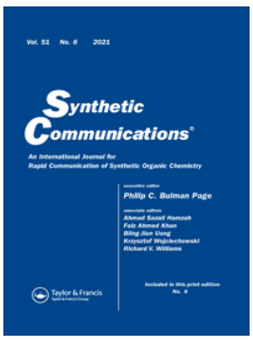

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Synthesis and antioxidant evaluation of some heterocyclic candidates from 3-(1,3-diphenyl-1*H*-pyrazol-4-yl)-2-(4-oxo-4*H*-benzo[*d*][1,3]oxazin-2-yl)propenonitrile

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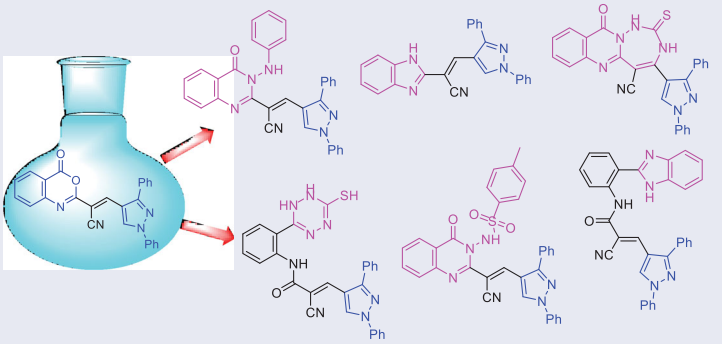
ABSTRACT

A new series of quinazoline derivatives bearing a 1,3-diphenylpyrazole core was synthesized starting from 3-(1,3-diphenyl-1*H*-pyrazol-4-yl)-2-(4-oxo-4*H*-benzo[*d*][1,3]oxazin-2yl)propenonitrile **(4)** through reactions with some nitrogen nucleophiles. Hydrazinolysis of **4** furnished the biquinazoline and diheterylazine derivatives depending on the reaction conditions. Noteworthy, the benzimidazole derivatives were obtained *via* treatment with 2-aminoaniline under different reaction conditions. Inspect of the reactions of **4** with hydrazinecarbothioamide and hydrazinecarbothiohydrazide provided thiosemicarbazide, triazepinoquinazoline, and mercaptotetrazine derivatives. The antioxidant screening disclosed that some of these compounds such as **3, 5, 11, 12,** and **13** exhibited significant potency.

GRAPHICAL ABSTRACT



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Introduction

The propenoyl chloride derivatives, prepared from hydrolysis of arylidine ethyl cyanoacetate with sodium hydroxide and then acidification followed by treating with thionyl chloride,[1–4] have been widely utilized for the synthesis of some valuable heterocyclic systems e.g., benzoxazinones, quinazolinones, quinolones, benzimidazoles, benzoxazoles,

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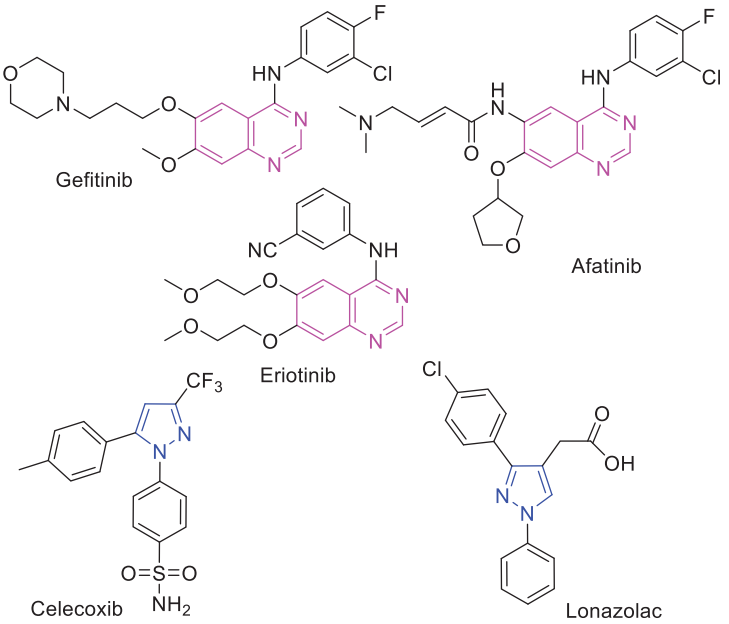


