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ORIGINAL PAPER

Synthesis, characterization, and bioassay of a new class of pyrazolyl/isoxazolyl oxadiazoles

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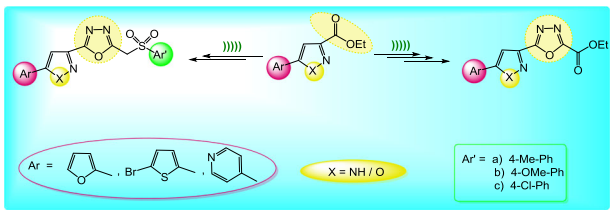
Abstract

This study aimed at describing a simple and facile synthesis of pyrazolyl/isoxazolyl 1,3,4-oxadiazole derivatives from the synthetic intermediates pyrazolyl/isoxazolyl carboxylates adopting conventional and ultrasound irradiation methods. In fact ultrasound-promoted synthesis led to the formation of title compounds in higher yields and in shorter reaction times when compared with conventional methods. All the compounds were characterized by IR, ^{1}H NMR, ^{13}C NMR, and mass spectra. The synthesized compounds were evaluated for their antioxidant and anti-inflammatory activities. The bioassay results indicated that some title compounds were found to be more potent than standard drugs. Amongst all the tested compounds furanyl/pyridinyl linked pyrazolyl/isoxazolyl methoxyphenylsulfonylmethyloxadiazoles were identified as potential antioxidant and anti-inflammatory agents.

Graphical abstract



Keywords Azole · Cyclization · Ultrasonication · Antioxidant activity · Anti-inflammatory activity · Structure–activity relationship

Introduction

The five-membered heterocyclic compounds with one or two nitrogen atoms particularly 1,3,4-oxadiazoles, pyrazoles, and isoxazoles represent an indispensable class of heteroaromatic compounds, as they are part of many biologically active pharmaceuticals vital for increasing the quality of life (Fig. 1).

Literature searches reveal that there are several methods for synthesis of 2,5-disubstituted 1,3,4-oxadiazoles either thermal/acid catalyzed cyclization of 1,2-diacylhydrazines [1] or by oxidative cyclization of semicarbazone/hydrazone in the presence of an oxidant [2] or by microwave irradiation of hydrazide and carboxylic acid mixture [3] or cyclization of acylthiosemicarbazides. 1,3,4-Oxadiazoles and its derivatives have been attracting great attention due to their wide range of biological properties including antioxidant [4], analgesic [5], anti-inflammatory [6], anticancer [7], antidiabetic [8], anticonvulsant [9], anti-HIV [10], antihypertensive [11], antiobesity [12], antibacterial

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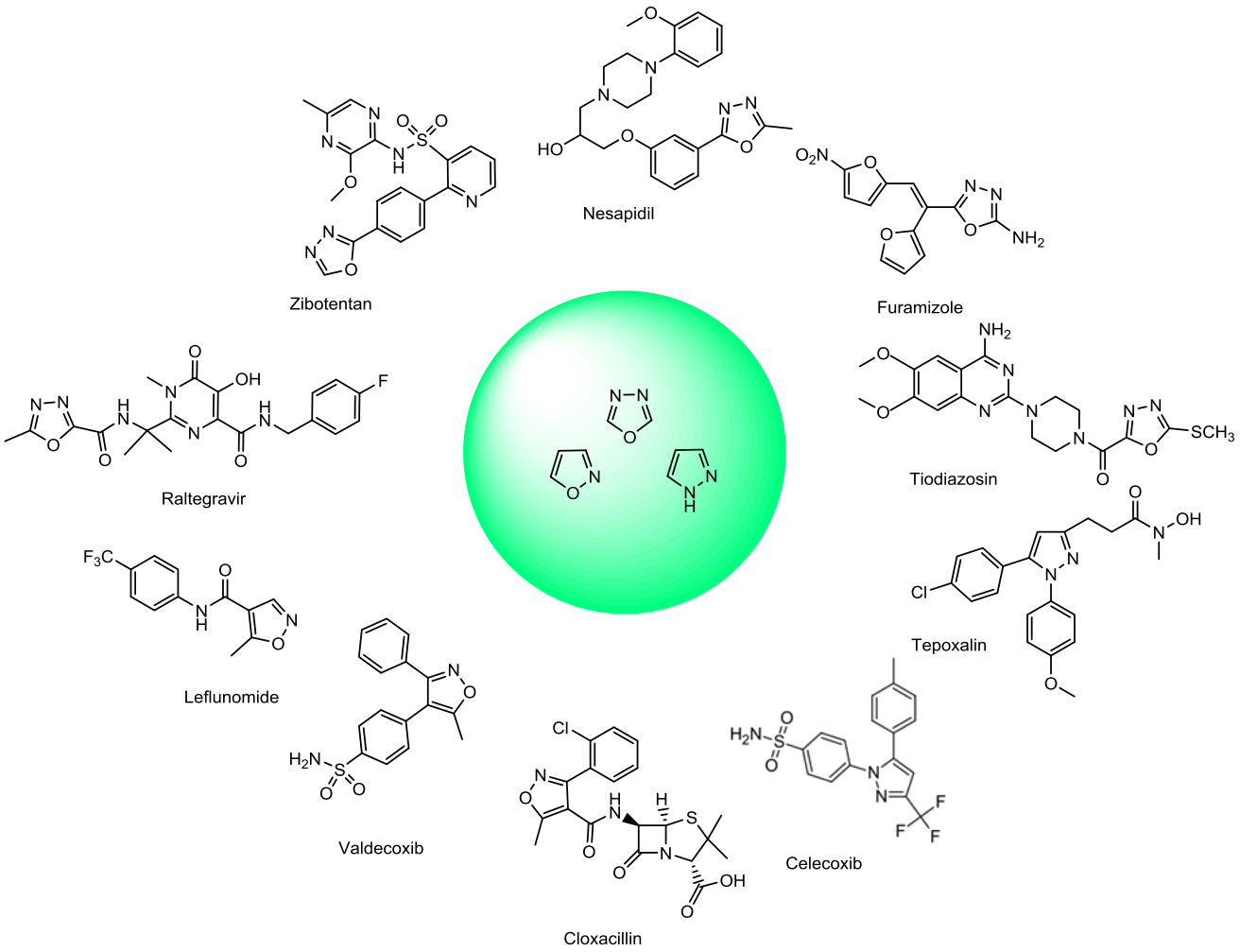


Fig. 1 Drugs containing pyrazole, isoxazole, and oxadiazole motifs

[13], antifungal [14], antitubercular [15], and cytotoxic [16] activities. Besides, many commercial drugs such as zibotentan [17], ataluren [18], raltegravir [19], tiodazosin [20], nesapidil [21], and furamizole [22] possess oxadiazole scaffold as major structural unit. They have also attracted interest in medicinal chemistry as surrogates for carboxylic acids, esters, and carboxamides [23]. On the other hand, a number of bioactive natural products and therapeutics are based on pyrazole and isoxazole motifs viz., celecoxib, tepoxalin, rimonabant, valdecoxib, leflunomide, and cloxacillin. In addition, pyrazoles and isoxazoles exhibit antibacterial [24], antioxidant [25], antidepressant [26], anticancer [27], antifungal [28], and anti-inflammatory [29] activities.

With this background heteroaromatic compounds have attracted researchers to synthesize these compounds by employing new innovative methods and techniques and to study their biological properties. Ultrasonic assisted organic synthesis, a green synthetic approach is a powerful technique to accelerate organic reactions [30, 31]. This can be considered as a processing aid in terms of energy conservation, waste minimization, more convenient and easily controlled compared to conventional heating. A large number of organic reactions can be carried out in high yields, shorter reaction time, and milder conditions under ultrasound irradiation. The characteristic feature of ultrasonicator is that the mechanical energy in the form of high-intensity, high-frequency sound waves is transferred to the reaction mixture. This results in the generation and the collapse of large number of minute bubbles throughout the mixture. This effect, which is known as cavitation, is responsible for the quick and thorough stirring of reaction mixture [32–35]. It can enhance chemical reaction, mass transfer. and offer potential for shorter reaction cycles which are inaccessible by conventional methods. Inspired by the remarkable biopotency of above mentioned heterocycles and in continuation of our interest in the synthesis of a variety of biologically active heterocycles [36–38], it is proposed to synthesize the molecules having two different pharmacophore units and to study their biological activity (Fig. 2).

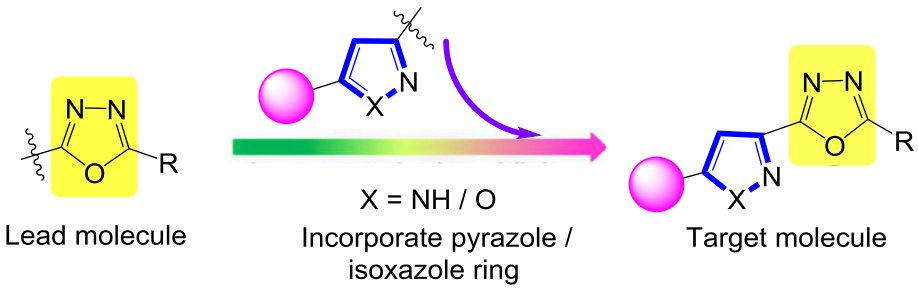


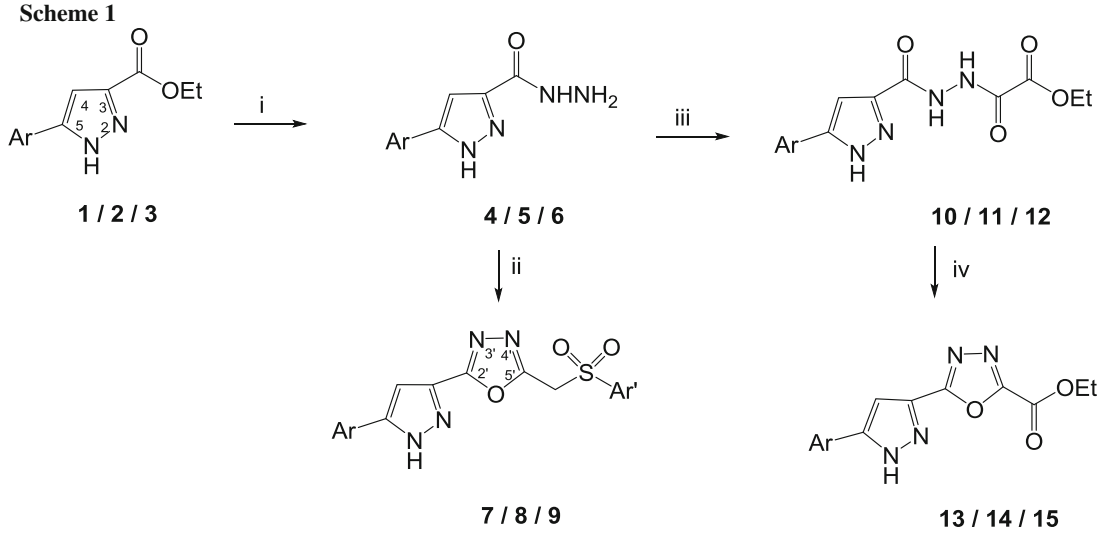
Fig. 2 Design strategy of the target compounds

