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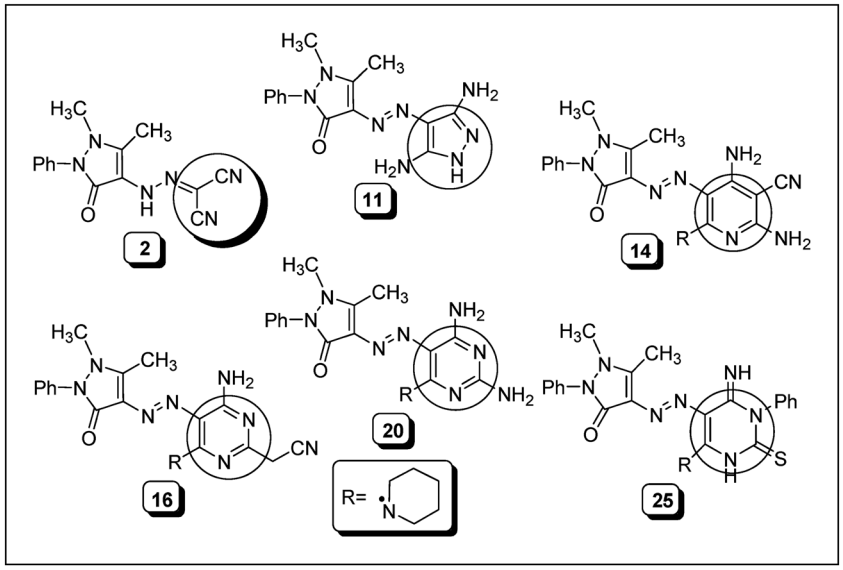

The starting (1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazol-4-yl)carbonohydrazonoyl dicyanide (**2**) was used as key intermediate for the synthesis of 3-amino-2-(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazol-4-ylazo)-[3-substituted]-1-yl-acrylonitrile derivatives (**3**–**10**). In addition, nitrile derivative **2** reacted with hydrazine hydrate or malononitrile to afford the corresponding 3,5-diaminopyrazole **11** and enaminonitrile derivative **13**, respectively. On the other hand, compound **3** was subjected to react with malononitrile, acetic anhydride, triethylorthoformate, *N,N*-dimethylformamide (DMF)-dimethylacetal, thiourea, and hydroxylamine hydrchloride to afford antipyrine derivatives **16**–**21**. Moreover, the reaction of enaminonitrile **3** with carbon disulfide in pyridine afforded the pyrimidine derivative **22**, whereas, in NaOH/DMF followed by the addition of dimethyl sulphate afforded methyl carbonodithioate **24**. The reaction of enaminonitrile derivatives **3**–**5** with phenylisothiocyanate afforded the thiopyrimidine derivatives **25a**–**c**. Finally, the enaminonitrile **4** reacted with 3-(4-chloro-phenyl)-1-phenyl-propenone to afford the pyridine derivative **27**. The newly synthesized compounds were characterized by elemental analyses and spectral data (IR, ^{13}C-NMR, ^{1}H–NMR, and MS).

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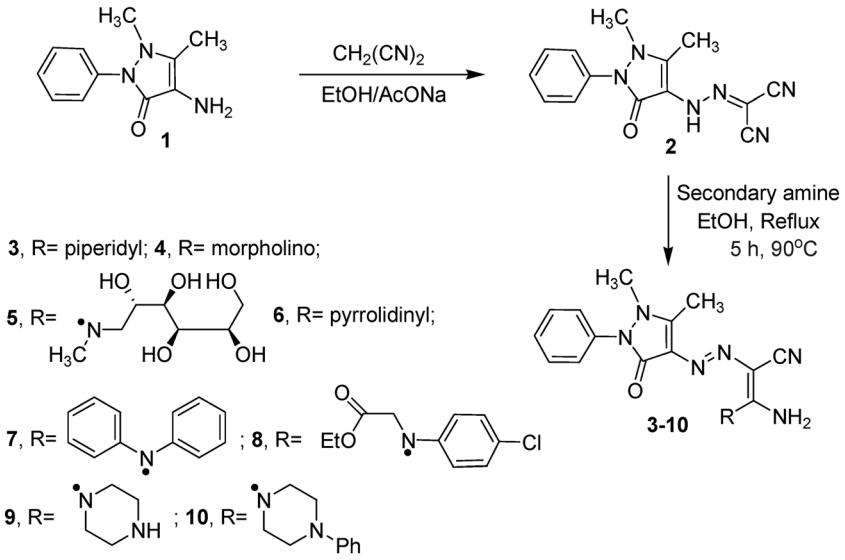
INTRODUCTION

In recent years, there has been increasing interest in the syntheses of heterocyclic compounds that have biological and commercial importances. Antipyrine compounds play an important role in modern organic synthesis, not only because they constitute a particularly useful class of heterocyclic compounds [1–3] but also because they are of great biological interest. They have been found to have biological [4], clinical [5], and pharmacological [6,7], activities. One of the most important derivatives of antipyrine is 4-aminoantipyrine (4AAP), which are used as a synthetic intermediate to prepare polyfunctionally substituted heterocyclic moieties with anticipated biological activity [8], analgesic [9,10], anti-inflammatory [10], antimicrobial [11–13], and anticancer [14] activities. It was of interest to study the reactivity of antipyrinylhydrazonomalononitrile toward different nitrogen nucleophiles as well as activated nitriles.

In continuation of our studies on the chemistry of enamino and activated nitriles [1,3,15,16], and as a part

Scheme 1



of our program directed toward developing new approaches to a variety of heterocycles incorporating the antipyrine moiety [1,3] of potential biological activity, we report here the scope and applicability of (1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazol-4-yl) carbonohydrazonoyl dicyanide as a unique precursor for the synthesis of some enaminonitriles and their behavior toward different reagents in which a antipyrine ring is incorporated.

