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Green synthesis and investigation of antioxidant ability new pyrazines

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Abstract: In this study, a new, easy and high yield procedure is investigated for the generation of pyrazine containing pyrrolo[2,1-a]isoquinoline derivatives using multicomponent reaction of phthalaldehyde or its derivatives, primary amines, □-haloalketones, electron deficient acetylenic compounds, ammonium acetate and KF/Clinoptinolite nanoparticles (KF/CP NPs) as catalyst in water at room temperature. The reactions of 2-hydroxy phthalaldehyde, primary amines, □-haloketones, electron deficient acetylenic compounds, and ammonium acetate in the presence of KF/CP NPs as catalyst in water at room temperature produce pyrazine derivatives in good yields. Also, in this work, antioxidant ability was studied for a number of prepared compounds employing the 2,2-diphenyl-1-picrylhydrazyl (DPPH) radical scavenging and power of compounds for reducing of ferric ion experiments and evaluating results with synthetic antioxidants (TBHQ and BHT). Comfortable, simple, fast and fresh procedure is the advantages of this study.

Keywords: Pyrazine containing Pyrrolo[2,1-a]isoquinoline, Antioxidant ability, Isoquinoline, Multi component reaction, Activated acetylenic compounds.

Introduction

Among the heterocyclic compounds that are shown in nature, pyrazines are a very important group. These compounds are also prepared in the laboratory as 1876 [1-3]. Different synthetic procedures have been reported to generate pyrazine derivatives that have biological properties [4-9].Another moiety in these synthesized molecules is Pyrrolo[2,1-*a*]isoquinoline moieties [10] that is exist in alkaloid groups, such as erythrina[11] and lamellarin [12], and in more simple pyrrolo[2,1-*a*]isoquinoline derivatives [13,14] with diverse biological activities in all of them. Furthermore, the value of pyrrolo[2,1-*a*]isoquinolines is more increased by their employing as intermediates for the generation of alkaloids [15] and for this reason, synthesis of these compounds is very important. The pyrrolo[2,1-a] isoquinoline derivatives have been generated many years ago before these compounds were separated as natural products.

pyrrolo[2,1-a]isoquinoline moiety also exist natural products which have been known for a long time. When the first report of their antitumor activity appeared, the importance and value of synthesized compounds with this moiety increased extremely. Among *N*-bridgehead heterocyclic compounds Pyrrolo[2,1-*a*]isoquinolines whichexist in some of natural products were considered for their biological activity such as crispine A, with imperative anticancer ability [16-19]. In recent times oleracein E [20, 21]and trolline [15] with pyrrolo[2,1-*a*]isoquinoline nucleus which were isolated from *traditional Chinese medicinal plants* were investigated.In addition, the important procedure for synthesis of complex molecules from simple compounds is multicomponent reactions (MCRs) [22-27]. This method is very important for medicinal and synthetic chemists and molecules that are prepared by this procedure are beautiful [28-30]. Use of eco-friendly, safe and cheap solvents and reagent in place of poisonous solvents, employing cheap reagents are the most attractive procedures for the synthesis of organic

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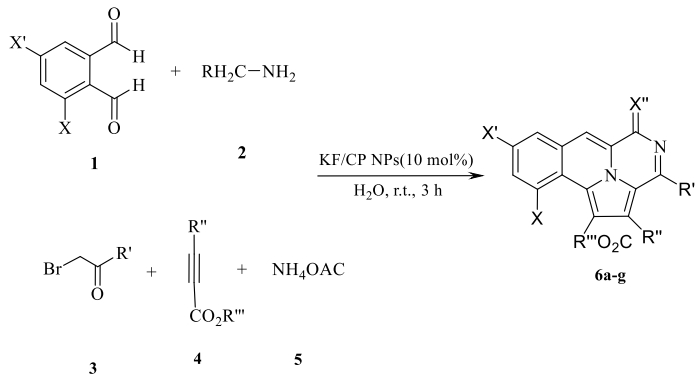
compounds [31]. The most of methods utilize expensive organic solvents and catalysts that employ multi- step synthetic methodologies [32-45]. Recently, there has been enormous emphasis on the green and sustainable chemistry, where high importance has given for the development of novel and eco-friendly methodologies that can decrease or remove the employ and production of dangerous industrial wastes. Water is an inexpensive solvent, is available in considerable levels and can enhance the rate of oranic reaction even for insoluble compounds in water. The products can separated from water media by using filtration. Recently, using KF (potassium fluoride) supported on zeolites such as clinoptilolite (CP) and clays as new natural and cheap solid base source are very interesting [46-54]. The CP with high internal surface is a natural zeolite. This zeolite is very interesting and valuable due to ability for cation exchanging especially for K^+.Therefore, in KF/Clinoptilolite fluoride anions is free and could be use as an effective base. Also, synthesis of potassium fluoride/Clinoptilolite (KF/CP) is very easy and simple and starting materials are used with no any pre-activation [55-57]. In continuation of our studies for discovering new methodes for synthesis of important heterocyclic organic compounds [58-61], we employ an effective multi component reaction of phthalaldehydes **1**, primary amines with electron withdrawing groups **2**, alkyl bromide **3**, activated acetylenic comompouds **4**, ammonium acetate **5**and catalytic amounts of KF/CP NPs in water at room temperature as green procedure for the preparation of new pyrazines**6** with excellent yields (Scheme 1). Additionally, because of existing pyrazine and isoquinoline core in these products, the antioxidant ability of some synthesized compounds were investigated by performing DPPH (2,2-diphenyl-1-picrylhydrazyl) radical trapping and reducing power of ferric ion experiments.

