

N-(Pyrazol-5-yl)cycanoacetamide in heterocyclic synthesis: synthesis of novel *N*-(pyrazol-5-yl)pyridine-3,5-dicarbonitrile, pyrazolo[1,5-*a*]- pyrido[3,2-*e*]pyrimidine-7-carbonitrile and pyrazolo[4,3-*e*]pyrido[1,2-*a*]- pyrimidine-6,8-dicarbonitrile moieties

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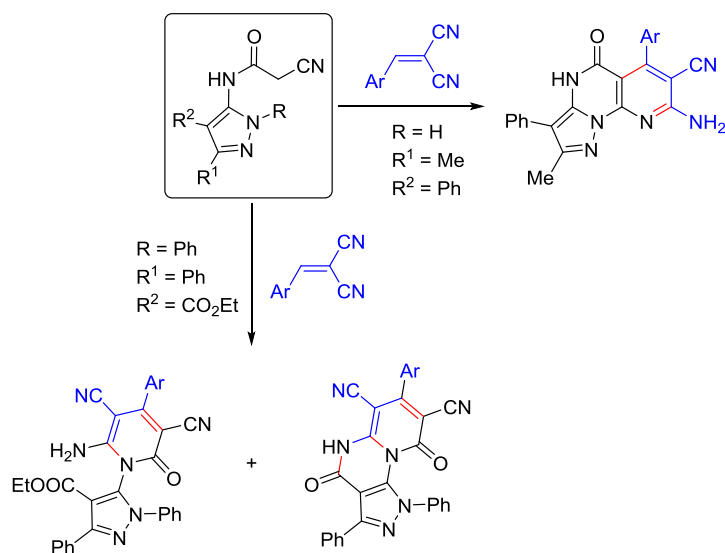
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Abstract

A novel series of interesting *N*-(pyrazol-5-yl)pyridine-3,5-dicarbonitrile, pyrazolo[1,5-*a*]pyrido[3,2-*e*]pyrimidine-7-carbonitrile and pyrazolo[4,3-*e*]pyrido[1,2-*a*]pyrimidine-6,8-dicarbonitrile derivatives were prepared *via* the versatile readily accessible 7-aminopyrazolo[1,5-*a*]pyrimidin-5(4*H*)-one or 2-cyano-*N*-(pyrazol-5-yl)acetamide derivatives with arylaldehydes and malononitrile in ethanol containing piperidine.



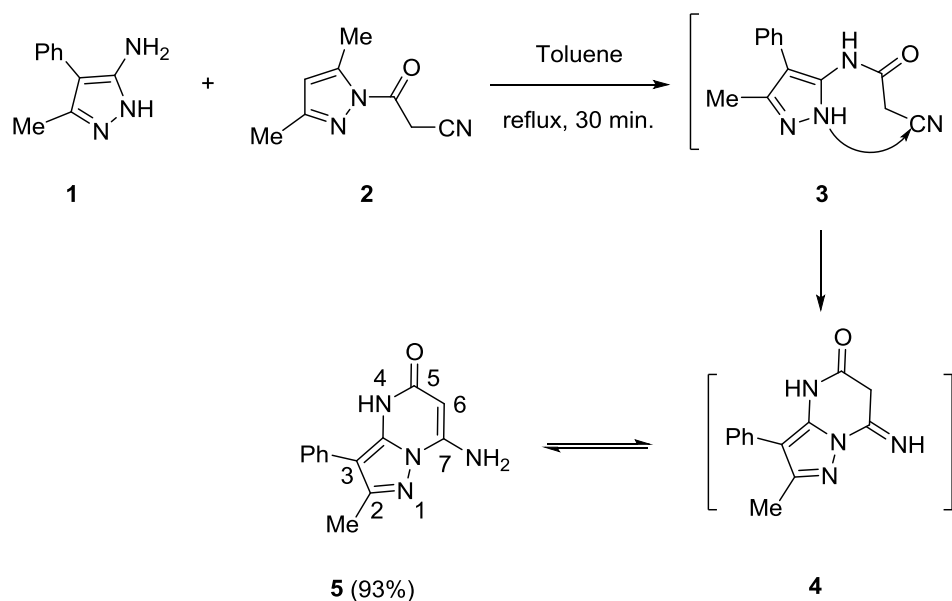
Keywords: 7-Aminopyrazolo[1,5-*a*]pyrimidin-5(4*H*)-one, *N*-(pyrazol-5-yl)cycanoacetamide, arylidene-malononitriles, Michael addition, *N*-(pyrazol-5-yl)pyridine-3,5-dicarbonitriles, pyrazolo[1,5-*a*]pyrido[3,2-*e*]pyrimidine-7-carbonitrile, pyrazolo[4,3-*e*]pyrido[1,2-*a*]pyrimidine-6,8-dicarbonitrile

Introduction

Cyanoacetamide derivatives are important precursors in the synthesis of a variety of pharmacologically active compounds and agrochemicals.¹ They were also found to exhibit significant bioactivities as antibacterial and antifungal agents.² In addition, they are versatile intermediates for the synthesis of wide variety of various nitrogen-containing heterocycles.³⁻⁶ Moreover, pyridine derivatives have attracted a continuing interest over the past years as they exhibit diverse biological activities that include antihistaminic,⁷ antihypertensive,⁸ antiviral,^{9,10} antitumor,^{11,12} and anti-inflammatory agents.¹³ Encouraged by the above findings and as a part of an ongoing research program on Michael addition reaction to acrylonitrile derivatives¹⁴⁻²⁶ we report herein the results of our investigations concerning the different reactivity patterns of 7-aminopyrazolo[1,5-*a*]pyrimidin-5-one and cyanoacetamides towards cinnamionitrile derivatives.

