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ARTICLE

Catalyst-free green synthesis and study of antioxidant activity of new pyrazole derivatives

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Abstract

In this research, a novel procedure for the synthesis of pyrazole derivatives in excellent yields was studied using catalyst-free multicomponent reaction of isoquinoline, activated acetylenic compounds, alkyl bromides, triphenylphosphine and hydrazine in water under ultrasonic irradiation at room temperature. The advantages of this procedure than to reported methods are short time of reaction, high yields of product, easy separation of product, clean mixture of reaction and green media for performing reaction. In addition, because of having pyrazole and isoquinoline core in the synthesized compounds, in this research, antioxidant activity of some synthesized compounds was investigated.

1 | INTRODUCTION

Sonochemistry as an original and valuable method has attracted increasing interest in accelerating organic reactions.[1–4] This procedure can be very efficient and is applicable to a broad variety of practical synthesis. Luche and coworkers have carried out a number of investigations, which provided the basis for using sonochemistry in organic synthesis.[5–8] The significant features of the ultrasound approach in organic reactions are improvement of reaction rates, formation of pure products with high yields and easier process. This method is also considered as a help in terms of energy protection and waste decreasing when compared with traditional methods.[9,10] Ultrasound has increasingly been used in organic synthesis. A large number of ultrasonic reactions can be carried out in higher yield, shorter reaction time or milder conditions. It is also observed that reactions under ultrasound irradiation are commonly easier to work-up than those in conventional stirring methods.[11–14] It should be mentioned that heterocyclic compounds are a highly valuable and unique class of compounds. These compounds demonstrate a broad spectrum of physical, chemical and biological characteristics.[15,16] In nature, heterocyclic compounds are widely distributed and display an important part in metabolism because of their structural nucleus occurring in various natural products, including hormones, antibiotics, alkaloids, vitamins and many others. [17–19] Among heterocyclic compounds, nitrogen-containing heterocycles are considerably found as a main structure in an enormous library of heterocycles and display several employments in natural science and other areas of science.[20] In addition, nitrogen-containing heterocycles are broadly displayed in natural products, for instance, vitamins, hormones and alkaloids.[21,22] Among them, pyrazole derivatives demonstrate a broad spectrum of biological activities such as anti-tubercular,[23] anti-AIDS,[24] anti-malarial,[22] anti-microbial,[25] antitumor,[26,27] anticancer[28] and antifungal.[20] In addition, pyrazoles have

also been found as promising anti-hyperglycemic,[29] anti-depressant,[30] anti-convulsant,[31] anti-pyretic,[32] anti-anxiety[33,34] and insecticidal agents.[35]

Herein, in continuation of our attempts to expand new synthetic procedure for important heterocyclic compounds,[36–48] we investigated synthesis of pyrazole derivatives in excellent yields (Scheme 1).

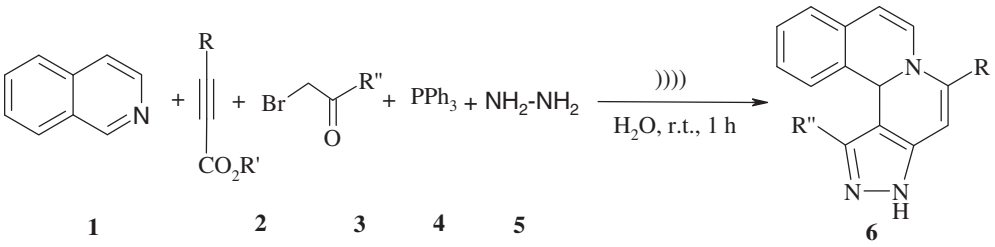
2 | RESULT AND DISCUSSION

In this work, generation of pyrazole derivatives **6** in excellent yield is performed using isoquinoline **1**, activated acetylenic comompouds **2**, alkyl bromide **3**, triphenylphosphine **4** and hydrazine **5** in water at room temperature under ultrasonic irradiation condition in short time (Scheme 1).

In the starting stage of this work, catalyst-free reaction of isoquinoline **1**, dimethyl acetylenedicarboxylate **2a**, ethyl bromopyruvate **3a**, triphenylphosphine **4** and hydrazine **5** was employed as a sample reaction to achieve the optimum conditions (Table 1). It should been mentioned that these reactions are experimented in both ultrasonic irradiation and conventional conditions and results were exhibited in Table 1. Surprisingly the yield of compound **6a** was obtained as 85% under ultrasonic irradiation in short time at room temperature (Table 1). By increasing the temperature, there was no significant change in the yield of reaction.

The structures of compounds **6** were confirmed by IR, ^{1}H NMR, ^{13}C NMR and mass spectral data. For example, the ^{1}H NMR spectrum of **6a** exhibited one singlet at 3.85 for methoxy protons, two singlets at 5.32 and 6.23 for methin proton and one broad singlet at 8.45 for NH proton along with signals for aromatic moiety at 6.87-8.15 ppm. In the ^{13}C NMR spectrum, the signals corresponding to the two carbonyl group of **6a** were observed at δ 162.3 and 164.8 ppm. Although there is no information about the mechanistic details, the reaction can been described by the mechanism proposed in Scheme 2.

First, isoquinoline **1** and activated acetylenic compounds **2** reacted under ultrasonic irradiation and generate intermediate **7**. The reaction of alkyl bromides **3** and triphenylphosphine **4** produces intermediate **8.** Intermediate **7** and intermediate **8** react together to produce intermediate **9**. Intermediate **9** convert into ylide **10** by losing hydrogen and intermolecular cyclization of **10** generates intermediate **11**. Intermediate **12** was produced by elimination of triphenylphosphine oxide from intermediate **11.** Hydrazine reacts with carbonyl group of **12** and converts into intermediate **13**. Finally, intermolecular cyclization and elimination of alcohol produce product **6** in excellent yields. These reactions are experimented by two procedures. In the first procedure, compound **12a** was separated and hydrazine **5** reacts with **12a** separately in water under ultrasonic irradiation after confirmation of the structure (Scheme 3). The structures of compounds **12a** were confirmed by IR, ^{1}H NMR, ^{13}C NMR and mass spectral data. The ^{1}H NMR spectrum of **12a** exhibited two singlets at 3.86 and 3.98 ppm for methoxy protons, one singlet at 5.32 for —CH proton, and one singlet at



