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Pyrazoles as Building Blocks in Heterocyclic Synthesis: Synthesis of Pyrazolo [3,4-*d*]pyrimidine, Pyrazolo[3,4-*e*][1,4]diazepine, Pyrazolo [3,4-*d*][1,2,3]triazine and Pyrolo [4,3-*e*][1,2,4]triazolo[1,5-*c*]pyrimidine Derivatives

A.-F.A. Harb*, H.H. Abbas and F.H. Mostafa
Chemistry Department, Faculty of Science (Qena), South Valley University,Qena, 83523, Egypt.

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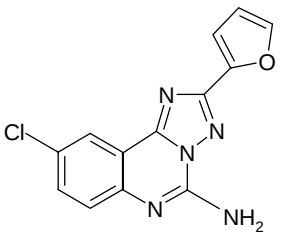
Several new pyrazolo[3,4-*d*]pyrimidine, pyrazolo[3,4-*e*][1,4]diazepine, pyrazolo[3,4-*d*][1,2,3]triazine and pyrolo[4,3-*e*][1,2,4]triazolo[1,5-*c*]pyrimidine derivatives were prepared by the reaction of the corresponding 5-amino-pyrazole-4-carbonitrile derivative with different organic reagents under different reaction conditions. Using IR, ^{1}H NMR, and mass spectra we have characterized all new compounds.

Keywords: Pyrazolo[3,4-*d*]pyrimidine, Pyrazolo[3,4-*e*][1,4]diazepine, Pyrazolo[3,4-*d*][1,2,3]-triazine, Pyrolo[4,3-*e*][1,2,4] diazole[1,5-*a*]pyrimidine, IR, ^{1}H NMR

INTRODUCTION

Azoloazines are biologically interesting molecules and their chemistry is now receiving considerable attention [1-3]. Furthermore, the considerable biological activities of pyrazole, and its annelated derivatives as antimycotics [4] antidepressants [5], fangicidal agents [6], herbicidal agents [7] are of increasing interest. Also, compounds containing the triazolo[1,5-*c*]pyrimidine moiety have attracted considerable attention due to their remarkable adenosine and benzodiazepine receptor affinity. Particularly, the 5-amino-9-chloro-2-(2-furyl)-1,2,4-triazolo[1,5-*c*]quinazoline **1** was found to be a highly potent adenosine antagonist [8], while the 9-chloro-2-(2-fluorophenyl)-1,2,4-triazolo[1,5-c]quinazolin-5 (6*H*)-one **2** displayed a very significant benzodiazepine binding activity [9]. This current pharmacological interest has stimulated our interest in the synthesis of several new and biologically active derivatives with these ring systems.



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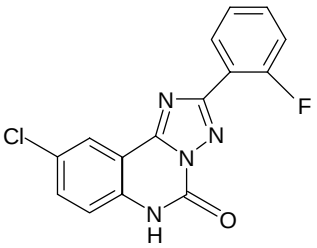

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EXPERIMENTAL SECTION

All melting points were uncorrected. IR. (KBr) spectra were recorded on a Shimadzu 408 spectrophotometer as a solid suspended in a potassium bromide disk. Mass spectra were recorded on GCMS QP1000 EX mass spectrometer with an ionization potential of 70 eV. ^{1}H NMR Spectra were recorded on a 90 MHz Varian EM-390 spectrometer with hexadeuterodimethylsulfoxide as a solvent, using Me_4Si as an internal standard. Chemical shift values (δ) are reported in

* Corresponding author. E-mail: funnytostos@hotmail.com

parts per million (ppm) relative to the residual signals of this solvent (δ 2.45). Microanalyses were performed on a LECO CHNS-932. The microanalytical data were obtained from the Microanalytical Data Unit at Cairo University.

5-Amino-1-(5,6-diphenyl-1,2,4-triazin-3-yl)-1*H*-pyrazole-4-carbonitrile (5). A mixture of 3-hydrazino-5,6-diphenyl-1,2,4-triazine, **3,** (13.2 g, 0.05 mol) and ethoxymethylenemalononitrile, **2,** (6.1 g, 0.05 mol) in absolute ethanol (100 ml) was heated under reflux for 30 min. The solvent was evaporated under vacuum and the residual solid was crystallized from ethanol to give 13.8 g (80%) of **5** as pale yellow needles: m.p.: 250 °C; IR (KBr) ν_{max}/cm^{-1} 3390, 3310, and 2225; MS: M^+; (rel int) 339.13 (100%). Anal. Calcd for $C_{19}H_{13}N_7$: C, 67.25; H, 3.83; N, 28.90. Found: C, 67.42; H, 3.91; N, 29.19.

6-Phenyl-1-(5,6-diphenyl-1,2,4-triazin-3-yl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-amine (6). A mixture of 3.39 g (0.01 mol) of **5**, with 1.10 g (0.01 mol) of benzonitrile and 0.50 g sodium methoxide in isopropanol (50 ml) was refluxed for 5 h with stirring. The reaction mixture was concentrated under reduced pressure and allowed to cool at room temperature, the yellow precipitate was separated, filtered off and crystallized from ethanol to give 2.8 g (63.3%) of **6** as deep yellow needles: m.p.: 324-325 °C; IR (KBr): ν_{max}/cm^{-1} 3430; ^1H NMR: δ_H 7.65-7.22 (m, 16H), 5.75 (s, 2H [D_2O changeable]); MS: M^+ (rel int) 442.19 (100%); Anal. Calcd for $C_{26}H_{18}N_8$: C, 70.58; H, 4.10; N, 25.32. Found: C, 70.49; H, 3.98; N, 25.13.

Ethyl-4-cyano-1-[5,6-diphenyl-1,2,4-triazin-3-yl]-1*H*-pyrazol-5-ylimidoformate (7). A mixture of compound **3** (3.39 g, 0.01 mol) and triethylorthoformate (2.50 ml) in redistilled acetic anhydride (25 ml) was heated under reflux for 2 h. The resulting solid, which formed on cooling, was collected by filtration and crystallized from ethanol to give 2.5 g (70%) of **5** as pale yellow crystals: m.p.: 243-244 °C; IR (KBr): ν_{max}/cm^{-1} 2220; ^1H NMR: δ_H 7.45-7.22 (m, 11H), 7.54 (d, 1H), 3.61 (q, 2H, J = 8 Hz), and 1.12 (t, 3H, J = 8 Hz); MS: M^+ (rel int) 395.17 (100%); Anal. Calcd for $C_{22}H_{17}N_7O$: C, 66.82; H, 4.33; N, 24.80. Found: C, 66.69; H, 4.38; N, 24.42.