Result and discussion

In this work, synthesis of pyrazines containing pyrrolo[2,1-*a*]isoquinolinederivatives in excellent yield **6** are performed using phthalaldehydes **1**, primary amine with electron withdrawing groups **2**, alkyl bromide **3**, activated acetylenic comompouds **4**, ammonium acetate **5** and catalytic amounts ofKF/clinoptilolite nanoparticles as basic catalyst in water at room temperature (Scheme **1**).



6	R	R'	R''	R'''	X	X'	X''	Yield of % **6**
a	CO_2Et	CO_2Et	CO_2Me	Me	H	Me	O	95
b	CN	4-MeO-C_6H_4	CO_2Me	Me	H	Me	NH	92
c	CN	4-Me-C_6H_4	CO_2Me	Me	H	Me	NH	90
d	CN	4-Br-C_6H_4	CO_2Me	Me	H	Me	NH	87
e	CO_2Et	4-NO_2-C_6H_4	CO_2Me	Me	MeO	H	O	85
f	CO_2Et	CO_2Et	CO_2Et	Et	Me	H	O	89
g	CO_2Et	CO_2Et	H	Me	Me	H	O	90

Scheme 1: Multi component reaction for the generation of pyrazine derivatives of **6**

The first step of this research is optimization the reaction and obtaining the best reaction conditions. For this purpose, the reaction of 5-methyl phthalaldehyde **1a**, primary amine **2a**, ethyl bromopyruvate **3a**, dimethyl acetylenedicarboxylate **4a** and ammonium acetate **5** was utilized as a model reaction for obtaining the best conditions (Table **1**). These reactions need to basic condition for carrying out and for this reason did not performed without base or basic catalyst even after 12 h (entry 1, Table **1**). In addition, the reaction mixture

is very busy in absence of catalyst. For confirmation of this point, 10 mol% Fe_3O_4-MNPs was added in the reaction mixture. By using this condition after 7 h, compound **6a** was produced in 80% yield (entry 15, Table 1). For more investigation about catalyst effect, different catalyst with basic property such as ZnO-nanorods, CuO-NPs, TiO_2-NPs, Me_3N, Al_2O_3, Et_3N and KF/CP NPs were utilized in this reaction. Thus, these results exhibited the KF/CP NPs is an effective green catalyst for performing model reaction. Then, for obtaining the best amounts of catalyst, the model reaction was done with 10-25 mol% of KF/CP NPs. By increasing the amount of catalyst from 15 mol% and temperature to 90 °C wasn't seen any significant change in the yield of reaction (entry 2, Table **1**).

Table 1. Optimization of catalyst and its amount, and temperature in the formation of **6a**

Entry	Catalyst	Temp.(°C)	catalyst (mol%)	Time (h)	Yield%[a]
1	none	r.t.	-	12	-
2	none	80	-	10	5
3	none	90	-	10	5
4	**KF/CP NPs**	**r.t.**	**10**	**3**	**95**
5	KF/CP NPs	80	10	3	97
6	KF/CP NPs	r.t.	15	3	95
7	KF/CP NPs	r.t.	20	3	93
8	Et_3N	r.t.	10	3	85
9	Me_3N	r.t.	10	3	90
10	Al_2O_3	r.t.	10	7	30
11	ZnO-NR	r.t.	10	5	58
12	ZnO-NR	90	15	5	60
13	CuO-NPs	r.t.	10	8	38
14	TiO_2-NPs	r.t.	10	7	15
15	Fe_3O_4-MNPs	r.t.	10	5	80

As expected, in the optimum conditions the yield of product **6a** after 3 h attained in 95% yield (entry4, Table **1**). The utilizing of catalytic amounts of KF/CP-NPs in these reactions is due to increasing the yield of reaction, be inexpensive, secure than to other catalyst and large quantity of clinoptilolite (CP). One of property of this catalyst is trapping the K^+ ion and therefore the F- ion act as base successfully. The ZnO-NPs, TiO_2-NPs activity as Lewis base catalyst is lower than F-. Performing these reactions with triethyl amine as basic catalyst caused to busy condition and product separation is not easy. Trimethylamine (TMA) than to triethylamine is better base and product produced with high yield in the presence of TMA. In KF/CP NPs, the F- ion is small, free and act better than to other catalyst. As well, the effects of some solvents was studied in model reaction. The results tabulated in Table **2** exhibitted that among the solvents, H_2O is the good media for performing these reaction.

