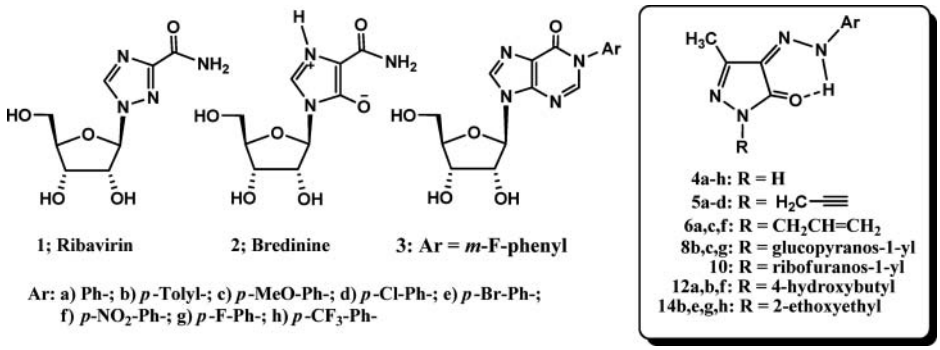

FIGURE 1 Biologically active nucleobase modified nucleosides.

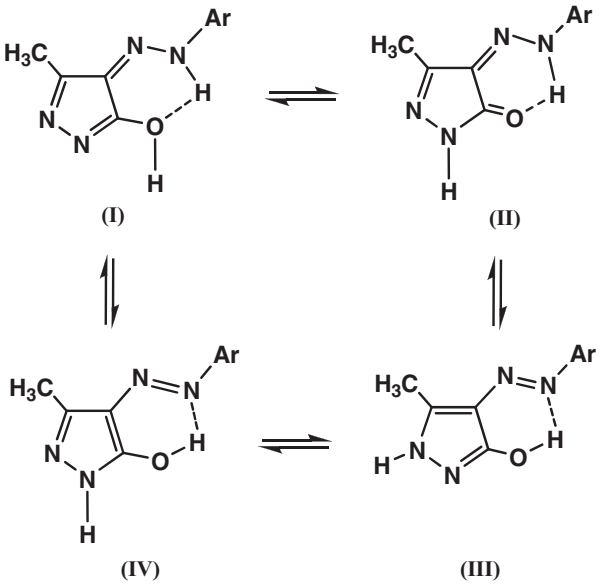

FIGURE 2 Possible tautomeric structures of 3-methyl-4-(arylhydrazono)-1H-pyrazol-5(4H)-one.

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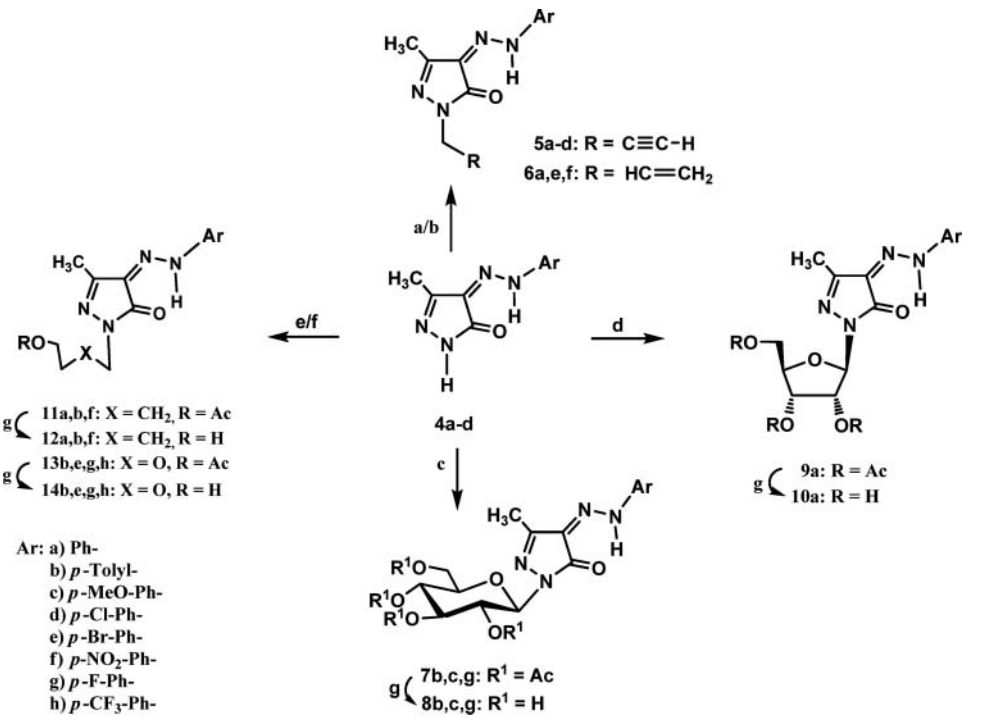
RESULTS AND DISCUSSION

Chemistry

1*H*-3-Methylpyrazolo-5-one[21] was coupled with aryldiazonium chlorides, according to the published procedure,[22–24] to give the corresponding 4-arylhydrazono-3-methylpyrazolo-5-one derivatives **4a–h**. 4-Arylhydrazonopyrazolo-5-one derivatives **4** may exist, in solution, in four tautomeric forms: I, II, III, and IV (Figure 2).[25] Literature reports conclude that, both in solid and liquid state (DMSO, $CHCl_3$, and pyridine), the equilibrium is in favor of the arylhydrazono tautomers.[26] Consequently, N^1, N^2, and *O*-alkylation is anticipated and the regioselectivity could be manipulated by altering the reaction conditions.

Khalil reported that Et_3N-assisted coupling of a 1*H*-3-trifluoromethyl-4-arylhydrazonopyrazolo-5-one with 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide in DMF gave a mixture of $N^2$and bis-N^1-*O*-glycosylated products.[14] *N*-versus *O*- Chemoselective alkylation of amides is largely dependent on the nature of the cation of the base, where alkali metals' [K^+ and Na^+] cations favor the *N*-alkylation.[27] Thus, treatment of **4a–c** with allyl bromide or propargyl bromide in the presence of K_2CO_3 in dry acetone gave the corresponding N^2-propargyl/allyl pyrazolone derivatives **5a–d,** and **6a,e, f,** respectively in good yields (Scheme 1). Spectroscopic data of compounds **5a–d** and **6a,e,f** support the N^2-alkylation site and the compounds exist in the hydrazo-keto form I rather than other possible tautomers (Figure 2). IR spectra of **5a**, for instance, showed absorption bands at 3480, 1645 cm^{-1} characteristic



SCHEME 1 [a]Reagents and conditions. (a) K_2CO_3, dry acetone, 15 minutes, r.t., then $BrCH_2CCH$, 6 hours, reflux temp.; (b) K_2CO_3, dry acetone, 15 minutes, r.t., then $BrCH_2CHCH_2$, 8 hours, reflux temp.; (c) K_2CO_3, dry acetone, 30 minutes, r.t., then 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide, overnight, r.t.; (d) (i) Silylation of **4a** [HMDS, $(NH_4)_2SO_4$, dry CH_2Cl_2, 12 hours, 80°C], (ii) $SnCl_4$, 1,2,3,4,6-tetra-*O*-acetyl-β-D-ribofuranose, CH_2Cl_2, overnight, r.t.; (e) K_2CO_3, dry DMF, 15 minutes, r.t., then $BrCH_2(CH_2)_2CH_2OAc$, 0 C°-r.t, 12 hours; (f) K_2CO_3, dry DMF, 15 minutes, r.t., then $BrCH_2OCH_2CH_2OAc$, 0°C, 12 hours, r.t.; (g) Et_3N, MeOH, r.t.

for ν NH of the hydrazo moiety, and the ν C = O of the pyrazolone ring. ^{1}H NMR spectrum of **5a** showed a signal at δ 12.24 ppm (exchangable with D_2O, hydrazono NH) and its ^{13}C NMR spectra showed a signal at 164.8 ppm (C = O, pyrazolone ring). In a similar manner, treatment of **4b,c,g** with 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide in the presence of K_2CO_3 in dry acetone gave the corresponding N^2-[(4-arylhydrazono)-3-methyl-1-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-1*H*-pyrazol-5(4*H*)-one **7b,c,g,** respectively, in good yields (Scheme 1). The N^2-β-D-configuration of the glycosides **7b,c,g** was supported by the large $J_{1',2'}$ = 8.28–8.62 Hz, and the appearance of the C-5 pyrazolone ring signals at δ 160.5–160.7 ppm in their ^{13}C-NMR spectra.