***N''*-[4-Cyano-1-(5,6-diphenyl-1,2,4-triazin-3-yl)-1*H*-pyrazol-5-yl]imidoformic hydrazide (8).** A suspension of **7** (3.95 g, 0.01 mol) in 25 ml benzene and hydrazine hydrate in 10 ml water was heated under reflux for one hour with stirring. After cooling, the precipitated product was filtered off and crystallized from ethanol to give 2.1 g (61%) of **8** as pale yellow crystals: m.p.: 230-231 °C; IR (KBr): ν_{max}/cm^{-1} 3500-3330, and 2225; ^1H NMR: δ_H 8.17 (br, 1H D_2O changeable), 7.60-7.22 (m, 12H), and 5.24 (br, 2H, D_2O changeable); MS: M^+ (rel int) 381.15 (100); Anal. Calcd.for $C_{20}H_{15}N_9$: C, 62.98; H, 3.96; N, 33.05. Found: C, 63.22; H, 3.8; N, 33.27.

1-(5,6-Diphenyl-1,2,4-triazin-3-yl)-4-imino-1,4-dihydro-5*H*-pyrazolo[3,4-*d*]pyrimidin-5-amine (9). A suspension of **8** (3.81 g; 0.01 mol) in dry benzene (50 ml) was heated under reflux for 3 h. After cooling, the precipitate was filtered off and crystallized from toluene to give 3.1 g (81.3%) of **9** as yellow needles, m.p.: 175-176 °C; IR (KBr). ν_{max}/cm^{-1} 3450-3330; ^1H NMR: δ_H 8.85 (s, 1H), 7.68-7.22 (m, 11H), 4.28 (br, 1H D_2O changeable), and 2.69 (br, 2H, D_2O changeable); MS: M^+ (rel int) 381.17 (100%); Anal. Calcd for $C_{20}H_{15}N_9$: C, 62.98; H, 3.96; N, 33.05. Found: C, 62.69; H, 3.71; N, 33.14.

7-(5,6-diphenyl-1,2,4-triazin-3-yl)-2-methyl-7*H*-pyrazolo[4,3-*e*][1,2,4]triazolo[1,5-*c*]pyrimidine (10). A suspension of either compound **8** (3.81 g; 0.01 mol) or compound **9** (3.81 g; 0.01 mol) in a mixture of acetic acid/acetic anhydride (20 ml/5 ml) was heated under reflux for 1 h. The precipitated product which formed on cooling and dilution with water was filtered off and crystallized from ethanol to give 2.8 g (69%) of **10** as pale green needles, m.p.: 207 °C; ^1H NMR: δ_H 8.96 (s, 1H), 7.65-7.22 (m, 11H), and 2.81 (s, 3H); MS: M^+ (rel int) 405, 12 (100%); Anal. Calcd for $C_{22}H_{15}N_9$: C, 65.18; H, 3.73; N, 31.09. Found: C, 64.87; H, 3.99; N, 30.84.

N-[1-(5,6-Diphenyl-1,2,4-triazin-3-yl)-4-imino-1,4-dihydro-5*H*-pyrazolo[3,4-d]pyrimidin-5-yl]benzamide (11). A suspension of compound **7** (3.95 g; 0.01 mol) and benzohydrazide (1.5g; 0.011 mol) in dry ethanol (30 ml) was refluxed for a few minutes. Then a precipitate began to separate from the initially clear solution. After heating for one hour, the reaction mixture was filtered, and the solid obtained was crystallized from dioxane to give 3.65 g (76%) of **11** as small cream-colored needles, m.p.: 270-271 °C; IR (KBr): ν_{max}/cm^{-1} 3150, and 1665. ^1H NMR: δ_H 10.43 (br, 1H, D_2O changeable), 9.32 (s, 1H D_2O changeable), 8.85 (s, 1H), and 7.62-7.27 (m, 16H); MS: M^+ (rel int) 485, 12 (100%); Anal. Calcd for $C_{27}H_{19}N_9O$: C, 66.79; H, 3.94; N, 25.97. Found: C, 66.91; H, 4.12; N, 25.83.

5-Amino-N^1-benzoyl-1-(5,6-diphenyl-1,2,4-triazin-3-yl)-1*H*-pyrazole-4-carbohydrazonamide (12). A suspension of

compound **9** (4.85 g, 0.01 mol) in 10% hydrochloric acid (100 ml) was stirred at 60 °C for 2 h to give a homogeneous solution. After cooling, the solution was treated with 10% sodium carbonate and the solid which formed was filtered off and crystallized from ethanol to give 2.9 g (61%) of **11** as pale yellow needles, m.p.: 196-198 °C: IR (KBr). ν_{max}/cm^{-1} 3450-3150 and 1665. ^1H NMR: δ_H 10.21 (bs, 1H, D_2O changeable), 6.80 (bs, 2H, D_2O changeable), 5.55 (bs, 2H, D_2O changeable) and 7.78-7.22 (m, 16H); MS: M^+ (rel int) 475, 19 (100%). Anal. Calcd for $C_{26}H_{21}N_9O$: C, 65.67; H, 4.45; N, 26.51. Found: C, 65.80; H, 4.22; N 26.25.