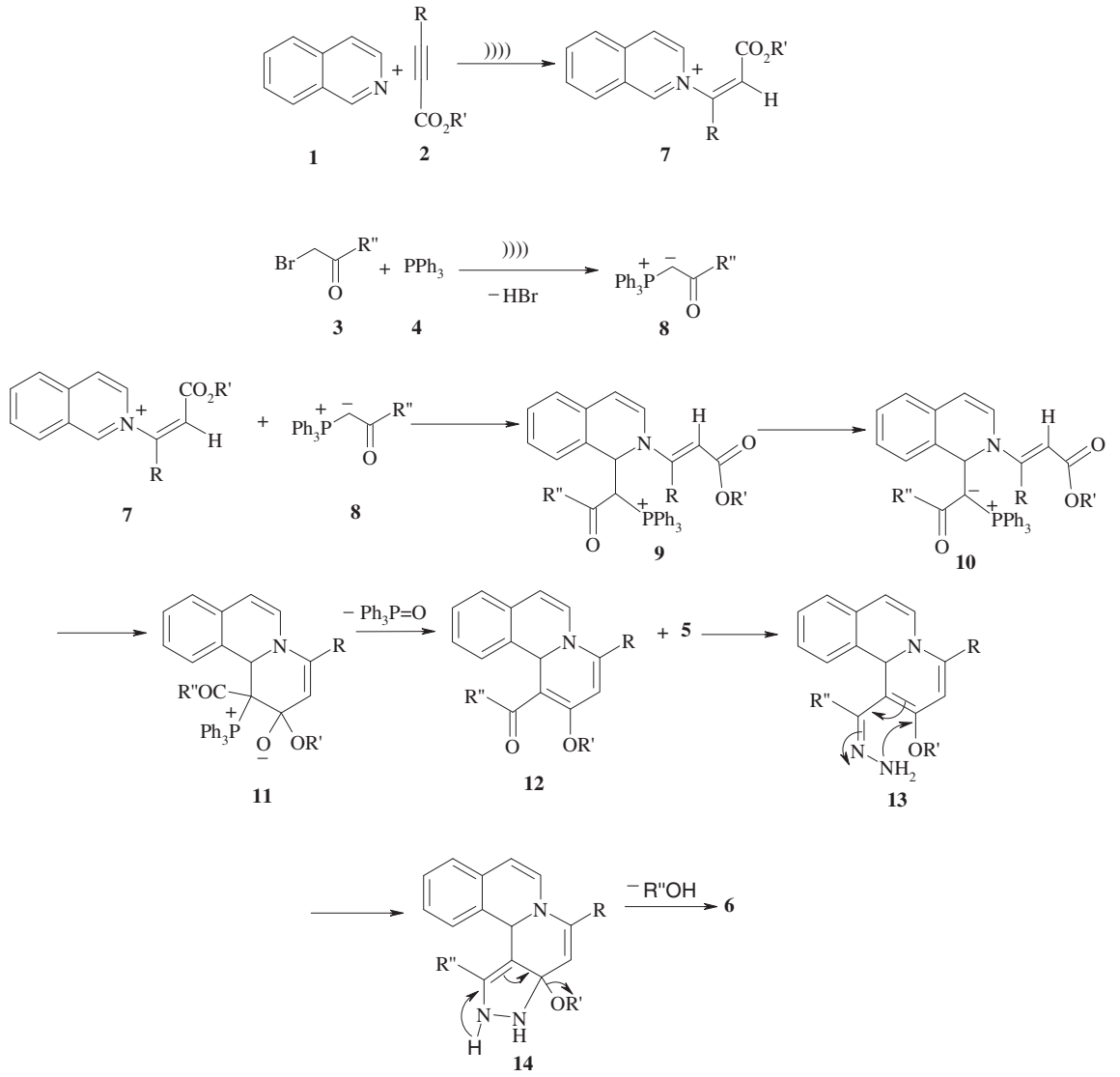
1 2 3 4 5 6

6	R	R'	R"	Yield % of **6**
a	CO_2Me	Me	CO_2Et	95
b	CO_2Et	Et	CO_2Et	92
c	H	Me	CO_2Et	90
d	CO_2Me	Me	4-MeO-C_6H_4	90
e	H	Me	4-MeO-C_6H_4	87
f	CO_2Et	Et	4-MeO-C_6H_4	90
g	CO_2Me	Me	4-Me-C_6H_4	87
h	CO_2Et	Et	4-Me-C_6H_4	85
i	CO_2Me	Me	4-Br-C_6H_4	83
j	CO_2Me	Me	4-NO_2-C_6H_4	80

SCHEME 1 Catalyst free synthesis of pyrazoles **6** under ultrasonic irradiation

TABLE 1 Optimization the reaction conditions for synthesis of **6a**

Entry	Solvent	Time/h Conventional conditions	Yield (%)	Time/min Ultrasonic irradiation	Yield (%)
1	-	6	45	2	58
2	**H_2O**	**2**	**75**	**60**	**95**
3	Toluene	3	48	2	75
4	CH_3CN	2	56	2	80
5	DMF	5	25	5	40
6	CH_2Cl_2	2	60	2	78
7	$CHCl_3$	2	63	2	80



SCHEME 2 proposed mechanism for preparation of **6**

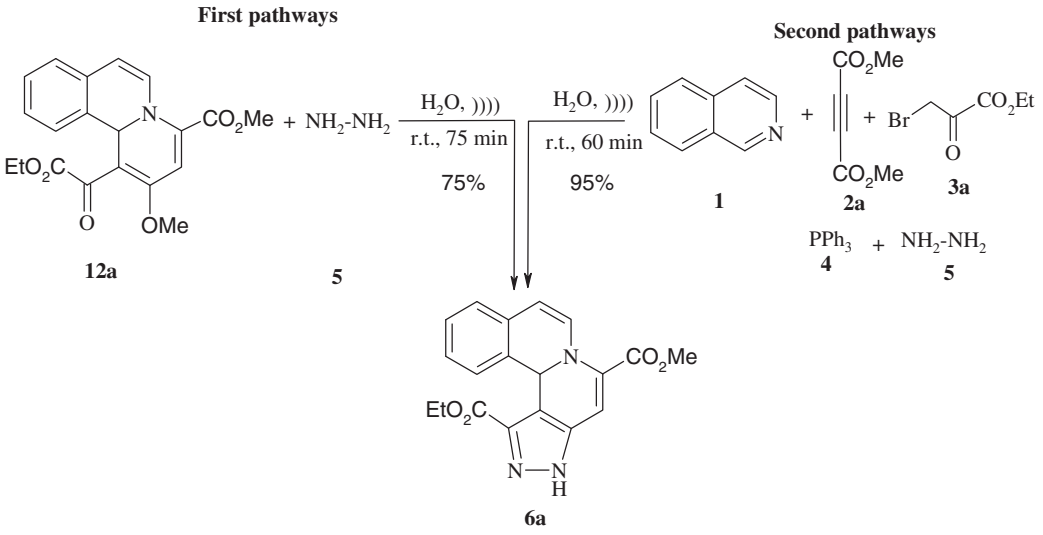
6.12 ppm for ═CH proton along with signals for aromatic moiety. In the ^{13}C NMR spectrum, the signals corresponding to the three carbonyl group of 6a were observed at δ 164.3, 165.6 and 176.6 ppm.

In the second procedure, all of compounds added together in one-pot and compounds **6** were produced. The results show that the product in two procedures is the same but the yield of reaction is completely different.

