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Graphical Abstract

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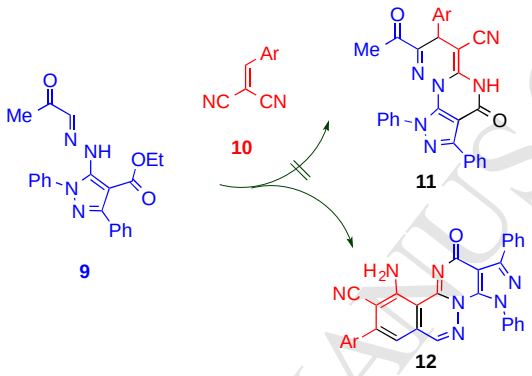

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Said A. S. Ghozlan[a] , Amr M. Abdelmoniem[a], Holger Butenschön[b] and Ismail A. Abdelhamid[a,b*]

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ABSTRACT

Azaenamine incorporating pyrazole-4-carboxylate is prepared and allowed to react with α,β-substituted nitriles. A new reactivity pattern was observed leading to the formation of substituted pyrazolo[4′,3′-5,6]pyrimido[2,1-*a*]phthalazine-9-carbonitriles, which can be considered as aromatic aza-steroid analogues

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1. Introduction

Arylhydrazones of type **1** can be regarded as azaenamines, they react similarly to enamines.[1-4] In this context, we managed to achieve a Michael addition of azomethine CH to cinnamonitriles followed by ring closure to the desired interesting pyridazine derivatives.[5-9] It was found that the reaction of **1a-d** (carrying electron-donating or weakly deactivating groups at the *ortho* position)[5-9] with **2** resulted in the formation of the 2,5-dihydropyridazine **3**. The constitution of **3** was established spectroscopically based on HMBC NMR measurements,[7] which revealed a correlation between the benzylic pyridazine proton and the carbonyl carbon atom. On the other hand, the reaction of **1e-f** (carrying an electron withdrawing group)[10] with **2** gave aminobenzene dicarbonitriles **4**. Thus, the nature of the substituent at the aryl substituent of the azaenamine controls the pathway of the reaction either to 2,5-dihydropyridazines **3** or to the aminobenzene dicarbonitrile **4** (Figure 1).

2. Results and Discussion

As a part of an ongoing research program we report the results of our investigations concerning the different reactivity patterns of substituted azaenamines towards cinnamonitrile derivatives **2** or **10**. In addition, we report a new synthesis of azaenamines containing the pyrazole-4-carboxylate substructure. Thus, it was found that coupling acetoacetic acid (**7**), which had been obtained by hydrolysis of **5** *via* the potassium salt **6**, with 4-(ethoxycarbonyl)-1,3-diphenyl-1*H*-pyrazole-5-diazonium chloride (**8**) afforded the corresponding pyruvaldehyde-1-arylhydrazone **9** in 73% yield (Scheme 1).

Our work showed that, while a variety of substituted azaenamines yielded 2,5-dihydropyridazines,[5-9] pyrazolyl-azaenamine **9** reacted differently yielding pyrazolo[4′,3′-5,6]pyrimido[2,1-*a*]phthalazine-9-carbonitrile derivatives **12** rather than the expected compounds **11** (Scheme 2). The constitutions of compounds **12** were established spectroscopically. For example, the IR spectrum indicated the presence of a CN group (ν = 2206 cm^{-1}), only one CO group (ν = 1650 cm^{-1}) and a characteristic broad band at ν = 3440 cm^{-1}, whichrefers to the NH_2 group. The ^{1}H NMR spectrum of compound **12a** revealed the absence of methyl protons and showed a broad singlet at δ = 7.23 ppm (2 H) assigned to NH_2 group, as well as a singlet at δ = 8.87 (1 H) ppm referring to the pyridazine CH. The multiplet at δ = 7.40-7.70 (5 H) ppm was assigned to the aryl protons. The ^{13}C NMR spectrum showed the carbnonyl carbon signal at δ = 163.1 ppm, that for the pyridazine CH at δ = 153.6 ppm, as well as the other signals of the carbon atoms of the aromatic system.