Table 2. Selecting the best temperature and solvent for the preparation of **6a**

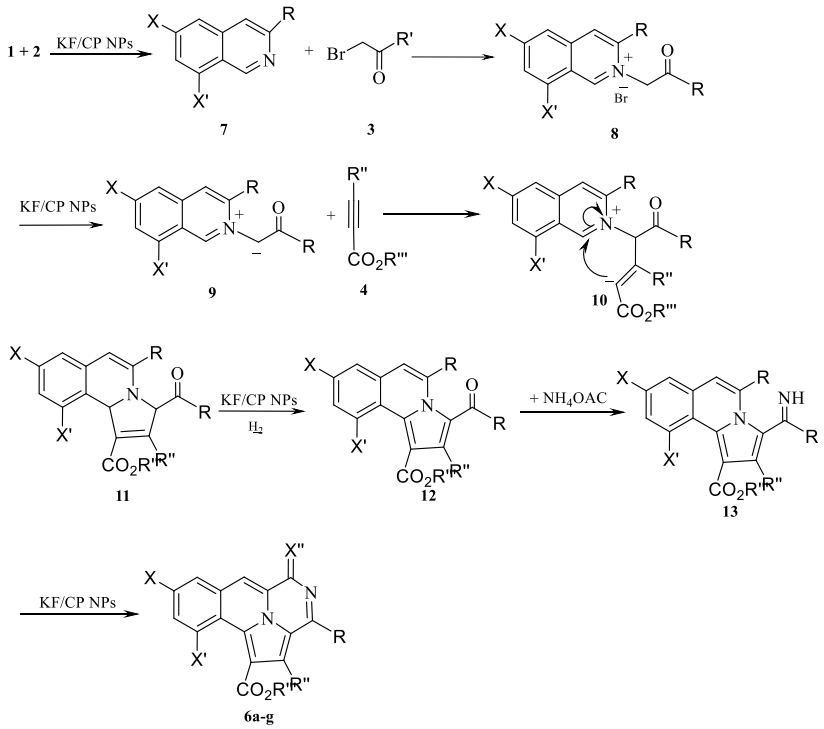
Entry	Solvent	Temp. (°C)	Time (h)	Yield%[a]
1	EtOH	r.t.	8	---
2	EtOH	90	8	5
3	CH_2Cl_2	r.t.	5	75
4	CH_2Cl_2	40	5	75
5	**H_2O**	**r.t.**	**3**	**95**
6	H_2O	80	3	97
7	H_2O	90	3	97
8	Solvent-free	r.t.	3	85
10	DMf	r.t.	10	25

As shown in the Tables 1 and 2, the best conditions for the synthesis of pyrazine derivatives is water as solvent and room temperature in the presence of catalytic amounts of KF/CP NPs (10 mol%) .The KF/CP NPs as catalyst was used some times in model reaction (the synthesis of compound **6a**). The outcomes displayed that this catalyst can be used three times without significant change in yield of **6a** (Table **3**).

Table 3. The reusability of KF/CP NPs

Run	% Yield[a]
1st	95
2nd	93
3nd	90
4nd	87

For evaluation of reusability of KF/CP NPs as catalyst, after completion of reaction, the KF/CP NPs was separated by filteration and cleaned with mixture of ethanol and water (1:1). After drying the catalyst, it was used in the modelreaction again. For the confirmation the structure of synthesized compounds **6**,theIR, ^{1}H NMR, ^{13}C NMR, and mass spectral data were employed. For instance, the ^{1}H NMR spectrum of **6a** exhibited one singlet at 2.25 ppm for methyl protons and two singlets at 3.75 and 3.83 ppm for methoxy protons, two singlets at 7.64 and 7.78 for methin protons along with signals for aromatic moiety. In the ^{13}C NMR spectrum, the signals corresponding to the four-carbonyl group of **6a** observed at δ161.2, 162.3, 164.7 and 168.2 ppm. The IR spectrum of **6a** display characteristic C=O bands. Although there isn't any data for the details of mechanism, the proposed mechanism for the reaction is investigated in Scheme **2**.



Scheme 2. Suggested mechanism for the generation of **6**.