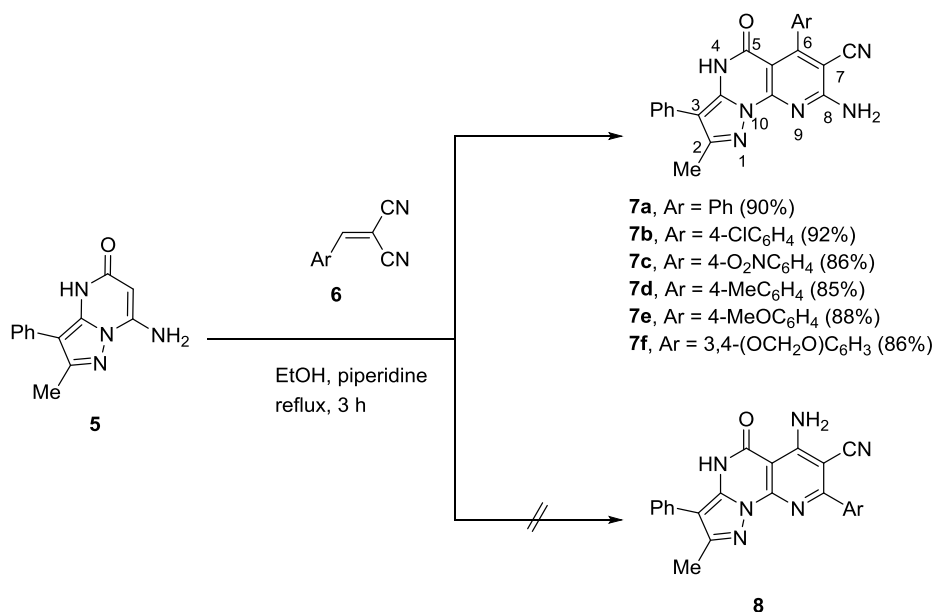
Results and Discussion

The reaction of 3-methyl-4-phenyl-1*H*-pyrazol-5-amine **1** with 3-(3,5-dimethyl-1*H*-pyrazol-1-yl)-3-oxopropanenitrile **2** in toluene at reflux afforded 7-amino-2-methyl-3-phenylpyrazolo[1,5-*a*]pyrimidin-5(4*H*)-one **5** via the non-isolable cyanoacetamide intermediate **3** (Scheme 1). The most probable approach includes the initial attack of exocyclic amino group nitrogen of **1** to compound **2** in toluene at reflux followed by ring closure of the presumable cyanoacetamide intermediate **3** to *N*-1 with formation of 7-aminopyrazolo[1,5-*a*]pyrimidin-5(4*H*)-one **5** via intermediacy of the imine **4**. The structure of compound **5** is verified by the different spectral tools. Thus, IR spectrum indicated the absence of CN group. It also featured the presence of amino and NH signals at ν 3412, 3102 cm^{-1} . ¹H NMR spectrum indicated singlet signal integrated by one proton at δ 4.98 ppm for H6. It also indicated the amino group and aromatic protons as multiplets in the region δ 7.18-7.43 ppm. The NH group appeared as broad singlet at δ 11.02 ppm. It is worth-mentioning that there is literature precedence for similar reaction in a publication by El-Feky *et al.*²⁷ (compounds **15a-f** therein) and Warnhoff *et al.*²⁸ (compound **7d** therein).



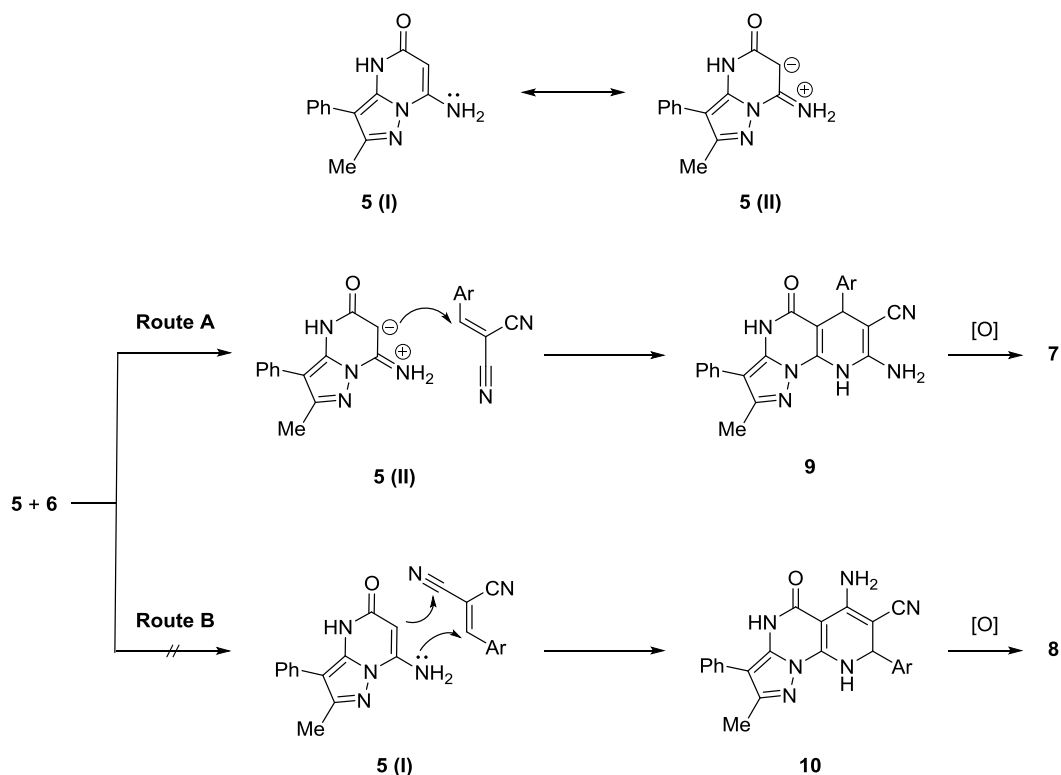
Scheme 1 Synthesis of 7-aminopyrazolo[1,5-*a*]pyrimidin-5(4*H*)-one **5**.

The reactivity of compound **5** was then investigated in Michael addition reaction towards activated cinnamitrile derivatives **6a-f**. It can be noticed from the structure of compound **5** that there are two nucleophilic centers at which the addition to activated double bond reagent **6** can initiate. These centers are amino group and the enamine β -carbon (H6). Thus, two isomeric products would be probably produced by the reaction of compound **5** with different cinnamitrile derivatives **6** *via* routes A and B (Scheme 2). Route A encompasses the nucleophilic addition of β -carbon of the enamine **5** to the activated double bond of **6** followed by cyclization involving the amino group of **5** to give 8-amino-6-aryl-pyrazolo[1,5-*a*]pyrido[3,2-*e*]pyrimidine-7-carbonitrile **7**. Route B involves the initial addition of the amino group of the enamine **5** to the β -carbon of the activated double bond of **6** followed by cyclization affected by β -carbon of the enamine **5** to form 6-amino-8-aryl-pyrazolo[1,5-*a*]pyrido[3,2-*e*]pyrimidine-7-carbonitrile **8**. Route A was approved based on literature similarities^{29,30} (cf. scheme 3).