7-(5,6-Diphenyl-1,2,4-triazin-3-yl)-2-phenyl-7*H*-pyrazolo[4,3-*e*][1,2,4]triazolo[1,5-*c*]pyrimidin-5-amine (13). Compound **12** (4.75 g, 0.01 mol) was finely ground with guanidine carbonate (1.8 g, 0.1 mol) in a mortar. The mixture was heated at 170-180 °C (oil bath) under reduced pressure for 2 h. After cooling, the mixture was vigorously stirred in boiling water (100 ml) over 30 minutes, and then filtered. The solid was collected, washed with water and cold methanol, and then crystallized from ethyl acetate to give 2.1 g (43%) of **13** as yellow crystals. M.p.: 228-230 °C; IR (KBr): ν_{max}/cm^{-1} 3450-3250 cm^{-1}. ^1H NMR: δ_H 9.50 (bs, 2H, D_2O changeable) and 7.71-7.22 (m, 16H); MS: M^+ (rel int) 482.12 (100%). Anal. Calcd for $C_{26}H_{18}N_{10}$: Calcd. C, 67.21; H, 3.76; N, 29.03. Found: C, 67.62; H, 3.91; N, 29.26.

1-(5,6-Diphenyl-1,2,4-triazin-3-yl)-4-(3-phenyl-1*H*-1,2,4-triazol-5-yl)-1*H*-pyrazol-5-amine (14). To a suspension of compound **12** (4.75 g, 0.01 mol) in ethanol (50 ml), 1 ml of acetic acid was added. The mixture was heated for 5 h, and then concentrated to dryness at reduced pressure. The residue was treated with diluted ammonium hydroxide. The formed precipitate was then crystallized from toluene to give 2.9 g (63.5%) of **14** as yellow crystals, m.p.: 148 °C; IR (KBr): ν_{max}/cm^{-1} 3450-3150. ^1H NMR: δ_H 11.62 (s, 1H D_2O changeable), 6.73 (s, 2H, D_2O changeable), and 7.58-7.22 (m, 16H); MS: M^+ (rel int) 457.19 (100%). Anal. Calcd for $C_{26}H_{19}N_9$: C, 68.26; H, 4.19; N, 27.55. Found: C, 67.97; H, 3.94; N, 27.29.

7-(5,6-Diphenyl-1,2,4-triazin-3-yl]-2-phenyl-5-methyl-7*H*-pyrazolo-[4,3-*e*][1,2,4]triazolo[1,5-*c*]pyrimidine (15). Acetyl chloride (1.56 g, 0.02 mol) was dropwise added to a stirred, cooled solution of **14** (4.57 g, 0.01 mol) in glacial acetic acid (50 ml). The reaction mixture was stirred at 90 °C for 2 h, then, the acetic acid was removed under reduced pressure and sodium carbonate (10% final concentration) was added to achieve alkalinity. The precipitated solid which formed was filtered off and crystallized from dimethylformamide to give 4.0 g (85%) of **15** as white crystals, m.p.: 248-250 °C; IR (KBr): ν_{max}/cm^{-1} 3450-3150. ^1H NMR: δ_H 7.55-7.22 (m, 16H), and 2.43 (s, 3H); MS: M^+ (rel int) 481.18 (100%). Anal. Calcd for $C_{28}H_{19}N_9$: C, 69.84; H, 3.98; N, 26.18. Found: C, 67.14; H, 4.21; N 26.39.

5-Chloromethyl-7-(5,6-diphenyl-1,2,4-triazin-3-yl)-2-phenyl-7*H*-pyrazolo[4,3-*e*][1,2,4]tri-azolo[1,5-*c*]pyrimidine (16). Chloroacetyl chloride (1.6 ml, 0.02 mol) was added dropwise to a stirred, cooled solution of **14** (4.57 g, 0.01 mol) in glacial acetic acid (50 ml). The mixture was stirred at 80 °C for 2 h; then the solvent was removed by vacuum, and 10% sodium carbonate solution was added to the residue to achieve alkalinity. The solid product which formed was filtered off and crystallized from ethanol to give 4.1 g (79.5%) of **15** as yellow crystals, m.p.: 276 °C; ^1H NMR: δ_H 7.50-7.22 (m, 16H) and 4.60 (s, 2H); MS M^+ (rel int) 515.14 (100%), and M^++ 2 (rel int) 517.13 (30%). Anal. Calcd for $C_{28}H_{18}ClN_9$: C, 65.18; H, 3.52; Cl, 6.87; N, 24.43. Found: C, 65.19; H, 3.25; Cl, 6.6; N, 24.58.

7-(5,6-Diphenyl-1,2,4-triazin-3-yl)-2-phenyl-5-(piperidin-1-ylmethyl)-7H-pyrazolo[4,3-e][1,2,4]triazolo[1,5-c] pyrimidine (17). Compound 16 (5.16 g, 0.01 mol) in piperidine (20 ml) was heated with stirring in a water bath for 10 h. Excess amine was removed and the resulting residue was directly crystallized from toluene to give 4.3g (76%) of **17** as yellow flakes, m.p.: 223-224 °C; ^1H NMR: δ_H 7.65-7.22 (m, 16H), 3.64 (s, 2H), and 2.42-1.55 (m, 10H); MS: M^+ (rel int) 564.32 (100%), and M^++ 1 (rel int) 565.40 (35%). Anal. Calcd for $C_{33}H_{18}N_{10}$: C, 70.20; H, 5.00; N 24.81. Found: C, 70.52; H, 5.28; N 24.99.

1-(5,6-Diphenyl-1,2,4-triazin-3-yl)-5-(2-ethoxy-4-oxo-1,3-thiazolidin-3-yl)-1H-pyrazole-4-carbonitrile (18). A suspension of **7** (3.95 g; 0.01 mol) and mercapto-acetic acid (1.38 g, 0.015 mol) in 25 ml dry benzene was stirred under reflux for 3 h. Excess solvent was removed and the nearly pure product that formed was isolated and crystallized from toluene to give 3.2 g (68.3%) of **18** as pale yellow flakes, m.p.: 201 °C; IR (KBr): ν_{max}/cm^{-1} 2223, and 1685. ^1H NMR: δ_H 7.62-7.22 (m, 11H), 5.98 (s, 1H), 3.41 (q, 2H, J = 10.8 Hz)

3.33 (s, 2H), and 1.12 (t, 3H, J = 10.8 Hz); MS: M^+ (rel int) 469.12 (100%), and M^++ 1 (rel int) 470.14 (29%). Anal. Calcd for $C_{24}H_{19}N_7O_2S$: C, 61.39; H, 4.08; N, 20.88; S, 6.82. Found: C, 61.52; H, 4.19; N, 20.65; S, 6.71.

