

Some New Heterocycles from the Reaction of 4-Carboxaldehyde-2-Phenyl-2H-1,2,3-Triazole Malononitrile

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ABSTRACT

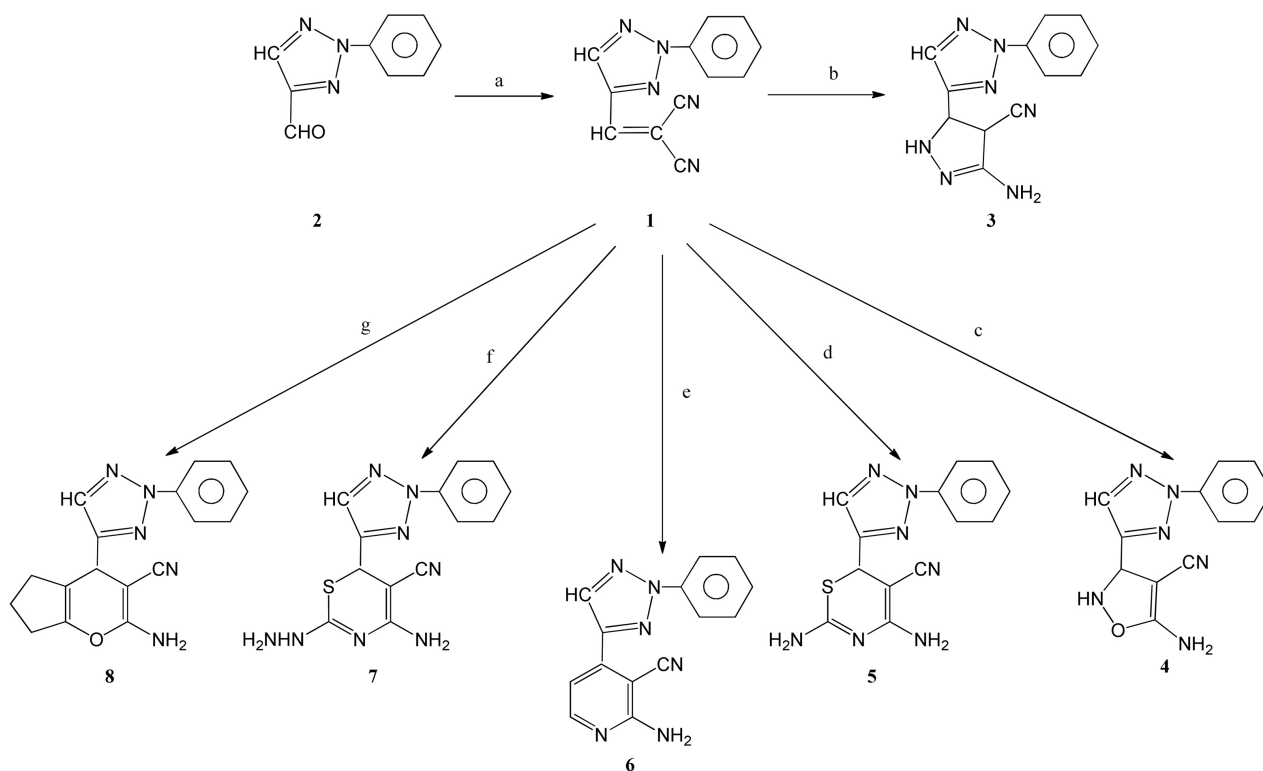
Reaction of 4-carboxaldehyde-2-phenyl-2H-1,2,3-triazole 1 with malononitrile in presence of piperidine afforded the triazolomalonitrile 2 which on treatment with hydrazine hydrate, gave 3-amino-5-(2-phenyl-2H-1,2,3-triazol-4-yl)-4,5-dihydro-1-H-pyrazole-4-carbonitrile 3 and with hydroxylamine, gave 5-amino-3-(2-phenyl-2H-1,2,3-triazol-4-yl)-2,3-dihydroisoxazole-4-carbonitrile 4, and with thiourea, gave 2,4-diamino-6-(2-phenyl-2H-1,2,3-triazol-4-yl)-6H-1,3-thiazine-5-carbonitrile 5. Similarly, reaction of 2 with ethanol amine, gave 2-amino-4-(2-phenyl-2H-1,2,3-triazol-4-yl)nicotinonitrile 6, and with thiosemicarbazide, gave 4-amino-2-hydrazinyl-6-(2-phenyl-2H-1,2,3-triazol-4-yl)-6H-1,3-thiazine-carbonitrile 7. Similar reaction of 2 with cyclopentanone gave, 2-amino-4-(2-phenyl-2H-1,2,3-triazol-4-yl)-4,5,6,7-tetrahydrocyclopenta [6] pyran-3-carbonitrile 8. In addition, reaction of 1 with hydrazine hydrate, gave the 4 hydrazone which on treatment with another mole of 1 gave 10 and with 3-carboxaldehyde-1-phenyl-4,5-pyrazolinedione 4 phenylhydrazone gave compound 11.