Initially, isoquinoline derivatives **7** [63]produced from the reaction of phthalaldehyde or its derivatives **1**and primary amines **2** with withdrawing group in the presence of KF/Clinoptilolite nanoparticles. Then, α-haloketone **3** reacts with isoquinoline **7** in the presence of KF/CP NPs and produce intermediate **9** with elimination of HBr. Negative charge in intermediate **9** attack to compounds **4** as nucleophile and produce intermediate **10**. By intermolecular cyclization, elimination of hydrogen and oxidation process of intermediate **10** produced compounds**12**. The reaction of compounds **12** with ammonium acetate **5**, generated imine **13** that NH of imine react with R group and cyclization are take place and product **6** are produced (Scheme 2)**.** Green reaction conditions; employing a small amount of nanocatalyst, high yield, short time of reaction, and simple work-up, which are in good agreement with some principles of green chemistry are

some advantages of our procedure. It should mentioned the isoquinoline convert to N-oxide in the presence of air and for this reason yield of reaction was low and should be used more than other reagent. For this reason, in this procedure isoquinoline is produced *in situe* and used in the reactions. The scanning electron microscopy images (SEM) Figure **1** and X-ray diffraction patterns (XRD) Figure **2** used for evaluation and confirmation of the construction and particle size of potassium fluoride/Clinoptilolite nanoparticles.

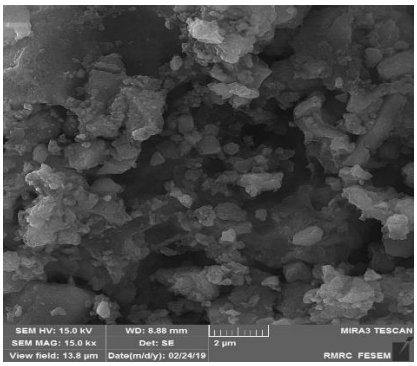


Figure 1. The image of scanning electron microscopy of green KF/CP NPs

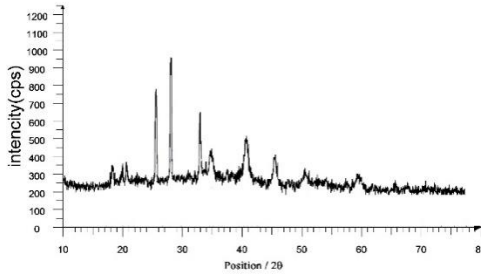


Figure 2 The X-ray diffraction spectra image of green KF/CP nanoparticles

The particles size of KF/Clinoptilolite nanoparticles has been calculated by the equation of Debye–Scherrer's ($D=K\lambda/\beta\cos\theta$) [64-64]and attained 35 nm.

By using EDS technique was performed elemental analysis of the synthesized KF/CP NPs and confirmed the structure of this catalyst (Figure 3). As shown in Figure 3, K and F peaks of KF/CP NPs indicate a successful synthesis. In addition, the presence of carbon peak in the EDS spectrum confirmed the presence of organic compounds at the nanoscale.

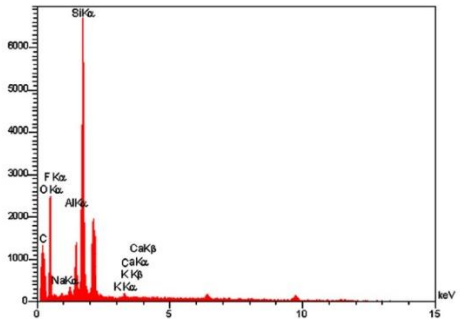


Figure 3. EDS image of green KF/CP NPs

The transmission electron microscopy analysis used for achieving the high quality and apparent size, form and structural picture of the KF/CP NPs (Figure 4). TEM image exhibited the size of the synthesized KF/CP NPs to be less than 40 nm.

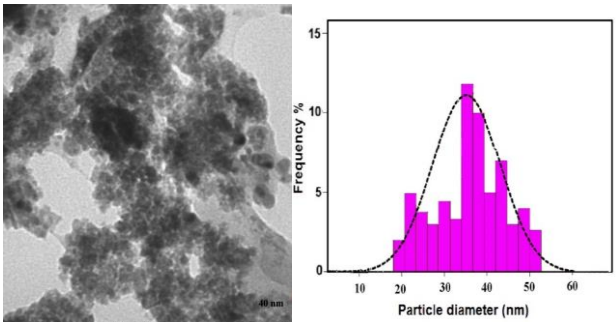


Figure 4. TEM image of the green KF/CP NPs

Evalution of antioxidant ability employing diphenyl-2-picrylhydrazyl (DPPH)

For the confirmation of antioxidant ability or power of compounds to take free radicals of a number of prepared pyrazines and confirmation the antioxidant ability of them in foods and biological structure [66-67],diphenyl-2-picrylhydrazyl (DPPH) radical trapping experiment is widely used. In these test, taking one electron or the hydrogen atom of synthezied compounds was performed by DPPH radical and basis of free radical trapping show an valuation of antioxidant capacity. The antioxidant ability of **6a, 6c, 6d** and **6g** was considered basis of their electron or hydrogen donating power to the DPPH radical. The absorption of DPPH radical was seen about 517 nm but absorption of it decreases when using an one electron or hydrogen from antioxidant or a radical typs. In this work, the antioxidant ability or power of compounds **6a, 6c, 6d** and **6g** for taking free radicals was evaluated than to synthesized antioxidant such as BHT and TBHQ at various concentrations. Overall, the trapping power of one electron or one hydrogen by DPPH was obtained TBHQ≈BHT>**6c**>**6g**>**6a**>**6d** respectively (Figure **5**).

