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Multi-component synthesis and invitro biological assessment of novel pyrrole derivatives and pyrano[2,3-c]pyrazole derivatives using Co_3O_4 nanoparticles as recyclable nanocatalyst

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In this study, Co_3O_4 nanoparticles were used as nanocatalyst for two different series of nitrogen-containing heterocyclic compounds, including pyrrole (Pyo) derivatives and pyrano [2, 3-c]pyrazole (Pya[2, 3-c]Pyz) derivatives. In the synthesis of derivatives, using 15 mol% and 10 mol% of the catalyst for Pyo derivatives and Pya[2, 3-c]Pyz derivatives, respectively, an efficiency between 83% and 96%, were observed. In addition, novel derivatives of Pyo and Pya[2,3-c]Pyz were synthesized and their structures were confirmed. In general, the advantages of using cobalt nanoparticles compared to previous reports include the synthesis of new derivatives, lower temperature used in the synthesis of derivatives, shorter synthesis time and high efficiency. The biological properties of the synthesized products, such as antibacterial, antifungal, and antioxidant properties, were tested and investigated. In antibacterial and antifungal tests, IZD, MIC, MBC, and MFC were measured and reported. In antioxidant activity, IC_{50} was calculated and reported. High reusability, green and environmentally friendly, synthesis of new derivatives and synthesis of products with higher efficiency and shorter time were the important benefits of using cobalt nanoparticles as a catalyst. In antioxidant tests, the IC_{50} for synthesized Pyo derivatives and Pya[2, 3-c] Pyz derivatives were between 12.2 and 13.71 μg/mL, and 16.18–17.75 μg/mL, respectively. In antimicrobial testes, the MIC for synthesized Pyo derivatives and Pya[2, 3-c]Pyz derivatives were between 2 and 4,096 μg/mL, and 2–2048 μg/mL, respectively. The results showed that the antioxidant property of Pyo derivatives were more than Pya[2, 3-c] Pyz derivatives, but the antimicrobial effect of Pya[2,3-c]

Pyz derivatives were more than Pyo derivatives. The antioxidant results proved that the activity of Pyo derivatives and Pya[2, 3-c] Pyz derivatives does not depend on the substitutions of the derivatives and is close to each other. Therefore, based on this, a proposed mechanism for stability of DPPH by Pyo derivatives and Pya[2, 3-c] Pyz derivatives were suggested. Finally, based on the more stable resonance structures of Pyo derivatives, compared to Pya[2, 3-c] Pyz derivatives, its high antioxidant property was justified. Pya[2, 3-c] Pyz derivatives has two heterocyclic rings connected together pyrano and pyrazole, but Pyo derivatives has only one heterocyclic ring (pyrrole). So high antimicrobial property of Pya[2, 3-c] Pyz derivatives compared to Pyo derivatives can be attributed to having two bioactive heterocyclic rings.

KEYWORDS

green chemistry, multi-component reaction, antimicrobial evaluation, antioxidant evaluation, Co3O4 nanoparticles, pyrrole derivatives, Pyrano[2,3-c]pyrazole derivatives

1 Introduction

Pyrrole (Pyo) is a five-member heterocyclic compound with one nitrogen in its structure. Biological activity such as anticancer, antitumor, anti-inflammatory, antiviral, antimicrobial, antituberculosis, and antioxidant have been reported from compounds containing Pyo derivatives (Petri et al., 2020; Zhou et al., 2020; Boichuk et al., 2021; Rawat et al., 2021; Reddy et al., 2021; Jeelan Basha et al., 2022). Pyo derivatives were found abundantly in nature. For example, Pyo derivatives were found in marine-derived fungi, such as *Penicillium citrinum* and *Aspergillus sclerotiorum* (Seipp et al., 2021). The use of Pyo derivatives as solvents for resin, polymerization processes, and erosion inhibitors is prevalent in industries (Bhardwaj et al., 2015).

Another five-member heterocyclic compound that has two nitrogen atoms in positions one and two in its structure is pyrazole. Pyrazole derivatives are present in the construction of commercial drugs such as Celecoxib and Fomepizole (Alam et al., 2015). Other biological properties reported for this heterocyclic compound include anticancer activity, antiviral, antimicrobial activity, anticonvulsant and antidepressant activity, anti-inflammatory activity, and antimicrobial activity (Faria et al., 2017; Faisal et al., 2019). Many multi-ring structures containing pyrazole derivatives with five-member heterocyclic compounds, such as pyrazolopyridine derivatives, pyrazolopyrimidine derivatives, pyranopyrazole derivatives, etc., have been reported with biological properties (Faisal et al., 2019; Rao and Chanda, 2020; Biswas and Das, 2022).

Pyrano [2,3-c]pyrazole (Pya[2,3-c]Pyz) derivatives, which are formed by connecting two heterocyclic compounds of pyran and pyrazole, is a heterocyclic compound with outstanding biological properties that retain the properties of both heterocyclic compounds of pyrazole and pyran. Several methods have been reported for synthesizing Pya[2,3-c]Pyz derivatives, including, the use of various metals and metal oxides (Muthuraja et al., 2017; Veeramani et al., 2018; Vairaperumal et al., 2019). The previous literature demonstrated that this heterocyclic compound has various biological properties, including anticancer, anti-malarial agents, anticonvulsant, analgesic, antimicrobial, and anti-inflammatory (Biswas and Das, 2022).

Pyrans, which play an essential role in the properties of Pya[2,3-c]Pyz derivatives, are 6-membered heterocyclic compounds containing one oxygen. The most important natural compound containing pyran is vitamin E, essential for humans (Garazd and Garazd, 2016).

Several methods have been reported for Pya[2,3-c]Pyz derivatives and Pyo derivatives, but multicomponent reactions are the most important method and scientists have focused on it. Multicomponent reactions that are one-pot reactions align with the rules of green chemistry (Baral et al., 2020; Sikandar and Zahoor, 2021). In addition to the green nature of multi-component reactions, it is possible to mention the convenience of the synthesis steps of the final product, high efficiency, and cost-effectiveness in terms of economy, etc (Javahershenas and Nikzat, 2023). In multicomponent reactions, the suitable catalyst plays a key role (Costanzo et al., 2018; Rahimi et al., 2022).

Using metal oxide nanoparticles is a suitable option as a catalyst in these reactions (Damera et al., 2023; Soltani et al., 2023). Cobalt oxide nanoparticles are a good choice due to their high catalytic properties. This oxidized metal catalyst has been used in the synthesis of heterocyclic compounds and organic reactions such as, arylidene barbituric and Meldrum's acid derivatives, benzochromenes derivatives, and Ugi adduct from aryl alcohols (Chacko and Shivashankar, 2017; Shahbazi et al., 2019; Yahyazadehfar et al., 2019; Kafi-Ahmadi et al., 2021).

Considering the importance of using green chemistry for the synthesis of Pyo derivatives and Pya[2,3-c]Pyz derivatives, with biological properties, novel Pyo derivatives and Pya[2,3-c]Pyz derivatives were synthesized using cobalt oxide nanoparticles as a green, efficient, and recyclable catalyst during a multicomponent reaction. In studying biological activities, *in vitro* antioxidant and *in vitro* antimicrobial properties of synthesized derivatives were evaluated.

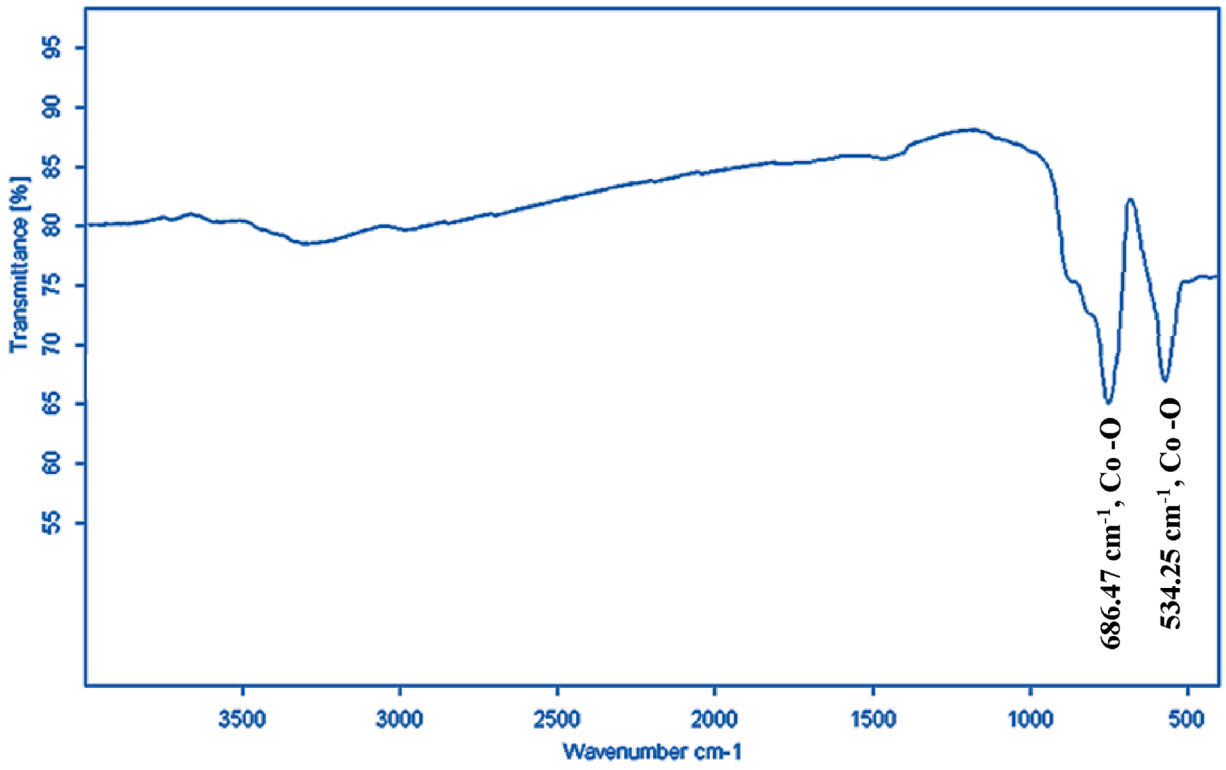

FIGURE 1
The FTIR spectrum of Co_3O_4 nanoparticles.

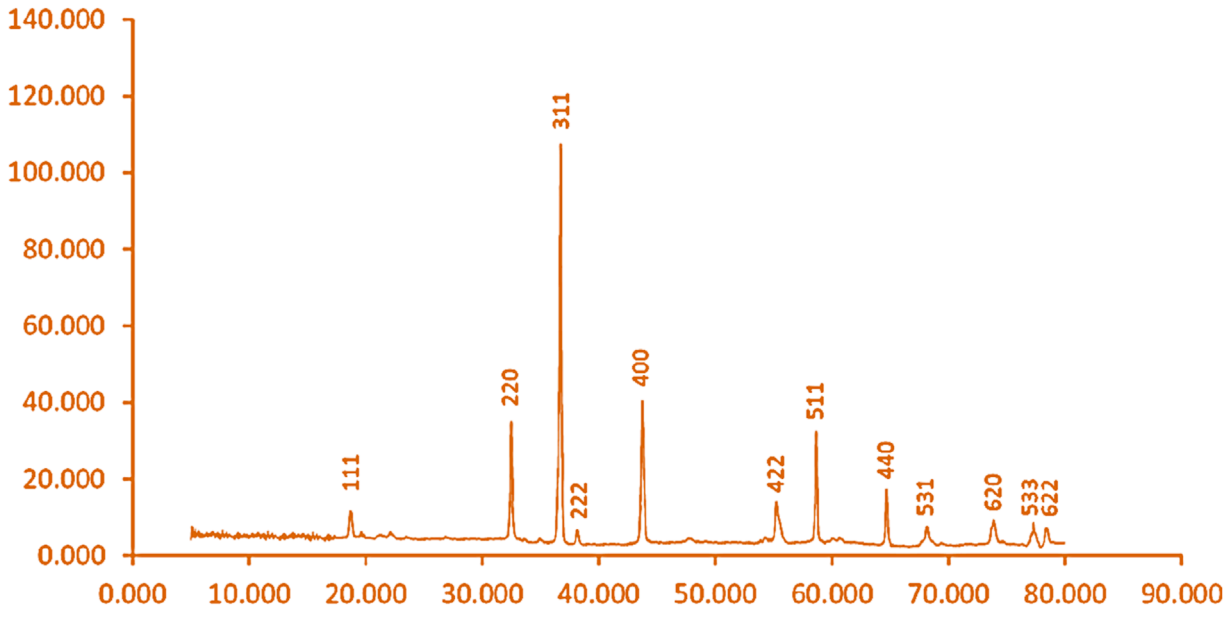

FIGURE 2
The XRD pattern of Co_3O_4 nanoparticles.