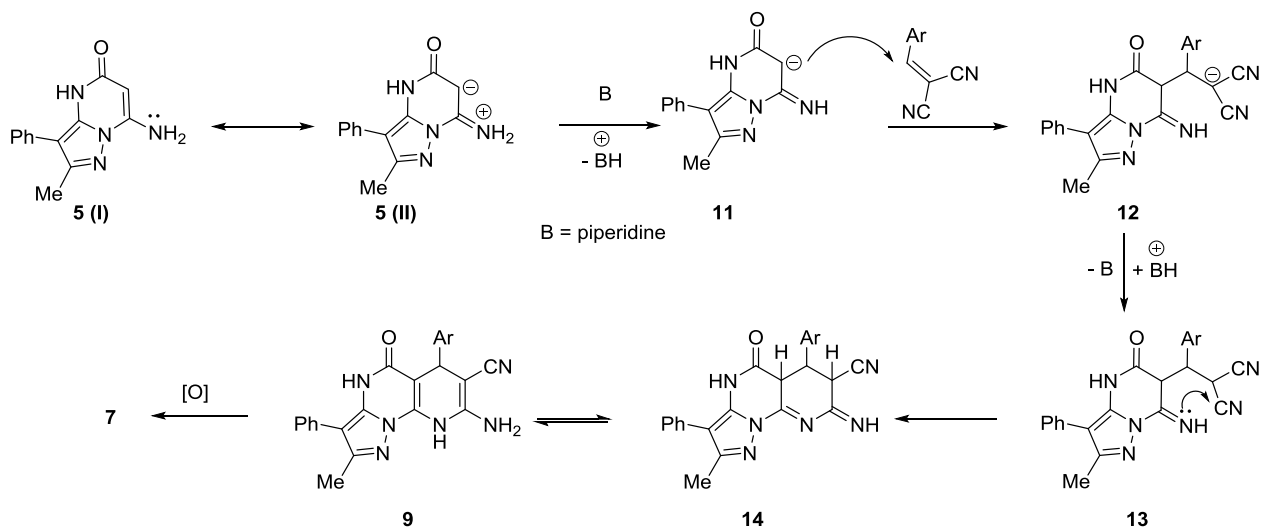


Scheme 2 The reaction of 7-aminopyrazolo[1,5-*a*]pyrimidin-5(4*H*)-one **5** with arylidene malononitriles **6a-f**.

It is noteworthy to mention that the delocalization of nitrogen lone pair in the cyclic enamine **5** acquires the β -carbon negative charge **5II**. Piperidine acts as a basic catalyst and serves as a carrier for the labile protons affording the carbanion **11**, which affects Michael type addition reaction to the activated double bond in compound **6** giving the Michael adduct **12**. Compound **12** abstracts the proton again from the basic catalyst giving intermediate **13**. Nucleophilic addition of NH to cyano group leads to the formation of the cyclic intermediate **14**. Isomerization followed by oxidation gives the final isolable products **7** (Scheme 4).



Scheme 3 Proposed routes for the reaction of **5** with arylidenemalononitriles **6a-f**

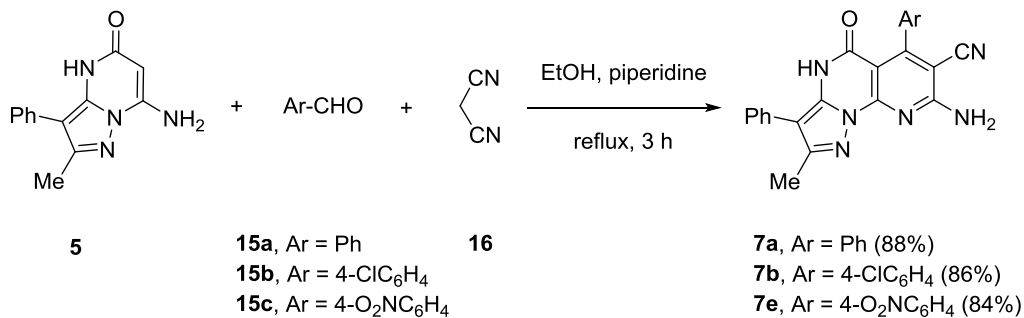


Scheme 4 Proposed mechanism for synthesis of compounds **7a-f**.

Thus, the reaction of compound **5** with cinnamonitriles **6a-f** follows route **A** that gives compounds **7a-f**. The structures of compounds **7** were characterized spectroscopically. For example, the mass spectrum of compound **7e** involves a molecular ion peak at m/z 422. IR spectrum of compound **7e** shows the presence of amino and NH stretches at ν 3461, 3303 and 3204 cm^{-1} as well as characteristic bands at ν 2224 cm^{-1} and ν 1678 cm^{-1} relative to cyano and carbonyl groups, respectively. The ^1H NMR spectrum reveals pyrazole methyl singlet at δ 2.27 ppm, methoxy protons at δ 3.83 ppm, broad peak at δ 7.80 ppm assigned to amino protons and a broad singlet at δ 11.30 ppm assigned to pyrazole NH. The aromatic protons appeared at their expected

positions. The ^{13}C NMR spectrum displays characteristic peaks at δ 14.6 ppm for pyrazole methyl, δ 55.5 ppm for methoxy carbon and amide carbonyl at δ 161.4 ppm besides the other different carbon signals.