IR spectra of compounds **7b,c,g** showed absorption bands (ν C = O) at 1660–1669 cm^{-1} supporting their hydrazo-keto structures. Silylation of the pyrazolin-3-one derivative, **4a** followed by treatment with 1,2,3,5-tetra-*O*-acetyl-β-D-ribofuranose in the presence of $SnCl_4$ gave the N^2-pyrazolone ribofuranosyl derivative **9a** in good yield (Scheme 1). The ^{1}H NMR signal

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of the anomeric proton of **9a** appeared at δ 6.19 ppm (d, $J_{1',2'}$5.8 Hz), indicating the β-configuration of the nucleoside analogue. The IR spectrum showed absorption bands at 3480 cm^{-1} (ν NH, hydrazo) and 1653 cm^{-1} (ν C = O, pyrazolone) supporting the keto-hydrazo structure of the nucleobase. Treatment of **4a,b,f** with 4-bromobuty acetate[28] in the presence of K_2CO_3 in DMF afforded N^2-acyclonucleosides **11a,b,f**, respectively, in high yields (Scheme 1). Spectroscopic analysis of these compounds supports the N^2, keto-hydrazo structure (Figure 2, structure II) of the alkylated pyrazolone derivatives **11**. For instance, the ^{1}H-NMR spectrum of **11b** showed the hydrazo-N*H* signal at δ 13.23 ppm, the C-5 pyrazolone signal appeared at δ 164.5 ppm in the^{13}C-NMR spectrum, and a characteristic (ν C = O) IR absorption band appeared at 1649 cm^{-1}. Reaction of the 4-arylhydrazonopyrazolones, **4b,e,g,h** with 2-acetoxyethoxymethyl bromide[29] gave the corresponding N^2-acyclonuclosides **13b,e,g,h**, respectively, in good yields. The structures of **13b,e,g,h** were confirmed by their ^{1}H NMR and ^{13}C NMR, IR and elemental analysis. Conventional deprotection of **7b,c,g; 9a; 11a,b,f,** and **13b,e,g,h** using Et_3N in methanol gave the corresponding nucleosides **8b,c,g**; **10a**; **12a,b,f**, and **14b,e,g,h,** respectively, in good yields (Scheme 1).

Biology

The antimicrobial activities of **4b,d,e,f,g, 7b,c**, **8a, 110a**, **12a,b**, **13b** and **14a,d** were assessed against *Aspergillus flavus, Penicillium sp., and Escherichia coli* according to published procedures.[30] The antimicrobial activity of the tested compounds is expressed by the diameter of inhibition zone (cm)

TABLE 1 Antimicrobial activity of compounds **4b,d,e,f,g; 7b,c; 8a; 12a,b; 13b,** and **14a,d** against *Aspergillus flavus*, *Penicillium sp.,* and *Escherichia coli*

Compd.	*Escherichia coli*	*Penicillium sp.*	*Aspergillus flavus*
4b	0.4	0.7	0.8
4d	0.3	0.5	0.4
4e	0.4	0.3	0.5
4f	0.2	0.1	ND
4g	0.1	ND	ND
7b	0.3	0.4	0.3
7c	0.4	0.3	0.5
8a	0.7	0.6	0.7
11a	0.3	0.1	0.3
12a	0.5	0.5	0.8
11b	0.4	0.3	0.4
13b	0.2	0.2	0.5
14a	0.4	0.3	0.4
14d	0.3	0.4	0.8
Griseofulvin	**NA**	0.9	1.2
Ampicillin	0.8	NA	NA

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around the well. 3-Methyl-4-arylhydrazono-pyrazolones **4d, 4e,** the glucopyranoside **7c**, and the acyclic nucleoside derivative **13b** showed moderate inhibitory effect on the growth of *Aspergillus flavus* and *Penicillium sp.*(0.5 cm) compared with griseofulvin. Significant antifungal activity against *Aspergillus flavus* and *penicillium sp.* was observed with **4b, 8a, 12a, and 14a,d** (Table 1). A significant antibacterial activity against *Escherichia coli* was observed with **6a** while compounds **4b, 4e, 7c**, **12a,b** showed moderate inhibitory activity.

Conclusions

We have synthesized a series of 3-methyl-4-(arylhydrazono)-1*H*-pyrazol-5(4*H*)-one, bearing electron donating/electron withdrawing substituents on the aryl moiety, their N^2-alkyl, N^2-glycosyl derivatives, and evaluated their antimicrobial activity against *Aspergillus flavus* and *penicillium sp. and Escherichia coli.* Among the tested compounds, 3-methyl-4-(arylhydrazono)-1*H*-pyrazol-5(4*H*)-one (**4b)**, bearing electron donating and lipophilic substituent on the aryl moiety, showed the highest antimicrobial activity. However, the pattern was reversed with the acylic nucleosides **13a** and **14d**. Further biological antiviral and anticancer evolutions of the synthesized compounds are under way and will be published in due course.

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EXPERIMENTAL

General Procedures

All melting points are uncorrected and were measured using an Electrothermal IA 9100 apparatus. The IR spectra (KBr disc) were recorded on a Pye Unicam Sp-3-300 and Shimadzu FTIR 8101 PC infrared spectrophotometer. The ^{1}H and ^{13}C NMR spectra were recorded on Varian Mercury VX-NMR 300 MHz spectrometer. Chemical shifts are expressed δ (ppm) scale using TMS as internal reference and coupling-constant values are given in Hz. Elemental analysis was determined on a Perkin Elmer 240.

Antimicrobial Evaluation

The antimicrobial evaluation was conducted with minor modifications to the published procedure.[29] The tested compounds were dissolved in dimethylsulfoxide to obtain a solution of 1 μg/mL concentration. After seeding of the ceded-solid medium by the microbial suspension (10 mL/250 medium), the plates were incubated overnight for germination, then 500 μL of each tested compound were pipetted to the wells of the plate cultures. Blanks of dissolving solvent were done for each organism. The cultures were incubated for 7 days at 30°C for fungal growth and for 2 days at 37°C for bacterial growth. The antimicrobial activity was expressed by the diameter

of inhibitory zone around the wells compared to griseofulvin and ampicillin as standard antifungal and antibacterial agents, respectively.