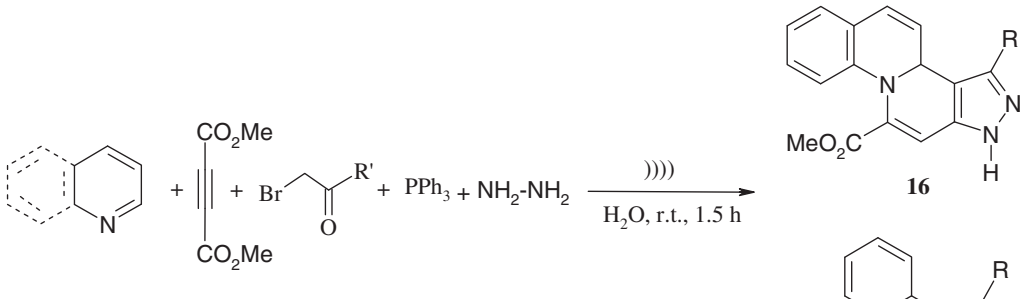
As shown in results in Scheme 3, the yield of reactions in the second procedure is more than the first procedure, which is one of the advantages of multicomponent reactions. In multi-step reactions, the yield of final product due to separation of some intermediate is low.

Under similar conditions, synthesis of another pyrazole derivatives **16** and **17**, respectively, in good yield is carried out using quinoline or pyridine **15**, dimethyl acetylenedicarboxylate **2a**, alkyl bromide **3**, triphenylphosphine **4** and hydrazine **5** in water at room temperature under ultrasonic irradiation condition in short time (Scheme 4).

The structures of compounds **16a** were confirmed by IR, ^{1}H NMR, ^{13}C NMR and mass spectral data. The ^{1}H NMR spectrum of **16a** exhibited one singlet at 3.87 ppm for methoxy protons, one singlet at 5.62 (1 H, d, ^3J = 6.5 Hz, CH) ppm for -CH proton, and one singlet at 6.27 ppm for ═CH proton along with signals for aromatic moiety. In the ^{13}C NMR spectrum, the signals corresponding to —CH group and the two carbonyl group of **16a** were observed at δ 48.5 (CH), 161.4 (C═O), 167.3 (C═O) ppm, respectively. In addition, the structures of compounds **17a** were confirmed by IR, ^{1}H NMR, ^{13}C NMR and mass spectral data. The ^{1}H NMR spectrum of **17a** showed exhibited one singlet at 3.78 ppm for methoxy protons, one singlet at 5.45 (1 H, d, ^3J = 7.5 Hz, CH) ppm for -CH proton, one singlet at 6.32 ppm for ═CH proton and one singlet at 8.52 for NH proton along with signals for aromatic moiety. In the ^{13}C NMR spectrum, the signals corresponding to —CH group and two



SCHEME 3 Synthesis of pyrazole **6a** by two procedures



16, 17	R	Yield % of **16**	Yield % of **17**
a	CO_2Et	90	95
b	4-MeO-C_6H_4	87	92

SCHEME 4 Synthesis of pyrazole **16** and **17** using quinoline and pyridine, respectively

carbonyl group of **16a** were observed at δ 46.3 (CH) and 161.2 (C═O), 164.3 (C═O) ppm, respectively.

2.1 | Study of antioxidant activity employing Diphenyl-2-picrylhydrazyl (DPPH)

For the confirmation of antioxidant ability or power of compounds to take free radicals of some synthesized compounds and their antioxidant properties in foods and biological systems,[49,50] diphenyl-2-picrylhydrazyl (DPPH) radical trapping experiment is widely used. In this experiment, taking one electron or the hydrogen atom of synthesized compounds was performed by DPPH radical and shows a valuation of antioxidant capacity basis of free radical trapping. The antioxidant ability of **6a–d** was investigated based on their electron or hydrogen donating powers to the DPPH radical. The absorption of DPPH radical was observed in area 517 nm but when DPPH radical is decreased using an antioxidant or radical types, its absorption decreases. In this research, the antioxidant ability or power of compounds **6a–d** for taking free radicals was compared with synthesized antioxidants such as BHT and TBHQ at different concentrations (Figure 1).

As shown in Figure 1, the new synthesized compounds in all concentrations (200-1000 ppm) have good distinctions than to BHT and TBHQ but, at concentration (1000 ppm), have excellent free radical trapping power than to BHT and TBHQ. Among selected synthesized compounds, **6c** was shown excellent radical trapping activity relative to standards (BHT and TBHQ).

2.2 | Reducing power of ferric ions (Fe^{3+}) by some synthesized compounds (FRAP)

The power of reducing ferric ions (Fe^{3+}) by some pyrazole derivatives such as **6a–d** is calculated by the amount of reduction of Fe^{3+}/ferricyanide complex to the Fe^{2+}/ ferrous at 700 nm.[51] As shown in Figure 2, in this test, compound **6c** was shown very good reducing ability than to standard antioxidants such as BHT and TBHQ.

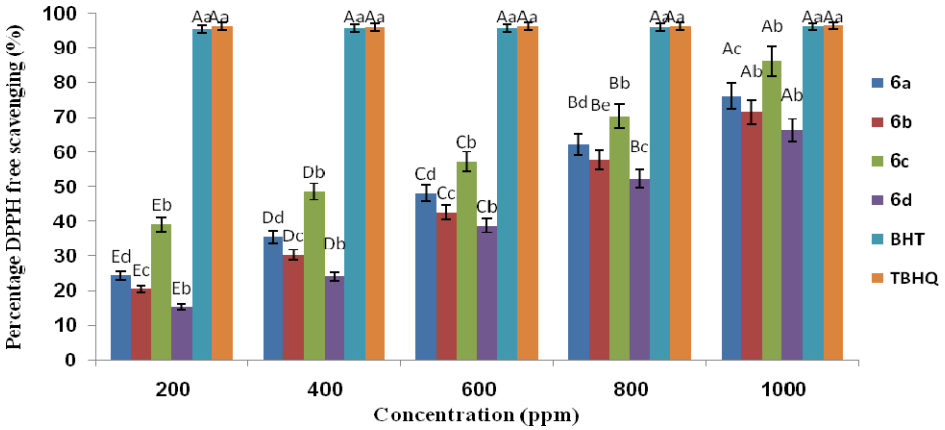


FIGURE 1 Radical scavenging activity of **6a–d** [Color figure can be viewed at wileyonlinelibrary.com]

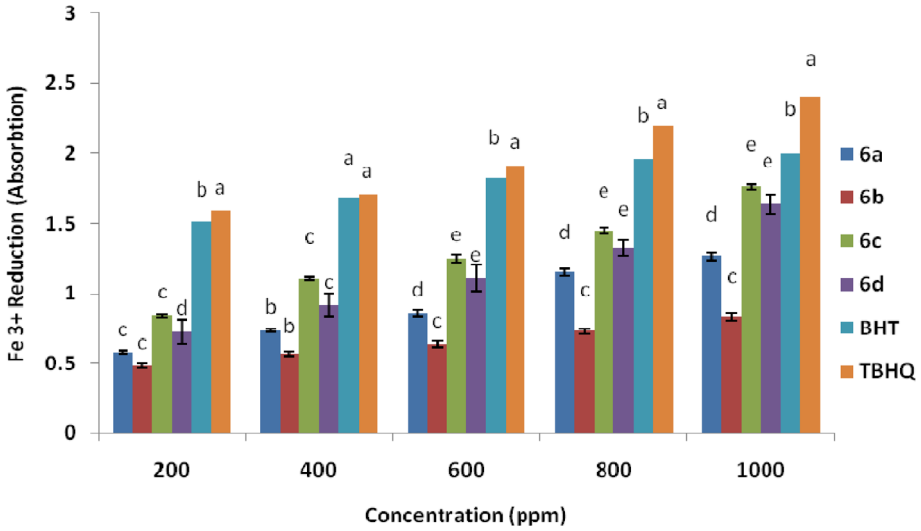


FIGURE 2 Reducing power of ferric ions (Fe^{3+}) (FRAP) by compounds **6a–d** [Color figure can be viewed at wileyonlinelibrary.com]