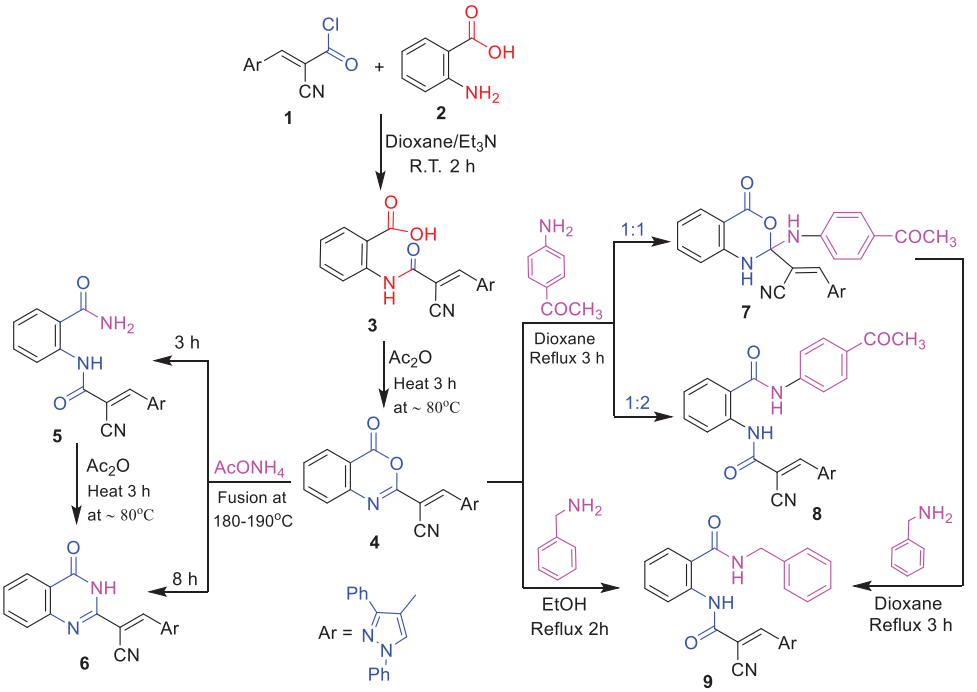
Figure 1. Some pyrazole and quinazoline-based drugs.

oxadiazoles, pyridopyrimidines, and pyrazolones.[1–7] Pyrazoles possess robust biological and pharmacological effects e.g., antiviral, anticancer, antimicrobial, antioxidant, and insecticidal.[1,2,8–16] Hence, the synthesis of pyrazole-based heterocycles is an effective synthetic strategy for the drug development process. Meanwhile, quinazolinone scaffolds are found in both natural products and pharmaceuticals.[17–23] Some pyrazole and quinazoline-based drugs are displayed in Figure 1. Enthused by these facts and as an extension of our study,[24–31] the present work aimed to combine both benzoxazinone and pyrazole skeletons in one framework as an attempt to obtain novel pyrazole-based heterocycles of enhanced antioxidant activity through reactions with some mono and bidentate nitrogen nucleophiles like ammonium acetate, benzylamine, 4-aminoacetophenone, 2-methylpropan-1-amine, dodecan-1-amine, 4-methylaniline, methyl 4-aminobenzoate, hydrazine hydrate, phenylhydrazine, 4-methylbenzenesulfonohydrazide, thiophene-2-carbohydrazide, 1,2-diaminoethane, 2-aminoethanol, 2-aminoaniline, hydrazinecarbothioamide, and hydrazinecarbothiohydrazide.

Results and discussion

Chemistry

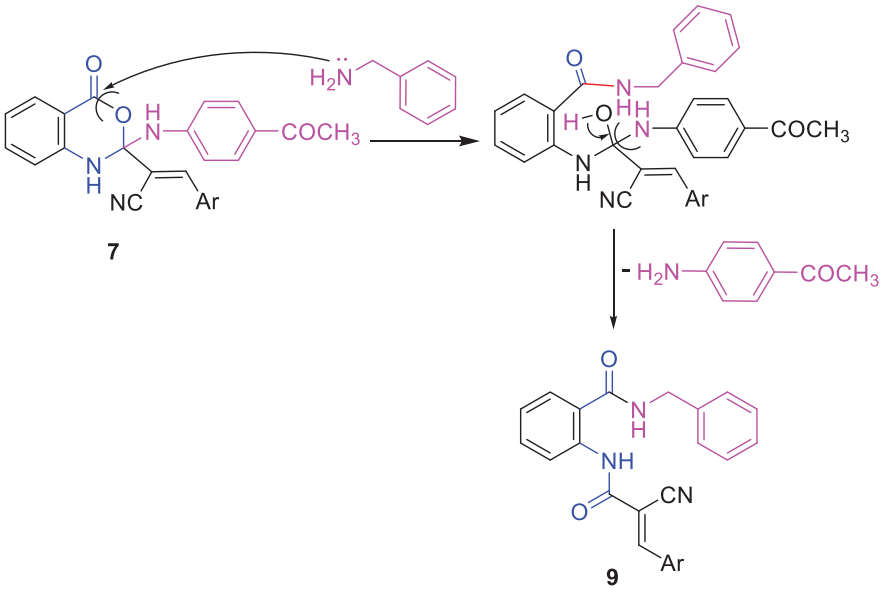
Aiming to tribute a novel series of heterocyclic cores combining 1,3-diphenylpyrazole and quinazoline moieties, 2-cyanopropenoyl chloride encompassing a pyrazole core **1**[1] was treated with anthranilic acid **2** at ambient temperature to afford propenylamide derivative **3** which was successfully transformed into the benzoxazinone derivative **4** via heating with acetic anhydride. IR spectrum of amide **3** lacked the carbonyl functionality of the acid chloride moiety, conserved the nitrile functionality at ν 2210 cm^{-1}, and