RESULTS AND DISCUSSION

The key precursor (1,5-dimethyl-3-oxo-2-phenyl-2, 3-dihydro-1*H*-pyrazol-4-yl)carbonohydrazonoyl dicyanide (**2**) [1,17,18] was prepared by diazo-coupling of 4-aminoantipyrine (**1**) with malononitrile in ethanolic sodium acetate solution at 0–5°C. Compound **2** reacted with different secondary amines namely; (piperidine, morpholine, *N*-methylglucamine, pyrrolidine, diphenyl amine, ethyl 2-(4-chlorophenylamino)acetate, piperazine, and 1-phenylpiperazine) in refluxing ethanol to afford the corresponding 1:1 acyclic enaminonitrile adducts **3**–**10**, respectively (Scheme 1).

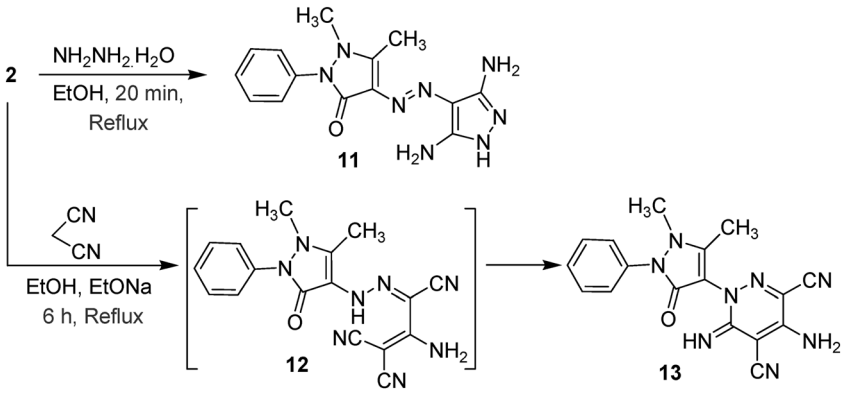
Furthermore, we investigated the reactivity of **2** toward hydrazine hydrate to obtain the pyrazole derivatives. Thus, an equimolar amount of hydrazine hydrate reacted with nitrile derivative **2** to afford the corresponding 3,5-diaminopyrazole derivative **11**. Moreover, we have also investigated the possible utility of compound **2** to develop a facile and convenient route to polyfunctionally pyridazine derivative **13** with expected biological activities [19]. Thus, compound **2** reacted with malononitrile in refluxing sodium ethoxide to yield the corresponding enaminonitrile derivative **13** *via* the intermediate **12**, which produced by nucleophilic addition of the active methylene group in malononitrile to nitrile function in **2** followed by heterocyclization (Scheme 2). The IR spectrum displayed the presence of a broad absorption bands at 3336 and 3214 cm^{-1} characteristic to the NH_2 and NH functions. The mass spectrum showed a molecular ion peak at *m/z* 346 (M^+, 4.3%).

In addition, the reaction of enaminonitrile **3** with malononitrile in ethanolic sodium ethoxide solution afforded the corresponding pyrimidine derivative **16**. The ^{1}H-NMR spectrum revealed singlet signal for two methylene protons at δ 4.13 ppm beside one amino group at δ 8.1 ppm as expected. Based on these data, it seemed that compound **16** was formed *via* the intermediate **15** as shown in Scheme 3. Similar behavior has been reported [20].

When compound **3** was heated in refluxing acetic anhydride, the diacetyl derivative **17** was obtained. Moreover, the reaction of enaminonitrile **3** with triethyl orthoformate afforded the ethoxymethylideneamino derivative **18**. The reaction of **3** with *N,N*-dimethylformamide-dimethylacetal (DMF-DMA) in dry xylene afforded *N, N*-dimethyl-formamidine derivative **19**.

The reaction of **3** with thiourea in ethanol-DMF mixture catalyzed by triethylamine afforded the pyrimidine derivative **20** *via* H_2S elimination. In a similar manner, the reaction of **3** with hydroxyl amine hydrochloride in ethanol catalyzed by triethylamine afforded the pyrazole derivative **21** (Scheme 3).

