Utility of Enaminonitriles in Heterocyclic Synthesis: Synthesis of Some New Azepine, Azocine, and Pyrroldione Derivatives

Ahmed A. Fadda and Khaled M. Elattar*

Chemistry Department, Faculty of Science, Mansoura University, El-Gomhoria Street, 35516 Mansoura, Egypt
*E-mail: khaledelattar2@yahoo.com

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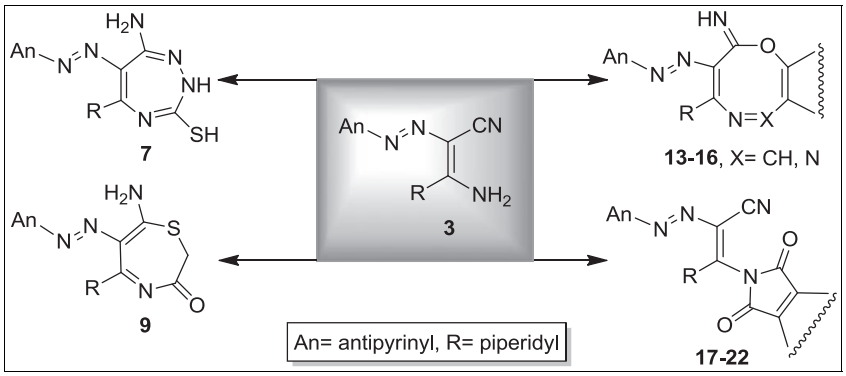

Reactions of enaminonitrile derivative **3** with a variety of reagents lead to the syntheses of novel 1,2,4-triazepin **7**, 1,4-thiazepinone **9**, oxazocines **13**, **14**, oxadiazocines **15**, **16**, and pyrroldiones **17–22** with the aim to explore the use of this exceptionally reactive enaminonitrile **3** in heterocyclic synthesis. Newly synthesized compounds were characterized by elemental analyses and spectral data (IR, ^{1}H-NMR, ^{13}C-NMR, and MS).

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INTRODUCTION

Enaminonitriles are important intermediates for the preparation of heterocyclic compounds possessing diverse biological activities. They are of particular interest as very promising reagents for cascade heterocyclization, which will undoubtedly become one of the main approaches to the targeted synthesis of heterocycles in the near future, in the rapidly rising field of combinatorial chemistry [1–7].

Chemistry of cyclic enaminonitriles and enaminoesters has been reviewed in 1992 by Wamhoff [8]. Although the chemistry of enamines was recently reviewed in several reports, little attention has been paid to the chemistry of enaminonitriles [9–12]. Several of these enaminonitriles have been investigated and found to exhibit a wide range of bioactivities including antitumor [13], antimicrobial [14], antiviral [15], analgesic, and anti-inflammatory drugs [16], and others, and their bioactivity diversities have been reported in these contexts.

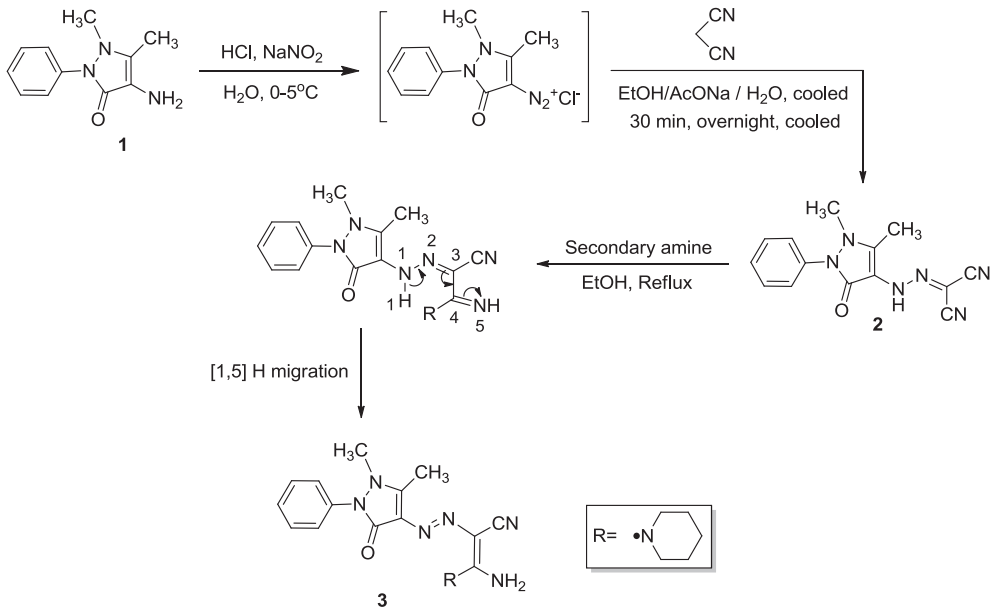
In this work, we report here the scope and applicability of 2-[(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazol-4-yl)-hydrazono]malononitrile as a unique precursor for the synthesis of some previously unreported enaminonitriles in which antipyrine ring is incorporated.

RESULTS AND DISCUSSION

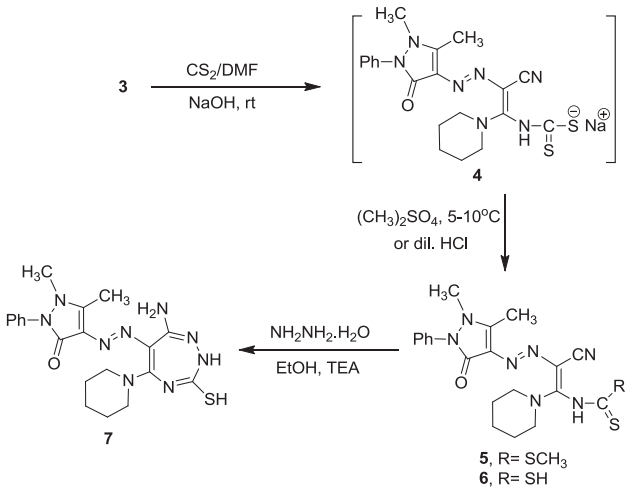
The synthetic strategies adopted to obtain the target compounds are depicted in Schemes 1–7. The key precursor 2-[(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazol-4-yl)-hydrazono] malononitrile (**2**) [17] was prepared by diazo-coupling of 4-aminoantipyrine (**1**) with malononitrile in ethanolic sodium acetate solution at 0–5°C. Compound **2** reacted with piperidine in refluxing ethanol to afford the corresponding 1:1 acyclic enaminonitrile adduct **3**, respectively. The formation of enaminonitrile **3** was illustrated through the initial addition of the secondary amines to cyano function to form the imino form followed by [1,5] H migration to form the enamine form (Scheme 1).

