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Synthesis and antioxidant screening of new 2-cyano-3-(1,3-diphenyl-1*H*-pyrazol-4-yl)acryloyl amide derivatives and some pyrazole-based heterocycles

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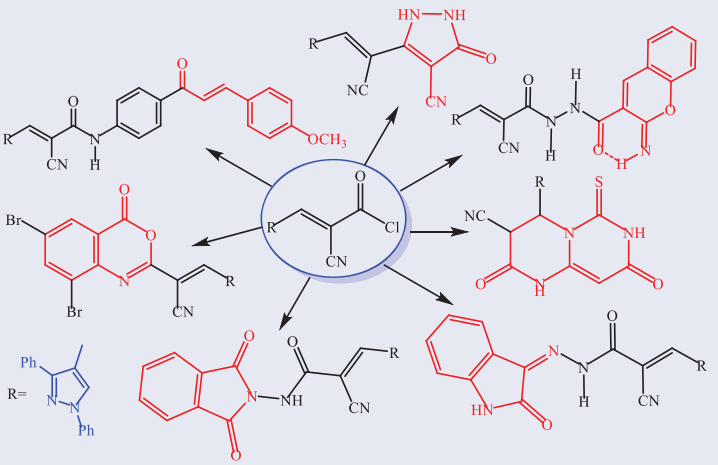
ABSTRACT

The high functionality compound namely 2-cyano-3-(1,3-diphenyl-1*H*-pyrazol-4-yl)acryloyl chloride **(1)** was utilized as a building block synthon *via* reactions with some nitrogen and sulfur nucleophilic reagents. The present work was planned to study the effect of 2-cyano group on the reactivity and stability of C_2–C_3 double bond toward different strong-to-weak nucleophiles, in addition to its facility of nucleophilic addition at C_2–C_3 double bond to construct new heterocyclic derivatives. The proclivity toward some mono-, 1,2-, 1,3-, 1,4-, and 1,5-binucleophiles was investigated. The reaction with 2-cyanoacetohydrazide was mainly dependent on the reaction conditions. Some new heterocycles integrated with pyrazole scaffold were successfully synthesized, such as benzoxazinone, indoline, isoindoline, pyrazolone, chromene, and pyrimidopyrimidine derivatives. Some of the newly synthesized compounds were screened for their antioxidant activity using ABTS method, and the results revealed that some compounds exhibited promising inhibitory antioxidant activity.

GRAPHICAL ABSTRACT



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Introduction

Pyrazole scaffolds are important heterocycles in the fields of medicine and pharmacology. The survey of the literature reveals that many pyrazole derivatives have been used for pharmacological applications, such as anti-HIV, antiviral, anticancer, antimicrobial, antidepressant, and antioxidant.[1–16] Thus, incorporation of the pyrazole scaffold represents an important synthetic strategy in the rational drug development process. Some pyrazole-based drugs are depicted in Figure 1. The recent widespread utilization of 2-cyanoacryloyl chloride derivatives in the design and synthesis of highly important products such as precursors of pharmaceutical intermediates[17–20] enthused us to employ new derivatives of these categories for the synthesis of new analogous of 2-cyanoacrylamides besides some interesting heterocycles bearing 1,3-diphenylpyrazole moiety such as benzoxazinone, isoindoline, indoline, pyrazolone, chromene, and pyrimidopyrimidine derivatives which might exhibit pharmacological effects.

Results and discussion

The requisite acid chloride namely 2-cyano-3-(1,3-diphenyl-1*H*-pyrazol-4-yl)acryloyl chloride **(1)** was synthesized[21] and submitted to react with different mono-, 1,2-, 1,3-, 1,4-, and 1,5-binucleophiles in an attempt to obtain some new heterocycles (Schemes 1–3). Indeed, stirring **1** with some aromatic primary amines such as 4-aminobenzenesulfonamide, methyl 4-aminobenzoate, and 4-aminoacetophenone in dioxane and triethylamine at ambient temperature afforded the 2-cyanoacrylamide derivatives **2a–c**,