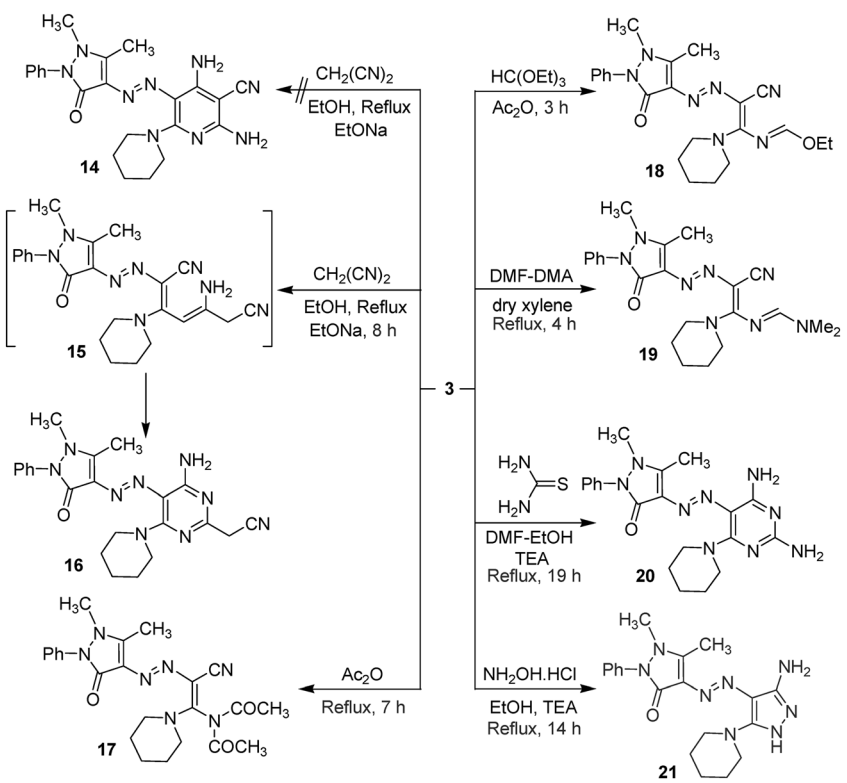
Scheme 2



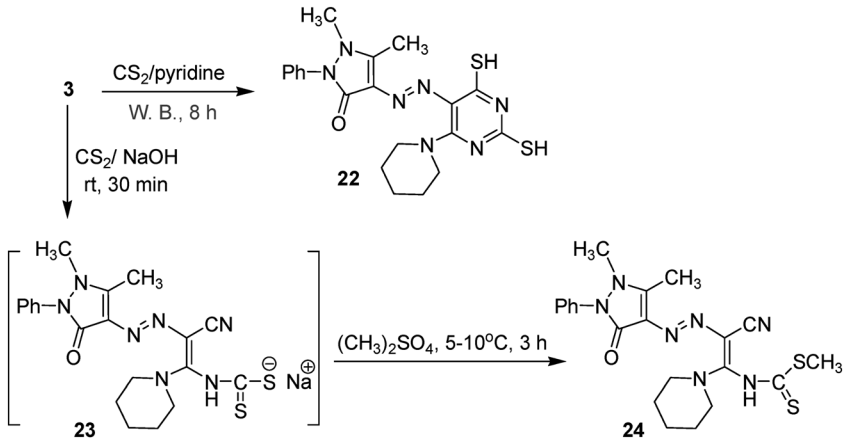
The reaction of **3** with carbon disulfide in pyridine proceeded by the addition of carbon disulfide to the amino group, followed by cyclization through nucleophilic attack of the sulfur atom to the cyano group, which subsequently underwent rearrangement to give the pyrimidinedithiole derivative **22**, similar behavior has been reported [21,22]. On the other hand, the reaction of **3** with carbon disulphide in sodium hydroxide solution simultaneously in a vigorously stirred solution of enaminonitrile **3** in dimethylformamide led to the formation of the sodium salt of enaminonitrile **23**, which was methylated with dimethyl sulphate to get [2-cyano-2-(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazol-4-ylazo)-1-piperidin-1-yl-vinyl]-dithio-carbamic acid methyl ester (**24**) (Scheme 4).

The enaminonitrile moiety in **3**–**5** proved to be highly reactive toward nitrogen nucleophiles. Thus, compounds **3**–**5** were refluxed with phenyl isothiocyanate in ethanol/DMF catalyzed by few drops of triethylamine to afford the corresponding pyrimidinethione derivative **25a**–**c** (Scheme 5). The structures of **25a**–**c** were elucidated on the basis of elemental analyses and spectral data. The ^{1}H-NMR spectra of **25a**–**c** together with their mass spectra

Scheme 3



Scheme 4



gives a more conformational data for the proposed structures (cf. Experimental section).

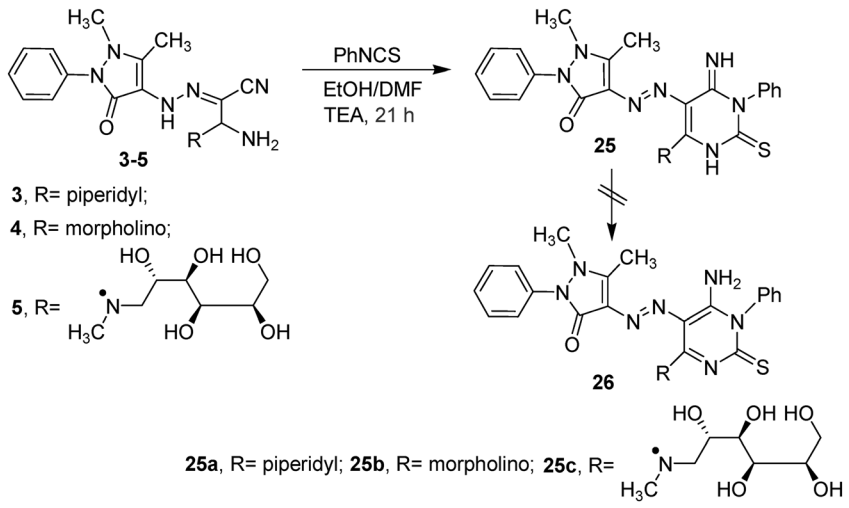
Finally, the pyridine derivative **27** was achieved *via* the reaction of enaminonitrile **4** with 3-(4-chloro-phenyl)-1-phenyl-propenone in DMF-EtOH catalyzed by triethylamine (Fig. 1).

EXPERIMENTAL

All melting points are recorded on Gallenkamp electric melting point apparatus. The IR spectra υ cm^{-1} (KBr) were on Perkin Elmer Infrared Spectrophotometer Model 157, Grating. The ^{13}C-NMR and ^{1}H-NMR spectra were run on Varian Spectrophotometer at 100 and 400 MHz using TMS as an internal reference and DMSO-d_6 as solvent. The mass spectra (EI) were run at 70 eV with JEOL JMS600 equipment and/or a Varian MAT 311 A Spectrometer. Elemental analyses (C, H, and N) were carried out at the Micro Analytical Center of Cairo Univ., Giza, Egypt. The results were found to be in good agreement (±0.3%) with the calculated values. 2-[(1,5-Dimethyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazol-4-yl)-hydrazono]-malononitrile (**2**) [1,17,18]; (93%), mp 140°C; yellowish orange crystals; ^{1}H-NMR (400 MHz, DMSO-d_6): δ, 2.26 (s, 3H, CH_3), 3.25 (s, 3H, N—CH_3), 7.35–7.56 (m, 5H, Ph), 12.1 (br, s, 1H, NH); ms: (*m/z*, %): 281 (M^++1, 4.3), 280 (M^+, 13.4), 188 (5.2), 91 (8.1), 56 (100.0).