It is worth-mentioning that compounds **12** can be viewed as 7,8,11,15,16-pentazasteroid derivatives as shown in Figure 2. It was reported that replacement one or more carbon atoms of a steroid molecule by heteroatoms brings about notable modifications of its biological activity; numerous studies exist, which deal with total and partial syntheses of heterosteroids as well as their physiological activities.[11-21] Figure 2 shows also that the oxidation of testosterone leads to the formation of steroidal phenanthrenes[21] that are similar to our products.

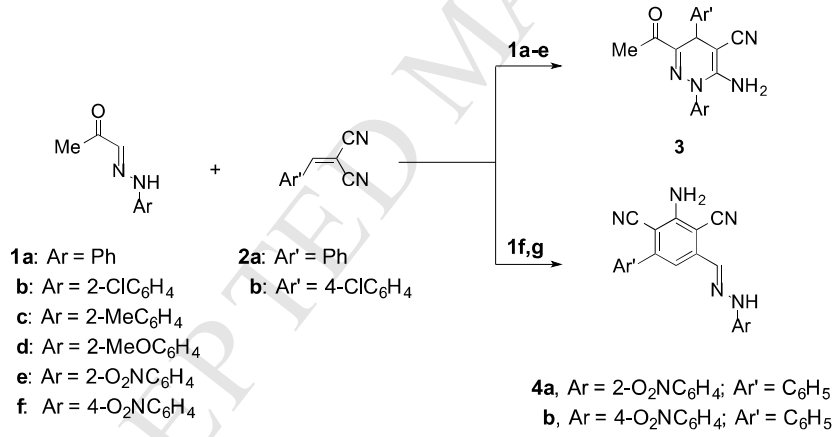
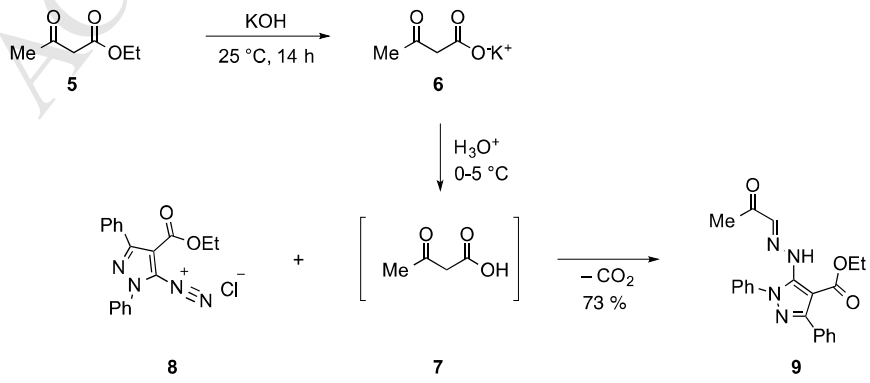
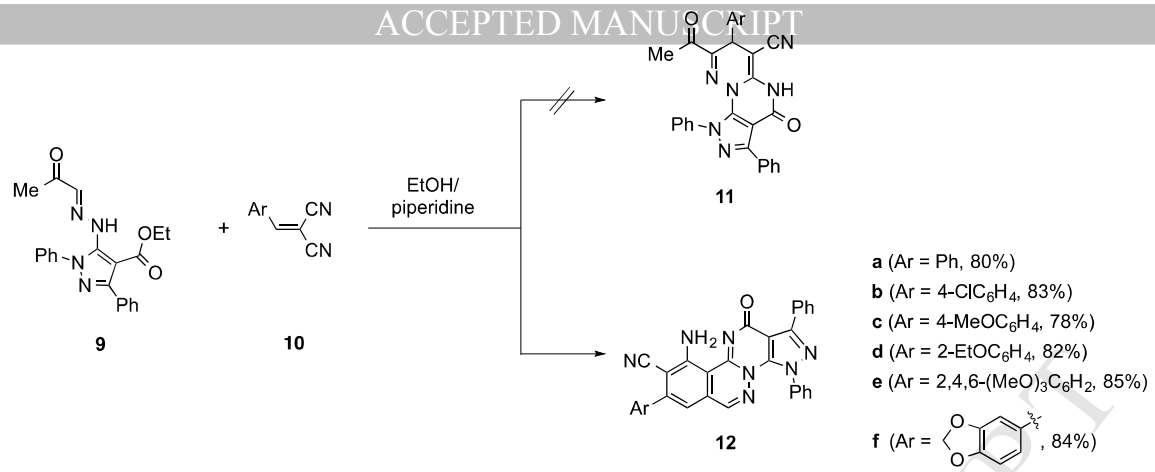