Results and discussion

Chemistry

The synthetic route to prepare a new class of pyrazolyl/isoxazolyl 1,3,4-oxadiazoles was synthesized from the synthetic intermediates pyrazolyl/isoxazolyl carboxylates by exploiting ester functionality adopting conventional and ultrasonication methodologies as illustrated in Schemes 1, 2 and Table 1. The reaction of ethyl 5-(furan-2-yl)-1*H*-pyrazole-3-carboxylate (**1**), ethyl 5-(5-bromothiophen-2-yl)-1*H*-pyrazole-3-carboxylate (**2**), and ethyl 5-(pyridin-4-yl)-1*H*-pyrazole-3-carboxylate (**3**) with hydrazine hydrate in methanol afforded 5-(furan-2-yl)-1*H*-pyrazole-3-carbohydrazide (**4**), 5-(5-bromo-thiophen-2-yl)-1*H*-pyrazole-3-carbohydrazide (**5**), 5-(pyridin-4-yl)-1*H*-pyrazole-3-carbohydrazide (**6**), respectively. In the ^{1}H NMR spectra of **4**, **5**, and **6** the absence of triplet and quartet due to ethoxy moiety and presence of two broad singlets at δ = 9.69, 9.79, 9.71 ppm (NH) and at 4.42, 4.48, 4.37 ppm (NH_2) indicated the formation of acid hydrazide. The cyclocondensation of acid hydrazide 4, 5, and 6 with arylsulfonylacetic acid in the presence of phosphorus oxychloride produced 2-[5-(furan-2-yl)-1*H*-pyrazol-3-yl]-5-arylsulfonylmethyl-1,3,4-oxadiazole (**7**), 2-[5-(5-bromothiophen-2-yl)-1*H*-pyrazol-3-yl]-5-arylsulfonyl-methyl-1,3,4-oxadiazole (**8**), and 2-[5-(pyridin-4-yl)-1*H*-pyrazol-3-yl]-5-arylsulfonyl-methyl-1,3,4-oxadiazole (**9**), respectively. The ^{1}H NMR spectra of **7a**, **8a**, and **9a** displayed a sharp singlet at 4.15, 4.23, 4.12 ppm (CH_2) and a broad singlet at 11.74,

Scheme 1



i) $NH_2NH_2.H_2O$ / MeOH / Δ or)))
ii) $Ar'SO_2CH_2COOH$ / $POCl_3$ / Δ or)))
iii) Ethyl 2-chloro-2-oxoacetate / THF / r.t. or)))
iv) $POCl_3$ / Δ or)))

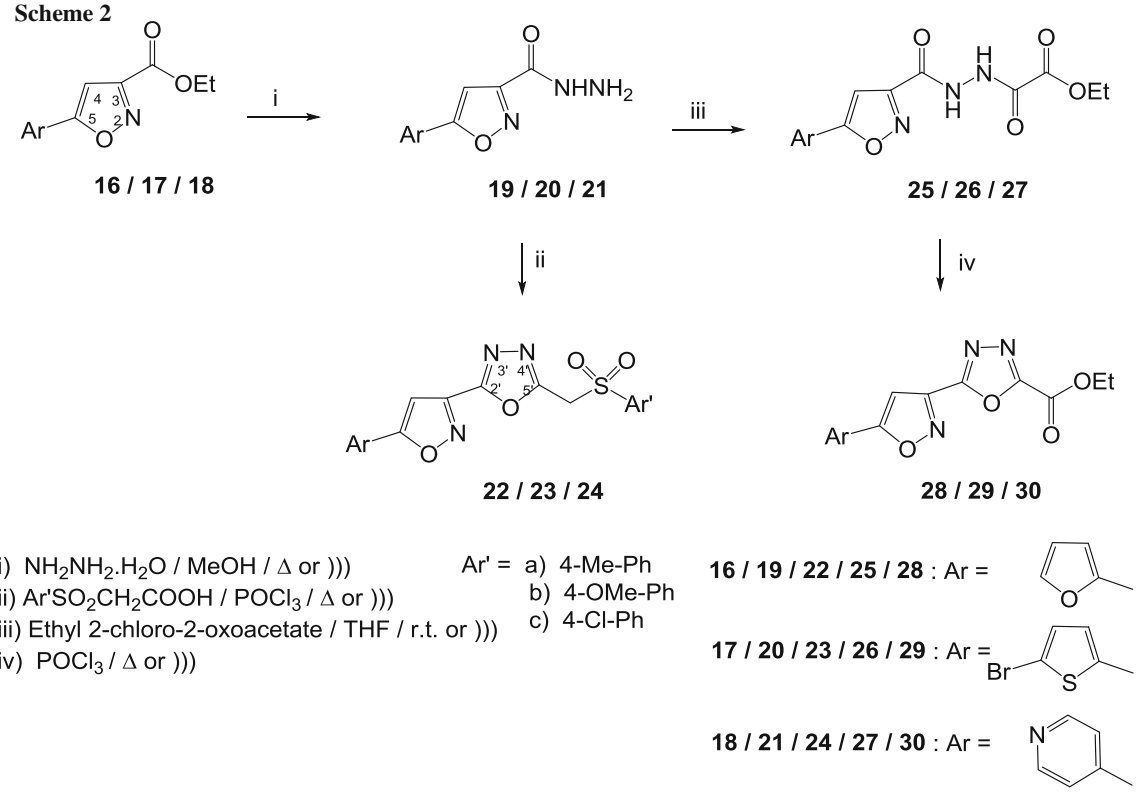
Ar' = a) 4-Me-Ph
b) 4-OMe-Ph
c) 4-Cl-Ph

1 / 4 / 7 / 10 / 13 : Ar =

2 / 5 / 8 / 11 / 14 : Ar =

3 / 6 / 9 / 12 / 15 : Ar =

Scheme 2



11.93, 11.82 ppm (NH), respectively. Besides, a singlet due to C_4–H of pyrazole ring appeared at downfield region and merged with aromatic protons. The signals due to NH disappeared on deuteration.

On the other hand, the treatment of compounds **4**, **5**, and **6** with ethyl 2-chloro-2-oxoacetate in tetrahydrofuran led to the formation of ethyl 2-[2-[5-(furan-2-yl)-1*H*-pyrazole-3-carbonyl]hydrazinyl]-2-oxoacetate (**10**), ethyl 2-[2-[5-(5-bromothiophen-2-yl)-1*H*-pyrazole-3-carbonyl]hydrazinyl]-2-oxoacetate (**11**), and ethyl 2-[2-[5-(pyridin-4-yl)-1*H*-pyrazole-3-carbonyl]hydrazinyl]-2-oxoacetate (**12**), respectively. The ^{1}H NMR spectra of **10**, **11**, and **12** exhibited a triplet at 1.21, 1.24, 1.26 ppm and a quartet at 4.22, 4.26, 4.18 ppm due to methyl and methylene protons of ester group and a singlet due to C_4–H of pyrazole appeared at much downfield region and merged with aromatic protons. Moreover, three broad singlets observed at 11.86, 11.82, 11.94; 9.80, 9.91, 9.78, and 9.98, 10.08, 9.84 ppm accounted for NH of pyrazole, CONH, and NHCOCOOEt, respectively. The signals of highly acidic protons disappeared when D_2O was added. Furthermore, the cyclocondensation of compounds **10**, **11**, and **12** with $POCl_3$ resulted in ethyl 5-[5-(furan-2-yl)-1*H*-pyrazol-3-yl]-1,3,4-oxadiazole-2-carboxylate (**13**), ethyl 5-[5-(5-bromothiophen-2-yl)-1*H*-pyrazol-3-yl]-1,3,4-oxadiazole-2-carboxylate (**14**), and ethyl 5-[5-(pyridin-4-yl)-1*H*-pyrazol-3-yl]-1,3,4-oxadiazole-2-carboxylate (**15**) (Scheme 3). The ^{1}H NMR spectra of **13**, **14**, and **15** showed a triplet at 1.34, 1.28, 1.33 ppm (CH_3) and a quartet at 4.27, 4.31, 4.34 ppm (OCH_2) in addition to the signals of aromatic protons. A broad singlet was also observed at 11.98, 11.80, 11.91 ppm (NH), which disappeared on deuteration.

Adopting similar methodology the condensation of ethyl 5-(furan-2-yl)isoxazole-3-carboxylate (**16**), ethyl 5-(5-bromothiophen-2-yl)isoxazole-3-carboxylate (**17**), and ethyl 5-(pyridin-4-yl)isoxazole-3-carboxylate (**18**) with hydrazine hydrate in methanol provided 5-(furan-2-yl)isoxazole-3-carbohydrazide (**19**), 5-(5-bromothiophen-2-yl)isoxazole-3-carbohydrazide (**20**), and 5-(pyridin-4-yl)isoxazole-3-carbohydrazide (**21**), respectively. The absence of signals due to ester group in ^{1}H NMR spectra of **19**, **20**, and **21** confirmed the formation of acid hydazide. Two broad singlets were also observed at 9.98, 10.02, 9.91 ppm, and 4.54, 4.62, 4.58 ppm due to NH and NH_2, respectively, which disappeared on deuteration.

Moreover, 2-[5-(furan-2-yl)-isoxazol-3-yl]-5-arylsulfonylmethyl-1,3,4-oxadiazole (**22**), 2-[5-(5-bromothiophen-2-yl)-isoxazol-3-yl]-5-arylsulfonylmethyl-1,3,4-oxadiazole (**23**), and 2-[5-(pyridin-4-yl)-isoxazol-3-yl]-5-arylsulfonylmethyl-1,3,4-oxadiazole (**24**) were obtained by cyclocondensation of acid hydrazide **19**, **20**, and **21** with arylsulfonyl acetic acid in the presence of $POCl_3$. The ^{1}H

Table 1 Synthesis of pyrazolyl/isoxazolyl 1,3,4-oxadiazole derivatives **7**–**15** and **22**–**30** under conventional and ultrasonication methods

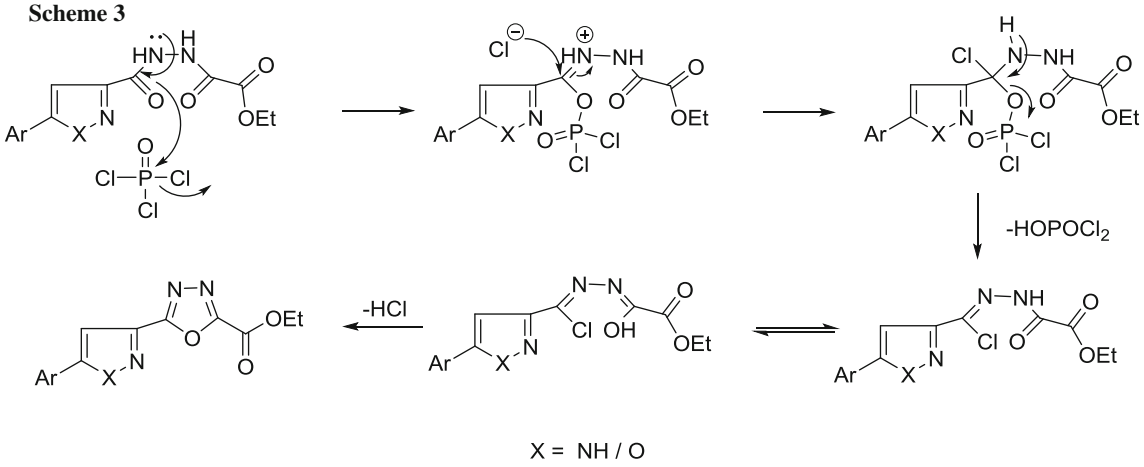
Product	Time/h	Time/min	Yield/%	
	Conventional	Ultrasound	Conventional	Ultrasound
7a	6.5	38	74	91
7b	6	30	72	94
7c	7.5	40	69	92
8a	8	43	66	89
8b	7.5	46	63	85
8c	9	50	68	90
9a	7	35	65	86
9b	6.5	31	60	82
9c	8.5	37	68	87
10	10	48	70	89
11	13	40	73	93
12	16	45	67	84
13	22	90	61	82
14	22	80	72	90
15	24	95	64	94
22a	4.5	21	62	83
22b	6	33	66	95
22c	5.5	28	63	86
23a	5	23	68	80
23b	6.5	27	72	94
23c	7	35	68	89
24a	5	24	62	86
24b	6	26	71	88
24c	5.5	30	73	92
25	12	25	64	83
26	10	36	69	91
27	14	40	58	79
28	20	90	71	90
29	22	85	69	87
30	24	75	67	85