1. INTRODUCTION

Our continuous studies have demonstrated the utilization of carbohydrates specially L-ascorbic acid and its analogs in the synthesis of heterocycles including pyrazoles, triazoles, imidazoles and isoxazolines [1-5]. The observation that triazole and pyrazole derivatives are biologically active compounds [6-10] specially as insecticides and antinflammatory has promoted the extension of our study to synthesize a new series of this class of compounds in the hope of producing more effective chemotherapeutic agents.

2. RESULTS AND DISCUSSION

Condensation of 4-carboxaldehyde-2-phenyl-2H-1,2,3-triazole **1** (obtained from the oxidation of D-glucosozone with copper sulphate followed by periodate oxidation) with molononitrile in the presence of triethylamine, afforded the triazolomethylene malononitrile **2** whose ^1H NMR spectrum showed two singlets at δ 7.99 and 8.53 for the ethylenic proton and the C5-H triazole ring respectively. Treatment of **2** with hydrazine hydrate in presence of piperidine, afforded the bicyclic compound, namely, 3-amino-5-(2-phenyl-2H-1,2,3-triazol-4-yl)-4,5-dihydro-1H-pyrazole-4-carbonitrile **3** (Scheme 1) whose structure was confirmed from its spectra and elemental analysis. Its ^1H NMR spectrum showed a singlet of two proton intensity at δ 5.35 due to NH_2 group, a doublet at δ 7.68 (C5'-H) a doublet at 8.33 (C4'-H) and a ginglet at 8.41 (C5-H). The reaction of **2** with hydroxylamine hydrochloride, afforded the bicyclic compound **4** namely, 5-amino-3-(2-phenyl-2H-1,2,3-triazol-4-yl)-2,3-dihydroisoxazole-4-carbonitrile whose structure was confirmed by ^1H NMR which revealed a singlet at δ 5.53 due to NH_2 group, a singlet of one proton intensity at δ 7.56 (C5-H) and a singlet at δ 8.39 (C5-H). Furthermore treatment of **2** with thiourea in the presence of piperidine, gave 2,4-diamino-6-(2-phenyl-2H-1,2,3-triazol-4-yl)-6H-1,3-thiazine-5-carbonitrile **5** whose structure was also confirmed by elemental analysis and NMR data. The ^1H NMR showed two singlets of one proton intensity each at δ 8.20 (C6-H) and 8.48 (C5-H). The reaction of **2** with ethanol amine, afforded 2-amino-4-(2-phenyl-2H-1,2,3-triazol-4-yl)nicotinonitrile **6** whose ^1H NMR revealed two doublets of one proton intensity each at δ 7.25 (C5'-H) and 7.89 (C5-H). Moreover, treatment of **2** with thiosemicarbazide in presence of piperidine, gave 4-amino-2-hydrazinyl-6-(2-phenyl-2H-1,2,3-triazol-4-yl)-6H-1,3-thiazine carbonitrile **7** whose structure was confirmed by ^1H NMR which showed three singlets of one proton intensity each at δ 8.20 (C6-H), 8.60 (C5-H) and 11.69(NH). Finally treatment



