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Synthesis and antimicrobial evaluation of some heterocyclic compounds from 3-aryl-1-phenyl-1*H*-pyrazole-4-carbaldehydes

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Abstract: A new series of chalcones, pyrazolinyl-pyrazoles, pyrazole-4-carbaldehyde oximes, pyrazole-4-carbonitriles, 5-pyrazolyl-1,2,4-triazolidine-3-thiones, and Knoevenagel condensation products was synthesized from 3-aryl-1-phenyl-1*H*-pyrazole-4-carbaldehydes. Most reactions were carried out either without solvent or in the presence of water as a green solvent. The structure of synthesized compounds was characterized by spectral and elemental analysis. The synthesized compounds were tested *in vitro* for their antimicrobial activity against *Escherichia coli*, *Staphylococcus aureus*, and *Candida albicans* in comparison with imipenem (intravenous β-lactam antibiotic) and clotrimazole (antifungal medication) as reference drugs by using the agar diffusion technique. 3-Aryl-1-phenyl-1*H*-pyrazole-4-carbonitriles **8b**, **8c**, and **8d** showed significant antifungal activity against the fungus *C. albicans*.

Keywords: antimicrobial activity; chalcones; green solvent; pyrazole-4-carbaldehyde; pyrazole-4-carbonitriles; solvent-free.

1 Introduction

Pyrazole nucleus is a unique structural scaffold that acts as an interesting template for combinatorial as well as medicinal chemistry [1–6]. Many pyrazole derivatives (Fig. 1) have already found their application as nonsteroidal anti-inflammatory drugs clinically, such as antipyrine or phenazone, metamizole or dipyrone, aminopyrine or aminophenazone, phenylbutazone, sulfinpyrazone, and oxyphenbutazone. Moreover, a number of biologically active compounds have been synthesized from pyrazole-4-carbaldehydes. These compounds showed antimicrobial [7], antitumor, antiangiogenic [8], antiviral [9], antitubercular [10], and antiparasitic activity [11]. On the other hand, the use of water as environmentally benign solvent and solvent-free reactions represent very powerful green chemical procedures from both the economic and synthetic points of view [12]. These methods may reduce the burden of organic solvent disposal. The use of water in organic synthesis represents a remarkable benefit since it is an innocuous, non-flammable, inexhaustible, and abundantly available solvent. Water as the reaction medium is immiscible with most organic compounds and thus offers ease of product isolation.

In combination with these findings, the aim of the present work was to synthesize some heterocyclic compounds from 3-aryl-1-phenyl-1*H*-pyrazole-4-carbaldehydes either in water or under solvent-free conditions with evaluation of their antimicrobial activities against some microorganisms.

2 Results and discussion

In our previous work, a number of chalcone derivatives were obtained by Claisen-Schmidt condensation of aliphatic or aromatic ketones with aromatic aldehydes in the presence of a base [13]. In this work 3-aryl-1-phenyl-1*H*-pyrazole-4-carbaldehydes (**2**) were prepared in good yields by Vilsmeier-Haack reaction of 1-phenyl-2-(1-phenylethylidene)hydrazine (**1**) with $POCl_3$ in dimethylformamide (DMF) (Scheme 1) [14–16]. Treatment of **2** with substituted acetophenones in the presence of potassium hydroxide gave chalcone derivatives **3a–3d** in good yields. Their infrared (IR) spectra showed absorption bands at 1647–1660, 1583–1600, and 1506–1534 cm^{-1} due to C=O, C=N, and C=C groups, respectively. The ^1H NMR spectra of **3a–3d** showed a singlet at $\delta = 8.34–8.41$ ppm for the 5-H of pyrazole ring, a doublet at $\delta = 7.87–8.00$ ppm for the β-vinylic proton, and the aromatic protons in the region of $\delta = 7.29–8.37$ ppm. In case of **3d** two geometrical isomers (*E* and *Z*) were obtained in a ratio of 10:1. The β-vinylic

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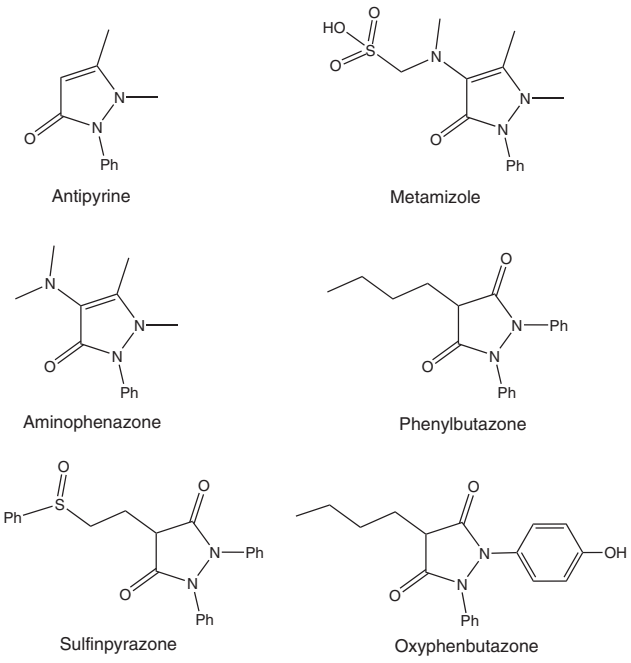
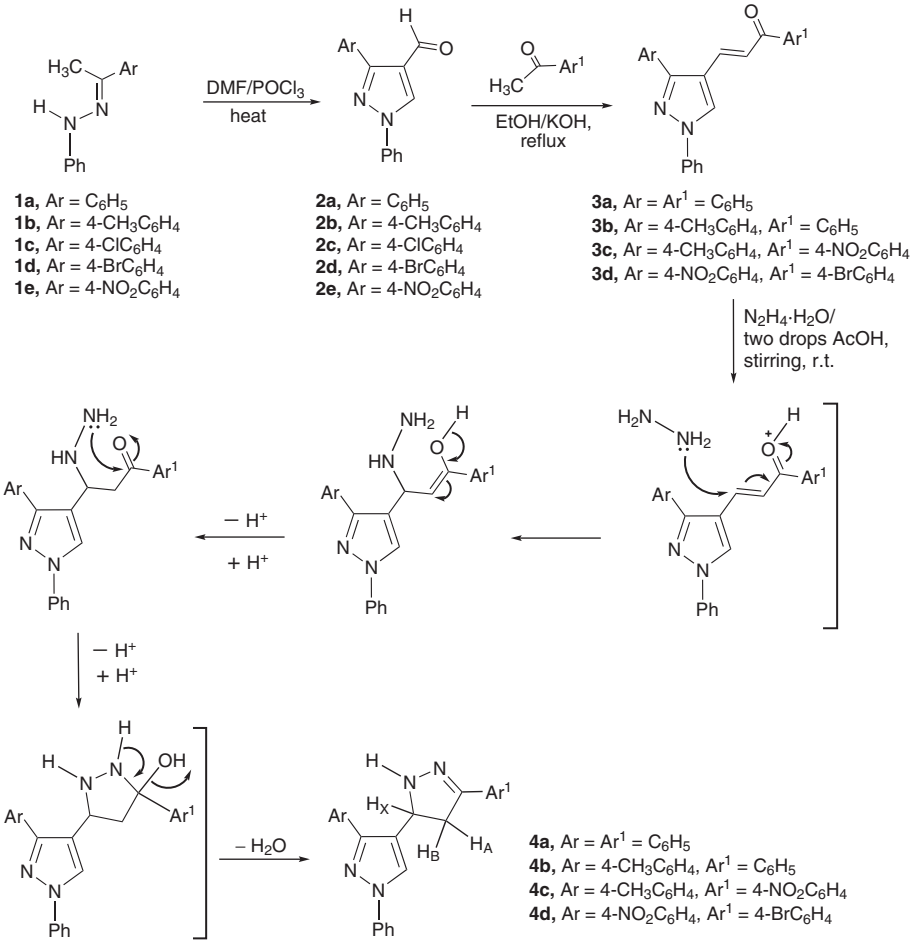


