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A facile synthesis of 3-amino-2,5-dihydropyridazines and 4-deazatoxoflavin analogues via [3+3] atom combination

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ABSTRACT

Michael addition reactions of arylhydrazone derivatives with different functionalized *α*-cyanoacrylamides were conducted and yielded new pyridazine-4-carboxamide compounds. A further reaction with acetic anhydride was investigated resulting in the formation of a 4-deazatoxoflavin analogue. A one step synthesis of 4-deazatoxoflavin was also carried out by reacting azaenamine with *N*-carbamoyl-2-cyano-3-phenylacrylamide to give deazatoxoflavin. Unambiguous structural elucidation was done using 2D-HMBC spectroscopy.

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1. Introduction

The biological importance of pyridazines and their fused compounds as antimicrobial and anticancer agents rendered them a target of enormous scientific efforts [1-5]. The synthetic approaches of pyridazines involve two main strategies: the first one (Figure 1, method A) is the cycloaddition of diazomethane derivatives to cyclopropene compounds [6-10], and the other method (Figure 1, method B) is the retro Diels-Alder cycloaddition of substituted 1,2,4,5-tetrazines to functionalized dienophiles [11-16]. Both methods, in spite of their prevalence in literature, have various disadvantages of expensive starting materials, tedious experimental work, hazard reagents, etc. A third relatively new method to synthesize dihydropyridazines (Figure 1, method C) implies a [3+3] atom combination of arylhydrazones to activated acrylonitrile derivatives yielding 3-amino-2,5-dihydropyridazines [17-21]. In this case, the nitrogen lone pair resonance makes the azomethine carbon relatively electron rich and enamine-like reactivity takes place [22,23].

The present work aims at studying the potency of [3+3] atom combination reaction of azaenamines, as Michael donors, with various *α*-cyanoacrylamides as an interesting strategy for the synthesis of partially unsaturated aminopyridazines. Also, extending these reactions to prepare some novel pyrimido [4,5-*c*]pyridazines (4-deazatoxoflavin analogues) is also investigated.

2. Experimental

2.1. Instrumentation

Melting points were measured with a Stuart melting point apparatus and are uncorrected. The IR spectra were recorded as potassium bromide pellets using a FT-IR Bruker-vector 22 spectrophotometer. All the ^{1}H and ^{13}C NMR spectra were recorded with a Varian Gemini NMR spectrometer at 400 and 100 MHz, respectively, using TMS as internal standard. The samples were dissolved in DMSO-d_6 or $CDCl_3$ and the chemical shifts are reported as δ in ppm. Electron ionization mass spectra (EI-MS) were measured on a Shimadzu GCMS-QP-1000 EX mass spectrometer at 70 eV. The elemental analyses were performed at the Microanalytical Center, Cairo University.

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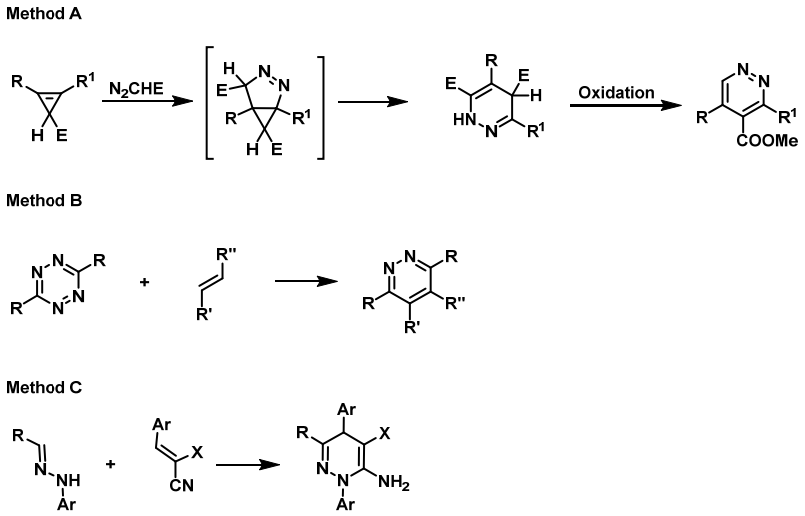


Figure 1. General synthetic strategies of pyridazine ring systems.

2.2. Synthesis

Azaenamines **1a**,**b** were prepared in a similar procedure to that reported by Reynolds *et al*. [24]. All *α*-cyanoacrylamide derivatives (**2a**-**e** and **16**) in this paper were prepared via a typical Knoevenagel condensation procedure [25]. The synthetic strategies, physical data and spectral characterization of the newly synthesized products are stated below.