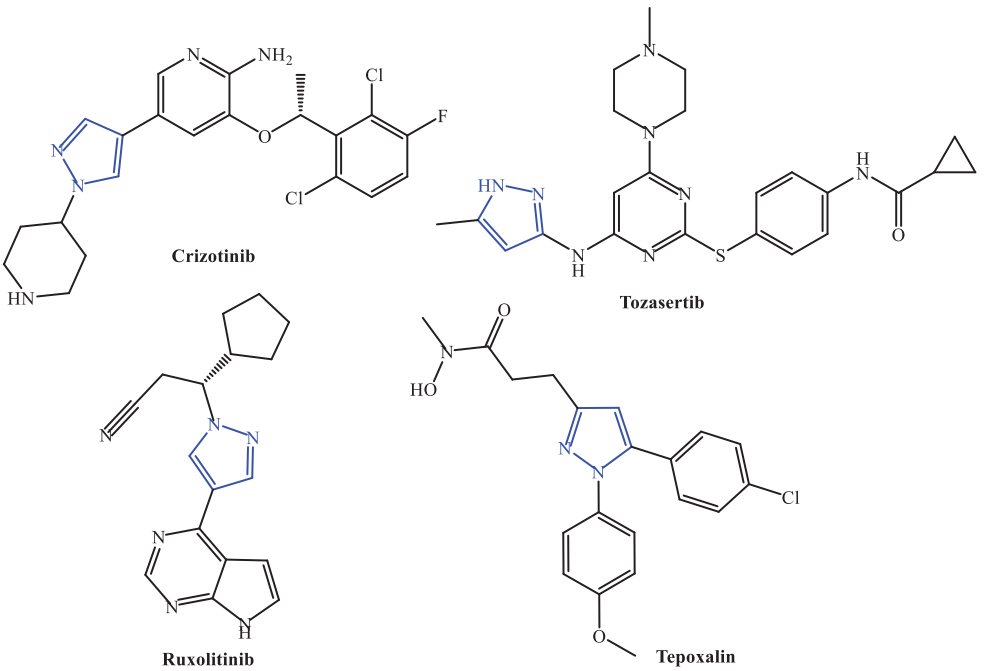


Figure 1. Some FDA-approved drugs based on the pyrazole ring.

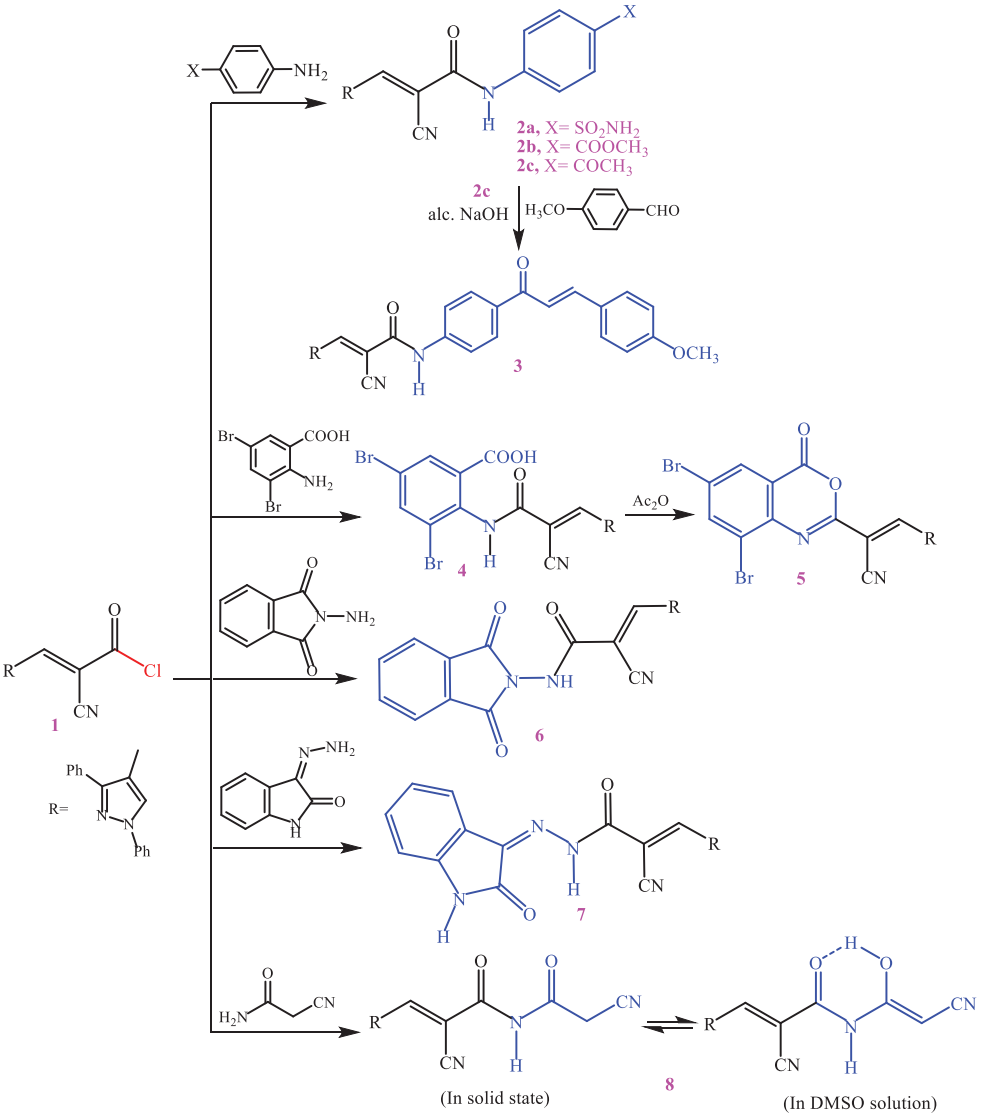
respectively, in good yields. The IR spectra retained the absorption bands for nitrile functions, and displayed the absence of carbonyl group of the acid chloride moiety and the presence of amide functionalities. The ^{1}H NMR spectra retained the singlet signal for olefinic proton. On the other hand, chalcone derivative **3** was prepared as canary-yellow crystals *via* treating the acetyl derivative **2c** with 4-methoxybenzaldehyde in alcoholic sodium hydroxide at room temperature. The ^{1}H NMR spectrum of chalcone **3** lacked to methyl singlet signal of acetyl group and showed a singlet signal for $-OCH_3$ group as well as CH = CH signals (cf. Experimental).