On the other hand, treatment of a vigorously stirred solution of enaminonitrile **3** in DMF with carbon disulphide and sodium hydroxide solution led to the formation of the sodium salt of enaminonitrile **4**, which was methylated with dimethyl sulfate to obtain methyl mercaptan derivative **5**. Furthermore, refluxing of **5** with hydrazine hydrate in ethanol catalyzed by TEA led to the formation of 1,2,4-triazepin derivative **7**. The formation of **7** was preceded by the addition of amino group in hydrazine hydrate to the cyano function in enaminonitrile derivative **3** follow by cyclization via the elimination of methyl mercaptan molecule (Scheme 2). The structures **5** and **7** were established on the basis of elemental analyses and spectral data. The IR spectrum of compound **5** showed characteristic absorption band at 1178 cm^{-1} due to (C═S) group, whereas the IR spectrum of compound **7** showed the band at 2400 cm^{-1} due to (SH) group and the absence of the bands corresponding to cyano and (C═S) functions. The ^{1}H-NMR spectrum of compound **5** revealed four singlet signals at δ

Scheme 1. Synthesis of acyclic enaminonitrile derivative **3**.



Scheme 2. Routes for the synthesis of 1,2,4-triazepin derivative **7**.



2.44, 2.91, 3.10, and 7.97 ppm corresponding to (CH_3), (SCH_3), (N–CH_3), and (NH) protons, respectively, and the expected signals of piperidyl and aromatic protons. Moreover, the ^{1}H-NMR spectrum of compound **7** revealed the absence of the signal at δ 2.91 ppm of SCH_3 protons and revealed five singlet signals at δ 1.63, 2.41, 3.08, 4.15, and 7.1 ppm corresponding to (SH), (CH_3), (N–CH_3), (NH), and (NH_2) protons, respectively. The assigned structures **5** and **7** were further supported by the appearance of their respective molecular ion peaks in the mass spectra at *m/z* 455 (M^+, 29.6%) and 440 ($M^+ + 1$, 9.4%), respectively.

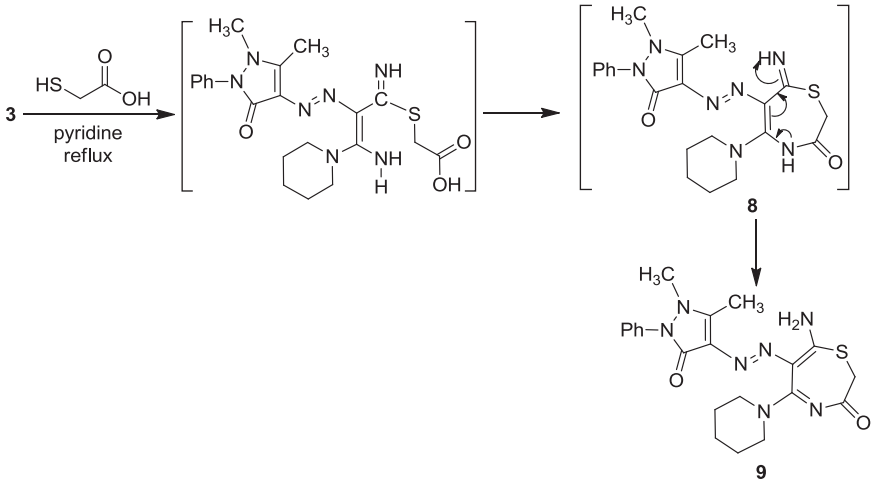
Moreover, acidification of **4** by dilute hydrochloric acid yielded the corresponding methanedithioic acid derivative **6**, which upon heating with hydrazine hydrate in ethanol in the presence of a catalytic amount of TEA (five drops) afforded 1,2,4-triazepin **7** (Scheme 2). This reaction probably involves the addition of the amino group of hydrazine hydrate to cyano group in compound **3** followed by cyclization of the adduct to give **7**. The structure of methanedithioic acid derivative **6** was established on the basis of elemental analysis and spectral data. The IR spectrum showed a band at 2350 cm^{-1} due to the SH group. Also, its mass spectrum showed the molecular ion peak at *m/z* 357 (M^+-piperidyl, 4.7%) corresponding the molecular formula ($C_{20}H_{23}N_7OS_2$).

On the other hand, the reaction of enaminonitrile derivative **3** with thioglycolic acid in refluxing pyridine afforded 1,4-thiazepinone **9**. The formation of structure **9** via the addition of the SH group in thioglycolic acid to cyano group then cyclization by elimination of water molecule followed by rearrangement of structure **8** took place (Scheme 3). The structure of **9** was confirmed by elemental analysis and spectral data. The IR spectrum showed absorption bands at 3343, 3251 cm^{-1} due to (NH_2) group. Its mass spectrum showed the molecular ion peak at *m/z* 439 (M^+, 16.7).

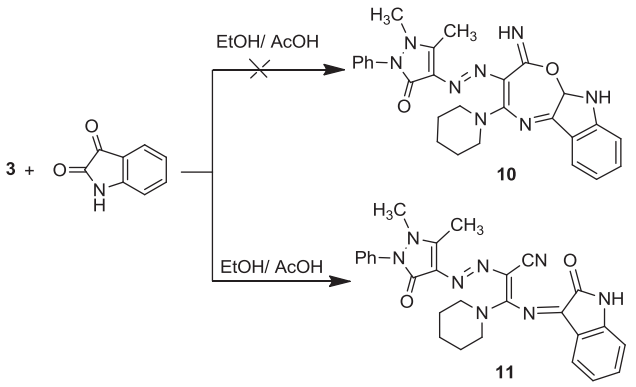
The reaction of compound **3** with isatin in refluxing ethanol containing few drops of glacial acetic acid furnished the corresponding Schiff base **11** instead of the oxazepine derivative **10** (Scheme 4). The formation of compound **11** is indicated by the disappearance of absorption band due to NH_2 in its IR spectrum. The molecular ion peak recorded in the mass spectrum was at *m/z* 480 ($M^+ - CH_3$, 10.2%), which is in agreement with the molecular formula ($C_{27}H_{26}N_8O_2$).