Fig. 1: Some examples of marketed drugs containing pyrazole moiety.

proton of the *E*-isomer appeared at a relatively higher field ($\delta = 7.89$ ppm) than the *Z*-isomer ($\delta = 8.00$ ppm).

Solvent-free reaction of chalcone derivatives **3a–3d** with hydrazine hydrate in the presence of a catalytic amount of glacial acetic acid was achieved at room temperature to give 3-aryl-4-(3-aryl-4,5-dihydro-1*H*-pyrazol-5-yl)-1-phenyl-1*H*-pyrazoles (**4a–4d**) in 78–92% yields. The reaction time was reduced from 9–10 to 4–6 h, when it compared with the classical heating method [17]. The ^{1}H NMR spectra of **4a–4d** showed a singlet at $\delta = 7.78$–8.35 ppm due to 5-H of pyrazole ring, two signals for two diastereotopic protons of pyrazoline ring (CH_A and CH_B) at $\delta = 3.11$–3.28 and 3.50–3.89 ppm, and a triplet or doublet of doublets at $\delta = 5.25$–5.55 ppm for the CH_X proton due to *vicinal* coupling with two magnetically non-equivalent protons of methylene group at position 4 of pyrazoline ring.

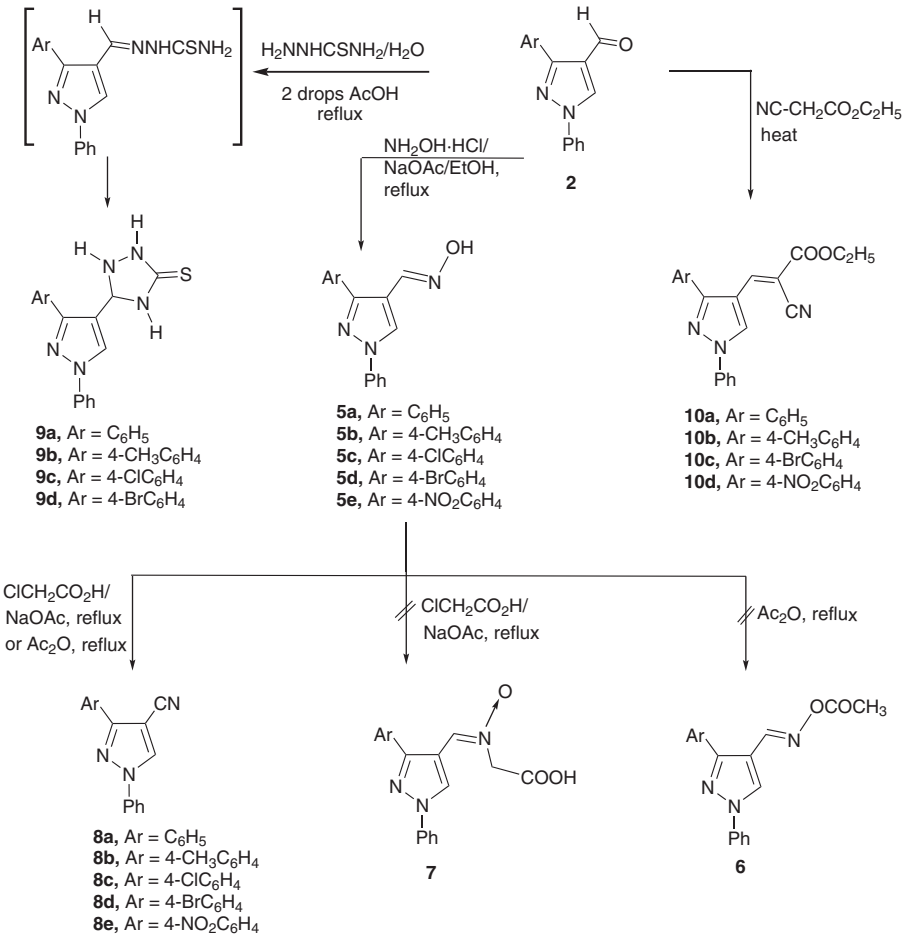
Compounds **2a–2e** were easily converted into the corresponding oximes **5a–5e** by treatment with hydroxylamine. The literature survey revealed that ^{1}H NMR spectra is one of the most reliable methods for structure



Scheme 1: Synthesis of pyrazolinyl-pyrazoles under solvent-free conditions.

determination of isomeric oximes since the difference between chemical shifts of protons in the aldoxime group ($\delta_{OH}-\delta_{CH}$) is specifically for *syn* and *anti* isomers [18]. The reported difference was ~3.0 ppm for *syn* and ~4.0 ppm for *anti* isomers. In the ^{1}H NMR spectrum of 1,3-diphenyl-1*H*-pyrazole-4-carbaldehyde oxime (**5a**), there was only one signal for OH group proton, and the $\delta_{OH}-\delta_{CH}$ difference was found to be 2.59 ppm, which is typical of *syn* isomer. On the other hand, it was reported that *syn*-aldoximes reacted with acetic anhydride to form acetyl derivatives **6**, while *anti* isomers under similar conditions were converted into nitriles *via* elimination of water [19]. Moreover, nitrone derivative **7** was obtained on treatment of *syn* or *anti*-aldoxime with haloacetic acid [20]. However, we found that the reaction of oximes **5a–5e** with either acetic anhydride or 2-chloroacetic acid gave exclusively pyrazole-4-carbonitriles **8a–8e** (Scheme 2). Thus, compound **5** behaved like *anti*-aldoximes, and the assignment of oximes to be *syn* or *anti* isomers on the basis of ^{1}H NMR data is not absolutely reliable.