In turn, the benzoxazinone derivative integrated with pyrazole scaffold **5** was successfully synthesized *via* condensation of the acid chloride **1** with 3,5-dibromo-2-aminobenzoic acid in dioxane and triethylamine at room temperature to produce the corresponding acrylamide derivative **4** followed by heating with freshly distilled acetic anhydride (Scheme 1). The IR spectrum of benzoxazinone **5** revealed the appearance of the stretching absorption band for the lactone carbonyl group and the absence of NH group.

Also, it was interesting to synthesize one framework contains both pyrazole and isoindoline or indoline moieties to construct compounds **6** and **7** *via* treatment of the acid chloride **1** with *N*-aminophthalimide and isatin monohydrazone, respectively (Scheme 1). The IR spectrum of compound **6** showed the following absorption bands (ν, cm^{-1}): 3339 (NH), 2212 (C≡N), 1794, 1738 (C=O due to vibrational coupling), 1703 (C=O amide). The IR of compound **7** exhibited the following absorption bands (ν, cm^{-1}): 3323, 3229 (2NH), 2209 (C≡N), 1708 (C=O oxoindoline), 1678 (C=O amide). Their ^{1}H NMR spectra were in good agreement with the assigned structures. 2-cyanoacetamide condensed with **1** to afford the corresponding imide derivative **8** as yellow crystals. Its IR spectrum displayed the stretching absorption bands for two C≡N groups ν 2239 and 2207 cm^{-1}, as well as C=O groups at ν 1736, 1701 cm^{-1} (attributable for vibrational coupling). In DMSO solution, examination of its ^{1}H NMR spectrum revealed its existence in the enol form as the predominant form due to intramolecular chelated H-bond in six-membered ring (cf. Experimental).