Figure 1 The substituent effect on the reaction of azaenamines **1a-f** with cinnamonitrile derivatives **2a**,**b**



Scheme 1 The synthesis of azaenamine **9**



Scheme 2 The reaction of azaenamine **9** with cinnamonitrile derivatives **10**

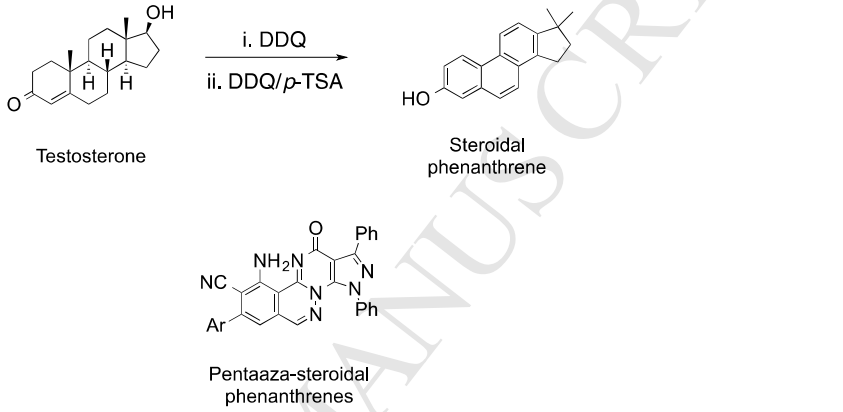


Figure 2. Steroidal phenanthrenes[21] produced by oxidation of testosterone resemble the azasteroids reported in this study

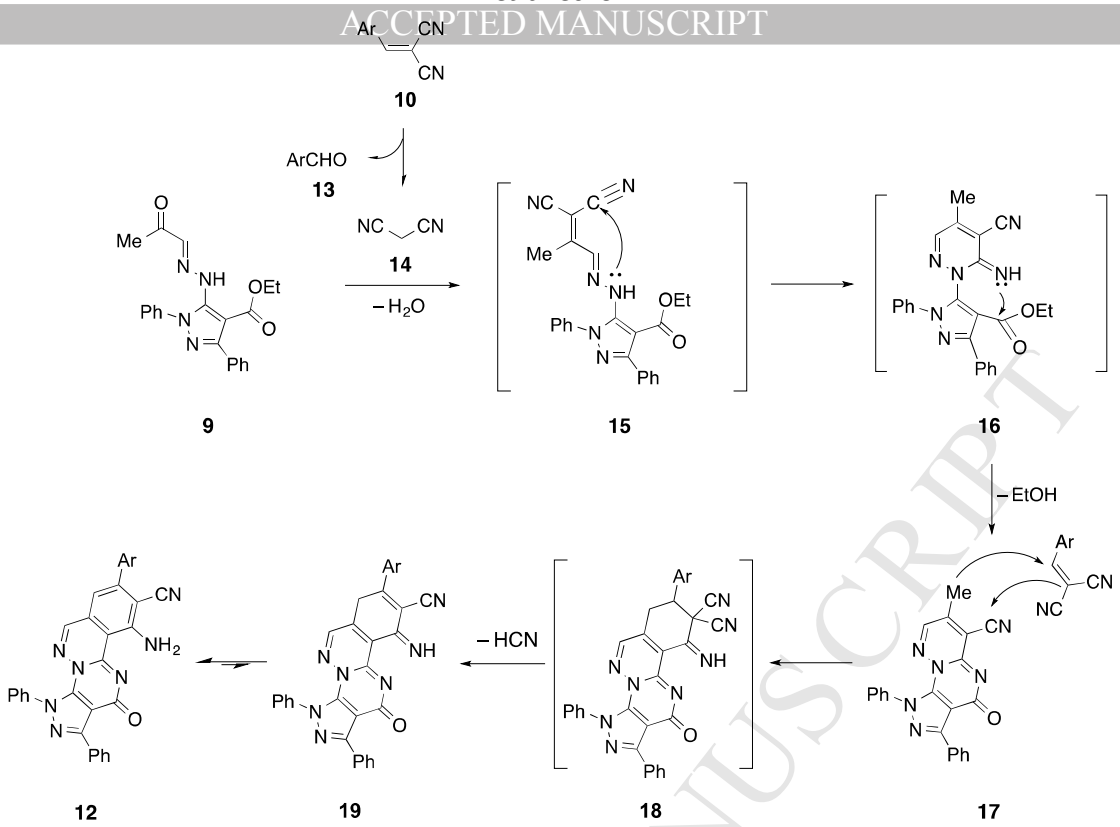
A possible pathway of the formation of compounds **12** is shown in Scheme 3. It is clear that the azomethine CH carbon atom in compound **9** is less nucleophilic than the methyl carbon atom due to the presence of electron withdrawing group at the pyrazole ring, and thus the CH will be inactive towards Michael acceptors **10.** These exist in equilibrium with malononitrile and aldehyde in wet solvents.[22,23] Compound **9** presumably condenses with malononitrile (**14**) to yield intermediate **15**, which cyclizes to **17** *via* intermediate **16**. Compound **17** then reacts further with **10** to give products **12**. A similar sequence has been reported.[10,24-29] Thus, while pyrazolyl-azaenamine **9** leads to the formation of pentaaza steroidal phenanthrene derivatives **12**, the azaenamines of type **1e,f** yield phthalazine derivatives (compound **9a** therein).[10]