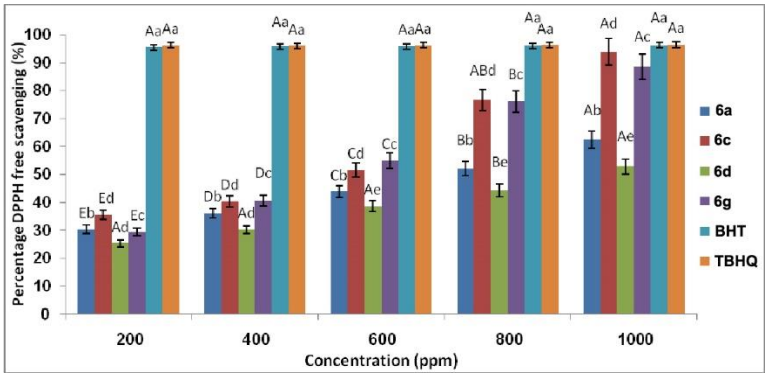


Figure 5. scavenging activity of radical by **6a, 6c, 6d** and **6g**

As shown in Figure 5, the new synthesized compounds in all concentrations have good distinctions in comparison with BHT and TBHQ. Among selected synthezied compounds, **6c** was shown excellent radical trapping activity than to standards (BHT and TBHQ).

The potential of synthesiaed copmpounds by Ferric ions (Fe^{3+}) reducing

The ability of reducing ferric ions (Fe^{3+}) by some synthesized compounds such as **6a, 6c, 6d** and **6g** are calculated by the quantity of Fe^{3+}/ferricyanide reduced to the Fe^{2+}/ ferrous at 700 nm [68].As shown in Figure6, in this investigation, reducing ability of compound **6c** are good in comparison with standard antioxidants such as BHT and TBHQ. The reducing activity trend of the samples was as follows: TBHQ>BHT>**6c**>**6a**>**6g**>**6d**. It shows that the **6c** had the isoquinoline core with stronger iron chelating power that lead to more reducing potential. The results are shown in Figure 6.

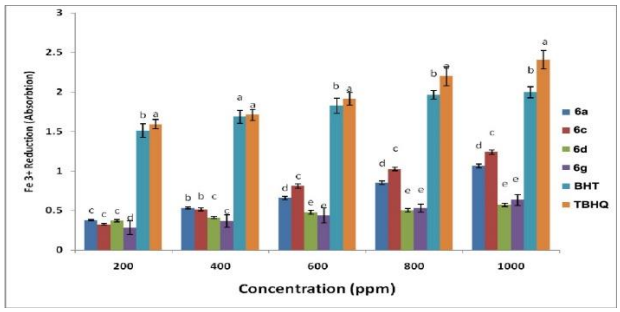


Figure 6. Antioxidant power (FRAP) of compounds **6a, 6c, 6d** and **6g** toreducing ferric ions (Fe^{3+})

Conclusion

In conclusion, we studied a convenient, clean, and environmentally method involving phthalaldehyde or its derivatives, primary amines, α-haloketones, electron deficient acetylenic compounds, ammonium acetate and KF/CP NPs as catalyst in water at room temperature. The our procedure for synthesis of pyrazine derivatives has many advantages such as excellent yield, simple, using low amount of catalyst and short time, mild and clean reaction. Also, the power of antioxidant for compounds **6a, 6c, 6d** and **6g** compounds were calculated by DPPH radical trapping and ferric reducing power analyzes. Among them, compound **6c** demonstrate good DPPH radical trapping and reducing ability in comparison with standard antioxidants BHT and TBHQ.

Experimental

KF/CP NPs was synthesized in agreement with reported in the literature [64, 65].

General procedure for preparation of compounds 6a–k

To a stirred mixture of phthalaldehyde or its derivatives **1** (2 mmol) and primary amines **2** (2 mmol) was added alkyl bromide **3** (2 mmol)and KF/CP NPs (15 mol%) after 30 min at room temperature in water (5mL). After 20 min activated actylenic compounds **4** (2

mmol) was added to previous mixture. After 2 h, ammonium acetate **5** (2 mmol) was added in the presence of basic catalyst. The reaction is completed and progress of the reaction is confirmed by TLC. Finally, the solid residue was collected by filtration and washed with EtOAc for separation of KF/CP NPs. After evaporating solvent, the residue was purified by column chromatography (8:1 hexane/EtOAc) to afforded pure title compounds.