2.2.1. Synthesis of 6-acetyl-3-amino-N,2,5-triphenyl-2,5-dihydropyridazine-4-carboxamide (8a)

A mixture of azaenamine **1a** (162 mg, 1 mmol) and activated cyanoacrylamide derivative **2a** (248 mg, 1 mmol) was heated at reflux in dioxane (10 mL) in the presence of piperidine (0.2 mL, 2 mmol) for 5 h. The solvent was evaporated under reduced pressure and the collected solid was crystallized from ethanol:dioxane mixture (5:1, *v*:*v*, 10 mL) to give compound **8a** (Scheme 1). Yield: 375 mg, 915 mmol, 91%. Color: Bright yellow crystals. M.p.: 190-192 °C. FT-IR (KBr, ν, cm^{-1}): 3360, 3181 (NH) (br, CONH and NH_2), 1673 (CO) ($COCH_3$), 1634 (CO) (CONH). ^1H NMR (400 MHz, DMSO-d_6, δ, ppm): 2.39 (s, 3H, C*H*$_3$), 5.72 (s, 1H, pyridazine-*H*), 6.96-7.59 (m, 17H, Ar-*H* and N*H*$_2$), 9.05 (br s, 1H, N*H*). ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): 25.6 (CH_3), 33.4 (CH), 66.6 (C), 78.4 (C), 121.4 (CH), 123.1 (CH), 126.2 (CH), 127.2 (CH), 127.7 (CH), 128.1 (CH), 128.6 (CH), 129.1 (CH), 130.0 (CH), 140.1 (C), 143.3 (C), 146.5 (C), 151.2 (C), 167.9 (C), 196.9 (C). MS (EI, *m/z* (%)): 411 [(M+1)$^+$] (1), 410 [M$^+$] (2), 366 (1), 333 (8), 318 (10), 291 (100), 248 (22), 93 (7), 77 (23). HRMS (EI) calcd. for $C_{25}H_{22}N_4O_2$: 410.1743; found: 410.1766. Anal. calcd. for $C_{25}H_{22}N_4O_2$: C, 73.15; H, 5.40; N, 13.65. Found: C, 73.09; H, 5.36; N, 13.42%.

2.2.2. Synthesis of 6-acetyl-3-amino-2,5-diphenyl-N-(p-tolyl)-2,5-dihydropyridazine-4-carboxamide (8b)

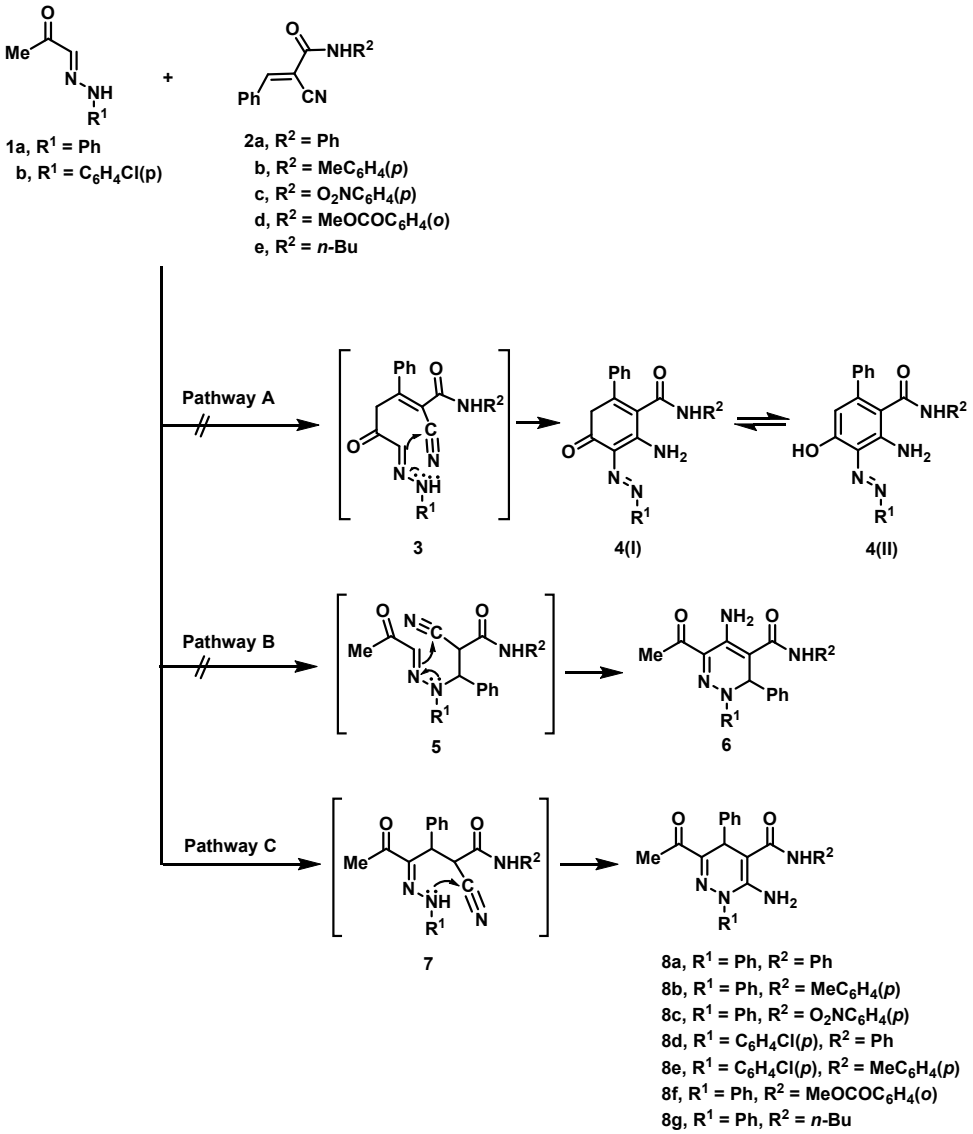
Following the procedure given for compound **8a**, azaenamine **1a** (162 mg, 1 mmol) and cyanoacrylamide derivative **2b** (262 mg, 1 mmol) were reacted in dioxane (10 mL) in presence of piperidine (0.2 mL, 2 mmol). Crystallization of the isolated product from ethanol:dioxane mixture (5:1, *v*:*v*, 10 mL) afforded the compound **8b** (Scheme 1). Yield: 382 mg, 901 mmol, 90%. Color: Golden yellow crystals. M.p.: 198-200 °C. IR (KBr, ν, cm^{-1}): 3392 (NH) (br, CONH and NH_2), 1631 (CO) (br, $COCH_3$ and CONH). ^1H NMR (400 MHz, DMSO-d_6, δ, ppm): 2.23 (s, 3H, C*H*$_3$), 2.36 (s, 3H, C*H*$_3$CO), 5.65 (s, 1H, pyridazine-*H*), 7.03-7.56 (m, 16H, Ar-*H* and N*H*$_2$), 8.95 (br s, 1H, N*H*). ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): 20.9 (CH_3), 25.3 (CH_3), 33.4 (CH), 78.4 (C), 121.4 (CH), 126.1 (CH), 127.2 (CH), 127.7 (CH), 128.1 (CH), 128.9 (CH), 129.0 (CH), 129.9 (CH), 132.0 (C), 137.4 (C), 140.7 (C), 143.3 (C), 146.5 (C), 150.7 (C), 167.9 (*C*ONH), 196.5 (*C*OCH_3). MS (EI, *m/z* (%)): 424 [M$^+$] (5), 318 (10), 290 (100), 248 (15), 214 (4), 106 (5), 77 (21). HRMS (EI) calcd. for $C_{26}H_{24}N_4O_2$: 424.1899; found: 424.1876. Anal. calcd. for $C_{26}H_{24}N_4O_2$: C, 73.56; H, 5.70; N, 13.20. Found: C, 73.49; H, 5.66; N, 13.18%.