In an attempt to support this pathway we managed to isolate the intermediate **17** in 92 % yield through the direct reaction of **9** with malononitrile (**14**). The reaction of compound **17** with arylidene malononitriles **10** gave products **12** in similar yields (Scheme 4). In support of this, carrying out the reaction in anhydrous ethanol in an inert atmosphere resulted in the formation of a very small amount of the product. Moreover, using anhydrous toluene instead of ethanol afforded no products.

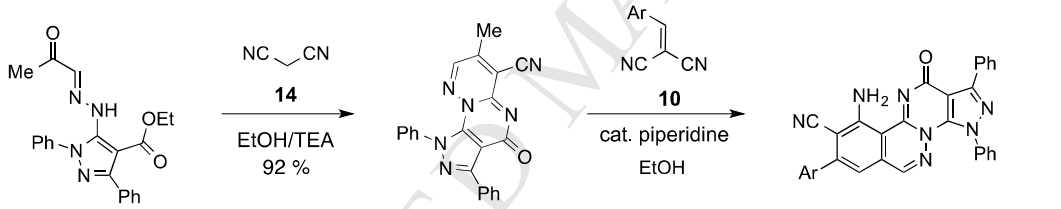
Compounds **12** could be also obtained in a three component reaction of equimolar amounts of arylaldehyde **13**, malononitrile (**14**), and azaenamine **9** in ethanol/piperidine (Scheme 5).

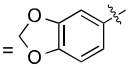
The difference in reactivity between azaenamines **1** and **9** may be explained by the reduction in nucleophilicity of the hydrazone carbon atom by decreased lone pair donation from the hydrazone NH group attached to the 4-nitrophenyl or to the pyrazole group, the latter being electron withdrawing because of the ethoxycarbonyl substituent.

In conclusion, the electron-withdrawing nature of the carboxylic ester at the pyrazole ring in **9** renders the hydrazone CH inactive towards electrophiles. A new reaction path is thus followed leading to novel pyrazolo[3′,4′-4,5]pyrimido[2,3-*a*]phthalazine-9-carbonitrile derivatives **12**, which can be considered as pentaaza-steroidal phenanthrene analogues. The effect of substituents at the pyrazole and other heterocyclic ring substituted azaenamines is subject of current research in our laboratories.

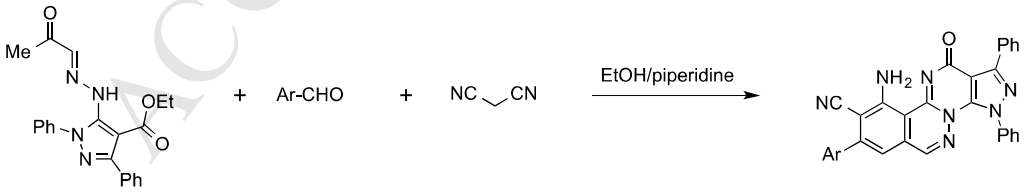


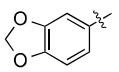
Scheme 3 A plausible mechanism for the reaction of pyrazolyl-azaenamine **5** with arylidene-malononitrile derivatives **6**