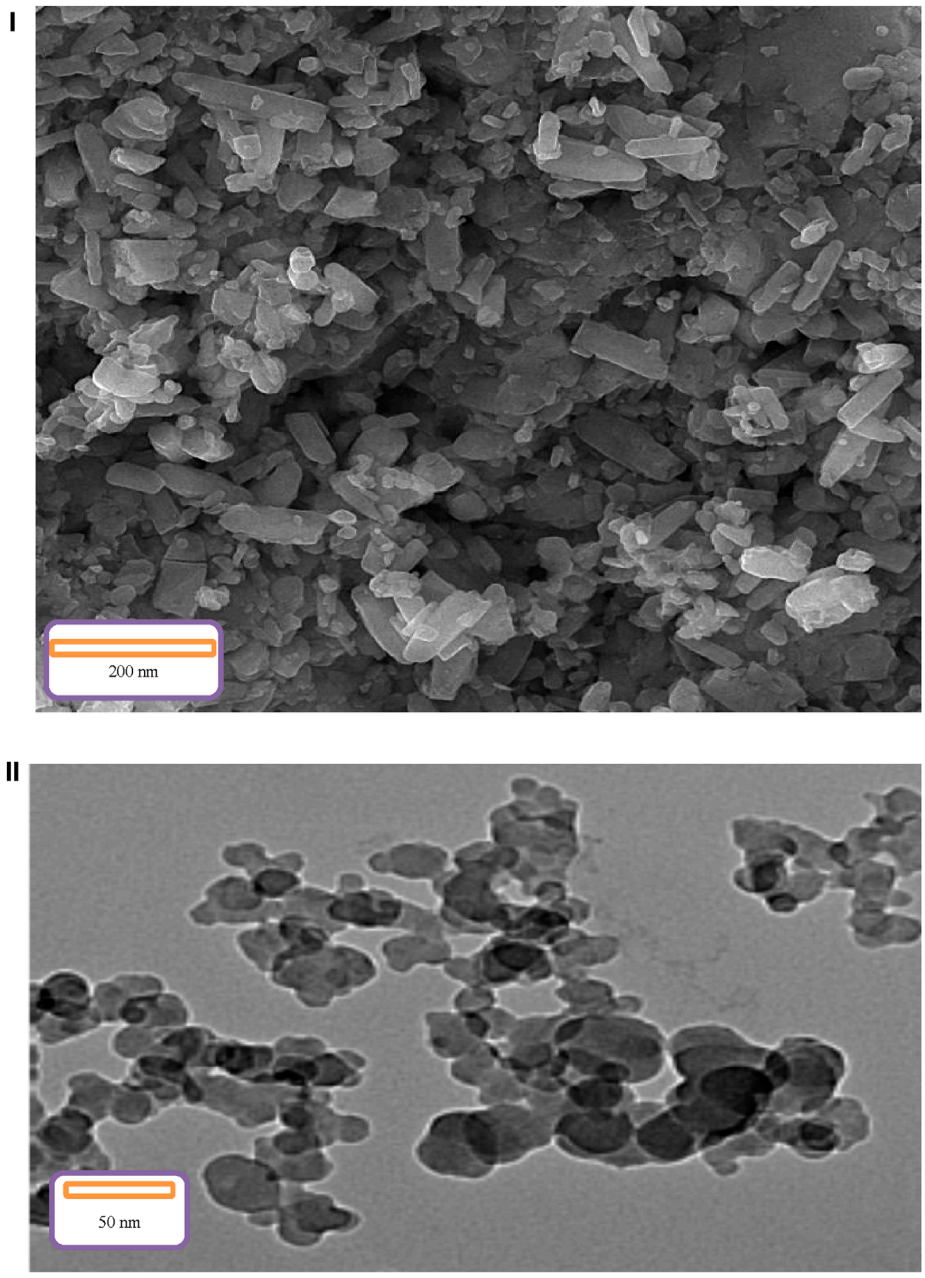

FIGURE 3
The SEM (I) and TEM (II) images of Co_3O_4 nanoparticles.

2 Experimental

2.1 Materials and structure verification equipment

The required solvents, materials, and antibiotics were prepared from Merck and Sigma. The microorganisms studied were prepared from ATCC (American Type Culture Collection).

Fourier transform infra-red spectra of Co_3O_4 nanoparticles and synthesized derivatives were recorded using Nicolet IS10. The Shimadzu XRD-7000 was used for X-ray diffraction of Co_3O_4 nanoparticles. The scanning electron microscope image of Co_3O_4 nanoparticles using Gemini SEM 500 was prepared. The carbon and hydrogen nuclear magnetic resonance of synthesized derivatives using Bruker FT-NMR ultra shield- 400 spectrometer were obtained. The melting points of a synthesized compound using Electrothermal IA9200 were obtained. Element analysis of synthesized derivatives using Thermo FlashSmart CHNS/O elemental analyzer was done. The Shimadzu UV-3600 Plus was used in biological evaluations.

2.2 Synthesis of Co_3O_4 nanoparticles

To synthesize Co_3O_4 nanoparticles, in a flask containing 100 mL of double distilled water, 1 g pluronic F-127 was added and stirred

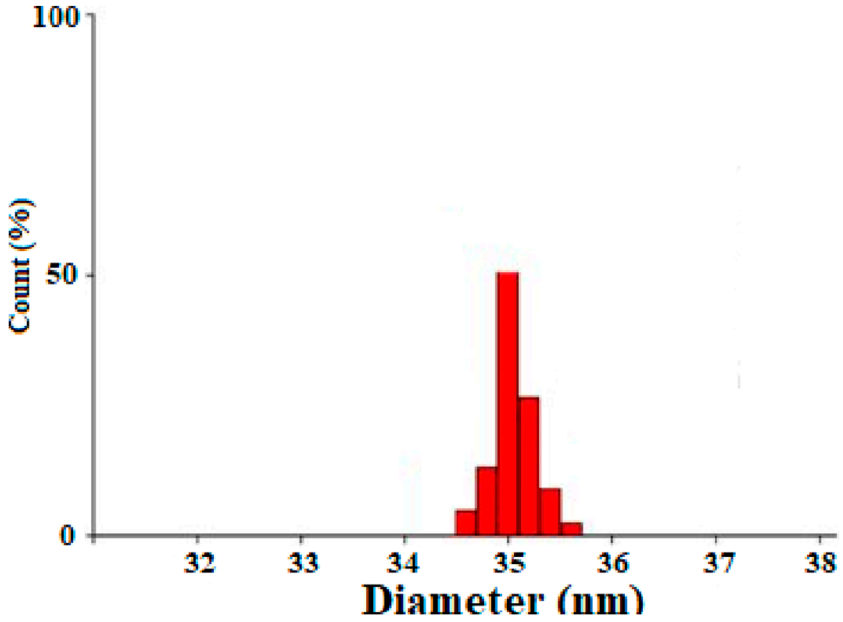

FIGURE 4
The DSL analysis of Co_3O_4 nanoparticles.

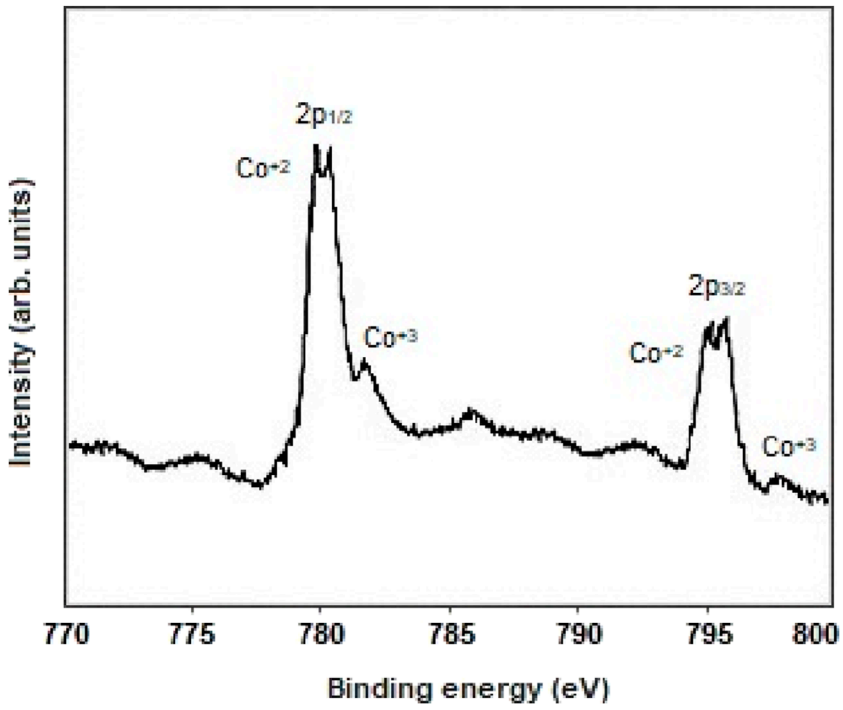

FIGURE 5
The XPS analysis of Co_3O_4 nanoparticles.

(1,000 rpm) at room temperature for 30 min. Then add 100 mL of cobalt nitrate solution (0.1 M) and stir) at room temperature for 30 min. Drop by drop, add 100 mL of NaOH solution 2 M and stir at 100°C for 72 h. In the next step, methanol (100 mL) was added to the mixture and stirred at room temperature for 4 h. The mixture was kept at room temperature for 12 h. The sediments were separated using Whatman filter paper and washed with double distilled water until they reached pH 7. Sediments obtained dried in an oven at

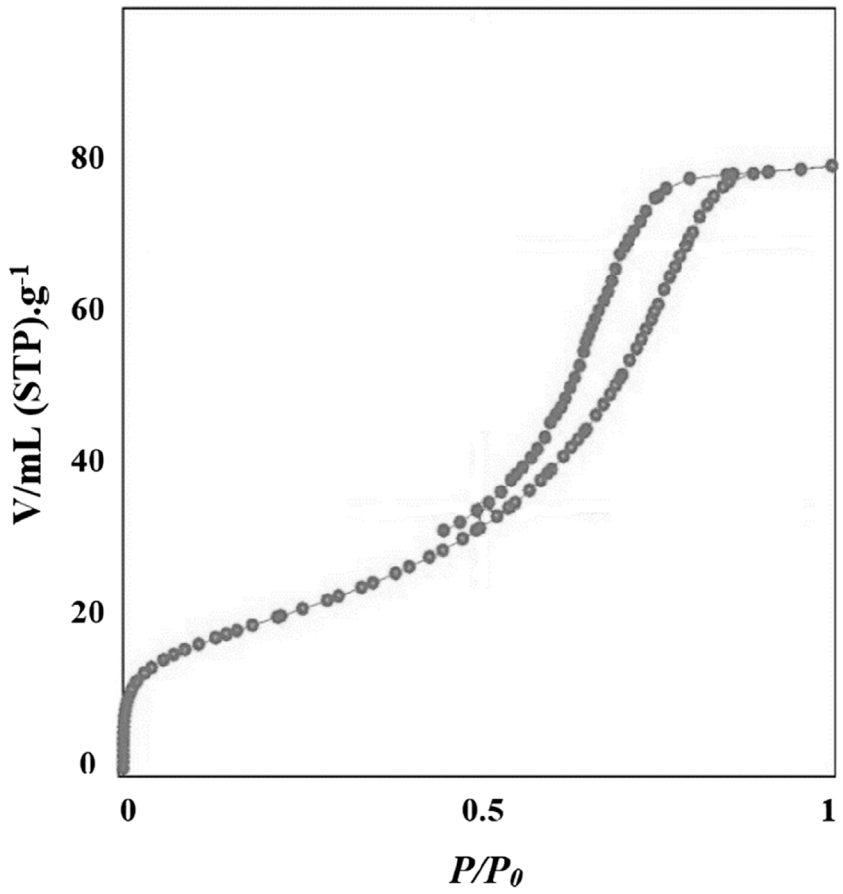

FIGURE 6
The nitrogen adsorption/desorption isotherms of Co_3O_4 nanoparticles.