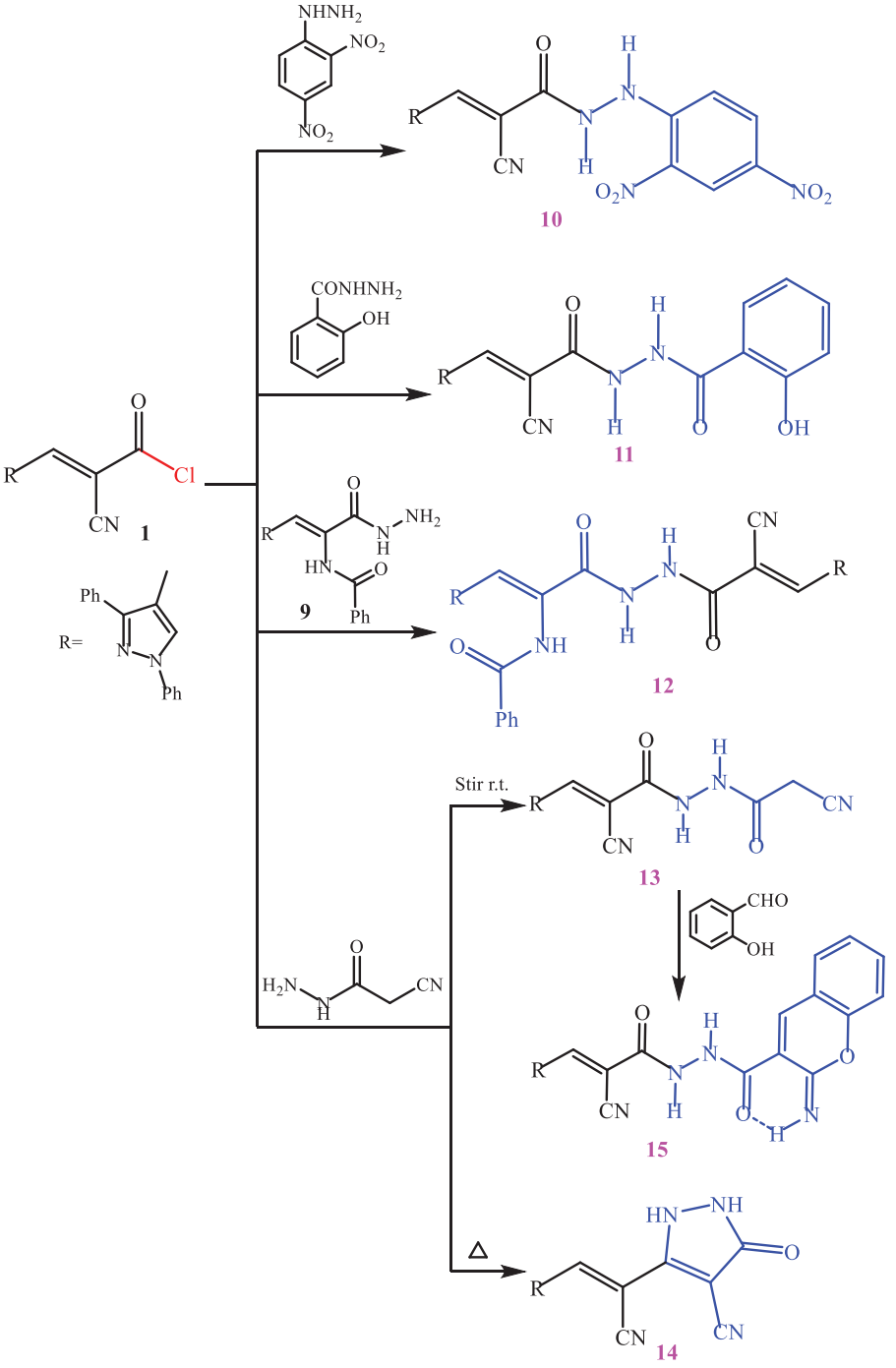
The reactions of the acid chloride **1** toward some 1,2-binucleophiles were investigated. Indeed, treating **1** with 2,4-dinitrophenylhydrazine, 2-hydroxybenzohydrazide, and *N*-(1-(1,3-diphenyl-1*H*-pyrazol-4-yl)-3-hydrazinyl-3-oxoprop-1-en-2-yl)benzamide **(9)** afforded the hydrazide derivatives **10–12**, respectively. The ^{1}H NMR spectrum of compound **10** provided two exchangeable broad singlet signals for two NH protons at δ 11.15 and 10.29 ppm. The ^{1}H NMR spectra of compounds **11** and **12** exhibited three exchangeable broad singlet signals (cf. Experimental).

It was fortunate that the reaction of the acid chloride **1** with 2-cyanoacetohydrazide was mainly dependent on the reaction conditions. Thus, carrying out the reaction at ambient temperature furnished the hydrazide derivative **13**. While at refluxing conditions, the pyrazolone derivative **14** was obtained. The IR spectrum of compound **13** provided the absorption bands for C≡N groups at ν 2263 and 2212 cm^{-1} and C=O groups at ν 1717 and 1675 cm^{-1}. The ^{1}H NMR spectrum of compound **13** showed a singlet signal for methylene protons which disappeared in that of compound **14**. The iminochromene derivative **15** was built upon treating the nitrile derivative **13** with salicylaldehyde in the presence of a catalytic amount of piperidine.