A very limited number of synthetic methods were reported for the preparation of 5-aryl-1,2,4-triazolidine-3-thiones [21–24]. However, 1,2,4-triazolidine-3-thiones bearing a pyrazole nucleus at position 5 have never been reported yet. In the present work, heating of **2** with thiosemicarbazide in water as a green solvent afforded the 5-(3-aryl-1-phenyl-1*H*-pyrazol-4-yl)-1,2,4-triazolidine-3-thiones (**9a–9d**) in excellent yields. The respective thiosemicarbazones have never been isolated under these reaction conditions. This result was evidenced from spectral data. The IR spectrum of compound **9b** showed absorption bands at 3305, 3297, and 3158 cm^{-1} due to NH groups; which were further confirmed by the presence of three D_2O-exchangeable protons at $\delta = 7.78$, 8.23, and 11.31 ppm in its ^{1}H NMR spectrum. It also showed two singlet peaks at $\delta = 8.18$ and 9.14 ppm for the 5-H of triazolidine ring and 5-H of pyrazole ring, respectively. The structure of **9b** was also proved by ^{13}C NMR, which exhibited signals at $\delta = 117.70$ and 178.08 ppm due to C-5 of triazolidine ring and thiocarbonyl (C=S) group, respectively.



Scheme 2: Synthetic routes of pyrazole derivatives from pyrazole-4-carbaldehydes.

The advantages of this eco-friendly reaction are the ease of reaction work-up and excellent yield of products.

Knoevenagel condensation is one of the most important C–C bond-forming reactions. The reaction is catalyzed by bases or acids, and in many of these methods relatively harsh conditions and expensive reagents are involved. We report herein a simple eco-friendly method for Knoevenagel condensation of **2** with ethyl 2-cyanoacetate without using a solvent and basic or acidic catalyst to give ethyl 3-(3-aryl-1-phenyl-1*H*-pyrazol-4-yl)-2-cyanopropenoate (**10a–10d**) in 83–97% yields. The IR spectra of **10a–10d** showed stretching vibrational bands at 2218–2219 and 1722–1724 cm^{-1} characteristic for C≡N and C=O groups, respectively. The ^1H NMR spectrum of **10a** showed a singlet at $\delta = 9.14$ ppm for 5-H of pyrazole ring, a singlet at $\delta = 8.13$ ppm for an olefinic (CH=C) proton, and a triplet and quartet at $\delta = 1.38$ and 4.34 ppm for the ethyl group in addition to aromatic protons which resonated in $\delta = 7.39$–7.84 ppm. The structure of newly synthesized compounds was supported by their analytical and spectral data (Experimental section).

The synthesized compounds were tested *in vitro* for their antimicrobial activities against *Escherichia coli* (ATCC-8739), *Staphylococcus aureus* (ATCC-6538P), and *Candida albicans* (ATCC-2091) by agar well-diffusion method using clotrimazole and imipenem as standard drugs [25, 26]. The results are shown in Tables 1 and 2 as growth inhibition zones (IZ) in millimeters (mm), minimal inhibitory concentrations (MIC) in micrograms per milliliter (μg mL^{-1}), and percentage of inhibition. The pyrazolinyl-pyrazole **4d** and pyrazole-4-carbonitrile **8c** exhibited low activity against *E. coli*. Compound **8d** showed moderate activity against *S. aureus*. On the other hand, the tested compounds showed growth IZ against *C. albicans* in the following ranking: **8d** > **8b** = **8c** > **9d** > **9c** = **10d**. It is clear that pyrazole-4-carbonitriles **8b**, **8c**, and **8d** have promising activity against *C. albicans*. Furthermore, 5-pyrazolyl-1,2,4-triazolidine-3-thiones **9d** bearing a bromophenyl substituent at position 3 of the pyrazole ring possessed moderate activity, while compounds **9c** and **10d** had the lowest activity against this strain. The MICs and inhibition level of the active compounds ranged at 31.25–125 μg mL^{-1} and 41.17–82.35%, respectively.

3 Experimental section

3.1 Materials and measurements

Commercially available chemicals were purchased from Sigma Aldrich. Melting points were measured in open capillary tubes using an Electro-thermal apparatus IA9100 and are uncorrected. Microanalyses were performed on an elemental Euro EA 3000 analyzer at the

Table 1: *In vitro* antifungal activity of synthetic compounds against *C. albicans*.[a]

Compound	IZ (mm)	MIC (μg mL^{-1})	% Inhibition	Compound	IZ (mm)	MIC (μg mL^{-1})	% Inhibition
8b	25	125.0	70.58	**9c**	20	31.25	41.17
8c	25	62.5	70.58	**9d**	23	62.50	58.82
8d	27	62.5	82.35	**10d**	20	62.50	41.17
DMF	13	–	–	Clotrimazole	17	–	–

[a]The diameter of growth inhibition zone (IZ) is accurately measured in three different directions, and its mean was calculated; % inhibition = [IZ(testing compound) – IZ(DMF)]/[IZ(clotrimazole)] × 100.

Table 2: *In vitro* antibacterial activity of synthetic compounds against *S. aureus* and *E. coli*.[a]

S. aureus				*E. coli*			
Compound	**IZ (mm)**	**MIC (μg mL^{-1})**	**% Inhibition**	**Compound**	**IZ (mm)**	**MIC (μg mL^{-1})**	**% Inhibition**
8d	20	62.5	40.00	**4d**	16	62.5	23.07
9c	15	62.5	23.33	**8c**	18	62.5	30.76
9d	15	62.5	23.33	DMF	10	–	–
10d	11	62.5	10.00	Imipenem	26	–	–
DMF	8.0	–	–				
Imipenem	30	–	–				

[a]See footnote a of Table 1 for growth inhibition zone and calculation of % inhibition.

Regional Center for Mycology and Biotechnology, Al-Azhar University, Egypt. IR spectra were recorded using the potassium bromide disk on a Perkin Elmer Spectrum RX I and Bruker Tensor 37 FTIR spectrometers. ^{1}H NMR and ^{13}C NMR spectra were measured on a Jeol EAC 500 MHz spectrophotometer. The chemical shifts are reported in δ units, and coupling constants (J) are given in hertz. Reaction time was monitored by thin layer chromatography (TLC) using Alugram Sil G UV_{254} silica gel plates, and chloroform-ethanol (9:1 or 19:1) was used as eluents. The spots were detected by using UV light absorption. Antimicrobial tests were measured in the Pharmaceutical Microbiology Department, Faculty of Pharmacy, Alexandria University.