In summary, multicomponent reaction of isoquinoline, quinoline or pyridine with activated acetylenic compounds, alkyl bromides, triphenylphosphine and hydrazine in water under ultrasonic irradiation at room temperature produced pyrazole derivatives in excellent yields. Also, the antioxidant activities of **6a–d** were evaluated by DPPH radical scavenging and ferric reducing power analyzes. The compounds **6c** exhibit excellent DPPH radical scavenging activity and FRAP compared with synthetic antioxidants BHT and TBHQ. The significant benefits of our method are green reaction conditions, high yield, short reaction time and easy work-up, which are in good agreement with some principles of green chemistry.

3 | EXPERIMENTAL

All chemicals used in this work were prepared from Fluka (Buchs, Switzerland) and were used without further purification. Melting points were measured on an Electrothermal 9100 apparatus. Elemental analyses for C, H and N were performed using a Heraeus CHN—O-Rapid analyzer. Mass spectra were recorded on a FINNIGAN-MAT 8430 spectrometer operating at an ionization potential of 70 eV. IR spectra were measured on a Shimadzu IR-460 spectrometer. ^{1}H and ^{13}C NMR spectra were measured with a BRUKER DRX-500 AVANCE spectrometer at 500.1 and 125.8 MHz, respectively. ^{1}H and ^{13}C spectra were obtained for solutions in $CDCl_3$ using TMS as internal standard or 85% H_3PO_4 as external standard.

3.1 | General procedure for preparation of compounds 6a–j

The mixture of isoquinoline **1** (2 mmol) and activated acetylenic compounds **2** (2 mmol) stirred in water (3 mL) under ultrasonic irradiation. After 10 min the mixture of alkyl bromide **3** and triphenylphosphine **4** that is mixed for 20 min in water (3 mL) under ultrasonic irradiation was added to previous mixture. After 20 minutes, hydrazine (2.5 mmol) was added to mixture and stirred for 10 minutes under ultrasonic irradiation. After completion, the reaction is monitored by TLC, and the solid residue was separated by filtration and washed with Et_2O to afforded pure title compound **6**.

1-Ethy-5-methyl3,12b-dihydropyrazolo[4′,3′:3,4]pyrido [2,1-a]isoquinoline-1,5-dicarboxylate (**6a**). Yellow powder, mp 163°C-165°C, Yield: 0.67 g (95%). IR (KBr) (ν_{max}/cm^{-1}): 1739, 1738, 1695, 1587, 1489, 1295 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): 1.28 (3 H, t, ^3J = 7.4 Hz, CH_3), 3.85 (3 H, s, MeO), 4.26 (2 H, q, ^3J = 7.4 Hz, CH_2O), 5.32 (1 H, s, CH), 6.23 (1 H, s, CH), 6.87 (1 H, d, ^3J = 7.6 Hz, CH), 7.12 (1 H, d, ^3J = 7.6 Hz, CH), 7.25 (1 H, t, ^3J = 7.6 Hz, CH), 7.42 (1 H, t, ^3J = 7.6 Hz, CH), 7.65 (1 H, d, ^3J = 7.8 Hz, CH), 8.15 (1 H, d, ^3J = 7.6 Hz, CH), 8.45 (1 H, s, NH) ppm. ^{13}C NMR (125.7 MHz, $CDCl_3$): 13.9 (Me), 51.3 (CH), 52.6 (MeO), 62.4 (CH_2O), 86.7 (CH), 106.3 (CH), 115.8 (C), 125.3 (CH), 126.6 (CH), 127.2 (CH), 127.8 (CH), 128.3 (CH), 134.2 (C), 138.6 (C), 140.2 (C), 141.5 (C), 142.3 (C), 162.3 (C═O), 164.8 (C═O) ppm. MS (EI, 70 eV): *m/z* (%) = 351 (M^+, 15), 320 (68), 129 (100), 31 (100). Anal. calcd for $C_{19}H_{17}N_3O_4$ (351.36): C, 64.95; H, 4.88; N, 11.96. Found: C, 65.12; H, 4.98; N, 12.18%.

Diethy-5-methyl3,12b-dihydropyrazolo[4′,3′:3,4]pyrido [2,1-a]isoquinoline-1,5-dicarboxylate (**6b**). Yellow powder, mp 166°C-168°C, Yield: 0.67 g (92%). IR (KBr) (ν_{max}/cm^{-1}): 1738, 1735, 1692, 1585, 1487, 1286 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): 1.25 (3 H, t, ^3J = 7.4 Hz, CH_3), 1.32 (3 H, t, ^3J = 7.4 Hz, CH_3), 4.23 (2 H, q, ^3J = 7.4 Hz, CH_2O), 4.28 (2 H, q, ^3J = 7.4 Hz, CH_2O), 5.35 (1 H, s, CH), 6.24 (1 H, s, CH), 6.93 (1 H, d, ^3J = 7.7 Hz, CH), 7.15 (1 H, d, ^3J = 7.7 Hz, CH), 7.32 (1 H, t, ^3J = 7.7 Hz, CH), 7.46 (1 H, t, ^3J = 7.6 Hz, CH), 7.68 (1 H, d, ^3J = 7.8 Hz, CH), 8.17 (1 H, d, ^3J = 7.6 Hz, CH), 8.46 (1 H, s, NH) ppm. ^{13}C NMR (125.7 MHz, $CDCl_3$): 13.9 (Me), 14.2 (Me), 51.3 (CH), 61.5 (CH_2O), 62.6 (CH_2O), 87.3 (CH), 106.5 (CH), 116.3 (C), 125.5 (CH), 127.2 (CH), 127.8 (CH), 128.3 (CH), 128.7 (CH), 134.5 (C), 139.3 (C), 140.5 (C), 141.6 (C), 142.7 (C), 162.5 (C═O), 165.2 (C═O) ppm. MS (EI, 70 eV): *m/z* (%) = 365 (M^+, 15), 320 (68), 129 (100), 45 (100). Anal. calcd for $C_{20}H_{19}N_3O_4$ (365.39): C, 65.74; H, 5.24; N, 11.50. Found: C, 65.95; H, 5.43; N, 11.67%.

