Indian Journal of Heterocyclic Chemistry
Vol. 28 - Number 03 (Jul-Sep 2018) 379-384

ISSN (Print) : 0971-1627
ISSN (Online) : 2456-4311

Synthesis and Biological Evaluations of Some New Oxadiazole–piperidine Hybrid Derivatives as Antioxidant Agents

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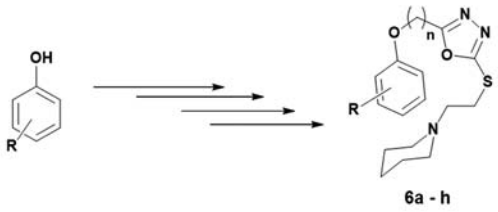
ABSTRACT A series of some new 1,3,4-oxadiazole-2-thiol derivatives (**6a-h**) containing cyclic secondary amine such as piperidine ring was expeditiously synthesized by alkylation of 1,3,4-oxadiazol-2-thiol derivatives with chloroethyl piperidine hydrochloride. The 1,3,4-oxadiazole-2-thiols were effectively synthesized by cyclization reaction of acid hydrazide derivatives with carbon disulfide. The target compounds **6a-h** were preliminarily screened for *in vitro* antioxidant activities using various *in vitro* antioxidant assays including 2,2′-diphenyl-1-picrylhydrazyl, nitric oxide, and hydrogen peroxide methods. The results showed that the compounds exhibited promising antioxidant property in the three methods at 50, 75, and 100 µM. Among the tested compounds, the compounds **6a** and **6b** having chloro substituent in the benzene ring displayed greater radical scavenging activity.



6a;a: R=4-Cl, n=1 is **the** higher radical scavenging activity than others substitutents

KEYWORDS Oxadiazole–piperidine, Synthesis, Antioxidant activity.

INTRODUCTION

Reactive oxygen species (ROS) are highly reactive molecules that encompass singlet oxygen superoxide anion radical, hydrogen peroxide (H_2O_2), ($^1O_2$), and hydroxyl radical (·OH) that could be generated by normal metabolic process or from exogenous elements.[1]

ROS has various pathological processes and can motive many diseases, which include atherosclerosis, cardiovascular disease, diabetes, and cancer.[2] Furthermore, ROS is related to qualitative decay of ingredients, which cause toxicity, rancidity, and destruction of critical biochemical pieces in physiologic metabolism.[3] Hence, it is significant to develop effective harmless antioxidants to scavenge free radicals inside the human body.

1,3,4-Oxadiazole and its derivatives have a high potential for biological activity and have drawn much attention during the present decades.[4–7] They have a wide range of pharmacological applications including potential antitumor and antioxidant activities.[8-10]

The literature survey has revealed that the structural modification of [1,3,4]-oxadiazole-2-thiols by the introduction of nitrogen-containing heterocycles can further enhance the antioxidant activity of candidate compounds.[11,12]

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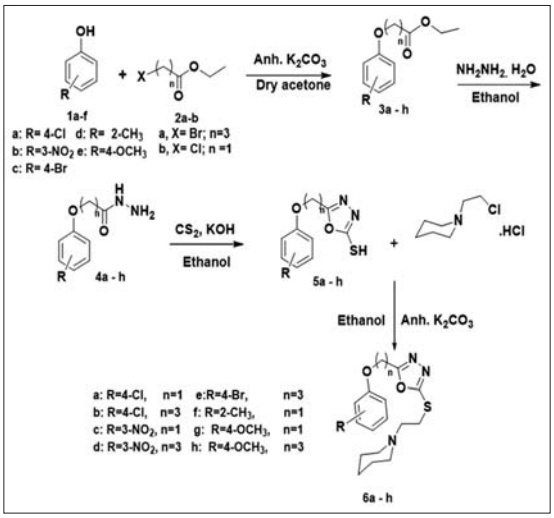
The piperidine analogs are an attractive drug template because of its significant biological applications as antioxidant, antihistaminic, anti-inflammatory, fungicidal, bactericidal, anticancer, analgesic, CNS stimulant, and depressant activities.[13-16] Thus, piperidine moiety-containing molecules play an essential role in the field of medicinal chemistry.