3.2 General procedure for synthesis of chalcones 3a–3d

A mixture of carbaldehyde **2a**, **2b**, or **2e** (5 mmol) and acetophenone derivative (5 mmol) was dissolved in ethanol (15 mL), and then aqueous potassium hydroxide (20%, 1.0 mL) was added. The reaction mixture was heated under reflux for 3–5 h. It was kept to attain ambient temperature, and the separated solid was filtered, washed with water, dried, and recrystallized from a mixture of chloroform and ethanol.

3.2.1 3-(1,3-Diphenyl-1*H*-pyrazol-4-yl)-1-phenylprop-2-en-1-one (3a)

Yellow crystals, yield 77% (1.349 g), m. p. 140–141°C. – IR (KBr): ν = 1659 (C=O), 1592 (C=N), 1533 (C=C) cm^{-1}. – ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.36 (s, 1 H, 5-H of pyrazole ring), 7.95 (d, J = 8 Hz, 2 H, Ar-H), 7.88 (d, J = 16 Hz, 1 H, C*H*=CHCO), 7.79 (d, J = 8 Hz, 2 H, Ar-H), 7.70–7.72 (m, 2 H, Ar-H), 7.34–7.58 (m, 12 H, Ar-H and CH=C*H*CO). – $C_{24}H_{18}N_2O$ (350.41): calcd. C 82.26, H 5.18, N 7.99; found C 82.33, H, 5.09, N 8.04.

3.2.2 1-Phenyl-3-[1-phenyl-3-(*p*-tolyl)-1*H*-pyrazol-4-yl] prop-2-en-1-one (3b)

Yellow crystals, yield 85% (1.548 g), m. p. 170–172°C. – IR (KBr): ν = 1647 (C=O), 1591 (C=N), 1534 (C=C) cm^{-1}. – ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.34 (s, 1 H, 5-H of pyrazole ring), 7.95 (d, J = 7 Hz, 2 H, Ar-H), 7.87 (d, J = 16 Hz, 1 H, C*H*=CHCO), 7.79 (d, J = 7 Hz, 2 H, Ar-H), 7.29–7.61 (m, 11 H, Ar-H and CH=C*H*CO), 2.43 (s, 3 H, CH_3). – $C_{25}H_{20}N_2O$ (364.44): calcd. C 82.39, H 5.53, N 7.69; found C 82.44, H 5.46, N 7.71.

3.2.3 1-(*p*-Nitrophenyl)-3-[1-phenyl-3-(*p*-tolyl)-1*H*-pyrazol-4-yl]prop-2-en-1-one (3c)

Yellow crystals, yield 72% (1.473 g), m. p. 190–191°C. – IR (KBr): ν = 1660 (C=O), 1583 (C=N), 1525 (C=C) cm^{-1}. – ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.37 (s, 1H, 5-H of pyrazole ring), 8.30 (d, J = 8 Hz, 2 H, Ar-H), 8.06 (d, J = 8 Hz, 2 H, Ar-H), 7.91 (d, J = 15 Hz, 1 H, C*H*=CHCO), 7.78 (d, J = 8 Hz, 2 H, Ar-H), 7.57 (d, J = 8 Hz, 2 H, Ar-H), 7.48 (t, J = 8 Hz, 2 H, Ar-H), 7.34 (t, J = 8 Hz, 1 H, Ar-H), 7.28–7.31 (m, 3 H, Ar-H and CH=C*H*CO), 2.43 (s, 3 H, CH_3). – $C_{25}H_{19}N_3O_3$ (409.44): calcd. C 73.34, H 4.68, N 10.26; found C 73.33, H 4.67, N 10.24.

3.2.4 (*E*/*Z*)-1-(*p*-Bromophenyl)-3-[3-(*p*-nitrophenyl)-1-phenyl-1*H*-pyrazol-4-yl]prop-2-en-1-one (3d)

Colorless – yellow crystals, yield 89% (2.11 g), m. p. 210–212°C. – IR (KBr): ν = 1659 (C=O), 1600 (C=N), 1506 (C=C) cm^{-1}. – ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.39, 8.41 (2s, 2 H, 5-H of pyrazole ring), 7.89 (d, J = 14 Hz, 1 H, C*H*=CHCO of *E*-isomer), 8.00 (d, J = 9 Hz, 1 H, C*H*=CHCO of *Z*-isomer), [8.35 (d, J = 8 Hz, Ar-H), 8.28 (d, J = 8 Hz, Ar-H), 8.06 (d, J = 8 Hz, Ar-H), 7.90 (d, J = 8 Hz, Ar-H), 7.85–7.87 (m, Ar-H), 7.80 (d, J = 8 Hz, Ar-H), 7.74 (d, J = 8 Hz, Ar-H), 7.68 (d, J = 8 Hz, Ar-H), 7.62–7.65 (m, Ar-H), 7.54–7.57 (m, Ar-H), 7.52 (t, J = 8 Hz, Ar-H), 7.42–7.47 (m, Ar-H and CH=C*H*CO), 7.32–7.37 (m, Ar-H and CH=C*H*CO), total integral = 28 H]. – ^{13}C NMR (125 MHz, [D_6]DMSO): δ = 118.88, 119.43, 122.49, 124.70, 127.89, 128.15, 129.89, 130.04, 130.33, 130.80, 132.44, 134.33, 137.02, 138.82, 139.27, 147.90 (Ar-C, CH=CH, C-4 and C-5 of pyrazole ring), 151.08 (C-3 of pyrazole ring), 188.22 (C=O).

3.3 General procedure for synthesis of pyrazolinyl-pyrazoles 4a–4d

A mixture of chalcone derivatives **3a**–**3d** (1.0 mmol), hydrazine hydrate (5 mL, 80%) and two drops of glacial acetic acid was stirred at room temperature for 4–6 h until the reaction was completed; the reaction progress was monitored by TLC using chloroform-ethanol (9:1). The resulting mixture was added to cold water (20 mL) with

vigorous stirring for 5 min. The separated solid was filtered and recrystallized from a mixture of chloroform and ethanol.