Scheme 1. Synthesis and reactions of the benzoxazinone derivative **4**.

disclosed bands for ν NH at 3200 cm^{-1}, ν C=O of carboxylic acid and amide at 1702 and 1686 cm^{-1}, respectively. Further corroboration for the designated structure was acquired from the ^{1}H NMR spectrum that provided two exchangeable singlet signals (COOH and NH protons) at δ 13.40 and 12.29 ppm, respectively. Meanwhile, the IR spectrum of benzoxazinone **4** exhibited a band for lactone C=O moiety at ν 1768 cm^{-1}. Full analysis of its ^{1}H NMR spectrum supported the assigned structure (cf. Experimental). The benzoxazinone **4** was utilized under different conditions following different aspects for the construction of other heterocyclic systems. Initially, it underwent aminolysis with monodentate and bidentate nucleophiles. The reaction involved a nucleophilic attack of the co-reactant amine at position-4 of the benzoxazin-4-one ring. Firstly, ammonolysis of benzoxazinone **4** was found to depend on the reaction circumstances. Indeed, a fusion of benzoxazinone **4** with ammonium acetate for 3 h afforded the benzamide derivative **5**. When the reaction time was extended for 8 h, the quinazolinone **6** was obtained as a sole product (cf. Scheme 1). Spectroscopically, IR spectra lacked the lactone absorption band. ^{1}H NMR spectrum of **5** disclosed two exchangeable singlet signals, one of them is integrated to two protons for NH_2 group at δ 8.40 ppm and the other is integrated to one proton of NH group at δ 12.98 ppm. Otherwise, the ^{1}H NMR spectrum of quinazolinone derivative **6** displayed NH proton as an exchangeable singlet signal at δ 12.77 ppm.

On the other hand, 4-aminoacetophenone reacted with benzoxazinone **4** under two different conditions. Indeed, treating an equimolar mixture of them in boiling dioxane acquired *2-(2-((4-acetylphenyl)amino)-4-oxo-1,4-dihydro-2H-benzo[d][1,3]oxazin-2-yl)-3-(1,3-diphenylpyrazol-4-yl)acrylonitrile* (**7**). This product could be demonstrated *via*