Based on the above observations, it was thought worthwhile to prepare new compounds that contain oxadiazole and piperidine ring systems with a view to produce promising antioxidant agents. Therefore, several hybrids were synthesized and investigated for the antioxidant activities using several determination methods 2,2′-diphenyl-1-picrylhydrazyl (DPPH), nitric oxide (NO), and H_2O_2 radical scavenging assays.

RESULTS AND DISCUSSION

Chemistry

The general synthetic route for the preparation of the title compounds **6a–h** is illustrated in **Scheme 1**. Initially, phenoxyacetic/butyric acid ethyl esters **3a-h** were obtained by the condensation of substituted phenols **1a-e** with **2a-b** in the presence of anhydrous K_2CO_3 and confirmed by the disappearance of OH stretching and appearance of carbonyl stretching band for the ester group at 1733–1742 cm^{-1} in the infrared (IR) absorption spectra. The proton NMR observations revealed that broad singlet for OH proton was disappeared and a triplet and quartet for CH_3 and CH_2 protons at 1.32–135 and 4.21–4.33 δ, respectively, were appeared.[7] Compounds **3a-h** were treated with the slight excessive equivalent amount of hydrazine hydrate to produced phenoxyacetic/butyric acid hydrazide derivatives **4a-h**, and the chemical structure of **4a-h** was established by the appearance of NH_2 stretching band of amide at 3309–3323 cm^{-1} in the IR spectra. In proton NMR, the appearance of NH_2 and NH protons at 3.83–3.91 and 8.40–8.46 δ, respectively, and disappearance of triplet and quartet peaks for CH_3 and CH_2 protons have confirmed the formation



Scheme 1: Synthesis of 1-[2-(5-phenoxymethyl-[1,3,4] oxadiazol-2-ylsulfanyl)-ethyl]-piperidines (6a-h)

of the acid hydrazide derivatives **4a-h**. 1,3,4-oxadiazol-2-thiols **5a-h** were prepared by cyclization of acid hydrazide derivatives **4a-h** with carbon disulfide in the presence of KOH which were clearly evident with the disappearance of carbonyl and NH_2 stretching band in the IR spectra. The appearance of SH proton at 10.72–10.76 δ and the disappearance of NH_2 and NH protons of amide in the NMR spectra also confirmed the product. Finally, compounds **5a-h** were subjected to alkylation with chloroethyl piperidine hydrochloride in the presence of anhydrous K_2CO_3 to afford the title compounds **6a–h**. This was supported by the disappearance of SH stretching in the IR spectra as well as by the disappearance of SH proton and appearance of methylene protons of piperidine at 1.54–1.58 and 2.36–2.41 δ in the NMR spectra. Further, the mass spectral data of these compounds displayed molecular ion peaks which confirmed their molecular weights.

Biology

Oxadiazole–piperidine derivatives **6a-h** were tested for the antioxidant property by DPPH, NO, and H_2O_2 radical scavenging assays using ascorbic acid as standard antioxidant. The experiments were carried out at three different concentrations in triplicates; the results are expressed as mean ± standard deviation (SD) and were summarized in **Table 1-3**. The structure-antioxidant activity relationship of the synthesized compounds revealed that compounds **6a-h** exhibited promising antioxidant property in the three methods at 50, 75, and 100 µM concentrations but showed less activity compared with the ascorbic acid. The scavenging effect gradually increases with the increasing concentrations of test compounds. Among the compounds tested, the compounds **6a** and **6b** having chloro substituent in the benzene ring displayed greater radical scavenging activity. The compounds **6c, 6d,** and **6e** having two nitro and bromo substituents in the benzene ring showed moderate radical scavenging abilities, while **6f, 6g,** and **6h** having methyl and methoxy substituent, respectively, in the benzene ring showed poor radical scavenging abilities in comparison with the standard antioxidant ascorbic acid. However, compound **6a** having a chloro substituent exhibited higher radical scavenging activity than **6b** which has the same group, but it has single CH_2 while **6b** has three CH_2. Remarkably**,** compounds **6c, 6d, 6g,** and **6h** which displayed moderate activity showed less activity with increasing substitutions of CH_2. Hence, increasing aliphatic chain length in compounds **6a-h** would obviously decrease the scavenging efficacy of the compounds. Moreover, due to electron-donating substituents of methoxy and methyl, stereochemical factors of *ortho* substitution of methyl substituent might cause for lower activity associated with the compounds **6g, 6h,** and **6f**.

