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Facile synthetic approaches for new series of pyrazole-4-carbonitrile derivatives

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Abstract Aldol condensation of 3-acetyl-1-(4-fluorophenyl)-5-phenyl-1*H*-pyrazole-4-carbonitrile with benzaldehyde afforded 1-(4-fluorophenyl)-5-phenyl-3-((*E*)-3-phenylacryloyl)-1*H*-pyrazole-4-carbonitrile, which in turn reacted with a series of 1,2- and 1,3-binucleophiles to afford new substituted pyrazoles, pyrimidines, and condensed azolopyrimidine derivatives attached to pyrazole scaffold at position 3. Moreover, multicomponent condensation reactions (MCRs) were used as an alternative method, and ^{1}H–^{13}C heteronuclear single quantum coherence (HSQC) in addition to heteronuclear multiple-bond correlation (HMBC) spectra were used for full confirmation of a selected example of these compounds. The reactivity of 1-(4-fluorophenyl)-5-phenyl-3-((*E*)-3-phenylacryloyl)-1*H*-pyrazole-4-carbonitrile towards active methylene derivatives, including malononitrile and ethyl cyanoacetate, was explored and afforded 2-amino-6-(4-cyano-1-(4-fluorophenyl)-5-phenyl-1*H*-pyrazol-3-yl)-4-phenylpyridine-3-carbonitrile and ethyl 6-(4-cyano-1-(4-fluorophenyl)-5-phenyl-1*H*-pyrazol-3-yl)-1,2-dihydro-2-oxo-4-phenylpyridine-3-carboxylate, respectively.

Keywords Pyrazole-4-carbonitrile · Binucleophiles · Chalcone · Multicomponent condensation reactions (MCRs) · Pyrimidine

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Introduction

A great deal of interest has been focused on synthesis of functionalized pyrazole derivatives due to their diverse biological applications. They are known to exhibit antioxidant, antiandrogen, anesthetic, antidiabetic, antifungal, and antiinflammatory activities [1–3]. Additionally, some pyrazole derivatives show potential anticancer and antibacterial activities [4, 5]. Previously, we synthesized several 4-cyano-1,5-diphenylpyrazoles attached to different heterocyclic ring systems at position 3 and tested their antiestrogenic effects and cytotoxic properties against estrogen-dependent tumors [6, 7]. Compounds **A**, **B**, and **C** (Fig. 1) are examples of the synthesized compounds, showing significant cytotoxic activity in the nanomolar range against certain types of breast and ovarian tumor with tolerable toxicity [6, 7].

On the other hand, nitrogen-containing 1,2- and 1,3-binucleophiles are important reagents in heterocyclic chemistry, and their reactions with electrophiles are considered as facile synthetic approaches for obtaining diverse heterocyclic systems containing azole and condensed azole moieties [8–11]. In view of these observations and in continuation of our current interest in synthesis of polysubstituted heterocycles [12–16], we describe herein a facile synthesis of a novel class of pyrazole-4-carbonitrile-based heterocycles starting from 3-acetyl-1-(4-fluorophenyl)-5-phenyl-1*H*-pyrazole-4-carbonitrile (**3**). In this study, we prepared 1-(4-fluorophenyl)-5-phenyl-3-((*E*)-3-phenylacryloyl)-1*H*-pyrazole-4-carbonitrile (**4**) and studied its reactivity towards a series of nitrogen-containing 1,2- and 1,3-binucleophiles, in addition to carbonitrile active methylene derivatives. Moreover, we applied multicomponent condensation reactions (MCRs) as an alternative method for preparation of selected examples of these compounds.

Results and discussion

Synthesis of the versatile, hitherto unreported 3-acetyl-1-(4-fluorophenyl)-5-phenyl-1*H*-pyrazole-4-carbonitrile (**3**) was achieved through the synthetic pathway presented in Scheme 1. The pyrazole-4-carbonitrile (**3**) underwent aldol

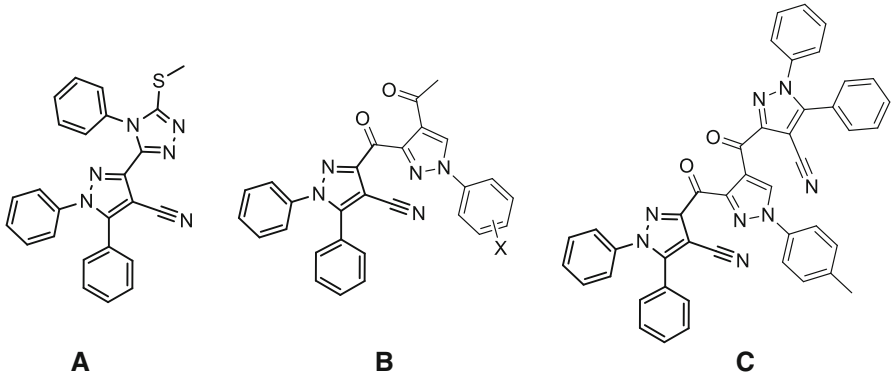
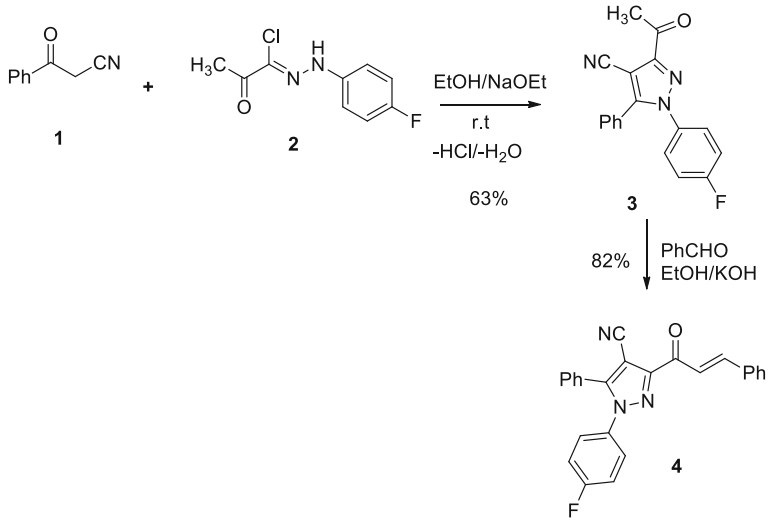