General Procedure for Preparation of Pyrazolone Derivatives (4a–h)

To a solution of ethyl acetoacetate (10.1 mL, 0.1 mol) in absolute ethanol (100 mL) was added hydrazine hydrate (3.5 mL, 0.1 mol) in absolute ethanol (15 mL) dropwise at room temperature. Then the mixture was heated for 30 minutes at 60°C. The mixture was cooled to room temperature and the precipitate was filtered, washed with ice-cold ethanol to give (7.46 g, 76%) of 1*H*-3-methylpyrazolo-5-one[19] as pale yellow solid. To a solution of 1*H*-3-methylpyrazolo-5-one (0.98 g, 10 mmol) and sodium acetate (1.64 g, 20 mmol) in ethanol (50 mL) was added an aqueous solution of aryl diazonium salt (10 mmol) dropwise at 0°C. The reaction mixture was stirred at room temperature for 3 hour and the formed precipitate was collected by filtration, washed several times with cold water, dried, and recrystallized from ethanol to give the corresponding 4-arylhydrazonopyrazolones **4a–h**.[31]

3-Methyl-4-(2-phenylhydrazono)-1H-pyrazol-5(4H)-one (4a)[31a]

Orange crystals, 80% yield; mp 198–199°C (lit. > 200°C); ^{1}H NMR δ_H ($CDCl_3$, 300 MHz) 2.27 (3H, s, C*H*$_3$), 7.14-7.44 (5H, m, Ar-*H*), 9.23 (1H, s, N*H*-pyrazolinone ring), 13.36 (1H, br s, N*H*-hydrazone). Anal. Calcd. for $C_{10}H_{10}N_4O$: C, 59.40; H, 4.98; N, 27.71. Found: C, 59.35; H, 4.89; N, 27.59.

3-Methyl-4-(2-p-tolylhydrazono)-1H-pyrazol-5(4H)-one (4b)[31b]

Orange crystals, 77% yield; mp 196–197°C (lit 195–196°C); ^{1}H NMR δ_H ($CDCl_3$, 300 MHz) 2.24 (3H, s, C*H*$_3$), 2.35 (3H, s, C*H*$_3$), 7.17 (2H, d, J = 8.6 Hz, Ar-*H*), 7.29 (2H, d, J = 8.6 Hz, Ar-H), 9.17 (1H, s, N*H*-pyrazolinone ring), 13.39 (1H, br s, N*H*-hydrazone). Anal. Calcd for $C_{11}H_{12}N_4O$: C, 61.09; H, 5.59; N, 25.91. Found: C, 60.97; H, 5.48; N, 25.79.

4-[2-(4-Methoxyphenyl)hydrazono]-3-methyl-1H-pyrazol-5(4H)-one (4c)[31c]

Yellow crystals, 89% yield; mp 195–197°C; ^{1}H NMR δ_H ($CDCl_3$,300 MHz) 2.25 (3H, s, C*H*$_3$), 3.75 (3H, s, OC*H*$_3$), 5.66 (1H, s, N*H*-pyrazolinone ring), 6.90 (2H, d, J = 8.8 Hz, Ar-*H*), 7.31 (2H, d, J = 8.8 Hz, Ar-*H*), 13.51 (1H, br, N*H*-hydrazone). Anal. Calcd for $C_{11}H_{12}N_4O_2$: C, 56.89; H, 5.21; N, 24.12. Found: C, 56.74; H, 5.18; N, 24.09.

4-[2-(3-Chlorophenyl)hydrazono]-3-methyl-1H-pyrazol-5(4H)-one (4d)[31a]

Orange crystals; 84% yield; mp 213–214°C; ^{1}H NMR δ_H ($CDCl_3$, 300 MHz) 2.27 (3H, s, C*H*$_3$), 5.67 (1H, s, N*H*-pyrazolinone ring), 7.05–7.82 (4H, m, Ar-*H*), 13.54 (1H, s, NH, hydrazone). Anal. Calcd for $C_{10}H_9ClN_4O$: C, 50.75; H, 3.83; N, 23.67. Found: C, 50.67; H, 3.79; N, 23.60.

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4-[2-(4-Bromophenyl)hydrazono]-3-methyl-1H-pyrazol-5(4H)-one (4e)[31c]

Orange crystals; 89% yield; mp 229–230°C (lit 231–232°C); ^{1}H NMR δ_H ($CDCl_3$, 300 MHz) 2.24 (3H, s, C*H*$_3$), 7.26 (2H, d, J = 8.8 Hz, Ar-*H*), 7.49 (2H, d, J = 8.8 Hz, Ar-*H*), 7.70 (1H, s, N*H*-pyrazolinone), 13.35 (1H, brs, N*H*-hydrazone). Anal. Calcd for $C_{10}H_9BrN_4O$: C, 42.73; H, 3.23; N, 19.93. Found: C, 42.76; H, 3.20; N, 19.88.

3-Methyl-4-[2-(4-nitrophenyl)hydrazono]-1H-pyrazol-5(4H)-one (4f)[31c]

Orange crystals; 81% yield; mp 259–260°C (Lit. 260°C); ^{1}H NMR δ_H (DMSO-d_6, 300 MHz) 2.18 (3H, s, C*H*$_3$), 7.76 (2H, d, J = 9.0 Hz, Ar-*H*), 8.26 (2H, d, J = 9.0 Hz, Ar-*H*), 13.26 (1H, brs, N*H*-hydrazone). Anal. Calcd for $C_{10}H_9N_5O_3$: C, 48.58; H, 3.67; N, 28.33. Found: C, 48.46; H, 3.72; N, 28.39.

4-[2-(4-Fluorophenyl)hydrazono]-3-methyl-1H-pyrazol-5(4H)-one (4g)

Yellow crystals; 90% yield; mp 212–214°C; ^{1}H NMR δ_H (DMSO-d_6, 300 MHz) 2.14 (3H, s, C*H*$_3$), 7.26 (2H, m, Ar-*H*), 7.59 (2H, m, Ar-*H*), 11.53 (1H, s, N*H*-hydrazone). Anal. Calcd for $C_{10}H_9FN_4O$: C, 54.54; H, 4.12; N, 25.44. Found: C, 54.67; H, 4.09; N, 25.37.

3-Methyl-4-[2-(3-(trifluoromethyl)phenylhydrazono]-1H-pyrazol-5(4H)-one (4h)

Yellow crystals; 89% yield; mp 203–205°C; ^{1}H NMR δ_H (DMSO-d_6, 300 MHz) 2.15 (3H, s, CH_3), 7.47 (1H, d, J = 7.5 Hz, Ar-*H*) 7.61 (1H, t, J = 7.5 Hz, Ar-*H*), 7.89 (2H, m, Ar-H), 11.59 (1H, s, NH-hydrazone). Anal. Calcd for $C_{11}H_9F_3N_4O$: C, 48.89; H, 3.36; N, 20.73. Found: C, 49.01; H, 3.29; N, 20.68.

3-Methyl-4-(2-phenylhydrazono)-1-(prop-2-ynyl)-1H-pyrazol-5(4H)-one (5a)

A mixture of **4a** (1.2 g, 5.94 mmol) and K_2CO_3 (1.23 g, 8.9 mmol) in dry acetone (15 mL) was stirred for 30 minutes at room temperature. Propargyl bromide (80 wt.% in toluene, 1.1 mL, 7.1 mmol) was added and the reaction mixture was heated for 6 hours at reflux temperature. The mixture was cooled down to room temperature and poured onto ice water, the precipitate was collected by filtration and crystallized from ethanol to give **5a** (1.11 g, 78% yield) as yellow crystals; mp 121–122°C; ^{1}H NMR δ_H (DMSO-d_6, 300 MHz) 2.59 (3H, s, C*H*$_3$), 3.35 (1H, s, ≡C*H*), 4.94 (2H, d, J= 7.2 Hz, N C*H*$_2$CCH), 7.42–7.70 (5H, m, Ar-*H*), 11.30 (1H, s, N*H*-hydrazone); ^{13}C NMR δ_C (DMSO-d_6, 75 MHz) 10.7, 56.5, 76.8, 78.5, 121.8, 123.4, 129.6, 130.1, 139.3, 153.5, 154.4; Anal. Calcd for $C_{13}H_{12}N_4O$: C, 64.99; H, 5.03; N, 23.32. Found: C, 65.01; H, 4.96; N, 23.21.