EXPERIMENTAL SECTION

Melting points were determined on a Thomas Hoover capillary melting point apparatus with a digital thermometer. IR spectra were recorded as Potassium bromide Discs on Shimadzu Fourier-transform infrared (FT-IR) 8300 spectrometer. ^{1}H-NMR spectra were recorded on Bruker spectrophotometer at 400 MHz in $CDCl_3$; values (δ) are given

Table 1: DPPH radical scavenging ability of the compounds 6a-h relative to the standard antioxidant ascorbic acid

Compound	% radical scavenging activity		
	50 µg/mL	75 µg/mL	100 µg/mL
6a	60.24±1.20	63.55±1.24	65.81±1.61
6b	55.78±1.14	58.75±1.47	60.44±1.08
6c	36.68±0.63	37.36±0.86	39.36±1.46
6d	40.13±0.68	41.32±0.67	44.52±1.15
6e	51.84±0.86	55.92±1.42	59.87±1.61
6f	24.15±1.17	27.86±1.21	29.81±1.26
6g	26.84±0.71	27.50±0.77	29.39±1.37
6h	24.12±0.56	25.93±0.78	27.28±1.15
Ascorbic acid	77.15±0.45	80.95±0.39	83.82±0.81

Values were the means of three replicates±S.D. SD: Standard deviation, DPPH: 2,2′-diphenyl-1-picrylhydrazyl

Table 2: NO radical scavenging ability of the compounds 6a-h relative to the standard antioxidant ascorbic acid

Compound	% radical scavenging activity		
	50 µg/mL	75 µg/mL	100 µg/mL
6a	64.56±0.98	67.55±1.13	68.81±1.56
6b	56.74±0.87	57.75±0.94	59.44±1.28
6c	41.51±0.74	43.34±0.85	44.79±1.59
6d	52.77±0.65	54.56±0.69	56.13±1.07
6e	56.67±0.81	58.92±1.21	59.87±1.53
6f	28.85±1.05	29.65±0.99	30.98±1.34
6g	27.73±0.89	29.17±0.81	32.46±1.39
6h	26.55±0.60	27.64±0.75	28.35±1.25
Ascorbic acid	78.23±0.17	81.46±1.37	82.79±0.80

Values were the means of three replicates±S.D. SD: Standard deviation, NO: Nitric oxide

Table 3: H_2O_2 radical scavenging ability of the compounds 6a-h relative to the standard antioxidant ascorbic acid

Compound	% radical scavenging activity		
	50 µg/mL	75 µg/mL	100 µg/mL
6a	61.34±1.18	63.23±1.43	64.18±1.44
6b	52.74±1.07	54.68±1.17	56.12±1.31
6c	38.75±1.16	39.19±1.06	41.±1.35
6d	47.19±0.89	48.56±0.86	50.19±1.25
6e	51.04±1.22	53.82±1.15	55.87±1.29
6f	23.66±1.30	24.16±1.09	27.56±1.39
6g	25.99±1.11	27.56±0.98	30.54±1.28
6h	19.78±0.93	22.54±1.11	24.88±1.32
Ascorbic acid	77.68±0.51	79.27±1.29	83.16±0.44

Values were the means of three replicates±S.D. SD: Standard deviation, H_2O_2: Hydrogen peroxide

in parts per million (ppm) downfield from tetramethylsilane (TMS) as internal reference standard. ^{13}C-NMR spectra were recorded using the same spectrophotometers that used for recording ^{1}H NMR. Mass spectra were obtained with a VG70-70H spectrophotometer. The elemental analysis of the compounds was performed on a PerkinElmer 2400 Elemental Analyzer.

Chemistry

General synthetic procedure for phenoxyacetic/butyric acid ethyl ester derivatives (3a-h)

A mixture of substituted phenols **1a-e** (0.75 mol) and **2a-b** (0.10 mol) in dry acetone (50 ml) with K_2CO_3 (0.10 mol) was refluxed for 10–14 h. The solvent was removed by distillation. The crude was triturated with cold water to remove potassium carbonate and extracted with ether. The ether layer was washed with 10% sodium hydroxide solution followed by water and then dried over anhydrous sodium sulfate and evaporated to afford compounds **3a-h.**

(4-Chlorophenoxy)acetic acid ethyl ester (3a)

Yield 90%; FT-IR (cm^{-1}): 1738 (C=O); ^{1}H-NMR ($CDCl_3$): δ: 1.35 (t, 3H, CH_3 of ester), 4.21 (q, 2H, CH_2 of ester), 5.01 (s, 2H, OCH_2), 7.32 (d, 2H, Ar-H), 7.49 (d, 2H, Ar-H); liquid chromatography–mass spectrometry (LC-MS) m/z 214 (M^+), 216 (M+2). Anal. Calcd. for $C_{10}H_{11}ClO_3$: C, 55.96; H, 5.17. Found: C, 55.49; H, 5.27%.