On the other hand, cyclocondensation of enaminonitrile derivative **3** with salicyaldehyde or 2-hydroxy-1-naphthaldehyde in refluxing ethanol in the presence of a catalytic

Scheme 3. Synthesis of 1,4-thiazepinone **9**.



Scheme 4. Reaction of enaminonitrile derivative **3** with isatin.

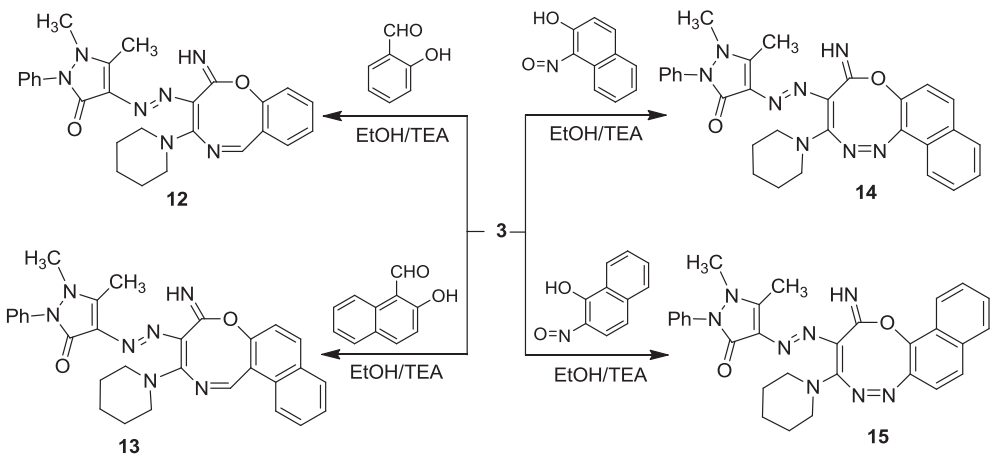


amount of TEA afforded [1,5]oxazocine derivatives **12** and **13**, respectively (Scheme 5). The reaction proceeded initially via condensation of amino group of compound **3** with aldehyde group followed by the addition of hydroxyl group in the aldehyde derivatives to cyano function. The formation of both compounds is indicated by the presence of (C═N) groups in the IR spectra at ν 1527 and 1541 cm^{-1}, respectively, besides no bands of hydroxyl and cyano groups were observed. The mass spectra gave an additional evidence for both structures formation in which the molecular ion peaks appeared at *m/z* 387 (M^+ – piperidyl, 2%) and 438 (M^+ – piperidyl, 7.3%), respectively.

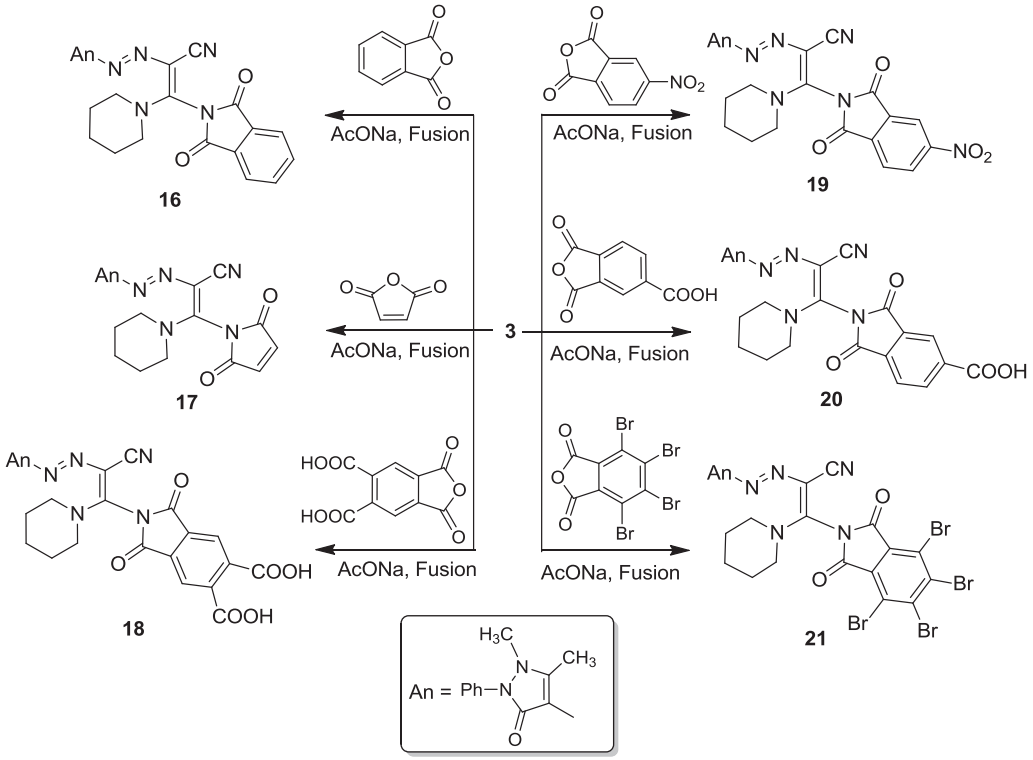
In a similar manner, enaminonitrile derivative **3** underwent cycloaddition with 1-nitroso-2-naphthol or 2-nitroso-1-naphthol in refluxing ethanol in the presence of a catalytic amount of TEA to yield [1,4,5]oxadiazocine derivatives **14** and **15**, respectively (Scheme 5). The structures of oxadiazocine derivatives **14** and **15** were confirmed on the basis of elemental analyses and spectral data. The mass spectra showed the molecular ion peaks at *m/z* 520 (M^+, 3.7%) and 505 ($M^+ - CH_3$, 38.5%), respectively.