Scheme 1. Reagents and conditions: (a) $\text{CH}_2(\text{CN})_2$, EtOH, triethylamine, Δ , 2 h; (b) $\text{NH}_2\text{NH}_2\cdot\text{H}_2\text{O}$, EtOH, piperidine, Δ , 2 h; (c) $\text{NH}_2\text{OH}\cdot\text{HCl}$, EtOH, piperidine, Δ , 2H; (d) NH_2CSNH_2 , EtOH, piperidine, Δ , 2 h; (e) $\text{NH}_2\text{CH}_2\text{CH}_2\text{OH}$, EtOH, piperidine, Δ , 2 h; (f) $\text{NH}_2\text{NHCSNH}_2$, piperidine, Δ , 2 h; (g) cyclopentanone, EtOH, piperidine, Δ , 2 h.

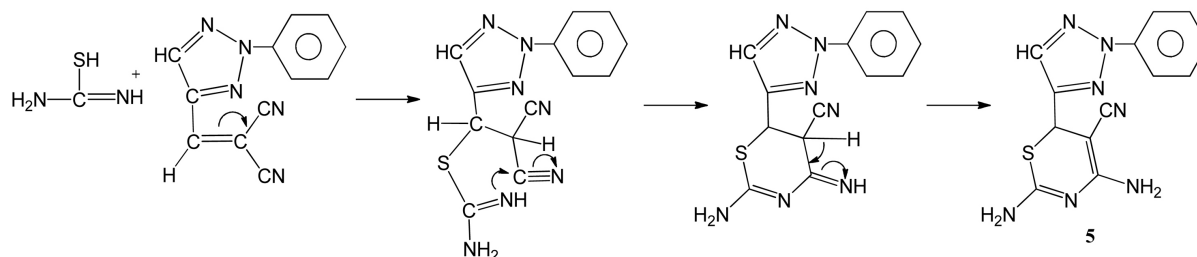
of **2** with cyclopentanone gave 2-amino-4-(2-phenyl-2H-1,2,3-triazol-4-yl)-4,5,6,7-tetrahydrocyclopenta [b] pyran-3-carbonitrile **8**. Its structure was established from its elemental analysis and ¹H NMR data which revealed two singlets of one proton intensity each at δ 8.42 (C5-H) and 8.57 (C5'-H) in addition to the expected proton signals. The reaction course leading to compounds **3-7** **Scheme 2** from the triazole methylenemalononitrile can be assumed to proceed via the addition of the mercapto or amino groups at the ethylenic double bonds and thne nucleophilic attack of the amino or imino groups to the cyclized product except for the reaction of ethanol-amine, the reaction may proceed through the elimination of water molecule and nucleophilic attack of the amino group followed by elimination of H₂ by auto oxidation. In addition, the reaction course leading to the formation of **8** from the triazole methylenemalononitrile **Scheme 2** can be assumed to proceed through the formation of carbanion followed by nucleophilic addition at the ethylenic bond and cyclization to give **8**. The reaction of 4-carboxaldehyde-2-phenyl-2H-1,2,3-triazole **1** with hydrazine hydrate, afforded 4-carboxaldehyde-4-hydrazone **9** which upon treatment with equivalent amount of **1** afforded 1,2-bis[(2-phenyl-2H-1,2,3-triazol-4-yl) methylen] hydrazine **10**. Similarly treatment of **9** with 3-carboxaldehyde-1-phenyl-4,5-pyrazolinedione-4-phenylhydrazono, gave 1-phenyl-3-[2-phenyl-2H-1,2,3-triazol-4-yl]-methylenehydrazonomethyl]-4-(phenylhydrazono)-1H-pyrazol-5(4H)-one **11** (**Scheme 3**).