Synthesis of 3-amino-2-(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazol-4-ylazo)-[3-substituted]-1-yl-acrylonitrile derivatives (3–10). ***General procedure.*** A mixture of (1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazol-4-yl)carbono-hydrazonoyl dicyanide (**2**) (1.4 g, 5 mmol) and the appropriate secondary amine namely; piperidine (0.49 mL, 5 mmol), morpholine (0.43 mL, 5 mmol), *N*-methylglucamine (0.98 g, 5 mmol), pyrrolidine (0.41 mL, 5 mmol), diphenyl amine (0.85 g, 5 mmol), ethyl 2-(4-chlorophenylamino)acetate (1.07 g, 5 mmol), piperazine (0.43 g, 5 mmol), or 1-phenylpiperazine (0.81 g, 5 mmol) in ethanol (15 mL) was refluxed for 5 h. The reaction mixture was left to cool, and the precipitated solid was filtered off, dried, and recrystallized from EtOH-DMF (2:1) mixture to afford the corresponding acyclic enaminonitrile derivatives **3–10**.

Scheme 5



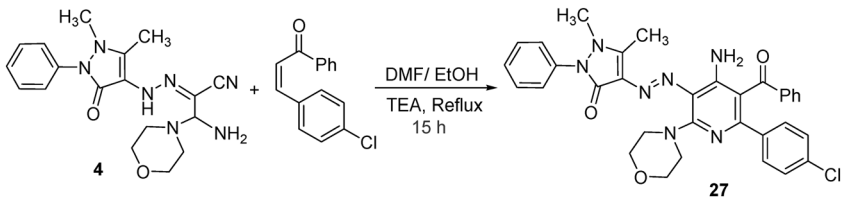


Figure 1. Reaction of enaminonitrile **4** with 3-(4-chloro-phenyl)-1-phenyl-propenone: Synthesis of aminopyridine derivative **27**.

3-Amino-2-(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazol-4-ylazo)-3-piperidin-1-yl-acrylonitrile (3). Yield: 91%, mp 209°C; dark green crystals; IR (KBr) ύ (cm^{-1}), 3392, 3334 (NH_2), 3189 (NH), 2960 (C—H, stretching), 2171 (CN), 1639 (CO), 1448 (N=N); ^{1}H-NMR (400 MHz, DMSO-d_6): δ, 1.58–1.69 (m, 6H, $3CH_2$, piperidine), 2.63 (s, 3H, CH_3), 3.16 (s, 3H, N—CH_3), 3.52–3.62 (m, 4H, $2CH_2$, piperidine), 7.13 (br., s, 2H, NH_2), 7.31–7.52 (m, 5H, Ph); ms: (*m/z*, %): 367 (M^+, 2.3), 366 (M^+-1, 14.5), 338 (12.2), 280 (11.0), 215 (11.0), 189 (77.9), 152 (100.0), 86 (12.8), 63 (26.7). *Anal.* Calcd. for $C_{19}H_{25}N_7O$ (367.45): C, 62.10; H, 6.86; N, 26.68%. Found: C, 62.23; H, 6.91; N, 26.76%.

3-Amino-2-(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazol-4-ylazo)-3-morpholin-4-yl-acrylonitrile (4). Yield: 83%, mp 232°C; light brown crystals; IR (KBr) ύ (cm^{-1}), 3385, 3337 (NH_2), 3197 (NH), 2967 (C—H, stretching), 2186 (CN), 1637 (CO), 1470 (N=N); ^{1}H-NMR (400 MHz, DMSO-d_6): δ, 2.22–2.25 (m, 4H, $2CH_2$, morpholine), 2.44 (s, 3H, CH_3), 3.10 (s, 3H, N—CH_3), 3.58–3.74 (m, 4H, $2CH_2$, morpholine), 7.24 (br, s, 2H, NH_2), 7.36–7.51 (m, 5H, Ph); ms: (*m/z*, %): 368 (M^+-1, 6.7), 367 (M^+-2, 15.5), 275 (7.7), 214 (13.4), 188 (14.6), 108 (24.6), 96 (17.8), 56 (100.0). *Anal.* Calcd. for $C_{18}H_{23}N_7O_2$ (369.42): C, 58.52; H, 6.28; N, 26.54%. Found: C, 58.61; H, 6.33; N, 26.61%.

3-Amino-2-(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazol-4-ylazo)-3-[methyl-(2,3,4,5,6-pentahydroxy-hexyl)-amino]-acrylonitrile (5). Yield: 83%, mp 205°C; dark yellow crystals; IR (KBr) ύ (cm^{-1}), 3451, 3436 (OH), 3358, 3301 (NH_2), 2954 (C—H, stretching), 2186 (CN), 1648 (CO), 1459 (N=N); ^{1}H-NMR (400 MHz, DMSO-d_6): δ, 2.47 (s, 3H, CH_3), 3.16 (s, 3H, N—CH_3), 3.35–3.41 (m, 5H, CH_2—N—CH_3), 3.86–3.93 (m, 2H, CH_2O), 4.36–5.14 (br, m, 5H, 5OH), 7.33 (br, s, 2H, NH_2), 7.35-7.53 (m, 5H, Ph); ms: (*m/z*, %): 439 (M^+-2-$2H_2O$, 100.0), 438 (97.0), 282 (78.8), 279 (48.5), 241 (93.9), 178 (69.7), 163 (57.6), 144 (63.6), 104 (45.5), 94 (15.2), 57 (30.3). *Anal.* Calcd. for $C_{21}H_{31}N_7O_6$ (477.51): C, 52.82; H, 6.54; N, 20.53%. Found: C, 52.91; H, 6.59; N, 20.72%.

3-Amino-2-(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazol-4-ylazo)-3-pyrrolidin-1-yl-acrylonitrile (6). Yield: 88%, mp 229°C; light brown sheets; IR (KBr) ύ (cm^{-1}), 3367, 3272 (NH_2), 3183 (NH), 2944, 2875 (C—H, aliphatic), 2173 (CN), 1641 (CO), 1467 (N=N); ^{1}H-NMR (400 MHz, DMSO-d_6): δ, 1.92–2.09 (m, 4H, $2CH_2$, pyrrolidine), 2.44 (s, 3H, CH_3), 3.10 (s, 3H, N—CH_3), 3.50–3.69 (m, 4H, $2CH_2$, pyrrolidine), 6.73 (br., s, 2H, NH_2), 7.31–7.51 (m, 5H, Ph). *Anal.* Calcd. for $C_{18}H_{23}N_7O$ (353.42): C, 61.17; H, 6.56; N, 27.74%. Found: C, 61.26; H, 6.61; N, 27.83%.