NMR spectra of **22a**, **23a**, **24a** displayed a singlet at 4.18, 4.21, and 4.22 ppm (CH_2), respectively. In addition, a singlet due to C_4–H of isoxazole appeared at downfield region and merged with aromatic protons. However, the resultant acid hydrazide **19**, **20**, and **21** was treated with ethyl 2-chloro-2-oxoacetate followed by THF gave ethyl 2-[2-[5-(furan-2-yl)isoxazole-3-carbonyl]hydrazinyl]-2-oxoacetate (**25**), ethyl 2-[2-[5-(5-bromothiophen-2-yl)isoxazole-3-carbonyl]hydrazinyl]-2-oxoacetate (**26**), and ethyl 2-[2-[5-(pyridin-4-yl)isoxazole-3-carbonyl]hydrazinyl]-2-oxoacetate (**27**). The ^{1}H NMR spectra of **25**, **26**, and **27** presented a triplet at 1.24, 1.26, 1.20 ppm (CH_3), a quartet at 4.19, 4.24, 4.17 ppm (OCH_2), and two broad singlets at 9.96, 9.94, 9.89 ppm (CONH) and 10.29, 10.05, 10.07 ppm (NHCOCOOEt). The signals due to NH disappeared on deuteration. The cyclized products ethyl 5-[5-(furan-2-yl)isoxazol-3-yl]-1,3,4-oxadiazole-2-carboxylate (**28**), ethyl 5-[5-(5-bromothiophen-2-yl)isoxazol-3-yl]-1,3,4-oxadiazole-2-carboxylate (**29**), and ethyl 5-[5-(pyridin-4-yl)isoxazol-3-yl]-1,3,4-oxadiazole-2-carboxylate (**30**) were synthesized by the cyclocondensation of diacyl hydrazide **25**, **26**, and **27** in the presence of $POCl_3$. The ^{1}H NMR spectra of **28**, **29**, and **30** showed a triplet and a quartet at 1.39, 1.32, 1.35 ppm and 4.35, 4.25, 4.39 ppm due to CH_3 and OCH_2 groups apart from signals due to C_4–H of isoxazole and other aromatic protons. It was observed that target compounds were obtained in shorter reaction times and in higher yields under ultrasonication than in conventional method. The structures of all the target compounds were further ascertained by IR, ^{13}C NMR, mass, and microanalyses.

Antioxidant activity

The observed data on the antioxidant activity of the test compounds and the standard drug are shown in Tables 2, 3 and 4 and Fig. 3. The results revealed that compounds **7b**, **9b**, **22b**, and **24b** showed greater radical scavenging activity in all the three methods when compared with the standard drug ascorbic acid. The compounds **7a**, **8a**, **8b**, **9a**, **22a**, **23a**, **23b**, **24a** exhibited good activity, whereas **10**, **11**, **12**, **25**, **26**, **27**, **28**, **30** displayed moderate activity. On the other hand, the compounds **7c**, **13**, **14**, **15**, **22c**, **29** exhibited low activity. However, the other compounds showed no activity. The structure–activity relationship indicated that isoxazole derivatives exhibited higher radical scavenging activity than pyrazole derivatives. Moreover, it was observed that electron donating substituents on the phenyl ring increases the activity. This may be due to mesomeric effect of methoxy group and inductive effect of methyl substituent. It was also noticed that with increasing electron donating effect the antioxidant activity increases. In fact, methoxy-substituted compounds displayed higher activity than methyl-substituted ones. Besides the compounds having chloro and bromo substituents exhibited least activity which indicated that with increasing electron withdrawing effect the activity decreases. On the other hand, the compounds **10**, **11**, **12**, **25**, **26**, and **27** exhibited higher activity than compounds **13**, **14**, **15**, **28**, **29**, and **30**. This may be due to the increasing number of chromophoric groups. In general, pyrazole in combination with furan/pyridine and isoxazole in combination with furan/pyridine displayed excellent activity than the thiophene-linked compounds. The free radical scavenging activity of the compounds **7b**, **9b**, **22b**, and **24b** was measured at different concentrations and monitored the change in absorbance at 10, 20, and 30 min in DPPH method (Table 5). It was perceived that at these 10-min intervals the values are very close and the results exemplified that the antioxidant

Scheme 3



activity is independent of time. The IC_{50} value of the standard drug ascorbic acid in DPPH method was found to be 17.03 μg/cm,[3] whereas IC_{50} values of compounds **7b**, **9b**, **22b**, and **24b** were found to be 16.69, 16.88, 16.16, and 16.41 μg/cm[3], respectively. It was also observed that radical scavenging activity increases with increase in concentration in all the three methods.

Statistical analysis

All experiments are performed in triplicate (n = 3), and an ANOVA test (Microsoft Excel) is used to compare the mean values across compounds and concentrations. The results represented mean ± standard deviation (SD) of three replicated determinations. The descriptive analysis is supported by the statistical analysis. The following inferences are supported through ANOVA analysis. Since the p value of rows (compounds) is less than 0.05 (α) cannot reject the null hypothesis, and so we conclude (with 95% confidence) that there is significant difference in radical scavenging activity exhibited by the compounds for different concentrations. Since the p value of columns (concentrations) is less than 0.05 (α) cannot reject the null hypothesis, and so we conclude (with 95% confidence) that there is significant difference in radical scavenging activity displayed across the compounds. Besides, the p value (interactions) is less than 0.05, indicating that there are significant differences in the interaction between compounds and concentrations.

Anti-inflammatory activity

The results (Table 6) indicated that the compounds **7b**, **9b**, **22b**, and **24b** showed significant anti-inflammatory activity. However, **22b** displayed anti-inflammatory activity equal to the standard drug phenylbutazone. The structure–activity relationship of the synthesized compounds revealed that isoxazolyl oxadiazoles exhibited greater activity than pyrazolyl oxadiazoles. In general, it was observed that electron donating methyl and methoxy substituents on the phenyl ring enhance the anti-inflammatory activity.

Conclusion

In summary, a series of new heteroaryl pyrazolyl/isoxazolyl 1,3,4-oxadiazole derivatives were designed and synthesized in good yields and in shorter reaction times adopting a green approach—ultrasound irradiation. The entire series of the compounds were characterized by IR, NMR, and mass spectral parameters. The title compounds were evaluated for their antioxidant and anti-inflammatory activities. The activity results showed that the methoxy substituted 1,3,4-oxadiazoles is a promising template for antioxidant and anti-inflammatory activities. It was also observed that the furanyl/pyridinyl pyrazolyl/isoxazolyl 1,3,4-oxadiazole displayed promising antioxidant and anti-inflammatory activities than the thiophenyl/pyrazolyl/isoxazolyl 1,3,4-oxadiazoles. Moreover, compounds having electron donating groups on the phenyl ring enhances the activity, when compared with the electron withdrawing groups. As a result of this study, compounds **7b**, **9b**, **22b**, and **24b** were identified as lead compounds for both activities and may be used for further studies.

Experimental

All the chemicals were purchased from commercial sources and used without further purification. Ultrasonication was performed in a Bandelin Sonorex RK 102H ultrasonic bath operating at frequency of 35 kHz. Melting points were determined in open capillaries on a Mel-Temp apparatus.

Table 2 The in vitro antioxidant activity of compounds **7–15** and **22–30** in DPPH method

Compound	Concentration/μg cm^{-3}				IC_{50}/μmol cm^{-3}
	25 Mean ± SD	50 Mean ± SD	75 Mean ± SD	100 Mean ± SD	Mean ± SD
7a	69.28 ± 0.19	73.85 ± 0.13	76.06 ± 0.21	78.56 ± 0.15	18.04 ± 0.15
7b	74.87 ± 0.24	78.03 ± 1.26	79.15 ± 0.23	82.34 ± 0.10	16.69 ± 0.24
7c	48.76 ± 0.10	52.15 ± 0.30	56.30 ± 0.31	59.33 ± 1.24	25.63 ± 0.30
8a	63.96 ± 0.31	68.38 ± 0.34	71.06 ± 0.28	74.26 ± 0.24	19.54 ± 0.31
8b	65.09 ± 0.16	69.67 ± 0.23	71.91 ± 0.27	75.68 ± 1.31	19.20 ± 0.28
8c	–	–	–	–	–
9a	68.94 ± 0.30	72.13 ± 0.27	74.41 ± 0.26	78.35 ± 0.34	18.13 ± 0.19
9b	74.04 ± 0.23	77.25 ± 0.32	77.86 ± 0.32	81.06 ± 0.26	16.88 ± 0.24
9c	–	–	–	–	–
10	58.81 ± 1.23	64.67 ± 1.81	68.81 ± 0.30	69.14 ± 0.23	21.25 ± 0.12
11	56.95 ± 0.27	60.84 ± 0.24	64.71 ± 0.30	66.28 ± 0.26	21.94 ± 0.25
12	57.25 ± 0.32	62.88 ± 0.18	67.17 ± 1.71	68.96 ± 0.31	21.83 ± 0.30
13	53.26 ± 0.29	56.74 ± 0.19	61.28 ± 0.28	62.65 ± 0.12	23.46 ± 0.29
14	44.37 ± 1.72	49.53 ± 0.30	53.35 ± 0.19	57.92 ± 0.32	50.47 ± 0.31
15	52.93 ± 0.32	55.70 ± 0.25	59.12 ± 0.27	61.05 ± 1.90	23.61 ± 1.84
22a	72.08 ± 0.24	76.11 ± 1.51	77.30 ± 1.37	80.67 ± 0.20	17.34 ± 0.31
22b	77.31 ± 0.23	79.23 ± 0.13	82.72 ± 0.14	85.21 ± 0.12	16.16 ± 0.17
22c	49.09 ± 0.26	53.11 ± 0.21	57.61 ± 1.80	60.17 ± 0.30	25.46 ± 0.29
23a	66.38 ± 0.30	71.21 ± 0.20	73.82 ± 0.24	76.34 ± 0.28	18.83 ± 0.24
23b	67.61 ± 1.41	70.94 ± 0.30	74.19 ± 0.3.6	77.10 ± 1.91	18.48 ± 1.87
23c	–	–	–	–	–
24a	71.73 ± 0.31	75.08 ± 0.18	76.81 ± 0.31	79.12 ± 0.34	17.42 ± 0.24
24b	76.16 ± 0.32	78.94 ± 1.36	81.54 ± 0.21	84.05 ± 0.31	16.41 ± 0.19
24c	–	–	–	–	–
25	62.07 ± 0.23	66.30 ± 0.35	70.08 ± 1.52	72.40 ± 0.21	20.13 ± 0.30
26	57.03 ± 0.29	61.04 ± 0.27	65.93 ± 0.32	67.74 ± 0.34	21.91 ± 0.27
27	61.54 ± 0.30	64.14 ± 0.32	69.40 ± 0.29	70.19 ± 0.17	20.31 ± 0.22
28	55.70 ± 1.41	59.62 ± 0.30	62.33 ± 0.31	66.10 ± 0.19	22.44 ± 0.23
29	45.63 ± 0.18	50.71 ± 0.27	54.92 ± 0.26	58.89 ± 0.25	49.29 ± 0.26
30	55.61 ± 0.26	57.59 ± 0.30	62.21 ± 0.12	63.97 ± 0.21	22.47 ± 0.21
Ascorbic acid	73.37 ± 0.31	76.86 ± 0.24	78.79 ± 0.34	80.78 ± 0.32	17.03 ± 0.19
Blank	–	–	–	–	–