100°C for 60 min. Finally, it was placed in a muffle furnace at a temperature of 500°C for 4 h (Sadasivan et al., 2013; Uddin and Baig, 2019).

2.3 Synthesis of pyrrole (pyo) derivatives

1 mmol cyclohexanamine or phenylmethanamine, 1 mmol dimethyl but-2-ynedioate or diethyl but-2-ynedioate were added to the 2 mL water/ethanol (1:1) and were stirred at room temperature for 15 min. To the mixture, 10 mol percent of Co_3O_4 nanoparticles, 1 mmol of formaldehyde and 1 mmol of aromatic amine nanoparticles were added and stirred at room temperature. After the completion of the reaction, which was monitored by TLC, acetone (5 mL) was added to the mixture, and by using Whatman filter paper, Co_3O_4 nanoparticles were separated. The desired product, which was in solution, was isolated by removing the solvents under vacuum at room temperature. A recrystallization technique in water/ethanol (1:1) was used to purify the synthesized derivatives.

Separated Co_3O_4 nanoparticles were washed thrice with ethanol and water and placed in the oven at 100°C for 24 h for reuse.

2.3.1 Ethyl 4-(benzylamino)-5-oxo-1-(p-tolyl)-2,5-dihydro-1H-pyrrole-3-carboxylate (5d)

Yield: 89%; White powder; FT-IR (KBr, cm^{-1}): 3,275, 1,672, 1,628, 1,564, 1,351; ^{1}H NMR (DMSO-*d6*, 400 MHz), δ (ppm):1.34 (t, J = 8.4 Hz, 3H, CH_3), 2.41 (s, 3H, CH_3), 3.26–3.29 (m, 2H, OCH_2), 4.41 (s, 2H, NCH_2), 5.14 (s, 2H, NCH_2), 6.69 (s, 1H, NH), 7.10 (*d*, J = 7.6 Hz, 2H, Ar-H), 7.25–7.32 (m, 7H, Ar-H); ^{13}C NMR (DMSO-*d6*, 100 MHz), δ (ppm):14.7, 20.6, 46.1, 48.3, 51.4, 97.6, 119.8, 127.7, 127.2, 128.6, 129.2, 134.9, 136.3, 139.8, 164.5, 165.1; Element analysis. Calcd for $C_{21}H_{22}N_2O_3$: C, 71.98; H, 6.33; N, 7.99; O, 13.70; Found: C, 71.96; H, 6.31; N, 7.98; O, 13.75.

2.3.2 Ethyl 4-(benzylamino)-1-(4-methoxyphenyl)-5-oxo-2,5-dihydro-1H-pyrrole-3-carboxylate (5f)

Yield: 87%; Light yellow powder; FT-IR (KBr, cm^{-1}): 3,301, 1,682, 1,637, 1,549, 1,377; ^{1}H NMR (DMSO-*d6*, 400 MHz), δ (ppm): 1.29 (t, J = 7.4 Hz, 3H, CH_3), 3.34–3.38 (m, 2H, CH_2), 3.79 (s, 3H, OCH_3), 4.46 (s, 2H, NCH_2), 5.19 (s, 2H, NCH_2), 6.63 (s, 1H, NH), 6.87 (*d*, J = 8.4 Hz, 2H, Ar-H), 7.31–7.34 (m, 5H, Ar-H), 7.59 (*d*, J = 8.4 Hz, 2H, Ar-H); ^{13}C NMR (DMSO-*d6*, 100 MHz), δ (ppm):15.16, 46.4, 48.5, 51.7, 55.9, 95.1, 114.6, 120.6, 121.3, 127.4, 127.8, 128.5, 131.2, 135.1, 157.6, 164.4, 165.7; Element analysis.

TABLE 1 Optimization of catalyst, solvent, and temperature in synthesis pyrrole (Pyo) (5a) and pyrano [2, 3-c]pyrazole (Pya[2, 3-c]Pyz) (10a).

Product	mol% of catalyst	Solvent	Temperature (°C)	Tim (min)	Yield (%)
5a	0	EtOH	25	60	20
10a				30	27
5a	5	EtOH	25	60	65
10a				30	80
5a	10	EtOH	25	60	81
10a				**15**	**92**
5a	15	EtOH	25	**40**	**93**
10a				30	91
5a	20	EtOH	25	40	93
10a				30	91
5a	25	EtOH	25	60	90
10a				30	90
5a	50	EtOH	25	60	90
10a				30	83
5a	100	EtOH	25	60	85
10a				30	80
5a	15	H_2O	25	60	22
10a	10			30	42
5a	15	MeOH	25	60	58
10a	10			30	44
5a	15	**1:1 (H_2O/EtOH)**	**25**	**40**	**96**
10a	10			15	92
5a	15	DMF	25	60	42
10a	10			30	36
5a	15	**1:1 (H_2O/EtOH)**	**40**	60	90
10a	10			**12**	**95**
5a	15	1:1 (H_2O/EtOH)	50	60	85
10a	10			12	95
5a	15	1:1 (H_2O/EtOH)	60	60	78
10a	10			12	90

(Continued on the following page)

TABLE 1 (*Continued*) Optimization of catalyst, solvent, and temperature in synthesis pyrrole (Pyo) (5a) and pyrano [2, 3-c]pyrazole (Pya[2, 3-c]Pyz) (10a).

Product	mol% of catalyst	Solvent	Temperature (°C)	Tim (min)	Yield (%)
5a	15	1:1 (H_2O/EtOH)	70	60	77
10a	10			15	85
5a	15	1:1 (H_2O/EtOH)	Reflux	60	75
10a	10			30	85

Bolded values are correspond to obtained optimal conditions.

Calcd for $C_{21}H_{22}N_2O_4$: C, 68.84; H, 6.05; N, 7.65; O, 17.46; Found: C, 68.87; H, 6.04; N, 7.63; O, 17.46.

2.3.3 Methyl 4-(cyclohexylamino)-5-oxo-1-(p-tolyl)-2,5-dihydro-1H-pyrrole-3-carboxylate (5k)

Yield: 92%; White powder; FT-IR (KBr, cm^{-1}): 3,324, 1,677, 1,625, 1,531, 1,386; ^1H NMR (DMSO-*d6*, 400 MHz), δ (ppm): 1.07–1.22 (m, 8H, CH_2), 1.41–1.47 (m, 2H, CH_2), 2.36 (s, 3H, CH_3), 3.17–3.22 (m, 1H, CH), 3.71 (s, 3H, OCH_3), 4.35 (s, 2H, NCH_2), 6.54 (s, 1H, NH), 7.11–7.16 (m, 2H, Ar-H), 7.51–7.58 (m, 2H, Ar-H); ^{13}C NMR (DMSO-*d6*, 100 MHz), δ (ppm): 20.5, 24.3, 25.6, 34.5, 48.5, 50.7, 59.3, 100.5, 119.7, 129.3, 134.2, 136.1, 164.3, 165.6; Element analysis. Calcd for $C_{19}H_{24}N_2O_3$: C, 69.49; H, 7.37; N, 8.53; O, 14.61; Found: C, 69.51; H, 7.35; N, 8.49; O, 14.65.

2.4 Synthesis of pyrano [2,3-c]pyrazole (Pya[2,3-c]Pyz) derivatives

10 mol percent of Co_3O_4 nanoparticles, 1 mmol ethyl acetoacetate, 1 mmol phenylhydrazine were added to the 2 mL water/ethanol (1:1) and were stirred at 50°C. After the completion of the reaction, which was monitored by TLC, 1 mmol of malononitrile and 1 mmol of aldehyde were added and stirred at 50°C. After the completion of the reaction, which was monitored by TLC and cooled to room temperature, acetone (5 mL) was added to the mixture, and by using Whatman filter paper, Co_3O_4 nanoparticles were separated. The desired product, which was in solution, was isolated by removing the solvents under vacuum at room temperature. A recrystallization technique in water/ethanol (1:1) was used to purify the synthesized derivatives.

Separated Co_3O_4 nanoparticles were washed thrice with ethanol and water and placed in the oven at 100°C for 24 h for reuse.

2.4.1 6-amino-3-methyl-1-phenyl-4-(3, 4, 5-trimethoxyphenyl)-1,4-dihydropyrano [2,3-c]pyrazole-5-carbonitrile (10e)

Yield: 90%; Light yellow powder; FT-IR (KBr, cm^{-1}): 3,431, 3,392, 3,112, 2,946, 2,911, 2,197, 1,663, 1,521, 1,452, 1,327,

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TABLE 2 Synthesized pyrrole (Pyo) derivatives using Co_3O_4 nanoparticles.

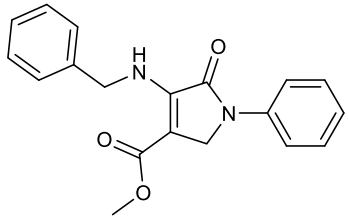
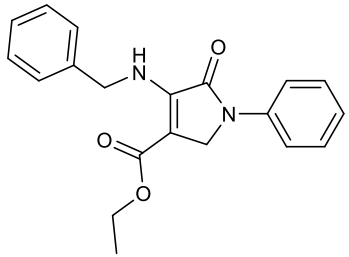
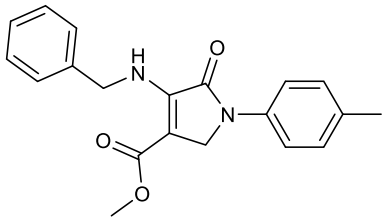
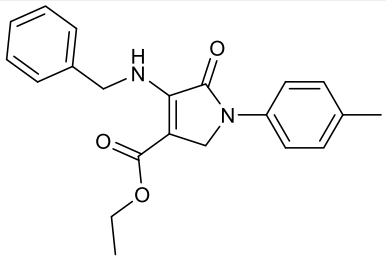
Product	R_1	R_2	Aryl	Structure	Time (min)	Yield (%)	Mp (°C)	
							Found	Reported
5a	$-CH_2-C_6H_5$	Me	$-C_6H_5$		40	96	141–142	140–141 (Khan et al., 2012)
5b	$-CH_2-C_6H_5$	Et	$-C_6H_5$		45	95	129–131	131–133 (Mohamadpour, 2022)
5c	$-CH_2-C_6H_5$	Me	$4\text{-Me-}C_6H_4$		55	95	144–146	145–147 (Khan et al., 2012)
5d	$-CH_2-C_6H_5$	Et	$4\text{-Me-}C_6H_4$		90	89	152–154	Novel

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TABLE 2 (*Continued*) Synthesized pyrrole (Pyo) derivatives using Co_3O_4nanoparticles.