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3-Methyl-1-(prop-2-ynyl)-4-(2-p-tolylhydrazono)-1H-pyrazol-5(4H)-one (5b)

Compound **5b** was synthesized from **4b** in a similar manner as described for **5a**, 85% yield; yellow crystals; mp 110–112°C; ^{1}H NMR δ_H (DMSO-d_6, 300 MHz) 2.32 (3H, s, CH_3), 2.57 3H, (s, CH_3), 3.32 (1H,s, ≡CH), 4.81 (2H, s, NCH_2), 7.22 - 7.90 (4H, m, Ar-H), 11.50 (1H, s, NH). ^{13}C NMR δ_C (DMSO-d_6, 75 MHz) 10.8, 21.4, 56.5, 76.7, 78.5, 96.6, 116.1, 121.8, 130.1, 130.5, 151.2, 160.9. Anal. Calcd for $C_{14}H_{14}N_4O$ (245.29): C, 66.21; H, 5.62; N, 22.03. Found: C, 66.28; H, 5.94; N, 21.96.

4-[2-(4-Methoxyphenyl)hydrazono]-3-methyl-1-(prop-2-ynyl)-1H-pyrazol-5 (4H)-one (5c)

Compound **5c** was synthesized from **4c** (1.2 g, 5.94 mmol) in a similar manner as described for the synthesis of **5a,** in 83% yield**:** yellow crystals; mp 108–110°C; ^{1}H NMR δ_H (DMSO-d_6, 300 MHz) 2.59 (3H,brs, CH_3), 3.33 (1H, s, C≡CH), 3.82 (3H, s, OCH_3), 4.93 (2H, d, J = 7.23 Hz, NCH_2), 7.04 (2H,d, J = 8.8 Hz, Ar-H), 7.70 (2H, d, J = 8.9 Hz, Ar-H), 11.35 (1H, s, NH). ^{13}C NMR δ_C (DMSO-d_6, 75 MHz) 10.77, 55.9, 56.5, 76.7, 79.7, 99.9, 114.8, 123.5, 138.4, 147.6, 154.4, 161.1. Anal. Calcd for $C_{14}H_{14}N_4O_2$: C, 62.21; H, 5.22; N, 20.73. Found: C, 62.35; H, 5.18; N, 20.68.

4-[2-(3-Chlorophenyl)hydrazono]-3-methyl-1-(prop-2-ynyl)-1H-pyrazol-5 (4H)-one (5d)

Compound **5d** was synthesized from **4d** in a similar manner as described for **5c**, 83% yield; yellow crystals; mp 148–150°C; ^{1}H NMR δ_H (DMSO-d_6, 300 MHz) 2.61 (3H,s, CH_3), 3.60 (1H, d, J = 2.4 Hz, C≡CH), 4.97 (2H, s, NCH_2), 7.41–7.61 (4H, m, Ar-H), 12.9 (1H, s, NH-hydrazone). ^{13}C NMR δ_C (DMSO-d_6, 75 MHz) 11.3, 56.8, 76.9, 78.6, 101.9, 117.4, 124.7, 128.3, 130.8, 132.8, 137.5, 149.3, 156.2. Anal. Calcd. for $C_{13}H_{11}ClN_4O$ (274.71): C, 56.84; H, 4.04; N, 20.40. Found: C, 56.85; H, 4.02; N, 20.43.

1-Allyl-3-methyl-4-(2-phenylhydrazono)-1H-pyrazol-5(4H)-one (6a)

A mixture of **4a** (1.0 g, 4.95 mmol) and K_2CO_3 (1.0 g, 8.9 mmol) in dry acetone (10 mL) was stirred for 30 minutes at room temperature. Allyl bromide (0.5 mL, 5.45 mmol) was added and the reaction mixture was heated for 8 hours at reflux temperature. The mixture was cooled down to room temperature and poured onto ice water. EtOAc (40 mL) was added to the mixture and the organic phase was separated, dried over $MgSO_4$, and evaporated. The residue was purified by a silica gel column (eluate; 7% MeOH in CH_2Cl_2) to give **6a** (1.g, 85%) as a yellow foam; ^{1}H NMR δ_H (DMSO-d_6, 300 MHz) 2.25 (3H, s, CH_3), 4.66 (1H, m, CH_{2a}CH = CH_2), 4.77 (1H, m, CH_{2b}CH = CH_2), 5.00 – 5.49 (m, 2H, CH_2CH = CH_2), 6.06 (m, 1H, CH_2CH = CH_2), 7.36–7.69 (m, 5H, Ar-H), 12.24 (1H, s, NH); ^{13}C NMR δ_C (DMSO-d_6, 75 MHz) 11.6, 32.8, 113.9, 117.5, 122.5, 128.7, 129.5, 132.8,

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143.5, 148.4, 164.8; Anal. Calcd. for $C_{13}H_{14}N_4O$: C, 64.45; H, 5.82; N, 23.13. Found: C, 64.39; H, 5.71; N, 22.91.

1-Allyl-4-[2-(4-methoxyphenyl)hydrazono]-3-methyl-1H-pyrazol-5(4H)-one (6c)

Compound **6c** was synthesized from **4c**, in a similar manner as described for the synthesis of **6a**, in 78% yield: yellow foam; IR (KBr) 3480 cm^{-1} (ν NH), 1645 cm^{-1} (ν C = O); ^1H NMR δ_H (DMSO-d_6, 300 MHz) 2.55 (3H, s, CH_3), 3.81 (3H, s, OCH_3), 4.69 (2H, m, $CH_2CH = CH_2$), 4.97–5.42 (2H, m, $CH_2CH = CH_2$), 6.04 (1H, m, $CH_2CH = CH_2$), 7.04 (2H, d, J= 8.4 Hz, Ar-*H*), 7.67 (2H, d, J= 8.44 Hz, Ar-*H*), 12.35 (1H, s, N-*H*); Anal. Calcd. for $C_{14}H_{16}N_4O_2$: C, 61.75; H, 5.92; N, 20.58. Found: C, 61.64; H, 5.87; N, 20.42.

1-Allyl-3-methyl-4-[2-(4-nitrophenyl)hydrazono]-1H-pyrazol-5(4H)-one (6f)

Compound **6f** was synthesized from **4f**, in a similar manner as described for the synthesis of **6a**, in 75% yield: yellow foam; ^1H NMR δ_H (DMSO-d_6, 300 MHz) 2.55 (3H, s, CH_3), 4.68 (1H, d, $CH_{2a}CH = CH_2$, J = 5.1 Hz), 4.77 (1H, d, J = $CH_{2b}CH = CH_2$, 5.1 Hz), 5.02–5.47 (2H, m, $CH_2CH = CH_2$), 6.00 (1H, m, $CH_2CH = CH_2$), 7.83 (2H, d, Ar-*H*, J= 8.42 Hz), 8.35 (2H, d, Ar-*H*, J= 8.4 Hz), 12.21 (1H, s, NH); ^{13}C NMR δ_C (DMSO-d_6, 75 MHz) 11.6, 32.9, 113.4, 117.3, 124.6, 128.8, 132.5, 137.8, 148.5, 149.4, 164.8; Anal. Calcd. for $C_{13}H_{13}N_5O_3$: C, 54.35; H, 4.56; N, 24.38. Found: C, 54.29; H, 4.48; N, 24.31.

