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ARTICLE

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Green synthesis of pyrido[2,1-*a*]isoquinolines and pyrido[1,2-*a*]quinolins using Fe_3O_4-MNPs as efficient nanocatalyst: Study of antioxidant activity

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Abstract

In this work, synthesis of pyrido[2,1-*a*]isoquinolines and pyrido[1,2-*a*]quinolins in excellent yield using multicomponent reaction of phthalaldehyde, methyl amine, methyl malonyl chloride, alkyl bromides, and triphenylphosphine in the presence of catalytic amount of Fe_3O_4-MNPs with aqueous sodium hydroxide at 80°C was investigated. The reduction of ferric chloride solution with *Clover Leaf* water extract caused to synthesis of magnetic iron oxide nanoparticles (Fe_3O_4-MNPs) as a green method. As well, antioxidant activity was studied for the some newly synthesized compounds such as **6a**, **6c**, **9b**, and **9c** using the DPPH radical trapping and reducing of ferric ion experiments and comparing results with synthetic antioxidants (TBHQ and BHT). As a result, compounds **6a**, **6c**, **9b**, and **9c** show good DPPH radical trapping and excellent reducing strength of ferric ion.

1 | INTRODUCTION

Green chemistry is a chemical procedure that decreases or removes application and production of hazardous chemicals from the environment. Organic solvents that are needed for performing some organic reactions are often toxic and expensive. For this reason, elimination of these solvents is a suitable work for nature. Therefore, performing organic reactions in water as solvent has received wonderful notice in recent years.[1] For synthesis of heterocyclic compounds using multicomponent reactions (MCRs), design of new procedures has more attention in the last decade. In MCRs, organic compounds were generated in a few steps or in a one-pot procedure.[2–4] Isoquinoline or isoquinoline derivatives are one of the important heterocyclic compounds that have outstanding moiety in medicinal chemistry and display a broad variety of biological and pharmacological properties.[5–11] Isoqunoline derivatives are the main group of heterocycle compounds because of their existence in nature[12–16] and their pharmacological activities including antifungal[17] antibacterial,[18] antitumor,[19] anti-inflammatory,[20] anticonvulsant,[21–23] analgesic,[24,25] and antitubercular[26] activities. Furthermore, isoquinoline derivatives are the new group of cancer chemotherapeutic agents along with considerable therapeutic performance anti solid tumor.[27–29] As well, isoquinoline derivatives have a chief location in asymmetric catalysis and photochemistry as ligands.[30] For the first time, isoquinoline was separated in 1885 by Hoogewerf and van Dorp from coal tar.[31] A number of procedures exist for the synthesis of isoquinoline ring that can be well modified to generate some of different functionalized isoquinolines. Conventional methods for the preparation of isoquinoline such as Bischer–Napieralski, Pictet–Spengler, and Pomeranz–Fritsch reactions often have disadvantages such as low yields, a limited substrate scope, and hard reaction conditions. Recently, organic chemists show a much attention to nanocatalysis. These compounds display enhanced catalytic activity compared with their bulk-sized types.[32,33] Another topic in this work is investigation of synthesized compounds power

in terms of antioxidant activity. Usually, the compounds that have antioxidant activity because of their reductive properties and chemical structure employ as transitional metals chelators, and negative effect of free radicals could be eliminate via these compounds. These compounds in addition to their antioxidant activity could prevent or reduce many diseases such as cardiovascular, inflammatory bowel syndrome, cancer, ageing, and Alzheimer.[34–36] In recent times, new and efficient synthetic antioxidant compounds for protective of humans against these diseases were discovered and experimented by biologists and medicinal and food chemist. At present, bacteria that are stable in the presence of drug have created substantial problems in the performance of many communicable diseases. Therefore, discovering new ways to fight against these pathogens are important. For this reason, recent studies have focused on the study of the antibacterial effects of new synthesized compounds. Herein, in continuation of our studies for discovering new procedure for synthesis of important organic compounds with biological activity,[37–45] in this research, we carry out the synthesis of new derivatives of isoquinoline **6** via the reaction of phthalaldehyde **1**, methyl amine **2**, methyl malonyl chloride **3**, alkyl bromides **4**, and triphenylphosphine **5** in the presence of catalytic amount of Fe_3O_4-MNPs and aqueous sodium hydroxide at 80°C in excellent yields (Scheme 1).

2 | RESULT AND DISCUSSION

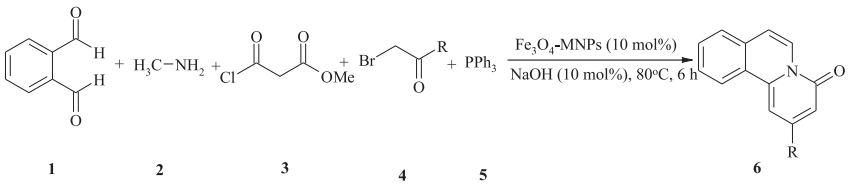
For choosing the best of reaction conditions, reaction of phthalaldehyde **1**, methyl amine **2**, methyl malonyl chloride **3**, ethyl bromopyruvate **4a**, and triphenylphosphine **5** was chosen as a sample reaction (Scheme 1). It was discovered the yield of this reaction with any catalyst is 10% (Table 1, entry 1). By adding a catalyst to mixture of reaction, the yield of **6a** is risen. For selecting the best catalyst, several catalysts such as commercial zinc oxid (ZnO-CM), zinc oxid nanorod (ZnO-NR), zinc oxid nanoparticles (ZnO-NPs), Fe_3O_4-MNPs, CuO-NPs, TiO_2-NPs, and potassium fluoride/clinoptilolite nanoparticles (KF/CP NPs) are experimented. The results of our optimization investigation in type and amount of catalyst are showed in Table 1. As shown in Table 1, the yield of the desirable product was increased when Fe_3O_4-MNPs was employed (Table 1, entry 12). The yield increased naturally with 10 mol% of catalyst, but additional increase in amount of catalyst did not change yield of product. The best reaction temperature when Fe_3O_4-MNPs were employed is 80°C because of increasing the temperature of any effect on the reaction time and yield. The catalyst can be reused five times without loss of activity by separating from the mixture of reaction by filtering.