(–) no activity, (±) standard deviation

The IR spectra were recorded on a Thermo Nicolet IR 200 FT-IR spectrometer as KBr pellets and the wave numbers were given in cm^{-1}. The ^{1}H NMR spectra were recorded in DMSO-d_6 on a Bruker-400 spectrometer (400 MHz). The ^{13}C NMR spectra were recorded in DMSO-d_6 on a Bruker spectrometer operating at 100 MHz. All chemical shifts are reported in δ (ppm) using TMS as an internal standard. The high-resolution mass spectra were recorded on micromass Q-TOF micromass spectrometer using electrospray ionization. The microanalyses were performed on a Perkin–Elmer 240C elemental analyzer. The progress of the reaction was monitored by TLC using silica gel plates (silica gel 60 F254 0.25 mm) and components were visualized by observation under UV light (254 and 365 nm). The antioxidant activity was carried out using Shimadzu UV-2450 spectrophotometer. The starting compounds ethyl 5-(heteroaryl)-1*H*-pyrazole-3-carboxylates **1–3**, 5-(heteroaryl)-1*H*-pyrazole-3-carbohydrazides **4–6**, ethyl 5-(heteroaryl)isoxazole-3-carboxylates **16–18**, and 5-(heteroaryl)-1*H*-isoxazole-3-carbohydrazides **19–21** were prepared as per the literature precedents [39].

Table 3 The in vitro antioxidant activity of compounds **7–15** and **22–30** in H_2O_2 method

Compound	Concentration/μg cm^{-3}				IC_{50}/μmol cm^{-3}
	25 Mean ± SD	50 Mean ± SD	75 Mean ± SD	100 Mean ± SD	Mean ± SD
7a	72.32 ± 1.21	75.69 ± 0.45	77.85 ± 0.55	79.73 ± 0.63	17.28 ± 0.83
7b	77.08 ± 0.71	79.17 ± 0.57	81.25 ± 0.24	83.79 ± 0.87	16.21 ± 0.32
7c	49.56 ± 0.66	54.50 ± 0.61	56.53 ± 0.69	59.42 ± 0.21	25.22 ± 1.01
8a	65.22 ± 0.79	69.66 ± 0.26	71.67 ± 0.31	74.18 ± 0.92	19.16 ± 1.23
8b	66.96 ± 0.44	70.97 ± 0.29	73.45 ± 0.43	75.79 ± 0.71	18.66 ± 0.41
8c	–	–	–	–	–
9a	70.49 ± 0.68	74.17 ± 0.25	76.52 ± 1.27	77.91 ± 1.14	17.73 ± 0.73
9b	76.91 ± 1.14	79.84 ± 0.68	80.79 ± 0.75	83.35 ± 0.74	16.25 ± 0.60
9c	–	–	–	–	–
10	60.27 ± 0.78	65.15 ± 0.29	66.72 ± 0.32	70.83 ± 0.60	20.74 ± 0.41
11	57.30 ± 0.40	61.91 ± 0.26	63.85 ± 0.49	66.14 ± 0.23	21.81 ± 0.51
12	59.62 ± 0.48	64.02 ± 0.42	65.27 ± 0.37	69.51 ± 0.56	20.96 ± 0.66
13	53.47 ± 0.84	58.74 ± 0.22	59.18 ± 0.52	62.17 ± 2.5	23.37 ± 1.03
14	46.83 ± 0.51	51.64 ± 1.90	53.73 ± 0.24	57.47 ± 1.07	48.41 ± 0.43
15	52.10 ± 0.31	56.46 ± 0.32	58.04 ± 0.30	61.70 ± 0.92	23.99 ± 0.30
22a	74.37 ± 0.42	77.25 ± 0.98	79.16 ± 0.37	82.43 ± 0.64	16.80 ± 0.59
22b	78.23 ± 0.68	82.73 ± 0.39	83.94 ± 0.42	85.07 ± 0.33	15.97 ± 0.28
22c	50.71 ± 0.54	55.31 ± 0.21	57.60 ± 0.57	60.16 ± 0.69	24.64 ± 0.72
23a	67.24 ± 0.80	71.74 ± 0.86	73.50 ± 0.95	76.57 ± 0.74	18.59 ± 0.31
23b	69.15 ± 0.92	72.53 ± 1.06	74.01 ± 0.31	77.80 ± 0.65	18.07 ± 0.46
23c	–	–	–	–	–
24a	73.56 ± 1.08	76.31 ± 0.72	78.53 ± 0.30	80.27 ± 0.24	16.99 ± 0.48
24b	77.74 ± 0.40	81.36 ± 0.24	83.08 ± 0.51	84.22 ± 0.99	16.07 ± 0.67
24c	–	–	–	–	–
25	63.78 ± 0.67	68.77 ± 1.34	69.71 ± 0.38	73.67 ± 0.36	19.59 ± 0.81
26	58.42 ± 0.55	62.46 ± 0.30	64.52 ± 0.26	67.88 ± 0.47	21.39 ± 0.46
27	62.93 ± 0.47	66.38 ± 0.19	68.10 ± 0.26	71.46 ± 0.42	19.86 ± 0.37
28	56.65 ± 0.77	59.07 ± 1.36	61.60 ± 0.56	66.62 ± 0.32	22.06 ± 0.59
29	47.20 ± 1.24	52.82 ± 1.07	54.41 ± 0.43	58.15 ± 0.61	47.33 ± 0.20
30	54.83 ± 0.35	58.13 ± 0.24	60.76 ± 1.03	64.55 ± 0.29	22.79 ± 1.25
Ascorbic acid	75.17 ± 0.76	78.23 ± 0.35	80.28 ± 0.42	82.34 ± 1.32	16.62 ± 0.27
Blank	–	–	–	–	–

(–) no activity, (±) standard deviation

General procedures for the synthesis of 5-(furan-2-yl)-1*H*-pyrazole-3-carbohydrazide (4), 5-(5-bromothiophen-2-yl)-1*H*-pyrazole-3-carbohydrazide (5), and 5-(pyridin-4-yl)-1*H*-pyrazole-3-carbohydrazide (6)

Conventional method

A solution of ethyl 5-(furan-2-yl)-1*H*-pyrazole-3-carboxylate (**1**), ethyl 5-(5-bromothiophen-2-yl)-1*H*-pyrazole-3-carboxylate (**2**), or ethyl 5-(pyridin-4-yl)-1*H*-pyrazole-3-carboxylate (**3**) (1.0 mmol) and hydrazine hydrate (2.0 mmol) in 3 cm^3 methanol were taken in a 100-cm^3 round bottomed flask fitted with reflux condenser and refluxed on a water bath for 4–6 h. It was cooled and the solid separated was filtered, dried, and recrystallized from methanol.

Ultrasonication method

Compound 1, 2, or 3 (1.0 mmol), hydrazine hydrate (2.0 mmol), and 4 cm^3 methanol were subjected to ultrasound irradiation for 42–55 min. The progress of the reaction was monitored by TLC. After completion of the reaction, the contents were cooled and poured onto crushed ice. The solid separated was filtered on a Buchner funnel,

Table 4 The in vitro antioxidant activity of compounds **7–15** and **22–30** in NO method

Compound	Concentration/μg cm^{-3}				IC_{50}/μmol cm^{-3}
	25 Mean ± SD	50 Mean ± SD	75 Mean ± SD	100 Mean ± SD	Mean ± SD
7a	75.71 ± 0.26	78.53 ± 1.06	80.93 ± 0.80	82.28 ± 0.65	16.51 ± 0.46
7b	79.53 ± 0.47	81.78 ± 0.19	84.86 ± 0.92	86.20 ± 0.42	15.71 ± 0.37
7c	55.31 ± 0.05	60.71 ± 0.03	61.160.01	63.60 ± 0.28	22.59 ± 0.26
8a	70.20 ± 0.40	73.18 ± 0.24	75.07 ± 0.51	77.30 ± 0.99	17.80 ± 0.67
8b	71.28 ± 0.48	75.55 ± 0.72	76.16 ± 1.08	78.05 ± 0.24	17.53 ± 0.30
8c	–	–	–	–	–
9a	74.23 ± 0.20	76.69 ± 1.07	79.47 ± 1.24	80.93 ± 0.61	16.83 ± 0.43
9b	78.85 ± 0.41	81.20 ± 0.95	83.38 ± 0.66	84.66 ± 0.35	15.85 ± 0.29
9c	–	–	–	–	–
10	65.87 ± 0.57	70.62 ± 0.39	71.68 ± 0.42	73.35 ± 0.33	18.97 ± 0.28
11	62.20 ± 0.95	67.49 ± 0.21	68.63 ± 0.68	70.32 ± 0.69	20.09 ± 0.72
12	64.59 ± 0.31	69.89 ± 0.86	70.90 ± 0.54	71.63 ± 0.74	19.35 ± 0.31
13	58.62 ± 0.41	63.50 ± 0.35	64.92 ± 0.74	66.57 ± 0.18	21.32 ± 1.12
14	52.12 ± 0.37	56.60 ± 0.52	58.85 ± 0.23	60.26 ± 0.29	23.98 ± 0.34
15	57.19 ± 0.59	62.67 ± 1.36	62.24 ± 0.77	65.30 ± 0.32	21.85 ± 0.56
22a	77.60 ± 0.58	80.15 ± 0.31	82.11 ± 0.92	84.32 ± 0.26	16.10 ± 0.46
22b	81.65 ± 0.29	83.10 ± 0.32	85.69 ± 0.60	88.51 ± 0.41	15.30 ± 0.78
22c	56.83 ± 0.26	61.18 ± 0.49	62.71 ± 0.23	64.49 ± 0.51	21.99 ± 0.40
23a	72.14 ± 0.42	75.25 ± 0.37	77.27 ± 0.55	79.81 ± 0.34	17.32 ± 0.45
23b	73.57 ± 0.48	76.31 ± 0.71	78.62 ± 0.63	80.79 ± 0.27	16.99 ± 0.57
23c	–	–	–	–	–
24a	76.42 ± 0.69	79.04 ± 0.31	80.76 ± 0.92	83.52 ± 0.35	16.35 ± 0.29
24b	80.87 ± 0.56	82.63 ± 0.43	85.03 ± 0.66	87.43 ± 0.54	15.45 ± 0.25
24c	–	–	–	–	–
25	68.59 ± 0.34	72.33 ± 0.83	73.53 ± 1.26	76.85 ± 0.95	18.22 ± 0.70
26	63.14 ± 0.91	68.21 ± 0.60	69.52 ± 0.35	71.26 ± 0.43	19.79 ± 1.03
27	67.75 ± 0.27	71.40 ± 0.15	72.94 ± 0.17	74.17 ± 0.46	18.45 ± 0.43
28	60.97 ± 0.41	66.78 ± 0.32	67.80 ± 1.27	68.09 ± 0.73	20.50 ± 0.44
29	53.79 ± 0.68	58.05 ± 1.01	59.29 ± 0.75	61.55 ± 0.60	23.23 ± 0.22
30	59.41 ± 1.21	64.94 ± 0.66	66.31 ± 0.87	67.81 ± 0.25	21.04 ± 0.61
Ascorbic acid	78.36 ± 1.23	80.18 ± 1.14	82.23 ± 0.83	84.89 ± 0.67	15.95 ± 0.79
Blank	–	–	–	–	–

(–) no activity, (±) standard deviation

washed with cold water, dried, and recrystallized from methanol to get 4, 5, 6.