2.2.3. Synthesis of 6-acetyl-3-amino-N-(4-nitrophenyl)-2,5-diphenyl-2,5-dihydropyridazine-4-carboxamide (8c)

Following the procedure given for compound **8a**, azaenamine **1a** (162 mg, 1 mmol) and cyanoacrylamide derivative **2c** (293 mg, 1 mmol) were reacted in dioxane (10 mL) in presence of piperidine (0.2 mL, 2 mmol). Crystallization of the isolated product from ethanol:dioxane mixture (5:1, *v*:*v*, 10 mL) afforded the compound **8c** (Scheme 1). Yield: 398 mg, 877 mmol, 88%. Color: Orange solid. M.p.: 192-194 °C. IR (KBr, ν, cm^{-1}): 3460 (NH) (br, CONH and NH_2), 1684 (CO) ($COCH_3$), 1644 (CO) (CONH). ^1H NMR (400 MHz, DMSO-d_6, δ, ppm): 2.37 (s, 3H, C*H*$_3$CO), 5.76 (s, 1H, pyridazine-*H*), 7.17-8.16 (m, 16H, Ar-*H* and N*H*$_2$), 9.56 (br s, 1H, N*H*). ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): 25.3 (CH_3), 33.2 (CH), 77.9 (C), 120.0 (CH), 124.9 (CH), 126.3 (CH), 127.3 (CH), 127.6 (CH), 128.4 (CH), 129.1 (CH), 130.1 (CH), 140.5 (C), 141.7 (C), 143.2 (C), 147.0 (C), 151.9 (C), 168.1 (C), 196.7 (C). MS (EI, *m/z* (%)): 455 [M$^+$] (3), 409 (9), 318 (12), 290 (100), 248 (13), 92 (27), 77 (30). HRMS (EI) calcd. for $C_{25}H_{21}N_5O_4$: 455.1594; found: 455.1578. Anal. calcd. for $C_{25}H_{21}N_5O_4$: C, 65.93; H, 4.65; N, 15.38. Found: C, 65.88; H, 4.63; N, 15.36%.

2.2.4. Synthesis of 6-acetyl-3-amino-2-(4-chlorophenyl)-N,5-diphenyl-2,5-dihydropyridazine-4-carboxamide (8d)

Following the procedure given for compound **8a**, azaenamine **1b** (196 mg, 1 mmol) and cyanoacrylamide derivative **2a** (248 mg, 1 mmol) were reacted in dioxane (10 mL) in presence of piperidine (0.2 mL, 2 mmol). Crystallization of the isolated product from ethanol:dioxane mixture (5:1, *v*:*v*, 10 mL) afforded the compound **8d** (Scheme 1). Yield: 414 mg, 932 mmol, 93%. Color: Pale yellow solid. M.p.: 194-196 °C.



Scheme 1

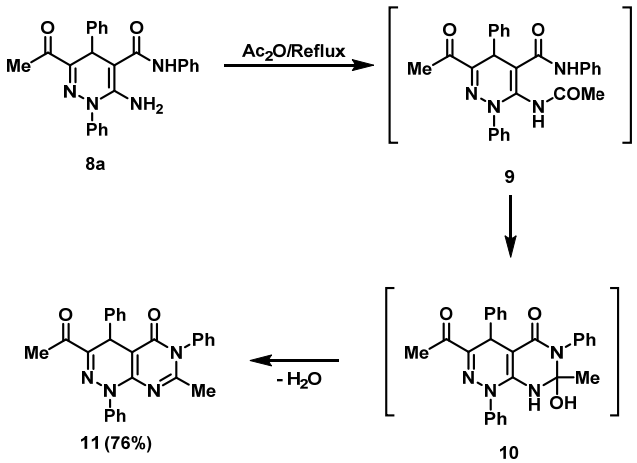
IR (KBr, ν, cm^{-1}): 3321 (NH) (br, CONH and NH_2), 1649 (CO) ($COCH_3$), 1625 (CO) (CONH). ^1H NMR (400 MHz, DMSO-d_6, δ, ppm): 2.36 (s, 3H, C*H*$_3$CO), 5.67 (s, 1H, pyridazine-*H*), 6.97-7.58 (m, 16H, Ar-*H* and N*H*$_2$), 9.03 (br s, 1H, N*H*). MS (EI, *m/z* (%)): 447 (1) [$(M+2)^+$], 446 (1), 445 [M^+] (4), 409 (8), 430 (12), 368 (23), 318 (34), 290 (100), 186 (14), 77 (53). HRMS (EI) calcd. for $C_{25}H_{21}ClN_4O_2$: 446.1324 [$(M+2)^+$], 444.1353 [M^+]; found: 446.1315 [$(M+2)^+$], 444.1346 [M^+]. Anal. calcd. for $C_{25}H_{21}ClN_4O_2$: C, 67.49; H, 4.76; N, 12.59. Found: C, 67.47; H, 4.73; N, 12.58%.

