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Synthesis of imidazole derivatives: Ester and hydrazide compounds with antioxidant activity using ionic liquid as an efficient catalyst

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Abstract

The pyrrolidinium hydrogen sulfate (PHS) was used as an excellent ionic liquid catalyst for the preparation of many imidazoles moiety, which have biologically application via one-pot multicomponent reaction. Imidazoles were afforded through the reaction of equimolar from 1,2-diphenylethane-1,2-dione, ammonium acetate, different aromatic aldehydes, and ethyl glycinate hydrochloride. This method has the advantages of giving excellent yield, shortened reaction times, and ease of establishment. Moreover, the yielded of imidazoles components can be purified and crystallized by a nonchromatographic technique, and the catalyst can be reused. These entire novel synthesized components have been identified by spectral data: IR, NMR and mass spectra. These compounds have an in vivo antioxidant activity on experimental animals (rats).

1 | INTRODUCTION

Through the last few years, the preparation of imidazole derivatives had a great attention in synthetic organic chemistry because of comprehensive abundance of applications in the industrial, pharmaceutical, and medicinal chemistry.[1] Moreover, they have various biological applications such as analgesic, antiallergic, antibacterial, antifungal, anthelmintic, antiprotozoal, anti-inflammatory, and antituberculosis activity.[2–4] These imidazole derivatives normally found in multiple forms such as Olmesartan and Losartan.[5]

Owing to the versatile biological activities of substituted imidazoles, several classical methods for their synthesis have been reported.[6–9] In a typical procedure, benzil or benzoin, aldehydes, amines, and ammonium acetate are used in the presence of strong protic acid and organo catalyst. These homogeneous catalysts have limitations due to the use of corrosive reagents, polar organic solvents, and the necessity of neutralization of the strong acid media.[10] More several modifications were then introduced to the classical procedure using acidic Al_2O_3,[11] HY/silicagel,[12] $NiCl_2.6H_2O$,[13] iodine[14] and $Yb(OTf)_3$,[15] and boric acid using ultrasound irradiation,[16] and potassium dihydrogen phosphate.[17] However, all are plagued by the limitations of poor yield, longer reaction time, difficult work-up, and effluent pollution. Therefore, the development of a new mild method to overcome these disadvantages was necessary.[18]

In recent years, environmentally friendly reaction processes have been strongly studied from the green chemistry point of view. Scientists paid great attention to ionic liquids as green reaction solvents used in organic synthesis and introduced as a favorable alternative.[19] Ionic liquid is defined as lucid organic salts, which have melting point below 100°C and quieted completely of ions.[20] They consist of inorganic anions and organic cations where appropriate combination of cation and anion can strengthen the polarity and hydrophilicity/hydrophobicity of ionic liquids.[21–25] Their application extensively reviewed as catalytic phase in diverse organometallic reactions.[26] Beside employment of ionic liquids as alternate solvents, lately, further work has supported the new functionality of ionic liquids, which referred to as "task specific ionic liquids"

(TSIL). This attempt introduced the ionic liquids as a true working system in the reaction rather than just reaction media.[27,28]

Herein, a simple, highly versatile, and efficient synthesis of tetrasubstituted imidazoles is achieved by four component cyclocondensation of 1,2-dicarbonyl compounds, aldehydes, primary amine, and ammonium acetate in thermal and solvent free condition using acidic ionic liquid pyrrolidinium hydrogen sulfate (PHS) as a catalyst. The advantages of PHS are cost effectiveness, reusability, nonflammability, high viscosity, thermal and oxidative stability, good solvation power, nonvolatility, and being ecofriendly catalyst.[29] The key advantages of this process are cost effectiveness of catalyst, reusability of catalyst, easy work-up and purification of products by nonchromatographic methods, excellent yields, and very short time reactions (20-50 minutes).[30]

2 | RESULTS AND DISCUSSION

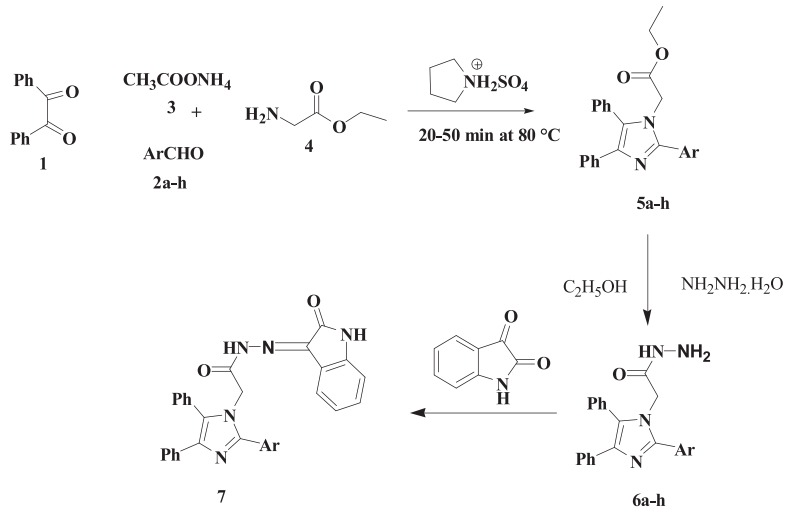
Regard to previous literature review, we are found that imidazoles derivatives have pharmaceutical and biological activity.[31] So, we are decided to research the capacity of the ionic liquid for preparation of multisubstitute dimidazoles (**5**) in a good yield. The reaction between 1,2-diphenylethane-1,2-dione (**1**), aromatic aldehydes (**2a-h**), ammonium acetate (**3**), and ethyl glycinate (**4**) in the presence of ionic liquid was illustrated in (Scheme 1, Table 1). All the novel components are checked with IR and NMR analysis. The method was found to be simple, expeditious, and environmentally friendly.