3.3.1 1,3-Diphenyl-4-(3-phenyl-4,5-dihydro-1*H*-pyrazol-5-yl)-1*H*-pyrazole (4a)

Yellow crystals, yield 92% (0.334 g), m. p. 218–220°C. – IR (KBr): $\nu = 3440$ (NH), 1593 (C=N), 1497 (C=C) cm^{-1}. – ^1H NMR (500 MHz, $CDCl_3$): $\delta = 7.81$ (d, $J = 8$ Hz, 2 H, Ar-H), 7.78 (s, 1 H, 5-H of pyrazole ring), 7.73 (d, $J = 8$ Hz, 2 H, Ar-H), 7.64 (d, $J = 8$ Hz, 2 H, Ar-H), 7.51 (t, $J = 8$ Hz, 2 H, Ar-H), 7.19–7.45 (m, 5 H, Ar-H and NH), 7.10 (d, $J = 8$ Hz, 2 H, Ar-H), 6.79 (t, $J = 8$ Hz, 1 H, Ar-H), 5.52, 5.55 (dd, $J_{AX} = 6$ Hz, $J_{BX} = 12$ Hz, 1 H, pyrazoline-H_X), 3.83, 3.89 (dd, $J_{AB} = 16$ Hz, $J_{BX} = 12$ Hz, 1 H, pyrazoline-H_B), 3.24, 3.28 (dd, $J_{AB} = 16$ Hz, $J_{AX} = 6$ Hz, 1 H, pyrazoline-H_A). – $C_{24}H_{20}N_4$ (364.44): calcd. C 79.10, H 5.53, N 15.37; found C 79.17, H 5.44, N 15.36.

3.3.2 1-Phenyl-4-(3-phenyl-4,5-dihydro-1*H*-pyrazol-5-yl)-3-(*p*-tolyl)-1*H*-pyrazole (4b)

Pale yellow crystals, yield 79% (0.298 g), m. p. 210–211°C. – IR (KBr): $\nu = 3438$ (NH), 1597 (C=N), 1501 (C=C) cm^{-1}. – ^1H NMR (500 MHz, $CDCl_3$): $\delta = 8.18$ (s, 1 H, 5-H of pyrazole ring), 7.71 (d, $J = 8$ Hz, 2 H, Ar-H), 7.67–7.69 (m, 2 H, Ar-H), 7.59 (d, $J = 8$ Hz, 2 H, Ar-H), 7.41 (d, $J = 8$ Hz, 2 H, Ar-H), 7.34–7.37 (m, 2 H, Ar-H), 7.24–7.27 (m, 4 H, Ar-H), 5.25 (t, $J = 10$ Hz, 1 H, pyrazoline-H_X), 3.75 (broad s, 1 H, NH), 3.53, 3.58 (dd, $J_{AB} = 17$ Hz, $J_{BX} = 10$ Hz, 1 H, pyrazoline-H_B), 3.16, 3.19 (dd, $J_{AB} = 17$ Hz, $J_{AX} = 6$ Hz, 1 H, pyrazoline-H_A), 2.39 (s, 3H, CH_3). – ^{13}C NMR (125 MHz, [D_6]DMSO): $\delta = 21.42$ (CH_3), 40.08 (C-4 of pyrazoline ring), 56.58 (C-5 of pyrazoline ring), 113.84, 118.63, 119.51, 123.33, 126.32, 126.80, 127.50, 128.38, 129.13, 129.26, 129.39, 129.89, 130.00, 130.38, 132.88, 138.13, 139.75, 145.21 (Ar-C, C-4 and C-5 of pyrazole ring), 148.20 (C-3 of pyrazole ring), 150.24 (C-3 of pyrazoline ring). – $C_{25}H_{22}N_4$ (378.47): calcd. C 79.34, H 5.86, N 14.80; found C 79.39, H 5.79, N 14.86.

3.3.3 4-[3-(*p*-Nitrophenyl)-4,5-dihydro-1*H*-pyrazol-5-yl]-1-phenyl-3-(*p*-tolyl)-1*H*-pyrazole (4c)

Pale yellow crystals, yield 81% (0.342 g), m. p. 213–215°C. – IR (KBr): $\nu = 3341$ (NH), 1595 (C=N), 1509 (C=C) cm^{-1}. – ^1H NMR (500 MHz, $CDCl_3$): $\delta = 8.20$ (d, $J = 8$ Hz, 2 H, Ar-H), 8.06 (s, 1 H, 5-H of pyrazole ring), 7.77 (d, $J = 8$ Hz, 2 H, Ar-H), 7.70 (d, $J = 8$ Hz, 2 H, Ar-H), 7.57 (d, $J = 8$ Hz, 2 H, Ar-H), 7.41 (t, $J = 8$ Hz, 2 H, Ar-H), 7.25–7.27 (m, 3 H, Ar-H), 7.17 (broad s, 1 H, NH), 5.25 (t, $J = 8$ Hz, 1 H, pyrazoline-H_X), 3.50–3.52 (m, 1 H, pyrazoline-H_B), 3.11–3.13 (m, 1 H, pyrazoline-H_A), 2.39 (s, 3 H, CH_3). – $C_{25}H_{21}N_5O_2$ (423.47): calcd. C 70.91, H 5.00, N 16.54; found C 70.94, H 4.93, N 16.61.

3.3.4 4-[3-(*p*-Bromophenyl)-4,5-dihydro-1*H*-pyrazol-5-yl]-3-(*p*-nitrophenyl)-1-phenyl-1*H*-pyrazole (4d)

Pale yellow crystals, yield 78% (0.380 g), m. p. 206–208°C. – IR (KBr): $\nu = 3308$ (NH), 1595 (C=N), 1506 (C=C) cm^{-1}. – ^1H NMR (500 MHz, $CDCl_3$): $\delta = 8.35$ (s, 1 H, 5-H of pyrazole ring), 8.28 (d, $J = 9$ Hz, 2 H, Ar-H), 7.95 (d, $J = 9$ Hz, 2 H, Ar-H), 7.71 (d, $J = 8$ Hz, 2 H, Ar-H), 7.28-7.69 (m, 8 H, Ar-H and NH), 5.31 (t, $J = 9$ Hz, 1 H, pyrazoline-H_X), 3.58, 3.63 (dd, $J_{AB} = 17$ Hz, $J_{BX} = 10$ Hz, 1 H, pyrazoline-H_B), 3.19, 3.25 (dd, $J_{AB} = 17$ Hz, $J_{AX} = 7$ Hz, 1 H, pyrazoline-H_A). – $C_{24}H_{18}BrN_5O_2$ (488.34): calcd. C 59.03, H 3.72, Br 16.36, N 14.34; found C 58.99, H 3.67, Br 16.37, N 14.31.

3.4 General procedure for synthesis of pyrazole-4-carbaldehyde oximes 5a–5e

To a solution of **2a**–**2e** (1.0 mmol) in ethanol (20 mL), hydroxylamine hydrochloride (0.069 g, 1.0 mmol) and anhydrous sodium acetate (0.082 g, 1.0 mmol) were added. The mixture was heated under reflux for 5 h; the reaction progress was monitored by TLC using chloroform-ethanol (9:1). The product that separated out on cooling was filtered and recrystallized from ethanol.