In previous publications [18–21], it has been reported that fusion of acid anhydrides with amino group in the

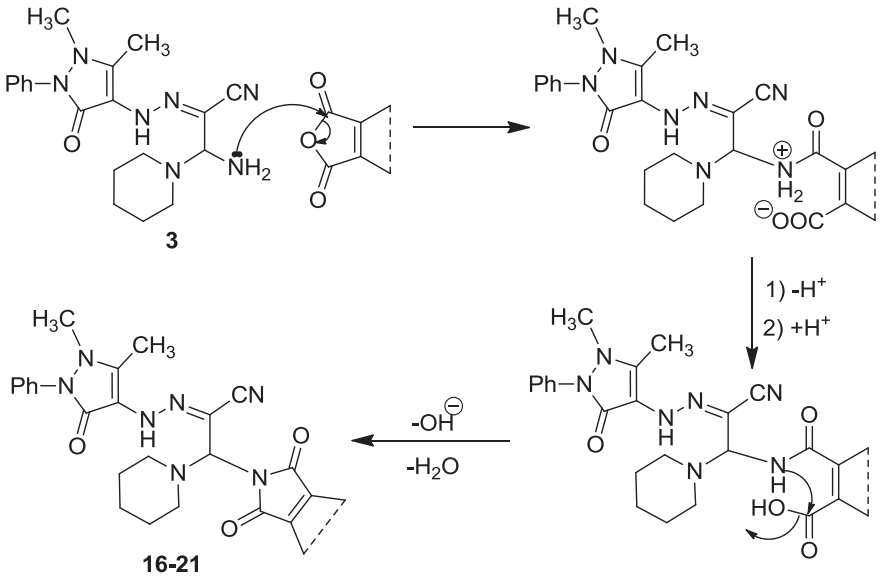
Scheme 5. Synthesis of [1,5]oxazocine and [1,4,5]oxadiazocine derivatives **12–15**.



Scheme 6. Synthesis of pyrroldione derivatives **16–21**.



Scheme 7. Mechanism of formation of pyrroldione derivatives **16–21**.



presence of sodium acetate gave the corresponding pyrroldione derivatives via ammonolysis followed by cyclization. In the present work, fusion of the enaminonitrile **3** with different anhydride derivatives, namely, phthalic anhydride, maleic anhydride, 1,2,4,5-benzene tetracarboxylic anhydride, 4-nitrophthalic anhydride, 1,2,4-benzene tricarboxylic anhydride, or tetrabromophthalic anhydride in the presence of freshly fused sodium acetate afforded the corresponding pyrroldione derivatives **16–21**, respectively (Scheme 6). The structures of compounds **16–21** were elucidated on the basis of elemental analysis and spectral data. The infrared spectrum showed the absence of ν (NH_2) and the presence

of bands at $\nu = 1690–1680\,cm^{-1}$ corresponding to (amide C═O) and bands at $\nu = 2210–2190\,cm^{-1}$ corresponding to ν (C ≡ N) functions. Also, the mass spectra of compounds **16–21** showed the molecular ion peaks at $m/z = 497$ ($M^+ + 2$, 21.2%), 430 ($M^+ - CH_3$, 35.7%), 536 [$M^+ - (H_2O, 2CH_3)$, 4.2%], 541 ($M^+ + 1$, 17.9%), 497 ($M^+ - CO_2$, 7.7%), and 818 ($M^+ + 7$, 5.7%), respectively, which are in agreement with the molecular formula of the investigated compounds **16–21**. The general mechanistic consideration for the formation of the corresponding pyrroldione derivatives **16–21** is shown in Scheme 7.

EXPERIMENTAL

All melting points are recorded on Gallenkamp electric melting point apparatus. The IR spectra $\nu\,cm^{-1}$ (KBr) were on PerkinElmer infrared spectrophotometer model 157, Grating. The ^{13}C-NMR and ^{1}H-NMR spectra were run on Varian spectrophotometer at 100 and 400 MHz, respectively, using TMS as an internal reference and using 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 Microanalytical Center of Cairo University, Giza, Egypt. The results were found to be in good agreement with the calculated values.

2-[(1,5-Dimethyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazol-4-yl)-hydrazono]malononitrile (2) [17]. Yield (93%), mp 140°C; yellowish orange crystals; ^{1}H-NMR (400 MHz, DMSO-d_6): δ_{ppm}, 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 (*Z*)-3-amino-2-((*E*)-(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazol-4-yl)diazenyl)-3-(piperidin-1-yl) acrylonitrile (3). A mixture of **2** (1.4 g, 5 mmol) and piperidine (0.49 mL, 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 derivative **3**. Yield (91%), mp 209°C; dark green crystals; IR (KBr) 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_{ppm}, 1.58–1.69 (m, 6H, $3CH_2$, piperidine, $J = 7.2$ Hz), 2.63 (s, 3H, CH_3), 3.16 (s, 3H, N–CH_3), 3.52–3.62 (m, 4H, $2CH_2$, piperidine, $J = 7.2$ Hz), 7.13 (br s, 2H, NH_2), 7.31–7.52 (m, 5H, Ph); ^{13}C-NMR (100 MHz, DMSO-d_6): δ_{ppm}, 173.2 (C–NH_2), 160.4 (CO), 160.1 (C–CH_3), 136.5, 129.1, 119.5 (Ar–C), 114.8 (CN), 113.0, 95.7 (C–CN), 46.8, 25.9, 25.7 ($5CH_2$, piperidine), 39.8 (N–CH_3), 13.1 (CH_3). MS: (*m/z*, %): 367 ($M^+ + 2$, 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 $C_{19}H_{23}N_7O$ (365.43): C, 62.45; H, 6.34; N, 26.83%. Found: C, 62.52; H, 6.38; N, 26.94%.