TABLE 1 Optimization of reaction condition for the formation of **6a**

Entry	Catalyst	Mol % of Catalyst	Yield (%)
1	None	None	10
2	ZnO-CM	10	25
3	ZnO-CM	15	25
4	ZnO-NR	10	52
5	ZnO-NR	15	54
6	KF/clinoptilolite NPs	10	68
7	KF/clinoptilolite NPs	15	68
8	TiO_2-NPs	10	45
9	TiO_2-NPs	15	45
10	CuO-NPs	10	—
11	CuO-NPs	20	—
12	**Fe_3O_4-MNPs**	**10**	**87**
13	Fe_3O_4-MNPs	15	87
14	Fe_3O_4-MNPs	20	85
15	ZnO-NP	15	60

The bold entry is the best condition for reaction.

For the synthesis of Fe_3O_4-MNPs, the aqueous extract of *Clover Leaf* was used. For confirming the structure of Fe_3O_4MNPs, field emission scanning electron microscopy (FESEM) (Figure 1) and X-ray diffraction (XRD) (Figure 2) image are taken for nanostructure. FESEM



6	R	Yied % of 6
a	CO_2Et	87
b	4-MeO-C_6H_4	80
c	4-Me-C_6H_4	89
d	4-Br-C_6H_4	85
e	4-NO2-C_6H_4	83

SCHEME 1 Multicomponent reaction for the synthesis of pyrido[2,1-*a*] isoquinoline derivatives of **6**

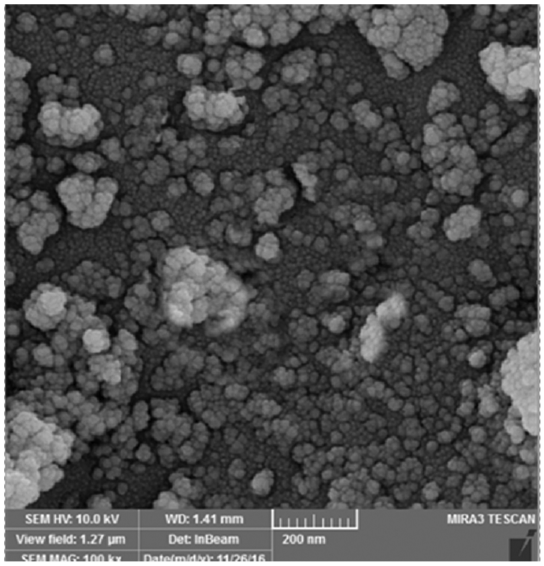


FIGURE 1 Field emission scanning electron microscopy (FESEM) images of Fe_3O_4-MNPs

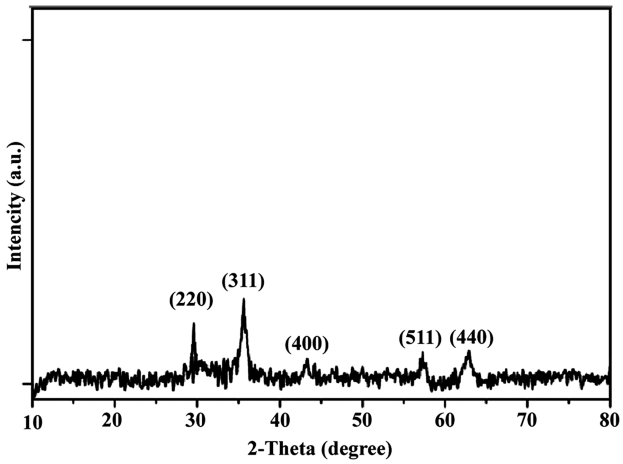


FIGURE 2 X-ray diffraction (XRD) powder pattern of Fe_3O_4 MNPs

image of Fe_3O_4-MNPs displays spherical morphology with uniform-sized particles.

The XRD model of the Fe_3O_4-MNPs is showed in Figure 2. The peaks at $2\theta = 30.4°$, 35.6°, 43.1°, 57.5°, and 62.7° can be showed to (220), (311), (400), (511), and (440) planes of cubic Fe_3O_4 (JCPDS 19-0629). The half-value size of the Fe_3O_4-MNPs is calculated 16 nm.

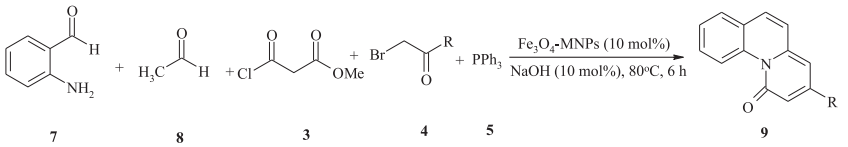
The new derivatives of isoquinoline **6** was prepared via the reaction of phthalaldehyde **1**, methyl amine **2**, methyl malonyl chloride **3**, alkyl bromides **4**, and triphenylphosphine **5** in the presence of catalytic amount of Fe_3O_4-MNPs and aqueous sodium hydroxide at 80°C in excellent yields (Scheme 1).

The products were produced in solid state, and no impurities were seen after purification. Structures of products were confirmed by IR, ^{1}H NMR, and ^{13}C NMR. For example, the ^{1}H NMR spectrum of **6a** showed two singlets at $\delta = 6.53$ and 7.23 ppm for methin proton along with signals for aromatic moiety. The ^{13}C NMR spectrum of **6a** showed carbonyl group at 163.2 and 175.3 ppm in agreement to the proposed structure. Under similar conditions, the new derivatives of quinoline **9** are prepared via the reaction of 2-aminobenzaldehyde **7**, acetaldehyde **8**, methyl malonyl chloride **3**, alkyl bromides **4**, and triphenylphosphine **5** in the presence of catalytic amount of Fe_3O_4-MNPs and aqueous sodium hydroxide at 80°C in excellent yields (Scheme 2).

The ^{1}H-NMR, ^{13}CNMR, mass spectroscopy, and Fourier transform infrared (FTIR) of compound **9** are given for confirming the structure of them. Although we could not prove the mechanism of the reaction between isoquinoline or quinoline, methyl malonyl chloride, alkyl bromides, and triphenylphosphine in the presence of Fe_3O_4-MNPs, a possible explanation is proposed in Scheme 3. Fe_3O_4-MNPs have Lewis acid sites and Lewis basic sites (O^{2-}).[46,47] It plays an important role in increasing the electrophilic character of the carbonyl group. Initially, phetalaldehyde **1** and methyl amine **2** react together and produce isoquinoline **10** asintermediate. Intermediate **10** reacted as nucleophile with methyl malonyl chloride **3** and generated intermediate **11**. In other pot, alkyl bromide **4** and triphenylphosphine **5** reacted together in the presence of Fe_3O_4-MNPs and produced intermediate **12** by elimination of HBr. Intermediate **12** was attached to intermediate **11** and produced intermediate **13**. Intramolecular cyclization of intermediate **14** and elimination of triphenylphosphine oxide produce intermediate **16**. In the presence of hydroxide ion and heating, carbon dioxide was eliminated from intermediate **17**, and compound **6** was produced. In these reactions, the chief benefits of our method are high atom economy, green reaction conditions, use a small amount nanocatalyst, higher yield, shorter reaction times, and easy work-up, which are in good agreement with some principles of green chemistry.