Fig. 1 Pyrazoles having potent anticancer activity

condensation with benzaldehyde, in the presence of potassium hydroxide, to afford 1-(4-fluorophenyl)-5-phenyl-3-((*E*)-3-phenylacryloyl)-1*H*-pyrazole-4-carbonitrile (**4**) (Scheme 1). The infrared (IR) spectrum of compound **3** exhibited nitrile and carbonyl bands at 2230 and 1696 cm^{-1}, respectively. The ^{1}H nuclear magnetic resonance (NMR) spectrum of **3** revealed signal at δ 2.60 ppm due to CH_3 protons, in addition to a characteristic multiplet in the region δ 7.29–7.52 ppm due to nine aromatic protons. In the IR spectrum of chalcone **4**, the carbonyl group was shifted from 1696 as in compound **3** to 1665 cm^{-1}. The ^{1}H NMR spectrum of the chalcone **4** revealed two doublet signals at δ 6.72 and 7.54 ppm, corresponding to 2CH protons ($J = 17$ Hz). The mass spectrum of compound **4** revealed a molecular ion peak at *m*/*z* 393. The structure of the isolated chalcone was assigned as the *E*-isomer based on the 2CH proton coupling constant value ($J = 17$ Hz).

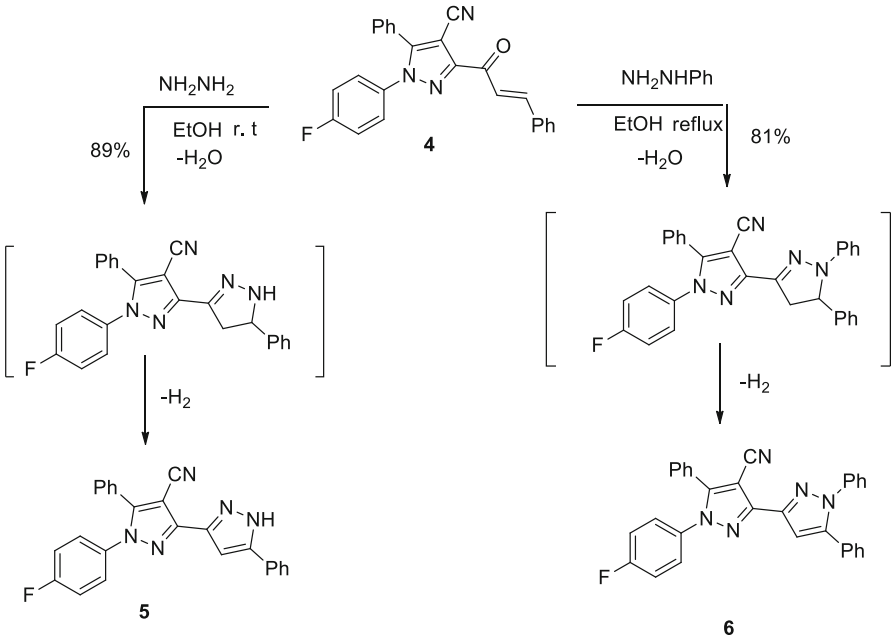
Addition of nitrogen-containing reagents that possess two nucleophilic centers provides an efficient route to convert 1-(4-fluorophenyl)-5-phenyl-3-((*E*)-3-phenylacryloyl)-1*H*-pyrazole-4-carbonitrile (**4**) to functionalized heterocycles. Thus, treatment of the chalcone (**4**) with hydrazine and with phenylhydrazine afforded the corresponding bipyrazole derivatives **5** and **6**, respectively, as shown in Scheme 2. The formation of bipyrazole derivatives **5** and **6** is assumed to proceed via a sequence of condensation reaction of amino group of the appropriate hydrazine derivative with the carbonyl group of the chalcone **4** with loss of water, followed by 1,4-nucleophilic Michael-type addition of the other nucleophilic center of hydrazines with subsequent cyclization then oxidative aromatization to afford the bipyrazole **5** and **6**. The reactions of chalcone with arylhydrazines to afford the corresponding pyrazolines or pyrazoles were well established and confirmed by x-ray diffraction analysis [17]. The structures of the products **5** and **6** were



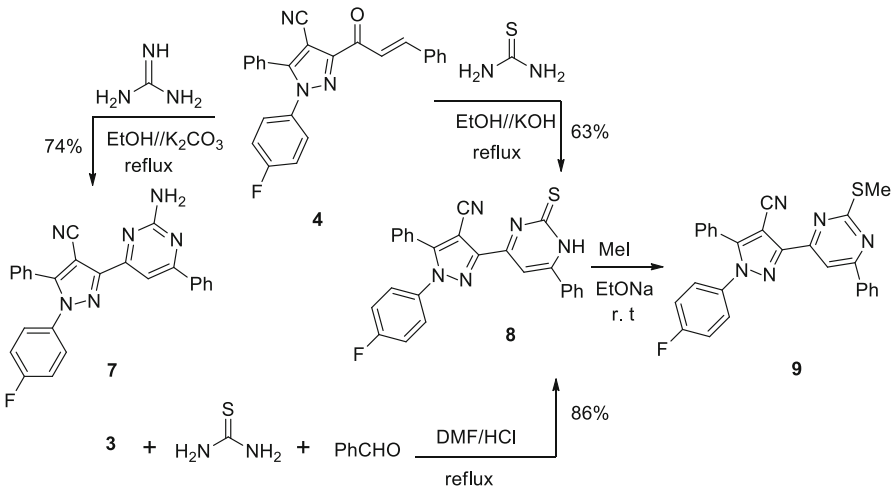
Scheme 1 Synthetic route to compounds **3** and **4**

confirmed on the basis of their elemental analyses and spectral data (see "Experimental" section).