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 (5). To a vigorously stirred solution of enaminonitrile **3** (7.35 g, 0.02 mol) in DMF (10 mL) at RT, 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 sulfate (1.9 mL, 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 **5**. Yield (88%). mp 152°C; orange powder, 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_{ppm}, 1.59–1.71 (m, 6H, $3CH_2$, piperidine, $J = 7.2$ Hz), 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, $J = 7.2$ Hz), 7.15–7.50 (m, 5H, Ar–H), 7.97 (br, s, 1H, NH), ^{13}C-NMR (100 MHz, DMSO-d_6): δ_{ppm}, 195.1 (C═S), 174.2 (C–NH), 160.4 (C═O), 160.1 (C–CH_3), 136.6, 130.5, 129.1, 123.0, (Ar–C), 103.7 (C–N═N), 113.0 (CN), 88.2 (C–CN), 51.6, 26.2, 24.1 ($5CH_2$, piperidine), 39.8 (N–CH_3), 25.7 (S–CH_3), 15.1 (CH_3). MS: (*m/z*, %): 455 (M^+, 60.1) 239 ,(24.2) 288 ,(30.4) 384 ,(29.6), 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 (*Z*)-2-cyano-2-((*E*)-(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazol-4-yl)diazenyl)-1-(piperidin-1-yl)vinylcarbamo-dithioic acid (6). To a vigorously stirred solution of enaminonitrile **3** (7.35 g, 0.02 mol) in DMF (10 mL) at RT, 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. Dilute hydrochloric acid 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 methanedithioic acid derivative **6**. Yield (68%); mp 148–150°C; red powder; IR (KBr) cm^{-1}: 3187 (NH), 2350 (SH), 2198 (CN), 1643 (C═O), 1565 (C═N), 1415 (N═N), 1224 (C═S); ^{13}C-NMR (100 MHz, DMSO-d_6): δ_{ppm}, 194.8 (C═S), 174.3 (C–NH), 160.4 (C═O), 160.1 (C–CH_3), 136.1, 131.2, 129.1, 125.0, (Ar–C), 104.3 (C–N═N), 114.2 (CN), 88.3 (C–CN), 51.6, 26.7, 24.0 ($5CH_2$, piperidine), 39.6 (N–CH_3), 25.9 (S–CH_3), 14.7 (CH_3). MS: (*m/z*, %): 357 (M^+ – piperidyl, 4.7%), 220 (6.3), 188 (25.6), 112 (8.1), 119 (12.8), 100 (18.6), 95 (16.3), 77 (30.2), 56 (100.0). *Anal.* Calcd for $C_{20}H_{23}N_7OS_2$ (441.57): C, 54.40; H, 5.25; N, 22.20%. Found: C, 54.47; H, 5.31; N, 22.28%.

Synthesis of 4-((*E*)-((1*E*,3*E*,5*E*)-7-amino-3-mercapto-5-(piperidin-1-yl)-2*H*-1,2,4-triazepin-6-yl)diazenyl)-1,5-dimethyl-2-phenyl-1*H*-pyrazol-3(2*H*)-one (7). Method A: A mixture of **5** (2.28 g, 5 mmol) and hydrazine hydrate (0.24 mL, 5 mmol) in ethanol (15 mL) in the presence of catalytic amount of TEA (five drops) was refluxed for 8 h and until the evaluation of methyl mercaptan odor. The reaction mixture was allowed to cool at RT. The separated solid product was filtered, dried, and recrystallized from ethanol to furnish **7**.

Method B: A mixture of methanedithioic acid derivative **6** (2.21 g, 5 mmol) and hydrazine hydrate (0.24 mL, 5 mmol) in ethanol (15 mL) in the presence of catalytic amount of TEA (five drops) was refluxed for 12 h. The reaction mixture was allowed to cool to RT. The separated solid product was filtered, dried, and recrystallized from ethanol to furnish **7**. Yield (A, 79%; B, 68%). mp 220°C; yellowish green needles; IR (KBr) cm^{-1}: 3341, 3211 (NH_2), 3088 (NH), 2400 (SH), 1649 (C═O), 1518 (C═N), 1492 (N═N); ^{1}H-NMR (400 MHz, DMSO-d_6): δ_{ppm}, 1.03–1.08 (m, 6H, $3CH_2$, piperidine, $J = 7.2$ Hz), 1.63 (s, 1H, SH), 2.41 (s, 3H, CH_3), 3.08 (s, 3H, N–CH_3), 3.44–3.56 (m, 4H, $2CH_2$, piperidine, $J = 7.2$ Hz), 4.15 (s, 1H, NH), 7.1 (s, 2H, NH_2), 7.32–7.52 (m, 5H, Ar–H); ^{13}C-NMR (100 MHz,

DMSO-d_6): δ_{ppm}, 164.7 (C=O), 164.6 (C–SH), 160.6 (C–CH_3), 153.4 (N–C=C), 151.2 (C–NH_2), 136.5, 129.1, 124.1, 123.0, (Ar–C), 104.5 (C–N=N), 88.3 (N=N–C), 46.8, 25.9, 24.8 ($5CH_2$, piperidine), 39.8 (N–CH_3), 13.9 (CH_3). MS: (*m/z*, %): 440 ($M^+ + 1$, 109 ,(40.6) 118 ,(12.5) 201 ,(26.6) 203 ,(9.4 (14.1), 91 (29.7), 84 (43.8), 70 (15.6), 56 (100.0). *Anal*. Calcd for $C_{20}H_{25}N_9OS$ (439.54): C, 54.65; H, 5.73; N, 28.68%. Found: C, 54.73; H, 5.69; N, 28.74%.

Synthesis of (4*E*,6*E*)-7-amino-6-((*E*)-(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazol-4-yl)diazenyl)-5-(piperidin-1-yl)-1,4-thiazepin-3(2*H*)-one (9). A solution of **3** (1.47 g, 4 mmol) and thioglycolic acid (0.28 g, 4 mmol) in pyridine (15 mL) was refluxed on a water bath for 12 h and allowed to stand at RT for 1 day. The solution was then triturated with aqueous ethanol (50 mL). The precipitated solid was filtered off and recrystallized from ethanol to afford **9**. Yield (74%); mp 172°C; brown powder; IR (KBr) cm^{-1}: 3282, 3261 (NH_2), 1635 (2C=O), 1492 (C=N), 1448 (N=N); ^{13}C-NMR (100 MHz, DMSO-d_6): δ_{ppm}, 197.3 (C=O), 165.1 (C–NH_2), 160.4 (C=O), 160.1 (C=N), 159.8 (C–CH_3), 136.8, 129.7, 123.3, 122.2 (Ar–C), 103.4 (C–N=N), 78.3 (C=C–NH_2), 46.8, 26.2, 24.1 ($5CH_2$, piperidine), 35.8 (N–CH_3), 32.4 (CH_2), 13.3 (CH_3). MS: (*m/z*, %): 439 (M^+, 16.7), 175 (20.0), 146 (20), 132 (20.0), 121 (40), 111 (53.3), 100 (40), 86 (20.0), 76 (100). *Anal*. Calcd for $C_{21}H_{25}N_7O_2S$ (439.53): C, 57.38; H, 5.73; N, 22.31%. Found: C, 57.46; H, 5.80; N, 22.37%.