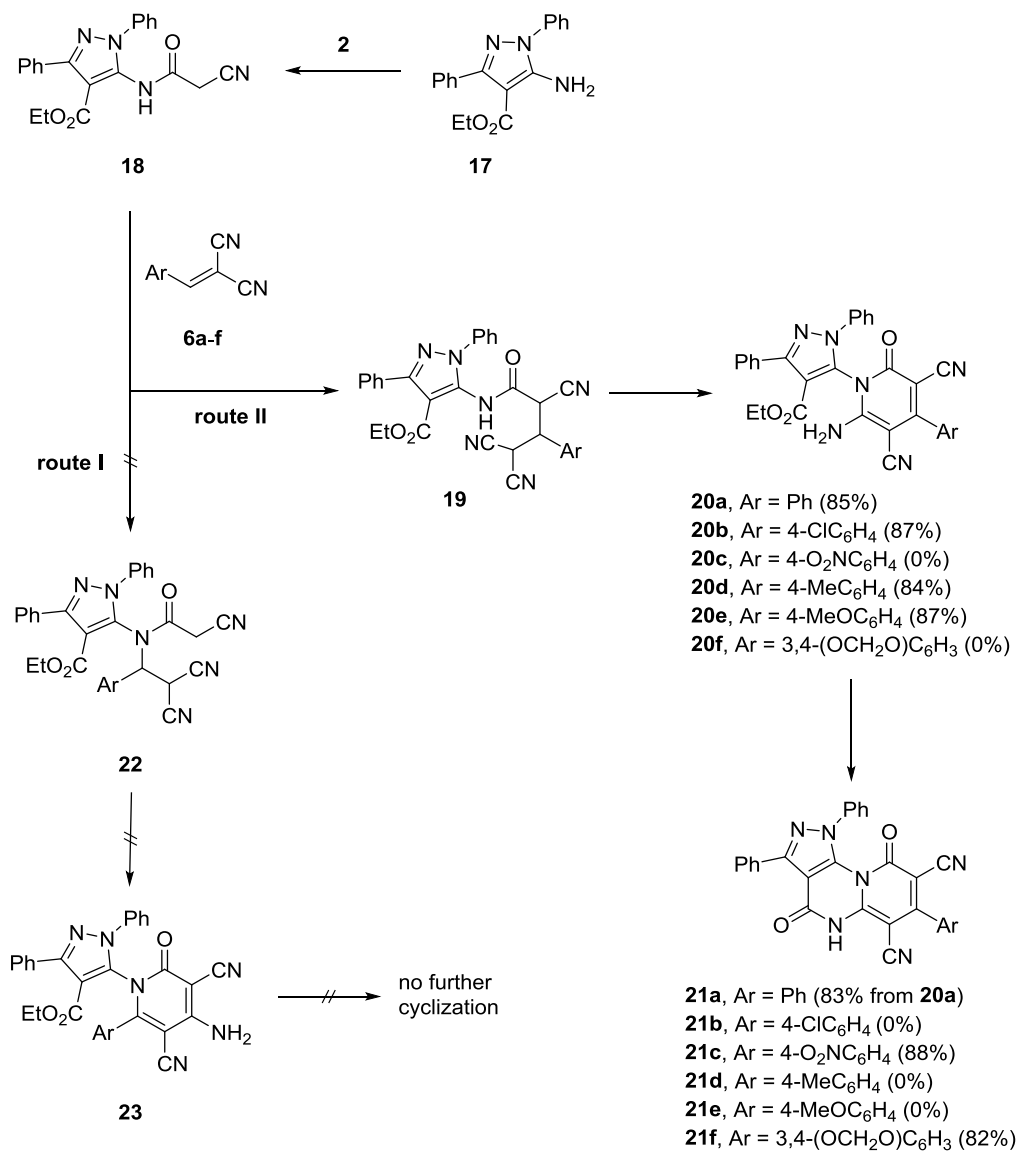
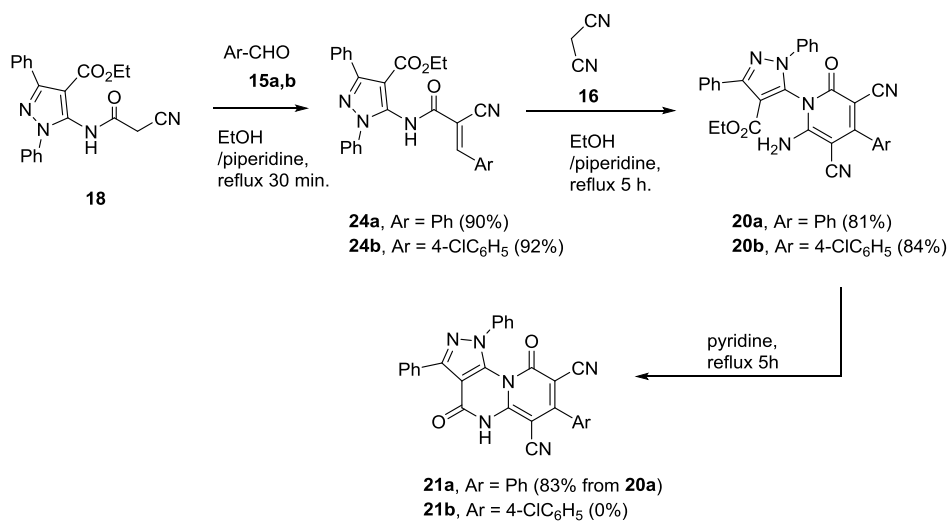
Furthermore, compounds **7a-c** could be successfully synthesized *via* one-pot reaction of compound **5**, aromatic aldehydes (**15a-c**) and malononitrile (**16**) (Scheme 5).



Scheme 5 One-pot synthesis of compounds **7**.

In an extension to this work, ethyl 5-(2-cyanoacetamido)-1,3-diphenyl-1*H*-pyrazole-4-carboxylate containing an ester group on pyrazole ring **18** was prepared according to a previously reported procedure^{22,31} *via* the reaction of aminopyrazole **17** with **2**. Then, we investigated the Michael addition of **18** to activated cinnamionitriles **6a-f**. Also, there are two possible routes (I and II), where only further cyclization including NH₂ and ester group occurs in case of route II, while in route I no further cyclization would occur. Thus, the reaction of **18** with **6** results in the formation of compounds **20** *via* the Michael addition intermediate **19**. Subsequent cyclization of **20** *via* ethanol elimination gave the tricyclic tetrahydropyrazolo[4,3-*e*]pyrido[1,2-*a*]pyrimidine-6,8-dicarbonitriles **21** (Scheme 5). It is noteworthy to mention that compound **20a** obtained in ethanol at reflux in the presence of piperidine as a basic catalyst was subsequently cyclized in pyridine to give **21a**. On the other hand, derivatives **20b** and **20e** did not cyclize in pyridine to **21b** and **21e**. We have also found that compounds **21c** and **21f** are obtained directly in the cyclized form without separation of **20c** and **20f** when heated either in ethanol / piperidine or pyridine at reflux (Scheme 6).

Moreover, the reaction of **18** with aldehydes **15a,b** gave 2-cyano-*N*-(1*H*-pyrazol-5-yl)acrylamide derivatives **24a,b** (Scheme 7). Subsequent reaction of **24a,b** with malononitrile (**16**) yielded **20a,b**. Compound **20a** was readily cyclized into **21a** by heating in pyridine at reflux for 5 h. However, cyclization of **20b** to **21b** did not succeed (Scheme 7). Structure of compounds **20** and **21** was readily established based the ^1H NMR spectra. The ^1H NMR of **20a** indicated the presence of triplet and quartet peaks characteristic for the ethoxy group as well as a broad singlet at δ 8.39 ppm for NH₂ group. On the other hand, compound **21a** revealed the absence of OEt group. Moreover, it featured the absence of NH₂ group and the presence of NH signal at δ 4.40 ppm.

Scheme 6 Reaction of *N*-(pyrazol-5-yl)cynoacetamide **18** with arylidene malononitriles **6a-f**.Scheme 7 Reaction of arylidene derivatives **24a,b** with malononitrile (**16**).

Conclusions

7-Aminopyrazolo[1,5-*a*]pyrimidin-5-one and cyanoacetamides bearing pyrazole moiety behave like C-nucleophiles affecting facile, regioselective Michael addition reactions with various cinnamionitrile derivatives yielding different *N*-(pyrazol-5-yl)pyridine-3,5-dicarbonitrile, pyrazolo[1,5-*a*]pyrido[3,2-*e*]pyrimidine-7-carbonitriles as well as pyrazolo[4,3-*e*]pyrido[1,2-*a*]pyrimidine-6,8-dicarbonitrile derivatives.

Experimental Section

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

7-Amino-2-methyl-3-phenylpyrazolo[1,5-*a*]pyrimidin-5(4*H*)-one (5). Applying a similar procedure to that previously reported^{22,31}. A mixture of 3-methyl-4-phenyl-1*H*-pyrazol-5-amine **1** (1730 mg, 10 mmol) and 3-(3,5-dimethyl-1*H*-pyrazol-1-yl)-3-oxopropanenitrile **2** (1960 mg, 12 mmol) in dry toluene (30 mL) was heated at reflux for 3 h. The crude isolated product was purified by crystallization from ethanol. Yellow crystals (2230 mg, 93%), mp 248–250 °C, IR (KBr): ν 3412, 3102 (NH and NH₂), 1681 (CO) cm⁻¹, ^1H NMR (400 MHz, DMSO- d_6): δ 2.30 (s, 3H, CH₃), 4.98 (s, 2H, CH), 7.18 (br s, 2H, NH₂), 7.22–7.43 (m, 5H, ArH), 11.02 (br s, 1H, NH) ppm, ^{13}C NMR (100 MHz, DMSO- d_6): δ 13.2 (CH₃), 76.0 (=CH), 101.9, 120.5, 125.9 (Ar-CH), 128.3 (Ar-CH), 128.8 (Ar-CH), 131.1, 139.0, 149.5, 161.8 (CO) ppm, MS (EI, 70 eV): m/z 240 [M]⁺, Anal. Calcd for C₁₃H₁₂N₄O: C, 64.99; H, 5.03; N, 23.32. Found: C, 64.63; H, 4.79; N, 23.09.