3-Ethyl1,2-dimethyl8-methyl-5-oxo-5H-benzo[g]pyrazino[2,1,6-cd]indolizine-1,2,3-tricarboxylate (6a):

Pall yellow powder, mp 132-134˚C, Yield: 0.78 g (95%). IR (KBr) (ν_{max}/cm^{-1}): 1743, 1735, 1698, 1585, 1487, 1293 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): 1.25 (3 H, t, ^3J = 7.4 Hz, CH_3), 2.25 (3 H, s, Me), 3.75 (3 H, s, MeO), 3.83 (3 H, s, MeO), 4.25 (2 H, q, ^3J = 7.4 Hz, CH_2O), 7.02 (1 H, d, ^3J = 7.6 Hz, CH), 7.64 (1 H, s, CH), 7.78 (1 H, s, CH), 8.03 (1 H, d, ^3J = 7.6 Hz, CH) ppm. ^{13}C NMR (125.7 MHz, $CDCl_3$):14.2 (Me), 21.3 (Me), 51.6 (MeO), 52.3 (MeO), 61.4 (CH_2O), 96.3 (C), 107.3 (CH), 108.6 (C), 118.3(C), 126.3 (C), 126.9 (CH), 128.3 (C), 131.4 (CH), 134.5 (CH), 138.2 (C), 139.4 (C), 144.2 (C), 151.4 (C), 161.2 (C=O), 162.3 (C=O), 164.7 (C=O), 168.2 (C=O) ppm. MS (EI, 70 eV): *m*/*z* (%) = 422 (M$^+$, 15), 391(87), 129 (100), 31 (100). Anal. Calcd for $C_{22}H_{18}N_2O_7$ (422.39): C, 62.56; H, 4.30; N, 6.63. Found: C, 62.73; H, 4.42; N, 6.83 %.

Dimethyl5-imino-3-(4-methoxyphenyl)-8-methyl-5H-benzo[g]pyrazino[2,1,6-cd]indolizine-1,2-dicarboxylate (6b):

Yellow powder, mp 143-145˚C, Yield: 0.79 g (92%). IR (KBr) (ν_{max}/cm^{-1}): 1740, 1736, 1696, 1588, 1468, 1295 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): 2.23 (3 H, s, Me), 3.78 (3 H, s, MeO), 3.85 (3 H, s, MeO), 3.89 (3 H, s, MeO), 6.24 (1 H, s, NH), 6.85 (2 H, d, ^3J = 7.8 Hz, 2 CH), 7.02 (1 H, d, ^3J = 7.7 Hz, CH), 7.34 (1 H, s, CH), 7.65 (1 H, s, CH), 7.83 (1 H, d, ^3J = 7.6 Hz, CH), 8.08 (2 H, d, ^3J = 7.6 Hz, 2 CH), ppm. ^{13}C NMR (125.7 MHz, $CDCl_3$):21.4 (Me), 51.3 (MeO), 52.4 (MeO), 55.6 (MeO), 92.3 (C), 105.6 (CH), 110.4 (CH), 114.2 (2 CH), 119.3 (C), 125.4 (C), 126.2 (CH), 128.3 (2 CH), 130.2 (C), 131.5 (CH), 132.3 (C), 135.2 (CH), 139.2 (C), 140.4 (C), 141.2 (C), 155.6 (C), 158.6 (C), 161.8 (C=O), 162.6 (C=O), 163.4 (C=O) ppm. MS (EI, 70 eV): *m*/*z* (%) = 431 (M$^+$, 10), 302 (86), 129 (100), 31 (100). Anal. Calcd. for $C_{26}H_{21}N_3O_5$ (455.46): C, 68.56; H, 4.65; N, 9.23. Found: C, 68.72; H, 4.83; N, 9.42 %.

Dimethyl5-imino-3-(4-methylphenyl)-8-methyl-5H-benzo[g]pyrazino[2,1,6-cd]indolizine-1,2-dicarboxylate (6c):

Yellow powder, mp 138-140˚C, Yield: 0.77 g (90%). IR (KBr) (ν_{max}/cm^{-1}): 1738, 1735, 1695, 1587, 1478, 1290 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): 2.28 (3 H, s, Me), 2.52 (3 H, s, Me), 3.75 (3 H, s, MeO), 3.83 (3 H, s, MeO), 6.32 (1 H, s, NH), 7.15 (1 H, d, ^3J = 7.6 Hz, CH), 7.38 (2 H, d, ^3J = 7.7 Hz, 2 CH), 7.42 (1 H, s, CH), 7.68 (1 H, s, CH), 7.85 (1 H, d, ^3J = 7.6 Hz, CH), 8.25 (2 H, d, ^3J = 7.6 Hz, 2 CH) ppm. ^{13}C NMR (125.7 MHz, $CDCl_3$):21.5 (Me), 22.3 (Me), 51.4 (MeO), 52.6 (MeO), 93.4 (C), 105.7 (CH), 110.4 (CH), 119.4 (C), 124.7 (C), 126.3 (CH), 128.7 (2 CH), 129.3 (C), 130.4 (2 CH), 131.2 (CH), 131.8 (C), 132.6 (C), 134.8 (CH), 139.2 (C), 140.6 (C), 141.3 (C), 142.3 (C), 156.2 (C), 162.3 (C=O), 163.6 (C=O) ppm.. MS (EI, 70 eV): *m*/*z* (%) = 429 (M$^+$, 10), 300 (86), 129 (100), 31 (100). Anal. Calcd for $C_{26}H_{21}N_3O_4$ (439.46): C, 71.06; H, 4.82; N, 9.56. Found: C, 71.23; H, 4.97; N, 9.75 %.