4-[2-(4-Fluorophenyl)hydrazono]-3-methyl-1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-1H-pyrazol-5(4H)-one (7g)

Dry K_2CO_3 (0.56 g, 5.45 mmol) was added to a solution of **4g** (1.0 g, 4.54 mmol) in dry acetone (15 mL) and the mixture was stirred for 30 minutes at room temperature. A solution of 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide (3.32 g, 8.18 mmol) in dry acetone (20 mL), was added and the reaction mixture was further stirred overnight at room temperature. The solvent was evaporated under reduced pressure and the residue was crystallized from EtOH to give **7g** (2.25 g, 75% yield) as yellow crystals; mp 130–131°C; IR (KBr) 3476 cm^{-1} (ν NH), 1747 cm^{-1} (ν C = O, ester), 1670 cm^{-1} (ν C = O, amide); ^1H NMR δ_H (DMSO-d_6, 300 MHz) 1.89, 1.99, 2.00, and 2.03 (12H, 4s, Ac), 2.13 (3H, s, CH_3-pyrazolinone), 3.98 (1H, m, H-5'a), 4.2 (1H, dd, H-6', $J_{5',6'}$ = 4.55, $J_{6',6"}$ = 11.89 Hz), 4.32 (1H, dd, H-6", $J_{5',6'}$ = 3.55, $J_{6',6"}$11.89 Hz), 5.18 (2H, m, H-2′, H-4′), 5.98 (1H, d, $J_{1',2'}$ = 8.62 Hz, H-1′), 7.21 (d, 2H, Ar-*H*, J = 8.9 Hz), 7.62 (2H, d, Ar-*H*, J = 8.9 Hz), 11.5 (1H, s, N*H*); ^{13}C NMR δ_C (DMSO-d_6, 75 MHz) 12.0, 20.7, 20.8, 20.9, 21.1, 69.6, 70.5, 71.8, 72.1, 73.6, 81.2, 116.6, 116.9, 117.9, 118.0, 160.5, 169.2, 169.5, 169.7, 169.8, 170.2, 170.4; Anal. Calcd. for $C_{24}H_{27}FN_4O_{10}$: C, 52.36; H, 4.94; N, 10.18. Found: C, 52.27; H, 4.87; N, 10.02.

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4-[2-(4-(Methoxyphenyl)hydrazono]-3-methyl-1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-1H-pyrazol-5(4H)-one (7c)

Compound **7c** was synthesized from **4c** and 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide, in a similar manner described for **7f,** in 69% yield; yellow crystals; mp 148–150°C; ^{1}H NMR δ_H (DMSO-d_6, 300 MHz) 1.99 (3H, s, Ac), 2.00 (3H, s, Ac), 2.07 (3H, s, Ac), 2.14 (3H, s, Ac) 2.18 (3H, s, CH_3), 3.78 (3H, s, OCH_3), 3.9 (1H, m, H-5'), 4.14 (1H, dd, H-6', $J_{5',6'} = 4.62$, $J_{6',6'} = 11.72$ Hz), 4.21 (1H, dd, H-6", $J_{5',6} = 2.76$, $J_{6',6'} = 11.72$ Hz), 4.95 (2H, m, H-2'and H-4'), 5.44 (1H,t, H-3', J 9.58 Hz), 5.96 (1H, d, H-1'), 7.02 (2H, d, Ar-*H*, J= 8.9 Hz), 7.48 (2H, d, Ar-*H*, J = 8.9 Hz), 11.50 (1H, s, NH, J = 8.3 Hz); ^{13}C NMR δ_C (DMSO-d_6, 75 MHz) 12.0, 20.7, 20.8, 20.9, 30.8, 61.8, 68.1, 69.1, 70.5, 71.8, 72.1, 81.4, 126.0, 122.1, 128.3, 135.4, 157.5, 160.7, 169.2, 169.5, 169.7, 169.9, 170.4; Anal. Calcd. for $C_{25}H_{30}N_4O_{11}$: C, 53.38; H, 5.38; N, 9.69. Found: C, 53.27; H, 5.26; N, 9.54.

4-[2-(p-Tolylhydrazono)-3-methyl-1-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-1H-pyrazol-5(4H)-one (7b)

Compound **7b** was synthesized from **4b** and 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide, in a similar manner described for **7f,** in 83% yield; yellow crystals; mp 139–141°C; IR (KBr) 3470 cm^{-1}(ν NH), 1745 cm^{-1} (ν C = O, ester), 1660 cm^{-1} (ν C = O, amide); ^{1}H NMR δ_H (DMSO-d_6, 300 MHz) 1.87 (3H, s, Ac), 1.97 (3H, s, Ac), 1.99 (3H, s, Ac), 2.04 (3H, s, Ac), 2.35 (3H, s, CH_3), 2.45 (3H,s, CH_3), 3.98 (1H, m, H-5′), 4.18 (1H, dd, H-6′, $J_{5',6"} = 4.68$, $J_{6',6"} = 11.72$ Hz), 4.21(1H, dd, H-6", $J_{5',6"} = 2.76$, $J_{6',6"} = 11.72$ Hz,), 5.93 (1H, d, H-1′, J = 8.29 Hz), 12.80 (1H, brs, NH); Anal. Calcd. for $C_{25}H_{30}N_4O_{10}$: C, 54.94; H, 5.53; N, 10.25. Found: C, 54.82; H, 5.47; N, 10.17.

4-(2-(4-Fluorophenyl)hydrazono)-1-(β-D-glucopyranosyl)-3-methyl-1H-pyrazol-5(4H)-one (8g)

Triethylamine (0.5 mL, 3.63 mmol) was added to a solution of **7g** (2 g, 3.63 mmol) in MeOH (15 mL). The mixture was stirred overnight at room temperature and the volatiles were evaporated and co-evaporated with MeOH under reduced pressure. The residue was crystallized from ethanol to give **8g** (1.1 g, 83% yield) as yellow crystals; mp 178–180°C; ^{1}H NMR δ_H (DMSO-d_6, 300 MHz) 2.27 (3H,s, C*H*$_3$), 3.13–3.34 (6H, m, H-6," H-6," H-5, H-4', H-3'and H-2'), 4.50 (1H, brt, 6'-OH), 5.00 (1H, brd, 4′-OH), 5.20 (1H, brd, 3′-OH), 5.47 (1H, brd, 2'-OH), 5.61 (1H, d, H-1′, $J_{1',2'} = 7.83$ Hz), 7.23–7.69 (4H, m, Ar-*H*), 11.53 (1H, s, N*H*); Anal. Calcd. for $C_{16}H_{19}FN_4O_6$: C, 50.26; H, 5.01; N, 14.65. Found: C, 50.21; H, 4.98; N, 14.52.