2.1 | Study of antioxidant activity employing DPPH

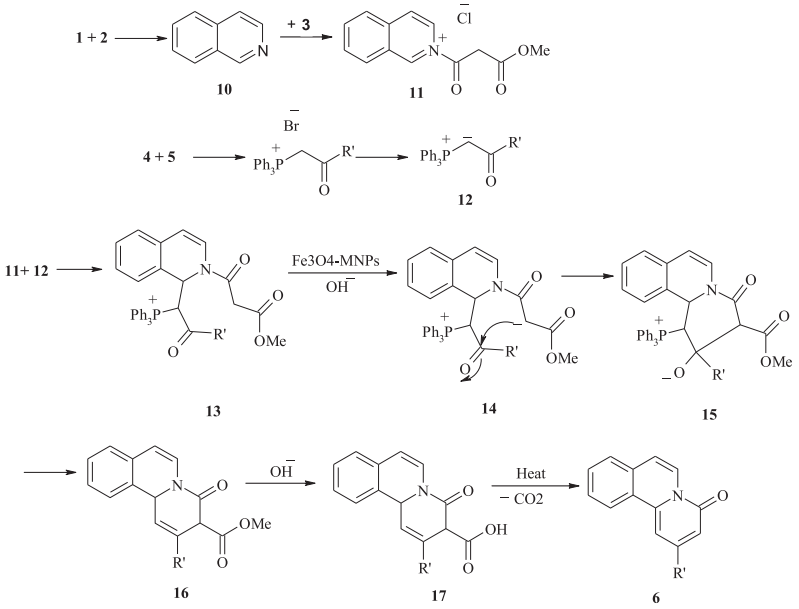
For determination of antioxidant activity of some synthesized compounds and their antioxidant property in foods and biological systems[48,49] as well as power of compounds to take free radicals, diphenyl-2-picrylhydrazyl (DPPH) radical trapping experiment is widely used. In these experiment, the DPPH radical takes the hydrogen atom (or one electron) of synthesized compounds **6a**, **6c**, **9b**, and **9c** and gives an evaluation of antioxidant activity basis of free radical trapping. The absorption of



7 8 3 4 5 9

9	R	Yied % of 9
a	CO_2Et	75
b	4-MeO-C_6H_4	70
c	4-Me-C_6H_4	72

SCHEME 2 Multicomponent reaction for the synthesis of pyrido[1,2-*a*]quinoline derivatives of **9**



10 11 12 13 14 15 16 17 6

SCHEME 3 Propose mechanism for preparation of **6**

DPPH radical was observed area 517 nm but when DPPH radical is reduced by an antioxidant or a radical species its absorption decreases. As shown from the results, free radical trapping activity of compounds **6a**, **6c**, **9b**, and **9c** is weaker than to BHT and TBHQ. Therefore, concentration and structure were key factors on the DPPH trapping activity ($P < .05$) (Figure 3). Normally, the DPPH scavenging ability of these compounds was attained TBHQ > BHT > **9b** > **9c** > **6a** > **6c**, respectively. The free radical trapping power had been enhanced from 200 to 1000 ppm. So, by rising concentration in all samples, the free radical activity was raised. For instance, compound **9b** with a concentration of 1000 ppm had 42.30% inhibition, while a concentration of 200 ppm of compound **9b** was exhibited 22.10% free radical inhibition.

2.2 | Ferric ions (Fe^{3+}) reducing potential

Reducing power of the synthesized compounds was determined by calculating the exchange amount of Fe^{3+}/ferricyanide complex to the Fe^{2+}/ferrous form at 700 nm.[48] The reducing power of compounds **6a**, **6c**, **9b**, and **9c** compared with synthetic antioxidants (BHT and TBHQ) is shown in Figure 2. The bigger reducing power means higher absorbance of the compounds. The reducing activity order of compounds **5a**, **5c**, **7b**, and **7c** was as following: TBHQ > BHT> **9b** > **6c** > **6a** > **9b** (Figure 4). In all of them, the increasing concentration enhanced ferric ions reducing power. Compound **9b** shows very good reducing activity compared with standards (BHT and TBHQ).

In summary, the procedure described here provides a suitable one-pot method for the preparation of isoquinoline and quinoline derivatives in good yield in the presence of Fe_3O_4-MNPs in water and 80°C. Also, compound **9b** was shown a noteworthy radical trapping activity and very good reducing activity relative to standards (BHT and TBHQ) by investigation of antioxidant activity. Moreover, easy work-up of catalyst and product, performing reactions in water, and reusability of catalyst make this method an interesting option to other approaches.

3 | EXPERIMENTAL

All chemicals were prepared from Fluka or Merck and employed with any further purification. We prepared Fe_3O_4 MNPs through literature method.[50] The

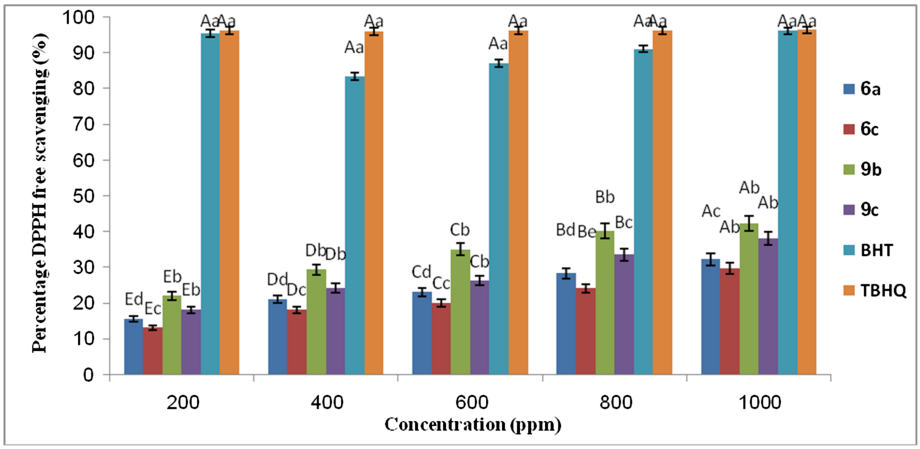


FIGURE 3 Radical trapping activity (RSA) of compounds **6a**, **6c**, **9b**, and **9c** [Color figure can be viewed at wileyonlinelibrary.com]