General procedures for synthesis of compounds (7a-f)

Method A. A mixture of compound **5** (240 mg, 1 mmol) and arylidene malononitrile **6** (1 mmol) was heated at reflux in EtOH (20 mL) containing piperidine (0.2 mL, 2 mmol) for 5 h. The solvent was evaporated at reduced pressure and then treated with aq. HCl (10 mL). The resulting solid was filtered, dried and crystallized from EtOH/dioxane (5 mL, 3:1, v/v).

Method B. A mixture of compound **5** (240 mg, 1 mmol), aromatic aldehyde **15** (1 mmol) and malononitrile **16** (66 mg, 1 mmol) was heated at reflux in EtOH (20 mL) containing piperidine (0.2 mL, 2 mmol) for 5 h. The solvent was evaporated at reduced pressure and then treated with aq. HCl (10 mL). The resulting solid was filtered, dried and crystallized from EtOH/dioxane (5 mL, 3:1, v/v).

8-Amino-2-methyl-5-oxo-3,6-diphenyl-4,5-dihydropyrazolo[1,5-*a*]pyrido[3,2-*e*]pyrimidine-7-carbonitrile (7a). Yellow crystals (353 mg, 90%), mp > 300 °C, IR (KBr): ν 3441, 3280, 3143 (NH₂ and NH), 2209 (CN), 1682 (CO) cm⁻¹, ^1H NMR (400 MHz, DMSO- d_6): δ 2.30 (s, 3H, CH₃), 7.23–7.46 (m, 10H, Ar-H), 7.83 (br s, 2H, NH₂), 11.30 (br s, 1H, NH) ppm, ^{13}C NMR (100 MHz, DMSO- d_6): δ 13.8 (CH₃), 90.5, 112.6, 115.8, 116.0 (2CN), 125.7 (Ar-CH), 127.4 (Ar-CH), 127.7 (Ar-CH), 127.9 (Ar-CH), 128.1 (Ar-CH), 128.6 (Ar-CH), 132.0, 134.2, 138.1, 144.5, 149.5, 151.3 (CO), 160.5 ppm, MS (EI, 70 eV): m/z 392 [M]⁺, Anal. Calcd for C₂₃H₁₆N₆O: C, 70.40; H, 4.11; N, 21.42. Found: C, 70.19; H, 3.96; N, 21.20.

8-Amino-6-(4-chlorophenyl)-2-methyl-5-oxo-3-phenyl-4,5-dihydropyrazolo[1,5-*a*]pyrido[3,2-*e*]pyrimidine-7-carbonitrile (7b). Yellow crystals (392 mg, 92%), mp > 300 °C, IR (KBr): ν 3394, 3335, 3238 (NH₂ and NH), 2211

(CN), 1637 (CO) cm^{-1} , ^1H NMR (400 MHz, DMSO- d_6): δ 2.32 (s, 3H, CH_3), 7.18-7.53 (m, 9H, Ar-H), 7.75 (br s, 2H, NH_2), 11.30 (br s, 1H, NH) ppm, ^{13}C NMR (100 MHz, DMSO- d_6): δ 14.6 (CH_3), 90.1, 101.5, 102.6, 116.2 (2CN), 125.8 (Ar-CH), 128.0 (Ar-CH), 128.6 (Ar-CH), 128.9 (Ar-CH), 129.9 (Ar-CH), 132.7, 132.9 (2Ar-C), 137.6, 150.0, 151.9, 158.7 (CO), 160.9 ppm, MS (EI, 70 eV): m/z 426 $[\text{M}]^+$, Anal. Calcd for $\text{C}_{23}\text{H}_{15}\text{ClN}_6\text{O}$: C, 64.72; H, 3.54; N, 19.69. Found: C, 64.36; H, 3.31; N, 19.42.

8-Amino-2-methyl-6-(4-nitrophenyl)-5-oxo-3-phenyl-4,5-dihydropyrazolo[1,5- α]pyrido[3,2- e]pyrimidine-7-carbonitrile (7c). Orange crystals (376 mg, 86%), mp > 300 °C, IR (KBr): ν 3460, 3278, 3110 (NH_2 and NH), 2206 (CN), 1684 (CO) cm^{-1} , ^1H NMR (400 MHz, DMSO- d_6): δ 2.33 (s, 3H, CH_3), 7.18-8.28 (m, 11H, Ar-H and NH_2), 11.30 (br s, 1H, NH) ppm, ^{13}C NMR (100 MHz, DMSO- d_6): δ 14.8 (CH_3), 89.2, 101.6, 102.9, 116.0 (2CN), 123.1 (Ar-CH), 125.5 (Ar-CH), 128.5 (Ar-CH), 128.7 (Ar-CH), 129.5 (Ar-CH), 133.4, 146.6, 147.3, 149.9, 151.9, 157.4, 160.7, 162.0 ppm, MS (EI, 70 eV): m/z 437 $[\text{M}]^+$, Anal. Calcd for $\text{C}_{23}\text{H}_{15}\text{N}_7\text{O}_3$: C, 63.16; H, 3.46; N, 22.42. Found: C, 62.88; H, 3.11; N, 22.20.

8-Amino-2-methyl-5-oxo-3-phenyl-6-(*p*-tolyl)-4,5-dihydropyrazolo[1,5- α]pyrido[3,2- e]pyrimidine-7-carbonitrile (7d). Yellow crystals (345 mg, 85%), mp > 300 °C, IR (KBr): ν 3451, 3295, 3181 (NH_2 and NH), 2210 (CN), 1630 (CO) cm^{-1} , ^1H NMR (400 MHz, DMSO- d_6): δ 2.33 (s, 3H, CH_3), 2.37 (s, 3H, CH_3), 7.14-7.56 (m, 9H, Ar-H), 7.66 (br s, 2H, NH_2), 11.30 (br s, 1H, NH) ppm, MS (EI, 70 eV): m/z 406 $[\text{M}]^+$, Anal. Calcd for $\text{C}_{24}\text{H}_{18}\text{N}_6\text{O}$: C, 70.92; H, 4.46; N, 20.68. Found: C, 70.61; H, 4.17; N, 20.48.