1,3-Binucleophiles were used to obtain pyrazole ring attached to six-membered heterocycles. Thus, treatment of 1-(4-fluorophenyl)-5-phenyl-3-((*E*)-3-phenylacryloyl)-1*H*-pyrazole-4-carbonitrile (**4**) with guanidine under reflux temperature



Scheme 2 Synthetic route to compounds **5** and **6**



Scheme 3 Synthetic route to compounds **8** and **9**

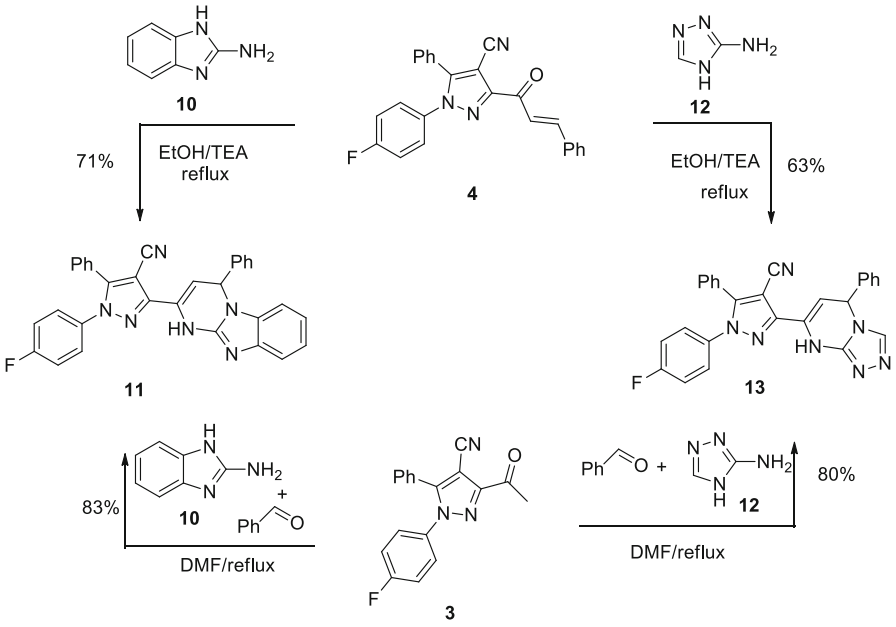
afforded a single product identified as 3-(2-amino-6-phenylpyrimidin-4-yl)-1-(4-fluorophenyl)-5-phenyl-1*H*-pyrazole-4-carbonitrile (**7**). The IR spectrum of compound **7** showed amino and nitrile absorption bands at 3430–3320 and 2231 cm^{-1}, respectively. Its ^1H NMR spectrum revealed D_2O-exchangeable signal at 2.60 ppm and CH proton signal at 7.52 ppm, corresponding to NH_2 and CH pyrimidine protons, respectively.

To obtain pyrazole-ring-attached thiopyrimidine ring, we treated the chalcone **4** with thiourea, in the presence of EtONa, to afford the thiopyrimidine derivative **8** in 63 % yield. The latter compound was also obtained by one-pot multicomponent acid-catalyzed synthesis by treatment of the acetylpyrazole **3** with excess thiourea (3 equiv.) in dimethylformamide (DMF), in the presence of HCl (Scheme 3). The ^1H NMR spectrum of compound **8** revealed a singlet signal at 8.19 ppm and D_2O-exchangeable signal at δ 8.31 ppm, due to CH-pyrimidine and NH protons, respectively. The IR spectrum of the latter product revealed the lack of absorption band corresponding to carbonyl group and showed a band at 2230 cm^{-1} corresponding to nitrile function. Its mass spectrum revealed a molecular ion peak at *m*/*z* 449. The formation of compound **8** can be explained on the basis of Michael-type addition of NH_2 group to the double bond in the chalcone **4**, to afford nonisolable thiouriedo intermediate followed by oxidative intramolecular cyclization to afford compound **8** (Scheme 3). Treatment of compound **8** with methyl iodide in the presence of EtONa afforded the corresponding *S*-methylated product **9** (Scheme 3).

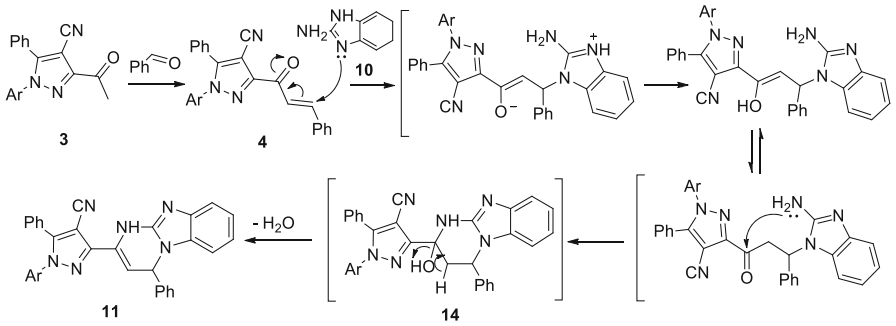
Electron-rich aminoheterocycles are important reagents in heterocyclic synthesis, and their reactions with electrophiles are considered as widespread facile synthetic approaches for preparation of different classes of heterocycles containing azole moiety. Herein, we used 2-aminotriazole and 2-aminobenzimidazole as examples of 1,3-binucleophiles. Thus, treatment of the chalcone **4** with 2-aminobenzimidazole (**10**) and with 2-amino-1*H*-1,3,4-triazole (**12**) furnished the corresponding 1-(4-fluorophenyl)-5-phenyl-3-(4-phenyl-1,4-dihydropyrimido[1.2-*a*]benzimidazol-2-yl)-1*H*-pyrazole-4-carbonitrile (**11**) and 1-(4-fluorophenyl)-3-(5,8-dihydro-5-phenyl-[1,2,4]triazolo[4,3-*a*]pyrimidin-7-yl)-5-phenyl-1*H*-pyrazole-4-carbonitrile (**13**), respectively.

Furthermore, we applied a three-component one-pot synthesis protocol to obtain the same products by reaction of the acetylpyrazole derivative **3**, benzaldehyde, and the appropriate heterocyclic amines **10** or **12**, which afforded, in each case, the corresponding dihydropyrimidine (DHP) derivative **11** and **13**, respectively, in high yields (Scheme 4).