morphology of nanoparticles of Fe_3O_4 MNPs was characterized by scanning electron microscopy (SEM) using a Holland Philips XL30 microscope. Crystalline structure of Fe_3O_4 MNPs was characterized by XRD analysis at room temperature using a Holland Philips Xpert X-ray powder diffractometer, with CuKα radiation (λ = 0.15406 nm), with 2θ ranging from 20° to 80°. The average crystallite size was calculated using Scherrer formula; $D = 0.9\lambda/\beta \cos\theta$, where D is the diameter of the nanoparticles, λ (CuKα) = 1.5406 Å, and β is the full width at half-maximum of the diffraction lines. ^{1}H NMR and ^{13}C NMR spectra were obtained with a Bruker FT-500 spectrometer in chloroform-d1, and tetramethylsilane (TMS) was used as an internal standard. Electron ionization mass spectra were recorded on a Finnigan Mat TSQ-70 spectrometer operating at an ionization potential 70 eV. Infrared (IR) spectra were acquired on a Nicollet Magna 550-FT spectrometer. Melting points were measured on an Electrothermal 9100 apparatus. Elemental analyses were carried out with a Perkin-Elmer model 240-C apparatus. The results of elemental analyses (C, H, N) were within ±0.4% of the calculated values.

3.1 | Preparation of Fe_3O_4-MNPs

Dried *Clover Leaf* (10 g) was drench in water (200 mL) at 80°C. After 2 hours, the mixture was filtered, and water essential oil was used for preparation of Fe_3O_4-MNPs as following: 100 mL of water extract of *Clover Leaf* was taken in a 250 two-neck round-bottom flask, and $FeCl_3$ (2 mmol) and $FeCl_2$ (1 mmol) were added. Then, the solution of NH_4OH (9*M*, 10 mL) was then injected dropwise into the mixture with vigorous stirring under N_2 atmosphere for 1 hour at room temperature. The resultant solution was a black color precipitate. The precipitate was separated by applying external magnetic field and

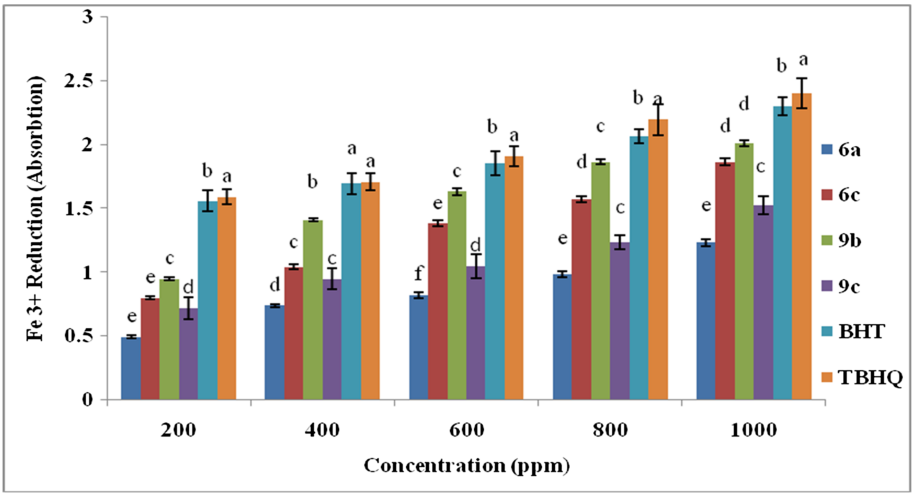


FIGURE 4 Ferric ions (Fe^{3+}) reducing antioxidant power (FRAP) of compounds **6a**, **6c**, **9b**, and **9c** [Color figure can be viewed at wileyonlinelibrary.com]

washed with water for several times as well as dried in oven at 80°C for 24 hours.

3.2 | General procedure for preparation of compound 6

To a stirred mixture of phthalaldehyde **1** (2 mmol) and methyl amine **2** (2 mmol) on solvent-free condition, after 30 minutes of methyl malonyl chloride **3** (2 mmol) and water (3 mL) as solvent was added gently at 80°C. In other pot alkyl bromide **4** (2 mmol) and triphenylphosphine **5** (2 mmol) was mixed in the presence of Fe_3O_4-MNPs (10 mol%) at 80°C on solvent-free condition for 45 minutes. After this time, mixture of second pot was added to first pot and let to be stirred for 30 minutes. After completion of the reaction (4 h; TLC control (hexane: AcOEt, 6:1), the solution of sodium hydroxide (10 mol%) was added to final mixture at 80° C, and mixture was stirred for 3 hours. After completion of the reaction (2 h; TLC control (hexane: AcOEt, 8:1), the Fe_3O_4 MNPs were separated by external magnet. After removing solvent, the residue was purified by column chromatography (8:1 hexane/EtOAc) to afforded pure title compounds.

3.2.1 | Ethyl 4-oxo-4*H*-pyrido[2,1-*a*] isoquinoline-2-carboxylate (6a)

Yellow powder, mp 97°C to 99C, yield: 0.46g (87%). IR (KBr) (ν_{max}/cm^{-1}): 1738, 1735, 1694, 1589, 1487, 1292 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): 1.38 (3H, t, ^3J = 7.4 Hz, Me), 4.25 (2H, q, ^3J = 7.4 Hz, CH_2O), 6.53 (1H, s, CH), 7.12 (1H, d, ^3J = 7.5 Hz, CH), 7.23 (1H, t, ^3J = 7.6 Hz, CH), 7.23 (1H, s, CH), 7.38 (1H, t, ^3J = 7.6 Hz, CH), 7.68 (1H, d, ^3J = 7.6 Hz, CH), 7.78 (1H, d, ^3J = 7.6 Hz, CH), 8.85 (1H, d, ^3J = 7.5 Hz, CH) ppm. ^{13}C NMR (125.7 MHz, $CDCl_3$): 14.2 (Me), 61.4 (CH_2O), 103.2 (CH), 110.7 (CH), 113.4 (CH), 121.4 (CH), 125.3 (CH), 126.8 (CH), 128.4 (CH), 129.5 (CH), 131.2 (C), 136.4 (C), 140.2 (C), 146.3 (C), 163.2 (C=O), 175.3 (C=O) ppm. MS, *m/z* (%): 267 (M^+, 15), 222 (68), 129 (100), 45 (100). Anal. Calcd. for $C_{16}H_{13}NO_3$ (267.28): C 71.90, H 4.90, N 5.24; Found: C 72.03, H 5.06, N 5.36.