Dimethyl5-imino-3-(4-bromophenyl)-8-methyl-5H-benzo[g]pyrazino[2,1,6-cd]indolizine-1,2-dicarboxylate (6d):

Yellow powder, mp 168-171˚C, Yield: 0.88 g (87%). IR (KBr) (ν_{max}/cm^{-1}): 1740, 1698, 1574, 1483, 1287 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): 2.42 (3 H, s, CH_3), 3.75 (3 H, s, MeO), 3.83 (3 H, s, MeO), 6.48 (1 H, s, NH), 7.16 (1 H, d, ^3J = 7.6 Hz, CH), 7.36 (1 H, s, CH), 7.54 (1 H, s, CH), 7.75 (1 H, d, ^3J = 7.8 Hz, CH), 7.98 (2 H, d, ^3J = 7.8 Hz, 2 CH), 8.06 (2 H, d, ^3J = 7.8 Hz, 2 CH) ppm. ^{13}C NMR (125.7 MHz, $CDCl_3$):21.4 (Me), 51.6 (MeO), 52.4 (MeO), 93.4 (C), 105.2 (CH), 110.3 (CH), 119.4 (C), 124.8 (C), 125.3 (C), 126.3 (CH), 129.4 (2 CH), 130.2 (C), 130.8 (CH), 131.7 (2 CH), 132.3 (C), 133.8 (C), 135.6 (CH), 139.2 (C), 139.7 (C), 140.3 (C), 156.2 (C), 161.4 (C=O), 163.7 (C=O) ppm. MS (EI, 70 eV): *m*/*z* (%) = 505 (M$^+$+2, 10), 503 (M$^+$, 10), 473 (86), 129 (100), 31 (100). Anal. Calcd for $C_{25}H_{18}BrN_3O_4$ (504.33): C, 59.54; H, 3.60; N, 8.33. Found: C, 59.75; H, 3.78; N, 8.56 %.

Dimethyl10-methyl-3-(4-nitrophenyl)-5-oxo-5H-benzo[g]pyrazino[2,1,6-cd]indolizine-1,2-dicarboxylate (6e):

Yellow powder, mp 192-194˚C, Yield: 0.80 g (85%). IR (KBr) (ν_{max}/cm^{-1}): 1742, 1738, 1698, 1593, 1486, 1284 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): 2.53 (3 H, s, Me), 3.78 (3 H, s, MeO), 3.85 (3 H, s, MeO), 7.22 (1 H, d. ^3J = 7.6 Hz, CH), 7.53 (1 H, t, ^3J = 7.6 Hz, CH), 7.74 (1H, d, ^3J = 7.6 Hz, CH), 7.85 (1 H, s, CH), 8.14 (2 H,

d, ^3J = 7.8 Hz, CH), 8.27 (2 H, d, ^3J = 7.8 Hz, 2 CH) ppm. ^{13}C NMR (125.7 MHz, $CDCl_3$):21.3 (Me), 51.4 (MeO), 52.6 (MeO), 95.8 (C), 106.3 (C), 108.4 (CH), 117.3 (C), 124.2 (2 CH), 125.3 (CH), 126.7 (CH), 130.4(CH), 131.6 (2 CH), 132.2 (C), 133.6 (C), 134.5 (C), 140.3 (C), 141.2 (C), 143.6 (C), 148.3 (C), 155.8 (C), 161.8 (C=O), 162.4 (C=O), 168.4 (C=O) ppm. MS (EI, 70 eV): *m*/*z* (%) = 471 (M^+, 10), 440 (86), 129 (100), 31 (100). Anal. Calcd for $C_{25}H_{17}N_3O_7$ (471.42): C, 63.69; H, 3.63; N, 8.91. Found: C, 63.84; H, 3.86; N, 9.12 %.

Triethyl10-methyl-5-oxo-5H-benzo[g]pyrazino[2,1,6-cd]indolizine-1,2,3-tricarboxylate (6f):