1-(5,6-Diphenyl-1,2,4-triazin-3-yl)-8-ethoxy-1*H*-pyrazolo[4,3-*e*][1,3]thiazolo[3,4-*a*]pyrimidin-4(5*H*)-one (19). A suspension of compound **18** (4.69 g; 0.01 mol) and sodium methoxide (1.0 g) in ethanol (50 ml) was heated under reflux for 3 h. Excess solvent was removed until dryness and the remnant was triturated with hot water. The resulting solid that formed was filtered and crystallized from ethanol to give 3.4 g (72%) of **19** as yellow crystals. m.p.: 172 °C; IR (KBr): ν_{max}/cm^{-1} 3325, and 1690. ^1H NMR: δ_H 10.06 (bs, 1H, D_2O changeable), 7.48-7.10 (m, 11H), 5.13 (s, 1H), 5.13 (s, 1H), 4.19 (s, 1H), 3.50 (q, 2H, J = 10.5 Hz), and 1.13 (t, 3H, 2H, J = 10.5 Hz); MS: M^+ (rel int) 469.18 (100%), and M^++ 1 (rel int) 470.10 (35%). Anal. Calcd for $C_{24}H_{19}N_7O_2S$: C, 61.39; H, 4.08; N, 20.88; S, 6.82. Found: C, 61.12; H, 3.89; N, 20.75; S, 7.03.

5-Amino-1-(5,6-diphenyl-1,2,4-triazin-3-yl)-1*H*-pyrazole-4-carboxamide (**20**)**.** To a solution of compound **5** (3.4 g, 0.01 mol) in a mixture of acetone-water (1: 1, 30 ml), urea-hydrogen peroxide adduct (UHP) (0.04 mole) and anhydrous K_2CO_3 (0.14 gm) were added. The resulting suspension was stirred at room temperature for 1 h. After completion of the reaction, acetone was removed under vacuum. Water (10 ml) was added to the residue and the solid which was formed was filtered off, washed with water, dried and crystallized from ethanol to give 3.15 g (89.6%) of **20** as yellow crystals. m.p.: 157-176 °C; IR (KBr): ν_{max}/cm^{-1} 3450-3215, and 1655. ^1H NMR: δ_H 7.56-7.20 (m, 11H), 6.51 (bs, 2H, D_2O changeable), and 5.34 (s, 2H, D_2O changeable); MS: M^+ (rel int) 357.19 (100%). Anal. Calcd for $C_{19}H_{15}N_7O$: C, 63.86; H, 4.23; N, 27.44. Found: C, 62.02; H, 3.96; N, 27.32.

1-(5,6-Diphenyl-1,2,4-triazin-3-yl]-1,5-dihydro-4*H*-pyrazolo[3,4-*d*]pyrimidin-4-one (21). A suspension of **20** (3.57 g; 0.01 mol) and triethylorthoformate (30 ml) in redistilled acetic anhydride (30 ml) was heated under reflux for 2 h. After completion of the reaction, the solvent was removed and the solid that formed was collected and crystallized from a toluene-ethanol mixture to give 2.6 g (69%) of **21** as brown crystals, m.p.: 276-277 °C; IR (KBr): ν_{max}/cm^{-1} 3320, and 1695. ^1H NMR: δ_H 9.73 (b s, 1H, D_2O changeable), 8.90 (s, 1H), and 7.85-7.25 (m, 11H); MS: M^+ (rel int) 367.13 (100%). Anal. Calcd for $C_{20}H_{13}N_7O$: C, 65.39; H, 3.57; N, 26.69. Found: C, 65.37; H, 3.39; N, 26.78.

Ethyl{[4-(aminocarbonyl)-1-(5,6-diphenyl-1,2,4-triazin-3-yl)-1*H*-pyrazol-5-yl]amino}(oxo)acetate (22). A suspension of **20** (3.57 g; 0.01 mol) and diethyloxalate (4.38 g; 0.03 mol) in ethanol (50 ml) was heated under reflux for 10 h. The reaction mixture was cooled and the solid that formed was collected and crystallized from ethanol to give 2.9 g (61%) of **22** as yellow crystals, m.p.: 104 °C; IR (KBr): ν_{max}/cm^{-1} 3450-3250, and 1710-1660. ^1H NMR: δ_H 10.21 (s, 1H, D_2O changeable), 7.58-7.22 (m, 11H) 6.27 (s, 2H, D_2O changeable), 4.15 (q, 2H, J = 10.2 Hz), and 1.31 (t, 3H, J = 10.2 Hz); MS: M^+ (rel int) 457.12 (100%). Anal. Calcd for $C_{23}H_{19}N_7O_4$: C, 60.39; H, 4.19; N, 21.43. Found: C, 60.47; H, 3.99; N, 21.25.

Ethyl 1-(5,6-diphenyl-1,2,4-triazin-3-yl)-4-oxo-4,5-dihydro-1*H*-pyrazolo[[3,4-*d*]pyrimidine-6-carboxylate (23). A suspension of compound **22** (4.6 g; 0.01 mol) in glacial acetic acid (50 ml) was heated under reflux for 3 h. Excess solvent was removed until dryness and the remnant was triturated with hot water. The resulting solid was filtrated and crystallized from ethanol to give 3.2 g (73%) of **23** as brown crystals, m.p.: 225 °C; IR (KBr): ν_{max}/cm^{-1} 3330, 1715, and 1640 cm^{-1}. ^1H NMR: δ_H 9.83 (s, 1H, D_2O changeable), 7.40-7.10 (m, 11H), 4.35 (q, 2H, J = 10.4 Hz), and 1.22 (t, 3H, J = 10.4 Hz); MS: M^+ (rel int) 439.13 (100%). Anal. Calcd for $C_{23}H_{17}N_7O_3$: C, 62.87; H, 3.90; N, 22.31. Found: C, 62.62; H, 3.79; N, 22.33.