The structures of the dihydropyrimidine (DHP) derivatives **11** and **13** were established on the basis of their elemental analyses and spectral data; For example, the ^1H NMR spectrum of compound **11** revealed the presence of two doublet signals at δ 5.73 ppm and 6.50 ppm ($J = 4.2$ Hz) due to pyrimidine protons, in addition to D_2O-exchangeable signal at δ 10.11 due to NH group. The IR spectrum of compound **11** revealed absorption bands at 3442 and 2226 cm^{-1}, corresponding to NH and CN groups, respectively. The mass spectrum of the same product showed a peak at *m*/*z* 508, corresponding to its molecular ion. The formation of compound **11** can be explained by the reaction sequence outlined in Scheme 5.



Scheme 4 Synthetic route to compounds **11** and **13**



Scheme 5 Plausible mechanism for formation of compound **11**

The structure of compound **11** was fully confirmed by connectivities found in ^{1}H–^{13}C HSQC and HMBC 2-dimensional (2D) NMR spectral data, as shown in Fig. 2.

^{1}H–^{13}C HSQC and HMBC spectra of compound **11** are shown in Figs. 3 and 4, respectively.

The reactivity of compound **4** towards some active methylene compounds was also investigated. Thus, treatment of 1-(4-fluorophenyl)-5-phenyl-3-((*E*)-3-phenylacryloyl)-1*H*-pyrazole-4-carbonitrile (**4**) with malononitrile, in refluxing EtOH, in the presence of ammonium acetate, afforded a pale-yellow crystalline product identified as 2-amino-6-(4-cyano-1-(4-fluorophenyl)-5-phenyl-1*H*-pyrazol-3-yl)-4-

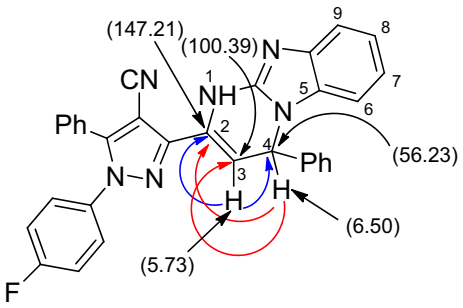


Fig. 2 ^{1}H–^{13}C HMBC correlations for compound **11**

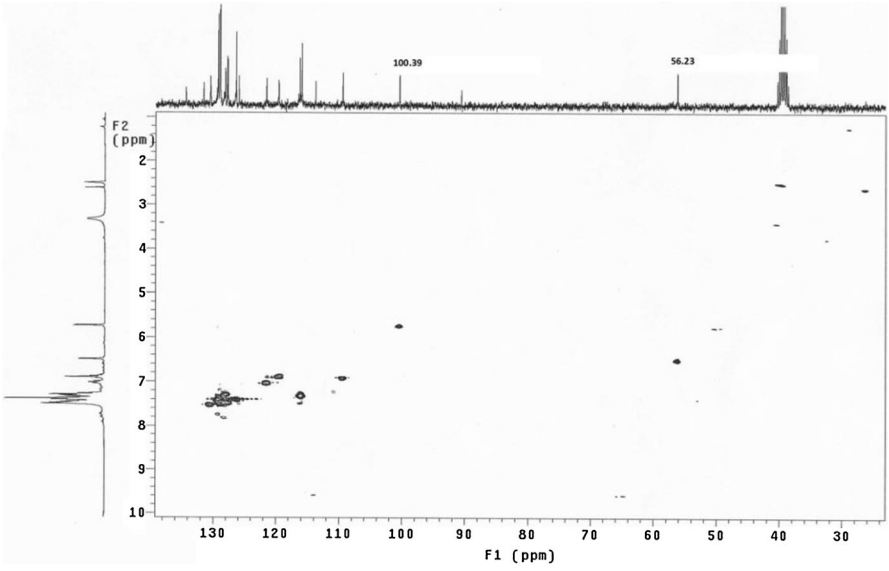


Fig. 3 ^{1}H–^{13}C HSQC spectrum of compound **11**

phenylpyridine-3-carbonitrile (**17**) (Scheme 6). The ^{1}H NMR spectrum of compound **17** showed D_2O-exchangeable signal at δ 3.31 ppm due to NH_2 group and a singlet signal at 8.35 ppm due to CH of pyridine ring. The IR spectrum of the same compound revealed absorption bands at 3470–3320 and 2227 cm^{-1}, corresponding to NH_2 and CN groups, respectively. The mass spectrum of **17** showed a peak at *m*/*z* 457, corresponding to its molecular ion.

Finally, treatment of the chalcone **4** with ethyl cyanoacetate, in EtONa solution, afforded ethyl 6-(4-cyano-1-(4-fluorophenyl)-5-phenyl-1*H*-pyrazol-3-yl)-1,2-dihydro-2-oxo-4-phenylpyridine-3-carboxylate (**20**) (Scheme 6). The ^{1}H NMR spectrum of the product **20** showed characteristic signals at δ 1.45, 4.11 ppm and D_2O-exchangeable signal at δ 10.5 ppm, corresponding to CH_3, CH_2, and NH protons, respectively. The IR spectrum of compound **20** revealed absorption bands at 3420,