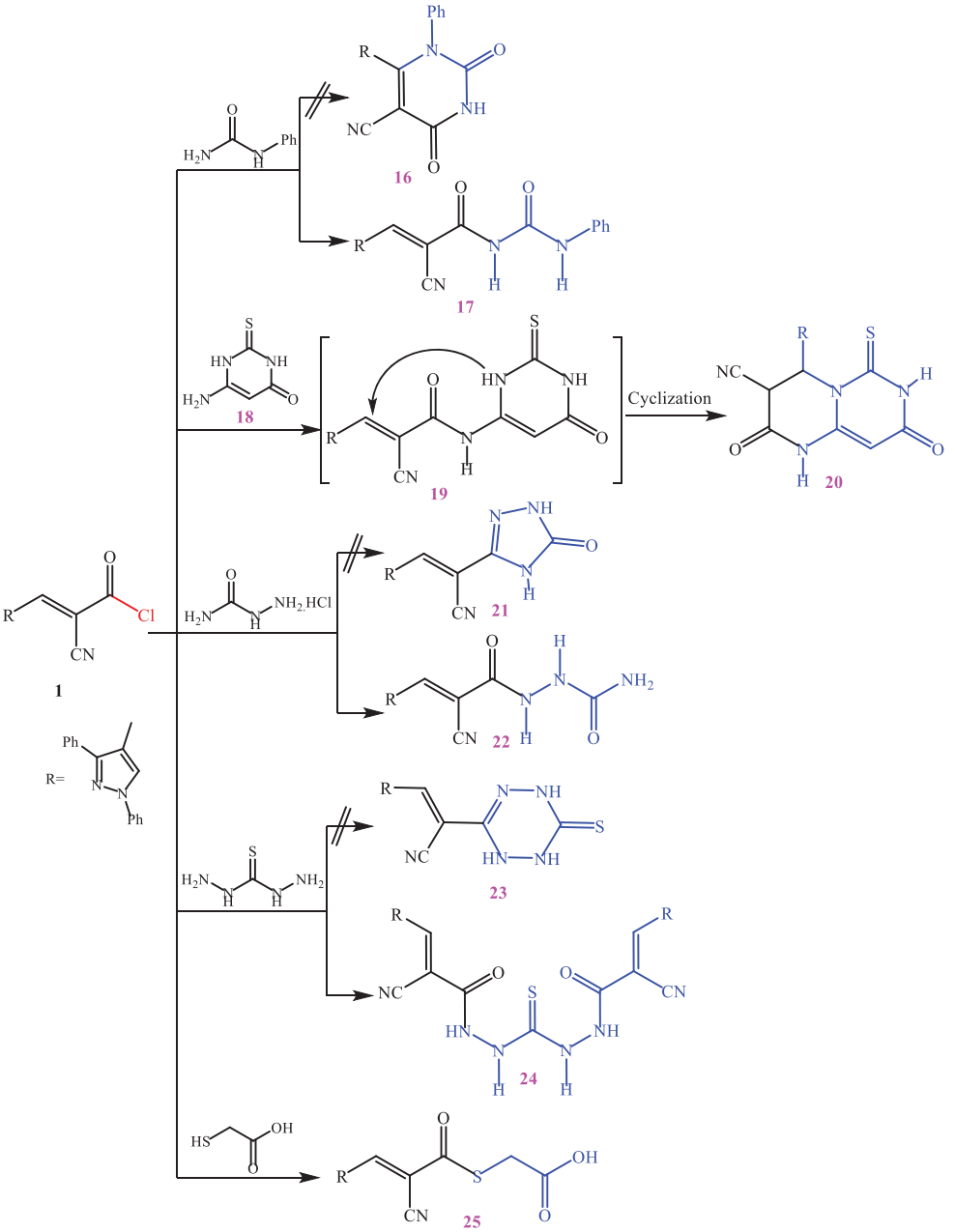
Scheme 1. Reactions of acid chloride **1** with some mono-nucleophiles.