1-(5,6-Diphenyl[1,2,4]triazin-3-yl]-6,7-diphenyl-1*H*-pyrazolo[3,4-*e*]diazepin-4-one (24). A mixture of compound **20** (3.57 g; 0.01 mol), benzoin (2.12 g; 0.01 mol) and anhydrous $ZnCl_2$ (0.5 g) was fused (oil bath) for 1 h. The reaction mixture was triturated with hot water and the resulting solid was crystallized from ethanol to give 4.4 g (73%) of **24** as pale yellow crystals, m.p.: 244 °C; IR (KBr): ν_{max}/cm^{-1} 1680. ^1H NMR: δ_H 7.66-7.20 (m, 21H); MS: M^+ (rel int) 531.20 (100%). Anal. Calcd for $C_{33}H_{21}N_7O$: C, 74.56; H, 3.98; N, 18.44. Found: C, 74.68; H, 3.91; N, 18.54.

1-(5,6-Diphenyl-1,2,4-triazin-3-yl]-6,7-diphenyl-1*H*-pyrazolo[4,3-*e*]pyrrolo[1,2-*a*]pyrimidin-4(5*H*)-one (27). A mixture of **20** (3.57 g; 0.01 mol) and benzoin (2.12 g; 0.01 mol) was heated under reflux for 1 h in a mixture of acetic

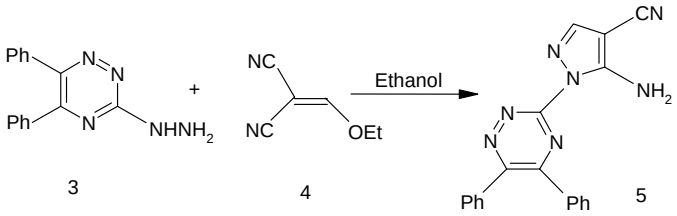
acid (20 ml), and acetic anhydride (20 ml). The reaction mixture was concentrated and the solid, which separated on cooling, was filtered off and crystallized from toluene to give 4.8 g (86%) of **27** as yellow crystals, m.p.: 216–217 °C; IR (KBr): ν_{max}/cm^{-1} 3330, and 1650. ^1H NMR: δ_H 9.78 (bs, 1H, D_2O changeable), and 7.60-7.2 (m, 22H); MS: M^+ (rel int) 557.20 (100%), and M^++ 1 (rel int) 558.21 (39%). Anal. Calcd for $C_{35}H_{23}N_7O$: C, 75.39; H, 4.16; N, 17.58. Found: C, 75.41; H, 3.89; N, 17.72.

7-(5,6-Diphenyl-1,2,4-triazin-3-yl]-3,7-dihydropyrazolo [3,4-*d*][1,2,3]triazin-4-one (28). To an ice cold solution of compound **20** (3.57 g; 0.01 mol) in an equal volume mixture of acetic acid and concentrated hydrochloric acid (25 ml), a solution of $NaNO_2$ (5 g; 0.07 mol) in ice cold water was added. After completion of the addition, the ice bath was removed and stirring continued for two more hours. The crude product was isolated and crystallized from toluene to give 2.3 g (60%) of **28** as orange needles. m.p.: 196-197 °C, IR (KBr): ν_{max}/cm^{-1} 3330, and 1654. ^1H NMR: δ_H 9.71 (bs, 1H, D_2O changeable), 7.59-7.22 (m, 11H); MS: M^+ (rel int) 368.12 (100%), and M^++ 1 (rel int) 369.11 (21.5%). Anal. Calcd for $C_{19}H_{12}N_8O$: C, 61.95; H, 3.28; N, 30.42. Found: C, 62.15; H, 3.10; N, 30.23.

1-(5,6-Diphenyl-1,3,4-triazin-3-yl)-5-methoxy-1*H*-pyrazole-4-carboxamide (29). Compound **28** (3.86 g; 0.01 mol) in 50 ml methanol was heated under reflux for 2 h. After completion of the reaction, the solvent was removed under vacuum and the remnant was isolated and crystallized from ethanol to give 2.1 g (56%) of **29** as yellow crystals, m.p.: 230 °C; IR (KBr): ν_{max}/cm^{-1} 3450-331, and 1645. ^1H NMR: δ_H 7.50-7.22 (m, 11H), 6.17 (s, 2H, D_2O changeable), and 3.12 (s, 3H); MS: M^+ (rel int) 372.14 (100%), and M^++ 1 (rel int) 373.14 (22.6%). Anal. Calcd for $C_{20}H_{16}N_6O_2$: C, 64.51; H, 4.33; N, 22.57. Found: C, 60.67; H, 4.29; N, 22.60.

RESULTS AND DISCUSSION

We have found that the 5-amino-1-(5, 6-diphenyl-1,2,4-triazen-3-yl)-pyrazole-4-carbonitrile **5**, (which resulted in an 80% yield, *via* the reaction of the known 5,6-diphenyl-3-hydrazenyl-1,2,4-triazole [10] **3** with ethoxymethylene-malononitrile **4** in refluxing ethanol, (Scheme 1) is an attractive starting material for the preparation of some new polycyclic azines. Thus, the treatment of compound **5** with