To the improvement of the reaction condition optimized, we investigated the model reaction further by different of the amount of the ionic liquid catalyst. We are noted that 4 mol % gave the highest products of 96%, and further increase were not beneficial to the process (Table 2).

The possible mechanism of the one-pot multicomponent cyclocondensation of 1,2-diphenylethane-1,2-dione, ethyl glycinate and the convenient aromatic aldehyde together with ionic liquid, in the presence of 1 mol of ammonium acetate contains a key coupling step of the intermediate of benzaldehyde imine (I). On the other hand, ethyl glycinate attack the activated benzil to form α-imino ketone (II). This is followed by the nucleophilic attack of the in situ generated imine to carbonyl of aryl ketoimine giving the intermediate (III). Their subsequent intramolecular interaction leads to cyclization and eventually to the formation of intermediate (IV), which dehydrates to the 1,2,4,5-tetrasubstituted imidazole (Scheme 2).

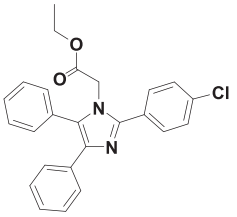
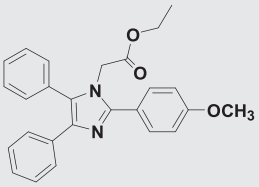
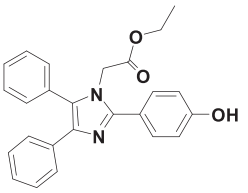
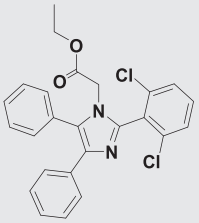
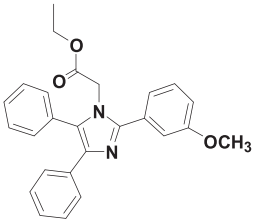
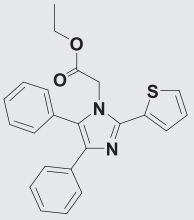
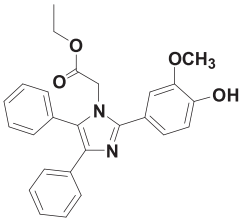
2.1 | Antioxidant activity

The antioxidant activities of the present compounds were determined using some oxidative stress biomarker assays. They included plasma malondialdehyde level (MDA), liver reduced glutathione content (GSH) and nitric oxide level (NO) in vivo on rats. All these oxidative stress biomarkers showed remarkable differences with all tested compounds. The most increased value of MDA level was recorded with compound **5a**, and the most decreased one was recorded with compound **7** in comparing with the control value (Figure 1A). The most increased value of liver GSH level is determined with **5b**, and the most decreased value is recorded with **5a** and **5e**, respectively, as compared with control value (Figure 1B). Compounds **5b** and **7** displayed the most increased effect of NO level; however, compound **5a** caused the most decreased effect as compared with control value (Figure 1C).



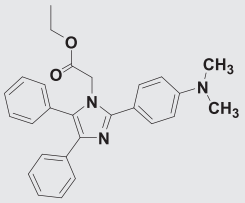
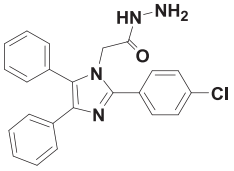
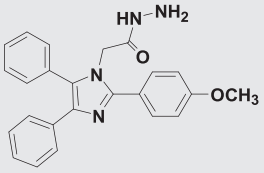
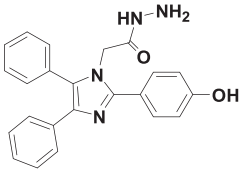
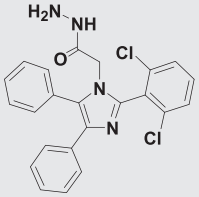
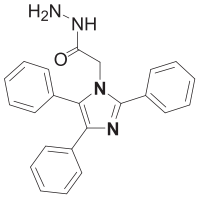
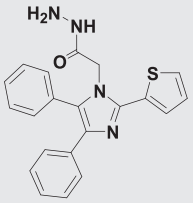
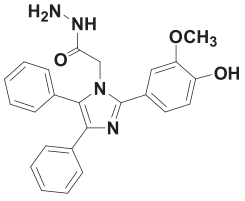
SCHEME 1 Optimization of the synthesis of 1,2,4,5-tetrasubstituted imidazoles **5a-h**, **6a-h**, and **7**

TABLE 1 List of 1,2,4,5-tetrasubstituted imidazole derivatives formed after addition of acidic ionic liquid pyrrolidinium hydrogen sulfate (PHS) (**5a-h**), after addition of hydrazine hydrate (**6a-h**), and after addition of isatin (**7**)

No	Formula, Mol. wt.	Scheme	M.P., °C	Reaction Time, min	Yield, %
5a	$C_{25}H_{21}ClN_2O_2$ (416.19)		121-123	37	96
5b	$C_{26}H_{24}N_2O_3$ (412.48)		114-116	44	92
5c	$C_{25}H_{22}N_2O_3$ (398.45)		151-153	38	90
5d	$C_{25}H_{20}Cl_2N_2O_2$ (451.34)		124-126	44	88
5e	$C_{26}H_{24}N_2O_3$ (412.48)		115-116	43	94
5f	$C_{23}H_{20}N_2O_2S$ (388.48)		124-125	55	94
5 g	$C_{26}H_{24}N_2O_4$ (428.48)		112-114	48	92
5 h	$C_{27}H_{27}N_3O_2$ (425.52)		114-115	55	93