1-(β-D-Glucopyranosyl)-4-[2-(4-methoxy)phenylhydrazono]-3-methyl-1H-pyrazol-5(4H)-one (8c)

Compound **7c** (0.8 g, 1.42 mmol) was deprotected, in a similar manner described for **8g,** to give **8c** (0.4 g, 83% yield) as yellow crystals; mp

172–173°C; ^{1}H NMR δ_H (DMSO-d_6, 300 MHz) δ 2.16 (3H,s, CH_3), 3.02–3.35 (6H, m, H-6′, H-6”, H-5′, H-4′, H-3′ and H-2′), 3.67 (3H, s, OCH_3), 4.32 (1H, t, 6′-OH), 4.81(1H, d, 4′-OH), 4.90 (1H, d, 3′-OH), 5.01 (1H, d, 2′-OH), 5.30 (1H, d, H-1′, $J_{1',2}$ 8.0 Hz), 7.01 (2H, d, Ar-H, J = 8.8 Hz), 7.50 (2H, d, Ar-H, J 8.8 Hz), 11.50 (1H, s, NH); Anal. Calcd. for $C_{17}H_{22}N_4O_7$: C, 51.77; H, 5.62; N, 14.21. Found: C, 51.45; H, 5.52; N, 14.19.

1-(β-D-Glucopyranosyl)-3-methyl-4(2-p-tolylhydrazono)-1-H-pyrazol-5(4H)-one (8b)

Compound **7b** (0.85 g, 1.55 mmol) was deprotected, in a similar manner described for **7f,** to give **7b** (0.5 g, 85% yield) as yellow crystals; mp 160–162°C; ^{1}H NMR δ_H (DMSO-d_6, 300 MHz) 2.14 (3H, s, CH_3), 2.35 (3H, s, CH_3), 3.10–3.64 (6H, m, H-6′, H-6′′, H-5′, H-4′, H-3′, and H-2′), 4.54 (1H, t, 6′-OH), 4.90 (1H, d, 4′-OH), 5.10 (1H, d, 3′-OH), 5. 21 (1H, d, 2′-OH), 5.56 (1H, d, H-1′, $J_{1',2}$ 7.98 Hz), 7.26 (2H, d, Ar-H, J 8.4 Hz), 7.60 (2H, d, Ar-H, J = 8.4 Hz), 12.50 (br s, 1H, NH); Anal. Calcd. for $C_{17}H_{22}N_4O_6$: C, 53.96; H, 5.89; N, 14.81. Found: C, 53.89; H, 5.77; N, 14.79.

3-Methyl-1-(2′,3′,5′-tri-O-acetyl-β-D-ribofuranolyl)-4-(2-phenylhydrazono)-1H-pyrazol-5(4H)-one (9a)

A mixture of **4a** (1.4 g, 6.92 mmol), ammonium sulfate (0.1 g), and of HMDS (30 mL) was heated for 12 hours at 80°C. The excess of HMDS evaporated and co-evaporated (dry xylene) under reduced pressure. A mixture of the silylated pyrazolone and 1,2,3,5-tetra-*O*-acetyl-β-D-ribofuranose (3.3 g, 10.4 mmol) was dissolved in dry CH_2Cl_2 (50 mL), and treated with a solution of $SnCl_4$ (1*M* in CH_2Cl_2; 13.84 mL) at room temperature. The reaction mixture was stirred for 18 hours at room temperature and then diluted with CH_2Cl_2 (100 mL), washed with saturated aqueous solution of $NaHCO_3$ (50 mL) and water (2 × 50 mL). The organic phase was separated, dried over (Na_2SO_4), and evaporated under reduced pressure. The residue was purified by a silica gel column chromatography (eluate; 4% MeOH in CH_2Cl_2) to give **9a** (2.3 g, 73% yield) as a pale yellow foam; IR (KBr) 3480 cm^{-1} (ν NH), 1749 cm^{-1} (ν C = O, Ac), 1653 cm^{-1} (ν C = O, amide); ^{1}H NMR δ_H (DMSO-d_6, 300 MHz) 2.07 (3H,s, Ac), 2.10 (3H, s, Ac), 2.12 (3H, s, Ac), 2.27 (3H, s, CH_3), 3.43 (1H, m, H-4′), 4.19 (1H, dd, H-5′, $J_{4',5'}$ = 3.5, $J_{5',5''}$ = 11.8 Hz), 4.30 (1H, dd, H-5”, $J_{4',5''}$ = 2.9, $J_{5',5''}$ = 11.8 Hz), 5.34 (2H, m, H-2′and H-3′), 6.19 (1H, d, H-1’, $J_{1',2}$ 6.9 Hz), 7.26–7.42 (5H, m, Ar-H), 13.4 (1H, br s, NH); Anal. Calcd. for $C_{21}H_{24}N_4O_8$: C, 54.78; H, 5.25; N, 12.17. Found: C, 54.59; H, 5.14; N, 12.10.

3-Methyl-1-(β-D-ribofuranosyl)-4-(2-phenylhydrazono)-1H-pyrazol-5(4H)-one (10a)

Compound **9a** (2 g, 4.34 mmol) was deprotected, in a similar manner described for **7d,** to give **10a** (1.15 g, 79% yield) as a pale yellow foam; ^{1}H

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NMR δ_H (DMSO-d_6, 300 MHz) 2.27 (3H, s, CH_3), 3.31 (5H, m, H-2′, H-3', H-4', H-5' and H-5"), 4.12 (1H, t, 5'-OH, $J = 5.4$ Hz), 4.26 (1H, d, 3'-OH), 4.30 (1H, d, 2′-OH), 5.52 (1H, d, H-1′, $J_{1',2'} = 6.6$ Hz), 7.17–7.69 (5H, m, Ar-*H*), 11.53 (1H, s, N*H*); Anal. Calcd. for $C_{15}H_{18}N_4O_5$: C, 53.98; H, 5.43; N, 16.76. Found: C, 53.86; H, 5.39; N, 16.58.

4-[3-Methyl-5-oxo-4(2-phenylhydrazono)-4,5-dihydro-1H-pyrazol-1-yl]butyl acetate (11a)

A solution of **4a** (1 g, 4.95 mmol), and dry K_2CO_3 (0.61 g, 5.93 mmol) in dry DMF (15 mL) was stirred for 15 minutes at room temperature. 4-Bromobutylacetate (0.6 mL, 5.94 mmol) was added at 0°C and the mixture was stirred overnight at room temperature. The insoluble material was filtered off and the filterate was evaporated under reduced pressure. The residue was then chromatographic on a silica gel column (eluate: 5% MeOH in CH_2Cl_2) to give **11a** (1.1 g, 72% yield) as orange foam; ^{1}H-NMR δ_H (DMSO-d_6, 300 MHz) 1.52 (2H, m, C*H*$_2$), 1.76 (2H, m, C*H*$_2$), 1.98 (3H, s, Ac), 2.53 (3H, s, CH_3), 3.99 (2H, m, C*H*$_2$N), 4.22 (2H, t, C*H*$_2$O), 6.66–7.38 (5H, m, Ar-*H*), 11.83 (1H, s, NH); ^{13}C NMR δ_C (DMSO-d_6. 75 MHz) 11.6, 20.7, 21.6, 26.0, 34.3, 64.6, 113.9, 122.4, 128.7, 129.5, 143.1, 148.2, 163.1, 170.2; Anal. Calcd. for $C_{16}H_{20}N_4O_3$: C, 60.75; H, 6.37; N, 17.71. Found: C, 60.74; H, 6.28; N, 17.69.