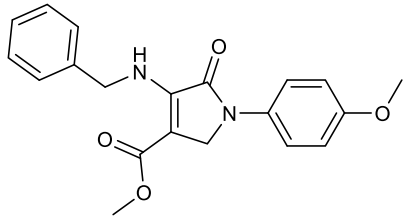
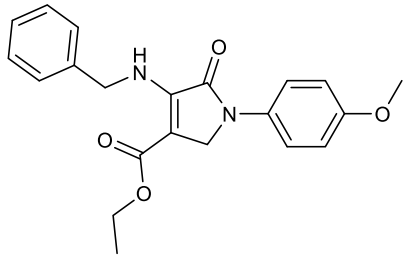
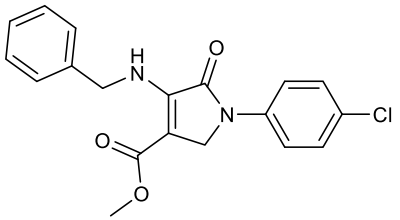
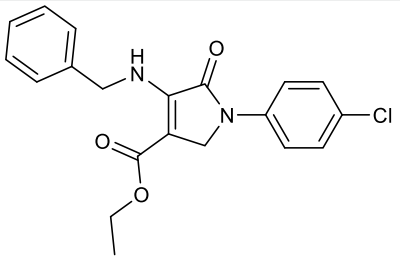
Product	R_1	R_2	Aryl	Structure	Time (min)	Yield (%)	Mp (°C)	
							Found	Reported
5e	$-CH_2-C_6H_5$	Me	4-OMe-C_6H_4		90	86	126–128	125–127 (Nickraftar et al., 2016)
5f	$-CH_2-C_6H_5$	Et	4-OMe-C_6H_4		115	87	140–143	Novel
5g	$-CH_2-C_6H_5$	Me	4-Cl-C_6H_4		120	88	145–147	147–148 (Khan et al., 2012)
5h	$-CH_2-C_6H_5$	Et	4-Cl-C_6H_4		125	83	142–143	140–142 (Khan et al., 2016)

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TABLE 2 (*Continued*) Synthesized pyrrole (Pyo) derivatives using Co_3O_4nanoparticles.

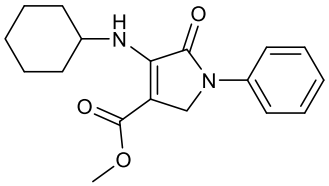
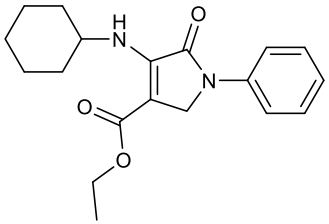
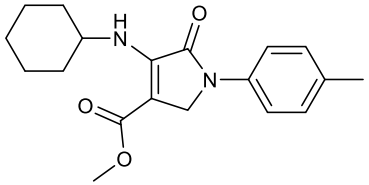
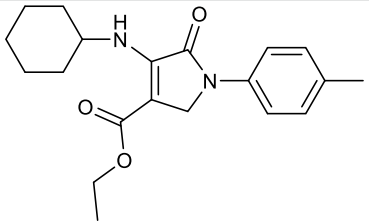
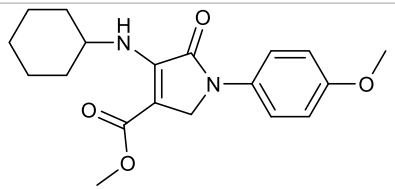
Product	R_1	R_2	Aryl	Structure	Time (min)	Yield (%)	Mp (°C)	
							Found	Reported
5i	$-C_6H_{11}$	Me	$-C_6H_5$		55	93	95–98	96–97 (Zhang et al., 2017)
5j	$-C_6H_{11}$	Et	C_6H_5		85	89	75–77	76–77 (Basirat et al., 2020)
5k	$-C_6H_{11}$	Me	4-Me-C_6H_4		90	92	118–120	Novel
5L	$-C_6H_{11}$	Et	4-Me-C_6H_4		80	90	105–108	105–107 (Sharghi et al., 2018)
5m	$-C_6H_{11}$	Me	4-OMe-C_6H_4		70	91	126–129	127–129 (Nickraftar et al., 2016)

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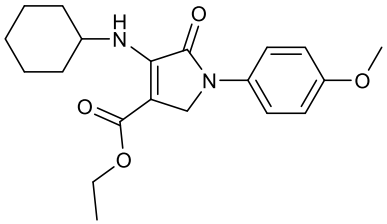
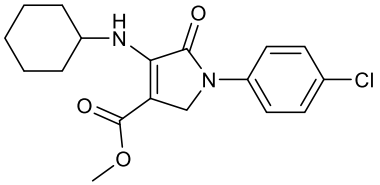
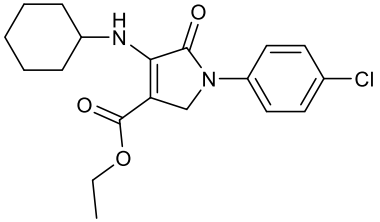
TABLE 2 (*Continued*) Synthesized pyrrole (Pyo) derivatives using Co_3O_4nanoparticles.

Product	R_1	R_2	Aryl (H)	Structure	Time (min)	Yield (%)	Mp (°C)	
							Found	Reported
5n	$-C_6H_{11}$	Et	4-OMe-C_6H_4		85	92	100–103	102–103 (Zhu et al., 2012)
5o	$-C_6H_{11}$	Me	4-Cl-C_6H_4		120	92	122–123	123–125 (Nickraftar et al., 2016)
5p	$-C_6H_{11}$	Et	4-Cl-C_6H_4		120	94	90–91	91–92 (Zhu et al., 2012)

15 mol % catalyst; 1:1 water/ethanol; 25°C.

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TABLE 3 Synthesized pyrano [2,3-c]pyrazole (Pya[2,3-c]Pyz) derivatives using Co_3O_4 nanoparticles.

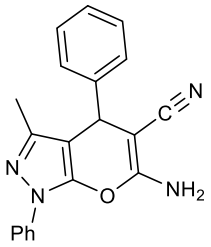
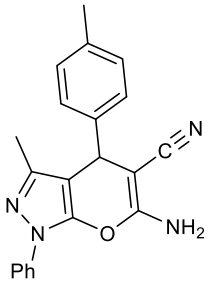
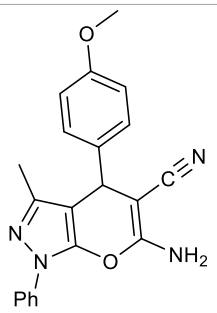
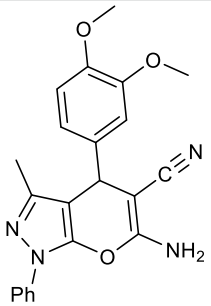
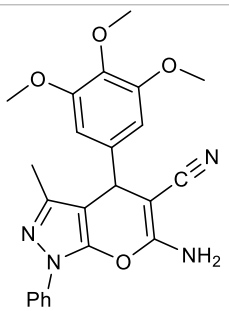
Product	R_3	Structure	Time (min)	Yield (%)	Mp (°C)	
					Found	Reported
10a	-C_6H_5		12	95	165–168	167–169 (Eftekhari Far and Nasr-Esfahani, 2020)
10b	–4-Me-C_6H_4		20	91	175–177	174–176 (Heravi et al., 2022)
10c	–4-OMe-C_6H_4		12	93	168–170	169–171 (Eftekhari Far and Nasr-Esfahani, 2020)
10d	–3,4-OMe-C_6H_3		15	89	190–193	193–195 (Shi et al., 2004)
10e	–3,4,5-OMe-C_6H_2		25	90	201–203	Novel

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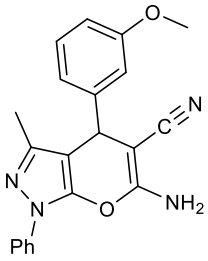
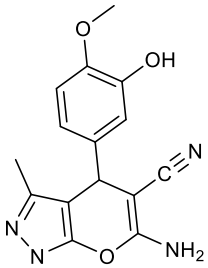
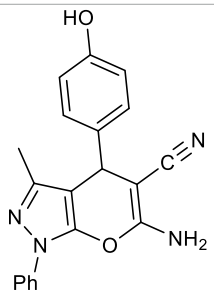
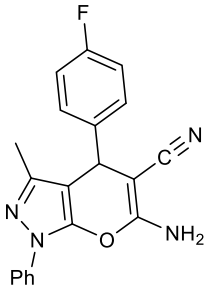
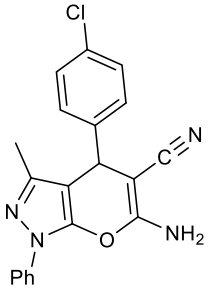
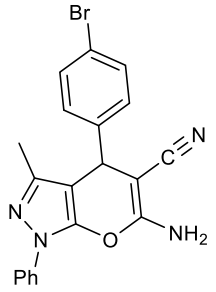
TABLE 3 (*Continued*) Synthesized pyrano [2,3-c]pyrazole (Pya[2,3-c]Pyz) derivatives using Co_3O_4 nanoparticles.

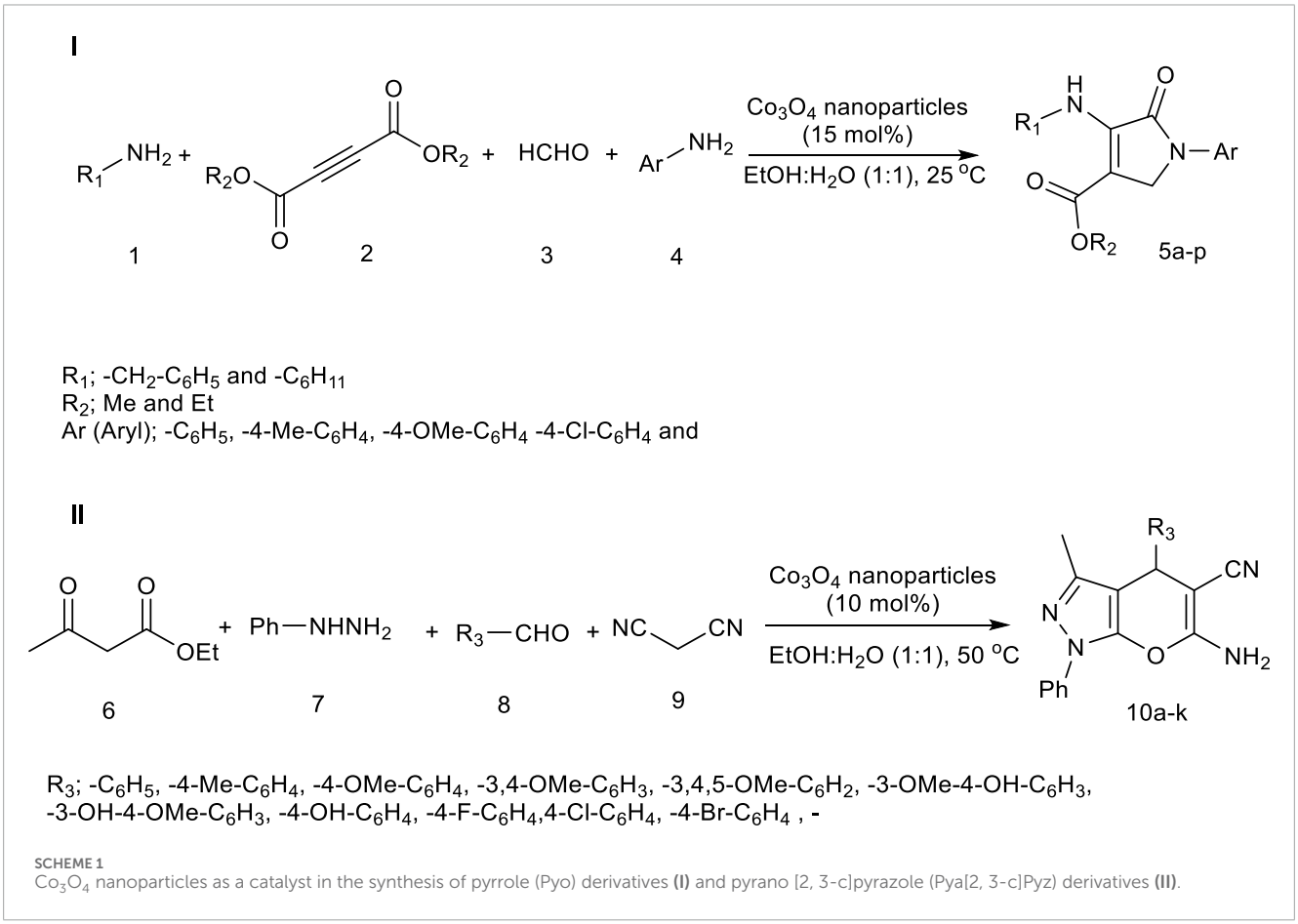
Product	R_3	Structure	Time (min)	Yield (%)	Mp (°C)	
					Found	Reported
10f	−3-OMe,4-OH-C_6H_3		25	89	182–185	182–184 (Eftekhari Far and Nasr-Esfahani, 2020)
10g	−3-OH,4-OMe-C_6H_3		30	87	176–179	Novel
10h	−4-OH-C_6H_4		20	90	207–210	208–210 (Eftekhari Far and Nasr-Esfahani, 2020)
10i	−4-F-C_6H_4		16	92	181–184	183–186 (Sameri et al., 2021)
10j	−4-Cl-C_6H_4		15	95	172–174	170–172 (Sameri et al., 2021)