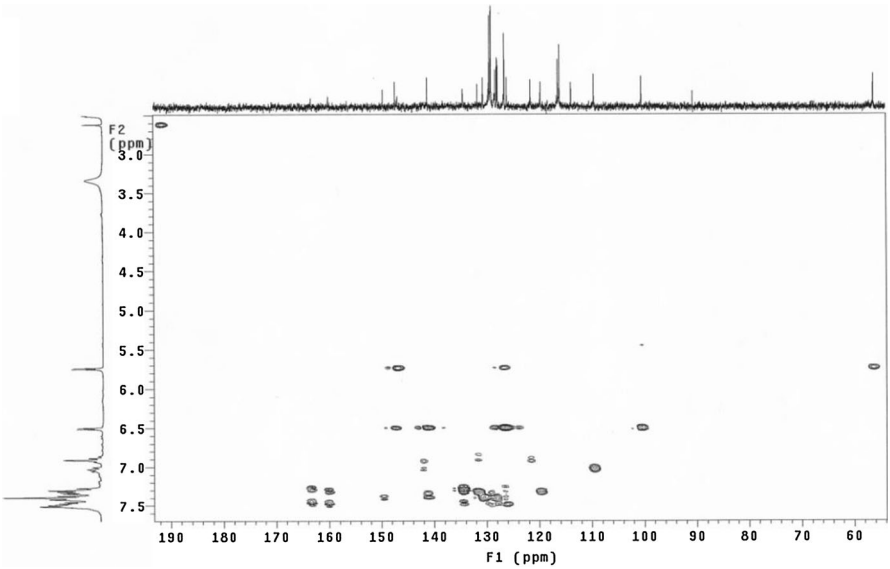


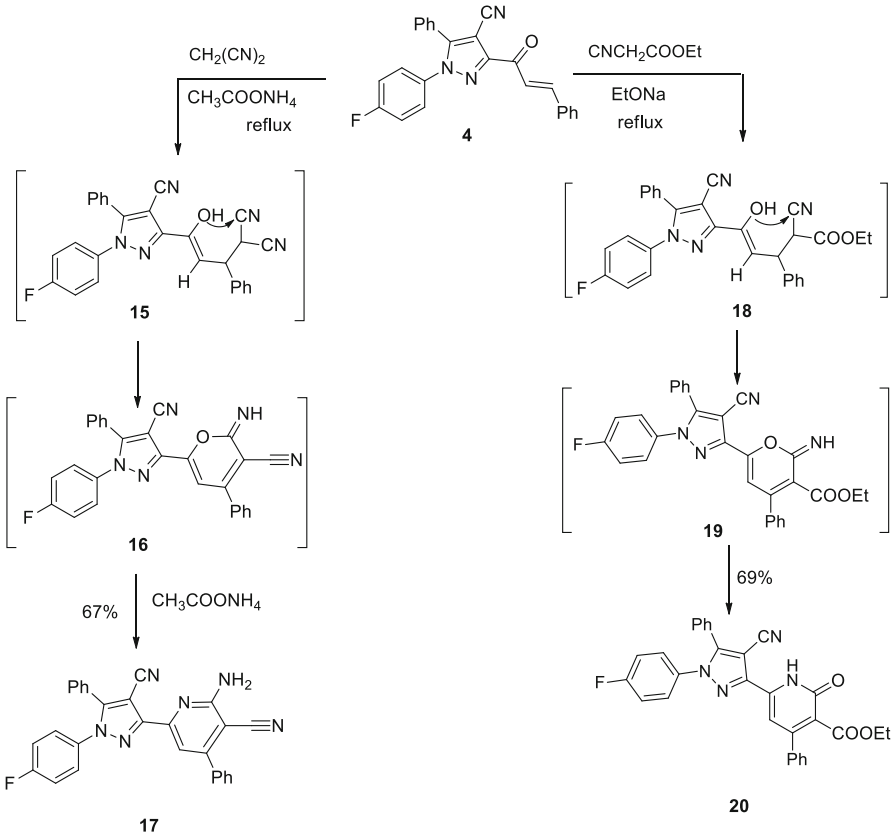
Fig. 4 ^{1}H–^{13}C HMBC spectrum of compound **11**

2238, 1743, and 1695 cm^{-1}, corresponding to NH, CN, and 2 carbonyl groups, respectively.

The formation of compounds **17** and **20** can be explained by the reaction sequence outlined in Scheme 6. First, cyclization of Michael adduct of the chalcone **4** with malononitrile or ethyl cyanoacetate affords the corresponding iminopyrane intermediates **16** and **19**, respectively. The latter intermediates underwent intermolecular rearrangement and cyclization with replacement of oxygen atom in the pyrane ring with nitrogen (in the reaction of malononitrile with chalcone **4** due to the presence of ammonium acetate).

Experimental

General All melting points were measured on a Gallenkamp melting point apparatus (Weiss–Gallenkamp, London, UK). The infrared spectra were recorded from potassium bromide disks on Pye Unicam SP 3300 and Shimadzu FT IR 8101 PC infrared spectrophotometers (Pye Unicam Ltd. Cambridge, UK and Shimadzu, Tokyo, Japan, respectively). The NMR spectra were recorded on a Varian Mercury VX-300 NMR spectrometer (Varian, Palo Alto, CA, USA). ^{1}H spectra were run at 300 MHz, and ^{13}C spectra were run at 75.46 MHz in deuterated chloroform ($CDCl_3$) or dimethyl sulfoxide (DMSO-d_6). Chemical shifts are given in parts per million and were related to the solvent. Mass spectra were recorded on a Shimadzu GCMS-QP 1000 EX mass spectrometer (Shimadzu, Tokyo, Japan) at 70 eV. Elemental analyses were carried out at the Micro-analytical Centre of Cairo University, Giza, Egypt and recorded on an Elementar-Vario EL (Germany)



Scheme 6 Synthetic route to compounds **17** and **20**

automatic analyzer. 3-Phenyl-3-oxopropanenitrile and 2-oxo-*N*-arylpropanehydrazonoyl chlorides (**2a**–**d**) were prepared by the following procedures reported in literature [18, 19].

3-Acetyl-1-(4-fluorophenyl)-5-phenyl-1*H*-pyrazole-4-carbonitrile (3)

Compound **3** was prepared using the well-known method [20]. To a stirred mixture of 3-phenyl-3-oxopropanenitrile (**1**) (4.35 g, 30 mmol) and sodium ethoxide solution (prepared from 0.69 g Na metal in 10 mL EtOH), *N*-(4-fluorophenyl)-2-oxopropane hydrazonoyl chloride (**2**) (6.42 g, 30 mmol) was added gradually with stirring. The reaction mixture was left to stir at room temperature for 12 h. The solid product was filtered off, washed with water, dried, and finally recrystallized from EtOH to afford pale-yellow crystals of **3**. Yield 5.77 g (63 %); yellow crystals; m.p.: 153–154 °C. IR (KBr, ν, cm^{-1}): 2230 (CN), 1696 (C=O), ^{1}H NMR (DMSO-d_6): δ 2.60 (s, 6H, $2CH_3$), 7.29–7.52 (m, 9H, Ar–H). ^{13}C NMR (DMSO-d_6): δ 23.11, 97.22, 115.11, 116.12, 122.8, 126.71, 128.32, 129.3, 132.11, 134.2, 163.14, 195.44.