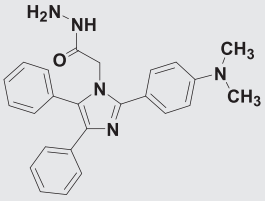
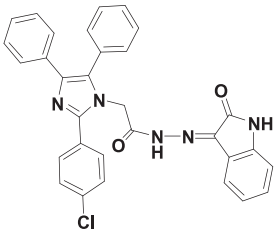
(Continues)

TABLE 1 (Continued)

No	Formula, Mol. wt.	Scheme	M.P., °C	Reaction Time, min	Yield, %
					
6a	$C_{23}H_{19}ClN_4O$ (402.88)		115	17	88
6b	$C_{24}H_{22}N_4O_2$ (398.46)		88-90	20	95
6c	$C_{23}H_{20}N_4O_2$ (384.43)		120-122	25	96
6d	$C_{23}H_{18}Cl_2N_4O$ (435.35)		113-114	33	95
6e	$C_{23}H_{20}N_4O$ (368.43)		110	35	91
6f	$C_{21}H_{18}N_4OS$ (374.46)		111-112	21	97
6 g	$C_{24}H_{22}N_4O_3$ (414.46)		113-115	33	91

(Continues)

TABLE 1 (Continued)

No	Formula, Mol. wt.	Scheme	M.P., °C	Reaction Time, min	Yield, %
6 h	$C_{25}H_{25}N_5O$ (411.50)		109-110	45	89
7	$C_{31}H_{22}ClN_5O_2$ (531.99)		154-156	25	93

2.2 | Experimental

2.2.1 | General methods for synthesis of PHS ionic liquid

Pyrrolidine (20 mmol) was added in the three-necked rounded bottom flask (150 mL), which have a magnetic stirrer. An equimolar concentrated H_2SO_4 was added slowly in a drop wise manner into this the flask at 0°C.After that, the reaction mixture was allowed to be stirred and heated at 80°Cfor 12 hours. Diethyl ether was used three times for washing the reaction mixture to expel the nonreacted compounds (nonionic residues) and dry using the rotary evaporator to acquire the viscous pure PHS.[32]

2.2.2 | General method for the synthesis of ethyl4,5-diphenyl-2-(substituted)-1*H*-imidazole-1-carboxylate (5a-h)

A mixture of 20-mmol aromatic aldehydes, 20-mmol 1,2-diphenylethane-1,2-dione, 20-mmol ammonium acetate, and 20-mmol ethyl glycinate were added to 4 mol % PHS ionic liquid as a catalyst. The reaction mixture was allowed toreflux foran appropriate time according to Table 1. After completion of the reaction, which was monitored by thin-layer chromatography (TLC), the mixture washed with water, the solid product purified by recrystallization from ethanol or methanol. While the ionic liquid in the filtrate can be regained after evaporating all solvents till oily mass of ionic liquid collected, ionic liquid now can be reused later for more reactions.

2.2.3 | General method for the synthesis of 2-(2-(substituted)-4,5-diphenyl-1*H*-imidazol-1-yl)acetohydrazide (6a-h)

To a solution of ethyl 4,5-diphenyl-2-(substituted)-1H-imidazole-1-carboxylate **5a-h** (5 mmol) in ethanol, hydrazine hydrate (5.1 mmol, 100%) was added slowly with persistent stirring. The reaction mixture allowed to reflux for 3 hours and cooled at 25°C. The separated product was collected with filtration, dried, and crystallized from methanol or ethanol.

2.3 | Animal treatment and experimental design

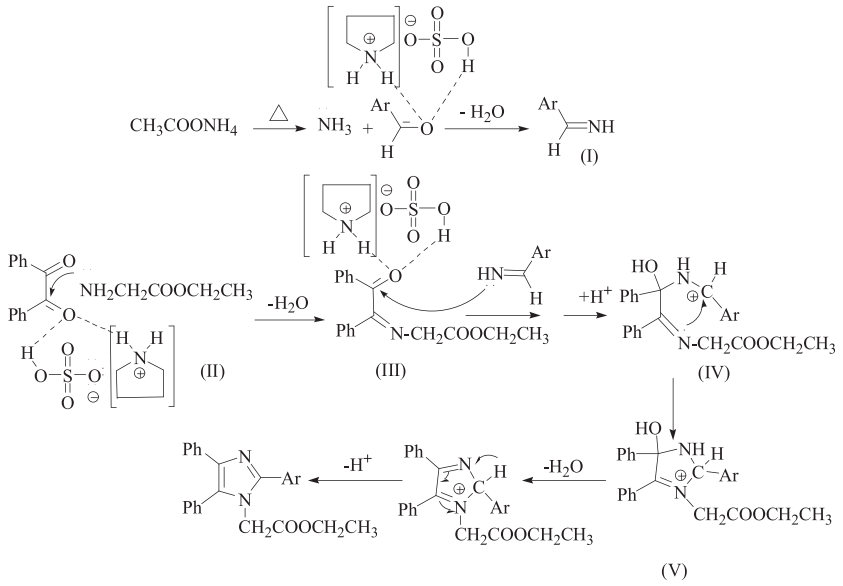
Male rats of body weight (160-180 g) were obtained from animal house, Sohag University, Egypt. They were housed and preserved on standard laboratory diet and water.