(Continued on the following page)

TABLE 3 (*Continued*) Synthesized pyrano [2,3-c]pyrazole (Pya[2,3-c]Pyz) derivatives using Co_3O_4 nanoparticles.

Product	R_3	Structure	Time (min)	Yield (%)	Mp (°C)	
					Found	Reported
10k	−4-BrC_6H_4		20	92	191–193	190–193 (Azarifar et al., 2018)

10 mol % catalyst; a 1:1 water/ethanol; 40°C.

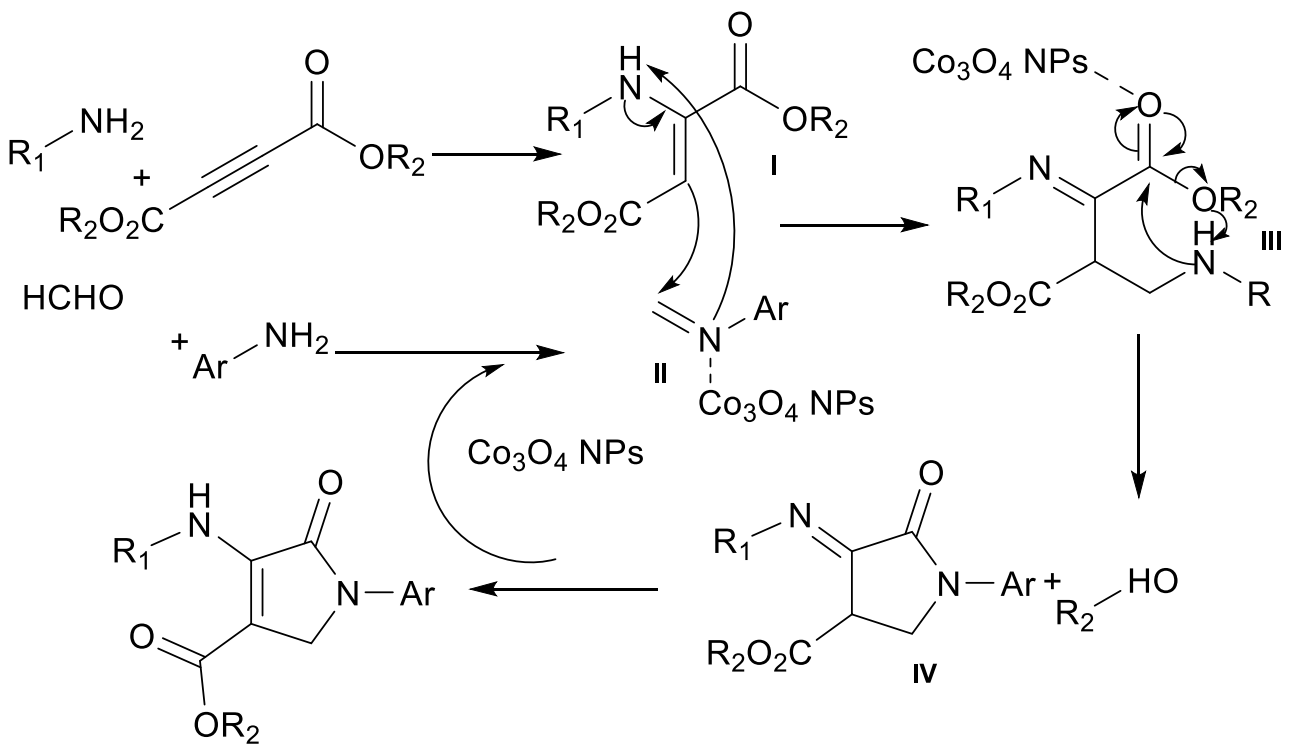


SCHEME 1
Co_3O_4 nanoparticles as a catalyst in the synthesis of pyrrole (Pyo) derivatives **(I)** and pyrano [2, 3-c]pyrazole (Pya[2, 3-c]Pyz) derivatives **(II)**.

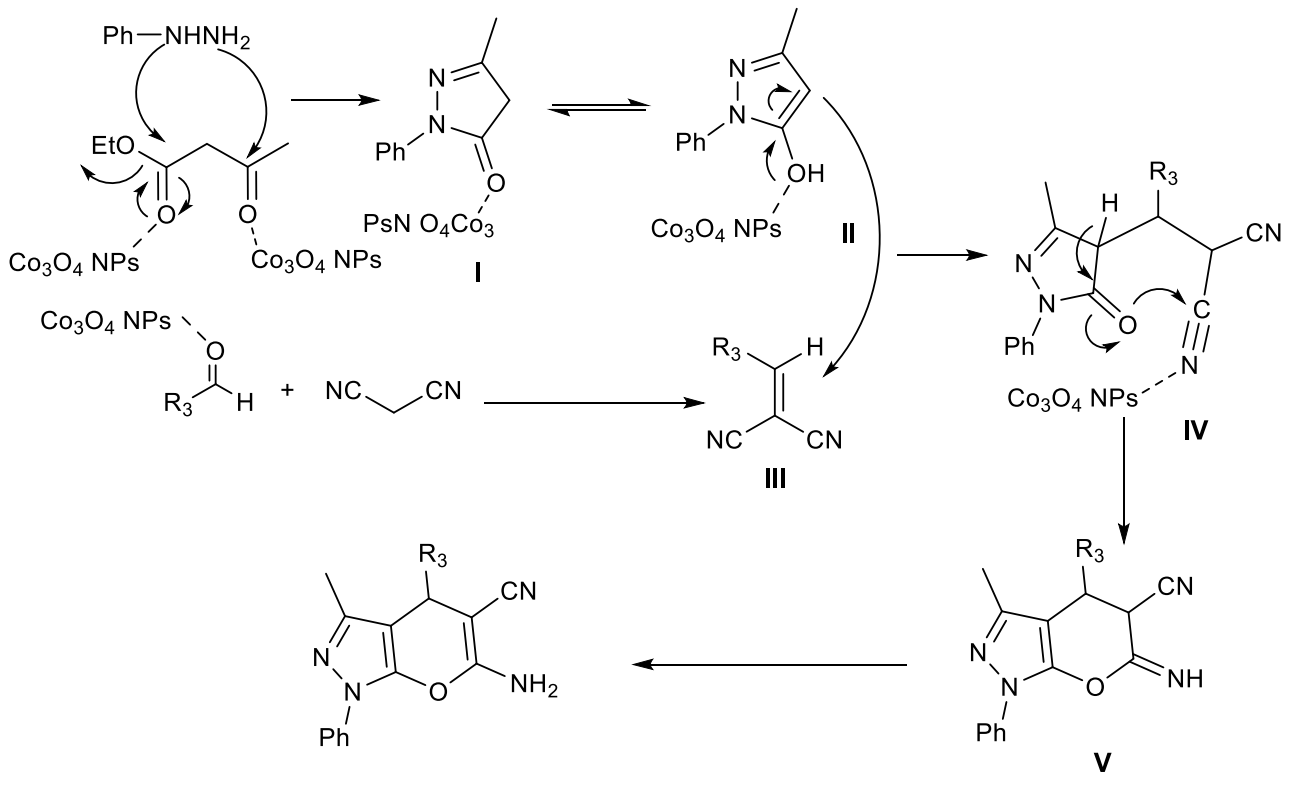
1,232, 1,146; ^{1}H NMR (300 MHz, DMSO-d6) δ = 1.91 (s, 3H, CH_3), 3.75 (s, 3H, OCH_3), 3.79 (s, 3H, OCH_3), 3.82 (s, 3H, OCH_3), 4.96 (s, 1H, -CH), 6.92 (s, 2H, Ar-H), 7.38 (s, 2H, NH_2), 7.65–7.79 (m, 5H, Ar-H); ^{13}C NMR (75 MHz, DMSO-d6) δ = 11.4, 33.9, 54.7, 55.3, 56.5, 59.6, 98.8, 111.7, 111.9, 119.7, 121.7, 122.3, 126.1 128.6, 129.4, 131.9, 137.7, 144.6, 145.5, 147.3, 148.7, 150.1, 163.2; Anal. Calcd for $C_{23}H_{22}N_4O_4$: C, 66.02; H, 5.30; N, 13.39; O, 15.29. Found: C, 66.05; H, 5.27; N, 13.42; O, 15.26.

2.4.2 6-amino-4-(3-hydroxy-4-methoxyphenyl)-3-methyl-1-phenyl-1,4-dihydropyrano [2,3-c]pyrazole-5-carbonitrile (10g)

Yield: 87%; yellow powder; FT-IR (KBr, cm^{-1}): 3,429, 3,301, 32,778, 3,106, 2,981, 2,937, 2,144, 1,652, 1,557, 1,474, 1,360, 1,237, 1,118; ^{1}H NMR (300 MHz, DMSO-d6) δ = 1.78 (s, 3H, CH_3), 3.65 (s, 3H, OCH_3), 4.85 (s, 1H, CH), 6.59 (d, 1H, J = 8.4 Hz, Ar-H), 6.62 (s, 1H, Ar-H), 6.71 (d, 1H, J = 8.4 Hz, Ar-H) 7.24 (s, 2H, NH_2), 7.35–7.76 (m, 5H, Ar-H), 8.67 (s, 1H,



SCHEME 2
Proposed mechanism and use of Co_3O_4 nanoparticles in synthesis pyrrole (Pyo) derivatives.



SCHEME 3
Proposed mechanism and use of Co_3O_4 nanoparticles in synthesis of pyrano [2, 3-c]pyrazole (Pya[2, 3-c]Pyz) derivatives.