3.2.2 | 2-(4-Methoxyphenyl)-4*H*-pyrido[2,1-*a*]isoquinolin-4-one (5b)

Yellow powder, mp 112°C to 114°C, yield: 0.48 g (80%). IR (KBr) (ν_{max}/cm^{-1}): 1737, 1694, 1627, 1568, 1425, 1274 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): 3.78 (3H, s, MeO), 6.58 (1H, s, CH), 6.82 (1H, s, CH), 6.92 (2H, d, ^3J = 7.6 Hz, 2 CH), 7.16 (2H, d, ^3J = 7.6 Hz, 2 CH), 7.22 (1H, d, ^3J = 7.6 Hz, CH), 7.32 (1H, t, ^3J = 7.6 Hz, CH), 7.42 (1H, t, ^3J = 7.6 Hz, CH), 7.82 (1H, d, ^3J = 7.6 Hz, CH), 7.93 (1H, d, ^3J = 7.6 Hz, CH), 8.62 (1H, d, ^3J = 7.6 Hz, CH) ppm. ^{13}C NMR (125.7 MHz, $CDCl_3$): 55.6 (MeO), 109.5 (CH), 110.4 (CH), 112.3 (2 CH), 113.2 (CH), 117.2 (CH), 126.2 (CH), 127.3 (CH), 128.4 (CH), 129.2 (CH), 130.5 (2 CH), 131.8 (C), 132.2 (C), 139.2 (C), 144.2 (C), 146.2 (C), 158.3 (C), 174.2 (C=O) ppm. MS, *m/z* (%): 301 (M^+, 10), 172 (84), 129 (100). Anal. Calcd. for $C_{20}H_{15}NO_2$ (301.34): C 79.72, H 5.02, N 4.65; Found: C 79.86, H 5.23, N 4.74.

3.2.3 | 2-(4-Methylphenyl)-4*H*-pyrido[2,1-*a*]isoquinolin-4-one (5c)

Yellow powder, mp 104°C to 106°C, yield: 0.51 g (89%). IR (KBr) (ν_{max}/cm^{-1}): 1735, 1698, 1642, 1578, 1436, 1284 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): 2.34 (3H, s, Me), 6.73 (1H, s, CH), 6.86 (1H, s, CH), 6.96 (1H, d, ^3J = 7.6 Hz, CH), 7.22 (1H, t, ^3J = 7.6 Hz, CH), 7.34 (2H, d, ^3J = 7.6 Hz, 2 CH), 7.42 (2H, d, ^3J = 7.6 Hz, 2 CH), 7.45 (1H, t, ^3J = 7.6 Hz, CH), 7.84 (1H, d, ^3J = 7.6 Hz, CH), 7.95 (1H, d, ^3J = 7.6 Hz, CH), 8.86 (1H, d, ^3J = 7.6 Hz, CH) ppm. ^{13}C NMR (125.7 MHz, $CDCl_3$): 20.4 (Me), 110.2 (CH), 111.7 (CH), 112.5 (CH), 116.5 (CH), 125.3 (CH), 126.4 (CH), 127.6 (CH), 128.5 (CH), 129.3 (2 CH), 130.4 (2 CH), 131.2 (C), 135.6 (C), 138.4 (C), 139.2 (C), 141.5 (C), 146.2 (C), 174.5 (C=O) ppm. MS, *m/z* (%): 285 (M^+, 15), 156 (68), 129 (100). Anal. Calcd. for $C_{20}H_{15}NO$ (285.34): C 84.19, H 5.30, N 4.91; Found: C 84.32, H 5.43, N 5.08.

3.2.4 | 2-(4-Bromophenyl)-4*H*-pyrido[2,1-*a*] isoquinolin-4-one (5d)

Pale yellow powder, mp 137°C to 139°C, yield: 0.59 g (85%). IR (KBr) (ν_{max}/cm^{-1}): 1736, 1692, 1663, 1584, 1456, 1278 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): 6.68 (1H, s, CH), 6.82 (1H, s, CH), 7.05 (1H, d, ^3J = 7.6 Hz, CH), 7.23 (1H, t, ^3J = 7.6 Hz, CH), 7.45 (1H, t, ^3J = 7.6 Hz, CH), 7.62 (2H, d, ^3J = 7.8 Hz, 2 CH), 7.45 (1H, t, ^3J = 7.6 Hz, CH), 7.82 (2H, d, ^3J = 7.8 Hz, CH), 7.88 (1H, d, ^3J = 7.6 Hz, CH), 7.93 (1H, d, ^3J = 7.6 Hz, CH), 8.92 (1H, d, ^3J = 7.6 Hz, CH) ppm. ^{13}C NMR (125.7 MHz, $CDCl_3$): 110.4 (CH), 111.5 (CH), 112.6 (CH), 116.8 (CH), 125.4 (CH), 126.5 (CH), 127.4 (CH), 128.2 (CH), 130.4 (2 CH), 131.2 (2 CH), 131.6 (C), 135.7 (C), 136.3 (C), 139.4 (C), 146.2 (C), 175.3 (C=O) ppm. MS, *m/z* (%): 350 (M^+, 10), 221 (58), 129 (100). Anal. Calcd. for $C_{19}H_{12}BrNO$ (350.21): C 65.16, H 3.45, N 4.00; Found: C 65.34, H 3.62, N 4.12.

3.2.5 | 2-(4-Nitrophenyl)-4*H*-pyrido[2,1-*a*] isoquinolin-4-one (5e)

Pale yellow powder, mp 168°C to 170°C, yield: 0.52 g (83%). IR (KBr) (ν_{max}/cm^{-1}): 1742, 1698, 1675, 1589, 1487, 1295 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): 6.57 (1H, s, CH), 6.84 (1H, s, CH), 7.12 (1H, d, ^3J = 7.6 Hz, CH), 7.25 (1H, t, ^3J = 7.6 Hz, CH), 7.46 (1H, t, ^3J = 7.6 Hz, CH), 7.65 (2H, d, ^3J = 7.8 Hz, 2 CH), 7.72 (1H, d, ^3J = 7.6 Hz, CH), 7.85 (1H, d, ^3J = 7.6 Hz, CH), 8.42 (2H, d, ^3J = 7.8 Hz, 2 CH), 8.92 (1H, d, ^3J = 7.6 Hz, CH) ppm. ^{13}C NMR (125.7 MHz, $CDCl_3$): 110.5 (CH), 111.6 (CH), 112.8 (CH), 116.4 (CH), 123.7 (2 CH), 125.2 (CH), 126.8 (CH), 127.4 (CH), 128.4 (CH), 131.5 (C), 132.4 (2 CH), 139.4 (C), 143.2 (C), 145.2 (C), 147.3 (C), 148.4 (C), 175.2 (C=O) ppm. MS, *m/z* (%): 316 (M^+, 20), 187 (62), 129 (100). Anal. Calcd. for $C_{19}H_{12}N_2O_2$ (350.21): C 72.15, H 3.82, N 8.86; Found: C 72.32, H 3.96, N 8.95.