12a (Ar = C_6H_5, 77%)
12b (Ar = 4-ClC_6H_4, 80%)
12c (Ar = 4-$MeOC_6H_4$, 76%)
12d (Ar = 2-$EtOC_6H_4$, 84%)
12e (Ar = 2,4,6-$(MeO)_3C_6H_2$, 83%)
12f (Ar =  , 82%)

Scheme 4 Synthesis of **17** and its subsequent reaction with arylidene-malononitrile derivatives **10a-f**



12a (Ar = Ph, 75%)
12b (Ar = 4-ClC_6H_4, 81%)
12c (Ar = 4-$MeOC_6H_4$, 72%)
12d (Ar = 2-$EtOC_6H_4$, 80%)
12e (Ar = 2,4,6-$(MeO)_3C_6H_2$, 82%)
12f (Ar =  , 78%)

Scheme 5 Three component reaction of pyrazolyl-azaenamine **9**, malononitrile (**10**) and arylaldehydes **13a-f** to compounds **12a-f**

3. Experimental Part

Melting points were determined with a Stuart melting point apparatus and are uncorrected. IR spectra were recorded as KBr pellets using a FTIR Bruker – vector 22 spectrophotometer. ^{1}H and ^{13}C NMR spectra were recorded in DMSO–d_6 as solvent with a Varian Gemini NMR spectrometer at 400 MHz and 100 MHz respectively using TMS as internal standard. Chemical shifts are reported as δ in ppm. Mass spectra were measured with a Shimadzu GCMS–QP–1000 EX mass spectrometer in EI (70 eV) mode. The elemental analyses were performed at the Micro analytical center, Cairo University.

3.1. Ethyl (E)-5-(2-(2-oxopropylidene)hydrazinyl)-1,3-diphenyl-1H-pyrazole-4-carboxylate (9)

Ethyl acetoacetate (1.28 mL, 10 mmol) was diluted with distilled water (250 mL). Then KOH (0.56 g, 10 mmol) was added, and the solution was stirred at 25 °C for 14 h. The resulting solution was cooled to 0 °C by addition of crushed ice and neutralized by addition of ice-cooled 50% conc. HCl (4 mL). 4-Ethoxycarbonyl-1,3-diphenyl-1*H*-pyrazole-5-diazonium chloride solution (prepared by a typical diazotization procedure as follows: Ethyl 5-amino-1,3-diphenyl-1*H*-pyrazole-4-carboxylate (3.07 g, 10 mmol) was dissolved in AcOH-HCl mixture (1:3, 4 mL). The internal temperature was cooled to 0 °C and a 5 mL aqueous solution of sodium nitrite (0.69 g, 10 mmol) was added dropwise keeping the temperature below 5 °C. The diazonium chloride solution was then added dropwise to the acetoacetic acid solution followed by a solution of sodium acetate (2.7 g, 20 mmol) in distilled water (100 mL). A pale yellow precipitate was separated and crystallized from ethanol to give **9** (2.74 g, 7.3 mmol, 73%) as yellow crystals (m. p. 148-150 °C).]; IR (KBr) ν 3269 (br), 3276, 3061, 2983, 1678, 1549, 1513, 1429, 1258, 1148, 1019, 697 cm^{-1}; 1H NMR (400 MHz, DMSO-d_6) δ (two forms) [(1.08 (H-bonded), 1.26 (free)] (3 H, t, J 7.2 Hz, $COOCH_2C\underline{H}_3$), [2.36 (shielded), 2.50 (deshielded)] (3 H, s, $COC\underline{H}_3$), [4.15 (H-bonded), 4.32 (free)] (2 H, q, J 7.2 Hz, $COOC\underline{H}_2CH_3$), 7.25-7.72 (10 H, m, Ar-H), 10.08 (1 H, br s, NH); MS (EI, 70 eV) *m/z* (%) 376 (2.2, M^+), 333 (42), 259 (22); HRMS (EI), calcd. for $[C_{21}H_{20}N_4O_3]^+$ (M^+) 376.1535; found 376.1528. . Anal. calcd. for $C_{21}H_{20}N_4O_3$ (376.4): C 67.01, H 5.36, N 14.88 %. Found: C 67.09, H 5.19, N 14.73 %.