Pall yellow powder, mp 135-137˚C, Yield: 0.78 g (89%). IR (KBr) (ν_{max}/cm^{-1}): 1743, 1735, 1698, 1585, 1487, 1293 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): 1.28 (3 H, t, ^3J = 7.4 Hz, CH_3), 1.32 (3 H, t, ^3J = 7.4 Hz, CH_3), 1.38 (3 H, t, ^3J = 7.4 Hz, CH_3), 2.45 (3 H, s, Me), 4.22 (2 H, q, ^3J = 7.4 Hz, CH_2O), 4.35 (2 H, q, ^3J = 7.4 Hz, CH_2O), 4.42 (2 H, q, ^3J = 7.4 Hz, CH_2O), 7.23 (1 H, d, ^3J = 7.6 Hz, CH), 7.45 (1 H, t, ^3J = 7.6 Hz, CH), 7.75 (1 H, d, ^3J = 7.6 Hz, CH), 7.84 (1 H, s, CH) ppm. ^{13}C NMR (125.7 MHz, $CDCl_3$):13.8 (Me), 14.1 (Me), 14.8 (Me), 21.6 (Me), 61.5 (CH_2O), 62.0 (CH_2O), 62.8 (CH_2O), 96.5 (C), 107.6 (CH), 108.2 (C), 118.5 (C), 125.3 (CH), 126.5 (CH), 128.5 (C), 131.7 (CH), 132.3 (C), 134.8 (C), 139.5 (C), 144.3 (C), 151.7 (C), 161.3 (C=O), 162.5 (C=O), 163.8 (C=O), 169.4 (C=O) ppm. MS (EI, 70 eV): *m*/*z* (%) = 450 (M^+, 15), 405 (84), 129 (100), 31 (100). Anal. Calcd for $C_{24}H_{22}N_2O_7$ (450.44): C, 63.99; H, 4.92; N, 6.22. Found: C, 64.16; H, 5.12; N, 6.43 %.

3-Ethyl1-methyl-10-methyl- 5-oxo-5H-benzo[g]pyrazino [2,1,6-cd]indolizine-1,3-dicarboxylate (6g):

Yellow powder, mp 123-125˚C, Yield: 0.66 g (90%). IR (KBr) (ν_{max}/cm^{-1}): 1740, 1738, 1693, 1587, 1485, 1282 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): 1.32 (3 H, t, ^3J = 7.4 Hz, CH_3), 2.47 (3 H, s, Me), 3.85 (3 H, s, MeO), 4.25 (2 H, q, ^3J = 7.4 Hz, CH_2O), 7.18 (1 H, d, ^3J = 7.6 Hz, CH), 7.46 (1 H, t, ^3J = 7.6 Hz, CH), 7.68 (1 H, d, ^3J = 7.6 Hz, CH), 7.76 (1 H, s, CH), 7.85 (1 H, s, CH) ppm. ^{13}C NMR (125.7 MHz, $CDCl_3$):13.8 (Me), 21.2 (Me), 51.2 (MeO), 61.4 (CH_2O), 90.4 (C), 107.4 (CH), 109.3 (CH), 117.2 (C), 118.3 (C), 125.8 (CH), 126.8 (CH), 131.6 (CH), 132.2 (C), 133.6 (C), 139.5 (C), 143.4 (C), 149.3 (C), 161.2 (C=O), 165.5 (C=O), 168.3 (C=O) ppm. MS (EI, 70 eV): *m*/*z* (%) = 364 (M^+, 15), 319 (64), 129 (100), 45 (100). Anal. Calcd for $C_{20}H_{16}N_2O_5$ (364.35): C, 65.93; H, 4.43; N, 7.69. Found: C, 66.14; H, 4.64; N, 7.85 %.

Radical scavenging experiment by DPPH for investigation of antioxidant activity

By employing of DPPH (2,2-Diphenyl-1-picrylhydrazyl) radical trapping experiment, antioxidant activity of some synthesized compounds **6a, 6c, 6d** and **6g** was measured [67].In this experiment different concentrations of **6a, 6c, 6d** and **6g** (200-1000 ppm) were added to a same volume of methanolic solution of DPPH (1 mM) and the mixtures were mixed and then put in a dark room. The maximum absorbance of the mixture was 517 nm after 30 min at room temperature. The synthesized compounds **6a, 6c, 6d** and **6g** was exchanged with 3 ml methanol in the control sample and butylated hydroxytoluene (BHT) and 2-tert-butylhydroquinone (TBHQ) were used as standard controls. The DPPH performance is calculated by the following formula [69].

$$I = [(AB-AS)/AB] \times 100$$

Where, I=DPPH inhibition (%), AB=absorbance of control sample (0 min) and AS=absorbance of an examined sample at the end of the reaction (after 30 min).

The power of reducing experiment

By the procedure of Yildirim et. al. [68],the power of **6a, 6c, 6d** and **6g** to reduce iron (III) was measured. The compounds **6a, 6c, 6d** and **6g** (1 ml) were combined with 2.5 ml of potassium ferricyanide ($K_3Fe(CN)_6$; 10 g/L) and 2.5 ml of phosphate buffer (0.2 M, pH 6.6) and stirred for 30 min at 50 °C. Then, 2.5 mL of trichloroacetic acid (10 % w/v) were added to the previous mixture and centrifuged for 10 min. Finally, supernatant (2.5 mL) and 0.5 ml $FeCl_3$ (1 g/L) was combined together in 2.5 ml of distilled water. The absorbance of samples was measured at 700 nm and higher absorbance attributed to higher reducing power.

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