Ethyl 3,12b-dihydropyrazolo[4′,3′:3,4]pyrido[2,1-a] isoquinoline-1-carboxylate (**6c**). Pale yellow powder, mp 142°C-144°C, Yield: 0.53 g (90%). IR (KBr) (ν_{max}/cm^{-1}): 1737, 1697, 1569, 1484, 1287 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): 1.34 (3 H, t, ^3J = 7.4 Hz, CH_3), 4.24 (2 H, q, ^3J = 7.4 Hz, CH_2O), 5.24 (1 H, s, CH), 5.63 (1 H, d, ^3J = 6.5 Hz, CH), 6.23 (1 H, d, ^3J = 6.5 Hz, CH), 6.65 (1 H, d, ^3J = 6.5 Hz, CH), 7.15 (1 H, d, ^3J = 6.5 Hz, CH), 7.35 (1 H, t, ^3J = 7.7 Hz, CH), 7.42 (1 H, t, ^3J = 7.6 Hz, CH), 7.65 (1 H, d, ^3J = 7.8 Hz, CH), 8.12 (1 H, d, ^3J = 7.6 Hz, CH), 8.38 (1 H, s, NH) ppm. ^{13}C NMR (125.7 MHz, $CDCl_3$): 14.0 (Me), 51.6 (CH), 61.7 (CH_2O), 98.3 (CH), 106.7 (CH), 109.2 (C), 123.4 (CH), 125.6 (CH), 126.7 (CH), 127.2 (CH), 127.8 (CH), 128.2 (CH), 132.3 (C), 136.4 (C), 138.2 (C), 140.4 (C), 163.7 (C═O) ppm. MS (EI, 70 eV): *m/z* (%) = 293 (M^+, 10), 248 (72), 129 (100), 45 (100). Anal. calcd for $C_{17}H_{15}N_3O_2$ (293.32): C, 69.61; H, 5.15; N, 14.33. Found: C, 69.83; H, 5.36; N, 14.52%.

Methy11-(4-methoxy phenyl) 3,12b-dihydropyrazolo [4′,3′:3,4]pyrido[2,1-a]isoquinoline-5-carboxylate (**6d**). Pale yellow powder, mp 146°C-148°C, Yield: 0.69 g (90%). IR

(KBr) (ν_{max}/cm^{-1}): 1739, 1695, 1568, 1486, 1293 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): 3.75 (3 H, s, MeO), 3.87 (3 H, s, MeO), 5.36 (1 H, s, CH), 6.03 (1 H, d, ^3J = 6.8 Hz, CH), 6.35 (1 H, s, CH), 6.97 (2 H, d, ^3J = 7.6 Hz, 2 CH), 7.08 (1 H, d, ^3J = 7.8 Hz, CH), 7.23 (1 H, t, ^3J = 7.8 Hz, CH), 7.35 (1 H, t, ^3J = 7.8 Hz, CH), 7.52 (1 H, d, ^3J = 7.8 Hz, CH), 7.67 (2 H, d, ^3J = 7.6 Hz, 2 CH), 7.96 (1 H, d, ^3J = 7.6 Hz, CH), 8.42 (1 H, s, NH) ppm. ^{13}C NMR (125.7 MHz, $CDCl_3$): 52.3 (MeO), 54.6 (CH), 55.6 (MeO), 97.2 (CH), 105.7 (CH), 113.4 (2 CH), 115.6 (C), 124.7 (CH), 127.2 (2 CH), 127.6 (CH), 127.9 (CH), 128.3 (CH), 128.5 (CH), 129.2 (C), 130.3 (C), 135.2 (C), 139.2 (C), 140.3 (C), 147.2 (C), 156.3 (C), 164.2 (C═O) ppm. MS (EI, 70 eV): *m*/*z* (%) = 385 (M^+, 15), 354 (48), 129 (100), 31 (100). Anal. calcd for $C_{23}H_{19}N_3O_3$ (385.42): C, 71.67; H, 4.97; N, 10.90. Found: C, 71.84; H, 5.18; N, 10.90%.

Ethy11-(4-methoxy phenyl) 3,12b-dihydropyrazolo [4′,3′:3,4]pyrido[2,1-a]isoquinoline-5-carboxylate (**6e**). Pale yellow powder, mp 153°C-154°C, Yield: 0.72 g (90%). IR (KBr) (ν_{max}/cm^{-1}): 1742, 1697, 1578, 1487, 1295 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): 1.23 (3 H, t, ^3J = 7.4 Hz, CH_3), 4.34 (2 H, q, ^3J = 7.4 Hz, CH_2O), 5.28 (1 H, s, CH), 6.12 (1 H, d, ^3J = 6.8 Hz, CH), 6.42 (1 H, s, CH), 7.03 (2 H, d, ^3J = 7.6 Hz, 2 CH), 7.15 (1 H, d, ^3J = 7.8 Hz, CH), 7.34 (1 H, t, ^3J = 7.8 Hz, CH), 7.48 (1 H, t, ^3J = 7.8 Hz, CH), 7.56 (1 H, d, ^3J = 7.8 Hz, CH), 7.73 (2 H, d, ^3J = 7.6 Hz, 2 CH), 8.06 (1 H, d, ^3J = 7.6 Hz, CH), 8.45 (1 H, s, NH) ppm. ^{13}C NMR (125.7 MHz, $CDCl_3$): 13.8 (Me), 53.8 (CH), 55.7 (MeO), 61.8 (CH_2O), 96.7 (CH), 106.4 (CH), 113.7 (2 CH), 116.3 (C), 125.3 (CH), 126.8 (2 CH), 127.8 (CH), 128.2 (CH), 128.5 (CH), 128.7 (CH), 129.6 (C), 130.5 (C), 135.6 (C), 139.4 (C), 140.5 (C), 147.7 (C), 156.5 (C), 163.8 (C═O) ppm. MS (EI, 70 eV): *m*/*z* (%) = 399 (M^+, 15), 354 (68), 129 (100), 45 (100). Anal. calcd for $C_{24}H_{21}N_3O_3$ (399.44): C, 72.16; H, 5.30; N, 10.52. Found: C, 72.34; H, 5.43; N, 10.73%.

1-(4-methoxy phenyl) 3,12b-dihydropyrazolo[4′,3′:3,4] pyrido[2,1-a]isoquinoline (**6f**). Yellow powder, mp 187°C-189°C, Yield: 0.57 g (87%). IR (KBr) (ν_{max}/cm^{-1}): 1695, 1624, 1567, 1458, 1236 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): 3.85 (3 H, s, MeO), 5.14 (1 H, s, CH), 6.05 (1 H, d, ^3J = 6.7 Hz, CH), 6.25 (1 H, d, ^3J = 6.8 Hz, CH), 6.42 (1 H, d, ^3J = 6.7 Hz, CH), 6.63 (1 H, d, ^3J = 6.8 Hz, CH), 6.75 (2 H, d, ^3J = 7.6 Hz, 2 CH), 7.17 (1 H, t, ^3J = 7.8 Hz, CH), 7.28 (1 H, t, ^3J = 7.8 Hz, CH), 7.42 (1 H, d, ^3J = 7.8 Hz, CH), 7.63 (2 H, d, ^3J = 7.8 Hz, CH), 7.85 (1 H, d, ^3J = 7.6 Hz, CH), 8.45 (1 H, s, NH) ppm. ^{13}C NMR (125.7 MHz, $CDCl_3$): 55.7 (MeO), 56.3 (CH), 98.6 (CH), 105.6 (CH), 112.2 (C), 113.5 (2 CH), 123.4 (CH), 124.8 (CH), 126.8 (2 CH), 127.3 (CH), 127.8 (CH), 128.4 (CH), 128.8 (CH), 129.3 (C), 136.4 (C), 138.4 (C), 140.7 (C), 147.2 (C), 158.9 (C) ppm. MS (EI, 70 eV): *m*/*z* (%) = 327 (M^+, 10), 198 (84), 129 (100). Anal. calcd for $C_{21}H_{17}N_3O$ (327.38): C, 77.04; H, 5.23; N, 12.84. Found: C, 77.23; H, 5.42; N, 12.98%.