3.2. General Procedures for Compounds 12a-f

Method A. A mixture of azaenamine **9** (0.38 g, 1 mmol) and arylidine malononitrile **10a-f** (1 mmol) was heated at reflux in EtOH (20 mL) in the presence of piperidine (0.2 mL) for 3 h. The solvent was evaporated at reduced pressure, and the crude product was collected and crystallized from the proper solvent.

Method B. A mixture of **17** (0.38 g, 1 mmol) and arylidene malononitrile **10a-f** (1 mmol) was refluxed in DMF (10 mL) in presence of piperidine (0.2 mL) for 3 h. The solvent was evaporated at reduced pressure, and the crude product was washed with 10% aq. HCl (10 mL) and then with distilled water (10 mL). The resulting solid was dried and crystallized from the proper solvent.

Method C. A mixture of azaenamine **9** (0.38 g, 1 mmol), malononitrile (**14**, 0.07 g, 1 mmol) and aryl aldehyde (**13**, 1 mmol) was heated at reflux in ethanol (20 mL) in presence of piperidene (0.2 mL). The solvent was then evaporated at reduced pressure, and the collected solid was crystallized from the proper solvent.

3.2.1. 10-Amino-12-oxo-1,3,8-triphenyl-3,12-dihydro-pyrazolo[4',3':5,6]pyrimido[2,1-*a*]phthalazine-9-carbonitrile (12a)

Crystallized from dioxane to give **12a** (0.40 g, 0.8 mmol, 80%, method A; 0.39 g, 0.8 mmol, 77%, method B; 0.38 g, 0.8 mmol, 75%, method C) as yellow crystals (m. p. > 300 ° C).]; IR (KBr) ν 3440, 3112, 3051, 2925, 2206, 1651, 1557, 1443, 1338, 1302, 1151, 1053, 764, 695 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.23 (2 H, br s, $N\underline{H}_2$), 7.40–7.70 (16 H, m, Ar-H), 8.87 (1 H, s, pyridazine C$\underline{H}$). ^{13}C NMR (100 MHz, DMSO-d_6) δ 96.7, 104.9 ($\underline{C}$CN), 106.2, 107.7, 114.6, 116.8 ($\underline{C}$N), 126.6, 127.4, 128.6, 129.1, 129.2, 129.6, 129.7, 129.8, 130.1, 130.9, 131.1, 137.8, 139.1, 142.9, 147.8, 149.5, 150.8 (Ar $\underline{C}$), 153.6 (pyridazine $\underline{C}$H), 163.1 ($\underline{C}$O). MS (EI, 70 eV) *m/z* (%) 505 (100, M^+), 504 (90), 428 (11), 410 (12), 327 (15), 260 (28), 245 (29); HRMS (EI) calcd. for $[C_{31}H_{19}N_7O]^+$ (M^+) 505.1651; found 505.1643. . Anal. calcd. for $C_{31}H_{19}N_7O$ (505.5): C 73.65, H 3.79, N 19.39 %. Found: C 73.54, H 3.68, N 19.25 %.

3.2.2. 10-Amino-8-(4-chlorophenyl)-12-oxo-1,3-diphenyl-3,12-dihydropyrazolo[4',3':5,6]pyrimido[2,1-*a*]phthalazine-9-carbonitrile (12b)

Crystallized from DMF to give **12b** (0.45 g, 0.8 mmol, 83%, method A; 0.43 g, 0.8 mmol, 80%, method B; 0.44 g, 0.8 mmol, 81%, method C) as yellow crystals (m. p. > 300 °C).]; IR (KBr) ν 3441 (br), 3114, 2205, 1650, 1557, 1445, 1338, 1307, 1241, 1151, 1054, 823, 755, 689 cm^{-1}; 1H NMR (400 MHz, DMSO-d_6) δ 7.22 (2 H, br s, $N\underline{H}_2$), 7.36–7.69 (15 H, m, Ar-H), 8.86 (1 H, br s, pyridazine C$\underline{H}$). MS (EI, 70 eV) *m/z* (%) 541 (26, $[M+2]^+$), 540 (44, $[M+1]^+$), 539 (57, M^+), 269 (15), 180 (15), 129 (11), 77 (100). HRMS (EI) cald. for $[C_{31}H_{18}ClN_7O]^+$ (M^+) 539.1261; found 539.1256. Anal. calcd. for $C_{31}H_{18}ClN_7O$ (540.0): C 68.95, H 3.36, Cl 6.57, N 18.16 %. Found: C 68.87, H 3.29, Cl 6.53, N, 18.13 %.