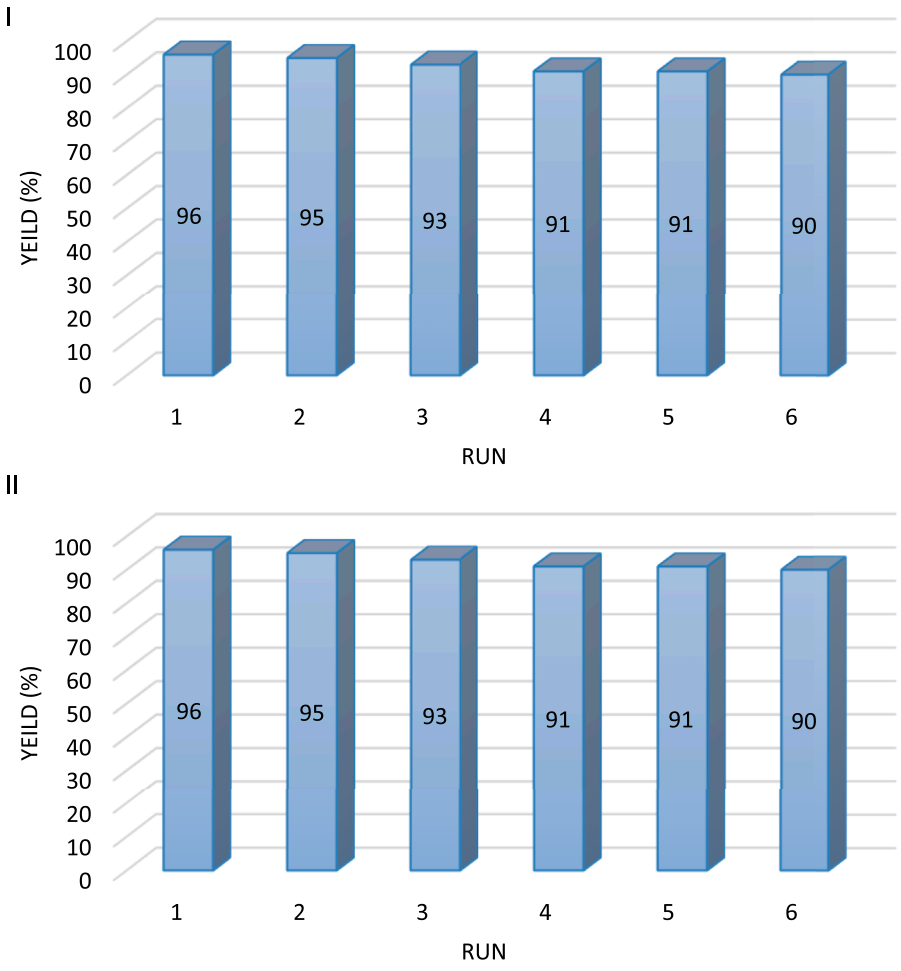


FIGURE 7
The ability to reuse of Co_3O_4 nanoparticles in synthesis pyrrole (Pyo) [**(I)**-5a] and pyrano [2, 3-c]pyrazole (Pya[2, 3-c]Pyz) [**(II)**-10a].

OH); ^{13}C NMR (75 MHz, DMSO-d6) δ = 13.4, 36.5, 55.9, 99.6, 112.7, 115.8, 117.1, 120.4, 121.7, 126.2, 129.5, 130.1, 135.2, 138.5, 144.7, 145.6, 146.1, 152.1, 160.8; Anal. Calcd for $C_{21}H_{18}N_4O_3$: C, 67.37; H, 4.85; N, 14.96; O, 12.82. Found: C, 67.40; H, 4.83; N, 14.98; O, 12.79.

2.5 *In vitro* antioxidant evaluation of derivatives

By using the DPPH method, *invitro* antioxidant evaluation of derivatives was tested. For this purpose, previously reported methods were used, and the initial concentration of derivatives was 25, 50, 75, and 100 μg/mL in methanol (Bhaskara Reddy et al., 2015; Hosseinzadegan et al., 2020a). In the evaluations, Eq. 1 was used for the percent inhibition of the derivatives.

$$\text{Percent inhibition} = (\text{Absorption of DPPH} - \text{Absorption of DDPH and sample}) / \text{Absorption of DPPH} \times 100 \quad (1)$$

Calculation of percent inhibition (I %) of DPPH free radical by derivatives.

2.6 *In vitro* antimicrobial evaluation of derivatives

The CLSI (Clinical and Laboratory Standards Institute) standards and guidelines to evaluate the antimicrobial and antifungal activity of the derivatives were used. For this purpose, previous studies were used, and Inhibition Zone Diameter, Minimum Inhibitory Concentration, Minimum Bactericidal Concentration, and Minimum Fungicidal Concentration were reported after the tests. The microorganism strains used were *Escherichia coli*, *Proteus mirabilis*, and *Yersinia enterocolitica* as Gram-negative bacteria, *Bacillus cereus*, *Staphylococcus aureus*, and *Rhodococcus equi* as Gram-positive bacteria, and *Candida albicans*, *Aspergillus fumigatus*, and *Fusarium oxysporum* as fungal (Etemadi et al., 2016; Moghaddam-Manesh et al., 2020; Abdieva et al., 2022).

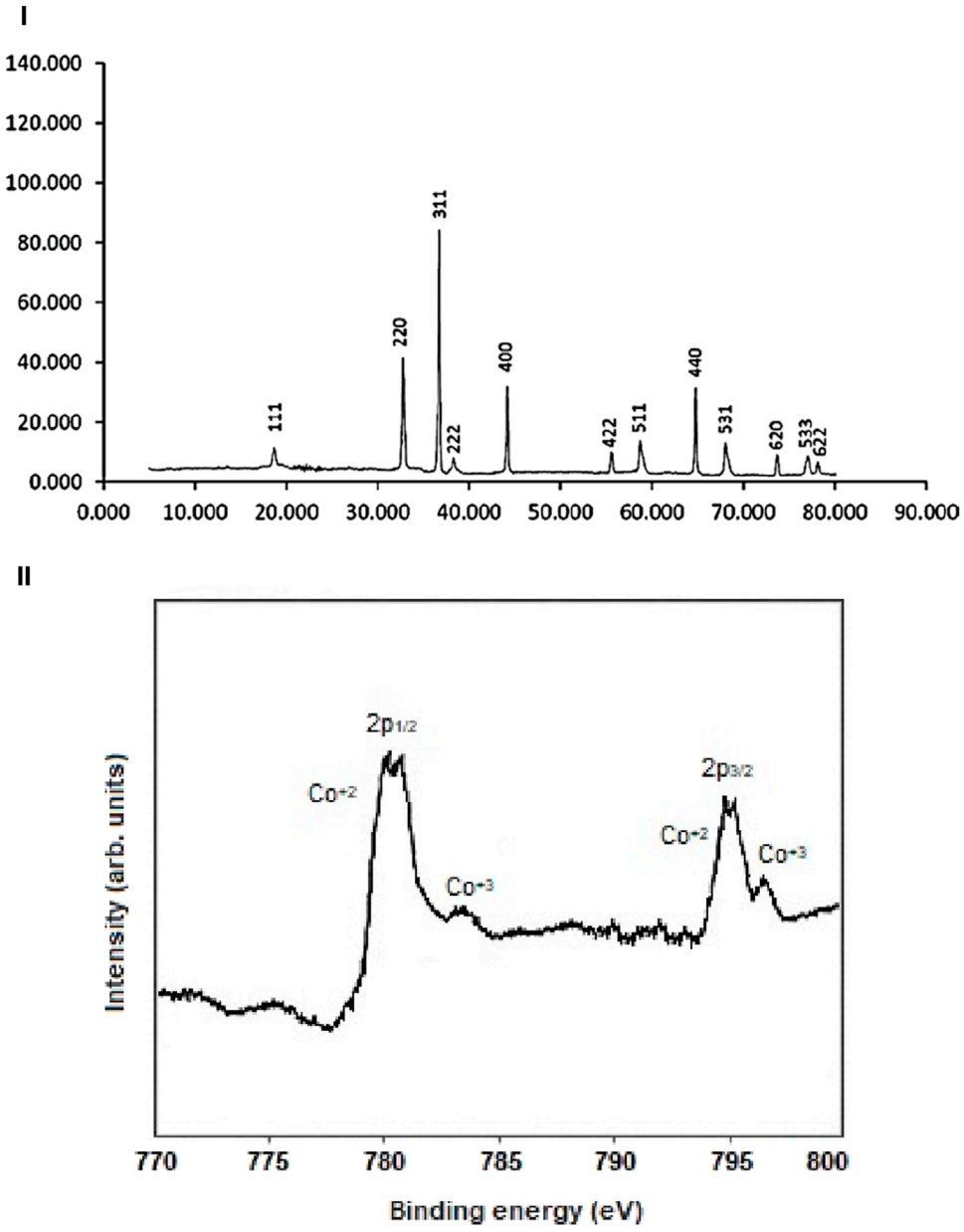


FIGURE 8
The XRD **(I)** and XPS **(II)** of Co_3O_4 nanoparticles after recycling.

3 Results and discussion

3.1 Verification of the structure and characterization of Co_3O_4 nanoparticles

Co_3O_4 nanoparticles, which were synthesized by the previously reported method using cobalt nitrate and Pluronic F-127 (Sadasivan et al., 2013; Uddin and Baig, 2019)., were used as catalysts for the synthesis of pyrrole (Pyo) derivatives and pyrano [2,3-c]pyrazole (Pya[2,3-c]Pyz) derivatives after confirming the structure. FTIR spectrum, XRD pattern, BET analysis, XPS analysis, DLS analysis, SEM, and TEM images were used to verify the structure and characterization of Co_3O_4 nanoparticles.

In the FTIR spectrum of Co_3O_4 nanoparticles (Figure 1), Peaks related to Co(III)–O and Co(II)–O were observed in regions 534.25 cm^{-1} and 686.47 cm^{-1} (Salavati-Niasari et al., 2009).

Using the XRD pattern of synthesized Co_3O_4 nanoparticles (Figure 2) and the Scherrer equation, the size of nanoparticles 31 nm was calculated. The peaks at 19.44°, 31.66°, 37.48°, 38.87°, 45.27°, 55.75°, 59.48°, 65.31°, 68.46°, 74.12°, 77.73°, and 78.35° due to plates to [111], [220], [311], [222], [400], [422], [511], [440], [531], [620], [533], and [622] in XRD pattern of synthesized Co_3O_4 were observed. The cubic Co_3O_4 spinel oxide and JCPDS card number 1467–42, for synthesized cobalt oxide nanoparticles, were observed in the XRD pattern (Sadasivan et al., 2013; Uddin and Baig, 2019).

TABLE 4 Comparison of recently reported conditions in the synthesis of pyrrole (Pyo) (5a) with Co_3O_4 nanoparticles.

Compound	Reported year	Reported yield (%)	Condition			Ref
			Reported catalyst	Reaction temperature (°C)	Reaction time (min)	
5a	This work	96	Co_3O_4 nanoparticles	40	25	-
5a	2020	86	aluminium potassium sulfate dodecahydrate	20	180	Mohamadpour (2020b)
5a	2020	90	N,N,N′,N′-tetramethyl-N,N′-bis(sulfo)ethane-1,2-diaminium mesylate	20	120	Basirat et al. (2020)
5a	2020	89	L-glycine	20	240	Mohamadpour (2020a)
5a	2018	92	Phthalic acid	20	210	Mohamadpour et al. (2018)

TABLE 5 Comparison of recently reported conditions in the synthesis of pyrano [2,3-c]pyrazole (Pya[2,3-c]Pyz) (10a) with Co_3O_4 nanoparticles.

Compound	Reported year	Reported yield (%)	Condition			Ref
			Reported catalyst	Reaction temperature (°C)	Reaction time (min)	
10a	This work	95	Co_3O_4 nanoparticles	40	15	-
10a	2020	93	Sulfonic acid immobilization on nanoparticles	Reflux (1:1 of H_2O:EtOH)	40	Eftekhari Far and Nasr-Esfahani (2020)
10a	2019	91	Yttriumiron garnet nanoparticles	80	20	Sedighinia et al. (2019)
10a	2016	87	Triphenyl phosphine	Reflux (H_2O)	120	Amine Khodja et al. (2016)
10a	2014	93	SnO_2 nanoparticles	25	150	Paul et al. (2014)

The same morphology of the synthesized Co_3O_4 nanoparticles was proved by using SEM and TEM images (Figure 3).