2.2.5. Synthesis of 6-acetyl-3-amino-2-(4-chlorophenyl)-5-phenyl-N-(p-tolyl)-2,5-dihydropyridazine-4-carboxamide (8e)

Following the procedure given for compound **8a**, azaenamine **1b** (196 mg, 1 mmol) and cyanoacrylamide derivative **2b** (262 mg, 1 mmol) were reacted in dioxane (10 mL) in presence of piperidine (0.2 mL, 2 mmol). Crystallization of the isolated product from ethanol:dioxane mixture (5:1, *v*:*v*, 10 mL) afforded the compound **8e** (Scheme 1). Yield: 403 mg, 880 mmol, 88%. Color: Beige solid. M.p.: 186-188 °C. IR (KBr, ν, cm^{-1}): 3410 (NH) (br, CONH and NH_2), 1678 (CO) ($COCH_3$), 1662 (CO) (CONH). ^1H NMR (400 MHz, DMSO-d_6, δ, ppm): 2.22 (s, 3H, C*H*$_3$), 2.36 (s, 3H, C*H*$_3$CO), 5.64 (s, 1H, pyridazine-*H*), 7.02-7.58 (m, 15H, Ar-*H* and N*H*$_2$), 8.96 (br s, 1H, N*H*). MS (EI, *m/z* (%)): 461 (2), 460 (1), 459 [M^+] (5), 444 (17), 424 (23), 416 (12), 401 (26), 380 (19), 318 (36), 290 (100), 166 (13), 92 (54), 77 (62). HRMS (EI) calcd. for $C_{26}H_{23}ClN_4O_2$: 460.1480 [$(M+2)^+$], 458.1510 [M^+]; found: 460.1522 [$(M+2)^+$], 458.1502 [M^+]. Anal. calcd. for $C_{26}H_{23}ClN_4O_2$: C, 68.04; H, 5.05; N, 12.21. Found: C, 68.06; H, 5.02; N, 12.17%.

2.2.6. Synthesis of methyl 2-(6-acetyl-3-amino-2,5-diphenyl-2,5-dihydropyridazine-4-carboxamido)benzoate (8f)

Following the procedure given for compound **8a**, azaenamine **1a** (162 mg, 1 mmol) and cyanoacrylamide derivative **2d** (306 mg, 1 mmol) were reacted in dioxane (10 mL) in presence of piperidine (0.2 mL, 2 mmol). Crystallization of the isolated product from ethanol:dioxane mixture (5:1, *v*:*v*, 10 mL) afforded the compound **8f** (Scheme 1).



Scheme 2

Yield: 399 mg, 853 mmol, 85%. Color: Bright yellow crystals. M.p.: 206-208 °C. IR (KBr, ν, cm^{-1}): 3410, 3307 (NH) (br, CONH and NH_2), 1685 (CO) ($COOCH_3$), 1644 (CO) (br, $COCH_3$ and CONH). ^1H NMR (400 MHz, DMSO-d_6, δ, ppm): 2.09 (s, 3H, CH_3CO), 3.91 (s, 3H, COOCH_3), 5.47 (s, 1H, pyridazine-*H*), 7.06-8.59 (m, 16H, Ar-*H* and NH_2), 10.91 (br s, 1H, N*H*). ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): 25.3 (CH_3), 34.2 (CH), 53.3 (CH_3), 77.9 (C), 115.4 (C), 120.7 (CH), 122.2 (CH), 126.2 (CH), 127.5 (CH), 128.0 (CH), 128.3 (CH), 129.2 (CH), 130.2 (CH), 131.2 (CH), 134.7 (CH), 140.5 (C), 142.1 (C), 142.2 (C), 146.5 (C), 151.8 (C), 167.8 (C), 168.5 (C), 196.7 (C). MS (EI, *m/z* (%)): 468 [M^+] (3), 453 (5), 425 (11), 440 (19), 409 (37), 394 (43), 360 (22), 318 (36), 290 (100), 248 (22), 146 (19), 77 (28). HRMS (EI) calcd. for $C_{27}H_{24}N_4O_4$: 468.1798; found: 468.1778. Anal. calcd. for $C_{27}H_{24}N_4O_4$: C, 69.22; H, 5.16; N, 11.96. Found: C, 69.18; H, 5.13; N, 11.98%.