8-Amino-6-(4-methoxyphenyl)-2-methyl-5-oxo-3-phenyl-4,5-dihydropyrazolo[1,5- α]pyrido[3,2- e]pyrimidine-7-carbonitrile (7e). Yellowish white crystals (371 mg, 88%), mp > 300 °C, IR (KBr): ν 3461, 3303, 3204 (NH_2 and NH), 2224 (CN), 1678 (CO) cm^{-1} , ^1H NMR (400 MHz, DMSO- d_6): δ 2.27 (s, 3H, CH_3), 3.82 (s, 3H, OCH_3), 6.96-7.42 (m, 9H, Ar-H), 7.80 (br s, 2H, NH_2), 11.30 (br s, 1H, NH) ppm, ^{13}C NMR (100 MHz, DMSO- d_6): δ 13.8 (CH_3), 55.5 (OCH_3), 91.4, 100.2, 103.4, 113.5 (Ar-CH), 116.0 (2CN), 128.8 (Ar-CH), 129.0 (Ar-CH), 129.6 (Ar-C), 129.7 (Ar-CH), 129.8 (Ar-CH), 130.8, 137.7, 150.0, 152.0, 157.8, 159.7, 161.4 ppm, MS (EI, 70 eV): m/z 422 $[\text{M}]^+$, Anal. Calcd for $\text{C}_{24}\text{H}_{18}\text{N}_6\text{O}_2$: C, 68.24; H, 4.29; N, 19.89. Found: C, 68.05; H, 4.11; N, 19.58.

8-Amino-6-(benzo[*d*][1,3]dioxol-5-yl)-2-methyl-5-oxo-3-phenyl-4,5-dihydropyrazolo[1,5- α]pyrido[3,2- e]pyrimidine-7-carbonitrile (7f). Yellow crystals (376 mg, 86%), mp > 300 °C, IR (KBr): ν 3458, 3380, 3202 (NH_2 and NH), 2223 (CN), 1681 (CO) cm^{-1} , ^1H NMR (400 MHz, DMSO- d_6): δ 2.30 (s, 3H, CH_3), 5.96 (s, 2H, OCH_2O), 6.61-7.41 (m, 8H, Ar-H), 7.61 (br s, 2H, NH_2), 11.51 (br s, 1H, NH) ppm, ^{13}C NMR (100 MHz, DMSO- d_6): δ 14.1 (CH_3), 91.1, 100.9 (OCH_2O), 101.6, 103.0, 108.2 (Ar-CH), 109.2 (Ar-CH), 116.1 (2CN), 121.7 (Ar-CH), 126.6 (Ar-CH), 128.8 (Ar-CH), 129.4 (Ar-CH), 131.6, 131.7, 147.0, 147.6, 150.0, 151.9, 158.7, 159.9, 161.2 ppm, MS (EI, 70 eV): m/z 436 $[\text{M}]^+$, Anal. Calcd for $\text{C}_{24}\text{H}_{16}\text{N}_6\text{O}_3$: C, 66.05; H, 3.70; N, 19.26. Found: C, 65.78; H, 3.44; N, 19.03.

Ethyl 5-(2-cyanoacetamido)-1,3-diphenyl-1*H*-pyrazole-4-carboxylate (18). Employing a similar procedure to that applied for compound 5. A mixture of ethyl 5-amino-1,3-diphenyl-1*H*-pyrazole-4-carboxylate 17 (3070 mg, 10 mmol) and 3-(3,5-dimethyl-1*H*-pyrazol-1-yl)-3-oxopropanenitrile 2 (1960 mg, 12 mmol) in dry toluene (30 mL) was heated at reflux for 3 h. The crude isolated product was purified by crystallization from ethanol.

Yellow crystals (3290 mg, 88%), mp 166-168 °C, IR (KBr): ν 3406, 3253, 3182 (free and H-bonded NH), 2261 (CN), 1748 (COO), 1677 (CONH) cm^{-1} , ^1H NMR (400 MHz, DMSO- d_6): δ 1.03 (t, 3H, 3J 7.2 Hz, CH_3CH_2), 3.99 (s, 2H, CH_2), 4.02 (q, 2H, 3J 7.2 Hz, CH_3CH_2), 7.21-7.39 (m, 10H, ArH), 10.42 (br s, 1H, NH) ppm, ^{13}C NMR (100 MHz, DMSO- d_6): δ 13.6 (CH_3CH_2), 25.9 (COCH_2), 59.7 (CH_3CH_2), 115.5, 125.5 (Ar-CH), 127.9 (Ar-CH), 128.1 (Ar-CH), 128.5 (CN), 128.9 (Ar-CH), 129.1 (Ar-CH), 130.3 (Ar-CH), 138.5 (2Ar-C), 145.4, 145.5, 161.8 (COO), 161.9 (CONH) ppm, MS (EI, 70 eV): m/z 374 $[\text{M}]^+$, Anal. Calcd for $\text{C}_{21}\text{H}_{18}\text{N}_4\text{O}_3$: C, 67.37; H, 4.85; N, 14.96. Found: C, 67.19; H, 4.63; N, 14.68.

General procedure for synthesis of compounds (20a, 20b, 20d and 20e). A mixture of compound **18** (375 mg, 1 mmol) and arylidene malononitrile **6** (1 mmol) was heated at reflux in EtOH (20 mL) containing piperidine (0.2 mL, 2 mmol) for 5 h. The solvent was evaporated at reduced pressure and then treated with aq. HCl (0.1 N, 20 mL). The resulting solid was filtered, dried and crystallized from EtOH/dioxane (5 mL, 3:1, v/v).

Ethyl 5-(6-amino-3,5-dicyano-2-oxo-4-phenylpyridin-1(2H)-yl)-1,3-diphenyl-1H-pyrazole-4-carboxylate (20a).

Yellow crystals (447 mg, 85%), mp 280-282 °C, IR (KBr): ν 3426 (br), 3297, 3206 (H-bonded and free NH₂), 2219 (CN), 1686 (COO), 1641 (CONH) cm⁻¹, ¹H NMR (400 MHz, DMSO-*d*₆): δ 1.01 (t, 3H, ³J 7.2 Hz, CH₃CH₂), 4.03 (q, 2H, ³J 7.2 Hz, CH₃CH₂), 7.29-7.62 (m, 15H, Ar-*H*), 8.39 (br s, 2H, NH₂) ppm, ¹³C NMR (100 MHz, DMSO-*d*₆): δ 14.0 (CH₃), 60.5 (CH₂), 75.5, 106.3, 115.8, 116.3 (CN), 126.1 (Ar-CH), 126.9 (Ar-CH), 128.7 (Ar-CH), 128.8 (Ar-CH), 129.2 (Ar-CH), 129.5 (Ar-CH), 130.1 (Ar-CH), 130.9 (Ar-CH), 131.3 (Ar-CH), 134.9, 136.1, 139.5, 140.5, 142.5, 148.5, 154.5, 157.8 (CONH), 160.7 (COO), 163.0 ppm, MS (EI, 70 eV): *m/z* 526 [M]⁺, Anal. Calcd for C₃₁H₂₂N₆O₃: C, 70.71; H, 4.21; N, 15.96. Found: C, 70.44; H, 4.03; N, 15.63.

Ethyl 5-(6-amino-4-(4-chlorophenyl)-3,5-dicyano-2-oxopyridin-1(2H)-yl)-1,3-diphenyl-1H-pyrazole-4-carboxylate 3b (20b).