TABLE 2 The amount of pyrrolidinium hydrogen sulphate catalyst for synthesis of imidazoles (MSI) $\mathbf{5_x}^{\mathbf{y}}$

Entry	Catalysts/mol %[b]	Yield, %[a]	Entry	Catalysts/mol %[b]	Yield, %[a]
5a	1	44	5a	4	96
5a	2	68	5a	5	96
5a	3	73	5a	6	96

[a]Isolated yields based on **5a**.

[b]Amount of catalyst used: 1, 2, 3, 4, 5, and 6 mol % catalyst.



SCHEME 2 The suggested mechanism of prepared multisubstitute dimidazoles (MSI) **5a-h**

Animals were categorized into three groups, each containing 6 to 8 animals. The first one (control) was received dimethyl sulfoxide (DMSO); however, methotrexate injection (7 mg/kg) was given intraperitoneally (*i.p*) daily for three sequential days to the positive control group. The third group was given tested compounds (150 mg/kg) dissolved in DMSO 1 hour before methotrexate daily for three consecutive days. After 24 hours from the last methotrexate injection, animals were anesthetized and dissected. Blood samples were collected via direct cardiac puncture, then centrifuged for 10 minutes at 3000 *g* to obtain sera. Livers were separated, homogenized in potassium phosphate buffer (0.05M, pH 7.4) and frozen at −20°C for analysis.[33,34] Animals handling and care was corresponding to the ethical standards confirmed by the Institutional Animal Ethics Committee guidelines, Sohag University, Egypt.

2.4 | Antioxidant assays

1. Thiobarbituric acid reactive substance (MDA) determination:

Determination of thiobarbituric acid reactive substances from the hepatic tissues was performed by using the method of Uchiyama and Mihara,[35] it was colorimetric calculated as MDA, which was applied based on the reaction of one molecule of MDA with two molecules of thiobarbituric acid.

2. Reduced GSH determination of:

Liver GSH was determined spectrophotometrically according to the method of Beutler et al.[36] Reduced GSH was used as a standard.

3. NO determination of:

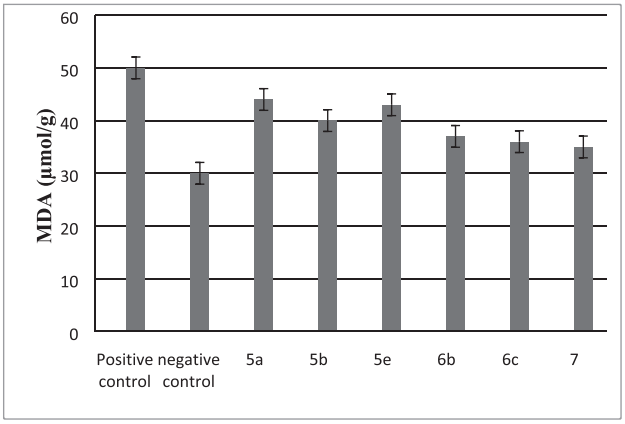
NO was estimated from plasma spectrophotometrically using sodium nitrite as a standard according to Griess reaction.[37]

2.4.1 | Ethyl 2-(2-(4-chlorophenyl)-4,5-diphenyl-1*H*-imidazol-1-yl)acetate (5a)

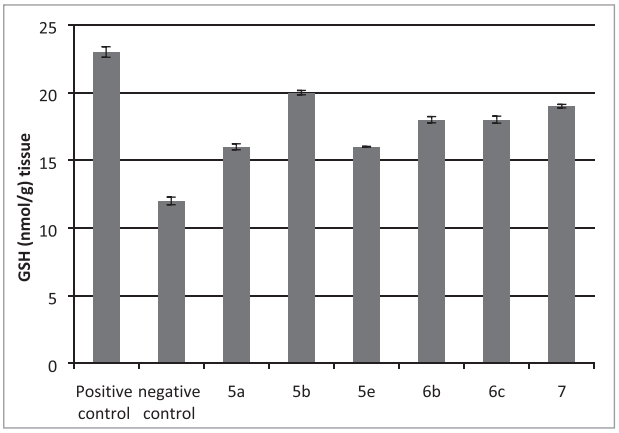
Yield 96%; m.p. 121-123°C; IR (λ max, cm^{-1}): 3024 ($CH_{arom.}$), 2944-2898 ($CH_{aliph.}$), 1735 (C═O), 1608 (C═N);^{1}H-NMR (DMSO-d_6), δ ppm: 7.72-7.15 (m,14H, $CH_{arom.}$), 4.66 (s, 2H, CH_2-C═O), 4.00 (q, 2H, O$\underline{CH_2}CH_3$), 1.01 (t, 3H, $OCH_2\underline{CH_3}$); ^{13}C-NMR (DMSO-d_6), δ ppm: 168.65, 146.71, 137.17, 134.61, 131.24, 130.74, 130.45, 129.72, 129.57, 129.33, 128.61, 126.92, 126.55, 61.85, 47.22, 14.23 ppm. Elemental Analysis: Calcd. C, 72.02; H, 5.08; N, 6.72. Found: 72.00; H, 5.02; N, 6.71.