Based on the TEM image, the samples gradually move from the tube state to the plate state, which indicates the completion of the nucleation cycle. According to information in SEM and TEM images, there are no evidences of agglomeration in the structures. It can be related to optimal preparation rout of the final products as well as the proportions of initial materials used in the procedure (Mirhosseini et al., 2022).

The particle size distribution of Co_3O_4 nanoparticles (Figure 4) was measured using dynamic light scattering (DLS) technique, and the average size of cobalt nanoparticles was 35 nm.

Figure 5 shows X-ray photoelectron spectroscopy analysis (XPS) of Co_3O_4 nanoparticles. The binding energy peaks related to the $2p_{1/2}$ of Cobalt and the $2p_{3/2}$ of Cobalt were observed in 780.1 eV and 795.4 eV, respectively (Fan et al., 2016; Yang et al., 2016; Aboelazm et al., 2018).

The nitrogen adsorption/desorption isotherms of Co_3O_4 nanoparticles are shown in Figure 6.

Based on the analysis, nitrogen adsorption/desorption isotherms were IV-type (Alfaifi et al., 2023) and its surface area was 18.21 $m^2\ g^{-1}$. The pore diameter, and pore volume of Co_3O_4 nanoparticles were 36.12 nm and 0.12 $cm^3\ g^{-1}$, respectively. The surface area is an important factor in the properties and activity of nanoparticles and depends on their synthesis method (Khan et al., 2019). As the surface area increases, the contact surface of the nanoparticle increases, thereby increasing its reactivity (Tee et al., 2022). So, the high surface area of Co_3O_4 nanoparticles can increase its catalytic properties.

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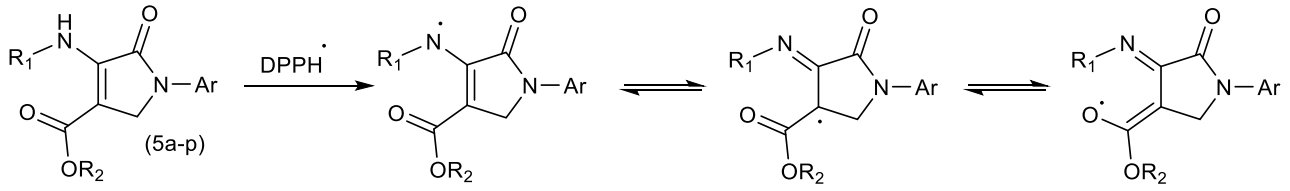
TABLE 6 The percent inhibition and IC_{50} of pyrrole (Pyo) derivatives and pyrano [2,3-c]pyrazole (Pya[2,3-c]Pyz) derivatives against DPPH free radical.

Derivatives	Percent inhibition/concentrati (μg/mL)				IC_{50} (μg/mL)	Derivatives	Percent inhibition/concentrati (μg/mL)				IC_{50} (μg/mL)
	5	10	15	20			5	10	15	20	
5a	44	48	55	57	13.68	5o	43	48	59	67	12.2
5b	42	45	54	60	13.71	5p	42	46	54	62	13.38
5c	43	46	52	65	13.16	*	*	*	*	*	*
5d	42	49	55	67	12.52	10a	23	36	42	55	17.29
5e	43	48	57	64	12.68	10b	29	31	43	55	17.42
5f	41	46	54	62	13.43	10c	23	34	46	57	16.57
5g	43	48	55	60	13.33	10d	24	33	41	58	17.07
5h	42	45	56	61	13.38	10e	26	37	44	59	16.17
5i	40	43	56	65	13.15	10f	26	37	45	57	16.39
5j	42	45	53	64	13.31	10g	22	35	45	58	16.47
5k	42	45	55	63	13.24	10h	21	34	40	55	17.75
5L	44	46	53	67	12.80	10i	25	32	47	59	16.21
5m	45	49	56	65	12.48	10j	21	37	48	60	16.18
5n	41	44	53	68	12.97						

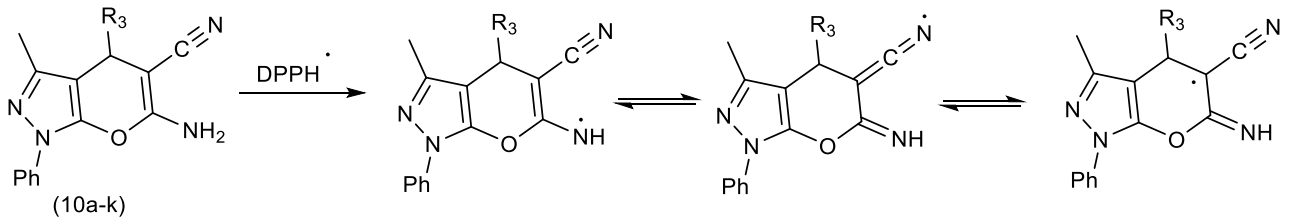


SCHEME 4
Suggested mechanism and resonance structures for DPPH free radical stabilization using pyrrole (Pyo) derivatives.

3.2 The results of the synthesis of pyrrole derivatives and pyrano [2,3-c]pyrazole derivatives

After confirming the structure of Co_3O_4 nanoparticles, their catalytic application was investigated in the synthesis of pyrrole (Pyo) derivatives and pyrano [2,3-c]pyrazole (Pya[2,3-c]Pyz) derivatives.

The optimization of reaction conditions, such as mol% of catalyst, solvent, and reaction temperature, was conducted to synthesize derivatives with the highest efficiency and conditions. For this purpose, the solvent and reaction temperature were maintained constant (ethanol solvent, room temperature), and the reactions were examined in conditions without catalyst, 5, 10, 15, 20, 25, 50, and 100 mol% of catalyst. The highest efficiency for synthesizing Pyo and Pya[2,3-c]Pyz was obtained when 15 mol% and 10 mol% of catalyst were used, respectively. Then, at a temperature of 25°C, the amount of 15 mol% of catalyst in the synthesis of Pyo and 10 mol% of Co_3O_4 nanoparticles in pyrano [2,3-c]pyrazole, using solvents of water, methanol, ethanol, 1:1 water/ethanol mixture, and dimethylformamide (DMF), reactions were carried out. The highest efficiency obtained in the reactions was when a 1:1 water/ethanol mixture was used. Finally, by keeping the amount of catalyst constant according to the previous step and using water/ethanol mixed solvent, the reactions were evaluated at 40°C, 50°C, 60°C, 70°C and reflux temperatures. The synthesis of Pyo at 25°C and Pya[2,3-c]Pyz at 40°C had the highest efficiency. The evaluation results are given in Table 1 for synthesizing Pyo and pyrano [2,3-c]pyrazole.



SCHEME 5
Suggested mechanism and resonance structures for DPPH free radical stabilization using pyrano [2, 3-c]pyrazole (Pya[2, 3-c]Pyz) derivatives.

Therefore, the optimal conditions, including using a 15 mol% catalyst, a 1:1 mixture of water/ethanol, and a temperature of 25 °C, were used to synthesize other Pyo derivatives (Table 2).

In synthesizing Pya[2,3-c]Pyz derivatives, optimal conditions, including 10 mol% of catalyst, 1:1 mixture of water/ethanol, and temperature of 40 °C were used (Table 3).

In all reactions to obtain optimal conditions in the synthesis of Pyo (5a), raw materials including cyclohexanamine, dimethyl but-2-ynedioate, formaldehyde and aniline have been used in the amount of 1 mol.

In all reactions to obtain optimal conditions in the synthesis of Pya[2,3-c]Pyz (10a), raw materials including ethyl acetoacetate, phenylhydrazine, malononitrile, and benzaldhyde have been used in the amount of 1 mol.

The structure of the derivatives has been confirmed using ^{1}H NMR, ^{13}C NMR, and element analysis.

Based on previous studies, Co_3O_4 nanoparticles act as Lewis acid catalysts in organic chemistry reactions (Rajabi et al., 2015; Gong et al., 2023). Here, too, Co_3O_4 nanoparticles enter the reaction as a Lewis acid, and Scheme 2 and 3 mechanisms are proposed for synthesizing Pyo derivatives and Pya[2,3-c]Pyz derivatives, respectively.

The but-2-ynedioate derivatives and aliphatic amine derivatives created intermediate (I). The formaldehyde and aromatic amine derivatives created intermediate (II). Intermediate (III) was synthesized from the reaction of intermediate (I) with intermediate (II). From the cyclization reaction of intermediate (III), and tautomerization (IV), the final product was synthesized.

First, using ethyl acetoacetate and phenylhydrazine, the pyrazole was synthesized that were equilibrium in two forms (I and II). Using condensation of malononitrile and aldehyde derivative, intermediate (III) was synthesized. The intermediate (IV) was formed from Michael addition reaction of intermediate (II) with intermediate (III). The final product was synthesized through the cyclization reaction of intermediate (IV) and tautomerization (V).

Risibility and reuse of the catalyst in synthesizing Pyo derivatives and Pya[2, 3-c]Pyz derivatives were investigated. The Co_3O_4 nanoparticles after separation, washing, and drying, were reuse in the synthesis of derivatives. The results of reuse and reusability of the catalyst up to six times are shown in Figure 7.

After recycling, the XRD and XPS of Co_3O_4 nanoparticles were prepared, and as can be seen in Figure 8, were similar to before being used as a catalyst.

According to the reported methods, a hot filtration test for Co_3O_4 nanoparticles was done, and results showed no enhancement in conversion was noticed in the filtrate (Babaei and Mirjalili, 2020).

Comparison of synthesis methods of derivatives Pyo and Pya[2,3-c]Pyz reported in recent literature with Co_3O_4 nanoparticles used in this study are given in Tables 4,5.

To summarize, nanoparticles have a high capacity to synthesize Pyo derivatives and Pya[2,3-c]Pyz derivatives with high efficiency and more suitable conditions than other catalysts (Table 5; Table 6). Suitable conditions include less reaction time, lower temperature used in the synthesis of derivatives and higher efficiency. The synthesis of new derivatives is another advantage of this study. It is suggested that nanoparticles can synthesize other heterocyclic compounds under suitable conditions as a recyclable green catalyst. The reason for the high catalytic property of cobalt nanoparticles, as explained in Section 3.1, can be attributed to its high active surface (Khan et al., 2019; Tee et al., 2022).

3.3 The antioxidant activity results

To check the antioxidant activity of derivatives, the DPPH method was used. 1 mL of derivatives with concentrations prepared as given in Section 2.5 was mixed with 4 mL of DPPH solution, and after half an hour of stirring in the dark, its absorbance was checked at 517 nm. The percent inhibition was calculated for each derivative concentration using the equation presented in Section 2.5, and the results are given in Table 6. In addition to percent inhibition, using concentration and percent inhibition, the value of IC_{50} for each of the derivatives was calculated (Beyzaei et al., 2018) and listed in Table 6.

Comparing the results of Pyo derivatives shows that the value of IC_{50} for them was very close, so it is not dependent on R_1, R_2, and Aryl groups. Therefore, mechanism Scheme 4 is suggested for DPPH free radical stability by Pyo derivatives. The IC_{50} value for Pya[2,3-c]Pyz derivatives was very close to each, and were not dependent on R_3 groups. Therefore, mechanism Scheme 5 is suggested for DPPH free radical stability by Pya[2,3-c]Pyz derivatives.

Although based on the proposed mechanisms, the resonance structures for Pyo derivatives and Pya[2,3-c]Pyz derivatives are equal in DPPH free radical stability, but as can be seen from the results, the antioxidant property of Pyo derivatives is more than that of Pya[2,3-c]Pyz derivatives. The obtained results are consistent with the proposed mechanisms because the resonance structures of Pyo derivatives are more stable than the resonance structures of

TABLE 7 The obtained IZD, MIC, and MBC values in antibacterial properties of pyrrole (Pyo) derivatives.