3.2.3. 10-Amino-8-(4-methoxyphenyl)-12-oxo-1,3-diphenyl-3,12-dihydropyrazolo[4',3':5,6]pyrimido[2,1-*a*]phthalazine-9-carbonitrile (12c)

Crystallized from dioxane to give **12c** (0.42 g, 0.8 mmol, 78%, method A; 0.41 g, 0.8 mmol, 76%, method B; 0.39 g, 0.7 mmol, 72%, method C) as bright yellow crystals (m. p. 292-294 °C). IR (KBr) ν 3440 (br), 3160, 3047, 2963, 2206, 1647, 1557, 1509, 1446, 1335, 1299, 1244, 1152, 1046, 838, 756, 688 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.87 (3 H, s, $OC\underline{H}_3$), 7.14–7.66 (15 H, m, Ar-H), 7.25 (2 H, br s, $N\underline{H}_2$), 8.91 (1 H, s, pyridazine C$\underline{H}$). ^{13}C NMR (100 MHz, DMSO-d_6) δ 55.9 ($O\underline{C}H_3$), 96.7, 105.0 ($\underline{C}$CN), 107.4, 114.7 ($\underline{C}$N), 126.7, 127.5, 128.5, 128.6, 129.6, 129.7, 130.0, 130.1, 130.6, 130.7, 131.0, 131.1, 139.2, 142.9, 147.9, 148.0, 150.5, 153.8 (pyridazine $\underline{C}$H), 160.9, 163.1 (Ar $\underline{C}$), 164.4 ($\underline{C}$O) MS (EI, 70 eV) *m/z* (%) 535 (37, $[M+1]^+$), 534 (100, M^+), 533 (90), 497 (23), 305 (23), 260 (63), 176 (30), 109 (23), 77 (60). HRMS (EI) calcd. for $[C_{32}H_{21}N_7O_2]^+$ (M^+) 535.1757; found 535.1765requires. Anal. calcd. for $C_{32}H_{21}N_7O_2$ (535.6): C 71.77, H 3.95, N 18.31. Found: C 71.69, H 3.86, N 18.25.

3.2.4. 10-Amino-8-(2-ethoxyphenyl)-12-oxo-1,3-diphenyl-3,12-dihydropyrazolo[4',3':5,6]pyrimido[2,1-a]phthalazine-9-carbonitrile (12d)

Crystallized from dioxane-DMF (5:2) to give **12d** (0.45 g, 0.8 mmol, 82%, method A; 0.46 g, 0.8 mmol, 84%, method B; 0.44 g, 0.8 mmol, 80%, method C) as brownish-yellow crystals (m. p. 288-290 °C). IR (KBr) ν 3407 (br), 3323, 3058, 2980, 2889, 2208, 1646, 1552, 1346, 1273, 1238, 1155, 1047, 970, 756, 659 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.53 (3 H, t, J 7.2 Hz, $COOCH_2C\underline{H}_3$), 4.22 (2 H, q, J 7.2 Hz, $COOC\underline{H}_2CH_3$), 7.07-8.00

(17 H, m, Ar-H, NH_2), 9.38 (1 H, s, pyridazine CH). MS (EI, 70 eV) *m/z* (%) 549 (47, M^+), 548 (45), 547 (47), 505 (13), 250 (13), 192 (21), 141 (24), 104 (42), 66 (100). HRMS (EI) calcd. for $[C_{33}H_{23}N_7O_2]^+$ (M^+); found 549.1902. Anal. calcd. for $C_{33}H_{23}N_7O_2$ (549.6): C 72.12, H 4.22, N 17.84 %. Found: C 72.08, H 4.14, N 17.77 %.