3-Amino-2-(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazol-4-ylazo)-3-diphenylamino-acrylonitrile (7). Yield: 75%, mp 98°C; light black powder; IR (KBr) ύ (cm^{-1}), 3352, 3271 (NH_2), 2179 (CN), 1644 (CO), 1472 (N=N); ^{1}H-NMR (400 MHz, DMSO-d_6): δ, 2.42 (s, 3H, CH_3), 3.18 (s, 3H, N—CH_3), 6.63–7.54 (m, 15H, Ar-H), 8.14 (br, s, 2H, NH_2). *Anal.* Calcd. for $C_{26}H_{25}N_7O$ (451.52): C, 69.16; H, 5.58; N, 21.71%. Found: C, 69.27; H, 5.63; N, 21.79%.

[1-Amino-2-cyano-2-(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazol-4-ylazo)-vinyl]-(4-chloro-phenyl)-amino]-acetic acid ethyl ester (8). Yield: 75%, mp 88–90°C; light black powder; IR (KBr) ύ (cm^{-1}), 3358, 3266 (NH_2), 2183 (CN), 1740 (C=O, ester), 1648 (CO), 1479 (N=N); ^{1}H-NMR (400 MHz, DMSO-d_6): δ, 1.29 (t, 3H, $CH_2\underline{CH_3}$, J = 7.2 Hz), 2.41 (s, 3H, CH_3), 3.18 (s, 3H, N—$\underline{CH_3}$), 3.82 (s, 2H, CH_2), 4.12 (q, 2H, $\underline{CH_2}CH_3$, J = 7.2 Hz), 6.2 (br, s, 2H, NH_2), 7.01–8.12 (m, 9H, Ar-H); ms: (*m/z*, %): 495 (M^+, 0.5), 447 (0.2), 214 (7.5), 212 (19.6), 141 (33.0), 139 (100.0), 56 (16.0). *Anal.* Calcd. for $C_{24}H_{26}ClN_7O_3$ (495.96): C, 58.12; H, 5.28; N, 19.77%. Found: C, 58.21; H, 5.34; N, 19.81%.

3-Amino-2-(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazol-4-ylazo)-3-piperazin-1-yl-acrylonitrile (9). Yield: 72%, mp 89–90°C; dark red powder; IR (KBr) ύ (cm^{-1}), 3450, 3379 (NH_2), 3159 (NH), 2929 (C—H, stretching), 2174 (CN), 1639 (CO), 1494 (N=N); ms: (*m/z*, %): 368 (M^+, 0.4), 343 (1.0), 228 (2.9), 201 (6.9), 189 (10.0), 160 (17.5), 135 (69.5), 73 (100.0), 65 (20.8). *Anal.* Calcd. for $C_{18}H_{24}N_8O$ (368.44): C, 58.68; H, 6.57; N, 30.41%. Found: C, 58.63; H, 6.51; N, 30.38%.

3-Amino-2-(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazol-4-ylazo)-3-(4-phenyl-piperazin-1-yl)-acrylonitrile (10). Yield: 86%, mp 230°C; yellow powder; IR (KBr) ύ (cm^{-1}), 3390, 3334 (NH_2), 2925, 2809 (C—H, aliphatic), 2173 (CN), 1610 (CO), 1490 (N=N); ^{1}H-NMR (400 MHz, DMSO-d_6): δ, 2.44 (s, 3H, CH_3), 3.10 (s, 3H, N—CH_3), 3.28–3.36 (m, 4H, $2CH_2$, piperazine), 3.72–3.82 (m, 4H, $2CH_2$, piperazine), 6.12 (br, s, 2H, NH_2), 6.81-7.53 (m, 5H, Ph); ms: (*m/z*, %): 444 (M^+, 5.0), 375 (0.4), 228 (46.6), 214 (65.3), 188 (82.4), 162 (59.7), 132 (94.7), 120 (100.0), 99 (67.3), 88 (42.7), 73 (81.9), 66 (24.3). *Anal.* Calcd. for $C_{24}H_{28}N_8O$ (444.53): C, 64.84; H, 6.35; N, 25.21%. Found: C, 64.92; H, 6.39; N, 25.27%.

Synthesis of 4-((3,5-diamino-1*H*-pyrazol-4-yl)diazenyl)-1,5-dimethyl-2-phenyl-1*H*-pyrazol-3(2*H*)-one (11). A solution of **2** (1.4 g, 5 mmol) and hydrazine hydrate (0.24 mL, 5 mmol) in ethanol (15 mL) was refluxed for 20 min. The reaction mixture was left to cool, and the precipitated solid was filtered off, dried, and recrystallized from a mixture of ethanol and DMF (1:2) to afford compound **11** as yellow crystals (88%). m.p.: > 300°C; IR (KBr): 3450, 3480 ($2NH_2$), 1640 (C=O); ^{1}H-NMR (400 MHz, DMSO-d_6): δ, 2.47 (s, 3H, CH_3), 3.20

(s, 3H, N—CH_3), 5.74 (br., s, 4H, $2NH_2$), 7.34–7.54 (m, 5H, Ph), 10.61 (br., s, 1H, NH); ms: (*m/z*, %): 313 (M^++1, 3.1), 312 (M^+, 14.8), 311 (M^+-1, 4.2), 284 (0.6), 299 (0.5), 215 (1.1), 188 (2.7), 111 (6.8), 56 (100.0). Anal. Calcd. for $C_{14}H_{16}N_8O$ (312.33): C, 53.84; H, 5.16; N, 35.88%. Found: C 53.74, H 5.19, N 35.84%.