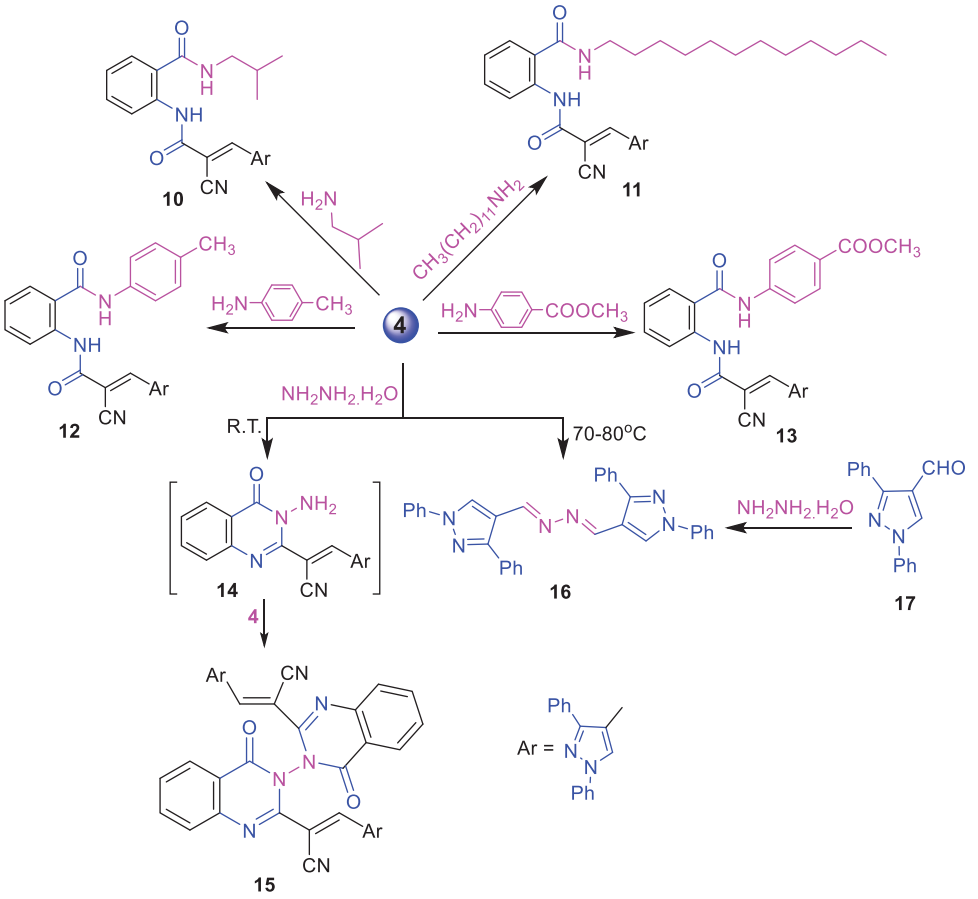


Scheme 2. Proposed pathway for transformation of compound **7** into compound **9**.

nucleophilic addition at position-2.[19] Whilst, using a double molar ratio of the amine, propenylamide derivative **8** was obtained as a sole product (cf. Scheme 1). IR spectrum of **7** conserved a lactone band at ν 1767 cm^{-1} which was disappeared in that of compound **8**. Compelling evidences for their structures were forthcoming from their ^1H NMR spectra (cf. Experimental). Treatment of benzoxazinone **4** with benzylamine in boiling ethanol provided the *N*-benzylamide derivative **9**. Meanwhile, benzylamine in boiling dioxane induced transformation of compound **7** into the amide derivative **9** which can be demonstrated via (Scheme 2). IR spectrum of **9** disclosed NH band at ν 3291 cm^{-1}, and the carbonyl absorption at ν 1686 cm^{-1}. Moreover, ^1H NMR spectrum of **9** offered two NH protons as two exchangeable singlet signals at δ 12.48 and 9.41 ppm.

In turn, treating the benzoxazinone **4** with 2-methylpropan-1-amine, dodecan-1-amine, 4-methylaniline or methyl 4-aminobenzoate acquired the propenylamide derivatives **10–13**, respectively (Scheme 3). The IR spectra retained the nitrile functionality, lacked lactone carbonyl absorption, and displayed the amide carbonyl absorption. Furthermore, the inspection of their ^1H NMR spectra was quite consistent with the proposed structures.

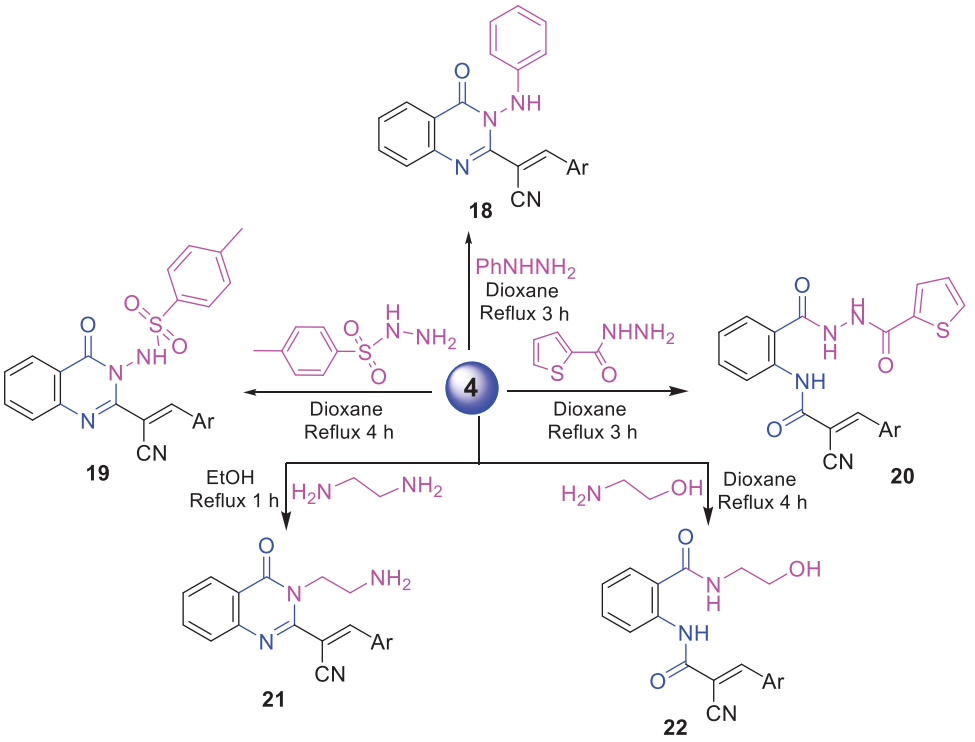
On the other hand, to investigate the behavior of benzoxazinone **4** with versatile 1,2- and 1,4-bidentate nucleophiles, compound **4** was submitted to react with hydrazine hydrate, phenylhydrazine, 4-toluenesulfonohydrazide, 1,2-diaminoethane, 2-aminoethanol, and 2-aminoaniline (cf. Schemes 3–5). Indeed, hydrazinolysis of **4** at ambient temperature in an ethanolic solution was not successful but in *N,N*-dimethylformamide solution, it furnished biquinazolinone derivative **15** (through a non-isolable intermediate **14**). In contrast, heating the reaction mixture at 70–80 °C in ethanol furnished the diheteryl azine **16** which was congruent in all aspects (mp., mixed mp., TLC) to an ethnic piece synthesized from treating pyrazole-4-carboxaldehyde **17** and hydrazine.[15]



Scheme 3. Synthesis of compounds **10–16**.