Yellow crystals (487 mg, 87%), mp > 300 °C, IR (KBr): ν 3438, 3349, 3317, 3212 (br, H-bonded and free NH₂), 2218 (CN), 1698 (COO), 1646 (CONH) cm⁻¹, ¹H NMR (400 MHz, DMSO-*d*₆): δ 1.00 (t, 3H, ³J 7.2 Hz, CH₃CH₂), 4.01 (q, 2H, ³J 7.2 Hz, CH₃CH₂), 7.30-7.72 (m, 14H, Ar-*H*), 8.59 (br s, 2H, NH₂) ppm, ¹³C NMR (100 MHz, DMSO-*d*₆): δ 13.9 (CH₃), 60.5 (CH₂), 75.5, 88.0, 109.3, 115.7, 116.2 (CN), 126.1 (Ar-CH), 128.5 (Ar-CH), 129.2 (Ar-CH), 129.5 (Ar-CH), 130.1 (Ar-CH), 130.4 (Ar-CH), 130.9 (Ar-CH), 131.3 (Ar-CH), 133.8, 135.9, 138.8, 142.5, 148.5, 157.7, 159.4 (CONH), 160.7 (COO), 161.8 ppm, MS (EI, 70 eV): *m/z* 560 [M]⁺, Anal. Calcd for C₃₁H₂₁ClN₆O₃: C, 66.37; H, 3.77; N, 14.98. Found: C, 66.09; H, 3.49; N, 14.76.

Ethyl 5-(6-amino-3,5-dicyano-2-oxo-4-(*p*-tolyl)pyridin-1(2H)-yl)-1,3-diphenyl-1H-pyrazole-4-carboxylate (20d).

White crystals (455 mg, 84%), mp > 300 °C, IR (KBr): ν 3309, 3208 (br, H-bonded and free NH₂), 2217 (CN), 1691 (COO), 1646 (CON) cm⁻¹, ¹H NMR (400 MHz, DMSO-*d*₆): δ 0.99 (t, 3H, ³J 7.2 Hz, CH₃CH₂), 2.44 (s, 3H, CH₃), 4.02 (q, 2H, ³J 7.2 Hz, CH₃CH₂), 7.31-7.48 (m, 14H, Ar-*H*), 8.59 (br s, 2H, NH₂) ppm, ¹³C NMR (100 MHz, DMSO-*d*₆): δ 13.8 (CH₃CH₂), 21.5 (CH₃), 60.5 (CH₃CH₂), 75.5, 87.9, 109.3, 115.9, 116.4 (CN), 126.2 (Ar-CH), 128.3 (Ar-CH), 128.5 (Ar-CH), 128.6, 129.2 (Ar-CH), 129.4 (Ar-CH), 129.8 (Ar-CH), 130.0 (Ar-CH), 130.9 (Ar-CH), 132.0, 138.8, 140.9, 142.5, 148.5, 157.7, 159.6 (CON), 160.8 (COO), 163.0 ppm, MS (EI, 70 eV): *m/z* 540 [M]⁺, Anal. Calcd for C₃₂H₂₄N₆O₃: C, 71.10; H, 4.48; N, 15.55. Found: C, 70.89; H, 4.21; N, 15.38.

Ethyl 5-(6-amino-3,5-dicyano-4-(4-methoxyphenyl)-2-oxopyridin-1(2H)-yl)-1,3-diphenyl-1H-pyrazole-4-carboxylate (20e).

Yellow crystals (445 mg, 87%), mp > 300 °C, IR (KBr): ν 3366, 3313, 3213 (br, H-bonded and free NH₂), 2214 (CN), 1692 (COO), 1648 (CONH) cm⁻¹, ¹H NMR (400 MHz, DMSO-*d*₆): δ 0.99 (t, 3H, ³J 7.2 Hz, CH₃CH₂), 3.87 (s, 3H, OCH₃), 4.00 (q, 2H, ³J 7.2 Hz, CH₃CH₂), 7.15-7.56 (m, 14H, Ar-*H*), 8.51 (br s, 2H, NH₂) ppm, ¹³C NMR (100 MHz, DMSO-*d*₆): δ 13.9 (CH₃CH₂), 55.9 (OCH₃), 60.5 (CH₃CH₂), 75.4, 87.8, 109.3, 114.6 (Ar-CH), 116.1, 116.6 (CN), 126.1 (Ar-CH), 126.8, 128.5 (Ar-CH), 128.6, 129.2 (Ar-CH), 129.5 (Ar-CH), 130.1 (Ar-CH), 130.3 (Ar-CH), 130.9 (Ar-CH), 138.8, 142.6, 148.4, 157.8, 159.6 (CON), 160.7 (COO), 162.6 ppm, MS (EI, 70 eV): *m/z* 556 [M]⁺, Anal. Calcd for C₃₂H₂₄N₆O₄: C, 69.06; H, 4.35; N, 15.10. Found: C, 68.81; H, 4.14; N, 14.89.

4,9-Dioxo-1,3,7-triphenyl-1,4,5,9-tetrahydropyrazolo[4,3-*e*]pyrido[1,2-*a*]pyrimidine-6,8-dicarbonitrile (21a).

Compound **20a** (250 mg, 0.5 mmol) was heated in pyridine (5 mL) at reflux for 5 h. The excess solvent was removed under vacuum. The collected residue was treated with aq. HCl (0.1 N, 20 mL) and the precipitate was filtered and washed thoroughly with distilled water (25 mL) and air-dried. The crude solid was crystallized from EtOH/dioxane (5 mL, 1:1, v/v). Yellow crystals (200 mg, 83%), mp > 300 °C, IR (KBr): ν 3440 (br, NH), 2214 (CN), 1685 (br, 2CO) cm⁻¹, ¹H NMR (400 MHz, DMSO-*d*₆): δ 4.40 (br s, 1H, NH), 7.34-7.60 (m, 15H, Ar-*H*) ppm, ¹³C NMR (100 MHz, DMSO-*d*₆): δ 81.7, 105.1, 116.5, 117.0 (2CN), 126.8 (Ar-CH), 126.9 (Ar-CH), 127.4 (Ar-CH), 128.5 (Ar-CH), 128.7 (Ar-CH), 129.0 (Ar-CH), 129.5 (Ar-CH), 129.6 (Ar-CH), 130.1 (Ar-CH), 131.2 (Ar-CH), 135.3,

139.0, 141.8, 144.4, 144.5, 148.0, 153.1 (CONH), 157.1 (CONH), 160.1 ppm, MS (EI, 70 eV): m/z 480 $[M]^+$, Anal. Calcd for $C_{29}H_{16}N_6O_2$: C, 72.49; H, 3.36; N, 17.49. Found: C, 72.13; H, 3.09; N, 17.22.