3. EXPERIMENTAL

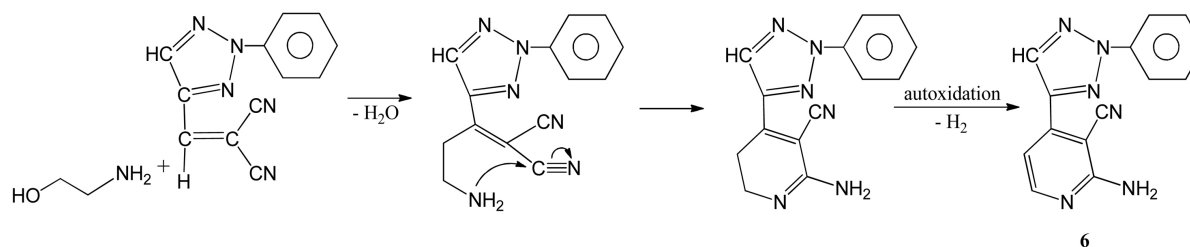
3.1. Apparatus and Materials

Melting points were determined on a Kofler block and tottoli (Büchi) apparatus and are uncorrected.

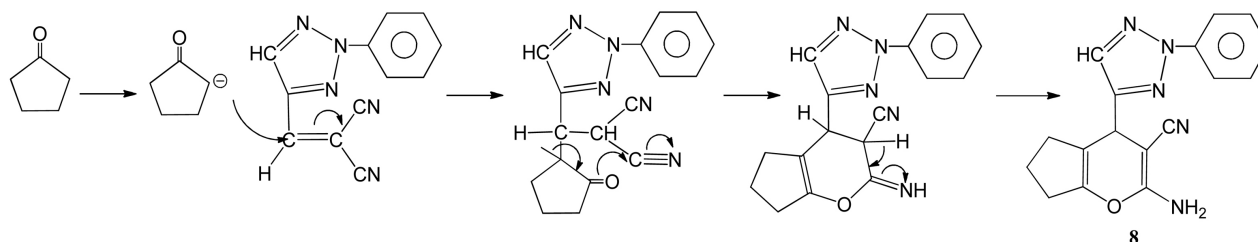
Mechanism of formation of compound 5



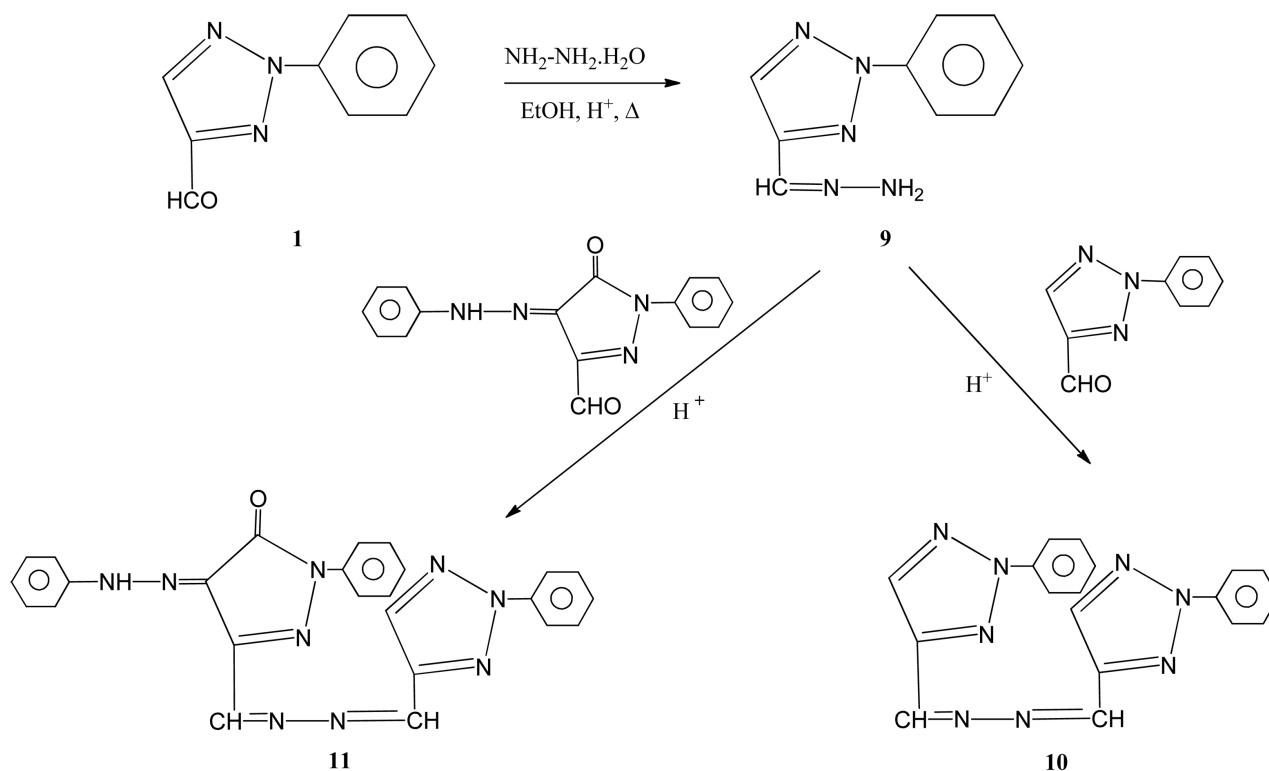
Mechanism of formation of compound 6



Mechanism of formation of compound 8



Scheme 2. Mechanisms of formation of compound 5, 6 and 8.



Scheme 3. Formation of compounds 9, 10 and 11.

Elemental analyses were carried out in the microanalytical laboratory of the Faculty of Science, Cairo University. The IR spectra of compounds were recorded on a Perkin-Elmer 580B spectrophotometer as potassium bromide pellets and frequencies are reported in cm^{-1} . The ^1H NMR spectra were recorded on a Camca 250 MHz spectrometer using TMS as internal standard. Mass spectra were recorded with LKB model 2091 spectrometer and intensities are given in parentheses as percentage of the base peak.

2-(2-Phenyl-2H-1,2,3-triazol-4-yl)methanimine (9) A solution of **1** (2 g, 11.5 mmol) in absolute ethanol (30 ml) was treated with malononitrile (0.94 g, 12 mmol) and few drops of triethylamine. The reaction mixture