Conducting the benzoxazinone **4** with phenylhydrazine or 4-toluenesulfonohydrazide in boiling dioxane produced quinazolinone derivatives **18** and **19**, respectively. Thiophene-2-carbohydrazide reacted with **4** in boiling dioxane to provide hydrazide derivative **20** (Scheme 4). Otherwise, treating 1,2-diaminoethane with **4** achieved the quinazolinone derivative **21**. The ^{1}H NMR spectrum of **21** exhibited only one exchangeable singlet signal for NH_2 protons at δ 4.05 ppm in addition to CH_2-CH_2 protons as two triplet signals. In contrast, 2-aminoethanol was reacted with benzoxazinone **4** in boiling dioxane to provide the benzamide derivative **22**. The ^{1}H NMR spectrum of **22** displayed two NH and OH protons at δ 12.51, 8.82, and 4.76 ppm (cf. Experimental).

Noteworthy, the reaction of **4** with 2-aminoaniline afforded products depending mainly on the reaction aspects. Indeed, performing the reaction in boiling ethanol/glacial acetic acid yielded the benzamide derivative **23** as a sole product. Meanwhile, a mixture of the benzamide derivative **23,** benzimidazole derivative **24**, and anthranilic acid **2** was obtained by conducting the reaction mixture in boiling acetic acid/fused sodium acetate. In turn, when the reaction was executed under fusion conditions, a mixture of benzimidazole **24** and anthranilic acid **2** was obtained instead of the benzimidazoquinazoline derivative **26**. Refluxing a solution of the benzamide derivative **23** in *n*-butanol for 4 h achieved the benzimidazole