On the other hand, condensation of acid chloride **1** with 1,3- and 1,4-binucleophiles was studied. Refluxing **1** with 1-phenylurea in benzene containing triethylamine failed to construct pyrimidinedione **16** and furnished the corresponding urea derivative **17** as yellow crystals. The structure of compound **17** was established from its IR spectrum which exhibited bands for NH groups and two bands for carbonyl groups at ν 1739 and 1674 cm^{-1} due to vibrational coupling. Its ^1H NMR spectrum provided two exchangeable singlet signals for two NH groups at δ 11.18 and 10.37 ppm. The synthesis of pyrimidopyrimidine derivative **20** was commenced from the reaction of acid chloride **1** with 6-amino-2-thioxo-2,3-dihydropyrimidin-4(1*H*)-one **(18)** in refluxing dioxane and triethylamine. The IR spectrum of compound **20** kept the nitrile function and exhibited absorption bands for NH, C=O, and C=S groups. In addition, the lack of olefinic



Scheme 2. Reactions of **1** with some 1,2-binucleophiles.

proton in its ^{1}H NMR spectrum emphasized the cyclization step and showed the presence of two exchangeable singlet signals for two NH groups, besides, two doublet signals in the upfield region corresponding to CH-CH group. The reaction could be extrapolated *via* first condensation to eliminate HCl molecule to afford acrylamide



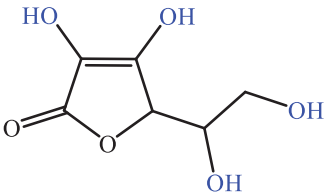
Scheme 3. Reactions of **1** with some 1,3-, 1,4-, and 1,5-binucleophiles and thioglycolic acid.

derivative **19** which underwent cyclization *in situ* to construct the fused heterocyclic product **20**.

Our work was extended to investigate the behavior of acid chloride **1** toward semicarbazide hydrochloride (as 1,4-binucleophile) and thiocarbohydrazide (as 1,5-binucleophile) in an attempt to synthesize triazole **21** and tetrazine **23** derivatives, respectively. However, the later reactions achieved the compounds **22** and **24**, respectively (Scheme 3). The existence of the absorption bands for NH, NH_2, and two carbonyl groups in the

Figure 2. Shape of crystals of compound **25**.

IR spectrum of compound **22** besides the nitrile function corroborated the open-chain structure. Furthermore, retaining of the singlet signal for the olefinic proton in its ^{1}H NMR spectrum and the presence of three exchangeable singlet signals for two NH and NH_2 protons supported the assigned structure. The structure of compound **24** was unequivocally proven from its IR spectrum which displayed the presence of an absorption band for the carbonyl group excluding the cyclization step (structure **23**). It is also worthy to mention that the ^{1}H NMR spectrum provided two exchangeable singlet signals for four NH protons. Finally, stirring a solution of the acid chloride **1** with mercaptoacetic acid (as sulfur nucleophile) in dry dioxane and triethylamine at room temperature furnished the thioester derivative, namely 2-((2-cyano-3-(1,3-diphenyl-1H-pyrazol-4-yl)acryloyl)thio)acetic acid **(25)** as faint-green crystals (cf. Scheme 3, Fig. 2). The IR spectrum retained the nitrile function at ν 2226 cm^{-1} and exhibited the absorption bands for OH at ν 3426 cm^{-1}, C=O acid at ν 1696 cm^{-1}, and C=O thioester at ν 1681 cm^{-1} (cf. Experimental).



Ascorbic acid

Figure 3. Structure of ascorbic acid.

Table 1. Antioxidant activity of some new compounds.

Compounds	Absorbance of samples	% inhibition
Control of ABTS	0.500	0
Ascorbic acid	0.058	88.4
2a	0.104	79.2
4	0.133	73.4
5	0.362	27.6
6	0.334	33.1
7	0.198	60.3
10	0.213	57.4
11	0.179	64.2
12	0.157	68.5
13	0.223	55.3
22	0.142	71.5
24	0.199	60.1

Antioxidant activity screening

The antioxidant activity of some new compounds was screened using ABTS [2,2′-azino-bis-(3-ethylbenzthiazoline-6-sulphonic acid)] assay.[22] Ascorbic acid (vitamin C) was used as a standard antioxidant (Fig. 3). The absorbance Abs(test) was measured, and the reduction in color intensity was expressed as % inhibition. The % inhibition for each compound was calculated from the following equation:

$$\%\ \text{inhibition} = \left[\text{Abs(control)} - \text{Abs(test)}/\text{Abs(control)}\right] \times 100.$$