Synthesis of 4-amino-1-(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazol-4-yl)-6-imino-1,6-dihydropyridazine-3,5-dicarbonitrile (13). A mixture of **2** (1.4 g, 5 mmol), malononitrile (0.33 g, 5 mmol), and freshly prepared sodium ethoxide [prepared by adding 1.0 g sodium metal into ethanol (20 mL)] in ethanol (20 mL) was refluxed for 6 h. The reaction mixture was left to cool and poured onto water. The formed solid product was filtered off, dried, and recrystallized from a mixture of ethanol and DMF (1:1) to give compound **13** as brown powder (71%). m.p.: above 300°C (dec); IR (KBr): 3336 (NH_2), 3214 (NH), 2200 (CN), 1633 (CO); ms: (*m/z*, %): 346 (M^+, 4.3), 313 (13.1), 185 (17.3), 83 (100.0). Anal. Calcd. for $C_{17}H_{14}N_8O$ (346.35): C, 58.95; H, 4.07; N, 32.35%. Found: C 58.89, H 4.13, N 32.42%.

Synthesis of [4-amino-5-(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazol-4-ylazo)-6-piperidin-1-yl-pyrimidin-2-yl]-acetonitrile (16). A mixture of **3** (1.84 g, 5 mmol) and malononitrile (0.33 g, 5 mmol) was added to freshly prepared sodium ethoxide solution [prepared by adding 1.0 g sodium metal into ethanol (20 mL)], the reaction mixture was refluxed for 8 h and left to cool overnight. The obtained solid product was collected by filtration, washed, and crystallized from ethanol to afford **16** as dark green crystals (78%). m.p.: 140–142°C; IR (KBr): 3456 (br, NH_2), 2209 (CN), 1650 (br, C═N, CO); ^{13}C-NMR (100 MHz, DMSO-d_6): δ, 174.31, 171.42, 167.20, 163.52, 161.30, 159.93, 154.6, 136.21, 130.22, 126.5, 126.43, 123.43, 117.63, 115.49, 115.36, 92.40, 86.36, 85.40, 53.61, 53.63, 53.61, 42.50, 25.91, 25.66, 25.37, 22.14, 11.63; ^{1}H-NMR (400 MHz, DMSO-d_6): δ, 1.53–1.67 (m, 6H, $3CH_2$, piperidine), 2.64 (s, 3H, CH_3), 3.12 (s, 3H, N—CH_3), 3.52–3.67 (m, 4H, $2CH_2$, piperidine), 4.13 (s, 2H, CH_2), 7.35–7.59 (m, 5H, Ph), 8.1 (br., s, 2H, NH_2); ms: (*m/z*, %): 433 (M^++2, 1.4), 391 (7.2), 375 (14.5), 343 (14.5), 278 (17.4), 254 (23.2), 213 (26.1), 186 (59.4), 129 (36.2), 84 (50.7), 73 (66.7), 57 (88.8). Anal. Calcd. for $C_{22}H_{25}N_9O$ (431.49): C, 61.24; H, 5.84; N, 29.21%. Found: C, 61.29; H, 5.87; N, 29.26%.

Synthesis of *N*-acetyl-*N*-[2-cyano-2-(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazol-4-ylazo)-1-piperidin-1-yl-vinyl]-acetamide (17). A mixture of **3** (1.84 g, 5 mmol) and acetic anhydride (20 mL) was heated under reflux for 7 h. The reaction mixture was poured into ice cold water, and the formed solid product was filtered, washed with ethanol, dried, and crystallized from ethanol to yield **17** as black crystals (65%). m.p.: 218°C; IR (KBr): 2960 (C—H, stretching), 2174 (CN), 1645 (CO), 1449 (N═N); ms: (*m/z*, %): 449 (M^+, 0.3), 342 (57.2), 324 (10.3), 309 (100.0), 215 (14.8), 169 (21.8), 84 (24.8), 73 (34.9), 56 (22.0). Anal. Calcd. for $C_{23}H_{27}N_7O_3$ (449.51): C, 61.46; H, 6.05; N, 21.81%. Found: C, 61.55; H, 6.11; N, 21.87%.

Synthesis of *N*-[2-cyano-2-(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazol-4-ylazo)-1-piperidin-1-yl-vinyl]-formimidic acid ethyl ester (18). A mixture of **3** (1.84 g, 5 mmol) and triethyl orthoformate (0.83 mL, 5 mmol) in acetic anhydride (10 mL) was refluxed on a water bath for 3 h. The reaction mixture was left to cool and poured into ice cold water. The formed solid product was filtered, dried, and crystallized from DMF-EtOH to yield **17** as brown powder (62%). m.p.: 176°C; IR (KBr): 2940 (C—H, stretching), 2934–2836 (CH, aliphatic), 2178 (CN), 1638 (CO), 1452 (N═N); ms: (*m/z*, %): 418 (M^+-3, 0.5), 350 (5.2), 295 (8.2), 255 (12.2), 229 (16.7), 188 (100.0), 151 (33.7), 122 (17.0), 88 (44.1). Anal. Calcd. for $C_{22}H_{27}N_7O_2$ (421.50): C, 62.69; H, 6.46; N, 23.26%. Found: C, 62.76; H, 6.51; N, 23.33%.

Synthesis of *N′*-[2-cyano-2-(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazol-4-ylazo)-1-piperidin-1-yl-vinyl]-*N,N*-dimethyl-formamidine (19). To a solution of compound **3** (1.47 gm, 4 mmol) in xylene (15 mL), DMF-DMA (0.53 mL, 4 mmol) was added. The reaction mixture was heated under reflux for 4 h, then filtered, and recrystallized from DMF-EtOH mixture to give **19** as brown powder (51%). m.p.: 94°C; IR (KBr): 2931, 2856 (C—H, aliphatic), 2177 (CN), 1637 (CO), 1616 (C═N); ms: (*m/z*, %): 419 (M^+-1, 0.5), 349 (6.3), 228 (13.7), 202 (28.1), 188 (100.0), 118 (32.9), 88 (54.4), 73 (67.0). Anal. Calcd. for $C_{22}H_{28}N_8O$ (420.51): C, 62.84; H, 6.71; N, 26.65%. Found: C, 62.93; H, 6.78; N, 26.72%.