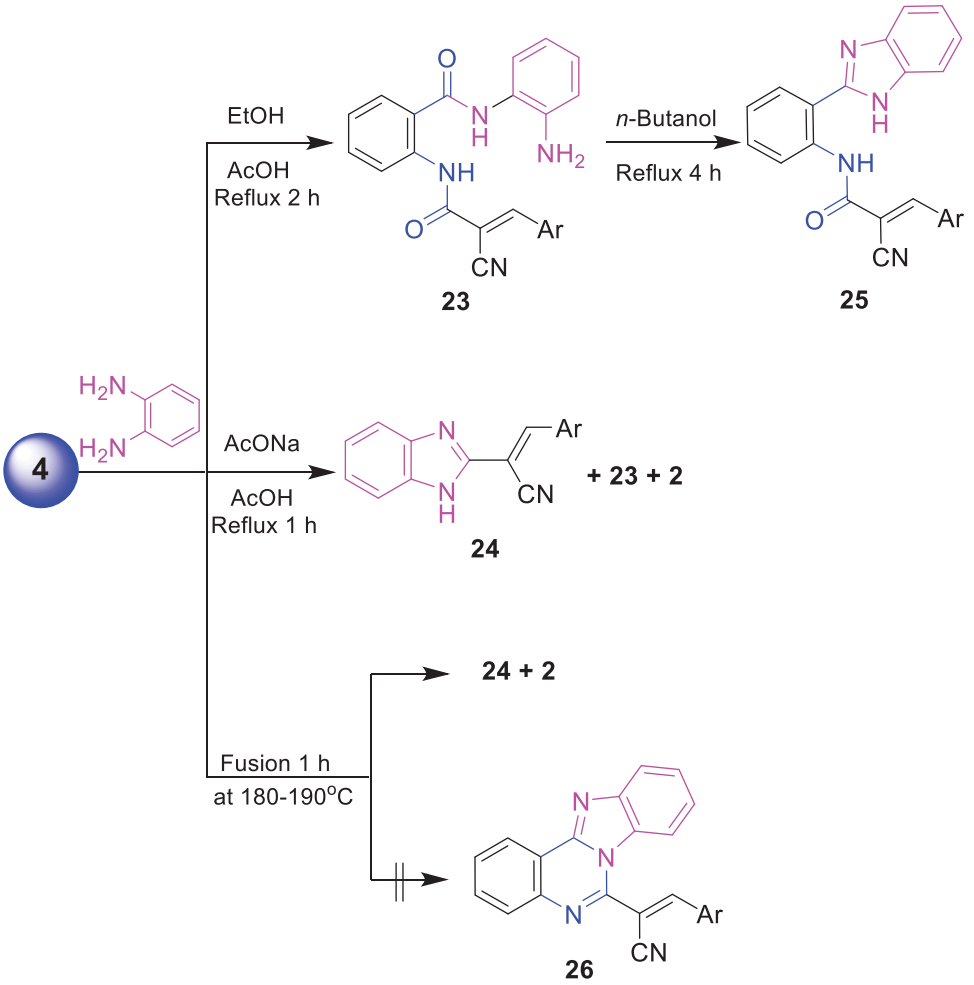


Scheme 4. Synthesis of compounds **18–22**.

derivative **25** as beige crystals (cf. Scheme 5). The IR spectrum of compound **23** retained the nitrile functionality and displayed bands for NH, NH_2 at ν 3390 and 3283 cm^{-1}, in addition to C=O group at ν 1686 cm^{-1}. Its ^1H NMR spectrum revealed the existence of two NH protons at δ 12.11 and 9.93 ppm, and NH_2 protons at δ 4.90 ppm. IR spectrum of **24** lacked carbonyl functionality, kept nitrile functionality at ν 2216 cm^{-1}, and showed a band for NH group at ν 3305 cm^{-1}. A compulsory clue for the presented structure was acquired from its ^1H NMR spectrum that offered the following signals: 13.07 (br.s, NH), 9.24 (s, C5-H pyrazole), 8.16 (s, CH=), in addition to the aromatic protons. Meanwhile, ^1H NMR spectrum of **25** acquired two NH protons of benzimidazole and amide groups at δ 14.20 and 12.29 ppm, respectively.

A plausible explanation for the formation of compounds **23** and **24** can be outlined in Scheme 6.[32,33] Evidently, the reaction involves the initial formation of benzamide derivative **23** by nucleophilic attack at position-4. This benzamide derivative passes through the intermediate **(I)** that possibly exists in equilibrium with its isomeric compound **(II)** whose cyclization and then cleavage would afford benzimidazole derivative **24** and anthranilic acid **2**.

Our work was expanded to inspect the reactions of benzoxazinone derivative **4** with hydrazinecarbothioamide and hydrazinecarbothiohydrazide. Thus, when **4** reacted with the former in boiling dioxane, the thiosemicarbazide derivative **27** was obtained. Accordingly, formation of **27** can be viewed via the initial nucleophilic attack of the free amino group of hydrazinecarbothioamide on the lactone carbonyl carbon atom followed by oxazinone ring opening. On the other hand, execution of the reaction in

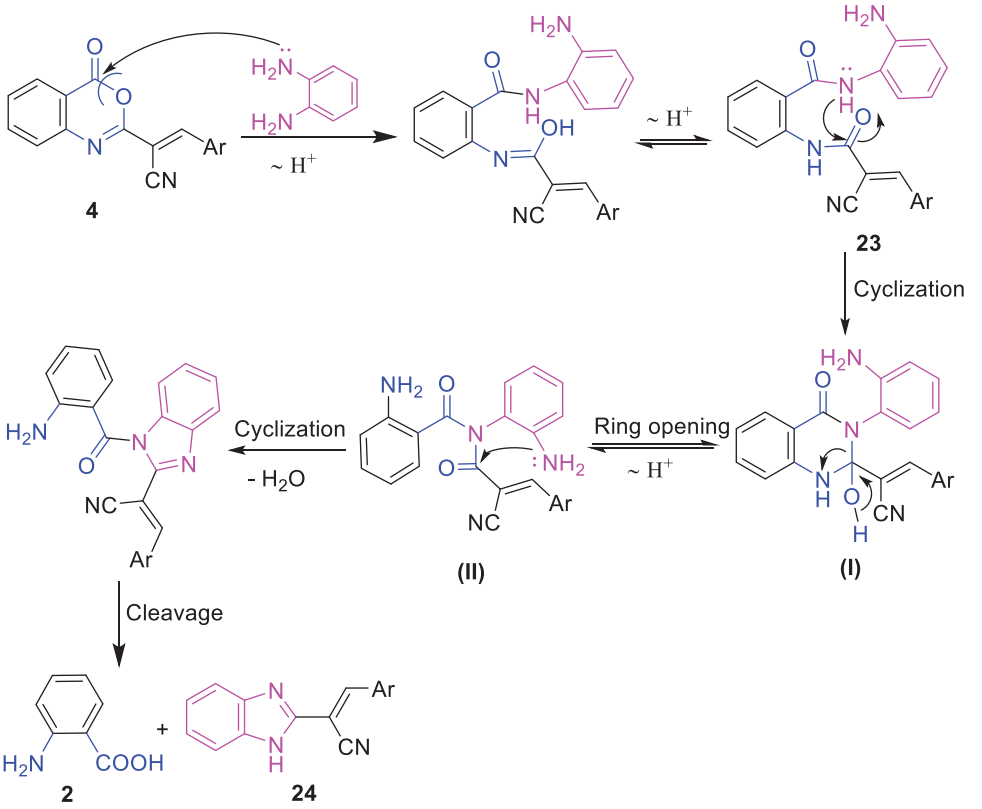


Scheme 5. Synthesis of compounds **23–25**.