was heated under reflux for 2 h, concentrated and left to cool. The yellow solid was filtered off, washed with ethanol and dried (1.85 g; 71%). It was recrystallized from ethanol as yellow needles m.p. $133^\circ\text{C} - 134^\circ\text{C}$; $\nu_{\text{max}}/\text{cm}^{-1}$ 2233 ($\text{C}\equiv\text{N}$) and 1609 ($\text{C}=\text{N}$); NMR: $\delta_{\text{H}}(\text{CDCl}_3)$ 7.99 (s, 1H, ethylinic proton), 7.40 - 8.14 (m, 5H, aromatic-H), 8.53 (s, 1H, C5-H); ^{13}C NMR (CDCl_3): δ 147, 138, 137, 119, 112, 84. Anal. Calc. for $\text{C}_{12}\text{H}_7\text{N}_5$: C, 65.16; H, 3.17; N, 31.67. Found: C, 65.32; H, 4.04; N, 31.87%.

3.2. General Procedure

A mixture of 2-(2-phenyl-2H-1,2,3-triazol-4-yl)methanimine **9** (0.3 g; 1.35 mmole) in absolute ethanol (20 ml) was treated with an equimolar amount of hydrazine hydrate, hydroxylamine hydrochloride, thiourea, ethanol amine, thiosemicarbazide or cyclopentanone and few drops of piperidine. The clear solution was heated under reflux for 2 h, concentrated, poured onto ice water and neutralized with acetic acid. The solid obtained was filtered off, washed with cold water, ethanol and dried. Each product was recrystallized from ethanol in needles.