Methy11-(4-methyl phenyl) 3,12b-dihydropyrazolo [4′,3′:3,4]pyrido[2,1-a]isoquinoline-5-carboxylate (**6g**). Yellow powder, mp 137°C-139°C, Yield: 0.69 g (87%). IR (KBr) (ν_{max}/cm^{-1}): 1736, 1687, 1585, 1487, 1295 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): 2.34 (3 H, s, Me), 3.78 (3 H, s, MeO), 5.42 (1 H, s, CH), 6.24 (1 H, d, ^3J = 6.5 Hz, CH), 6.37 (1 H, s, CH), 7.05 (1 H, d, ^3J = 6.5 Hz, CH), 7.23 (1 H, t, ^3J = 7.6 Hz, CH), 7.32 (1 H, t, ^3J = 7.6 Hz, CH), 7.42 (2 H, d, ^3J = 7.8 Hz, 2 CH), 7.54 (1 H, d, ^3J = 7.7 Hz, CH), 7.83 (2 H, d, ^3J = 7.6 Hz, 2 CH), 7.93 (1 H, d, ^3J = 7.6 Hz, CH), 8.38 (1 H, s, NH) ppm. ^{13}C NMR (125.7 MHz, $CDCl_3$): 22.3 (Me), 51.4 (MeO), 53.8 (CH), 96.6 (CH), 104.6 (CH), 114.6 (C), 124.2 (CH), 125.4 (CH), 127.3 (2 CH), 127.8 (CH), 128.2 (CH), 128.6 (CH), 129.2 (C), 129.7 (2 CH), 133.2 (C), 135.6 (C), 139.2 (C), 140.2 (C), 141.2 (C), 147.5 (C), 163.2 (C═O) ppm. MS (EI, 70 eV): *m*/*z* (%) = 369 (M^+, 15), 338 (68), 129 (100), 31 (100). Anal. calcd for $C_{23}H_{19}N_3O_2$ (369.42): C, 74.78; H, 5.18; N, 11.37. Found: C, 74.93; H, 5.34; N, 11.57%.

Ethy11-(4-methyl phenyl) 3,12b-dihydropyrazolo [4′,3′:3,4]pyrido[2,1-a]isoquinoline-5-carboxylate (**6h**). Yellow powder, mp 142°C-144°C, Yield: 0.72 g (85%). IR (KBr) (ν_{max}/cm^{-1}): 1738, 1695, 1569, 1485, 1293 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): 1.25 (3 H, t, ^3J = 7.4 Hz, CH_3), 2.36 (3 H, s, Me), 4.25 (2 H, q, ^3J = 7.4 Hz, CH_2O), 5.23 (1 H, s, CH), 6.09 (1 H, d, ^3J = 6.7 Hz, CH), 6.26 (1 H, s, CH), 7.08 (1 H, d, ^3J = 6.7 Hz, CH), 7.25 (1 H, t, ^3J = 7.6 Hz, CH), 7.37 (1 H, t, ^3J = 7.6 Hz, CH), 7.45 (2 H, d, ^3J = 7.8 Hz, 2 CH), 7.56 (1 H, d, ^3J = 7.7 Hz, CH), 7.87 (2 H, d, ^3J = 7.6 Hz, 2 CH), 7.96 (1 H, d, ^3J = 7.6 Hz, CH), 8.42 (1 H, s, NH). ^{13}C NMR (125.7 MHz, $CDCl_3$): 14.0 (Me), 22.3 (Me), 54.3 (CH), 61.5 (CH_2O), 96.5 (CH), 105.8 (CH), 116.3 (C), 124.8 (CH), 125.7 (CH), 127.2 (2 CH), 127.6 (CH), 128.0 (CH), 128.3 (CH), 129.2 (2 CH), 129.6 (C), 134.2 (C), 137.2 (C), 139.4 (C), 140.2 (C), 141.5 (C), 147.3 (C), 164.3 (C═O) ppm. MS (EI, 70 eV): *m*/*z* (%) = 399 (M^+, 15), 354 (68), 129 (100), 45 (100). Anal. calcd for $C_{24}H_{21}N_3O_2$ (383.44): C, 75.18; H, 5.52; N, 10.96. Found: C, 75.32; H, 5.67; N, 11.18%.

Methy11-(4-bromophenyl) 3,12b-dihydropyrazolo [4′,3′:3,4]pyrido[2,1-a]isoquinoline-5-carboxylate (**6i**). Yellow powder, mp 183°C-185°C, Yield: 0.69 g (83%). IR (KBr) (ν_{max}/cm^{-1}): 1735, 1696, 1597, 1492, 1292 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): 3.75 (3 H, s, MeO), 5.18 (1 H, s, CH), 6.09 (1 H, d, ^3J = 6.7 Hz, CH), 6.25 (1 H, s, CH), 7.08 (1 H, d, ^3J = 6.7 Hz, CH), 7.18 (1 H, t, ^3J = 7.6 Hz, CH), 7.29 (1 H, t, ^3J = 7.6 Hz, CH), 7.35 (2 H, d, ^3J = 7.7 Hz, 2 CH), 7.46 (2 H, d, ^3J = 7.7 Hz, 2 CH), 7.63 (1 H, d, ^3J = 7.6 Hz, CH), 7.87 (1 H, d, ^3J = 7.6 Hz, CH), 8.24 (1 H, s, NH) ppm. ^{13}C NMR (125.7 MHz, $CDCl_3$):

51.6 (MeO), 54.8 (CH), 96.2 (CH), 104.5 (C), 105.7 (CH), 124.3 (C), 125.2 (CH), 126.3 (CH), 127.2 (CH), 127.6 (CH), 128.2 (CH), 128.5 (2 CH), 128.7 (C), 130.6 (2 CH), 134.3 (C), 135.8 (C), 139.2 (C), 140.3 (C), 147.7 (C), 161.6 (C═O) ppm. MS (EI, 70 eV): m/z (%) = 436 (M^++2, 15), 434 (M^+, 15), 403 (56), 129 (100), 31 (100). Anal. calcd for $C_{22}H_{16}BrN_3O_2$ (434.29): C, 60.84; H, 3.71; N, 9.68. Found: C, 60.96; H, 3.87; N, 9.85%.