2.4.2 | Ethyl 2-(2-(4-methoxyphenyl)-4,5-diphenyl-1*H*-imidazol-1-yl)acetate (5b)

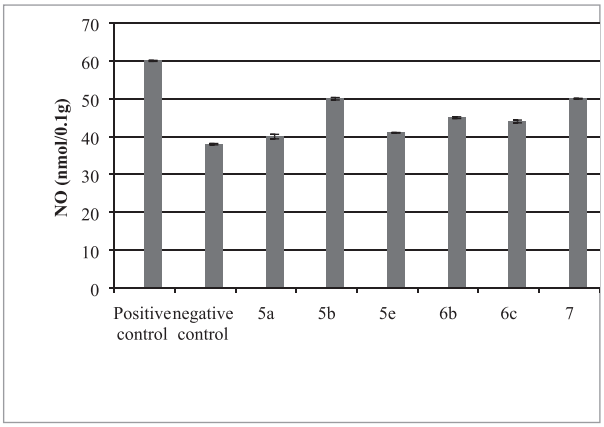
Yield 92%; m.p. 114-116°C; IR (λ max, cm^{-1}): ($CH_{arom.}$) 3055, 2955-2880 ($CH_{aliph.}$), 1735 (C═O), 1605 (C═N); ^{1}H-NMR (DMSO-d_6), δ ppm: 7.16-7.18 (m, 14H, $CH_{arom.}$), 4.60 (s, 2H, CH_2-C═O), 4.02 (q, 2H, O$\underline{CH_2}CH_3$), 3.82 (s, 3H, OCH_3), 1.02 (t, 3H, $OCH_2\underline{CH_3}$); ^{13}C-NMR (DMSO-d_6) δ ppm: 168.81, 160.32, 147.81, 136.73, 134.89, 131.26, 130.78, 130.48, 130.14, 130.05, 129.96, 129.66, 129.57, 128.56, 126.74, 126.52, 123.06, 114.65, 61.78, 55.71, 47.14, 14.26; DEPT 135 (300 MHz, DMSO-d_6): 61.78, 55.71 (CH_2) ppm disappeared. Elemental Analysis: Calcd. C, 75.71; H, 5.86; N, 6.79. Found: 75.69; H, 5.83; N, 6.75.



(A)



(B)



(C)

FIGURE 1 Antioxidant effects of imidazoles

2.4.3 | Ethyl 2-(2-(4-hydroxyphenyl)-4,5-diphenyl-1*H*-imidazol-1-yl)acetate (5c)

Yellow crystals; yield 90%; m.p. 151-153°C; IR (λ max, cm^{-1}): 3123 (OH), 3042 ($CH_{arom.}$), 2954-2865 ($CH_{aliph.}$), 1739 ($C{=}O_{ester}$), 1593 (C=N); ^{1}H-NMR (DMSO-d_6), δ ppm: 12.53 (s, 1H, OH), 8.03-7.04 (m, 14H, $CH_{arom.}$), 4.85 (s, 2H, CH_2-C=O), 4.23 (q, 2H, $O\underline{CH_2}CH_3$), 1.24 (t, 3H, $OCH_2\underline{CH_3}$); ^{13}C-NMR (DMSO-d_6), δ ppm: 168.66, 159.33, 148.72, 135.17, 134.61, 131.24,,130.77, 129.11, 128.82, 128.63, 128.11,127.51, 127.12, 126.90, 115.18, 65.14, 61.15, 14.53; DEPT 135 (300 MHz, DMSO-d_6): 65.14, 61.15 (CH_2) ppm disappeared. Elemental Analysis: Calcd. C, 75.36; H, 5.57; N, 7.03, Found: C, 75.34; H, 5.53; N, 7.00.

2.4.4 | Ethyl 2-(2-(2,6-dichlorophenyl)-4,5-diphenyl-1*H*-imidazol-1-yl)acetate (5d)

Yellow crystals; yield 88%; m.p. 124-126°C; IR (λ max, cm^{-1}): 3033 ($CH_{arom.}$), 2933-2814 ($CH_{aliph.}$), 1740 ($C{=}O_{ester}$), 1600 (C=N); ^{1}H-NMR (DMSO-d_6), δ ppm: 7.95-7.21 (m, 13H, $CH_{arom.}$), 4.65 (s, 2H, CH_2-C=O), 4.01 (q, 2H, $O\underline{CH_2}CH_3$), 1.03 (t, 3H, $OCH_2\underline{CH_3}$); ^{13}C-NMR (DMSO-d_6), δ ppm: 197.33, 168.65, 160.43, 147.12, 137.76, 134.71, 134.24, 130.76, 130.07, 130.01, 129.99, 129.69, 128.61, 121.63, 118.11, 117.95, 117.12, 63.17, 57.75, 43.23, 13.56 ppm. Elemental Analysis: Calcd. C, 66.53; H, 4.47; N, 6.21, Found: C, 66.49; H, 4.46; N, 6.19.

2.4.5 | Ethyl 2-(2-(3-methoxyphenyl)-4,5-diphenyl-1*H*-imidazol-1-yl)acetate (5e)

Yield 94%; m.p. 115-116°C; IR (λ max, cm^{-1}): 3041 ($CH_{arom.}$), 2934-2864 ($CH_{aliph.}$), 1754 ($C{=}O_{ester}$), 1605 (C=N); ^{1}H-NMR (DMSO-d_6), δ ppm:7.95-7.09 (m, 14H, $CH_{arom.}$), 4.65 (s, 2H, CH_2-C=O), 4.02 (q, 2H, $O\underline{CH_2}CH_3$), 3.85 (s, 3H, OCH_3), 1.02 (t, 3H, $OCH_2\underline{CH_3}$); ^{13}C-NMR (DMSO-d_6), δ ppm: 197.34,169.64, 160.53, 148.13, 138.12, 137.76, 134.71, 134.24, 131.27, 130.06, 130.02, 129.99, 129.69, 128.61, 126.55, 120.12, 118.11, 117.95, 117.12, 115.41, 61.81, 55.66, 47.23, 40.20, 14.25; DEPT 135 (300 MHz, DMSO-d_6): 61.81, 40.20 (CH_2) ppm disappeared. Elemental Analysis: Calcd. C, 75.71; H, 5.86; N, 6.79, Found: C, 75.70; H, 5.83; N, 6.75.