4-[3-Methyl-4-(2-p-tolylhydrazono]-4,5-dihydro-1H-pyrazol-1-yl)butyl acetate (11b)

Compound **11b** was synthesized from **1c,** in a similar manner as described for the synthesis of **11a,** in 85% yield**;** yellow foam; ^{1}H NMR δ_H (DMSO-d_6, 300 MHz) 1.52 (2H, m, C*H*$_2$), 1.78 (2H, m, C*H*$_2$), 1.88 (3H, s, C*H*$_3$), 1.98 (3H, s, Ac), 2.53 (3H, s, CH_3), 3.99 (2H, m, C*H*$_2$N), 4.22 (2H, t, C*H*$_2$O), 7.27 (2H, d, Ar-*H*, $J = 8.1$ Hz), 7.58 (2H, d, Ar-*H*, $J = 8.1$ Hz), 12.48 (1H, s, N*H*); ^{13}C NMR δ_C (DMSO-d_6) 11.6, 20.7, 21.3, 21.6, 26.1, 34.3, 64.7, 116.2, 128.7, 129.8, 131.2, 140.0, 148.2, 163.0, 170.3; Anal. Calcd. for $C_{17}H_{22}N_4O_3$: C, 61.80; H, 6.71; N, 16.96. Found: C, 61.69; H, 6.67; N, 16.82.

4-[3-Methyl-4-(2-(4-nitrophenyl)hydrazono]-5-oxo-4,5-dihydro-1H-pyrazol-1-yl)butyl acetate (11f)

Compound **11f** was synthesized from **4f**, in a similar manner as described for the synthesis of **11a,** in 80% yield**;** yellow foam; IR (KBr) 1739 cm^{-1} (C = O, ester), 1649 cm^{-1} (C = O, amide); ^{1}H NMR (DMSO-d_6) δ 1.58 (2H, m, CH_2), 1.79 (2H, m, CH_2), 1.98 (3H, s, $COCH_3$), 2.56 (3H, s, CH_3), 3.99 (2H, m, CH_2N), 4.24 (2H, t, CH_2O), 7.81 (2H, d, Ar-*H*, $J = 8.7$ Hz), 8.33 (2H, d, Ar-H, $J = 8.7$ Hz); Anal. Calcd for $C_{16}H_{19}N_5O_5$ (361.35): C, 53.18; H, 5.30; N, 19.38. Found: C, 53.20; H, 5.28; N, 19.37.

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1-(4-Hydroxybutyl)-3-methyl-4-(2-phenylhydrazono)-1H-pyrazol-5(4H)-one (12a)

Compound **11a** (0.95 g, 3 mmol) in MeOH (15 mL) was treated with Et_3N (0.5 mL, 3.2 mmol) and the mixture was stirred for 2 hours at room temperature. The volatiles were removed under reduced pressure and the residue was purified by silica gel column chromatography (eluate: 6% MeOH in CH_2Cl_2) to give **12a** (0.61g, 75% yield) as a yellow foam; ^{1}H NMR δ_H (DMSO-d_6, 300 MHz) 1.42–1.78 (4H, m, C*H*$_2$C*H*$_2$), 2.25 (3H, s, C*H*$_3$), 3.49 (2H, m, C*H*$_2$N), 3.96–4.21 (2H, m, C*H*$_2$O), 4.50 (1H, t, O*H*), 7.48–7.66 (5H, m, Ar-*H*); Anal. Calcd. for $C_{14}H_{18}N_4O_2$: C, 61.30; H, 6.61; N, 20.42. Found: C, 61.28; H, 6.59; N, 20.33.

1-(4-Hydroxybutyl)-3-methyl-4-(2-p-tolylhydrazono)-1H-pyrazol-5(4H)-one (12b)

Compound **11b** (0.75 g, 2.27 mmol) was deprotected, in a similar manner described for **11a,** to give **12b** (0.54 gm, 82% yield) as a yellow foam; ^{1}H NMR δ_H (DMSO-d_6, 300 MHz) 1.25 (2H, m, CH_2), 2.04 (2H, m, CH_2), 2.36 (3H, s, CH_3), 2.57 (3H, s, C*H*$_3$), 3.97 (2H, t, C*H*$_2$N), 4.22 (2H, t, C*H*$_2$O), 4.49 (1H, t, O*H*), 7.25 (2H, d, Ar-*H,* *J* 8.4 Hz), 7.69 (2H, d, *J* 8.4 Hz, Ar-*H*). Anal. Calcd. for $C_{15}H_{20}N_4O_2$: C, 62.48; H, 6.99; N, 19.43. Found: C, 62.39; H, 6.88; N, 19.38.

1-(4-Hydroxybutyl)-3-methyl-4-(2-(4-nitrophenyl)hydrazono)-1H-pyrazol-5(4H)-one (12f)

Compound **11f** (0.8 g, 2.21 mmol) was deprotected, in a similar manner described for **11a,** to give **12f** (0.56 g, 79% yield) as a yellow foam; ^{1}H NMR δ_H (DMSO-d_6, 300 MHz) 1.40–1.79 (4H, m, C*H*$_2$-C*H*$_2$), 2.54 (3H, s, C*H*$_3$), 3.47 (2H, m, C*H*$_2$N), 3.97–4.24 (2H, m, CH_2O), 4.49 (brt, 1H, OH, exchanged with D_2O), 7.78 (2H, d, Ar-H, J = 8.8 Hz), 8.29 (2H, d, Ar-*H,* J = 8.8 Hz). Anal. Calcd. for $C_{14}H_{17}N_5O_4$: C, 52.66; H, 5.37; N, 21.93. Found: C, 52.64; H, 5.29; N, 21.87.

2-[4-(2-(4-Fluorophenyl)hydrazono)-3-methyl-5-oxo-4,5-dihydro-1H-pyrazol-1-yl)methoxy]ethyl acetate (13g)

A mixture of **4g** (1.25 g, 5.68 mmol) and dry K_2CO_3 (0.88 g, 8.5 mmol) in dry DMF (15 mL) was stirred for 15 minutes at room temperature. (2-acetoxyethoxy)methyl bromide (1.45 g, 7.4 mmol) was added at 0°C and the mixture was stirred overnight at room temperature. The insoluble material was filtered off and the filtrate was evaporated under reduced pressure. The residue was purified by a silica gel column chromatography (eluate; 5% MeOH in CH_2Cl_2) to give **13g** (1.4 g, 75% yield) as a yellow syrup; IR (KBr) 3260 cm^{-1} (ν NH), 1740 cm^{-1} (ν C = O, ester), 1669 cm^{-1} (ν C = O, amide);

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^{1}H NMR δ_H (DMSO-d_6, 300 MHz) 1.99 (3H, s, CH_3CO), 2.58 (3H, s, CH_3), 4.38 (2H, t, OCH_2), 4.76 (2H, t, CH_2OCO), 4.98 (2H, s, NCH_2O), 7.23–7.73 (4H, m, Ar-*H*), 12.58 (1H, s, N*H*). ^{13}C NMR δ_C (DMSO-d_6, 75 MHz) 11.9, 21.2, 62.8, 66.2, 66.9, 116.2, 116.6, 116.9, 117.9, 118.0, 118.2, 118.3, 123.7, 137.1, 138.6, 147.3, 150.3, 157.9, 161.7; Anal. Calcd. for $C_{15}H_{17}FN_4O_4$: C, 53.57; H, 5.09; N, 16.66. Found: C, 53.47; H, 5.02; N, 16.54.