Synthesis of 4-(2,4-diamino-6-piperidin-1-yl-pyrimidin-5-ylazo)-1,5-dimethyl-2-phenyl-1,2-dihydro-pyrazol-3-one (20). A mixture of **3** (1.84 g, 5 mmol) and thiourea (0.38 g, 5mmol) in ethanol-DMF mixture (20 mL) in the presence of catalytic amount of triethylamine (5 drops) was refluxed for 19 h. The reaction mixture was left to cool. The formed solid product was filtered, dried, and crystallized from DMF-EtOH to furnish **20** as dark yellow powder (74%). m.p.: 93°C; IR (KBr): 3431, 3372 (br, $2NH_2$), 1639 (CO), 1458 (N═N); ms: (*m/z*, %): 405 (M^+-2, 1.2), 349 (11.5), 308 (10.9), 294 (100.0), 265 (51.1), 238 (39.1), 226 (98.3), 197 (78.5), 143 (47.3), 78 (60.1). Anal. Calcd. for $C_{20}H_{25}N_9O$ (407.47): C, 58.95; H, 6.18; N, 30.94%. Found: C, 59.03; H, 6.24; N, 30.97%.

Synthesis of 4-(5-amino-3-piperidin-1-yl-2*H*-[1,2,6]oxadiazin-4-ylazo)-1,5-dimethyl-2-phenyl-1,2-dihydro-pyrazol-3-one (21). A mixture of **3** (1.84 g, 5 mmol) and hydroxylamine hydrochloride (0.35 g, 5 mmol) in ethanol (15 mL) in the presence of catalytic amount of triethylamine (four drops) was refluxed for 14 h, and the reaction mixture was left to cool. The formed solid product was filtered, dried, and crystallized from ethanol to furnish **21** as yellow powder (68%). m.p.: 124°C; IR (KBr): 3346, 3298 (NH_2), 3116 (NH), 2936, 2859 (C—H, aliphatic), 1647 (CO), 1623 (C═N); ms: (*m/z*, %): 382 (M^++2, 3.1), 349 (13.8), 269 (41.5), 255 (19.4), 240 (100.0), 226 (35.7), 212 (43.2), 198 (22.9), 187 (62.2), 55(47.1). Anal. Calcd. for $C_{19}H_{24}N_8O$ (380.45): C, 59.98; H, 6.36; N, 29.45%. Found: C, 60.06; H, 6.47; N, 29.53%.

Synthesis of 4-(2,4-dimercapto-6-piperidin-1-yl-pyrimidin-5-ylazo)-1,5-dimethyl-2-phenyl-1,2-dihydro-pyrazol-3-one (22). A solution of **3** (1.47 g, 4 mmol) in a mixture of dry pyridine (25 mL) and carbon disulphide (10 mL) was refluxed on a water bath for 8 h and allowed to stand at room temperature for two days. The solution was then triturated with aqueous ethanol (50 mL). The precipitated solid was filtered off and recrystallized from DMF-EtOH mixture to

afford **22** as dark red crystals (81%). m.p.: 167°C; IR (KBr): 2573 (2SH), 1639 (CO), 1494 (N═N); ^{1}H-NMR (400 MHz, DMSO-d_6): δ, 1.58–1.68 (m, 6H, 3CH_2, piperidine), 2.42 (s, 3H, CH_3), 3.09 (s, 3H, N—CH_3), 3.55–3.65 (m, 4H, 2CH_2, piperidine), 7.17–7.52 (m, 7H, Ar-H, 2SH); ms: (*m/z*, %): 438 (M^+-3, 0.5), 342 (13.1), 187 (100.0), 144 (5.4), 121 (25.8), 88 (44.0), 56 (49.2). Anal. Calcd. for $C_{20}H_{23}N_7OS_2$ (441.57): C, 54.40; H, 5.25; N, 22.20%. Found: C, 54.51; H, 5.28; N, 22.27%.

Synthesis of [2-cyano-2-(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazol-4-ylazo)-1-piperidin-1-yl-vinyl]-dithiocarbamic acid methyl ester (24). To a vigorously stirred solution of enaminonitrile **3** (7.35 g, 0.02 mol) in dimethylformamide (10 mL) at room temperature, carbon disulphide (1.57 mL, 0.026 mol) and aqueous sodium hydroxide (1.2 mL, 20 mol solution) were added simultaneously over 30 min. Stirring was continued for a further 30 min. Dimethyl sulphate (1.9 mL g, 0.02 mol) was added dropwise to the reaction mixture with stirring at 5–10°C; it was further stirred for 3 h and poured into ice-water; the solid obtained was filtered, dried, and recrystallized from ethanol to afford **24** as orange powder (88%). m.p. 152°C; IR (KBr) cm^{-1}: 3151 (NH), 2173 (CN), 1641 (C═O), 1494 (N═N), 1178 (C═S); ^{1}H-NMR (400 MHz, DMSO-d_6): δ, 1.59–1.71 (m, 6H, 3CH_2, piperidine), 2.44 (s, 3H, CH_3), 2.91 (s, 3H, SCH_3), 3.10 (s, 3H, N—CH_3), 3.56–3.64 (m, 4H, 2CH_2, piperidine), 7.15–7.50 (m, 5H, Ar-H), 7.97 (br, s, 1H, NH), ms: (*m/z*, %): 455 (M^+, 29.6), 384 (30.4), 288 (24.2), 239 (60.1), 188 (43.5), 175 (57.8), 144 (47.8), 84 (78.8), 70 (45.2). Anal. calcd for $C_{21}H_{25}N_7OS_2$ (455.60): C, 55.36; H, 5.53; N, 21.52%. Found: C, 55.41; H, 5.58; N, 21.61%.