2.4.6 | Ethyl 2-(2-(thiophen-2-yl)-4,5-diphenyl-1*H*-imidazol-1-yl)acetate (5f)

Yield 73%; m.p. 210-212°C; IR (λ max, cm^{-1}): 3059 ($CH_{arom.}$), 2935 ($CH_{aliph.}$), 1740 (C=O), 1601 (C=N); ^{1}H-NMR (DMSO-d_6), δ ppm: 7.71-7.16 (m, 13H, $CH_{arom.}$), 3.38 (s, 2H, CH_2-C=O), 3.36 (q, 2H, $O\underline{CH_2}CH_3$), 1.09 (t, 3H, $OCH_2\underline{CH_3}$); ^{13}C-NMR (DMSO-d_6), δ ppm: 196.33,168.61, 161.55, 149.13, 140.13, 137.55, 136.34, 135.34, 136.25, 132.13, 130.02, 129.15, 128.15, 127.60, 125.14, 119.11, 117.09, 116.91, 114.11, 113.10, 60.09, 54.45, 44.20, 41.19, 14.12; DEPT 135 (300 MHz, DMSO-d_6): 60.09 (CH_2) ppm disappeared. Elemental Analysis: Calcd. C, 71.11; H, 5.19; N, 7.21; S, 8.25, Found: 71.09; H, 5.14; N, 7.18; S, 8.23.

2.4.7 | Ethyl 2-(2-(4-hydroxy-3-methoxyphenyl)-4,5-diphenyl-1*H*-imidazol-1-yl)acetate (5g)

Yield 88%; m.p. 112-114°C; IR (λ max, cm^{-1}): 3341 ($OH_{phenolic}$), 3045 ($CH_{arom.}$), 2941-2844 ($CH_{aliph.}$), 1721 ($C{=}O_{ester}$), 1601 (C=N); ^{1}H-NMR (DMSO-d_6), δ ppm: 90.14 (br, 1H, $OH_{phenolic}$) 7.91-7.12 (m, 13H, $CH_{arom.}$), 4.61 (s, 2H, CH_2-C=O), 4.00 (q, 2H, O$\underline{CH_2}CH_3$), 3.90 (s, 3H, OCH_3), 1.00 (t, 3H, $OCH_2\underline{CH_3}$); ^{13}C-NMR (DMSO-d_6), δ ppm: 197.34,169.64, 160.53, 148.13, 138.12, 137.76, 134.71, 134.24, 131.27, 130.06, 130.02, 129.99, 129.69, 128.61, 126.55, 120.12, 118.48, 117.84, 117.17, 115.26, 61.19, 55.14, 48.20, 47.23, 40.22, 14.21; DEPT 135 (300 MHz, DMSO-d_6): 61.81, 40.20 (CH_2) ppm disappeared. Elemental Analysis: Calcd. C, 72.88; H, 5.65; N, 6.54, Found: C, 72.85; H, 5.62; N, 6.51.

2.4.8 | Ethyl 2-(2-(4-(dimethylamino)phenyl)-4,5-diphenyl-1*H*-imidazol-1-yl)acetate (5h)

Yield 92%; m.p. 114-115°C; IR (λ max, cm^{-1}): ($CH_{arom.}$) 3050, 2951-2885 ($CH_{aliph.}$), 1741 (C=O), 1609 (C=N); ^{1}H-NMR (DMSO-d_6), δ ppm: 7.51-6.69 (m, 14H, $CH_{arom.}$), 4.61 (s, 2H, CH_2-C=O), 4.30 (q, 2H, O$\underline{CH_2}CH_3$), 2.95 (s, 6H, N $(CH_3)_2$), 1.01 (t, 3H, $OCH_2\underline{CH_3}$); ^{13}C-NMR (DMSO-d_6) δ ppm: 169.80, 163.14, 147.24, 136.12, 136.01, 134.16,132.72,130.48, 130.51, 130.05, 129.45, 129.02, 128.51, 126.74, 126.52, 123.06, 114.65, 61.78, 55.71, 40.26, 47.14, 14.26; DEPT 135 (300 MHz, DMSO-d_6): 61.78, 55.71 (CH_2) ppm disappeared. Elemental Analysis: Calcd. C, 76.21; H, 6.40; N, 9.87, found C, 76.18; H, 6.36; N, 9.85.