3.3 | General procedure for preparation of compound 9

To a stirred mixture of 2-aminobenzaldehyde **7** (2 mmol) and acetaldehyde **8** (2 mmol) on solvent-free conditions, after 30 minutes, methyl malonyl chloride **3** (2 mmol) and water (3 mL) as solvent were added at 80°C. In other pot, alkyl bromide **4** and triphenylphosphine **5** were mixed in the presence of Fe_3O_4-MNPs (10 mol%) at 80°C on solvent-free condition for 45 minutes. After this time, mixture of the second pot was added to the first pot and let to be stirred for 30 minutes. After completion of the reaction (4 h; TLC control [hexane: AcOEt, 5:1]), the solution of sodium hydroxide (10 mol%) was added to final mixture at 80°C, and mixture was stirred for 2 hours. After completion of the reaction (2 h; TLC control [hexane: AcOEt, 9:1]), the Fe_3O_4 MNPs were separated by external magnet. After removing solvent, the residue was purified by column chromatography (9:1, hexane: EtOAc) to afforded pure title compounds.

3.3.1 | Ethyl 1-oxo-1*H*-pyrido[1,2-*a*]quinoline-3-carboxylate (9a)

Yellow powder, mp 100°C 102°C, yield: 0.46 g (75%). IR (KBr) (ν_{max}/cm^{-1}): 1742, 1737, 1695, 1585, 1474, 1295 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): 1.16 (3H, t, ^3J = 7.4 Hz, Me), 4.32 (2H, q, ^3J = 7.4 Hz, CH_2O), 9.65 (1H, d, ^3J = 7.5 Hz, CH), 7.12 (1H, d, ^3J = 7.6 Hz, CH), 7.25 (1H, t, ^3J = 7.6 Hz, CH), 7.35 (1H, t, ^3J = 7.6 Hz, CH), 7.42 (1H, s, CH), 7.75 (1H, d, ^3J = 7.6 Hz, CH), 7.86 (1H, s, CH), 8.02 (1H, d, ^3J = 7.5 Hz, CH) ppm. ^{13}C NMR (125.7 MHz, $CDCl_3$): 13.8 (Me), 62.3 (CH_2O), 103.4 (CH), 118.2 (CH), 119.7 (CH), 122.4 (CH), 130.2 (C), 131.5 (CH), 132.3 (CH), 134.6 (CH), 135.2 (CH), 136.2 (C), 144.3 (C), 151.3 (C), 160.2 (C=O), 168.4 (C=O) ppm. MS, *m/z* (%): 267 (M^+, 10), 222 (86), 129 (100), 45 (100). Anal. Calcd. for $C_{16}H_{13}NO_3$ (267.28): C 71.90, H 4.90, N 5.24; Found: C 72.05, H 5.02, N 5.39.

3.3.2 | 1-(4-Methoxyphenyl)-1*H*-pyrido[1,2-*a*]quinolin-4-one (9b)

Yellow powder, mp 115°C to 117°C, yield: 0.42 g (70%). IR (KBr) (ν_{max}/cm^{-1}): 1738, 1697, 1643, 1578, 1446, 1284 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): 3.83 (3H, s, MeO), 6.85 (2H, d, ^3J = 7.6 Hz, 2 CH), 6.94 (1H, d, ^3J = 7.6 Hz, CH), 7.02 (1H, s, CH), 7.15 (1H, d, ^3J = 7.6 Hz, CH), 7.22 (1H, d, ^3J = 7.6 Hz, CH), 7.34 (2H, d, ^3J = 7.6 Hz, 2 CH), 7.38 (1H, s, CH), 7.47 (1H, t, ^3J = 7.6 Hz, CH), 7.65 (1H, d, ^3J = 7.6 Hz, CH), 7.95 (1H, d, ^3J = 7.6 Hz, CH) ppm. ^{13}C NMR (125.7 MHz, $CDCl_3$): 55.7 (MeO), 107.6 (CH), 112.3 (2 CH), 115.3 (CH), 118.4 (CH), 123.4 (CH), 127.8 (2 CH), 130.4 (C), 131.6 (CH), 132.2 (C), 133.4 (CH), 134.5 (CH), 135.4 (CH), 143.4 (C), 144.5 (C), 149.5 (C), 160.4 (C=O), 172.2 (C=O) ppm. MS, *m/z* (%): 301 (M^+, 15), 172 (62), 129 (100). Anal. Calcd. for $C_{20}H_{15}NO_2$ (301.34): C 79.72, H 5.02, N 4.65; Found: C 79.85, H 5.18, N 4.78.

3.3.3 | 1-(4-Methylphenyl)-1*H*-pyrido[1,2-*a*]quinolin-4-one (9c)

Yellow powder, mp 121°C to 123°C, yield: 0.41 g (72%). IR (KBr) (ν_{max}/cm^{-1}): 1742, 1698, 1656, 1584, 1468, 1352 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): 2.34 (3H, s, Me), 6.87 (1H, s, CH), 6.97 (1H, d, ^3J = 7.6 Hz, CH), 7.08 (1H, d, ^3J = 7.6 Hz, CH), 7.16 (1H, t, ^3J = 7.6 Hz, CH), 7.27 (2H, d, ^3J = 7.6 Hz, 2 CH), 7.32 (1H, s, CH), 7.42 (1H, t, ^3J = 7.6 Hz, CH), 7.53 (2H, d, ^3J = 7.6 Hz, 2 CH),7.65 (1H, d, ^3J = 7.8 Hz, CH), 8.04 (1H, d, ^3J = 7.6 Hz, CH) ppm. ^{13}C NMR (125.7 MHz, $CDCl_3$): 21.3 (Me), 107.2 (CH), 115.4 (CH), 118.5 (CH), 122.4 (CH), 128.2 (2 CH), 129.5 (2 CH), 130.2 (C), 131.4 (CH), 132.2 (CH), 133.6 (CH), 134.5 (CH), 136.3 (C), 138.2 (C), 141.2 (C), 144.3 (C), 149.7 (C), 161.2 (C=O) ppm. MS, *m/z* (%): 301 (M^+, 15), 172 (84), 129 (100). Anal. Calcd. for $C_{20}H_{15}NO_2$ (301.34): C 79.72, H 5.02, N 4.65; Found: C 79.87, H 5.16, N 4.76.