MS *m/z* (%): 305 [M^+] (19), 290 (100), 262 (10), 198 (40), 159 (20), 95 (47), 77 (30). Anal. Calcd. for $C_{18}H_{12}FN_3O$ (305.31): C, 70.81; H, 3.86; N, 13.76. Found: C, 70.92; H, 3.82; N, 13.65.

1-(4-Fluorophenyl)-5-phenyl-3-((*E*)-3-phenylacryloyl)-1*H*-pyrazole-4-carbonitrile (4)

A mixture of 3-acetyl-1-(4-fluorophenyl)-5-phenyl-1*H*-pyrazole-4-carbonitrile (**3**) (3.05 g, 10 mmol) and benzaldehyde (1.06 g, 10 mmol) in EtOH (10 mL) was treated with potassium hydroxide solution (0.5 g KOH in 2 mL water) and stirred at room temperature for 5 h. The solid product was filtered off, washed with EtOH, dried, and finally recrystallized from EtOH to afford pale-yellow crystals of 1-(4-fluorophenyl)-5-phenyl-3-((*E*)-3-phenylacryloyl)-1*H*-pyrazole-4-carbonitrile (**4**). Yield 3.2 g (82 %), yellow crystals; m.p.: 171–172 °C. IR (KBr, *v*, cm^{-1}): 2232 (CN), 1665 (C=O), ^{1}H NMR (DMSO-d_6): δ 6.72, 7.54 (2d, 2H, 2CH, $J = 17$ Hz), 6.75–7.29 (m, 14H, Ar–H). ^{13}C NMR (DMSO-d_6): δ 101, 115.12, 116.5, 120.22, 121.51, 126.11, 126.91, 128.2, 128.44, 129.10, 129.54, 131.21, 132.11, 135.42, 140.13, 145.12, 161.21, 181.21. MS *m/z* (%): 393 [M^+] (15), 392 (58), 358 (15), 323 (20), 245 (80), 149 (51), 95 (61), 77 (100). Anal. Calcd. for $C_{25}H_{16}FN_3O$ (393.41): C, 76.32; H, 4.10; N, 10.68. Found: C, 76.28; H, 4.15; N, 10.73.

1-(4-Fluorophenyl)-5-phenyl-3-(5-phenyl-1*H*-pyrazol-3-yl)-1*H*-pyrazole-4-carbonitrile (5)

A mixture of hydrazine hydrate (60 %, 1.5 mL) and 1-(4-fluorophenyl)-5-phenyl-3-(5-phenyl-1*H*-pyrazol-3-yl)-1*H*-pyrazole-4-carbonitrile (**4**) (0.39 g, 1 mmol) in EtOH (20 mL) was stirred at room temperature for 8 h. The solid precipitate was collected by filtration, washed with EtOH/H_2O mixture, dried, and finally recrystallized from EtOH to afford white solid of 1-(4-fluorophenyl)-5-phenyl-3-(5-phenyl-1*H*-pyrazol-3-yl)-1*H*-pyrazole-4-carbonitrile (**5**). Yield 0.35 g (89 %); m.p.: 224–226 °C; IR (KBr, *v*, cm^{-1}): 3346 (NH), 2228 (CN), ^{1}H NMR (DMSO-d_6): δ 7.24 (s, 1H, CH-pyrazole), 7.27–7.49 (m, 14H, Ar–H), 8.18 (s, 1H, NH-D_2O-exchangeable). ^{13}C NMR (DMSO-d_6): δ 105.11, 108.21, 116.02, 117.12, 120.22, 125.48, 126.12, 127.27, 127.45, 127.96, 130.23, 145.23, 145.46, 147.10, 147.11, 149.69, 161.22. MS *m/z* (%): 405 [M^+] (100), 330 (10), 262 (19), 198 (39), 151 (16), 115 (26), 95 (66), 77 (70). Anal. Calcd. for $C_{25}H_{16}FN_5$ (405.43): C, 74.06; H, 3.98; N, 17.27. Found: C, 74.13; H, 4.08; N, 17.33.

1-(4-Fluorophenyl)-5-phenyl-3-(1,5-diphenyl-1*H*-pyrazol-3-yl)-1*H*-pyrazole-4-carbonitrile (6)

To a solution of compound **4** (0.39 g, 1 mmol) in EtOH (20 mL) phenylhydrazine (0.11 g, 1 mmol) was added. The reaction mixture was refluxed with stirring for 10 h then left to cool. The solid product was collected by filtration, washed with EtOH, dried, and finally recrystallized from EtOH to afford pale-yellow crystals of compound **6**. Yield 0.39 g (81 %); m.p.: 300–302 °C; IR (KBr, *v*, cm^{-1}): 2225

(CN), ^{1}H NMR (DMSO-d_6): δ 6.75 (s, 1H, CH-pyrazole), 7.04–7.51 (m, 19H, Ar–H). ^{13}C NMR (DMSO-d_6): δ 89.95, 100.11, 114.05, 114.92, 120.59, 125.48, 126.23, 127.18, 127.35, 127.96, 130.23, 145.63, 145.66, 147.10, 147.11, 149.69, 161.41. MS *m/z* (%): 481 [M^+] (72), 406 (17), 242 (25), 149 (80), 121 (15), 95 (47), 77 (100). Anal. Calcd. for $C_{31}H_{20}FN_5$ (481.52): C, 77.32; H, 4.19; N, 14.54. Found: C, 77.21; H, 4.27; N, 14.63.