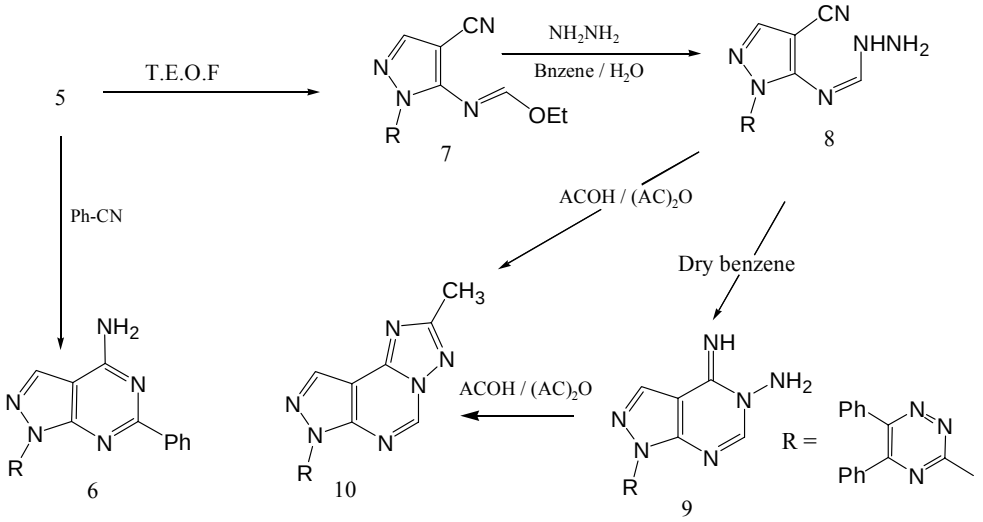


3 4 5

Scheme 1

benzonitrile in refluxing isopropanol containing a catalytic amount of sodium methoxide resulted in the formation of the corresponding 1-(5,6-diphenyl-1,2,4-triazin-3-yl)-*1H*-pyrazolo [3,4-*d*]pyrimidin-4-amine, compound **6,** with a 63.3% yield. The structure of compound **6** was established on the basis of elemental and spectral analyses of the isolated product. Thus, mass spectrum showed a m/z ratio of 442.19. The IR spectrum revealed absence of the cyano group that had appeared at 2225 cm^{-1} in the IR spectrum of compound **3**. In addition, the ^1H NMR spectrum showed the presence of the characteristic signals of one NH_2 group at δ = 5.75 ppm.

The ethyl-4-cyano-1-[5,6-diphenyl-1,2,4-triazin-3-yl]-1*H*-pyrazol-5-ylimidoformate, **7**, resulted in a 70% yield *via* treatment of compound **5** with triethylorthoformate (T.E.O.F.) in acetic anhydride. The structure of **7** was confirmed based on its elemental and spectral analyses. Heating of compound **7** with hydrazine hydrate in benzene-water mixture resulted in a 61% yield. The *N``*-[4-cyano-1-(5,6-diphenyl-1,2,4-triazin-3-yl)-1*H*-pyrazol-5-yl]imidoformic hydrazide, **8**, which transformed into the 1-(5,6-diphenyle-1,2,4-triazin-3-yl)-4-imino-1,4-dihydro-5*H*-pyrazolo[3,-4-*d*]pyrimidin-5-amine, **9** by heating in refluxing dry benzene resulted in an 81% yield. On heating of **9** in glacial acetic acid-acetic anhydride mixture, the 7-(5,6-diphenyl-1,2,4-triazin-3-yl)-2-methyl-7*H*-pyrazolo[4,3-*e*] [1,2,4]triazolo[1,5-*c*]pyrimidine, **10**, was obtained with a yield of 69% (Scheme 2). The structure of compound **10** was confirmed from its elemental and spectral analyses which showed the molecular ion peak at m/z ratio of 405, 12. Also, IR spectrum of **10** revealed the absence of the characteristic stretching vibrations due to the NH, NH_2, and CN groups, which appear at ν = 3450-3300, and 2225 cm^{-1} regions in the IR spectra of compounds **8** and **9**. In addition, the ^1H NMR spectrum of **10** showed the presence of the

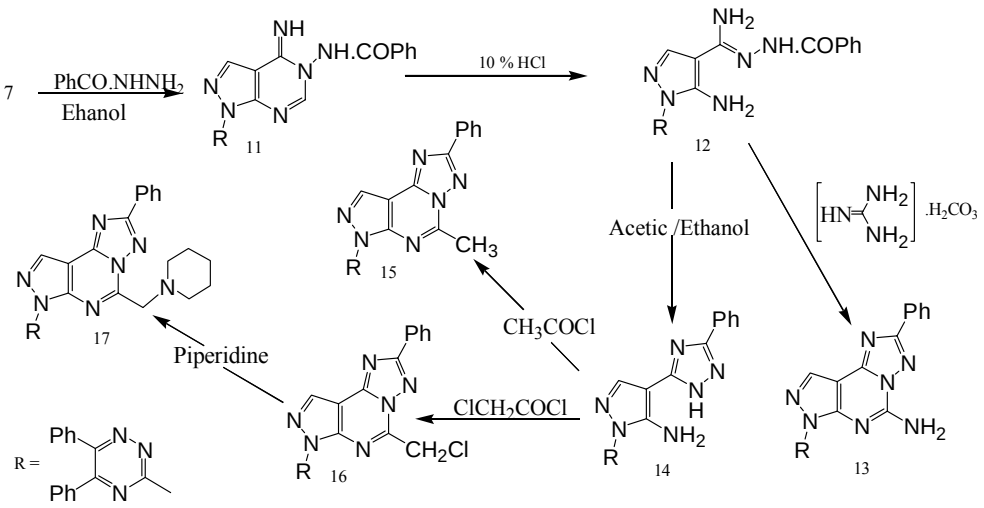


Scheme 2

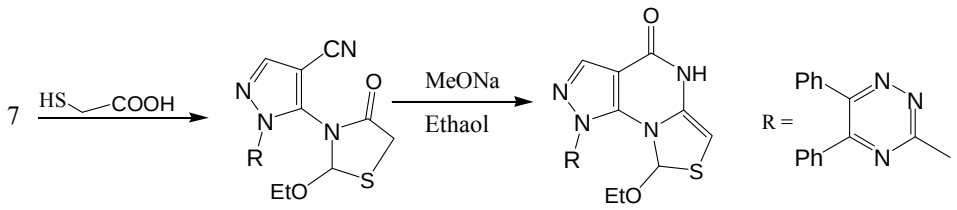
characteristic signals of a methyl group at δ = 2.81 ppm, beside a signal at δ = 8.96 ppm due to one proton.