General procedures for the synthesis of compounds 7a–7c, 8a–8c, and 9a–9c

Conventional method

A solution of **4**, **5**, or **6** (1.0 mmol), arylsulfonylacetic acid (1.0 mmol), and 3 cm^3 $POCl_3$ was taken in a 100-cm^3 round-bottom flask fitted with reflux condenser carrying a calcium chloride guard-tube and refluxed for 6–9 h. The excess $POCl_3$ was removed under reduced pressure and the residue was poured onto crushed ice. The resulting precipitate was filtered, washed with saturated sodium bicarbonate solution, and then with water, dried, and purified by column chromatography (silica gel 60–120 mesh) using ethyl acetate-hexane (1:3) as eluent.

Ultrasonication method

A mixture of **4**, **5**, or **6** (1.0 mmol), arylsulfonylacetic acid (1.0 mmol), and 3 cm^3 phosphorus oxychloride was subjected to ultrasound irradiation at a frequency of 35 kHz for 30–50 min at 45 °C. After completion of the reaction, the excess phosphorus oxychloride was removed under

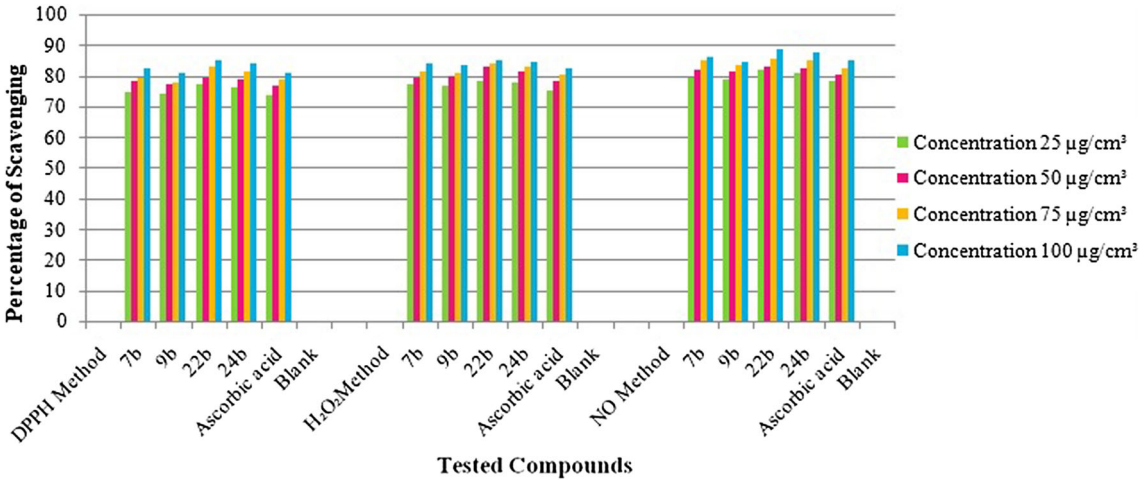


Fig. 3 The in vitro antioxidant activity of **7b**, **9b**, **22b**, and **24b** in all the three methods

Table 5 Antioxidant activity of the compounds **7b**, **9b**, **22b**, and **24b** at 10 min time intervals by DPPH scavenging method

Compound	10 min	20 min	30 min
7b	77.32	77.46	77.53
9b	75.80	76.04	76.21
22b	74.65	74.83	74.97
24b	79.27	79.38	79.52

reduced pressure and the residue was poured onto crushed ice. The separated solid was collected by filtration. It was washed with saturated sodium bicarbonate solution followed by water, dried, and purified by column chromatography (silica gel 60–120 mesh) using ethyl acetate-hexane (1:3) as eluent.

2-[5-(Furan-2-yl)-1*H*-pyrazol-3-yl]-5-(tosylmethyl)-1,3,4-oxadiazole (7a, $C_{17}H_{14}N_4O_4S$) White solid (0.33 g, 91%); m.p.: 176–178 °C; ^{1}H NMR (DMSO-d_6): δ = 2.55 (s, 3H, Ar–CH_3), 4.15 (s, 2H, CH_2), 6.69–8.07 (m, 8H, Ar–H), 11.74 (bs, 1H, pyrazole-NH) ppm; ^{13}C NMR (DMSO-d_6): δ = 21.4 (Ar–CH_3), 59.1 (CH_2), 104.2, 107.8, 114.3, 126.8, 131.2, 132.3, 134.3, 138.4, 141.5, 145.7, 156.8, 160.6, 162.5 ppm; IR (KBr): $\bar{\nu}$ = 1145, 1334 (SO_2), 1565 (C=N), 1600 (C=C), 3242 (NH) cm^{-1}; HRMS: *m/z* = 393.3736 ([M+Na]$^+$).

2-[5-(Furan-2-yl)-1*H*-pyrazol-3-yl]-5-[(4-methoxyphenyl)sulfonylmethyl]-1,3,4-oxadiazole (7b, $C_{17}H_{14}N_4O_5S$) White solid (0.36 g, 94%); m.p.: 187–189 °C; ^{1}H NMR (DMSO-d_6): δ = 3.95 (s, 3H, Ar–OCH_3), 4.21 (s, 2H, CH_2), 6.71–7.86 (m, 8H, Ar–H), 11.79 (bs, 1H, pyrazole-NH) ppm; ^{13}C NMR (DMSO-d_6): δ = 55.2 (Ar–OCH_3), 59.6 (CH_2), 104.9, 108.0, 114.7, 118.5, 130.1, 132.9, 133.6, 141.1, 145.2, 156.2, 156.4, 162.9, 164.2 ppm; IR (KBr): $\bar{\nu}$ = 1128, 1329 (SO_2), 1556 (C=N), 1610 (C=C), 3256 (NH) cm^{-1}; HRMS: *m/z* = 409.3710 ([M+Na]$^+$).

2-[5-(5-Bromothiophen-2-yl)-1*H*-pyrazol-3-yl]-5-[(4-chlorophenyl)sulfonylmethyl]-1,3,4-oxadiazole (7c, $C_{16}H_{11}ClN_4O_4S$) White solid (0.35 g, 92%); m.p.: 193–195 °C; ^{1}H NMR (DMSO-d_6): δ = 4.04 (s, 2H, CH_2), 6.91–8.01 (m, 8H, Ar–H), 11.96 (bs, 1H, pyrazole-NH) ppm; ^{13}C NMR (DMSO-d_6): δ = 60.2 (CH_2), 105.3, 108.2, 114.1, 128.2, 128.8, 133.1, 133.4, 138.1, 141.7, 146.5, 156.5, 160.2, 162.3 ppm; IR (KBr): $\bar{\nu}$ = 1122, 1325 (SO_2), 1560 (C=N), 1612 (C=C), 3227 (NH) cm^{-1}; HRMS: *m/z* = 413.7886 ([M+Na]$^+$).

2-[5-(5-Bromothiophen-2-yl)-1*H*-pyrazol-3-yl]-5-(tosylmethyl)-1,3,4-oxadiazole (8a, $C_{17}H_{13}BrN_4O_3S_2$) White solid (0.41 g, 89%); m.p.: 234–236 °C; ^{1}H NMR (DMSO-d_6): δ = 2.51 (s, 3H, Ar–CH_3), 4.23 (s, 2H, CH_2), 6.52–7.95 (m, 7H, Ar–H), 11.93 (bs, 1H, pyrazole-NH) ppm; ^{13}C NMR (DMSO-d_6): δ = 21.6 (Ar–CH_3), 59.5 (CH_2), 103.8, 113.5, 126.3, 128.7, 131.8, 132.5, 132.9, 135.7, 138.1, 143.7, 145.9, 160.9, 161.8 ppm; IR (KBr): $\bar{\nu}$ = 1134, 1337 (SO_2), 1587 (C=N), 1619 (C=C), 3263 (NH) cm^{-1}; HRMS: *m/z* = 488.3289 ([M+Na]$^+$).

2-[5-(5-Bromothiophen-2-yl)-1*H*-pyrazol-3-yl]-5-[(4-methoxyphenyl)sulfonylmethyl]-1,3,4-oxadiazole (8b, $C_{17}H_{13}BrN_4O_4S_2$) White solid (0.40 g, 85%); m.p.: 261–263 °C; ^{1}H NMR (DMSO-d_6): δ = 3.89 (s, 3H, Ar–OCH_3), 4.18 (s, 2H, CH_2), 6.47–7.93 (m, 7H, Ar–H), 11.87 (bs, 1H, pyrazole-NH) ppm; ^{13}C NMR (DMSO-d_6): δ = 55.8 (Ar–OCH_3), 60.9 (CH_2), 105.5, 113.8, 118.1, 128.0, 130.4, 132.3, 133.1, 133.8, 143.2, 145.3, 159.7, 161.4, 164.7 ppm; IR (KBr): $\bar{\nu}$ = 1136, 1331 (SO_2), 1584 (C=N), 1626 (C=C), 3210 (NH) cm^{-1}; HRMS: *m/z* = 504.3296 ([M+Na]$^+$).