3.4.1 *Anti*-1,3-diphenyl-1*H*-pyrazole-4-carbaldehyde oxime (5a) [27]

Colorless crystals, yield 88% (0.231 g), m. p. 155–157°C. – IR (KBr): $\nu = 3265$ (OH), 1597 (C=N), 1534 (C=C) cm^{-1}. – ^1H NMR (500 MHz, [D_6]DMSO): $\delta = 8.97$ (s, 1 H, CH=N), 7.79 (d, $J = 8$ Hz, 2 H, Ar-H), 7.68 (d, $J = 8$ Hz, 2 H, Ar-H), 7.58 (s, 1 H, 5-H of pyrazole ring), 7.43–7.51 (m, 5 H, Ar-H), 7.31–7.35 (m, 1 H, Ar-H), 6.38 (broad s, D_2O-exchangeable, 1 H, OH). ^{13}C NMR (125 MHz, [D_6]DMSO): $\delta = 111.96$, 119.59, 127.52, 129.18, 129.35, 130.17, 131.89, 132.46, 137.37 (Ar-C, C-4 and C-5 of pyrazole ring), 139.64 (CH=N), 152.53 (C-3 of pyrazole ring). – $C_{16}H_{13}N_3O$ (263.29): calcd. C 72.99, H 4.98, N 15.96; found C 73.05, H 5.01, N 15.92.

Aldoximes **5b**–**5e** [27] were formed as a mixture of *syn* and *anti* isomers. Their proton signals appeared in the region of $\delta = 6.35$–8.97 ppm, but the assignment was not

possible because they were highly overlapped with each other. They were used in the next step without further purification.

3.5 General procedure for synthesis of pyrazole-4-carbonitriles 8a–8e

Method a. A solution of aldoximes **5a**–**5e** (1.0 mmol) and anhydrous sodium acetate (0.164 g, 2 mmol) in acetic anhydride (10 mL) was heated on a boiling water bath for 3 h. The mixture was kept to cool and poured onto crushed ice (20 g) with occasional stirring. The separated product was filtered off, washed repeatedly with water, and recrystallized from a mixture of chloroform and ethanol.

Method b. A solution of **5a**–**5e** (1.0 mmol), 2-chloroacetic acid (0.094 g, 1.0 mmol) and anhydrous sodium acetate (0.082 g, 1.0 mmol) in DMF (10 mL) was heated under reflux for 17–21 h. The mixture was processed as above to give identical products to that obtained from method a.

3.5.1 1,3-Diphenyl-1*H*-pyrazole-4-carbonitrile (8a) [28]

Colorless crystals, yield 81% (0.198 g, method a), 76% (0.186 g, method b), m. p. 125–127°C. – IR (KBr): $\nu = 2227$ (C≡N), 1597 (C=N), 1532 (C=C) cm^{-1}. – ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 8.36$ (s, 1 H, 5-H of pyrazole ring), 8.07 (d, $J = 8$ Hz, 2 H, Ar-H), 7.74 (d, $J = 8$ Hz, 2 H, Ar-H), 7.41–7.54 (m, 6 H, Ar-H). – $C_{16}H_{11}N_3$ (245.28): calcd. C 78.35, H 4.52, N 17.13; found C 78.41, H 4.44, N 17.17.

3.5.2 3-(*p*-Tolyl)-1-phenyl-1*H*-pyrazole-4-carbonitrile (8b) [29]

Colorless crystals, yield 77% (0.199 g, method a), 67% (0.173 g, method b), m. p. 102–104°C. – IR (KBr): $\nu = 2223$ (C≡N), 1596 (C=N), 1530 (C=C) cm^{-1}. – ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 8.34$ (s, 1H, 5-H of pyrazole ring), 7.96 (d, $J = 8$ Hz, 2 H, Ar-H), 7.73 (d, $J = 8$ Hz, 2 H, Ar-H), 7.50 (t, $J = 8$ Hz, 2 H, Ar-H), 7.38 (t, $J = 8$ Hz, 1 H, Ar-H), 7.29 (d, $J = 8$ Hz, 2 H, Ar-H), 2.42 (s, 3 H, CH_3). – $C_{17}H_{13}N_3$ (259.31): calcd. C 78.74, H 5.05, N 16.20; found C 78.91, H 5.07, N 16.21.

3.5.3 3-(*p*-Chlorophenyl)-1-phenyl-1*H*-pyrazole-4-carbonitrile (8c) [29]

Colorless crystals, yield 72% (0.2 g, method a), 75% (0.209 g, method b), m. p. 138–140°C. – IR (KBr): $\nu = 2224$ (C≡N), 1599 (C=N), 1530 (C=C) cm^{-1}. – ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 8.36$ (s, 1 H, 5-H of pyrazole ring), 8.02 (d, $J = 8$ Hz, 2 H, Ar-H), 7.73 (d, $J = 8$ Hz, 2 H, Ar-H), 7.51 (t, $J = 8$ Hz, 2 H, Ar-H), 7.45 (d, $J = 8$ Hz, 2 H, Ar-H), 7.40 (t, $J = 8$ Hz, 1 H, Ar-H). – ^{13}C NMR (125 MHz, [D_6]DMSO): $\delta = 91.16$ (C-4 of pyrazole ring), 114.66 (C≡N), 119.85, 128.59, 129.47, 129.75, 130.27, 134.98, 136.93, 138.80 (Ar-C, C-5 of pyrazole ring), 151.96 (C-3 of pyrazole ring). – $C_{16}H_{10}ClN_3$ (279.72): calcd. C 68.70, H, 3.60, Cl 12.67, N 15.02; found C 68.61, H 3.54, Cl 12.91, N 14.93.

3.5.4 3-(*p*-Bromophenyl)-1-phenyl-1*H*-pyrazole-4-carbonitrile (8d)

Colorless crystals, yield 80% (0.259 g, method a), 83% (0.268 g, method b), m. p. 132–134°C. – IR (KBr): $\nu = 2224$ (C≡N), 1639 (C=N), 1598 (C=C) cm^{-1}. – ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 8.37$ (s, 1 H, 5-H of pyrazole ring), 7.95 (d, $J = 8$ Hz, 2 H, Ar-H), 7.73 (d, $J = 8$ Hz, 2 H, Ar-H), 7.61 (d, $J = 8$ Hz, 2 H, Ar-H), 7.51 (t, $J = 8$ Hz, 2 H, Ar-H), 7.41 (t, $J = 8$ Hz, 1 H, Ar-H). – ^{13}C NMR (125 MHz, [D_6]DMSO): $\delta = 91.16$ (C-4 of pyrazole ring), 114.66 (C≡N), 119.89, 123.71, 128.65, 128.84, 129.83, 130.31, 132.69, 136.98, 138.82 (Ar-C, C-5 of pyrazole ring), 152.06 (C-3 of pyrazole ring). – $C_{16}H_{10}BrN_3$ (324.17): calcd. C 59.28, H 3.11, Br 24.65, N 12.96; found C 59.24, H 3.03, Br 24.71, N 13.01.