3.2.5. 10-Amino-12-oxo-1,3-diphenyl-8-(2,4,6-trimethoxyphenyl)-3,12-dihydropyrazolo[4',3':5,6]pyrimido[2,1-*a*]phthalazine-9-carbonitrile (12e)

Crystallized from dioxane to give **12e** (0.51 g, 0.9 mmol, 85%, method A; 0.49 g, 0.8 mmol, 83%, method B; 0.485 g, 0.8 mmol, 82%, method C) as a reddish-yellow powder (m. p. 196-198 °C). IR (KBr) *v* 3425, 2941, 2206, 1655, 1619, 1582, 1554, 1506, 1451, 1411, 1388, 1344, 1285, 1247, 1148, 1125, 1055, 1009, 916, 794, 752, 694 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6) δ 3.80 (3 H, s, OCH_3), 3.89 (6H, s, 2 OCH_3), 7.01 (2 H, br s, NH_2), 7.31-7.46 (13 H, m, Ar-H), 8.85 (1 H, s, pyridazine CH). MS (EI, 70 eV) *m/z* (%) 595 (7, M^+), 303 (5), 216 (100), 161 (21), 116 (28), 73 (65). HRMS (EI) calcd. for $[C_{34}H_{25}N_7O_4]^+$ (M^+) 595.1968; found 595.1955. . Anal. calcd. for $C_{34}H_{25}N_7O_4$ (595.6): C 68.56, H 4.23, N 16.46 %. Found: C 68.42, H 4.18, N 16.38 %.

3.2.6. 10-Amino-8-(benzo[d][1,3]dioxol-5-yl)-12-oxo-1,3-diphenyl-3,12-dihydropyrazolo[4',3':5,6]pyrimido[2,1-a]phthalazine-9-carbonitrile (12f)

Crystallized from dioxane-DMF (5:2) to give **12f** (0.46 g, 0.8 mmol, 84%, method A; 0.45 g, 0.8 mmol, 82%, method B; 0.43 g, 0.8 mmol, 78%, method C) as faint brown powder (m. p. > 300 °C). ; [Found: C, 69.85; H, 3.42; N, 17.79.]; IR (KBr) *v* 3052, 2211, 1651, 1619, 1593, 1556, 1501, 1443, 1386, 1336, 1311, 1241, 1153, 1055, 1036, 928, 793, 758, 694 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6) δ 6.15 (2 H, s, -OCH_2O-), 7.09–7.47 (16 H, m, Ar-H, NH_2), 8.86 (1 H, br s, pyridazine CH). MS (EI, 70 eV) *m/z* (%) 560 (22, $[M+1]^+$), 549 (60, M^+), 307 (20), 274 (40), 205 (18), 129 (38), 77 (100). HRMS (EI) calcd. for $[C_{32}H_{19}N_7O_3]^+$ (M^+) 549.1549; found 549.1537. Anal. calcd. for $C_{32}H_{19}N_7O_3$ (549.6): C 69.94, H 3.49, N 17.84 %.

3.3. 7-Methyl-4-oxo-1,3-diphenyl-1,4-dihydropyrazolo[4',3':5,6]pyrimido[1,2-*b*]pyridazine-6-carbonitrile (17)

A mixture of azaenamine **9** (0.38 g, 1 mmol) and malononitrile (**14**, 0.07 g, 1 mmol) was heated at reflux in ethanol (20 mL) in the presence of triethylamine (0.3 mL) for 3 h. The solvent was evaporated at reduced pressure, and the crude product was collected and crystallized from dioxane to give **17** (0.35 g, 0.9 mmol, 92%) as green crystals (m. p. 288-290 °C) ; [Found:. requires]; IR (KBr) *v* 3057, 2912, 2207, 1647, 1615, 1557, 1432, 1330, 1156, 1056, 975, 758, 692 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6) δ 2.62 (CH_3), 7.45 (m, 10 H, Ar-H), 8.76 (s, 1 H, pyridazine CH). ^{13}C NMR (100 MHz, DMSO-d_6) δ 19.2 (CH_3), 106.3, 113.2, 113.9 (CN), 126.6, 127.2, 128.6, 129.8, 130.2, 131.1, 139.0, 143.0, 143.1, 144.6 (pyridazine CH), 146.3, 149.0, 149.1 (Ar-C), 163.8 (CO). MS (EI, 70 eV) *m/z* (%) 379 (4, $[M+1]^+$), 378 (63, M^+), 376 (100), 180 (2), 77 (40). HRMS (EI) calcd. for $[C_{22}H_{14}N_6O]^+$ (M^+) 378.1229; found 378.1243. Anal. calcd. for $C_{22}H_{14}N_6O$ (378.4): C 69.83, H 3.73, N 22.21 %. Found: C 69.79, H 3.68, N 22.18 %.

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