Table 6 The in vivo anti-inflammatory activity of compounds **7–15** and **22–30**

Compound	Edema volume ml (± SD)[a]	Edema inhibition (%)[c]
7a	0.30 (0.02)[b]	56
7b	0.22 (0.01)[b]	68*
7c	0.47 (0.01)[b]	31
8a	0.40 (0.01)[b]	42
8b	0.38 (0.02)[b]	44
8c	0.53 (0.02)[b]	23
9a	0.33 (0.02)[b]	52
9b	0.23 (0.01)[b]	67
9c	0.57 (0.01)[b]	17
10	0.50 (0.01)[b]	28
11	0.61 (0.02)[b]	11
12	0.42 (0.01)[b]	39
13	0.43 (0.02)[b]	37
14	0.52 (0.02)[b]	24
15	0.45 (0.01)[b]	34
22a	0.24 (0.01)[b]	65
22b	0.19 (0.01)[b]	72*
22c	0.46 (0.01)[b]	33
23a	0.37 (0.01)[b]	46
23b	0.35 (0.02)[b]	49
23c	0.55 (0.02)[b]	20
24a	0.29 (0.02)[b]	57
24b	0.21 (0.02)[b]	70*
24c	0.60 (0.01)[b]	13
25	0.42 (0.01)[b]	39
26	0.59 (0.02)[b]	14
27	0.39 (0.01)[b]	43
28	0.29 (0.01)[b]	57
29	0.51 (0.01)[b]	26
30	0.42 (0.01)[b]	39
Phenylbutazone	0.19 (0.01)[b]	72*
Control	0.69 (0.02)	–

*Statistically significant ($p < 0.05$, Mann–Whitney)

[a]Edema volume was measured 3 h after carrageenan injection and expressed as mean ± standard deviation

[b]Control edema volume = 0.69 (0.02)

[c]At 100 mg/kg (p.o.) percent edema inhibition was calculated by comparing edema volume with that of the respective vehicle-treated control animals

2-[5-(5-Bromothiophen-2-yl)-1*H*-pyrazol-3-yl]-5-[(4-chlorophenyl)sulfonylmethyl]-1,3,4-oxadiazole (8c, $C_{16}H_{10}BrClN_4O_3S_2$) Pale yellow solid (0.43 g, 90%); m.p.: 268–270 °C; ^{1}H NMR (DMSO-d_6): δ = 4.09 (s, 2H, CH_2), 6.58–8.02 (m, 7H, Ar–H), 11.92 (bs, 1H, pyrazole-NH) ppm; ^{13}C NMR (DMSO-d_6): δ = 60.4 (CH_2), 105.8, 113.3, 127.7, 128.4, 129.5, 132.2, 132.8, 133.5, 138.6, 143.5, 145.8, 159.5, 162.6 ppm; IR (KBr): $\bar{\nu}$ = 1129, 1332 (SO_2), 1578 (C=N), 1621 (C=C), 3254 (NH) cm^{-1}; HRMS: *m/z* = 508.7459 ([M+Na]$^+$).

2-[5-(Pyridin-4-yl)-1*H*-pyrazol-3-yl]-5-(tosylmethyl)-1,3,4-oxadiazole (9a, $C_{18}H_{15}N_5O_3S$) White solid (0.32 g, 86%); m.p.: 181–183 °C; ^{1}H NMR (DMSO-d_6): δ = 2.58 (s, 3H, Ar–CH_3), 4.12 (s, 2H, CH_2), 6.61–8.20 (m, 9H, Ar–H), 11.82 (bs, 1H, pyrazole-NH) ppm; ^{13}C NMR (DMSO-d_6): δ = 21.1 (Ar–CH_3), 60.1 (CH_2), 104.3, 125.7, 126.6, 131.5, 132.4, 134.8, 136.1, 138.3, 145.6, 147.5, 160.3, 161.2 ppm; IR (KBr): $\bar{\nu}$ = 1140, 1320 (SO_2), 1572 (C=N), 1617 (C=C), 3236 (NH) cm^{-1}; HRMS: *m/z* = 404.3991 ([M+Na]$^+$).

2-[5-(Pyridin-4-yl)-1*H*-pyrazol-3-yl]-5-[(4-methoxyphenyl)-sulfonylmethyl]-1,3,4-oxadiazole (9b, $C_{18}H_{15}N_5O_4S$) White solid (0.32 g, 82%); m.p.: 197–199 °C; ^{1}H NMR (DMSO-d_6): δ = 3.91 (s, 3H, Ar–OCH_3), 4.26 (s, 2H, CH_2), 6.49–8.09 (m, 9H, Ar–H), 11.92 (bs, 1H, pyrazole-NH) ppm; ^{13}C NMR (DMSO-d_6): δ = 54.6 (Ar–OCH_3), 59.3 (CH_2), 104.7, 118.8, 125.9, 126.5, 131.9, 132.8, 136.8, 145.4, 147.3, 160.8, 161.5, 164.5 ppm; IR (KBr): $\bar{\nu}$ = 1138, 1324 (SO_2), 1553 (C=N), 1630 (C=C), 3250 (NH) cm^{-1}; HRMS: *m/z* = 420.3995 ([M+Na]$^+$).

2-[5-(5-Bromothiophen-2-yl)-1*H*-pyrazol-3-yl]-5-[(4-chlorophenyl)sulfonylmethyl]-1,3,4-oxadiazole (9c, $C_{17}H_{12}ClN_5O_3S$) Pale yellow solid (0.34 g, 87%); m.p.: 203–205 °C; ^{1}H NMR (DMSO-d_6): δ = 4.17 (s, 2H, CH_2), 6.73–8.24 (m, 9H, Ar–H), 11.89 (bs, 1H, pyrazole-NH) ppm; ^{13}C NMR (DMSO-d_6): δ = 59.8 (CH_2), 105.4, 125.2, 128.7, 129.5, 133.6, 134.7, 136.4, 138.5, 146.1, 147.8, 159.1, 162.4 ppm; IR (KBr): $\bar{\nu}$ = 1125, 1326 (SO_2), 1564 (C=N), 1629 (C=C), 3223 (NH) cm^{-1}; HRMS: *m/z* = 424.8139 ([M+Na]$^+$).

General procedures for the synthesis of compounds 10–12

Conventional method

The compound **4**, **5**, or **6** (1.5 mmol) was dissolved in 20 cm^3 dry tetrahydrofuran and ethyl 2-chloro-2-oxoacetate (1.8 mmol) was added dropwise. The mixture was stirred at room temperature for 13–16 h (monitored by TLC). Then, the reaction mixture was poured onto crushed ice and extracted with dichloromethane. The solvent was removed under reduced pressure and the resultant residue was purified by recrystallization from acetone/methanol.

Ultrasonication method

To a solution of **4**, **5**, or **6** (1.5 mmol) in 20 cm^3 THF, ethyl 2-chloro-2-oxoacetate (1.8 mmol) was added and kept under ultrasonication for 28–42 min. The progress of the

reaction was monitored by TLC. After completion of the reaction, the contents of the flask were poured onto crushed ice and extracted with dichloromethane. Removal of the solvent under vacuum gave a residue which was purified by recrystallization from acetone/methanol.

Ethyl 2-[2-[5-(furan-2-yl)-1*H*-pyrazole-3-carbonyl]hydrazinyl]-2-oxoacetate (10, $C_{12}H_{12}N_4O_5$) White solid (0.39 g, 89%); m.p.: 152–154 °C; ^{1}H NMR (DMSO-d_6): δ = 1.21 (t, 3H, CH_3, J = 7.2 Hz), 4.22 (q, 2H, OCH_2, J = 7.2 Hz), 7.04–7.68 (m, 4H, Ar–H), 9.80 (bs, 1H, NH), 9.98 (bs, 1H, NH), 11.86 (bs, 1H, pyrazole-NH) ppm; ^{13}C NMR (DMSO-d_6): δ = 14.3 (CH_3), 61.1 (CH_2), 106.4, 109.1, 115.3, 136.8, 143.5, 148.2, 155.7, 159.7 (NHCO), 164.3 (CO), 164.9 (CONH) ppm; IR (KBr): $\bar{\nu}$ = 1583 (C=N), 1618 (C=C), 1665 (CO–NH), 1732 (CO–O), 3244 (NH) cm^{-1}; HRMS: m/z = 315.2415 ([M+Na]$^+$).

Ethyl 2-[2-[5-(5-bromothiophen-2-yl)-1*H*-pyrazole-3-carbonyl]hydrazinyl]-2-oxoacetate (11, $C_{12}H_{11}BrN_4O_4S$) White solid (0.54 g, 93%); m.p.: 189–191 °C; ^{1}H NMR (DMSO-d_6): δ = 1.24 (t, 3H, CH_3, J = 7.1 Hz), 4.26 (q, 2H, OCH_2, J = 7.1 Hz), 6.94–7.65 (m, 3H, Ar–H), 9.91 (bs, 1H, NH), 10.08 (bs, 1H, NH), 11.82 (bs, 1H, pyrazole-NH) ppm; ^{13}C NMR (DMSO-d_6): δ = 14.5 (CH_3), 61.5 (CH_2), 106.8, 115.1, 129.4, 131.8, 136.3, 143.9, 148.6, 158.9 (NHCO), 164.1 (CO), 164.5 (CONH) ppm; IR (KBr): $\bar{\nu}$ = 1580 (C=N), 1610 (C=C), 1649 (CO–NH), 1738 (CO–O), 3271 (NH) cm^{-1}; HRMS: m/z = 410.1989 ([M+Na]$^+$).

Ethyl 2-[2-[5-(pyridin-4-yl)-1*H*-pyrazole-3-carbonyl]hydrazinyl]-2-oxoacetate (12, $C_{13}H_{13}N_5O_4$) White solid (0.38 g, 84%); m.p.: 158–160 °C; ^{1}H NMR (DMSO-d_6): δ = 1.26 (t, 3H, CH_3, J = 7.2 Hz), 4.18 (q, 2H, OCH_2, J = 7.2 Hz), 7.10–8.16 (m, 5H, Ar–H), 9.78 (bs, 1H, NH), 9.84 (bs, 1H, NH), 11.94 (bs, 1H, pyrazole-NH) ppm; ^{13}C NMR (DMSO-d_6): δ = 13.9 (CH_3), 60.9 (CH_2), 106.3, 129.5, 135.7, 136.1, 148.3, 148.7, 158.5 (NHCO), 164.5 (CO), 164.9 (CONH) ppm; IR (KBr): $\bar{\nu}$ = 1585 (C=N), 1615 (C=C), 1658 (CO–NH), 1716 (CO–O), 3210 (NH) cm^{-1}; HRMS: m/z = 326.2670 ([M+Na]$^+$).

General procedures for the synthesis of compounds 13–15

Conventional method

A mixture of **10**, **11**, or **12** (1.5 mmol) and 5 cm^3 $POCl_3$ was taken in a 100-cm^3 round-bottomed flask fitted with reflux condenser carrying a calcium chloride guard-tube and refluxed for 22–24 h (monitored by TLC). After completion of the reaction, the contents of the flask were cooled to room temperature and poured onto crushed ice. The separated solid was filtered, washed with saturated sodium bicarbonate solution followed by water, and dried. It was purified by column chromatography (silica gel 60–120 mesh) using ethyl acetate-hexane (1:3) as eluent.

Ultrasonication method

The compound **10**, **11**, or **12** (1.5 mmol) and 5 cm^3 $POCl_3$ were subjected to ultrasound irradiation at a frequency of 35 kHz for 80–95 min at 40 °C. The progress of the reaction was monitored by TLC. After completion of the reaction, the contents of the flask were cooled to room temperature and poured onto crushed ice. The separated solid was filtered, washed with saturated sodium bicarbonate solution followed by water, and dried. It was purified by column chromatography (silica gel 60–120 mesh) using ethyl acetate-hexane (1:3) as eluent.

Ethyl 5-[5-(furan-2-yl)-1*H*-pyrazol-3-yl]-1,3,4-oxadiazole-2-carboxylate (13, $C_{12}H_{10}N_4O_4$) White solid (0.33 g, 82%); m.p.: 141–142 °C; ^{1}H NMR (DMSO-d_6): δ = 1.34 (t, 3H, CH_3, J = 6.8 Hz), 4.27 (q, 2H, OCH_2, J = 6.8 Hz), 7.11–8.01 (m, 4H, Ar–H), 11.98 (bs, 1H, pyrazole-NH) ppm; ^{13}C NMR (DMSO-d_6): δ = 14.8 (CH_3), 61.2 (CH_2), 103.3, 108.8, 114.5, 131.7, 140.4, 144.9, 153.2, 159.0, 159.4 (CO), 160.7 ppm; IR (KBr): $\bar{\nu}$ = 1579 (C=N), 1623 (C=C), 1725 (CO–O), 3238 (NH) cm^{-1}; HRMS: m/z = 297.2269 ([M+Na]$^+$).