The results are shown in Table 1 and revealed that all compounds were found to be potent. Compounds **2a, 4**, and **22** exhibited the most potent levels of activity with % inhibition = 79.2, 73.4, 71.5%, respectively, which is nearer to the standard antioxidant, ascorbic acid (% inhibition = 88.4%). Also, compounds **7, 10, 11, 12, 13**, and **24** displayed strong efficacy. On the other hand, compounds **5** and **6** have moderate antioxidant activity. These results may include the following structure–activity relationship (SAR's): (i) The presence of the pyrazole scaffold proved to be vital for remarkable potential inhibitory antioxidant activity. (ii) The incorporation of NH_2 and OH groups enhanced the antioxidant activity.[16,23,24] (iii) Cyclization of compound **4** to construct benzoxazinone derivative **5** retarded the activity.

Conclusion

Synthesis of some new *N*-heterocycles, e.g., benzoxazinone, indoline, isoindoline, pyrazolone, chromene, and pyrimidopyrimidine derivatives starting from 2-cyano-3-(1,3-diphenyl-1*H*-pyrazol-4-yl)acryloyl chloride, has been achieved and screened for their

antioxidant activity using ABTS method, and the results revealed that some compounds exhibited the promising inhibitory antioxidant activity.

Experimental

All reagents and solvents were purified and dried by standard techniques. Melting points were measured on a GALLENKAMP electric melting point apparatus and are uncorrected. IR spectra (ν, cm^{-1}) were recorded using potassium bromide disks on Fourier Transform Infrared Thermo Electron Nicolet iS10 Spectrometer (Thermo Fisher Scientific Inc., Waltham, MA, USA) at Chemistry Department, Faculty of Science, Ain Shams University. The ^1H NMR spectra were run at 300 MHz on a GEMINI NMR spectrometer (GEMINI, Manufacturing & Engineering Inc., Anaheim, CA, USA) and 400 MHz on a BRUKER NMR spectrometer (BRUKER, Manufacturing & Engineering Inc., Anaheim, CA, USA) using tetramethyl silane (TMS) as an internal standard in deuterated dimethyl sulfoxide (DMSO-d_6) at Faculty of Science and Faculty of Pharmacy, Cairo University, Giza, Egypt. Elemental analyses were carried out at the Microanalytical Unit, Faculty of Science, Ain Shams University, by using Perkin-Elmer 2400 CHN elemental analyzer and satisfactory analytical data (±0.4) were obtained for all compounds. The reactions were monitored by thin-layer chromatography (TLC) using Merck Kiesel gel $60F_{254}$ obtained from Fluka, Switzerland. The antioxidant activity was tested at the drugs department, Faculty of Pharmacy, Mansoura University, Mansoura, Egypt. The starting acid chloride namely 2-cyano-3-(1,3-diphenyl-1*H*-pyrazol-4-yl)acryloyl chloride **(1)** was previously prepared by us.[21]

General procedure for reaction with primary amines

To a stirred solution of acid chloride **1** (1 g, 3 mmol) in dry dioxane (10 mL) containing 2-drops of triethylamine, the suitable primary amines, namely 4-aminobenzenesulfonamide, methyl 4-aminobenzoate, and 4-aminoacetophenone (3 mmol) were added at room temperature. The reaction mixture was further stirred for 1 h. The precipitated solid was sucked and recrystallized from the suitable solvent to produce the corresponding 2-cyanoacrylamides **2a–c,** respectively.

2-Cyano-3-(1,3-diphenyl-1H-pyrazol-4-yl)-N-(4-sulfamoylphenyl)acrylamide (2a)

Pale-yellow crystals, m.p. 334–336 °C (ethanol), yield 84%. IR (KBr, ν, cm^{-1}): 3379, 3260 (NH, NH_2), 3066 (CH-aromatic), 2210 (C≡N), 1680 (C=O), 1346, 1161 (SO_2). ^1H NMR (DMSO-d_6, δ, ppm): 10.58 (br.s, 1H, NH, exchangeable), 9.23 (s, 1H, C5–H pyrazole), 8.19 (s, 1H, CH=), 7.97–7.94 (d, 2H, Ar-H, $J = 8.4\,Hz$), 7.81–7.47 (m, 12H, Ar-H), 7.28 (br.s, 2H, NH_2, exchangeable). Anal. Calcd. for $C_{25}H_{19}N_5O_3S$ (469.52): C, 63.95; H, 4.08; N, 14.92. Found: C, 63.88; H, 4.00; N, 14.91%.