2.2.7. Synthesis of 6-acetyl-3-amino-N-butyl-2,5-diphenyl-2,5-dihydropyridazine-4-carboxamide (8g)

Following the procedure given for compound **8a**, azaenamine **1a** (162 mg, 1 mmol) and cyanoacrylamide derivative **2e** (228 mg, 1 mmol) were reacted in dioxane (10 mL) in presence of piperidine (0.2 mL, 2 mmol). Crystallization of the isolated product from ethanol:dioxane mixture (5:1, *v*:*v*, 10 mL) afforded the compound **8g** (Scheme 1). Yield: 349 mg, 895 mmol, 89%. Color: Yellowish-white crystals. M.p.: 158-160 °C. IR (KBr, ν, cm^{-1}): 3411, 3173 (NH) (br, CONH and NH_2), 1678 (CO) ($COCH_3$), 1632 (CO) (CONH). ^1H NMR (400 MHz, DMSO-d_6, δ, ppm): 0.81 (t, 3H, CH_3CH$_2$), 1.13 (m, 2H, CH$_3$CH_2CH$_2$), 1.33 (m, 2H, CH$_3$CH$_2$CH_2CH$_2$), 2.34 (s, 3H, CH_3CO), 3.06 (m, 2H, CH$_2$CH_2NH), 5.28 (s, 1H, pyridazine-*H*), 7.03 (br s, 2H , NH_2), 7.05-7.53 (m, 11H, Ar-*H* and N*H*). ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): 14.6 (CH_3), 19.9 (CH_2), 25.3 (CH_3), 32.0 (CH_2), 33.5 (CH), 38.8 (CH_2), 78.6 (C), 126.0 (CH), 127.1 (CH), 127.7 (CH), 127.6 (CH), 128.8 (CH), 129.8 (CH), 140.9 (C), 143.2 (C), 145.8 (C), 149.4 (C), 168.8 (C), 196.6 (C). MS (EI, *m/z* (%)): 390 [M^+] (2); 347 (4), 313 (5), 290 (100), 248 (28), 231 (3), 77 (26). HRMS (EI) calcd. for $C_{23}H_{26}N_4O_2$: 390.2056; found: 390.2034. Anal. calcd. for $C_{23}H_{26}N_4O_2$: C, 70.75; H, 6.71; N, 14.35. Found: C, 70.77; H, 6.68; N, 14.34%.

2.2.8. Synthesis of 3-acetyl-7-methyl-1,4,6-triphenyl-4,6-dihydropyrimido[4,5-c]pyridazin-5(1H)-one (11)

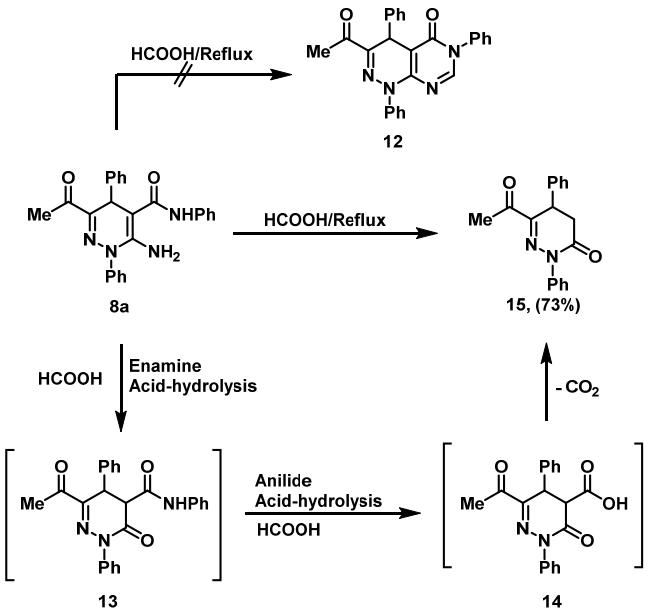
Compound **8a** (0.41 g, 1 mmol) was heated at reflux in acetic anhydride (10 mL, 106 mmol) for 5 h. The solvent was evaporated under reduced pressure and the residue was washed with 25% aq. ammonia solution (10 mL, 260 mmol) then filtered and washed with distilled water (20 mL). The crude dry product was crystallized from ethanol:dioxane (5:1, *v*:*v*, 10 mL) to give compound **11** (Scheme 2). Yield: 332 mg, 765 mmol, 76%. Color: Deep yellow solid. M.p.: 268-270 °C. IR (KBr, ν, cm^{-1}): 1664 (CO) ($COCH_3$), 1638 (CO) (CONH). ^1H NMR (400 MHz, DMSO-d_6, δ, ppm): 1.65 (s, 3H, CH_3), 2.42 (s, 3H, CH_3CO), 5.36 (s, 1H, pyridazine-*H*), 7.22-7.64 (m, 15H, Ar-*H*). ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): 24.5 (CH_3), 25.0 (CH_3), 34.0 (CH), 98.0 (C), 125.8 (CH), 127.3 (CH), 127.6 (CH), 127.9 (CH), 128.2 (CH), 128.7 (CH), 129.1 (CH), 129.3 (CH), 130.0 (CH), 137.7 (C), 141.7 (C), 141.9 (C), 144.2 (C), 150.2 (C), 158.7 (C), 161.4 (C), 196.2 (C). MS (EI, *m/z* (%)): 434 [M^+] (6), 420 (11), 391 (35), 357 (19), 318 (27), 290 (100), 168 (13), 91 (63), 77 (72). HRMS (EI) calcd. for $C_{27}H_{22}N_4O_2$: 434.1743; found: 434.1719. Anal. calcd. for $C_{27}H_{22}N_4O_2$: C, 74.64; H, 5.10; N, 12.89. Found: C, 74.61; H, 5.07; N, 12.90%.