Ethyl 5-[5-(5-bromothiophen-2-yl)-1*H*-pyrazol-3-yl]-1,3,4-oxadiazole-2-carboxylate (14, $C_{12}H_9BrN_4O_3S$) White solid (0.49 g, 90%); m.p.: 173–175 °C; ^{1}H NMR (DMSO-d_6): δ = 1.28 (q, 3H, CH_3, J = 7.0 Hz), 4.31 (q, 2H, OCH_2, J = 7.0 Hz), 6.86–8.08 (m, 3H, Ar–H), 11.80 (bs, 1H, pyrazole-NH) ppm; ^{13}C NMR (DMSO-d_6): δ = 14.6 (CH_3), 60.9 (CH_2), 103.8, 114.2, 128.4, 131.3, 132.9, 142.6, 144.1, 158.7, 159.1 (CO), 160.5 ppm; IR (KBr): $\bar{\nu}$ = 1566 (C=N), 1614 (C=C), 1720 (CO–O), 3235 (NH) cm^{-1}; HRMS: m/z = 392.1839 ([M+Na]$^+$).

Ethyl 5-[5-(pyridin-4-yl)-1*H*-pyrazol-3-yl]-1,3,4-oxadiazole-2-carboxylate (15, $C_{13}H_{11}N_5O_3$) White solid (0.40 g, 94%); m.p.: 155–157 °C; ^{1}H NMR (DMSO-d_6): δ = 1.33 (t, 3H, CH_3, J = 6.9 Hz), 4.34 (q, 2H, OCH_2, J = 6.9 Hz), 6.90–8.27 (m, 5H, Ar–H), 11.91 (bs, 1H, pyrazole-NH) ppm; ^{13}C NMR (DMSO-d_6): δ = 13.8 (CH_3), 61.5 (CH_2), 103.5, 123.5, 131.5, 135.9, 144.7, 146.9, 159.1, 159.7 (CO), 160.3 ppm; IR (KBr): $\bar{\nu}$ = 1561 (C=N), 1628 (C=C), 1718 (CO–O), 3249 (NH) cm^{-1}; HRMS: m/z = 308.2539 [M+Na]$^+$.

General procedures for the synthesis of 5-(furan-2-yl)isoxazole-3-carbohydrazide (19), 5-(5-bromothiophen-2-yl)isoxazole-3-carbohydrazide (20), and 5-(pyridin-4-yl)isoxazole-3-carbohydrazide (21)

Conventional method

The compound ethyl 5-(furan-2-yl)isoxazole-3-carboxylate (**16**), ethyl 5-(5-bromothiophen-2-yl)isoxazole-3-carboxylate (**17**), or ethyl 5-(pyridin-4-yl)isoxazole-3-carboxylate (**18**) (1.0 mmol) and hydrazine hydrate (2.0 mmol) in 3 cm^3 methanol was taken in a 100 cm^3 round-bottomed flask fitted with reflux condenser and refluxed on a water bath for 3–4 h. The contents were cooled and poured onto crushed ice. The solid separated was filtered, dried, and recrystallized from methanol.

Ultrasonication method

A mixture of **16**, **17**, or **18** (1.0 mmol), hydrazine hydrate (2.0 mmol), and 4 cm^3 methanol was taken and heated at reflux conditions under ultrasound irradiation at a frequency of 35 kHz for 38–50 min. The progress of the reaction was monitored by TLC. After completion of the reaction, the contents were cooled and poured onto crushed ice. The solid separated was filtered on a Buchner funnel, washed with cold water, dried, and recrystallized from methanol.

General procedures for the synthesis of compounds 22a–22c, 23a–23c, and 24a–24c

Conventional method

A mixture of **19**, **20**, or **21** (1.0 mmol) arylsulfonylacetic acid (1.0 mmol), and 3 cm^3 $POCl_3$ was taken in a 100-cm^3 round-bottomed flask fitted with reflux condenser carrying a calcium chloride guard-tube and refluxed for 4.5–7 h. The excess phosphorus oxychloride was removed under reduced pressure and the residue was poured onto crushed ice. The resulting precipitate was filtered, neutralized with saturated sodium bicarbonate solution and then with water, dried, and further purified by column chromatography (silica gel 60–120 mesh) using ethyl acetate-hexane (1:3) as eluent.

Ultrasonication method

To an equimolar (1.0 mmol) solution of **19**, **20**, or **21** and arylsulfonylacetic acid, 4 cm^3 $POCl_3$ was added and subjected to ultrasound irradiation for 21–35 min at 45 °C. After completion of the reaction, the excess phosphorus oxychloride was removed under reduced pressure and the residue was poured onto crushed ice. The separated solid was collected by filtration. It was washed with saturated sodium bicarbonate solution followed by water, dried, and purified by column chromatography (silica gel 60–120 mesh) using ethyl acetate-hexane (1:3) as eluent.

2-[5-(Furan-2-yl)isoxazol-3-yl]-5-(tosylmethyl)-1,3,4-oxadiazole (22a, $C_{17}H_{13}N_3O_5S$) White solid (0.30 g, 83%); m.p.: 180–182 °C; ^{1}H NMR (DMSO-d_6): δ = 2.59 (s, 3H, Ar–CH_3), 4.18 (s, 2H, CH_2), 6.92–8.06 (m, 8H, Ar–H) ppm; ^{13}C NMR (DMSO-d_6): δ = 21.8 (Ar–CH_3), 60.3 (CH_2), 107.3, 109.6, 115.4, 127.2, 131.7, 134.1, 138.6, 144.0, 149.3, 153.2, 154.6, 160.7, 162.0 ppm; IR (KBr): $\bar{\nu}$ = 1138, 1336 (SO_2), 1576 (C=N), 1617 (C=C) cm^{-1}; HRMS: *m/z* = 394.3557 ($[M+Na]^+$).

2-[5-(Furan-2-yl)isoxazol-3-yl]-5-[(4-methoxyphenyl)sulfonylmethyl]-1,3,4-oxadiazole (22b, $C_{17}H_{13}N_3O_6S$) White solid (0.36 g, 95%); m.p.: 188–190 °C; ^{1}H NMR (DMSO-d_6): δ = 3.98 (s, 3H, Ar–OCH_3), 4.26 (s, 2H, CH_2), 6.79–7.94 (m, 8H, Ar–H) ppm; ^{13}C NMR (DMSO-d_6): δ = 56.1 (Ar–OCH_3), 61.8 (CH_2), 107.7, 109.3, 115.0, 117.8, 128.1, 131.3, 144.9, 149.3, 153.6, 154.2, 160.9, 162.3, 165.1 ppm; IR (KBr): $\bar{\nu}$ = 1125, 1324 (SO_2), 1572 (C=N), 1623 (C=C) cm^{-1}; HRMS: *m/z* = 410.3563 ($[M+Na]^+$).

2-[5-(5-Bromothiophen-2-yl)isoxazol-3-yl]-5-[(4-chlorophenyl)sulfonylmethyl]-1,3,4-oxadiazole (22c, $C_{16}H_{10}ClN_3O_5S$) White solid (0.33 g, 86%); m.p.: 192–194 °C; ^{1}H NMR (DMSO-d_6): δ = 4.12 (s, 2H, CH_2), 6.70–8.13 (m, 8H, Ar–H) ppm; ^{13}C NMR (DMSO-d_6): δ = 60.5 (CH_2), 107.1, 109.1, 115.7, 126.3, 131.2, 134.8, 138.4, 144.3, 149.7, 153.8, 154.1, 160.1, 162.9 ppm; IR (KBr): $\bar{\nu}$ = 1162, 1320 (SO_2), 1567 (C=N), 1614 (C=C) cm^{-1}; HRMS: *m/z* = 414.7710 ($[M+Na]^+$).

2-[5-(5-Bromothiophen-2-yl)isoxazol-3-yl]-5-(tosylmethyl)-1,3,4-oxadiazole (23a, $C_{17}H_{12}BrN_3O_4S_2$) White solid (0.37 g, 80%); m.p.: 243–245 °C; ^{1}H NMR (DMSO-d_6): δ = 2.53 (s, 3H, Ar–CH_3), 4.21 (s, 2H, CH_2), 6.58–8.08 (m, 7H, Ar–H) ppm; ^{13}C NMR (DMSO-d_6): δ = 21.3 (Ar–CH_3), 60.6 (CH_2), 113.2, 126.9, 127.3, 130.8, 131.3, 134.5, 134.9, 138.8, 150.4, 153.1, 154.8, 161.3, 163.1 ppm; IR (KBr): $\bar{\nu}$ = 1136, 1325 (SO_2), 1573 (C=N), 1619 (C=C) cm^{-1}; HRMS: *m/z* = 489.3146 ($[M+Na]^+$).

2-[5-(5-Bromothiophen-2-yl)isoxazol-3-yl]-5-[(4-methoxyphenyl)sulfonylmethyl]-1,3,4-oxadiazole (23b, $C_{17}H_{12}BrN_3O_5S_2$) White solid (0.45 g, 94%); m.p.: 265–267 °C; ^{1}H NMR (DMSO-d_6): δ = 3.92 (s, 3H, Ar-OCH_3), 4.15 (s, 2H, CH_2), 6.43–8.00 (m, 7H, Ar–H) ppm; ^{13}C NMR (DMSO-d_6): δ = 55.7 (Ar–OCH_3), 59.2 (CH_2), 113.6, 118.3, 127.0, 128.6, 130.1, 131.2, 134.4, 149.9,

153.4, 154.3, 160.4, 162.7, 164.8 ppm; IR (KBr): $\bar{\nu}$ = 1143, 1319 (SO_2), 1575 (C=N), 1612 (C=C) cm^{-1}; HRMS: *m/z* = 505.3137 ($[M+Na]^+$).

2-[5-(5-Bromothiophen-2-yl)isoxazol-3-yl]-5-[(4-chlorophenyl)sulfonylmethyl]-1,3,4-oxadiazole (23c, $C_{16}H_9BrClN_3O_4S_2$) White solid (0.43 g, 89%); m.p.: 270–272 °C; ^{1}H NMR (DMSO-d_6): δ = 4.17 (s, 2H, CH_2), 6.51–7.14 (m, 7H, Ar–H) ppm; ^{13}C NMR (DMSO-d_6): δ = 60.9 (CH_2), 113.1, 126.5, 127.5, 130.7, 131.7, 134.1, 134.4, 138.9, 149.6, 153.7, 154.0, 160.8, 163.4 ppm; IR (KBr): $\bar{\nu}$ = 1162, 1320 (SO_2), 1597 (C=N), 1614 (C=C) cm^{-1}; HRMS: *m/z* = 509.7294 ($[M+Na]^+$).

2-[5-(Pyridin-4-yl)isoxazol-3-yl]-5-(tosylmethyl)-1,3,4-oxadiazole (24a, $C_{18}H_{14}N_4O_4S$) White solid (0.32 g, 86%); m.p.: 196–198 °C; ^{1}H NMR (DMSO-d_6): δ = 2.57 (s, 3H, Ar–CH_3), 4.22 (s, 2H, CH_2), 6.74–8.16 (m, 9H, Ar–H) ppm; ^{13}C NMR (DMSO-d_6): δ = 20.7 (Ar–CH_3), 59.7 (CH_2), 125.1, 126.5, 131.0, 134.7, 136.2, 138.3, 147.9, 149.5, 152.8, 154.9, 161.6, 163.6 ppm; IR (KBr): $\bar{\nu}$ = 1132, 1328 (SO_2), 1580 (C=N), 1622 (C=C) cm^{-1}; HRMS: *m/z* = 405.3827 ($[M+Na]^+$).