Synthesis of (*E*)-2-((*E*)-(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazol-4-yl) diazenyl)-3-((*Z*)-2-oxoindolin-3-ylideneamino)-3-(piperidin-1-yl)acrylonitrile (11). A mixture of **3** (1.84 g, 5 mmol) and isatin (0.74 g, 5 mmol) in ethanol (15 mL) containing few drops of glacial acetic acid was refluxed for 20 h. The reaction mixture was poured into ice-cold water. The formed solid product was filtered, dried, and crystallized from ethanol to yield **11**. Yield (83%). mp: 240°C; light brown powder; IR (KBr) cm^{-1}: 1641, 1679 (2CO), 1538 (C=N), 1417 (N=N); ^{13}C-NMR (100 MHz, DMSO-d_6): δ_{ppm}, 173.3 (N–C–N), 160.6 (C=O), 160.1 (C–CH_3), 153.7 (C=N), 141.2 (CO–NH), 143.2, 134.7, 131.3, 130.6, 124.8, 123.7, 121.6, 119.8, 117.8 (Ar–C), 114.8 (CN), 108.2 (C–CN), 103.5 (C–N=N), 39.9 (N–CH_3), 53.8, 26.8, 24.6 ($5CH_2$, piperidyl), 13.3 (CH_3). MS: (*m/z*, %): 480 ($M^+ - CH_3$, 10.2), 319 (14.3), 280 (14.3), 248 (30.6), 213 (38.8), 155 (30.6), 117 (61.2), 77 (100.0). *Anal*. Calcd for $C_{27}H_{26}N_8O_2$ (494.55): C, 65.57; H, 5.30; N, 22.66%. Found: C, 65.64; H, 5.33; N, 22.72%.

General procedure for the synthesis of benzo[*b*][1,5]oxazocin and naphtho[2,1-*b*][1,5]oxazocin derivatives 12 and 13. An equimolar amounts of enaminonitrile derivative **3** (1.84 g, 5 mmol) and aldehyde derivatives, namely, salicyaldehyde (0.53 mL, 5 mmol) or 2-hydroxy-1-naphthaldehyde (0.86 g, 5 mmol) in ethanol (20 mL) in the presence of catalytic amount of TEA (four drops) were refluxed for 13 and 15 h, respectively. The reaction mixture was left to cool at RT. The precipitated solid was filtered off, washed with ethanol, dried, and recrystallized from ethanol to yield oxazocine derivatives **12** and **13**, respectively.

4-((E)-((3E,5Z)-2-Imino-4-(piperidin-1-yl)-2H-benzo[b][1,5]oxazocin-3-yl)diazenyl)-1,5-di-methyl-2-phenyl-1H-pyrazol-3(2H)-one (12). Yield (69%). mp: 231°C; dark red crystals; IR (KBr) cm^{-1}: 3174, 3141 (NH_2), 1648 (CO), 1527 (C=N), 1452 (N=N), 1153 (C–O, stretching); ^{13}C-NMR (100 MHz, DMSO-d_6): δ_{ppm}, 164.6 (C=NH), 164.2 (N–C–N), 163.8 (N=C), 160.5 (C=O), 160.1 (C–CH_3), 158.3 (C–O), 136.7, 133.1, 133.7, 129.1, 122.3, 121.4, 119.8, 115.3 (Ar–C), 119.7 (C=C), 103.5 (C–N=N), 82.4 (C–N=N), 53.8, 27.2, 25.1 ($5CH_2$, piperidyl), 35.8 (N–CH_3), 25.9, 25.8, 25.7, 18.5, 13.2 (CH_3). MS: (*m/z*, %): 387 (M^+ – piperidyl, 2%), 386 ($M^+ - 2$, 4.0), 376 (6.0), 307 (17.4), 266 (12.1), 215 (13.4), 188 (15.4), 153 (12.1), 109 (11.4), 96 (14.8), 84 (23.5), 67 (22.8), 56 (100.0). *Anal*. Calcd for $C_{26}H_{27}N_7O_2$ (469.54): C, 66.51; H, 5.80; N, 20.88%. Found: C, 66.58; H, 5.86; N, 20.93%.

4-((E)-((1Z,3E)-5-Imino-3-(piperidin-1-yl)-5H-naphtho[2,1-b][1,5]oxazocin-4-yl)diazenyl)-1,5-dimethyl-2-phenyl-1H-pyrazol-3(2H)-one (13). Yield (74%). mp: 258°C; dark red crystals; IR (KBr) cm^{-1}: 3316, 3251 (NH_2), 1644 (CO), 1541 (C=N), 1423 (N=N); ^{13}C-NMR (100 MHz, DMSO-d_6): δ_{ppm}, 164.3 (C=NH), 164.0 (C=N), 163.5 (C=O), 160.7 (N–C–N), 160.3 (C–CH_3), 153.6 (C–O), 133.7, 133.6, 132.4, 131.8, 129.4, 128.2, 127.6, 124.1, 123.7, 122.7, 118.0, 116.8 (Ar–C), 109.4 (C=C), 103.5 (C–N=N), 83.1 (C–N=N), 53.6, 27.3, 25.2 ($5CH_2$, piperidyl), 39.8 (N–CH_3), 25.9, 25.8, 25.7, 13.8 (CH_3). MS: (*m/z*, %): 438 (M^+ – piperidyl, 7.3%), 280 (25.5), 210 (16.4), 188 (12.7), 170 (20.0), 119 (45.5), 96 (23.6), 77 (54.5), 56 (100.0). *Anal*. Calcd for $C_{30}H_{29}N_7O_2$ (519.6): C, 69.35; H, 5.63; N, 18.87%. Found: C, 69.42; H, 5.72; N, 18.95%.

General procedure for the synthesis of naphtho[(1,2-*b*) and (2,1-*b*)][1,4,5]oxadiazocin-3-yl)diazenyl)-1,5-dimethyl-2-phenyl-1*H*-pyrazol-3(2*H*)-one derivatives 14 and 15. An equimolar amounts of enaminonitrile derivative **3** (1.84 g, 5 mmol) and nitroso derivatives, namely, 1-nitroso-2-naphthol (0.87 g, 5 mmol) or 2-nitroso-1-naphthol (0.87 g, 5 mmol) in ethanol (15 mL) in the presence of catalytic amount of TEA (six drops) were refluxed for 12 and 13 h, respectively. The reaction mixture was left to cool at RT. The precipitated solid was filtered off, washed with ethanol, dried, and recrystallized from ethanol to yield oxadiazocine derivatives **14** and **15**, respectively.