2.2.9. Synthesis of 6-acetyl-2,5-diphenyl-4,5-dihydro pyridazin-3(2H)-one (15)

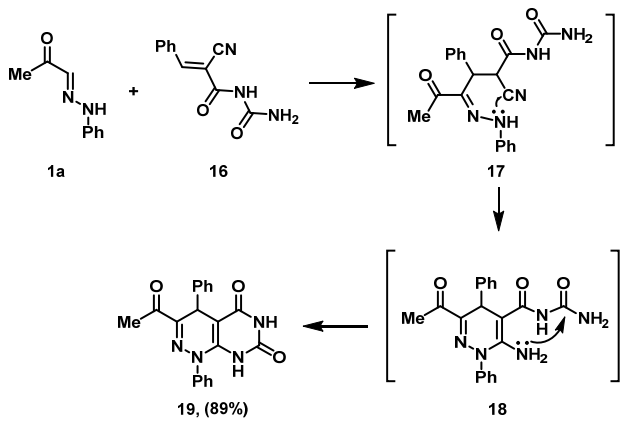
Compound **8a** (0.41 g, 1 mmol) was heated at reflux in formic acid (10 mL, 265 mmol) for 3 h. The excess solvent was removed at reduced pressure and the crude substance was treated with 25% aq. ammonia solution (10 mL, 260 mmol) then filtered and washed with water (20 mL). The dry solid was crystallized from ethanol (10 mL) to give compound **15** (Scheme 3). Yield: 212 mg, 726 mmol, 63%. Color: Colorless crystals. M.p.: 122-124 °C. IR (KBr, ν, cm^{-1}): 1705 (CO) ($COCH_3$), 1687 (CO) (CONPh). ^1H NMR (400 MHz, $CDCl_3$, δ, ppm): 2.50 (s, 3H, CH_3CO), 3.05 (m, 2H, CHCH_2), 4.71 (m, 1H, CHCH$_2$), 7.22-7.57 (m, 10H, Ar-*H*). ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 24.8 (*C*H$_3$CO), 35.0 (CH*C*H$_2$), 35.4 (*C*HCH$_2$), 124.8 (CH), 126.9 (CH), 127.4 (CH), 127.9 (CH), 128.8 (CH), 129.3 (CH), 137.5 (C), 140.4 (C), 150.4 (C), 164.8 (*C*ONPh), 196.0 (*C*OCH$_3$). MS (EI, *m/z* (%)): 292 [M^+] (15), 277 (10), 249 (35), 215 (22), 172 (14), 77 (100). HRMS (EI) calcd. for $C_{18}H_{16}N_2O_2$: 292.1212; found: 292.1123. Anal. calcd. for $C_{18}H_{16}N_2O_2$: C, 73.95; H, 5.52; N, 9.58. Found: C, 73.88; H, 5.48; N, 9.63%.

2.2.10. Synthesis of 3-Acetyl-1,4-diphenyl-6,8-dihydro pyrimido[4,5-c]pyridazine-5,7(1H,4H)-dione (19)

Following the procedure given for compound **8a**, azaenamine **1a** (162 mg, 1 mmol) and *N*-carbamoyl-2-cyano-3-phenylacrylamide **16** (0.22 g, 1.0 mmol) were reacted in dioxane (10 mL) in presence of piperidine (0.2 mL, 2 mmol).



Scheme 3



Mechanistic pathway for the reaction of azaenamine **1a** with (*E*)-*N*-carbamoyl-2-cyano-3-phenylacrylamide **2**.

Scheme 4

Crystallization of the isolated product from ethanol:dioxane mixture (5:1, *v*:*v*, 10 mL) afforded the compound **19** (Scheme 4). Yield: 319 mg, 886 mmol, 89%. Color: Canary-yellow crystals. M.p.: 290-292 °C. IR (KBr, ν, cm^{-1}): 1681 (CO) ($COCH_3$), 1619 (CO) (br, CONH and NHCONH). ^1H NMR (400 MHz, DMSO-d_6, δ, ppm): 2.36 (s, 3H, CH_3CO), 5.18 (s, 1H, pyridazine-*H*), 7.11-7.53 (m, 12H, Ar-*H* and 2N*H*). ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): 25.1 (CH_3), 33.3 (CH), 85.5 (C), 125.8 (CH), 126.0 (CH), 126.6 (CH), 127.7 (CH), 128.5 (CH), 128.7 (CH), 143.3 (C), 144.3 (C), 144.5 (C), 155.4 (C), 157.9 (C), 165.4 (C), 196.6 (C). MS (EI, *m/z* (%)): 360 [M^+] (13), 345 (24), 317 (47), 290 (100), 184 (16), 77 (72). HRMS (EI) calcd. for $C_{20}H_{16}N_4O_3$: 360.1222; found: 360.1188. Anal. calcd. for $C_{20}H_{16}N_4O_3$: C, 66.66; H, 4.48; N, 15.55. Found: C, 66.67; H, 4.50; N, 15.53%.

3. Results and discussion

As a part of sequential work aimed at manifesting the proper pattern of the azaenamine reactivity as nucleophilic carbon species towards activated cinnamonitriles [17-21], we report here the aza-Michael addition of azaenamines **1a**,**b** with *α*-cyano-*N*-arylacrylamide derivatives **2a**-**e**. The reaction may proceed through one of three reasonable pathways *A*, *B* or *C* (Scheme 1). Pathway *A*, involving the Michael addition of the nucleophilic acyl methyl carbon to activated acrylonitrile followed by ring closure caused by the attack of azomethine carbon to give **4** (**I**) and their tautomeric forms **4** (**II**) was readily excluded as the ^1H NMR spectrum revealed a characteristic peak at δ 2.39 ppm corresponding to the acetyl protons (Scheme 1). Thus, the reaction can take place according to either pathway *B*, that comprises the first addition of hydrazone lone pair to the activated double bond followed by azomethine carbon attack forming 5-amino-2,3-dihydropyridazines **6**, or pathway *C*, that employs a lone pair resonance causing the azomethine carbon to be nucleophilic and consequently, attack the activated acylonitriles to yield 3-amino-2,5-dihydropyridazines **8**.