On the other hand, compound **10** was obtained *via* heating of **8** in refluxing acetic anhydride-acetic acid mixture. By treatment of **7** with benzohydrazide in refluxing ethanol, the *N*-[4-imino-1-(5,6-diphenyl-1,2,4-triazin-3-yl)-1,4-dihydro-5*H*-pyrazolo[3,4-*d*]pyrimidin-5-yl] benzamide **11** was formed with a 76% yield, which was converted into 5-amino-N^1-benzoyl-1(5,6-diphenyl-1,2,4-triazin-3-yl)1*H*-pyra-zole-4-carbohydrazonamide **12,** with a 61% yield, in 10% hydrochloric acid. The proposed structures for **11** and **12** were supported by the following features: the IR spectrum of **11** revealed the absence of any nitrile band in the 2220 cm^{-1} region. In the mean time, the characteristic stretching vibrations due to amidic carbonyls at 1650 cm^{-1} region were present for both of these compounds. Also, the ^{1}H NMR spectrum of compound **12** revealed the presence of two amino groups signals at δ = 5.55, and 6.80 ppm, beside a broad signal at δ = 10.21 ppm for the NH proton. However, for compound **11**, the ^{1}H NMR spectrum revealed the presence of two signals at δ = 9.32, and 10.32 ppm due to two NH groups, in addition to one signal at δ = 8.85 ppm due to one proton.

The fusion of compound **12** with guanidine carbonate under somewhat reduced pressure yielded 7-(5,6-diphenyl-1,2,4-triazin-3-yl)-2-phenyl-7*H*-pyrazolo[4,3-*e*][1,2,4]triazolo, 5[1-*c*] pyrimidin-5-amine, **13**, with a 43% yield. Furthermore, the heating of compound **12** in 5% ethanolic acetic acid produced 1-(5,6-diphenyl-1,2,4-triazin-3-yl)-4-(3-phenyl-1*H*-1,2,4-triazol-5-yl)-1*H*-pyrazol-5-amine, **14**, with a 63% yield. Treatment of **14** with acetyl chloride and chloroacetyl chloride in refluxing glacial acetic acid produced 7-(5,6-diphenyl-1,2,4-triazin-3-yl]-2-phenyl-5-methyl-7*H*-pyrazolo-[4,3-*e*] [1, 2,4]triazolo[1,5-*c*] pyrimidine, **15**, with a 85% yield, and 5-chloromethyl-7-(5,6-diphenyl-1,2,4-triazin-3-yl)-2-phenyl-7*H*-pyrazolo[4,3-*e*][1,2,4]triazlo[1,5-*c*]pyrimidine **16** with a 79% yield. The following features supported the proposed structures for **13**, **14**, **15**, and **16**. The IR spectra of **13**, **14**, **15**, and **16** showed the absence of the amidic carbonyl bands in the a ν = 1650 cm^{-1} region which appeared in the IR spectrum of compound **12**. In addition, the ^{1}H NMR spectrum of compound **13** showed the appearance of only one NH_2 signal at δ = 9.50 ppm in compound **13**, and one NH_2 group signal at δ = 6.73 ppm in addition to one NH signal at δ = 11.62 ppm in compound **14** ^{1}H NMR spectrum. Furthermore, the ^{1}H NMR spectra revealed the appearance of one methyl signal at δ = 2.43 ppm in case of compound **15,** and one methylene signal at δ = 4.60 ppm in the case of compound **16**. On the other hand, treatment of compound **16** with an excess of piperidine afforded 7-(5,6-diphenyl-1,2,4-triazin-3-yl)-2-phe-nyl-5-(piperidin-1-ylmethyl)-7*H*-pyrazolo[4,3-*e*][1,2,4]tri-azolo[1,5-*c*]pyrimidine, **17**, with a 76% yield (Scheme 3), and its structure was confirmed on the basis of its elemental and



Scheme 3



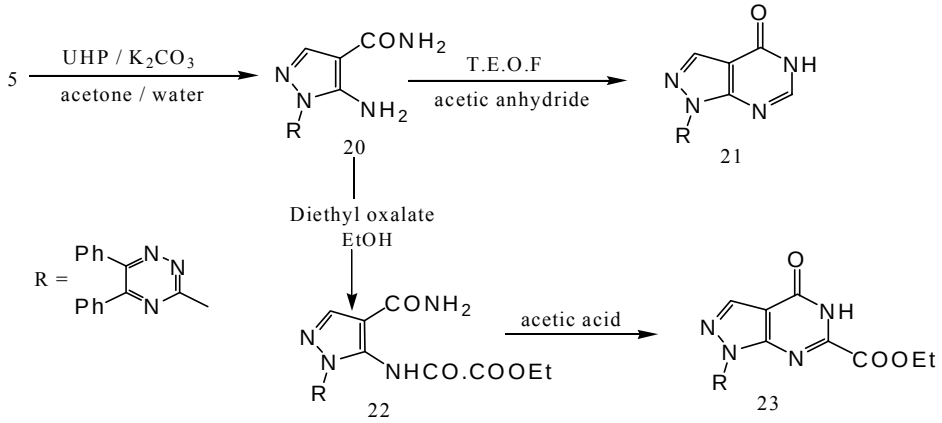
Scheme 4

spectral analyses. Thus, mass spectrum revealed an ion peak at m/z = 564.32. Also, the ^{1}H NMR spectrum showed the presence of the characteristic signals at δ = 2.42-1.55 ppm due to five CH_2 groups in addition to a singlet signal at δ = 3.64 ppm due to one CH_2 group.