3.5.5 3-(*p*-Nitrophenyl)-1-phenyl-1*H*-pyrazole-4-carbonitrile (8e) [28]

Colorless crystals, yield 71% (0.205 g, method a), 73% (0.211 g, method b), m. p. 154–156°C. – IR (KBr): $\nu = 2229$ (C≡N), 1600 (C=N), 1534 (C=C) cm^{-1}. – ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 8.43$ (s, 1 H, 5-H of pyrazole ring), 8.33 (d, $J = 8$ Hz, 2 H, Ar-H), 8.27 (d, $J = 8$ Hz, 2 H, Ar-H), 7.75 (d, $J = 8$ Hz, 2 H, Ar-H), 7.54 (t, $J = 8$ Hz, 2 H, Ar-H), 7.44 (t, $J = 8$ Hz, 1 H, Ar-H). – $C_{16}H_{10}N_4O_2$ (290.28): calcd. C 66.20, H 3.47, N, 19.30; found C 66.19, H 3.47, N 19.26.

3.6 General procedure for synthesis of 5-pyrazolyl-1,2,4-triazolidine-3-thiones 9a–9d

A suspension of **2a–2d** (1.0 mmol) in water (20 mL) was treated with thiosemicarbazide (0.091 g, 1.0 mmol) and two drops of glacial acetic acid. The mixture was heated under reflux for 3 h; the completion of the reaction was checked by TLC using chloroform-ethanol (9:1). The product that

separated out on cooling was filtered, washed with water, dried, and recrystallized from a mixture of chloroform and ethanol.

3.6.1 5-(1,3-Diphenyl-1*H*-pyrazol-4-yl)-1,2,4-triazolidine-3-thione (9a)

Colorless crystals, yield 95% (0.304 g), m. p. 195–196°C. – IR (KBr): $\nu = 3295$ (NH), 3264 (NH), 3147 (NH), 1597 (C=N), 1537 (C=C), 1216 (C=S) cm^{-1}. – ^1H NMR (500 MHz, [D_6]DMSO): $\delta = 11.31$ (s, 1 H, NH, D_2O-exchangeable), 9.17 (s, 1 H, 5-H of pyrazole ring), 8.24 (s, 1 H, NH, D_2O-exchangeable), 8.19 (s, 1 H, 5-H of triazolidine ring), 7.86 (d, $J = 8$ Hz, 2 H, Ar-H), 7.78 (s, 1 H, NH, D_2O-exchangeable), 7.64 (d, $J = 8$ Hz, 2 H, Ar-H), 7.52 (t, $J = 8$ Hz, 2 H, Ar-H), 7.48 (t, $J = 8$ Hz, 2 H, Ar-H), 7.42 (t, $J = 8$ Hz, 1 H, Ar-H), 7.34 (t, $J = 8$ Hz, 1 H, Ar-H). – $C_{17}H_{15}N_5S$ (321.40): calcd. C 63.53, H 4.70, N 21.79, S 9.98; found C 63.51, H 4.71, N 21.84, S 10.03.

3.6.2 5-[1-Phenyl-3-(*p*-tolyl)-1*H*-pyrazol-4-yl]-1,2,4-triazolidine-3-thione (9b)

Colorless crystals, yield 89% (0.298 g), m. p. 190–192°C. – IR (KBr): $\nu = 3305$ (NH), 3297 (NH), 3158 (NH), 1598 (C=N), 1541 (C=C), 1223 (C=S) cm^{-1}. – ^1H NMR (500 MHz, [D_6]DMSO): $\delta = 11.31$ (s, 1 H, NH, D_2O-exchangeable), 9.14 (s, 1 H, 5-H of pyrazole ring), 8.23 (s, 1 H, NH, D_2O-exchangeable), 8.18 (s, 1 H, 5-H of triazolidine ring), 7.85 (d, $J = 8$ Hz, 2 H, Ar-H), 7.78 (s, 1 H, NH, D_2O-exchangeable), 7.51–7.54 (m, 4 H, Ar-H), 7.33 (t, $J = 8$ Hz, 1 H, Ar-H), 7.28 (d, $J = 8$ Hz, 2 H, Ar-H), 2.35 (s, 3 H, CH_3). – ^{13}C NMR (125 MHz, [D_6]DMSO): $\delta = 21.40$ (CH_3), 117.70 (C-5 of triazolidine ring), 119.00, 127.45, 128.11, 128.53, 129.85, 130.19, 135.61, 138.59, 139.60 (Ar-C, C-4 and C-5 of pyrazole ring), 151.92 (C-3 of pyrazole ring), 178.08 (C=S). – $C_{18}H_{17}N_5S$ (335.43): calcd. C 64.45, H 5.11, N 20.88, S 9.56; found C 64.51, H 5.08, N 21.03, S 9.56.

3.6.3 5-[3-(*p*-Chlorophenyl)-1-phenyl-1*H*-pyrazol-4-yl]-1,2,4-triazolidine-3-thione (9c)

Colorless crystals, yield 97% (0.344 g), m. p. 193–194°C. – IR (KBr): $\nu = 3334$ (NH), 1602 (C=N), 1543 (C=C), 1221 (C=S) cm^{-1}. – ^1H NMR (500 MHz, [D_6]DMSO): $\delta = 11.31$ (s, 1 H, NH, D_2O-exchangeable), 9.16 (s, 1 H, 5-H of pyrazole ring), 8.24 (s, 1 H, NH, D_2O-exchangeable), 8.17 (s, 1 H, 5-H of triazolidine ring), 7.85 (d, $J = 8$ Hz, 2 H, Ar-H), 7.77 (s, 1 H, NH, D_2O-exchangeable), 7.67 (d, $J = 8$ Hz, 2 H, Ar-H), 7.51–7.55 (m, 4 H, Ar-H), 7.34 (t, $J = 7$ Hz, 1 H, Ar-H). – $C_{17}H_{14}ClN_5S$ (355.84): calcd. C 57.38, H 3.97, Cl 9.96, N 19.68, S 9.01; found C 57.32, H 3.96, Cl 10.17, N 19.61, S 9.03.