Methy11-(4-nitro phenyl) 3,12b-dihydropyrazolo [4′,3′:3,4]pyrido[2,1-a]isoquinoline-5-carboxylate (**6j**). Yellow powder, mp 198°C-200°C, Yield: 0.64 g (80%). IR (KBr) (ν_{max}/cm^{-1}): 1736, 1687, 1585, 1487, 1295 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): 3.76 (3 H, s, MeO), 5.24 (1 H, s, CH), 5.89 (1 H, d, ^3J = 6.8 Hz, CH), 6.23 (1 H, s, CH), 7.07 (1 H, d, ^3J = 6.8 Hz, CH), 7.22 (1 H, t, ^3J = 7.6 Hz, CH), 7.35 (1 H, t, ^3J = 7.6 Hz, CH), 7.43 (1 H, d, ^3J = 7.7 Hz, CH), 7.56 (2 H, d, ^3J = 7.8 Hz, 2 CH), 7.86 (1 H, d, ^3J = 7.7 Hz, CH), 8.18 (2 H, d, ^3J = 7.6 Hz, 2 CH), 8.53 (1 H, s, NH) ppm. ^{13}C NMR (125.7 MHz, $CDCl_3$): 51.8 (MeO), 54.3 (CH), 96.7 (CH), 105.3 (CH), 117.4 (C), 123.2 (2 CH), 125.2 (CH), 126.3 (CH), 127.5 (CH), 128.3 (CH), 128.5 (CH), 129.5 (2 CH), 129.6 (C), 135.4 (C), 139.3 (C), 140.2 (C), 141.4 (C), 147.3 (C), 149.2 (C), 161.6 (C═O) ppm. MS (EI, 70 eV): m/z (%) = 400 (M^+, 15), 369 (86), 129 (100), 31 (100). Anal. calcd for $C_{22}H_{16}N_4O_4$ (400.39): C, 66.00; H, 4.03; N, 13.99. Found: C, 66.23; H, 4.18; N, 14.18%.

Spectral data of intermediate **12a**. *Methyl 1-(2-ethoxy-2-oxoacetyl)-2-methoxy-11bH-pyrido[2,1-a]isoquinoline-4-carboxylate (**12a**):* Yellow powder, mp 158°C-160°C, Yield: 0.64 g (87%). IR (KBr) (ν_{max}/cm^{-1}): 1739, 1738, 1725, 1695, 1587, 1489, 1295 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): 1.36 (3 H, t, ^3J = 7.4 Hz, CH_3), 3.86 (3 H, s, MeO), 3.98 (3 H, s, MeO), 4.35-4.44 (2 H, m, CH_2O), 5.32 (1 H, s, CH), 6.12 (1 H, s, CH), 7.33 (1 H, d, ^3J = 7.6 Hz, CH), 7.61-7.81 (3 H, m, 3 CH), 8.77 (1 H, d, ^3J = 7.8 Hz, CH), 9.40 (1 H, d, ^3J = 7.6 Hz, CH) ppm. ^{13}C NMR (125.7 MHz, $CDCl_3$): 13.9 (Me), 41.2 (CH), 52.6 (MeO), 58.6 (MeO), 62.7 (CH_2O), 101.9 (CH), 116.6 (CH), 119.1 (C), 123.8 (C), 124.3 (CH), 125.7 (CH), 127.3 (CH), 128.4 (CH), 129.4 (CH), 130.1 (C), 133.8 (C), 160.6 (C), 164.3 (C═O), 165.6 (C═O), 176.6 (C═O) ppm. MS (EI, 70 eV): m/z (%) = 369 (M^+, 15), 338 (56), 129 (100), 31 (100). Anal. calcd for $C_{20}H_{19}NO_6$ (369.37): C, 65.03; H, 5.18; N, 3.79. Found: C, 65.18; H, 5.34; N, 3.92%.

3.2 | General procedure for preparation of compounds 16a–b and 17a–b

To a stirred mixture of quinoline or pyridine **15** (2 mmol) and dimethyl acetylenedicarboxylate **2a** (2 mmol) in water (3 mL) under ultrasonic irradiation was added after 10 minutes the mixture of alkyl bromide **3** and triphenylphosphine **4** that is mixed for 20 minutes in water (3 mL) under ultrasonic irradiation. After 20 minutes, hydrazine (2.5 mmol) was added to mixture and stirred for 10 minutes under ultrasonic irradiation. After completion, the reaction is monitored by TLC, and the solid residue was separated by filtration and washed with Et_2O to afforded pure title compound **16** and **17,** respectively.

3-Ethy-11-methyl1,3b-dihydropyrazolo[4′,3′:3,4]pyrido [1,2-a]quinoline-3,11-dicarboxylate (**16a**). Yellow powder, mp 152°C-154°C, Yield: 0.63 g (90%). IR (KBr) (ν_{max}/cm^{-1}): 1742, 1740, 1697, 1586, 1487, 1292 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): 1.25 (3 H, t, ^3J = 7.4 Hz, CH_3), 3.87 (3 H, s, MeO), 4.25 (2 H, q, ^3J = 7.4 Hz, CH_2O), 5.62 (1 H, d, ^3J = 6.5 Hz, CH), 6.27 (1 H, s, CH), 6.78 (1 H, d, ^3J = 6.8 Hz, CH), 7.06 (1 H, t, ^3J = 7.6 Hz, CH), 7.18 (1 H, d, ^3J = 7.6 Hz, CH), 7.34 (1 H, t, ^3J = 7.6 Hz, CH), 7.68 (1 H, d, ^3J = 7.8 Hz, CH), 7.86 (1 H, d, ^3J = 7.6 Hz, CH), 8.48 (1 H, s, NH) ppm. ^{13}C NMR (125.7 MHz, $CDCl_3$): 14.2 (Me), 48.5 (CH), 52.4 (MeO), 61.3 (CH_2O), 95.4 (CH), 109.2 (C), 117.2 (CH), 118.6 (CH), 122.3 (CH), 130.2 (C), 130.8 (CH), 131.2 (C), 131.6 (C), 132.3 (C), 133.4 (CH), 134.2 (CH), 141.2 (C), 161.4 (C═O), 167.3 (C═O) ppm. MS (EI, 70 eV): m/z (%) = 351 (M^+, 15), 320 (84), 129 (100), 31 (100). Anal. calcd for $C_{19}H_{17}N_3O_4$ (351.36): C, 64.95; H, 4.88; N, 11.96. Found: C, 65.16; H, 5.02; N, 12.23%.