3-Amino-5-(2-phenyl-2H-1,2,3-triazol-4-yl)-4,5-dihydro-1H-pyrazole-4-carbonitrile (3): (0.26 g; 81%); m.p. $180^\circ\text{C} - 181^\circ\text{C}$; IR: $\nu_{\text{max}}/\text{cm}^{-1}$ 3213 (NH_2), 2236 ($\text{C}\equiv\text{N}$) and 1612 ($\text{C}=\text{N}$); NMR: $\delta_{\text{H}}(\text{CDCl}_3)$ 5.35 (s, 2H, NH_2), 6.19 (s, 1H, pyrazole H), 7.39 - 8.17 (m, 5H, aromatic-H), 7.68 (d, 1H, $j_{5,4} = 9.4$ Hz, C5'-H), 8.33 (d, 1H, $J_{5,4} = 7.42$ Hz, C4'-H), 8.41 (s, 1H, C5-H). ^{13}C NMR (CDCl_3): 153, 136 - 134 (aromatic C), 133, 129,

128, 119. Anal. Calc. for $C_{12}H_{11}N_7$: C, 56.92; H, 4.35; N, 38.73. Found: C, 56.78; H, 4.42; N, 38.52%.

5-Amino-3-(2-phenyl-2H-1,2,3-triazol-4-yl)-2,3-dihydroisoxazole-4-carbonitrile (4) (0.3 g; 76%); m.p. 185°C - 186°C; IR: $\nu_{\max}/\text{cm}^{-1}$ 3417 (NH), 2221 ($C \equiv N$) and 1625 ($C=N$); NMR: $\delta_{\text{H}}(\text{CDCl}_3)$ 5.35 (s, 2H, NH_2), 7.42 - 8.51 (m, 5H, aromatic-H), 7.65 (s, 2H, NH_2), 7.65 (s, 1H, $\text{C5}'\text{-H}$), 8.39 (s, 1H, C5-H), 9.26 (s, 1H, isoxazole-NH). Anal. Calc. for $C_{12}H_{10}N_6O$: C, 56.69; H, 3.94; N, 33.07. Found: C, 56.46; H, 3.78; N, 33.21%.

2,4-Diamino-6-(2-phenyl-2H-1,2,3-triazol-4-yl)-6H-1,3-thiazine-5-carbonitrile (5) (0.3 g; 72%); m.p. 193°C - 194°C; IR: $\nu_{\max}/\text{cm}^{-1}$ 3362 (NH), 2236 ($C \equiv N$), and 1638 ($C=N$); NMR: $\delta_{\text{H}}(\text{DMSO-d}_6)$ 7.47 - 8.05 (m, 9H, aromatic- H^+ 2 NH_2), 6.69 (s, 1H, $\text{C5}'\text{-H}$), 8.48 (s, 1H, C5-H); Ms: m/z 297 (4.3), 296 (10.1), 295 (46.2), 237 (32.5), 171 (12.8), 119 (10.4), 92 (24.5), 91 (92), 90 (14.8), 77 (100), 66 (19.6), 65 (37.9), 64 (94.5), 63 (29.3), 52 (21.4), 51 (58.9). Anal. Calc. for $C_{13}H_{11}SN_7$: C, 52.52; H, 3.70; N, 32.29. Found: C, 52.36; H, 3.82; N, 33.06%.

2-Amino-4-(2-phenyl-2H-1,2,3-triazol-4-yl)-nicotinonitrile (6): (0.22 g, 63%); m.p. 190°C - 191°C; IR: $\nu_{\max}/\text{cm}^{-1}$ 3383 (NH), 2219 ($C \equiv N$) and 1626 ($C=N$); NMR: $\delta_{\text{H}}(\text{DMSO-d}_6)$ 6.87 (s, 2H, NH_2), 7.25 (d, 1H, $J_{5,6} = 8.2$ Hz, $\text{C5}'\text{-H}$), 7.45 - 8.06 (m, 5H, aromatic -H), 7.89 (d, 1H, $J_{6,5} = 9.2$ Hz., $\text{C6}'\text{-H}$), 8.65 (s, 1H, C5-H). Anal. Calc. for $C_{14}H_{10}N_6$: C, 64.12; H, 3.82; N, 32.06. Found: C, 64.36; H, 3.58; N, 31.96%.