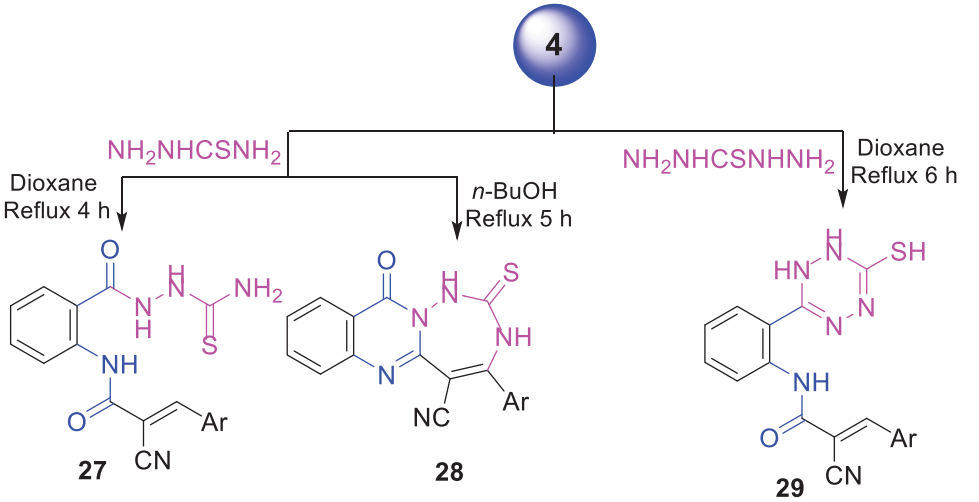
higher boiling point solvent like *n*-butanol provided triazepinoquinazoline derivative **28**. Presumably, the formation of **28** can be visualized via cyclization of **27** by elimination of water molecule followed by aza-Michael addition (which was enhanced by the higher boiling point solvent)[34] on the *β*-carbon of the activated nitrile. Finally, hydrazinecarbothiohydrazide was conducted with benzoxazinone **4** in boiling dioxane to produce mercaptotetrazine derivative **29** (Scheme 7).

Antioxidant screening

Some of the synthesized compounds were screened for their antioxidant activity using ABTS assay.[35] Ascorbic acid was utilized as a reference antioxidant drug. Ascorbic acid is protecting the double bonds and scavenging oxygen as the two free radicals formed at 2- and 3-positions may be intermediates in scavenging oxygen and inhibiting the radical formation at double bonds (cf. Figure 2). Absorption was recorded and the



Scheme 6. Suggested pathways for compounds **23** and **24**.



Scheme 7. Reactions of **4** with hydrazinecarbothioamide and hydrazinecarbothiohydrazide.

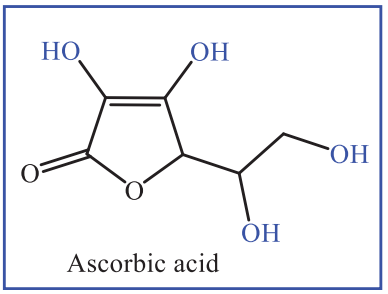


Figure 2. Ascorbic acid (standard antioxidant drug).

Table 1. Results of antioxidant activity of the examined compounds.

Samples	Absorbance	% Inhibition
Control of ABTS	0.500	0
Ascorbic acid	0.058	88.4
3	0.108	78.4
4	0.201	59.8
5	0.105	79.0
6	0.152	69.6
8	0.141	71.8
9	0.138	72.4
10	0.131	73.8
11	0.110	78.0
12	0.098	80.4
13	0.103	79.5
15	0.291	41.8

alleviation in the color intensity was expressed as percent inhibition which can be calculated *via* the attached equation below:

$$\%\ Inhibition = \frac{Abs(control) - Abs(test)}{Abs(control)} \times\ 100$$

The antioxidant results (cf. Table 1) disclosed that all tested compounds were potent. Compounds **3, 5, 11, 12,** and **13** were the most potent with % inhibition = 78.4, 79.0, and 78.0, 80.4 and 79.5%, respectively. Likewise, compounds **6, 8, 9,** and **10** displayed strong efficacy. Compounds **4** and **15** exhibited moderate activity. The antioxidant results may comprise the subsidiary structure-activity relationship: (i) Existence of a pyrazole moiety manifested to be pivotal for noteworthy inhibitory antioxidant activity. (ii) the presence of OH, NH, and NH_2 groups increased the capacity to scavenge free radicals and thus enhanced the antioxidant activity.[36,37]