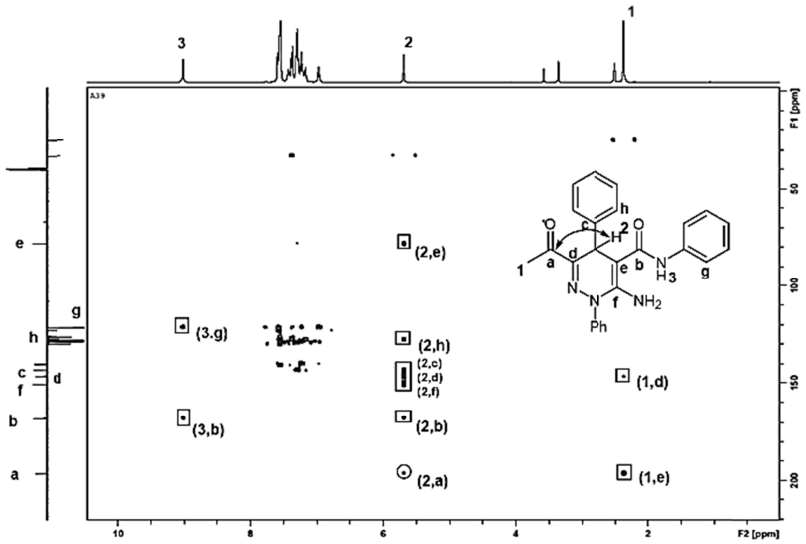


Figure 2. The HMBC spectrum of compound **8a**; the number refers to protons, the letters denotes the carbon atoms and the correlation is represented by parentheses. The correlation cross peaks between the methyl protons, pyridazine-*H*5 and amide proton with the different carbon atoms are enclosed in a square. The characteristic cross peak is enclosed in a circle for clarity.

Using the simple spectroscopic tools we cannot make an unambiguous decision concerning the exact chemical structure of the products, yet the inspection of the HMBC spectrum of compound **8a** supported the pathway *C* as it indicated a ^{3}J-cross coupling between pyridazine-*H*5 at δ 5.72 ppm and each of the acetyl carbonyl carbon atoms at δ 196.9 ppm and the carboxamide carbon atom at δ 167.9 ppm (Figure 2). Under the usual reaction conditions compounds **8** were obtained in high yield (Table 1). Further support of the constitution of the prepared compounds was established on the basis of the other spectroscopic tools. The mass spectrum of **8a** showed a molecular ion peak at *m/z* = 410 [M^{+}]. The IR spectrum of compound **8a** displayed broad NH_2 bands at ν = 3360 and 3181 cm^{-1}. The two bands at ν = 1673 and 1643 cm^{-1} were assigned to the ketone and amide carbonyl carbon atoms, respectively. The ^{1}H NMR spectrum exhibited a singlet signal at δ 2.39 ppm for the acyl methyl group, a singlet at δ 5.72 ppm for pyridazine-*H*5. The multiplet at δ 6.96-7.59 ppm integrated for 17 protons and was assigned to aromatic and amino group protons. In addition, the spectrum showed a broad signal at δ 9.05 ppm for the amide proton. The ^{13}C NMR spectrum showed a methyl signal at δ 25.6 ppm, a pyridazine-*C*5 signal at δ 33.4 ppm, a signal for the carbonitrile carbon atom at δ 121.4 ppm and two characteristic signals at δ 167.9 and 196.9 ppm for the carboxamide and ketonic carbonyl carbon atoms, respectively.

Table 1. The yield percentages of compounds **8a**-**g**.

Compound	R^{1}	R^{2}	Yield (%)
8a	Ph	Ph	92
8b	Ph	MeC_6H_4 (*p*)	90
8c	Ph	$O_2NC_6H_4$ (*p*)	88
8d	ClC_6H_4 (*p*)	Ph	92
8e	ClC_6H_4 (*p*)	MeC_6H_4 (*p*)	87
8f	Ph	$MeOCOC_6H_4$ (*o*)	90
8g	Ph	*n*-Butyl	89

The chemistry of pyrimido[4,5-*c*]pyridazines was not extensively investigated in literature [26-28]. Pyrimido[4,5-*c*]pyridazines could be regarded as analogues of 4-deaza-toxoflavin [29-34]. These compounds are extensively utilized in the field of the auto-recycling oxidation of amines and alcohols [35-37]. Moreover, toxoflavin has antibiotic properties and impedes the xanthene oxygenase [38]. In an extension of the program to prepare 4-deazatoxoflavin analogues through boiling compound **8a** in acetic anhydride, the pyrimido[4,5-*c*]pyridazine derivative **11** was obtained in good yield (Scheme 2). Compound **11** was characterized spectroscopically revealing the disappearance of NH and NH_2 signals and bands. Thus the ^{1}H NMR spectrum showed a singlet at δ 1.65 ppm for methyl, a singlet at δ 2.42 ppm for the acyl methyl and a singlet at δ 5.36 ppm for pyridazine-*H*5. The ^{13}C NMR spectrum showed two methyl signals at δ 24.4 and 25.0 ppm. It also featured signal at δ 34.0 ppm for pyridazine-*C*5. The signals at δ 161.3 and 196.1 ppm were assigned to carboxamide and acetyl carbonyl.