4-((E)-((1Z,3E)-5-Imino-3-(piperidin-1-yl)-5H-naphtho[2,1-b][1,4,5]oxadi-azocin-4-yl)diazenyl)-1,5-dimethyl-2-phenyl-1H-pyrazol-3(2H)-one (14). Yield (71%). mp: 256°C; dark gray powder; IR (KBr) cm^{-1}: 3109 (NH), 1652 (CO), 1423 (2 N=N); ^{13}C-NMR (100 MHz, DMSO-d_6): δ_{ppm}, 164.7 (C=NH), 160.8 (C=O), 160.3 (C–CH_3), 155.2 (C–O), 147.8 (N–C–N), 136.6, 135.5, 130.3, 130.1, 129.6, 129.0, 128.6, 127.0, 124.5, 123.7, 122.3, 119.6 (Ar–C), 102.7 (C–N=N), 95.3 (C–N=N), 39.8 (N–CH_3), 49.8, 26.2, 25.1 ($5CH_2$, piperidyl), 13.6 (CH_3). MS: (*m/z*, %): 520 (M^+, 3.7%), 466 (3.7), 364 (4.5), 329 (5.2), 280 (11.9), 214 (17.9), 188 (11.9), 151 (10.4), 119 (19.4), 84 (36.6), 56 (100.0). *Anal*. Calcd for $C_{29}H_{28}N_8O_2$ (520.59): C, 66.91; H, 5.42; N, 21.52%. Found: C, 66.86; H, 5.45; N, 21.56%.

4-((E)-((3E,5Z)-2-Imino-4-(piperidin-1-yl)-2H-naphtho[1,2-b][1,4,5]oxadi-azocin-3-yl)di-azenyl)-1,5-dimethyl-2-phenyl-1H-pyrazol-3(2H)-one (15). Yield (64%). mp: 234°C; dark green powder; IR (KBr) cm^{-1}: 3116 (NH), 1648 (CO), 1418 (2 N=N); ^{13}C-NMR (100 MHz, DMSO-d_6): δ_{ppm}, 165.8 (C=NH), 160.4 (C=O), 160.1 (C–CH_3), 153.7 (C–O), 147.8 (N–C–N), 134.6, 136.5, 131.9, 129.1, 127.0, 126.7, 123.6, 122.3, 121.0, 120.8 (Ar–C), 112.8 (C–N=N), 104.1, 95.3 (C–N=N), 35.8 (N–CH_3), 51.8, 26.3, 25.2 ($5CH_2$, piperidyl), 13.2 (CH_3). MS: (*m/z*, %): 505 ($M^+ - CH_3$, 38.5%), 281 (7.3), 212 (46.2), 183 (53.8), 103 (46.2), 88 (83.5), 72 (38.5), 54 (100.0). *Anal*. Calcd for $C_{29}H_{28}N_8O_2$ (520.59): C, 66.91; H, 5.42; N, 21.52%. Found: C, 66.96; H, 5.48; N, 21.59%.

General procedure for the synthesis of pyrroldione derivatives 16–21. An equimolar amounts of enaminonitrile derivative **3** (1.84 g, 5 mmol) and different anhydride derivatives, namely, phthalic anhydride (0.74 g, 5 mmol), maleic anhydride (0.49 g, 5 mmol), 1,2,4,5-benzene tetracarboxylic anhydride (1.18 g,

5 mmol), 4-nitrophthalic anhydride (0.97 g, 5 mmol), 1,2,4-benzene tricarboxylic anhydride (0.96 g, 5 mmol), or tetrabromophthalic anhydride (2.32 g, 5 mmol) in the presence of freshly fused sodium acetate (5 mmol) were fused in sand bath for 2 h. The reaction mixture was left to cool at RT. The precipitated solid was treated with concd HCl then washed with water, filtered off, dried, and recrystallized from ethanol to yield the corresponding pyrroldione derivatives **16–21**, respectively.

(E)-N′-(1,5-Dimethyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazol-4-yl)-2-(1,3-dioxoiso-indolin-2-yl)-2-(piperidin-1-yl) acetohydrazonoyl cyanide (16). Yield (71%). mp: 263°C; brown powder; IR (KBr) cm^{-1}: 1683 (C═O, amide), 1643 (CO), 2196 (CN); ^{13}C-NMR (100 MHz, DMSO-d_6): δ_{ppm}, 166.8 (2C═O), 160.4 (C═O), 161.2 (N–C–N), 160.1 (C–CH_3), 135.8, 134.5, 132.4, 130.5, 124.1, 123.6, 122.9 (Ar–C), 114.6 (CN), 113.2, 103.0 (C–N═N), 91.7 (C–CN), 35.7 (N–CH_3), 50.3, 25.9, 25.5 ($5CH_2$, piperidyl), 13.0 (CH_3). MS: (*m/z*, %): 497 ($M^+ + 2$, 21.2%), 388 (5.3), 333 (21.1), 229 (36.8), 186 (31.6), 147 (47.4), 93 (60.5), 56 (100.0). *Anal*. Calcd for $C_{27}H_{25}N_7O_3$ (495.53): C, 65.44; H, 5.09; N, 19.79%. Found: C, 65.37; H, 5.13; N, 19.86%.

(E)-N′-(1,5-Dimethyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazol-4-yl)-2-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)-2-(piperidin-1-yl) acetohydrazonoyl cyanide (17). Yield (76%). mp: 280°C; brown powder; IR (KBr) cm^{-1}: 1690 (C═O, amide), 1653 (CO), 2192 (CN); ^{13}C-NMR (100 MHz, DMSO-d_6): δ_{ppm}, 164.2, 161.3 (3C═O), 161.0 (N–C–N), 160.6 (C–CH_3), 136.5 (C═C), 134.6, 130.2, 125.1, 124.1 (Ar–C), 114.6 (CN), 103.2 (C–N═N), 92.3 (C–CN), 50.3, 25.9, 25.7 ($5CH_2$, piperidyl), 39.8 (N–CH_3), 13.5 (CH_3). MS: (*m/z*, %): 430 ($M^+ - CH_3$, 35.7%), 381 (35.7), 230 (50.0), 188 (100.0), 184 (71.4), 110 (64.3), 109 (50.0), 108 (35.7), 96 (64.3), 93 (64.3), 84 (50.0), 83 (71.4), 77 (28.6). *Anal*. Calcd for $C_{23}H_{23}N_7O_3$ (445.47): C, 62.01; H, 5.20; N, 22.01%. Found: C, 61.87; H, 5.12; N, 21.85%.