Conclusion

A novel series of pyrazole-based heterocyclic systems was prepared starting from the benzoxazinone building block **(4)** through reactions with some mono and bidentate nucleophiles. The reaction with ammonium acetate was mainly dependent upon the heating period. In contrast, the reaction with 4-aminoacetophenone was dependent upon whether equal or double molar ratios. Hydrazinolysis of **4** produced the

biquinazoline derivative **15** and the diheterylazine **16** depending on the reaction conditions. Noteworthy, the benzimidazole derivatives were obtained upon treatment with 2-aminoaniline under different reaction conditions. Finally, thiosemicarbazide, triazepinoquinazoline and mercaptotetrazine derivative **27–29** were achieved by conducting benzoxazinone **4** with hydrazinecarbothioamide and hydrazinecarbothiohydrazide. The antioxidant activity evaluation of some of the synthesized compounds revealed that some of them exhibiting significant potency as compared with ascorbic acid.

Experimental

General

Chemicals and solvents obtained from Sigma Aldrich, Merck, Fluka, and El-Nasr pharmaceutical chemicals companies were purified and dried by standard techniques. All melting points were measured on a GALLENKAMP electric melting point apparatus and are uncorrected. IR spectra (ν, cm^{-1}) were run at the Department of Chemistry, Faculty of Science, Ain Shams University utilizing KBr disks on FTIR Thermo Electron Nicolet iS10 infrared spectrometer (Thermo Fisher Scientific Inc., Waltham, MA, USA). ^{1}H NMR spectra (δ, ppm) were run at 300 *MHz* on a GEMINI NMR spectrometer (GEMINI, Manufacturing & Engineering Inc., Anaheim, CA, USA) utilizing tetramethylsilane (TMS) as an internal standard in deuterated dimethyl sulfoxide. Elemental analyses were run at Faculty of Science, Ain Shams University utilizing Perkin-Elmer 2400 CHN elemental analyzer. The starting 2-cyanopropenoyl chloride **1** was previously reported by us.[1]

2-(2-Cyano-3-(1,3-diphenyl-1H-pyrazol-4-yl)acrylamido)benzoic acid (3)

Anthranilic acid **2** (1.37 g, 0.01 mol) was added to a stirred solution of 2-cyanopropenoyl chloride derivative **1** (3.33 g, 0.01 mol) in dry dioxane (15 mL) containing triethylamine (3-drops) and the reaction mixture was further stirred at ambient temperature for 2 h. The precipitate was filtered off and then recrystallized from dioxane to produce propenylamide derivative **3** as pale-yellow crystals, mp. 292–290 °C, yield 88%. IR: 3426 (*br*.OH,NH), 2210 (CN), 1702 (CO acid), 1686 (CO amide). ^{1}H NMR: 13.40 (br.s, 1H, OH, exchangeable), 12.29 (br.s, 1H, NH, exchangeable), 9.22 (s, 1H, C5-H pyrazole), 8.62 (d, 1H, Ar-H, $J = 8.4\,Hz$), 8.25 (s, 1H, CH=), 8.07–7.22 (m, 11H, Ar-H), 7.47 (t, 1H, Ar-H, $J = 7.28\,Hz$), 7.24 (t, 1H, Ar-H, $J = 7.52\,Hz$). Anal. Calcd. for $C_{26}H_{18}N_4O_3$ (434.46): C, 71.88; H, 4.18; N, 12.90. found: C, 71.73; H, 4.04; N, 12.87%.

3-(1,3-Diphenyl-1H-pyrazol-4-yl)-2-(4-oxo-4H-benzo[d][1,3]oxazin-2-yl)propenonitrile (4)

A suspension of propenylamide derivative **3** (4.16 g, 0.01 mol) in acetic anhydride (5 mL) was heated on water bath at 80 °C for 3 h. A deposited solid after cooling was filtered off and then recrystallized from benzene to furnish the benzoxazinone **4** as yellow crystals, mp. 290–292 °C, yield 85%. IR: 2222 (CN), 1768 (CO). ^{1}H NMR: 9.28 (s, 1H, C5-H pyrazole), 8.18 (s, 1H, CH=), 8.13 (d, 1H, Ar-H, $J = 7.8\,Hz$), 7.99–7.61 (m,

12H, Ar-H), 7.49 (t, 1H, Ar-H, $J = 7.32\,Hz$). Anal. Calcd. for $C_{26}H_{16}N_4O_2$ (416.44): C, 74.99; H, 3.87; N, 13.45. Found: C, 74.84; H, 3.75; N, 13.47%.

Full Experimental details, tables, and spectroscopic data can be found at supplemental files.

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Disclosure statement

No potential conflict of interest was reported by the author(s).

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