2-[5-(Pyridin-4-yl)isoxazol-3-yl]-5-[(4-methoxyphenyl)sulfonylmethyl]-1,3,4-oxadiazole (24b, $C_{18}H_{14}N_4O_5S$) White solid (0.35 g, 88%); m.p.: 203–205 °C; ^{1}H NMR (DMSO-d_6): δ = 3.95 (s, 3H, Ar–OCH_3), 4.24 (s, 2H, CH_2), 7.56–8.21 (m, 9H, Ar–H) ppm; ^{13}C NMR (DMSO-d_6): δ = 55.5 (Ar–OCH_3), 60.1 (CH_2), 118.1, 125.6, 128.4, 131.7, 136.5, 147.2, 150.0, 153.9, 154.7, 159.8, 162.8, 164.3 ppm; IR (KBr): $\bar{\nu}$ = 1151, 1336 (SO_2), 1572 (C=N), 1617 (C=C) cm^{-1}; HRMS: *m/z* = 421.3816 ($[M+Na]^+$).

2-[5-(5-Bromothiophen-2-yl)isoxazol-3-yl]-5-[(4-chlorophenyl)sulfonylmethyl]-1,3,4-oxadiazole (24c, $C_{17}H_{11}ClN_4O_4S$) White solid (0.37 g, 92%); m.p.: 210–212 °C; ^{1}H NMR (DMSO-d_6): δ = 4.20 (s, 2H, CH_2), 6.84–8.30 (m, 9H, Ar–H) ppm; ^{13}C NMR (DMSO-d_6): δ = 59.9 (CH_2), 125.3, 126.1, 131.0, 134.5, 136.9, 138.2, 147.7, 149.8, 153.5, 154.4, 160.3, 162.5 ppm; IR (KBr): $\bar{\nu}$ = 1129, 1334 (SO_2), 1570 (C=N), 1630 (C=C) cm^{-1}; HRMS: *m/z* = 425.7996 ($[M+Na]^+$).

General procedures for the synthesis of compounds 25–27

Conventional method

To a solution of **19**, **20**, or **21** (1.5 mmol), 20 cm^3 dry THF, 1.8 cm^3 ethyl 2-chloro-2-oxoacetate were taken in a 100-cm^3 round-bottomed flask carrying a calcium chloride guard-tube and the mixture was stirred at laboratory temperature for 10–14 h. After completion of the reaction, the reaction mixture was poured onto crushed ice and extracted with dichloromethane. The solvent was removed under reduced pressure and the resultant residue was purified by recrystallization from acetone/methanol.

Ultrasonication method

The compound **19**, **20**, or **21** (1.5 mmol) was dissolved in 25 cm^3 THF. To this ethyl 2-chloro-2-oxoacetate (4.0 mmol) was added and subjected to ultrasound irradiation for 25–40 min. After completion of the reaction (monitored by TLC), the contents of the flask were poured onto crushed ice and extracted with dichloromethane. The solvent was removed in vacuo. The resultant residue was purified by recrystallization from acetone/methanol.

Ethyl 2-[2-[5-(furan-2-yl)isoxazole-3-carbonyl]hydrazinyl]-2-oxoacetate (25, $C_{12}H_{11}N_3O_6$) White solid (0.36 g, 83%); m.p.: 158–160 °C; ^{1}H NMR (DMSO-d_6): δ = 1.24 (t, 3H, CH_3, *J* = 6.4 Hz), 4.20 (q, 2H, OCH_2, *J* = 6.4 Hz), 7.29–7.68 (m, 4H, Ar–H), 9.96 (bs, 1H, NH), 10.29 (bs, 1H, NH) ppm; ^{13}C NMR (DMSO-d_6): δ = 14.6 (CH_3), 60.7 (CH_2), 105.3, 109.6, 116.4, 143.2, 151.7, 155.1, 157.6, 159.9 (NHCO), 164.7 (CO), 165.1 (CONH) ppm; IR (KBr): $\bar{\nu}$ = 1568 (C=N), 1625 (C=C), 1660 (CO–NH), 1726 (CO–O), 3235 (NH) cm^{-1}; HRMS: *m/z* = 316.2256 ($[M+Na]^+$).

Ethyl 2-[2-[5-(5-bromothiophen-2-yl)isoxazole-3-carbonyl]hydrazinyl]-2-oxoacetate (26, $C_{12}H_{10}BrN_3O_5S$) White solid (0.52 g, 91%); m.p.: 206–208 °C; ^{1}H NMR (DMSO-d_6): δ = 1.26 (t, 3H, CH_3, *J* = 6.4 Hz), 4.24 (q, 2H, OCH_2, *J* = 6.4 Hz), 7.01–7.71 (m, 3H, Ar–H), 9.94 (bs, 1H, NH), 10.05 (bs, 1H, NH) ppm; ^{13}C NMR (DMSO-d_6): δ = 14.8 (CH_3), 61.3 (CH_2), 105.7, 116.0, 129.8, 131.3, 136.8, 151.2, 157.4, 159.5 (NHCO), 164.2 (CO), 164.8 (CONH) ppm; IR (KBr): $\bar{\nu}$ = 1563 (C=N), 1620 (C=C), 1668 (CO–NH), 1720 (CO–O), 3257 (NH) cm^{-1}; HRMS: *m/z* = 411.1830 ($[M+Na]^+$).

Ethyl 2-[2-[5-(pyridin-4-yl)isoxazole-3-carbonyl]hydrazinyl]-2-oxoacetate (27, $C_{13}H_{12}N_4O_5$) White solid (0.36 g, 79%); m.p.: 163–165 °C; ^{1}H NMR (DMSO-d_6): δ = 1.20 (t, 3H, CH_3, *J* = 6.6 Hz), 4.17 (q, 2H, OCH_2, *J* = 6.6 Hz), 7.15–8.20 (m, 5H, Ar–H), 9.89 (bs, 1H, NH), 10.07 (bs, 1H, NH) ppm; ^{13}C NMR (DMSO-d_6): δ = 14.3 (CH_3), 61.5 (CH_2), 105.1, 120.7, 139.6, 142.1, 151.5, 159.0 (NHCO), 160.4, 164.9 (CO), 165.5 (CONH) ppm; IR (KBr): $\bar{\nu}$ = 1570 (C=N), 1622 (C=C), 1656 (CO–NH), 1729 (CO–O), 3266 (NH) cm^{-1}; HRMS: *m/z* = 327.2532 ($[M+Na]^+$).

General procedures for the synthesis of compounds 28–30

Conventional method

The compound **25**, **26**, or **27** (1.5 mmol) dissolved in 5 cm^3 $POCl_3$ was taken in a 100-cm^3 round-bottom flask fitted with reflux condenser carrying a calcium chloride guard-tube and refluxed for 20–24 h. The progress of the reaction was monitored by TLC. After completion of the reaction, the contents of the flask were cooled to room temperature and poured onto crushed ice. The resulting precipitate was filtered, washed with saturated sodium bicarbonate solution followed by water, and dried. It was purified by column chromatography (silica gel 60–120 mesh) using ethyl acetate-hexane (1:3) as eluent.

Ultrasonication method

To the compound **25**, **26**, or **27** (1.6 mmol) 5 cm^3 $POCl_3$ was added and kept under ultrasonication for 75–90 min at 40 °C. The progress of the reaction was monitored by TLC. After completion of the reaction, the contents of the flask were cooled to room temperature and poured onto crushed ice. The resulting precipitate was filtered, washed with saturated sodium bicarbonate solution followed by water and dried. It was purified by column chromatography (silica gel 60–120 mesh) using ethyl acetate-hexane (1:3) as eluent.

Ethyl 5-[5-(furan-2-yl)isoxazol-3-yl]-1,3,4-oxadiazole-2-carboxylate (28, $C_{12}H_9N_3O_5$) White solid (0.39 g, 90%); m.p.: 144–146 °C; ^{1}H NMR (DMSO-d_6): δ = 1.39 (t, 3H, CH_3, J = 6.4 Hz), 4.35 (q, 2H, OCH_2, J = 6.4 Hz), 6.92–8.21 (m, 4H, Ar–H) ppm; ^{13}C NMR (DMSO-d_6): δ = 14.7 (CH_3), 61.8 (CH_2), 106.8, 109.7, 115.4, 144.1, 149.2, 150.2, 153.3, 159.5 (CO), 159.9, 162.5 ppm; IR (KBr): $\bar{\nu}$ = 1575 (C=N), 1625 (C=C), 1697 (CO–O) cm^{-1}; HRMS: m/z = 298.2091 ([M+Na]$^+$).

Ethyl 5-[5-(5-bromothiophen-2-yl)isoxazol-3-yl]-1,3,4-oxadiazole-2-carboxylate (29, $C_{12}H_8BrN_3O_4S$) White solid (0.51 g, 87%); m.p.: 198–200 °C; ^{1}H NMR (DMSO-d_6): δ = 1.32 (t, 3H, CH_3, J = 6.8 Hz), 4.25 (q, 2H, OCH_2, J = 6.8 Hz), 6.91–8.15 (m, 3H, Ar–H) ppm; ^{13}C NMR (DMSO-d_6): δ = 14.1 (CH_3), 61.3 (CH_2), 105.8, 113.0, 127.2, 130.5, 134.8, 149.0, 153.9, 159.5, 160.4 (CO), 163.0 ppm; IR (KBr): $\bar{\nu}$ = 1562 (C=N), 1618 (C=C), 1712 (CO–O) cm^{-1}; HRMS: m/z = 393.1677 ([M+Na]$^+$).

Ethyl 5-[5-(pyridin-4-yl)isoxazol-3-yl]-1,3,4-oxadiazole-2-carboxylate (30, $C_{13}H_{10}N_4O_4$) White solid (0.38 g, 85%); m.p.: 156–158 °C; ^{1}H NMR (DMSO-d_6): δ = 1.35 (t, 3H, CH_3, J = 7.0 Hz), 4.39 (q, 2H, OCH_2, J = 7.0 Hz), 6.98–8.34 (m, 5H, Ar–H) ppm; ^{13}C NMR (DMSO-d_6): δ = 14.5 (CH_3), 60.7 (CH_2), 106.2, 125.2, 136.1, 147.5, 149.7, 154.2, 159.3 (CO), 160.1, 162.9 ppm; IR (KBr): $\bar{\nu}$ = 1559 (C=N), 1622 (C=C), 1716 (CO–O) cm^{-1}; HRMS: m/z = 309.2360 ([M+Na]$^+$).

Antioxidant activity

The compounds **7–15** and **22–30** were tested for antioxidant property by 2,2-diphenyl-1-picrylhydrazyl (DPPH), hydrogen peroxide (H_2O_2), and nitric oxide (NO) methods at four different concentrations 25, 50, 75, and 100 μg/cm^3 using ascorbic acid as the standard drug [40].

Anti-inflammatory activity

The in vivo anti-inflammatory activity of the title compounds **7–15** and **22–30** was studied using carrageenan-induced hind paw edema test in male albino rats (150–180 g) of Wistar strain at 100 mg/kg body weight using phenylbutazone as the standard [41].

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