(E)-2-(2-Cyano-2-(2-(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazol-4-yl)hydrazono)-1-(piperidin-1-yl)ethyl)-1,3-dioxoisoindoline-5,6-dicarboxylic acid (18). Yield (69%). mp: >300°C; brown powder; IR (KBr) cm^{-1}: 1687 (C═O, amide), 1662 (CO), 2207 (CN). ^{13}C-NMR (100 MHz, DMSO-d_6): δ_{ppm}, 168.4, 166.8, 161.4 (5C═O), 161.2 (N−C−N), 160.3 (C−CH_3), 137.4, 134.4, 133.3, 136.8, 130.7, 128.1, 124.4, 123.3 (Ar-C), 114.8 (CN), 103.0 (C−N═N), 91.6 (C−CN), 50.3, 26.8, 25.4 ($5CH_2$, piperidyl), 39.8 (N-CH_3), 26.0, 25.9, 25.8, 13.6 (CH_3). MS: (*m/z*, %): 536 [$M^+ - (H_2O, 2CH_3)$, 4.2%], 402 (7.6), 333 (5.9), 280 (11.0), 216 (23.7), 171 (9.3), 102 (45.8), 56 (100.0). *Anal*. Calcd for $C_{29}H_{25}N_7O_7$ (583.55): C, 59.69; H, 4.32; N, 16.80%. Found: C, 59.73; H, 4.41; N, 16.89%.

(E)-N′-(1,5-Dimethyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazol-4-yl)-2-(5-nitro-1,3-dioxoiso-indolin-2-yl)-2-(piperidin-1-yl) acetohydrazonoyl cyanide (19). Yield (81%). mp: 270°C; brown powder; IR (KBr) cm^{-1}: 1680 (C═O, amide), 1648 (CO), 2210 (CN); ^{13}C-NMR (100 MHz, DMSO-d_6): δ_{ppm}, 167.6, 161.7 (3C═O), 160.6 (N–C–N), 160.2 (C–CH_3), 152.3, 138.3, 133.7, 132.5, 130.6, 129.3, 128.2, 124.5, 123.0, 122.3 (Ar-C), 114.7 (CN), 103.0 (C–N═N), 92.7 (C–CN), 50.3, 26.8, 24.3 ($5CH_2$, piperidyl), 39.8 (N–CH_3), 25.9, 25.7, 25.6, 13.2 (CH_3). MS: (*m/z*, %): 541 ($M^+ + 1$, 17.9%), 540 ($M^+ - 2$, 21.4%), 240 (14.3), 227 (35.7), 199 (25.0), 188 (32.1), 173 (25.0), 142 (17.9), 119 (35.7), 84 (100.0), 56 (96.4). *Anal* Calcd for $C_{27}H_{24}N_8O_5$ (540.53): C, 59.99; H, 4.48; N, 20.73%. Found: C, 59.86; H, 4.53; N, 20.82%.

(E)-2-(2-Cyano-2-(2-(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazol-4-yl)hydrazono)-1-(piperidin-1-yl)ethyl)-1,3-dioxoisoindoline-5-carboxylic acid (20). Yield (76%). mp: 290°C; brown powder; IR (KBr) cm^{-1}: 1690 (C═O, amide), 1651 (CO), 2190 (CN); ^{13}C-NMR (100 MHz, DMSO-d_6): δ_{ppm}, 173.1, 169.8, 160.4 (4C═O), 160.1 (N–C–N), 159.7 (C–CH_3), 138.6, 136.7, 136.5, 134.9, 132.1, 126.9, 124.0, 123.5, 123.8 (Ar–C), 114.7 (CN), 103.8 (C–N═N), 92.0 (C–CN), 50.4, 26.8, 25.3 ($5CH_2$, piperidyl), 39.8 (N–CH_3), 26.1, 25.9, 25.8, 13.3 (CH_3). MS: (*m/z*, %): 497 ($M^+ - CO_2$, 7.7%), 329 (10.3), 119 (15.4), 104 (20.5), 84 (17.9), 77 (43.6), 64 (100.0), 56 (10.3). *Anal*. Calcd for $C_{28}H_{25}N_7O_5$ (539.54): C, 62.33; H, 4.67; N, 18.17%. Found: C, 62.39; H, 4.82; N, 18.22%.

(E)-N′-(1,5-Dimethyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazol-4-yl)-2-(piperidin-1-yl)-2-(4,5,6,7-tetrabromo-1,3-dioxoisoindolin-2-yl)aceto-hydrazonoyl cyanide (21). Yield (66%). mp: 295°C; brown powder; IR (KBr) cm^{-1}: 2203 (CN), 1688 (C═O, amide), 1641 (CO); ^{13}C-NMR (100 MHz, DMSO-d_6): δ_{ppm}, 167.2, 162.8 (3C═O), 160.5 (N–C–N), 160.1 (C–CH_3), 139.3, 134.8, 131.6, 125.6, 129.3, 124.2, 123.1 (Ar–C), 114.7 (CN), 102.7 (C–N═N), 92.7 (C–CN), 36.7 (N–CH_3), 50.2, 26.8, 25.3 ($5CH_2$, piperidyl), 13.3 (CH_3). MS: (*m/z*, %): 818 ($M^+ + 7$, 5.7), 729 (11.4%), 627 (14.3), 524 (17.1), 462 (25.7), 420 (17.1), 338 (20.0), 267 (25.7), 160 (14.3), 118 (20.0), 94 (25.7), 84 (100.0), 56 (56.7). *Anal*. Calcd for $C_{27}H_{21}Br_4N_7O_3$ (811.12): C, 39.98; H, 2.61; N, 12.09%. Found: C, 39.92; H, 2.57; N, 12.01%.

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