7-(4-Nitrophenyl)-4,9-dioxo-1,3-diphenyl-1,4,5,9-tetrahydropyrazolo[4,3-*e*]pyrido[1,2-*a*]pyrimidine-6,8-dicarbonitrile (21c). A mixture of compound **18** (375 mg, 1 mmol) and compound **6c** (200 mg, 1 mmol) was heated in pyridine (5 mL) at reflux for 5 h. The excess solvent was removed under vacuum. The collected residue was treated with aq. HCl (0.1 N, 20 mL) and the precipitate was filtered and washed thoroughly with distilled water (25 mL) and air-dried. The crude solid was crystallized from EtOH/dioxane (5 mL, 1:1, v/v).

Yellowish white crystals (462 mg, 88%), mp > 300 °C, IR (KBr): ν 3426 (br, NH), 2219 (CN), 1678 (CO-9), 1649 (CO-4) cm^{-1} , 1H NMR (400 MHz, DMSO- d_6): δ 4.04 (br s, 1H, NH), 7.32-8.14 (m, 14H, Ar-*H*) ppm, ^{13}C NMR (100 MHz, DMSO- d_6): δ 83.4, 84.5, 106.8, 117.8 (CN), 117.9 (CN), 124.1 (Ar-CH), 126.9 (Ar-CH), 128.1, 128.3 (Ar-CH), 129.1 (Ar-CH), 129.5 (Ar-CH), 129.6 (Ar-CH), 130.5 (Ar-CH), 131.3 (Ar-CH), 139.4, 140.6, 146.6, 148.5, 148.6, 154.3, 157.6 (CO-4), 158.0 (CO-9), 164.4 ppm, MS (EI, 70 eV): m/z 525 $[M]^+$, Anal. Calcd for $C_{29}H_{15}N_7O_4$: C, 66.29; H, 2.88; N, 18.66. Found: C, 66.03; H, 2.67; N, 18.48.

7-(Benzo[*d*][1,3]dioxol-5-yl)-4,9-dioxo-1,3-diphenyl-1,4,5,9-tetrahydropyrazolo[4,3-*e*]pyrido[1,2-*a*]pyrimidine-6,8-dicarbonitrile (21f). Applying the same procedure for synthesis of **21c** employing a mixture of compound **18** (375 mg, 1 mmol) and compound **6f** (200 mg, 1 mmol). The crude solid was crystallized from EtOH/dioxane (5 mL, 1:1, v/v). Yellow crystals (430 mg, 82%), mp 258-260 °C, IR (KBr): ν 3435 (br, NH), 2215 (CN), 1681 (CO-9), 1628 (CO-4) cm^{-1} , 1H NMR (400 MHz, DMSO- d_6): δ 4.02 (br s, 1H, NH), 6.17 (s, 2H, OCH₂O), 7.05-7.46 (m, 13H, Ar-*H*) ppm, ^{13}C NMR (100 MHz, DMSO- d_6): δ 81.8, 102.2 (OCH₂O), 105.1, 108.9 (Ar-CH), 109.2 (Ar-CH), 116.7 (CN), 117.2 (CN), 123.3 (Ar-CH), 126.8 (Ar-CH), 127.4, 128.5 (Ar-CH), 128.7, 129.4 (Ar-CH), 129.6 (Ar-CH), 130.1 (Ar-CH), 131.2 (Ar-CH), 139.0, 141.7, 147.7, 148.0, 149.3, 153.0, 157.1 (CO-4), 159.6 (CO-9), 166.5 ppm, MS (EI, 70 eV): m/z 524 $[M]^+$, Anal. Calcd for $C_{30}H_{16}N_6O_4$: C, 68.70; H, 3.07; N, 16.02. Found: C, 68.48; H, 2.88; N, 15.78.

General procedure for synthesis of compounds 24a,b. A mixture of **18** (375 mg, 1 mmol) and aromatic aldehyde **15** (1 mmol) was heated at reflux in absolute EtOH (20 mL) containing piperidine (0.2 mL, 2 mmol) for 30 min. The crude product was collected and crystallized from EtOH (5 mL).

Ethyl 5-(2-cyano-3-phenylacrylamido)-1,3-diphenyl-1*H*-pyrazole-4-carboxylate (24a). White crystals (415 mg, 90%), mp 210-212 °C, IR (KBr): ν 3431 (br, NH), 2211 (CN), 1698 (COO), 1678 (CONH) cm^{-1} , 1H NMR (400 MHz, DMSO- d_6): δ 1.01 (t, 3H, 3J 7.2 Hz, CH₃CH₂), 4.03 (q, 2H, 3J 7.2 Hz, CH₃CH₂), 7.25-8.05 (m, 16H, Ar-*H* and =C-*H*), 8.40 (br s, 1H, NH) ppm, ^{13}C NMR (100 MHz, DMSO- d_6): δ 14.2 (CH₃), 60.4 (CH₂), 106.5, 106.9, 117.5 (CN), 126.1 (Ar-CH), 128.3 (Ar-CH), 128.5 (Ar-CH), 128.9, 129.5 (Ar-CH), 129.6 (Ar-CH), 129.9 (Ar-CH), 130.8 (Ar-CH), 130.9 (Ar-CH), 132.2, 133.4 (Ar-CH), 139.0, 145.2, 146.7, 152.4 (=CH), 160.6 (CONH), 162.6 (CO₂Et) ppm, MS (EI, 70 eV): m/z 462 $[M]^+$, Anal. Calcd for $C_{28}H_{22}N_4O_3$: C, 72.71; H, 4.79; N, 12.11. Found: C, 72.49; H, 4.53; N, 11.94.

Ethyl 5-(3-(4-chlorophenyl)-2-cyanoacrylamido)-1,3-diphenyl-1*H*-pyrazole-4-carboxylate (24b). Yellow crystals (456 mg, 92%), mp 236-238 °C, IR (KBr): ν 3435 (br, NH), 2210 (CN), 1692 (COO), 1678 (CONH) cm^{-1} , 1H NMR (400 MHz, DMSO- d_6): δ 1.00 (t, 3H, 3J 7.2 Hz, CH₃CH₂), 4.03 (q, 2H, 3J 7.2 Hz, CH₃CH₂), 7.25-8.06 (m, 15H, Ar-*H* and =C-*H*), 8.38 (br s, 1H, NH) ppm, ^{13}C NMR (100 MHz, DMSO- d_6): δ 14.2 (CH₃), 60.4 (CH₂), 106.7, 107.1, 116.3 (CN), 126.1 (Ar-CH), 128.4 (Ar-CH), 128.8 (Ar-CH), 128.9, 129.5 (Ar-CH), 129.7 (Ar-CH), 130.0 (Ar-CH), 130.9 (Ar-CH), 131.1, 132.4 (Ar-CH), 137.9, 139.0, 146.0, 146.6, 151.1 (=CH), 160.4 (CONH), 162.6 (CO₂Et) ppm, MS (EI, 70 eV): m/z 496 $[M]^+$, Anal. Calcd for $C_{28}H_{21}ClN_4O_3$: C, 67.67; H, 4.26; N, 11.27. Found: C, 67.51; H, 4.10; N, 11.03.

Supplementary Material

The ^1H and ^{13}C NMR spectra of new compounds: this material can be found using the link "Supplementary Material" in the journal issue contents page.

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