General synthetic procedure for phenoxyacetic acid/butyric acid hydrazide derivatives (4a-h)

Hydrazine hydrate (0.060 mol) was added to the solution of compounds **3a-h** (0.045 mol) in ethanol (25 ml), and the reaction mixture was stirred at room temperature for 4 h. Reaction completion was monitored by thin-layer chromatography using hexane: ethyl acetate (2:1) as the mobile phase and allowed to stand overnight. Formed white crystals **4a-h** were filtered, washed, and after drying recrystallized from ethanol to give **4a-h**.

(4-Chlorophenoxy)acetic acid hydrazide (4a)

Yield 92%; mp 115–117°C; FT-IR (KBr, cm^{-1}): 3315 (NH_2), 3220 (NH), 1672 (C=O); ^{1}H NMR ($CDCl_3$): δ 3.85 (d, 2H, NH_2), 5.08 (s, 2H, OCH_2), 6.88 (d, 2H, Ar-H), 7.27 (d, 2H, Ar-H), 8.40 (t,1H, NH), LC-MS m/z 200 (M^+), 202 (M+2). Anal. Calcd. for $C_8H_9ClN_2O_2$: C, 47.89; H, 4.52; N, 13.96. Found: C, 47.78; H, 4.56; N, 14.08%.

General synthetic procedure for 5-phenoxymethyl/propyl-[1,3,4]oxadiazole-2-thiol derivatives (5a-h)

A mixture of hydrazides **4a-h** (4 mmol), carbon disulfide (4 ml), potassium hydroxide (8 mmol), and ethanol (50 ml) was heated under reflux until evolution of hydrogen sulfide was ceased (6–8 h). Afterward, the reaction mixture was cooled to room temperature. The solvent was evaporated at reduced pressure, and cold water was poured and acidified with diluted hydrochloric acid solution to bring the pH between 3 and 4. The precipitate thus separated out was allowed to stand overnight, filtered, washed, and after drying recrystallized from acetone.

5-(4-Chlorophenoxymethyl)[1,3,4]oxadiazole-2-thiol (5a) Yield 84%; mp 140–142°C; FT-IR (KBr, cm^{-1}): 1612 (C=N), 2557 (SH), 1164 (C-O-C); ^{1}H NMR ($CDCl_3$): δ 5.05

(s, 2H, OCH_2), 6.95 (d, *J* = 8.80 Hz, 2H, Ar-H), 7.32 (d, *J* = 8.85 Hz, 2H, Ar-H), 10.72 (s, 1H, SH); LC-MS m/z 242 (M^+), 244 (M+2). Anal. Calcd. for $C_9H_7ClN_2O_2S$: C, 44.54; H, 2.91; N, 11.54. Found: C, 44.70; H, 2.82; N, 11.65%.

5-[3-(4-Chlorophenoxy)propyl][1,3,4]oxadiazole-2-thiol (5b) Yield 82%; mp 147-149 °C; FT-IR (KBr, cm^{-1}): 1612 (C=N), 2557 (SH), 1164 (C-O-C); ^1H NMR ($CDCl_3$): δ 2.37 (m, 2H, CH_2), 2.92 (t, 2H, $COCH_2$), 4.23 (t, 2H, OCH_2), 6.95 (d, *J* = 8.80 Hz, 2H, Ar-H), 7.32 (d, *J* = 8.85 Hz, 2H, Ar-H), 10.72 (s, 1H, SH); LC-MS m/z 270 (M^+), 272 (M+2). Anal. Calcd. for $C_{11}H_{11}ClN_2O_2S$: C, 48.80; H, 4.10; N, 10.35. Found: C, 48.91; H, 4.03; N, 10.25%.