4-Amino-2-hydrazinyl-6-(2-phenyl-2H-1,2,3-triazol-4-yl)-6H-1,3-thiazine-5-carbonitrile (7): (0.3 g; 64%); m.p. 179°C - 181°C; IR: $\nu_{\max}/\text{cm}^{-1}$ 3202 (NH), 2241 ($C \equiv N$) and 1642 ($C=N$); NMR: $\delta_{\text{H}}(\text{DMSO-d}_6)$ 7.41 - 8.01 (m, 5H, aromatic -H), 8.13 (s, 2H, NH), 8.20 (s, 1H, $\text{C6}'\text{-H}$), 8.45 (s, 2H, NH_2), 8.60 (s, 1H, C5-H), 11.69 (s, 1H, NH). MS: m/z (%) 313 (86), 265 (16), 235 (66), 206 (36), 169 (31), 143 (18), 119 (17), 92 (21), 77 (100). Anal. Calc. for $C_{13}H_{12}SN_8$: C, 49.99; H, 3.87; N, 35.87. Found: C, 50.01; H, 3.58; N, 35.96%.

2-Amino-4-(2-phenyl-2H-1,2,3-triazol-4-yl)-4,5,6,7-tetrahydrocyclopenta[b]pyran-3-carbonitrile (8): (0.3 g; 63%) m.p. >270°C; IR: $\nu_{\max}/\text{cm}^{-1}$ 3365 (NH), 2236 ($C \equiv N$) and 1625 ($C=N$); NMR: $\delta_{\text{H}}(\text{DMSO-d}_6)$ 3.13 (m, 6H, 3 CH_2), 6.69 (s, 2H, exchangeable NH_2), 7.45 - 8.01 (m, 5H, aromatic-H), 8.42 (s, 1H, $\text{C4}'\text{-H}$), 8.57 (s, 1H, C5-H). Anal. Calc. for $C_{17}H_{15}N_5O$: C, 66.87; H, 4.95; N, 22.94. Found: C, 66.70; H, 4.80; N, 22.80%.

4-Carboxaldehyde-2-(phenyl-2H-1,2,3-triazole hydrazone (9): A solution of (1 g, 5.78 mmole) in ethanol (20 ml) was treated with hydrazine hydrate (2 ml) and acetic acid (1 ml) was heated under reflux for 2 h, concentrated and left to cool. The solid was filtered off, washed with ethanol and dried (0.65 g, 65%). It was recrystallized from ethanol as colorless needles, m.p. 115°C - 116°C; IR: $\nu_{\max}/\text{cm}^{-1}$ 3218 (NH) and 1600 ($C=N$). Anal. Calc. for $C_9H_9N_5$: C, 57.74; H, 4.85; N, 37.41. Found: C, 57.60; H, 4.70; N, 37.80%.

1,2-Bis[(2-phenyl-2H-1,2,3-triazol-4-yl)methylene hydrazine (10): A solution of **9** (1 g, 5.35 mmol) was treated with 4-carboxaldehyde-2-phenyl-2H-1,2,3-triazole (1 g; 5.78 mmol), boiled under reflux for 3 h, and left to cool. The solid was filtered off and washed with ethanol (yield 0.8 g, 60%). It was recrystallized from ethanol colorless needles, m.p. 218°C - 220°C; IR: $\nu_{\max}/\text{cm}^{-1}$ 1600 ($C=N$) Anal. Calc. for $C_{18}H_{14}N_8$: C, 63.15; H, 4.12; Found: C, 62.89; H, 4.53%.

1-phenyl-3-[(2-phenyl-2H-1,2,3-triazol-4-yl)methylene hydrazononemethyl]-4-(2-phenyl-hydrazono)-1H-pyrazol-5(4H)-one (11). A solution of **9** (1 g; 5.78 mmol) in ethanol was treated with 3-carboxaldehyde-1-phenyl-4,5-pyrazolinedione-4-(phenylhydrazine) (2 g; 6.53 mmol) was heated under reflux for 3 h, and left to cool. The solid filtered off, washed with ethanol and dried (1.1 g; 55%). It was recrystallized from ethanol in orange needles, m.p. 176°C - 177°C; IR: $\nu_{\max}/\text{cm}^{-1}$ 3200 (NH), 1659 (OCN) and 1595 ($C=N$). Anal. Calc. for $C_{25}H_{19}N_9O$: C, 65.07; H, 4.15. Found: C, 65.53; H, 4.31%.

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