3.4 | 1,1-Diphenyl-2-picrylhydrazyl radical trapping test

Radical trapping activity of **6a**, **6c**, **9b**, and **9c** was calculated by DPPH (2, 2-diphenyl-1-picrylhydrazyl) radical

trapping experiment according to the reported method by Shimada et al.[51] Different concentrations of **6a**, **6c**, **9b**, and **9c** (200-1000 ppm) were added to an equal volume of methanolic solution of DPPH (1 mmol/L). The mixtures were well shaken and then placed in a dark room. After 30 minutes at room temperature, the absorbance was recorded at 517 nm. The control samples **6a**, **6c**, **9b**, and **9c** were exchanged with 3 mL of methanol. Butylated hydroxytoluene (BHT) and 2-tertbutylhydroquinone (TBHQ) were employed as standard controls. The percentage inhibition of the DPPH radical was calculated according to the formula of Yen and Duh.[52]

3.5 | Reducing power experiment

The ability of compounds **6a**, **6c**, **9b**, and **9c** to reduce iron (III) was evaluated by the method of Yildirim et al.[53] Samples (1 mL) were mixed with 2.5 mL of phosphate buffer (0.2 mol/L, pH 6.6) and 2.5 mL of potassium ferricyanide ($K_3Fe(CN)_6$; 10 g/L) and display for 30 minutes at 50°C. Then, 2.5 mL of trichloroacetic acid (10% w/v) were added to the solution and centrifuged for 10 minutes. In the end, 2.5 mL of supernatant was mixed with 2.5 mL of distilled water and 0.5 mL of $FeCl_3$ (1 g/L). The absorbance of samples was measured at 700 nm. Higher absorbance means higher reducing power.

Each measurement was performed in triplicate. The data were analyzed by running one-way analysis of variance (ANOVA) using SPSS software version 18.0. A one-way ANOVA was used to estimate dissimilarity in the mean value of samples and control. All mean separations were carried out by Duncan multiple range test employing the importance level of 95% ($P < .05$).

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REFERENCES

[1] J. Tao, R. J. Kazlauskas, *Biocatalysis for Green Chemistry and Chemical Process Development*, John Wiley & Sons, Hoboken, NJ **2011**.

[2] J. Zhu, H. Bienaymé, *Multicomponent reactions*, Wiley-VCH, Veinheim **2005**.

[3] R. V. Orru, E. Ruijter, *Synthesis of heterocycles* via *multicomponent reactions II*, Springer, Berlin **2010**.

[4] A. Domling, W. Wang, K. Wang, *Chem. Rev.* **2012**, *112*, 3083.

[5] (a) S. Markmee, S. Ruchirawat, V. Prachyawarakorn, K. Ingkaninan, N. Khorana, *Bioorg. Med. Chem. Lett.* **2006**, *16*, 2170. (b) Q. Chao, L. Deng, H. Shih, L. M. Leoni, D. Genini, D. A. Carson, H. B. Cottam, *J. Med. Chem.* **1999**, *42*, 3860. (c) C. W. Wright, S. J. Marshall, P. F. Russell, M. M. Anderson, J. D. Phillipson, G. C. Kirby, P. L. Schiff, *J. Nat. Prod.* **2000**, *63*, 1638. (d) V. G. Kartsev, *Med. Chem. Res.* **2004**, *13*, 325. (e) P. Chen, D. Norris, K. D. Haslow, T. M. Dhar, W. J. Pitts, S. H. Watterson, D. L. Hollenbaugh, *Bioorg. Med. Chem. Lett.* **2003**, *13*, 1345. (f) P. Giri, K. G. Suresh, *Mini-Rev. Med. Chem.* **2010**, *10*, 568.

[6] (a) M. Tillhon, L. M. G. Ortiz, P. Lombardi, A. I. Scovassi, *Biochem. Pharmacol.* **2012**, *84*, 1260. (b) J. L. Vennerstrom, D. L. Klayman, *J. Med. Chem.* **1988**, *31*, 1084. (c) J. Guo, S. B. Wang, T. Y. Yuan, Y. J. Wu, Y. Yan, L. Li, G. H. Du, *Atherosclerosis* **2013**, *231*, 384. (d) C. W. W. Beecher, W. J. Kelleher, *Tetrahedron Lett.* **1983**, *24*, 469. (e) P. Giri, M. Hossain, G. S. Kumar, *Bioorg. Med. Chem. Lett.* **2006**, *16*, 2364. (f) M. Maiti, R. Nandi, K. Chaudhuri, *FEBS Lett.* **1982**, *142*, 280.

[7] (a) M. D. Rozwadowska, *Pol. J. Chem.* **1994**, *68*, 2271. (b) M. Chrzanowska, M. D. Rozwadowska, *Chem. Rev.* **2004**, *104*, 3341. (c) M. Chrzanowska, A. Grajewska, M. D. Rozwadowska, *Chem. Rev.* **2016**, *116*, 12369.

[8] Z. Xiang, T. Luo, K. Lu, J. Cui, X. Shi, R. Fathi, Z. Yang, *Org. Lett.* **2004**, *6*, 3155.

[9] T. Ngouansavanh, J. Zhu, *Angew. Chem. Int. Ed.* **2007**, *46*, 5775.

[10] C. Che, B. Yang, X. Jiang, T. Shao, Z. Yu, C. Tao, S. Lin, *J. Org. Chem.* **2014**, *79*, 436.

[11] Y. Chen, G. Feng, *Org. Biomol. Chem.* **2015**, *13*, 4260.

[12] T. Masao, Y. Okamoto, T. Kikuchi, K. Osaki, M. Nishikawa, K. Kamiya, Y. Sasaky, K. Matoba, K. Goto, *Chem. Pharm. Bull.* **1971**, *19*, 770.

[13] J. Kunitomo, M. Satoh, *Chem. Pharm. Bull.* **1982**, *30*, 2659.

[14] X. Zhang, W. Ye, S. Zhao, C.-T. Che, *Phytochemistry* **2004**, *65*, 929.

[15] T. R. Kane, C. Q. Ly, D. E. Kelly, J. M. Denner, *J. Comb. Chem.* **2004**, *6*(4), 564.