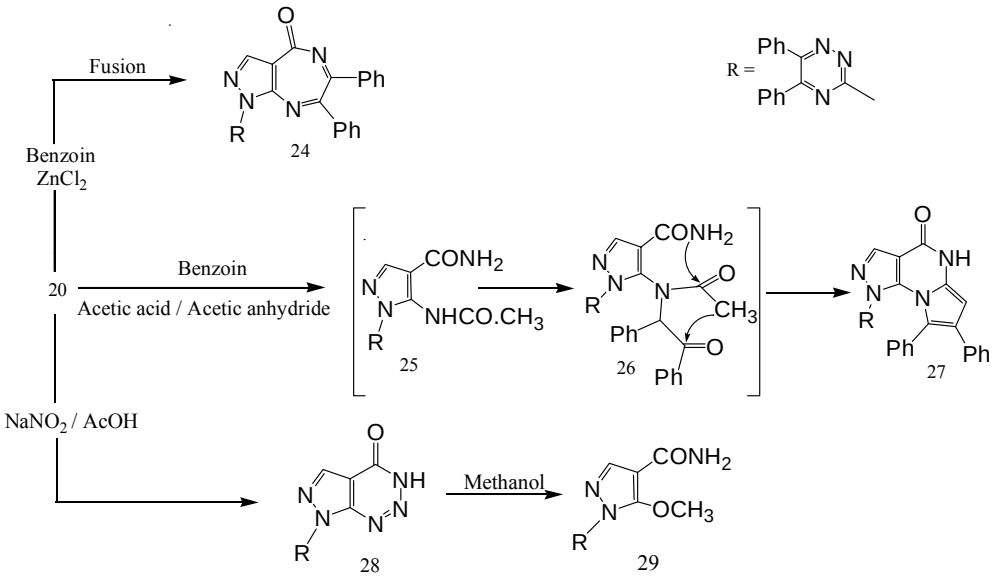
On treatment of **7** with mercaptoacetic acid in dry benzene, the 1-(5,6-diphenyl-1,2,4-triazin-3-yl)-5-(2-ethoxy-4-oxo-1,3-thiazolidin-3-yl)-1*H*-pyrazole-4-carbonitrile derivative **18** was obtained in 68% yield, which on heating in a refluxing ethanolic sodium methoxide solution afforded the 1-(5,6-diphenyl-1,2,4-triazin-3-yl)-8-ethoxy-1*H*-pyrazolo[4,3-*e*][1,3] thiazolo[3,4-*a*] pyrimidin-4(5H)-one, **19**, with a 72% yield (Scheme 4). Structures **18** and **19** were confirmed by the elemental analysis as well as the spectrometric studies. The ^{1}H NMR spectrum of compound **18** revealed the presence of a singlet signal at δ = 3.33 ppm due to one CH_2 group, and a singlet signal at δ = 5.98 ppm due to the thiazolidine C2-H, in addition to the characteristic triplet, quartet signals at δ = 1.12 and 3.41 ppm due to -OEt group. However, in the case of compound **19**, the ^{1}H NMR spectrum showed the broad signal for one NH proton at δ = 10.06 ppm, the characteristic triplet, quartet signals at δ = 3.50 ppm, and at δ = 1.13 ppm due to -OEt group, the presence of two singlet signals at δ = 5.13 and 4.19 ppm due to C8-H and C6-H. Also, the IR spectrum of compound **19** showed the absence of any cyano groups.

The urea-hydrogen peroxide adduct (UHP) [11], an inexpensive, stable, and easily handled reagent, has shown utility for mild and efficient transformation of nitriles into their corresponding amides [12]. So, compound **5** was converted into 5-amino-1-(5,6-diphenyl-1,2,4-triazin-3-yl)-1*H*-pyrazole-4-carboxamide, **20**, at room temperature with a 89% yield, using an excess of urea-hydrogen peroxide adduct (UHP) in the presence of a catalytic amount of potassium carbonate in an acetone-water mixture as a solvent. Heating of

20 with triethylorthoformate in refluxing acetic anhydride, resulted in the formation of 1-(5,6-diphenyl-1,2,4-triazin-3-yl)-1,5-dihydro-4*H*-pyrazolo [3, 4-*d*]pyrimidin-4-one, **21**, with a 69% yield. On the other hand, the heating of **20** with diethyl oxalate in refluxing ethanol yielded the ethyl {[4-(aminocarbonyl)-1-(5,6-diphenyl-1,2,4-triazin-3-yl)-1*H*-pyrazol-5-yl]amino}(oxo)acetate, **22**, which was converted into the ethyl 1-(5,6-diphenyl-1,2,4-triazin-3-yl)-4-oxo-4,5-dihydro-1*H*-pyrazolo[[3,4-*d*]pyrimidine-6-carboxylate, **23**, by heating it in refluxing glacial acetic acid resulting in a 73% yield (Scheme 5). Structures **20**, **21**, **22** and **23** were confirmed by the elemental and spectral analyses of the isolated products. The 6,7-diphenyl-1-(5,6-diphenyl-1,2,4-triazin-3-yl)pyrazolo [3,4-*e*][1,4]diazepin-4(1*H*)-one, **24,** was formed with a 73% yield by the fusion of **20** with benzoin in the presence of anhydrous $ZnCl_2$. The structure of **24** was confirmed by elemental and spectral analyses, which revealed an ion peak at m/z ratio of 531.20 as a base peak in the mass spectrum. Further reaction of **20** with benzoin n a refluxing glacial acetic acid-acetic anhydride mixture, afforded a product with a



Scheme 5



Scheme 6

molecular formula of $C_{35}H_{23}N_7O$ (m/z = 557.20). The ^1H NMR spectrum of the isolated product showed a broad band (exchanges with D_2O) for only one proton at δ = 9.18 ppm and a multiplet in the aromatic region due to 22 protons. According to these results, the 1-(5,6-diphenyl-1,2,4-triazin-3-yl]-7,8-diphenyl-1*H*-pyrazolo[4,3-*e*]pyrrolo[1,2-*a*]pyrimidin-4(1*H*)-one, **27**, is the suitable structure for the isolated product. Compound **27** may be formed *via* the first formation of the N-acetyl intermediate **25** which condenses with benzion to give the intermediate **26**. The latter then loses two molecules of water to give the isolated product **27** (Scheme 6).

Diazotization and self coupling of the amino amide **20** gave 7-(5,6-diphenyl-1,3,4-triazin-3-yl)-3,7-dihydro-*4H*-pyrazolo[3, 4-*d*][1,2,3]triazin-4-one, **28**, which was converted to the corresponding 1-(5,6-diphenyl-1,3,4-triazin-3-yl)-5-methoxy-1*H*-pyrazole-4-carboxamide, **29**, with a 56% yield on heating in absolute methanol (Scheme 6). Structures **28** and **29** were confirmed by spectral and elemental analyses. The ^1H NMR spectrum of **28** showed a broad band (exchanges with D_2O) for only one proton at δ = 9.71 ppm due to an NH group. However, the ^1H NMR spectrum of **29** showed, in addition to the broad signal for one NH_2 protons at δ = 6.17 ppm, a singlet signal at δ = 3.12 ppm due to one methyl group.

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