3-(2-Amino-6-phenylpyrimidin-4-yl)-1-(4-fluorophenyl)-5-phenyl-1*H*-pyrazole-4-carbonitrile (7)

To a mixture of **4** (0.39 g, 1 mmol) and guanidine hydrochloride (0.1 g, 1 mmol) in EtOH (20 mL) was added anhydrous potassium carbonate (0.14 g, 1 mmol). The resulting mixture was refluxed for 6 h and allowed to cool to room temperature, then diluted with water (30 mL). The formed solid product was collected by filtration, washed with water, dried, and finally recrystallized from EtOH to afford 3-(2-amino-6-phenylpyrimidin-4-yl)-1-(4-fluorophenyl)-5-phenyl-1*H*-pyrazole-4-carbonitrile (**7**). Yield 0.32 g (74 %); m.p.: 167–168 °C; IR (KBr, *v*, cm^{-1}): 3430–3320 (NH_2), 2231 (CN), ^{1}H NMR (DMSO-d_6): δ 2.60 (s, 2H, NH_2; D_2O-exchangeable), 7.29–7.49 (m, 14H, Ar–H), 7.52 (s, 1H, pyrimidine-H). ^{13}C NMR (DMSO-d_6): δ 92.11, 112.96, 115.14, 117.11, 120.57, 120.63, 125.62, 127.34, 127.43, 127.47, 129.23, 129.64, 129.88, 130.27, 131.47, 134.24, 150.73, 160.46, 163.71. MS *m/z* (%): 432 [M^+] (6), 358 (16), 245 (100), 184 (19), 148 (31), 106 (41), 95 (7), 77 (41). Anal. Calcd. for $C_{26}H_{17}FN_6$ (432.45): C, 72.21; H, 3.96; N, 19.43. Found: C, 72.32; H, 3.86; N, 19.32.

1-(4-Fluorophenyl)-3-(1,2-dihydro-6-phenyl-2-thioxopyrimidin-4-yl)-5-phenyl-1*H*-pyrazole-4-carbonitrile (8)

Method A 1-(4-Fluorophenyl)-5-phenyl-3-((*E*)-3-phenylacryloyl)-1*H*-pyrazole-4-carbonitrile (**4**) (0.395 g, 1 mmol) was added, with stirring at room temperature, to EtONa solution (0.023 g sodium metal in 10 mL EtOH). Thiourea (0.076 g, 1 mmol) was added, and the reaction mixture was refluxed for 12 h. The reaction mixture was diluted with water and acidified with 1 N HCl to pH 6. The solid product was collected by filtration, washed with water, dried, and finally recrystallized from EtOH to give yellow crystals of compound **8** (0.285 g, 63 %).

Method B To a stirred solution of benzaldehyde (0.11 g, 1 mmol), 3-acetyl-1-(4-fluorophenyl)-5-phenyl-1*H*-pyrazole-4-carbonitrile (**3**) (0.305 g, 1 mmol), and thiourea (0.076 g, 1 mmol) in DMF (10 mL) a few drops of HCl were added. The reaction mixture was refluxed for 3 h and allowed to cool, then diluted with 50 mL ice-cold water. The solid product was filtered off, washed with water, dried, and finally recrystallized from EtOH to give yellow crystals of 1-(4-fluorophenyl)-3-(1,2-dihydro-6-phenyl-2-thioxopyrimidin-4-yl)-5-phenyl-1*H*-pyrazole-4-carbonitrile (**8**) (0.39 g, 86 %). M.p.: 214–216 °C. IR (KBr, *v*, cm^{-1}): 3416 (NH), 2230 (CN), ^{1}H NMR (DMSO-d_6): δ 7.28–7.58 (m, 14H, Ar–H), 8.19 (s, 1H, CH-pyrimidine), 8.31 (s, 1H, NH-pyrimidine-D_2O-exchangeable). ^{13}C NMR (DMSO-d_6): δ 93.11, 107.12, 113.11, 116.4, 116.5, 122.13, 126.2, 127.5, 128.8, 128.5, 128.7,

129.2, 132.3, 133.11, 135.4, 150.11, 152.1, 161.4, 164.6, 176.2, 177.1. MS *m/z* (%): 449 [M^+] (19), 393 (18), 257 (35), 224 (40), 118 (21), 95 (51), 77 (100). Anal. Calcd. for $C_{26}H_{16}FN_5S$ (449.5): C, 69.47; H, 3.59; N, 15.58. Found: C, 69.27; H, 3.69; N, 15.48.

1-(4-Fluorophenyl)-3-(2-(methylthio)-6-phenylpyrimidin-4-yl)-5-phenyl-1*H*-pyrazole-4-carbonitrile (9)

To a mixture of the thiopyrimidine **8** (0.45 g, 1 mmol) and sodium ethoxide (0.023 g Na in 20 mL EtOH), methyl iodide (0.14 g, 1 mmol) was added. The reaction mixture was refluxed for 11 h, then left to cool to room temperature. The reaction mixture was diluted with water and acidified with hydrochloride acid to pH 6. The solid product was collected by filtration, washed with water, dried, and finally recrystallized from EtOH to afford compound **9**. Yield 0.42 g (91 %); m.p.: 147–148 °C; IR (KBr, *v*, cm^{-1}): 2230 (CN), ^{1}H NMR (DMSO-d_6): δ 2.73 (s, 3H, CH_3), 7.33–7.59 (m, 14H, Ar–H), 8.27 (s, 1H, pyrimidine-H). MS *m/z* (%): 463 [M^+] (33), 417 (23), 269 (66), 198 (47), 141 (27), 105, 95 (46) (50), 77 (80), 57 (100). Anal. Calcd. for $C_{27}H_{18}FN_5S$ (463.53): C, 69.96; H, 3.91; N, 15.11. Found: C, 69.92; H, 3.87; N, 15.13.

Reaction of 1-(4-fluorophenyl)-5-phenyl-3-((*E*)-3-phenylacryloyl)-1*H*-pyrazole-4-carbonitrile (4) with some heterocyclic amines

Method A To a mixture of the pyrazole-4-carbonitrile (**4**) (0.392 g, 1 mmol) and the appropriate heterocyclic amine **10** or **12** (1 mmol) in EtOH (20 mL) was added a few drops of triethylamine. The resulting mixture was refluxed for 5 h, then allowed to cool to room temperature. The formed solid product was collected by filtration, washed with EtOH, dried, and finally recrystallized from EtOH to afford compounds **11** and **13**, respectively.

Method B A mixture of benzaldehyde (0.107 g, 1 mmol), 3-acetyl-1-(4-fluorophenyl)-5-phenyl-1*H*-pyrazole-4-carbonitrile (**3**) (0.21 g, 1 mmol), and the appropriate heterocyclic amine **10** or **12** (1 mmol) in dry DMF (5 mL) was refluxed for 4–7 h until the reaction completed [monitored by thin-layer chromatography (TLC)], and 30 mL ice-cold water was then added. The solid product was filtered off, washed with water, then dried. The crude product was purified by recrystallization from EtOH to afford compounds **11** and **13**, respectively.