2.4.9 | 2-(2-(4-chlorophenyl)-4,5-diphenyl-1*H*-imidazol-1-yl)acetohydrazide (6a)

Crystalized as brown crystals from methanol; yield 89%; m.p. 115°C; IR (λ max, cm^{-1}): 3471, 3321, 3220 (NH, NH_2), 3041,3012 ($CH_{arom.}$), 2941 ($CH_{aliph.}$), 1665 (C=O), 1608 (C=N); ^{1}H-NMR (DMSO-d^6), δ ppm: 9.13 (s, 1H, NH), 7.76-7.14 (m, 14H, $CH_{arom.}$), 4.37 (s, 2H, CH_2-C=O), 4.33 (s, 2H, NH_2); ^{13}C-NMR (DMSO-d_6), δ ppm: 167.65, 148.14, 138.91, 137.13, 135.33, 131.28, 131.19, 130.84, 129.57, 129.14 128.57 126.75, 126.55, 46.58 ppm; DEPT 135 (300 MHz, DMSO-d_6): 46.58 (CH_2) ppm disappeared. Elemental Analysis: Calcd. C, 68.57; H, 4.75; N, 13.91, found C, 68.55; H, 4.72; N, 13.88,

2.4.10 | 2-(2-(4-Methoxyphenyl)-4,5-diphenyl-1*H*-imidazol-1-yl)acetohydrazide (6b)

Crystallized as crystals brown color from methanol; yield 95%; m.p. 88-90°C; IR (λ max, cm^{-1}): 3470, 3315, 3111 (NH, NH_2), 3045, 3010 ($CH_{arom.}$), 2931 ($CH_{aliph.}$), 1660 (C=O), 1610 (C=N); ^{1}H-NMR (DMSO-d^6), δ ppm: 9.13 (s, 1H, NH), 7.76-7.16 (m, 14H, $CH_{arom.}$), 4.37 (s, 2H, CH_2-C=O), 4.33 (s, 2H, NH_2), 3.8 (s, 3H, OCH_3); ^{13}C-NMR (DMSO-d_6), δ ppm: 167.99, 148.47, 138.91, 137.13, 135.33, 131.28, 131.19, 130.84, 129.57, 129.14 128.57 126.75, 126.55, 46.58 ppm; DEPT 135 (300 MHz, DMSO-d_6): 46.58 (CH_2) ppm disappeared. Elemental Analysis: Calcd. C, 72.34; H, 5.57; N, 14.06, found C, 72.33; H, 5.54; N, 14.02.

2.4.11 | 2-(2-(4-Hydroxyphenyl)-4,5-diphenyl-1*H*-imidazol-1-yl)acetohydrazide (6c)

Crystallized as pale yellowish crystals from DMF; yield 96%; m.p. 120-122°C; IR (λ max, cm^{-1}): 3472, 3324, 3200 (OH) (NH, NH_2), 3067-3013 ($CH_{arom.}$), 2975 ($CH_{aliph.}$), 1637 (C=O), 1610 (C=N); ^{1}H-NMR (DMSO-d_6), δ ppm: 12.55 (s, 1H, OH), 9.42 (s, 1H, NH), 8.04-7.07 (m, 14H, $CH_{arom.}$), 4.57 (s, 2H, CH_2-C=O), 4.35 (s, 2H, NH_2); ^{13}C-NMR (DMSO-d_6), δ ppm: 167.04, 157.45, 146.88, 142.14, 138.91, 137.13, 129.10, 128.81, 128.64 127.55, 127.11, 126.12, 115.20, 66.78 ppm; DEPT 135 (300 MHz, DMSO-d_6): 66.78 (CH_2) ppm disappeared. Elemental Analysis: Calcd. C, 71.86; H, 5.24; N, 14.57, found C, 71.84; H, 5.22; N, 14.54.

2.4.12 | 2-(2-(2,6-Dichlorophenyl)-4,5-diphenyl-1*H*-imidazol-1-yl)acetohydrazide (6d)

Crystallized as brownish crystal from methanol; yield 95%; m.p. 113-114°C; IR (λ max, cm^{-1}): 3024 ($CH_{arom.}$), 2944-2898 ($CH_{aliph.}$), 1639 (C=O), 1606 (C=N); ^{1}H-NMR (DMSO-d_6), δ ppm: 9.34 (s, 1H, NH), 7.98-7.00 (m, 13H, $CH_{arom.}$), 4.63 (s, 2H, CH_2-C=O), 4.25 (s, 2H, NH_2); ^{13}C-NMR (DMSO-d_6), δ ppm: 168.65, 146.71, 137.17, 134.61, 131.24,,130.74, 130.45, 129.72, 129.57, 129.33, 128.61, 126.92, 126.55, 61.85 ppm; DEPT 135 (300 MHz, DMSO-d_6): 61.85 (CH_2) ppm disappeared. Elemental Analysis: Calcd. C, 63.17; H, 4.15; N, 12.81, found C, 63.15; H, 4.12; N, 12.77.

2.4.13 | 2-(2,4,5-triphenyl-1*H*-imidazol-1-yl) acetohydrazide (6e)

Yield 90%; m.p. 110°C; IR (λ max, cm^{-1}):, 3454, 3354, 3210 (NH, NH_2), 3033 ($CH_{arom.}$), 2991 ($CH_{aliph.}$), 1664 (C═O), 1604 (C═N);^{1}H-NMR (DMSO-d_6), δ ppm: 9.06 (s,1H,NH), 8.12-7.14 (m,15H,$CH_{arom.}$), 4.38 (s,2H, $CH_{2aliph.}$), 4.25 (s, 2H, NH_2); ^{13}C-NMR (DMSO-d_6), δ ppm: 191.31,165.11, 164.12, 148.45, 141.54, 139.18, 137.41, 135.34, 136.25, 135.21, 132.13, 130.02, 129.15, 128.15, 127.60, 125.14, 119.11, 117.09, 116.91, 114.11, 113.10, 61.10; DEPT 135 (300 MHz, DMSO-d_6): 61.10 (CH_2) ppm disappeared. Elemental Analysis: Calcd. C, 74.98; H, 5.47; N, 15.21, found. C, 74.95; H, 5.44; N, 15.18.