[16] Z. Czarnocki, D. Suh, D. B. MacLean, P. G. Hultin, W. A. Szarek, *Can. J. Chem.* **1992**, *70*, 1555.

[17] E. J. Corey, D. Gin, *Tetrahedron Lett.* **1996**, *37*, 7163.

[18] J. S. Yadav, B. V. S. Reddy, K. S. Raj, A. R. Prasad, *Tetrahedron* **2003**, *59*(10), 1805.

[19] Z. Zalan, T. A. Martinek, L. Lazar, F. Fulop, *Tetrahedron* **2003**, *59*(46), 9117.

[20] J. D. Scott, R. M. Williams, *Chem. Rev.* **2002**, *102*, 1669.

[21] P. Craig, F. Nabenhauer, P. Williams, E. Macko, J. Toner, *J. Am. Chem. Soc.* **1952**, *74*, 1316.

[22] E. Yamato, M. Hirakura, S. Sugasawa, *Tetrahedron* **1966**, *22*, 129.

[23] M. Ohkubo, A. Kuno, K. Katsuta, Y. Ueda, K. Shirakawa, H. Nakanishi, I. Nakanishi, T. Kinoshita, H. Takasugi, *Chem. Pharm. Bull.* **1996**, *44*, 95.

[24] Hirobe, M.; Ohta, S.; Masukawa, Y. WIPO Patent Application WO9736588, Kind Code: A2, **1997**.

[25] M. Francisco, A. L. Nasser, L. Lopes, *Phytochemistry* **2003**, *62*, 1265.

[26] H. Kubota, T. Watanabe, A. Kakefuda, N. Masuda, K. Wada, N. Ishii, S. Sakamoto, S. Tsukamoto, *Bioorg. Med. Chem.* **2004**, *12*, 871.

[27] Y. Horiguchi, H. Kodama, M. Nakamura, T. Yoshimura, K. Hanezi, H. Hamada, T. Saritoh, T. Sano, *A Chem. Pharm. Bull.* **2002**, *50*, 253.

[28] H. Kumpaty, S. Bhattacharyya, E. Rehr, A. Gonzalez, *Synthesis* **2003**, *2003*, 2206.

[29] A. Hegedüs, Z. Hell, *Tetrahedron Lett.* **2004**, *45*, 8553.

[30] (a) N. W. Alcock, J. M. Brown, G. I. Hulmes, *Tetrahedron: Asymmetry* **1993**, *4*, 743. (b) C. W. Lim, O. Tissot, A. Mattison, M. W. Hooper, J. M. Brown, A. R. Cowley, D. I. Hulmes, A. Blacker, *J. Org. Process Res. Dev.* **2003**, *7*, 379. (c) B. A. Sweetman, H. Muller-Bunz, P. J. Guiry, *Tetrahedron Lett.* **2005**, *46*, 4643. (d) F. Durola, J.-P. Sauvage, O. S. Wenger, *Chem. Commun.* **2006**, *2006*, 171.

[31] S. Hoogewerf, Dorp VWA Collection of Work in Chemistry in the Netherlands, **1885**, 4(4).

[32] S. Rostamizadeh, M. Nojavan, R. Aryan, E. Isapoor, M. J. Azad, *Mol. Catal. A: Chem.* **2013**, *374–375*, 102.

[33] D. Beydoun, R. Amal, G. Low, S. J. McEvoy, *Nanopart. Res.* **1999**, *1*, 439.

[34] (a) B. Halliwell, *Free Radic. Res.* **1999**, *31*, 261. (b) F. Ahmadi, M. Kadivar, M. Shahedi, *Food Chem.* **2007**, *105*, 57.

[35] M. A. Babizhayev, A. I. Deyev, V. N. Yermakovea, I. V. Brikman, J. Bours, *Drugs R. D.* **2004**, *5*, 125.

[36] L. Liu, M. Meydani, *Nutr. Rev.* **2002**, *60*, 368.

[37] M. Rajabi, Z. S. Hossaini, M. A. Khalilzadeh, S. Datta, M. Halder, S. A. Mousa, *J. Photochem. Photobiol. B Biol.* **2015**, *148*, 66.

[38] I. Yavari, M. Sabbaghan, Z. S. Hossaini, *Chem. Mon.* **2008**, *139*, 625.

[39] I. Yavari, M. Sabbaghan, Z. S. Hossaini, *Synlett* **2008**, *2008*, 1153.

[40] I. Yavari, Z. S. Hossaini, M. Sabbaghan, M. Ghazanfarpour-Darjani, *Tetrahedron* **2007**, *63*, 9423.

[41] I. Yavari, M. Sabbaghan, Z. S. Hossaini, M. Ghazanfarpour-Darjani, *Helv. Chim. Acta* **2008**, *91*, 1144.

[42] F. Rostami-Charati, *Chin. Chem. Lett.* **2014**, *2014*, 169.

[43] F. Rostami-Charati, Z. S. Hossaini, M. A. Khalilzadeh, H. Jafaryan, *J. Heterocyclic Chem.* **2012**, *49*, 217.

[44] R. Hajinasiri, Z. S. Hossaini, F. Rostami-Charati, *Heteroat. Chem.* **2011**, *22*, 625.

[45] F. Rostami Charati, Z. S. Hossaini, M. R. Hosseini-Tabatabaei, *Phosphorus Sulfur Silicon Relat Elem A* **2011**, *186*, 1443.

[46] M. Hosseini-Sarvari, M. Tavakolian, *Appl. Catal. A* **2012**, *441-442*, 65.

[47] M. Hosseini-Sarvari, H. Sharghi, S. Etemad, *Helv. Chim. Acta* **2008**, *91*, 715.

[48] A. R. Saundane, M. K. Nandibeoor, *Monatsh Chem.* **2015**, *146*, 1751.

[49] A. M. Bidchol, *Food Bioproc. Tech.* **2011**, *4*, 1137.

[50] F. Shafaei, S. E. Babaei, A. S. Shahvelayati, F. Honarmand Janatabadi, *J. Chin. Chem. Soc.* **2019**.https://doi.org/10.1002/jccs.201800489

[51] K. Shimada, K. Fujikawa, N. T. Yahara, *J. Agric. Food Chem.* **1992**, *40*, 945.

[52] G. C. Yen, P. D. Duh, *J. Agric. Food Chem.* **1994**, *42*, 629.

[53] A. Yildirim, A. Mavi, A. A. Kara, *J. Agric. Food Chem.* **2001**, *49*, 4083.

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