Attempts to extend this methodology to synthesize the other targeted analogue **12** using formic acid have unexpectedly failed. Instead, tetrahydropyridazine **15** was obtained in 73 % yield. The formation of **15** presumably takes place via hydrolysis of the enamine group giving the intermediate **13**, which undergoes a hydrolytic anilide cleavage to form *β*-oxoacid derivative **14**, which then loses CO_2 to form the pyridazinone derivative **15** (Scheme 3). The identity of **15** has been confirmed by spectral data which indicated the presence of two sp^{3} carbon atoms in addition to the acetyl methyl group. Thus ^{1}H NMR spectrum exhibited a singlet at δ 2.5 ppm for the acyl methyl protons, a multiplet at δ 3.05 ppm for pyridazine-CH_2 and multiplet at δ 4.71 ppm for pyridazine-*H*5. The ^{13}C NMR spectrum showed the acetyl methyl signal at *δ* = 24.8 ppm, pyridazine-CH_2 signal at δ 35.0 ppm, pyridazine-*C*H signal at δ 35.4 ppm, amide and acetyl carbonyls appeared at δ 164.8 and 196.0 ppm, respectively.

In an attempt to affect a one pot synthesis of pyrimido[4,5-*c*]pyridazine derivatives, we treated pyruvaldehyde-1-phenylhydrazone **1a** with *N*-carbamoyl-2-cyano-3-phenyl-acrylamide **16** in dioxane at reflux in the presence of piperidine (Scheme 4). Similar to the aforementioned discussion, this reaction adopts *Pathway C* (Scheme 1) and the consti-tution of the product **19** can be assessed by HMBC showing ^{3}J-cross coupling between pyrimido[4,5-*c*]pyridazine-*H*4 at δ 5.18 ppm with acetyl carbonyl at δ 196.6 ppm and amide carbonyl at δ 165.4 ppm (Figure 3). Compound **19** was presumably formed as a result of Michael addition of **1a** to **16** giving **17**, which then cyclized to **18** followed by ammonia elimination.

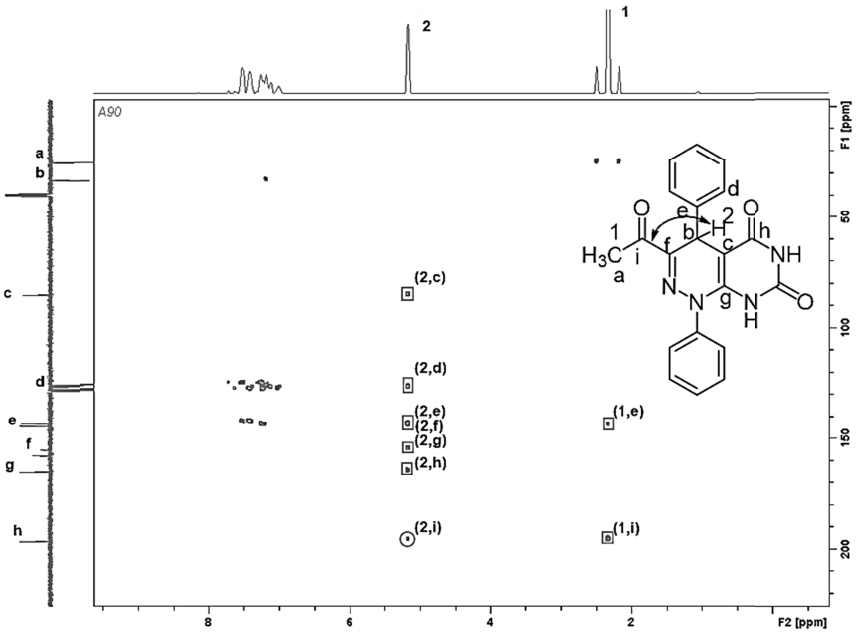


Figure 3. The HMBC spectrum of compound **19**; the number refers to protons, the letters denotes the carbon atoms and the correlation is represented by parentheses. The correlation cross peaks between the methyl protons, pyridazine-*H*5 and amide proton with the different carbon atoms are enclosed in a square. The characteristic cross peak is enclosed in a circle for clarity.

Compound **19** was also fully characterized through the different spectral tools: the mass spectrum showed a molecular ion peak at *m/z* = 360 [M+]. The IR spectrum indicated the presence of broad band at ν = 3424 cm^{-1} for N-H stretch of the two NH functional groups, acetyl absorption band at ν = 1681 cm^{-1} and a broad band at ν = 1619 cm^{-1} for the two amide groups. The ^{1}H NMR spectrum demonstrated a signal at δ 2.36 ppm for the acetyl protons, a singlet at δ 5.18 ppm for pyridazine-*H*4 and a multiplet at δ 7.11-7.53 ppm for the aromatic and two N*H* protons. The ^{13}C NMR fits with the deduced structure involved acyl methyl signal at δ 25.08 ppm, a pyridazine-*C*H signal at δ 33.34 ppm, two amide signals at δ 157.91 and 165.36 ppm and the acetyl carbonyl signal at δ 196.57 ppm.

4. Conclusion

Azaenamines were proven to be suitable *C*-nucleophilic candidates in Michael addition to various *α*-cyano-*N*-arylacrylamide derivatives **2a-c** in a regioselective manner yielding different *N*-Substituted 2,5-dihydropyridazine-4-carboxamide derivatives. The newly synthesized pyridazine compounds could be transformed by a simple acetylation procedure into pyrimido[4,5-*c*]pyridazine (deazatoxoflavin analogue) **15**. The formation of pyrimido[4,5-*c*]pyridazine compound in a single step was successfully achieved by the reaction of azaenamine with *N*-carbamoyl-2-cyano-3-phenylacrylamide under the same conditions.

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