1-(4-Fluorophenyl)-5-phenyl-3-(4-phenyl-1,4-dihydropyrimido[1.2-*a*]benzimidazol-2-yl)-1*H*-pyrazole-4-carbonitrile (11)

Yield: method A, 0.36 g (71 %); method B, 0.42 g (83 %); m.p.: 275–277 °C; IR (KBr, *v*, cm^{-1}): 3442 (NH), 2226 (CN), ^{1}H NMR (DMSO-d_6): **δ** 5.73 (d, 1H, CH, $J = 4.2$ Hz), 6.50 (d, 1H, CH, $J = 4.2$ Hz), 6.85–7.54 (m, 18H, Ar–H), 10.11 (s, 1H, NH, D_2O-exchangeable). ^{13}C NMR (DMSO-d_6): δ 56.23, 90.62, 100.39, 109.44, 113.74, 115.93, 116.24, 119.56, 121.50, 125.95, 126.41, 127.71, 127.83,

128.19, 128.93, 129.26, 129.34, 130.48, 131.56, 134.36, 141.11, 146.77, 147.20, 149.52, 160.03, 163.30. MS *m/z* (%): 508 [M^+] (6), 371 (16), 224 (100), 149 (19), 129 (31), 105 (41), 85 (7), 77 (41), 60 (100). Anal. Calcd. for $C_{32}H_{21}FN_6$ (508.55): C, 75.58; H, 4.16; N, 16.53. Found: C, 75.63; H, 4.22; N, 16.43.

1-(4-Fluorophenyl)-3-(5,8-dihydro-5-phenyl-[1,2,4]triazolo[4,3-*a*]pyrimidin-7-yl)-5-phenyl-1*H*-pyrazole-4-carbonitrile (13)

Yield 0.28 g (63 %); m.p.: 230–232 °C; IR (KBr, *v*, cm^{-1}): 3422 (NH), 2226 (CN), ^{1}H NMR (DMSO-d_6): δ 4.95 (d, 1H, CH), 6.11 (d, 1H, 2CH-pyrimidine), 6.95–7.44 (m, 14H, Ar–H), 8.25 (m, 1H, CH-triazole). 9.51 (s, 1H, NH, D_2O-exchangeable). ^{13}C NMR (DMSO-d_6): δ 55.11, 95.23, 105.2, 116.11, 118.2, 121.2, 127.3, 127.9, 128.0, 128.8, 129.0, 129.7, 133.3, 135.2, 139.2, 145.6, 146.3, 153.4, 161.2, 165.4, 167.3. MS *m/z* (%): 459 [M^+] (10), 457 (100), 228 (11), 129 (11), 95 (34), 77 (35). Anal. Calcd. for $C_{27}H_{18}FN_7$ (459.48): C, 70.58; H, 3.95; N, 21.34. Found: C, 70.63; H, 3.89; N, 21.31.

2-Amino-6-(4-cyano-1-(4-fluorophenyl)-5-phenyl-1*H*-pyrazol-3-yl)-4-phenylpyridine-3-carbonitrile (17)

To a mixture of compound **4** (0.392 g, 1 mmol) and malononitrile (0.066 g, 1 mmol) in EtOH (10 mL), ammonium acetate (0.62 g) was added. The reaction mixture was heated under reflux for 5 h, then poured into ice-cold water. The formed solid was collected by filtration, washed with water, dried, and finally recrystallized from EtOH/dioxane to afford compound **17**. Yield 0.31 g (67 %); m.p.: 200–202 °C; IR (KBr, *v*, cm^{-1}): 3470–3320 (NH_2), 2227 (CN), ^{1}H NMR (DMSO-d_6): δ 3.31 (s, 2H, NH_2; D_2O-exchangeable), 8.35 (s, 1H, pyridine-CH), 7.03–7.50 (m, 14H, Ar–H), ^{13}C NMR (DMSO-d_6): δ 92.22, 111.33, 111.5, 113.14, 115.01, 116.03, 117.43, 125.95, 127.17, 128.09, 128.44, 129.90, 130.19, 133.51, 149.96, 150.04, 160.11, 165.14, 166.81. MS *m/z* (%): 457 [M^+] (5), 443 (77), 263 (15), 148 (77), 104 (100) 77 (22). Anal. Calcd. for $C_{28}H_{16}FN_5O$ (457.46): C, 73.51; H, 3.53; N, 15.31. Found: C, 73.57; H, 3.49; N, 15.39.

Ethyl 6-(4-cyano-1-(4-fluorophenyl)-5-phenyl-1*H*-pyrazol-3-yl)-1,2-dihydro-2-oxo-4-phenylpyridine-3-carboxylate (20)

To a solution of the pyrazole-4-carbonitrile (**4**) (0.392 g, 1 mmol) and ethyl cyanoacetate (0.11 g, 1 mmol) in EtOH, sodium hydroxide (0.62 g) was added. The reaction mixture was heated under reflux for 5 h, then poured into ice-cold water and acidified with diluted HCl. The formed solid was collected by filtration, washed with water, dried, and finally recrystallized from EtOH/dioxane to afford ethyl 6-(4-cyano-1-(4-fluorophenyl)-5-phenyl-1*H*-pyrazol-3-yl)-1,2-dihydro-2-oxo-4-phenyl-pyridine-3-carboxylate (**20**).

Yield 0.35 g (69 %); m.p.: 175–177 °C; IR (KBr, *v*, cm^{-1}): 3420 (NH), 2238 (CN), 1743, 1695 (2C=O). ^{1}H NMR (DMSO-d_6): δ 1.45 (t, 3H, CH_3), 4.11 (q, 2H, CH_2), 6.95–7.39 (m, 14H, Ar–H), 8.01 (s, 1H, pyridine-H). 10.5 (s, 1H, NH; D_2O-

exchangeable), MS *m*/*z* (%): 505 [M^++1] (10), 504 [M^+] (5), 433 (3), 392 (99), 364 (26), 290 (37), 131 (31), 103 (95), 77 (100). Anal. Calcd. for $C_{30}H_{21}FN_4O_3$ (504.51): C, 71.42; H, 4.20; N, 11.11. Found: C, 71.39; H, 4.28; N, 11.17.

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