3.6.4 5-[3-(*p*-Bromophenyl)-1-phenyl-1*H*-pyrazol-4-yl]-1,2,4-triazolidine-3-thione (9d)

Colorless crystals, yield 96% (0.384 g), m. p. 215–217°C. – IR (KBr): $\nu = 3341$ (NH), 3155 (NH), 1618 (C=N), 1536 (C=C), 1220 (C=S) cm^{-1}. – ^1H NMR (500 MHz, [D_6]DMSO): $\delta = 11.30$ (s, 1 H, NH, D_2O-exchangeable), 9.15 (s, 1 H, 5-H of pyrazole ring), 8.24 (s, 1 H, NH, D_2O-exchangeable), 8.15 (s, 1 H, 5-H of triazolidine ring), 7.85 (d, $J = 8$ Hz, 2 H, Ar-H), 7.77 (s, 1 H, NH, D_2O-exchangeable), 7.68 (d, $J = 8$ Hz, 2 H, Ar-H), 7.60 (d, $J = 8$ Hz, 2 H, Ar-H), 7.52 (t, $J = 8$ Hz, 2 H, Ar-H), 7.35 (t, $J = 8$ Hz, 1 H, Ar-H). – $C_{17}H_{14}BrN_5S$ (400.30): calcd. C 51.01, H 3.53, Br 19.96, N 17.50, S 8.01; found C 50.89, H 3.53, Br 20.23, N 17.41, S 8.05.

3.7 General procedure for synthesis of Knoevenagel condensation products 10a–10d

In a dry test tube, carbaldehyde **2a**, **2b**, **2d**, or **2e** (5 mmol) was added to ethyl 2-cyanoacetate (0.53 mL, 5 mmol), and the mixture was heated over a boiling water bath for 2 h. The separated product was collected by filtration, washed with water, and dried. It was recrystallized from a mixture of chloroform and ethanol.

3.7.1 Ethyl 2-cyano-3-(1,3-diphenyl-1*H*-pyrazol-4-yl) propenoate (10a)

Colorless crystals, yield 83% (1.425 g), m. p. 118–120°C. – IR (KBr): $\nu = 2218$ (C≡N), 1722 (C=O), 1591 (C=N), 1528 (C=C) cm^{-1}. – ^1H NMR (500 MHz, $CDCl_3$): $\delta = 9.14$ (s, 1 H, 5-H of pyrazole ring), 8.31 (s, 1 H, CH=C), 7.83–7.84 (m, 2 H, Ar-H), 7.61–7.63 (m, 2 H, Ar-H), 7.49–7.54 (m, 5 H, Ar-H), 7.39 (t, $J = 8$ Hz, 2 H, Ar-H), 4.34 (q, $J = 7$ Hz, 2 H, CH_2-CH_3), 1.38 (t, $J = 7$ Hz, 3 H, CH_2-CH_3). – $C_{21}H_{17}N_3O_2$ (343.38): calcd. C 73.45, H 4.99, N 12.24; found C 73.44, H 5.03, N 12.23.

3.7.2 Ethyl 2-cyano-3-[1-phenyl-3-(*p*-tolyl)-1*H*-pyrazol-4-yl]propenoate (10b)

Colorless crystals, yield 95% (1.697 g), m. p. 132–133°C. – IR (KBr): $\nu = 2218$ (C≡N), 1724 (C=O), 1595 (C=N), 1536 (C=C) cm^{-1}. – ^1H NMR (500 MHz, $CDCl_3$): $\delta = 9.12$ (s, 1 H, 5-H of pyrazole ring), 8.30 (s, 1 H, CH=C), 7.82 (d, $J = 8$ Hz,

2 H, Ar-H), 7.50–7.53 (m, 4 H, Ar-H), 7.38 (t, J = 8 Hz, 1 H, Ar-H), 7.32–7.34 (d, J = 8 Hz, 2 H, Ar-H), 4.35 (q, J = 7 Hz, 2 H, CH_2-CH_3), 2.44 (s, 3 H, CH_3), 1.38 (t, J = 7 Hz, 3 H, CH_2-CH_3). – $C_{22}H_{19}N_3O_2$ (357.41): calcd. C 73.93, H, 5.36, N 11.76; found C 73.91, H 5.37, N 11.81.

3.7.3 Ethyl 3-[3-(*p*-bromophenyl)-1-phenyl-1*H*-pyrazol-4-yl]-2-cyanopropenoate (10c)

Pale yellow solid, yield 92% (1.942 g), m. p. 143–144°C. – IR (KBr): ν = 2219 (C≡N), 1722 (C=O), 1591 (C=N), 1522 (C=C) cm^{-1}. – ^{1}H NMR (500 MHz, $CDCl_3$): δ = 9.12 (s, 1 H, 5-H of pyrazole ring), 8.23 (s, 1 H, CH=C), 7.81–7.82 (m, 2 H, Ar-H), 7.65 (d, J = 8 Hz, 2 H, Ar-H), 7.49–7.54 (m, 4 H, Ar-H), 7.40 (t, J = 8 Hz, 1 H, Ar-H), 4.35 (q, J = 7 Hz, 2 H, CH_2-CH_3), 1.38 (t, J = 7 Hz, 3 H, CH_2-CH_3). – $C_{21}H_{16}BrN_3O_2$ (422.27): calcd. C 59.73, H 3.82, Br 18.92, N 9.95; found C 59.61, H 3.81, Br 19.11, N 9.94.

3.7.4 Ethyl 2-cyano-3-[3-(*p*-nitrophenyl)-1-phenyl-1*H*-pyrazol-4-yl]propenoate (10d)

Pale yellow solid, yield 97% (1.883 g), m. p. 164–165°C. – IR (KBr): ν = 2219 (C≡N), 1723 (C=O), 1600 (C=N), 1529 (C=C) cm^{-1}. – ^{1}H NMR (500 MHz, $CDCl_3$): δ = 9.16 (s, 1 H, 5-H of pyrazole ring), 8.38 (d, J = 8 Hz, 2 H, Ar-H), 8.24 (s, 1 H, CH=C), 7.82 (d, J = 8 Hz, 4 H, Ar-H), 7.53 (t, J = 8 Hz, 2 H, Ar-H), 7.43 (t, J = 8 Hz, 1 H, Ar-H), 4.36 (q, J = 7 Hz, 2 H, CH_2-CH_3), 1.41 (t, J = 7 Hz, 3 H, CH_2-CH_3). – $C_{21}H_{16}N_4O_4$ (388.38): calcd. C 64.94, H 4.15, N 14.43; found C 64.91, H 4.17, N 14.55.

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Graphical synopsis

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