Synthesis of 4-(2-(4-(substituted)-6-imino-1-phenyl-2-thioxotetrahydro-pyrimidin-5(6*H*)-ylidene)hydrazinyl)-1,5-dimethyl-2-phenyl-1*H*-pyrazol-3(2*H*)-ones (25a–c). An equimolar mixture of **3** (1.84 g, 5 mmol) or **4** (1.85 g, 5 mmol) or **5** (2.39 g, 5 mmol) and phenyl isothiocyanate (0.6 mL, 5 mmol) in EtOH-DMF mixture (3:1, 20 mL) in the presence of catalytic amount of TEA (four drops) was refluxed for 21 h. The reaction mixture was left to cool and poured into cold water for complete precipitation. The separated solid was filtered off, washed with water, dried well, and recrystallized from ethanol to yield pyrimidine derivatives **25a**–**c**.

4-(6-Amino-1-phenyl-4-piperidin-1-yl-2-thioxo-1,2-dihydro-pyrimidin-5-ylazo)-1,5-dimethyl-2-phenyl-1,2-dihydro-pyrazol-3-one (25a). Yield (50%). m.p. 157°C; IR (KBr) ύ (cm^{-1}), 3193 (NH), 2964 (C—H, stretching), 1643 (CO), 1452 (N═N), 1216 (C═S); ^{1}H-NMR (400 MHz, DMSO-d_6): δ, 1.55–1.67 (m, 6H, 3CH_2, piperidine), 2.61 (s, 3H, CH_3), 3.22 (s, 3H, N—CH_3), 3.53–3.66 (m, 4H, 2CH_2, piperidine), 7.38–7.56 (m, 5H, Ph), 10.86 (br, s, 2H, 2NH); ms: (*m/z*, %): 500 (M^+, 0.21), 284 (9.13), 283 (8.57), 227 (8.13), 200 (7.77), 109 (13.5), 84 (100.0), 77 (90.0). Anal. calcd for $C_{26}H_{28}N_8OS$ (500.62): C, 62.38; H, 5.64; N, 22.38%. Found: C, 62.46; H, 5.74; N, 22.43%.

4-(6-Amino-4-morpholin-4-yl-1-phenyl-2-thioxo-1,2-dihydro-pyrimidin-5-ylazo)-1,5-dimethyl-2-phenyl-1,2-dihydro-pyrazol-3-one (25b). Yield (57%). m.p. 193°C; IR (KBr) ύ (cm^{-1}), 3183 (NH), 2958 (C—H, stretching), 1647 (CO), 1462 (N═N), 1209 (C═S); ^{1}H-NMR (400 MHz, DMSO-d_6): δ, 2.24–2.29 (m, 4H, 2CH_2, morpholine), 2.43 (s, 3H, CH_3), 3.17 (s, 3H, N—CH_3), 3.34–3.71 (m, 4H, 2CH_2, morpholine), 6.93–7.51 (m, 5H, Ar-H), 10.81 (br, s, 2H, 2NH), ms: (*m/z*, %): 503 (M^+, 0.41), 286 (70.0), 271 (22.34), 229 (9.16), 200 (38.0), 168 (17.04), 86 (100.0), 77 (62.9). Anal. calcd for $C_{25}H_{26}N_8O_2S$ (502.59): C, 59.74; H, 5.21; N, 22.30%. Found: C, 59.81; H, 5.29; N, 22.37%.

4-{6-Amino-4-[methyl-(2,3,4,5,6-pentahydroxy-hexyl)-amino]-1-phenyl-2-thioxo-1,2-dihydro-pyrimidin-5-ylazo}-1,5-dimethyl-2-phenyl-1,2-dihydro-pyrazol-3-one (25c). Yield (60%). m.p. 187°C; IR (KBr) ύ (cm^{-1}), 3453, 3446 (OH), 3109 (NH), 2962 (C—H, stretching), 1658 (CO), 1446 (N═N), 1230 (C═S); ^{1}H-NMR (400 MHz, DMSO-d_6): δ, 2.47 (s, 3H, CH_3), 3.16 (s, 3H, N—CH_3), 3.01–4.52 (sugar moiety protons), 7.15–7.65 (m, 5H, Ph), 11.12 (br., s, 2H, 2NH); ms: (*m/z*, %): 590 [(M^+-2)-H_2O, 4.3], 589 (M^+-3-H_2O, 5.2), 181 (48.3), 136 (50.0), 93 (100.0), 51 (87.9). Anal. calcd for $C_{28}H_{34}N_8O_6S$ (610.68): C, 55.07; H, 5.61; N, 18.35%. Found: C, 55.13; H, 5.66; N, 18.40%.

Synthesis of 4-((4-amino-5-benzoyl-6-(4-chlorophenyl)-2-morpholinopyridin-3-yl)diazenyl)-1,5-dimethyl-2-phenyl-1H-pyrazol-3(2H)-one (27). A mixture of **4** (1.85 g, 5 mmol) and 3-(4-chloro-phenyl)-1-phenyl-propenone (1.21 g, 5 mmol) in DMF-EtOH mixture (15 mL, 1:3) in the presence of catalytic amount of triethylamine (5 drops) was refluxed for 15 h. The reaction mixture was poured into ice cold water, the formed solid product was filtered, dried, and crystallized from DMF-EtOH (1:4) to yield **27** as dark brown powder (67%). m.p.: 118–120°C; IR (KBr) ύ (cm^{-1}), 3388, 3346 (NH_2), 1683, 1637 (2CO), 1493 (N═N); ^{1}H-NMR (400 MHz, DMSO-d_6): δ, 2.43 (s, 3H, CH_3), 3.17 (s, 3H, N—CH_3), 3.55–3.93 (m, 8H, 4CH_2, morpholine), 7.05–8.35 (m, 16H, Ar-H, NH_2); ms: (*m/z*, %): 617 (M^++7, 1.6), 342 (24.9), 241 (100.0), 215 (36.7), 177 (34.7), 136 (19.5), 114 (10.8), 99 (42.0), 73 (93.7). Anal. Calcd. for $C_{33}H_{30}ClN_7O_3$ (608.09): C, 65.18; H, 4.97; N, 16.12%. Found: C, 65.24; H, 5.03; N, 16.17%.

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