5-(3-Nitrophenoxymethyl)[1,3,4]oxadiazole-2-thiol (5c) Yield 84%; mp 142–144°C; FT-IR (KBr, cm^{-1}): 1612 (C=N), 2557 (SH), 1164 (C-O-C); ^1H NMR ($CDCl_3$): δ 5.11 (s, 2H, OCH_2), 7.23 (d, *J* = 7.20 Hz, 2H, Ar-H), 7.45 (s, 1H, Ar-H), 7.62 (t, *J* = 8.80 Hz, 1H, Ar-H), 10.72 (s, 1H, SH); LC-MS m/z 254 (M+1). Anal. Calcd. for $C_9H_7N_3O_4S$: C, 42.69; H, 2.79; N, 16.59. Found: C, 42.73; H, 2.73; N, 16.57%.

5-[3-(3-Nitrophenoxy)propyl][1,3,4]oxadiazole-2-thiol (5d) Yield 80%; mp 144–146°C; FT-IR (KBr, cm^{-1}): 1612 (C=N), 2557 (SH), 1164 (C-O-C); ^1H NMR ($CDCl_3$): δ 2.42 (m, 2H, CH_2), 2.96 (t, 2H, $COCH_2$), 4.28 (t, 2H, OCH_2), 7.23 (d, *J* = 7.20 Hz, 2H, Ar-H), 7.45 (s, 1H, Ar-H), 7.62 (t, *J* = 8.80 Hz, 1H, Ar-H), 10.72 (s, 1H, SH); LC-MS m/z 282 (M+1). Anal. Calcd. for $C_{11}H_{11}N_3O_4S$: C, 46.97; H, 3.94; N, 14.94. Found: C, 47.17; H, 3.87; N, 15.15%.

5-[3-(4-Bromophenoxypropyl]-[1,3,4]oxadiazole-2-thiol (5e) Yield 76%; mp 141–143°C; FT-IR (KBr, cm^{-1}): 1612 (C=N), 2557 (SH), 1164 (C-O-C); ^1H NMR ($CDCl_3$): δ 2.39 (m, 2H, CH_2), 2.92 (t, 2H, $COCH_2$), 4.27 (t, 2H, OCH_2), 6.77 (d, *J* = 8.80 Hz, 2H, Ar-H), 7.36 (d, *J* = 8.85 Hz, 2H, Ar-H), 10.72 (s, 1H, SH); LC-MS m/z 315 (M^+), 317 (M+2). Anal. Calcd. for $C_{11}H_{11}BrN_2O_2S$: C, 41.92; H, 3.52; N, 8.89. Found: C, 41.85; H, 3.57; N, 8.80%.

5-o-Tolyloxymethyl[1,3,4]oxadiazole-2-thiol (5f) Yield 78%; mp 135–137°C; FT-IR (KBr, cm^{-1}): 1612 (C=N), 2557 (SH), 1164 (C-O-C); ^1H NMR ($CDCl_3$): δ 2.16 (s, 3H, CH_3), 5.04 (s, 2H, OCH_2), 6.82 (d, *J* = 8.80 Hz, 1H, Ar-H), 7.37 (d, *J* = 7.40 Hz, 1H, Ar-H), 7.54 (t, *J* = 8.80 Hz, 2H, Ar-H), 10.72 (s, 1H, SH); LC-MS m/z 223 (M+1). Anal. Calcd. for $C_{10}H_{10}N_2O_2S$: C, 54.04; H, 4.53; N, 12.60. Found: C, 54.18; H, 4.53; N, 12.51%.

5-(4-Methoxyphenoxymethyl)[1,3,4]oxadiazole-2-thiol (5g) Yield 83%; mp 133–135°C; FT-IR (KBr, cm^{-1}): 1612 (C=N), 2557 (SH), 1164 (C-O-C); ^1H NMR ($CDCl_3$): δ 3.76 (s, 3H, OCH_3), 5.06 (s, 2H, OCH_2), 6.89–7.05 (m, 4H, Ar-H), 10.72 (s, 1H, SH); LC-MS m/z 239 (M+1). Anal. Calcd. for $C_{10}H_{10}N_2O_3S$: C, 50.41; H, 4.23; N, 11.76. Found: C, 50.53; H, 4.19; N, 11.66%.