Methy3-(4-methoxy phenyl) 1,3b-dihydropyrazolo [4′,3′:3,4]pyrido[1,2-a]quinoline-11-carboxylate (**16b**). Pale yellow powder, mp 158°C-160°C, Yield: 0.67 g (87%). IR (KBr) (ν_{max}/cm^{-1}): 1738, 1692, 1575, 1487, 1295 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): 3.78 (3 H, s, MeO), 3.85 (3 H, s, MeO), 5.24 (1 H, d, ^3J = 6.4 Hz, CH), 6.28 (1 H, d, ^3J = 6.8 Hz, CH), 6.47 (1 H, s, CH), 6.98 (2 H, d, ^3J = 7.6 Hz, 2 CH), 7.12 (1 H, t, ^3J = 7.6 Hz, CH), 7.25 (1 H, d, ^3J = 7.6 Hz, CH), 7.38 (1 H, t, ^3J = 7.8 Hz, CH), 7.59 (1 H, d, ^3J = 7.6 Hz, CH), 7.74 (2 H, d, ^3J = 7.6 Hz, 2 CH), 7.86 (1 H, d, ^3J = 7.6 Hz, CH), 8.53 (1 H, s, NH) ppm. ^{13}C NMR (125.7 MHz, $CDCl_3$): 49.3 (CH), 52.6 (MeO), 55.7 (MeO), 98.4 (CH), 112.4 (C), 113.6 (2 CH), 117.2 (CH), 119.2 (CH), 122.6 (CH), 126.8 (2 CH), 127.2 (C), 130.4 (C), 131.2 (C), 131.8 (CH), 132.3 (C), 133.4 (CH), 134.2 (CH), 140.6 (C), 145.6 (C), 158.3 (C), 165.7 (C═O) ppm. MS (EI, 70 eV): m/z (%) = 385 (M^+, 15), 354 (62), 129 (100), 31 (100). Anal. calcd for $C_{23}H_{19}N_3O_3$ (385.42): C, 71.67; H, 4.97; N, 10.90. Found: C, 71.82; H, 5.20; N, 10.93%.

1-Ethy-5-methyl3,10a-dihydropyrazolo[4,3-a] quinolizine-1,5-dicarboxylate (**17a**). Yellow powder, mp 123°C-125°C, Yield: 0.67 g (95%). IR (KBr) (ν_{max}/cm^{-1}): 1739, 1737, 1697, 1586, 1464, 1296 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): 1.56 (3 H, t, ^3J = 7.4 Hz, CH_3), 3.78

(3 H, s, MeO), 4.36 (2 H, q, ^3J = 7.4 Hz, CH_2O), 5.45 (1 H, d, ^3J = 7.5 Hz, CH), 6.32 (1 H, s, CH), 6.94 (1 H, t, ^3J = 7.6 Hz, CH), 7.34 (1 H, t, ^3J = 7.5 Hz, CH), 7.45 (1 H, d, ^3J = 7.5 Hz, CH), 7.95 (1 H, d, ^3J = 7.5 Hz, CH), 8.52 (1 H, s, NH) ppm. ^{13}C NMR (125.7 MHz, $CDCl_3$): 13.8 (Me), 46.3 (CH), 52.5 (MeO), 62.3 (CH_2O), 94.6 (CH), 95.3 (CH), 108.4 (C), 115.2 (CH), 123.4 (CH), 127.5 (CH), 128.2 (C), 129.68 (C), 130.4 (C), 161.2 (C═O), 164.3 (C═O) ppm. MS (EI, 70 eV): *m/z* (%) = 301 (M^+, 10), 270 (84), 129 (100), 31 (100). Anal. calcd for $C_{15}H_{15}N_3O_4$ (301.29): C, 59.79; H, 5.02; N, 13.95. Found: C, 59.96; H, 5.24; N, 14.18%.

Methy1-(4-methoxy phenyl) 3,10a-dihydropyrazolo [4,3-a]quinolizine-5-carboxylate (**17b**). Pale yellow powder, mp 138°C-140°C, Yield: 0.55 g (92%). IR (KBr) (ν_{max}/cm^{-1}): 1743, 1698, 1586, 1488, 1296 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): 3.78 (3 H, s, MeO), 3.83 (3 H, s, MeO), 4.86 (1 H, d, ^3J = 6.8 Hz, CH), 6.42 (1 H, s, CH), 6.87 (1 H, t, ^3J = 7.5 Hz, CH), 7.05 (1 H, t, ^3J = 7.5 Hz, CH), 7.16 (1 H, d, ^3J = 7.5 Hz, CH), 7.22 (2 H, d, ^3J = 7.6 Hz, 2 CH), 7.64 (2 H, d, ^3J = 7.6 Hz, 2 CH), 8.07 (1 H, d, ^3J = 7.6 Hz, CH), 8.45 (1 H, s, NH) ppm. ^{13}C NMR (125.7 MHz, $CDCl_3$): 48.6 (CH), 52.3 (MeO), 55.2 (MeO), 94.2 (CH), 97.5 (CH), 112.3 (C), 113.5 (2 CH), 114.2 (CH), 122.5 (CH), 126.8 (2 CH), 127.5 (CH), 128.2 (C), 129.5 (C), 130.7 (C), 143.2 (C), 158.4 (C), 162.5 (C═O) ppm. MS (EI, 70 eV): *m/z* (%) = 335 (M^+, 15), 304 (86), 129 (100), 31 (100). Anal. calcd for $C_{19}H_{17}N_3O_3$ (335.36): C, 68.05; H, 5.11; N, 12.53. Found: C, 68.23; H, 5.32; N, 12.74%.

3.2.1 | Determination of antioxidant activity using radical trapping test by (DPPH)

The radical trapping experiment by DPPH was employed for valuation of antioxidant ability for some generated compounds such as **6a–d** as indicated by Shimada et al[50] procedure. For achieving to this purpose, different concentrations (200-1000 ppm) of compounds **6a–d** were added to DPPH methanolic solution (1 mmol/L) with an equal volume. The mixtures were mixed for 30 minutes at ambient temperature and after this time computed in a dark room. Then, the mixture absorbance was calculated and recorded at 517 nm. The compounds **6a–d** were exchanged with methanol (3 mL) in the standard type. The standard antioxidant such as Butylated hydroxytoluene (BHT) and 2-tertbutylhydroquinone (TBHQ) were employed as standard control sample. The percentage inhibition of the DPPH radical was measured using Yen and Duh[52] formula.

3.2.2 | Evaluation of reducing ability for synthesized compounds

The ability of reducing iron (III) was evaluated for the compounds **6a–d** using Yildirim et al method.[51] For this purpose, the samples (1 mL), phosphate buffer (2.5 mL, 0.2 mol/L, pH 6.6) and potassium ferricyanide ($K_3Fe(CN)_6$; 2.5 mL, 10 g/L) were combined together and sustained for 30 minutes at 50°C. Then, trichloroacetic acid (2.5 mL, 10% w/v) was added to the previous solution and centrifuged for 10 minutes. In the end, the supernatant (2.5 mL) was mixed with distilled water (2.5 mL) and $FeCl_3$ (0.5 mL, 1 g/L) and the samples absorbance was computed at 700 nm. The higher reducing power was attributed to higher absorbance. For accuracy of calculating, each calculation was performed in three times. The SPSS software version 18.0 was used for data analysis of compounds by running one way analysis of variance (ANOVA) that confirmed variation in the mean value of samples and control. All removing were done by Duncan multiple range tests employing the importance level of 95% ($P < .05$).

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