Methyl 4-(2-cyano-3-(1,3-diphenyl-1H-pyrazol-4-yl)acrylamido)benzoate (2b)

Yellow crystals, m.p. 310–312 °C (benzene), yield 82%. IR (KBr, ν, cm^{-1}): 3340 (NH), 3060 (CH-aromatic), 2939 (CH-aliphatic), 2211 (C≡N), 1719 (C=O ester), 1686 (C=O amide). ^{1}H NMR (DMSO-d_6, δ, ppm): 10.51 (br.s, 1H, NH, exchangeable), 9.18 (s, 1H, C5–H pyrazole), 8.11 (s, 1H, CH=), 7.96–7.94 (d, 2H, Ar-H, $J = 8.5\,Hz$), 7.80–7.45 (m, 8H, Ar-H), 7.34–7.30 (m, 4H, C_6H_4-CO), 3.70 (s, 3H, CH_3). Anal. Calcd. for $C_{27}H_{20}N_4O_3$ (448.48): C, 72.31; H, 4.50; N, 12.49. Found: C, 72.20; H, 4.43; N, 12.50%.

N-(4-Acetylphenyl)-2-cyano-3-(1,3-diphenyl-1H-pyrazol-4-yl)acrylamide (2c)

Yellow crystals, m.p. 300–302 °C (dioxane), yield 86%. IR (KBr, ν, cm^{-1}): 3342 (NH), 3059 (CH-aromatic), 2922 (CH-aliphatic), 2209 (C≡N), 1683 (C=O). ^{1}H NMR (DMSO-d_6, δ, ppm): 10.57 (br.s, 1H, NH, exchangeable), 9.22 (s, 1H, C5–H pyrazole), 8.19 (s, 1H, CH=), 7.98–7.95 (d, 2H, Ar-H, $J = 8.4\,Hz$), 7.97–7.94 (d, 2H, Ar-H, $J = 8.4\,Hz$), 7.83–7.80 (d, 2H, Ar-H, $J = 8.5\,Hz$), 7.71–7.56 (m, 8H, Ar-H), 2.49 (s, 3H, CH_3). Anal. Calcd. for $C_{27}H_{20}N_4O_2$ (432.48): C, 74.98; H, 4.66; N, 12.95. Found: C, 74.89; H, 4.50; N, 12.91%.

Synthesis of chalcone 3

To a mixture of the acetyl derivative **2c** (1.30 g, 3 mmol) and 4-methoxybenzaldehyde (0.40 g, 3 mmol) in ethanol (20 mL), 10% sodium hydroxide solution (5 mL) was added and stirred at 0–5 °C for 3 h. The precipitate formed was collected by filtration and recrystallized from benzene to furnish chalcone derivative **3**.

2-Cyano-3-(1,3-diphenyl-1H-pyrazol-4-yl)-N-(4-(3-(4-methoxyphenyl)acryloyl)phenyl)-acrylamide (3)

Canary yellow crystals, m.p. 270–272 °C, yield 58%. IR (KBr, ν, cm^{-1}): 3351 (NH), 3059 (CH-aromatic), 2924 (CH-aliphatic), 2208 (C≡N), 1683, 1658 (C=O). ^{1}H NMR (DMSO-d_6, δ, ppm): 10.60 (br.s, 1H, NH, exchangeable), 9.23 (s, 1H, C5–H pyrazole), 8.21 (s, 1H, CH=), 8.13–8.10 (d, 1H, COCH=CH, $J = 8.5\,Hz$), 7.97–7.42 (m, 18H, Ar-H), 7.04–7.01 (d, 1H, COCH=CH, $J = 8.4\,Hz$), 3.83 (s, 3H, $-OCH_3$). Anal. Calcd. for $C_{35}H_{26}N_6O_3$ (550.20): C, 76.35; H, 4.76; N, 10.18. Found: C, 76.35; H, 4.63; N, 10.21%.

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Disclosure statement

The authors declare no conflicts of interest.

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