2-[(3-Methyl-5-oxo-4-(2-p-tolylhydrazono)-4,5-dihydro-1H-pyrazol-1-yl) methoxy]ethyl acetate (13b)

Compound **13b** was synthesized from **4b,** in a similar manner as described for **13g,** in 85% yield; yellow foam; IR (KBr) 3230 cm^{-1} (ν NH), 1742 cm^{-1} (ν C = O, ester), 1657 cm^{-1} (ν C = O, amide); ^{1}H NMR δ_H ($CDCl_3$, 300 MHz) 1.32 (3H, s, CH_3), 2.06 (3H, s, CH_3CO), 2.63 (1H, s, CH_3), 4.18 (2H, t, CH_2), 4.50 (2H, m, CH_2OCO), 5.24 (2H, s, NCH_2O), 7.25 (2H, d, Ar-*H*, J= 8.4 Hz), 7.69 (2H, d, Ar-*H*, J = 8.4 Hz). ^{13}C NMR δ_C (DMSO-d_6, 75MHz) 11.6, 20.8, 63.3, 66.2, 83.2, 116.4, 128.5, 129.7, 131.8, 140.3, 148.5, 164.1, 170.5; Anal. Calcd. for $C_{16}H_{20}N_4O_4$ (332.35): C, 57.82; H, 6.07; N, 16.86. Found: C, 57.71; H, 5.96.08; N, 16.77.

2-[4-(2-(4-Bromophenyl)hydrazono]-3-methyl-5-oxo-4,5-dihydro-1H-pyrazol-1-yl)methoxy]ethyl acetate (13e)

Compound **13e** was synthesized from **4e,** in a similar manner as described for **13g,** in 83% yield; yellow foam; IR (KBr) 1735 cm^{-1} (ν C = O, ester), 1666 cm^{-1} (ν C = O, amide), 1235 cm^{-1} (ν C-O, ether); ^{1}H NMR δ_H ($CDCl_3$, 300 MHz) 2.05 (3H, s, *Ac*), 2.62 (3H,s, CH_3-pyrazolinone ring), 3.75 (2H, t, OCH_2), 4.21 (2H, t, CH_2OCO), 5.18 (2H, s, NCH_2O), 7.26 (2H, d, Ar-*H*, J= 8.3 Hz), 7.52 (2H, d, Ar-*H*, J = 8.3 Hz), 13.26 (1H, brs, N*H*). Anal. Calcd. for $C_{15}H_{17}BrN_4O_4$: C, 45.35; H, 4.31; N, 14.10. Found: C, 45.39; H, 4.27; N, 14.06.

2-[(3-Methyl-5-oxo-4-(2-(3-trifluoromethyl)phenyl)hydrazono)-4, 5-dihydro-1H-pyrazol-1-yl)methoxy]ethyl acetate (13h)

Compound **13h** was synthesized from **4h,** in a similar manner as described for **13g,** in 80% yield; yellow crystals; m. p 145–146°C; IR (KBr) 3301 cm^{-1}(ν NH), 1740 cm^{-1} (ν C = O, ester), 1668 cm^{-1} (ν C = O, amide). ^{1}H NMR δ_H (DMSO-d_6, 300 MHz) 2.04 (3H, s, Ac), 2.58 (3H, s, CH_3-pyrazolinone ring), 4.41 (2H, t, OCH_2), 4.72 (2H, t, CH_2OCO), 4.98 (2H, s, NCH_2O), 7.23–7.72 (4H, m, Ar-*H*), 13.12 (1H, brs, N*H*). ^{13}C NMR δ_C (DMSO-d_6, 300 MHz) 12.0, 34.7, 62.8, 66.2, 66.9, 99.9, 112.9, 120.1, 121.6, 129.6, 130.4, 130.8, 131.2, 142.9, 147.1, 157.6; Anal. Calcd. for $C_{16}H_{17}F_3N_4O_4$: C, 49.74; H, 4.44; N, 14.50. Found: C, 49.84; H, 4.41; N, 14.42.

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1-[(2-Hydroxyethoxy)methyl)-3-methyl-4-(2-p-tolylhydrazono]-1H-pyrazol-5(4H)-one (14b)

Compound **13b** (0.48 g, 1.44 mmol) was deprotected, in a similar manner described for **11a,** to give **14b** (0.34 g, 82% yield) as a yellow foam; ^{1}H NMR δ_H (DMSO-d_6, 300 MHz) 2.33 (3H, s, CH_3), 2.55 (3H, s, Ac), 3.74 (2H, t, CH_2OH), 4.25 (2H, t, OCH_2), 4.75(1H, t, OH), 4.98 (2H, s, NCH_2O), 7.28 (2H, d, Ar-H, J 8.32 Hz), 7.58 (2H, d, Ar-H, J 8.3 Hz), 12.52 (1H, s, NH). Anal. Calcd. for $C_{14}H_{18}N_4O_3$: C, 57.92; H, 6.25; N, 19.30. Found: C, 57.69; H, 6.36; N, 19.21.

4-(2-(4-Fluorophenyl)hydrazono)-1-[(2-hydroxyethoxy)methyl]-3-methyl-1H-pyrazol-5(4H)-one (14g)

Compound **13g** (0.54 g, 1.36 mmol) was deprotected in a similar manner described for **11a**, to give **14g** (0.3 g, 73% yield) as a yellow foam; ^{1}H NMR δH (DMSO-d_6, 300 MHz) 2.56 (3H, s, CH_3), 3.68 (2H, t, CH_2OH), 4.19 (2H, t, OCH_2), 4.52 (1H, t, OH), 5.16 (2H, s, NCH_2O), 7.29 (2H, d, Ar-H, J = 8.43 Hz), 7.49 (2H, d, Ar-H), 13.2 (1H, brs, NH). Anal. Calcd. for $C_{13}H_{15}FN_4O_3$: C, 53.06; H, 5.14; N, 19.04. Found: C, 52.96; H, 5.03; N, 14.94.

4-[2-(4-Bromophenyl)hydrazono)-1-(2-hydroxyethoxy)methyl]-3-methyl-1H-pyrazol-5(H)-one (14e)

Compound **13e** (0.42 g, 1.1 mmol) was deprotected, in a similar manner described for **11a,** to give **14e** (0.29 g, 78% yield) as a yellow foam; ^{1}H NMR δ_H ($CDCl_3$, 300 MHz) 2.26 (3H, s, CH_3), 3.69 (2H, t, CH_2OH), 4.21(2H, t, OCH_2), 4.49 (1H, brt, OH), 5.18 (2H, s, NCH_2O), 7.26 (2H, d, Ar-H), 7.52 (2H, d, Ar-H), 13.26 (1H, brs, NH). ^{13}C NMR δ_C (DMSO-d_6, 75 MHz) 11.7, 61.2, 69.5, 84.6, 116.8, 118.0, 128.5, 132.7, 142.0, 148.5, 164.5; Anal. Calcd. for $C_{13}H_{15}BrN_4O_3$: C, 43.96; H, 4.26; N, 15.77. Found: C, 43.95; H, 4.19; N, 15.61.

1-[(2-Hydroxyethoxy)methyl)-3-methyl-4-(2-(3-trifluoromethyl)-phenyl)hydrazono)-1H-pyrazol-5(4H)-one (14h)

Compound **13h** (0.51 g, 1.32 mmol) was deprotected, in a similar manner described for **11a,** to give **14h** (0.3 g, 68% yield) as a yellow foam; ^{1}H NMR δ_H (DMSO-d_6, 300 MHz) 2.54 (3H, s, CH_3), 3.70 (2H, t, CH_2OH), 4.23 (2H, t, OCH_2), 4.51 (1H, brt, OH), 5.28 (2H, s, NCH_2O), 7.23–7.85 (4H, m, Ar-H), 12.50 (1H, brs, NH). Anal. Cald. for $C_{14}H_{15}F_3N_4O_3$: C, 48.84; H, 4.39; N, 16.27. Found: C, 48.71; H, 4.27; N, 16.12.

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