Compound	Gram-negative strains									Gram-positive strains								
	Escherichia coli			*Proteus mirabilis*			*Yersinia* enterocolitica			*Bacillus* cereus			*Staphylococcus aureus*			Rhodococcus equi		
	IZD	MIC	MBC	IZD	MIC	MBC	IZD	MIC	MBC	IZD	MIC	MBC	IZD	MIC	MBC	IZD	MIC	MBC
5a	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	10.01	1,024	2048
5b	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	10.24	2048	4,096
5c	12.77	512	1,024	-	-	-	-	-	-	-	-	-	13.10	512	1,024	12.35	512	1,024
5d	10.15	2048	4,096	-	-	-	-	-	-	-	-	-	11.46	2048	4,096	10.80	1,024	1,024
5e	13.09	256	256	14.23	128	256	14.22	128	256	14.21	128	256	14.85	256	256	15.14	256	256
5f	11.78	256	512	14.55	512	512	14.57	512	512	14.67	512	512	14.29	256	512	14.83	512	1,024
5g	14.31	16	32	18.15	32	64	18.01	32	64	18.41	32	64	17.81	32	64	16.55	8	32
5h	15.85	4	16	17.88	32	64	17.83	32	64	17.93	32	64	16.95	16	32	17.67	4	8
5i	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	9.34	2048	4,096
5j	-	-	-	10.41	2048	4,096	10.42	2048	4,096	10.33	2048	4,096	-	-	-	-	-	-
5k	11.52	1,024	2048	13.22	1,024	2048	13.15	1,024	2048	13.17	1,024	2048	-	-	-	12.59	512	1,024
5L	10.97	2048	2048	-	-	-	-	-	-	-	-	-	12.83	2048	4,096	11.82	1,024	2048
5m	13.41	128	256	16.63	128	128	16.61	128	128	16.64	128	128	16.26	128	256	15.49	64	128
5n	13.72	64	128	16.27	64	128	16.37	64	128	16.29	64	128	16.31	64	64	16.17	32	64
5o	16.96	4	8	18.31	2	4	18.29	2	4	18.42	2	4	18.62	2	2	18.26	2	8
5p	17.14	8	8	16.92	8	16	16.83	8	16	16.99	8	16	19.33	4	8	16.89	2	4
Gentamicin	17.69	16	32	18.66	2	4	18.70	2	4	18.98	2	4	19.25	1	2	18.01	4	8

IZD, Inhibition Zone Diameter (mm); MIC, Minimum Inhibitory Concentration (μg/mL); MBC, Minimum Bactericidal Concentration (μg/mL).

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TABLE 8 The obtained IZD, MIC, and MBC values in antibacterial properties of pyrano [2,3-c]pyrazole (Pya[2,3-c]Pyz) derivatives.

Compound	Gram-negative strains									Gram-positive strains								
	Escherichia coli			*Proteus mirabilis*			*Yersinia* enterocolitica			*Bacillus* cereus			*Staphylococcus aureus*			Rhodococcus equi		
	IZD	MIC	MBC	IZD	MIC	MBC	IZD	MIC	MBC	IZD	MIC	MBC	IZD	MIC	MBC	IZD	MIC	MBC
10a	-	-	-	-	-	-	11.38	1,024	1,024	-	-	-	-	-	-	-	-	-
10b	-	-	-	-	-	-	11.16	512	1,024	-	-	-	-	-	-	-	-	-
10c	13.12	1,024	1,024	13.34	256	512	14.21	128	256	13.81	256	512	-	-	-	-	-	-
10d	14.21	512	1,024	13.49	256	256	14.53	128	256	13.79	128	256	15.21	512	512	14.17	512	1,024
10e	14.52	256	512	14.97	128	256	14.31	128	256	14.39	128	128	15.01	256	512	14.02	256	512
10f	15.57	32	64	16.12	64	64	15.72	64	128	16.92	64	64	17.53	64	128	17.06	32	64
10g	15.42	32	64	16.01	64	128	14.99	64	128	15.84	64	128	17.85	128	128	16.59	32	64
10h	14.27	64	128	15.41	128	256	13.81	128	128	15.09	64	128	14.12	128	256	14.31	128	128
10i	16.94	4	16	18.92	4	4	17.29	4	16	18.31	4	8	18.02	4	8	18.18	16	32
10j	17.37	2	4	18.52	2	4	18.01	2	2	19.25	2	4	18.25	2	2	17.14	4	8
10k	-	-	-	12.01	512	1,024	-	-	-	12.41	256	512	-	-	-	-	-	-
Gentamicin	17.69	16	32	18.66	2	4	18.70	2	4	18.98	2	4	19.25	1	2	18.01	4	8

IZD, Inhibition Zone Diameter (mm); MIC, Minimum Inhibitory Concentration (μg/mL); MBC, Minimum Bactericidal Concentration (μg/mL).

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TABLE 9 The obtained IZD, MIC, and MFC values in antifungal properties of pyrrole (Pyo) derivatives and pyrano [2,3-c]pyrazole (Pya[2,3-c]Pyz) derivatives.

Compound	*Candida* albicans			Aspergillus fumigatus			Fusarium oxysporum		
	IZD	MIC	MFC	IZD	MIC	MFC	IZD	MIC	MFC
5a	-	-	-	-	-	-	-	-	-
5b	-	-	-	-	-	-	-	-	-
5c	-	-	-	11.01	256	512	-	-	-
5d	9.33	2048	4,096	-	-	-	-	-	-
5e	11.47	256	512	-	-	-	10.51	512	512
5f	11.59	512	512	-	-	-	13.65	1,024	2048
5g	18.77	32	128	17.43	64	128	15.34	64	128
5h	14.35	64	64	18.92	64	128	16.28	128	128
5i	-	-	-	-	-	-	-	-	-
5j	-	-	-	-	-	-	-	-	-
5k	-	-	-	-	-	-	11.30	512	2048
5L	11.52	512	1,024	-	-	-	-	-	-
5m	13.66	128	256	16.91	128	256	16.26	512	512
5n	14.19	128	128	17.37	128	256	15.85	256	512
5o	19.41	32	64	19.69	32	64	17.93	64	64
5p	19.82	64	128	18.52	32	128	15.46	64	128
10a	-	-	-	-	-	-	-	-	-
10b	10.95	1,024	2048	-	-	-	-	-	-
10c	13.12	256	512	14.24	512	1,024	13.17	1,024	2048
10d	14.71	128	256	14.61	256	512	14.53	512	1,024
10e	14.62	128	128	15.72	256	512	14.19	512	512
10f	15.48	64	128	17.34	64	128	15.48	128	256
10g	14.97	64	128	14.83	128	256	14.19	128	256
10h	14.31	128	128	13.31	128	256	14.46	256	512
10i	19.27	16	64	18.77	32	64	18.12	64	64
10j	19.41	16	32	19.69	32	64	17.93	32	64
10k	11.67	512	1,024	-	-	-	-	-	-
Terbinafine	21.85	32	64	20.42	64	128	17.62	64	128

IZD, Inhibition Zone Diameter (mm); MIC, Minimum Inhibitory Concentration (μg/mL); MFC, Minimum Fungicidal Concentration (μg/mL).

Pya[2,3-c]Pyz derivatives (Hosseinzadegan et al., 2020b; Gani and Al-Obaidi, 2023).

3.4 The antimicrobial activity results

The bacterial and fungal strains mentioned in Section 2.6 were used in the evaluation and antimicrobial tests of synthesized Pyo derivatives and Pya[2,3-c]Pyz derivatives. The results of antibacterial activity (against Gram-positive strains and Gram-negative strains) of Pyo derivatives were given in Table 7, antibacterial activity (against Gram-positive strains and Gram-negative strains) of Pya[2,3-c]Pyz derivatives were presented in Table 8, and antifungal activity of derivatives Pyo derivatives and Pya[2,3-c]Pyz derivatives were shown in Table 9. In the investigation of the antibacterial activity of the derivatives IZD, MIC, and MBC, and the investigation of the antifungal activity of the derivatives, IZD, MIC, and MFC have been tested and reported. To comparison of antimicrobial studies, tests were performed on commercial drugs such as Gentamicin and Terbinafin.

The results proved that the antibacterial and antifungal properties of some synthesized Pyo derivatives and Pya[2,3-c]Pyz derivatives were more effective than commercial drugs. As shown in Tables 5–7, 5o and 10j were more effective than Gentamicin and Terbinafin.

Based on the results, in contrast to antioxidant activity, the high antimicrobial activity of Pya[2,3-c]Pyz derivatives compared to Pyo derivatives is significant and can be attributed to the heterocyclic rings present in their structure. Pyo derivatives contain one heterocyclic ring, but Pya[2,3-c]Pyz derivatives comprise two (Sharma et al., 2010; Al-Mulla, 2017).

The results of the antimicrobial activity of Pyo derivatives showed that they have more potent antibacterial properties than antifungal properties. The comparison of the antimicrobial effects of Pyo derivatives showed that the antimicrobial properties have a direct relationship with the substitutions of the aryl group and derivatives with chlorine, and methoxy had the highest effectiveness, respectively.

Comparing the antibacterial activity and antifungal activity of Pya[2,3-c]Pyz derivatives was similar to Pyo derivatives and antibacterial activity was more than antifungal activity. From the comparison of the antimicrobial activity of Pya[2,3-c]Pyz derivatives, it was also proved that the activity of derivatives has a direct relationship with R_3 groups. The derivatives with chlorine, fluorine, hydroxyl, methoxy, and bromine had the highest effectiveness, respectively.

4 Conclusion

In this study, Co_3O_4 nanoparticles were used as recyclable and green catalyst for the synthesis of pyrrole (Pyo) derivatives and pyrano [2,3-c]pyrazole (Pya[2,3-c]Pyz) derivatives and 5 novel derivatives were synthesized. Efficiency of 83%–96%, and 87%–95% in synthesizing Pyo derivatives and Pya[2,3-c]Pyz derivatives, respectively, were observed. Less synthesis time and higher efficiency compared to recent studies were the advantages of using Co_3O_4 nanoparticles. Recycling up to 6 times without noticeable change in efficiency was another advantage of using Co_3O_4 nanoparticles. Antioxidant tests of derivatives using DPPH free radical method and antimicrobial tests of derivatives on Gram-positive, Gram-negative bacterial strains, and fungal species were performed. In the antioxidant tests, percentage inhibition, and IC_{50}, and in antimicrobial tests, IZD, MIC, MBC, and MFC were investigated and reported. In antioxidant tests, it was proved that Pyo derivatives have a higher antioxidant activity than Pya[2,3-c]Pyz derivatives, which can be fully verified by the proposed mechanisms for the stability of DPPH free radicals according to their structure. The antimicrobial activity of Pyo derivatives and Pya[2,3-c]Pyz derivatives were the opposite of antioxidant activity. The Pya[2,3-c]Pyz derivatives were generally more effective on the studied species than Pyo derivatives. In antimicrobial activity, the derivatives with chlorine, fluorine, hydroxyl, and methoxy had the highest effectiveness. In antimicrobial activity, some derivatives, for example, 5o and 10j, have high effectiveness than Gentamicin and Terbinafin which are known as commercial drugs.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material, further inquiries can be directed to the corresponding author.

Author contributions

TA: Resources, Writing–review and editing. MJ: Writing–original draft. SS: Conceptualization, Writing–review and editing. MA: Supervision, Writing–review and editing. UA: Formal Analysis, Writing–review and editing. MS: Methodology, Writing–review and editing. FR: Project administration, Writing–review and editing. AA: Writing–original draft. IA: Writing–original draft, Writing–review and editing. AlA: Validation, Writing–original draft, Writing–review and editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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