2.4.14 | 2-(4,5-diphenyl-2-(thiophen-2-yl)-1*H*-imidazol-1-yl)acetohydrazide (6f)

Yield 97%; m.p. 111-112°C; IR (λ max, cm^{-1}): 3314, 3212, 3111 (NH, NH_2), 3012 ($CH_{arom.}$), 2934 ($CH_{aliph.}$), 1671 (C═O), 1602 (C═N); ^{1}H-NMR (DMSO-d_6), δ ppm: 9.25 (s,1H,NH), 7.70-7.16 (m,13H,$CH_{arom.}$), 4.49 (s, 2H, $CH_{2aliph.}$), 4.34 (s, 2H, NH_2); ^{13}C-NMR (DMSO-d_6), δ ppm: 191.31,165.11, 164.12, 148.45, 141.54, 139.18, 137.41, 135.34, 136.25, 135.21, 132.13, 130.02, 129.15, 128.15, 127.60, 125.14, 119.11, 117.09, 116.91, 114.11, 113.10, 61.10, 54.45, 44.20, 41.19, 15.14; DEPT 135 (300 MHz, DMSO-d_6): 61.10 (CH_2) ppm disappeared. Elemental Analysis: Calcd. C, 67.36; H, 4.85; N, 14.96; S, 8.56, found C, 67.33; H, 4.84; N, 14.93; S, 8.54.

2.4.15 | 2-(2-(4-hydroxy-3-methoxyphenyl)-4,5-diphenyl-1*H*-imidazol-1-yl) acetohydrazide (6g)

Yield 92%; m.p. 113-115°C; IR (λ max, cm^{-1}): 3500 (OH_{broad}), 3305-3200 (NH^+NH_2), 3061 ($CH_{arom.}$), 2938 ($CH_{aliph.}$), 1673(C═O), 1602 (C═N); ^{1}H-NMR (DMSO-d_6), δ ppm: 12.51 (s, 1H, OH), 9.33 (s, 1H, NH),7.72-6.92 (m, 14H, CH_{arom}),4.42 (s, 2H, CH_{2aliph}), 3.88 (s, 2H, NH_2);^{13}C-NMR (DMSO-d_6),δ ppm: 190.12, 169.14, 164.12, 149.45, 141.94, 139.14, 137.11, 135.30, 136.24, 135.00, 132.11, 130.09, 129.17, 128.75, 127.11, 125.14, 119.11, 117.41, 116.17, 114.14, 113.17, 63.11; DEPT 135 (300 MHz, DMSO-d_6): 63.11 (CH_2) ppm disappeared. Elemental Analysis: Calcd. C, 69.55; H, 5.35; N, 13.52, found C, 69.53; H, 5.31; N, 13.50.

2.4.16 | 2-(2-(4-(dimethylamino)phenyl)-4,5-diphenyl-1*H*-imidazol-1-yl) acetohydrazide (6h)

Yield 90%; m.p. 109°C; IR (λ max, cm^{-1}): 3350 (broad NH + NH_2), 3030 ($CH_{arom.}$), 2925-2801 ($CH_{aliph.}$), 1672 (C═O), 1611 (C═N); ^{1}H-NMR (DMSO-d_6), δ ppm: 9.10 (s, 1H, NH); 7.95-6.80 (m, 14H, $CH_{arom.}$); 4.35 (s, 2H, CH); 4.00 (s, 2H, NH_2); 2.97 (s, 6H, $2CH_3$); ^{13}C-NMR (DMSO-d_6), δ ppm: 188.91, 167.91, 148.14, 139.90, 136.53, 137.32, 130.17, 130.09, 130.01, 129.99, 129.19 128.17, 127.27, 126.23, 46.54, 45.12 ppm; DEPT 135 (300 MHz, DMSO-d_6): 46.54 (CH_2) ppm disappeared. Elemental Analysis: Calcd. C, 72.97; H, 6.12; N, 17.02, found C, 72.95; H, 6.10; N, 17.00.

2.4.17 | 2-(2-(4-chlorophenyl)-4,5-diphenyl-1*H*-imidazol-1-yl)-*N*′-(2-oxoindolin-3-ylidene)acetohydrazide (7)

Yield 93%; m.p. 228°C; crystalized as brownish crystals from methanol; yield 93%; m.p. 154-156°C; IR (λ max, cm^{-1}): 3317, 3161 (2NH), 3045-3010 ($CH_{arom.}$), 2976 ($CH_{aliph.}$), 1675, 1666 (2 C═O), 1608 (C═C); ^{1}H-NMR (DMSO-d_6), δ ppm: 12.7, 11.44 (s, 2H, 2NH.), 7.82-6.96 (m, 18H, $CH_{arom.}$), 5.21 (s, 2H, CH_2-C═O);^{13}C-NMR (DMSO-d_6), δ ppm: 197.33, 188.31, 168.65, 167.51, 164.44, 160.43, 157.61, 147.12, 145.44, 137.76, 134.71, 134.24,,130.76, 130.07, 130.01, 129.99, 129.69, 128.61, 121.63, 118.11, 117.95, 117.12, 63.14 ppm. Elemental Analysis: Calcd. C, 69.99; H, 4.17; N, 13.16, found C, 69.95; H, 4.14; N, 13.12.

3 | CONCLUSION

Series of imidazole derivatives were synthesized by using the good catalyst PHS through a multicomponent reaction. The reaction was carried out in short time, giving very high yield products, as compounds (**5a** and **6f**; 96% and 97%) respectively, that have in vivo antioxidant activity on experimental animals (rats).

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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