5-[3-(4-Methoxyphenoxy)propyl]-[1,3,4]oxadiazole-2-thiol (5h) Yield 77%; mp 148–150°C; FT-IR (KBr, cm^{-1}): 1612 (C=N), 2557 (SH), 1164 (C-O-C); ^1H NMR ($CDCl_3$): δ 2.36 (m, 2H, CH_2), 2.90 (t, 2H, $COCH_2$), 3.76 (s, 3H, OCH_3), 4.22 (t, 2H, OCH_2), 6.89–7.05 (m, 4H, Ar-H), 10.76 (s, 1H, SH); LC-MS m/z 267 (M+1). Anal. Calcd. for $C_{12}H_{14}N_2O_3S$: C, 54.12; H, 5.30; N, 10.52. Found: C, 54.25; H, 5.27; N, 10.61%.

General synthetic procedure for 1-[2-(5-phenoxymethyl-[1,3,4]oxadiazol-2-ylsulfanyl)-ethyl]piperidine derivatives (6a-h)

A mixture of 5-phenoxymethyl/propyl-[1,3,4]oxadiazole-2-thiols (**5a–h**) (2 mmol), chloroethyl piperidine hydrochloride (5 mmol), and anhydrous potassium carbonate (5 mmol) in ethanol (30 ml) was heated under reflux for 15–24 h. After completion of the reaction, the reaction mixture was cooled down, and excess of solvent was evaporated under reduced pressure. The residue obtained was triturated with cold water to precipitate the desired target compounds **6a-h** which were recrystallized from ethanol.

2-((4-Chlorophenoxy)methyl)-5-((2-(piperidin-1-yl) ethyl)thio)-1,3,4-oxadiazole (6a) Yield 70%; mp. 83–85°C; FT-IR (KBr, cm^{-1}): 1333 (C=N), 1272 (C-O-C); ^1H NMR ($CDCl_3$): δ 1.56 (m, 6H, $2CH_2$ of piperidine ring), 2.36 (t, 4H, CH_2NCH_2 of piperidine ring), 2.75 (t, 2H, N CH_2), 3.41 (t, 2H, CH_2S), 5.12 (s, 2H, OCH_2), 7.21–8.04 (m, 4H, Ar-H); ^{13}C-NMR ($CDCl_3$): δ 25.45, 26.32, 28.17, 50.67, 55.88, 59.80, 64.53, 118.44, 129.35, 132.57, 158.21; LC-MS m/z 353 (M^+), 355 (M+2). Anal. Calcd. for $C_{16}H_{20}ClN_3O_2S$: C, 54.31; H, 5.70; N, 11.87. Found: C, 54.47; H, 5.58; N, 11.59%.

2-(3-(4-Chlorophenoxy)propyl)-5-((2-(piperidin-1-yl) ethyl)thio)-1,3,4-oxadiazole (6b) Yield 73%; mp. 87-89°C; FT-IR (KBr, cm^{-1}): 1333 (C=N), 1272 (C-O-C); ^1H NMR ($CDCl_3$): δ 1.58 (m, 6H, $2CH_2$ of piperidine ring), 2.15 (m, 2H, CH_2), 2.39 (t, 4H, CH_2NCH_2 of piperidine ring), 2.86 (t, 2H, NCH_2), 2.90 (t, 2H, CH_2), 3.35 (t, 2H, CH_2S), 3.90 (t, 2H, OCH_2), 7.27-8.11 (m, 4H, Ar-H); ^{13}C-NMR ($CDCl_3$): δ 21.16, 26.89, 27.77, 29.99, 48.96, 59.85, 64.55, 72.46, 79.16, 118.90, 123.65, 130.78, 156.23; LC-MS m/z 381 (M^+), 383 (M+2). Anal. Calcd. for $C_{18}H_{24}ClN_3O_2S$: C, 56.61; H, 6.33; N, 11.00. Found: C, 56.63; H, 6.30; N, 10.81%.

2-((3-Nitrophenoxy)methyl)-5-((2-(piperidin-1-yl)ethyl)thio)-1,3,4-oxadiazole (6c) Yield 70%; mp. 81-83°C; FT-IR (KBr, cm^{-1}): 1336 (C=N), 1276 (C-O-C); ^1H NMR ($CDCl_3$): δ 1.56 (m, 6H, $2CH_2$ of piperidine ring), 2.41 (t, 4H, CH_2NCH_2 of piperidine ring), 2.90 (t, 2H, CH_2N), 3.53 (t, 2H, CH_2S), 5.34 (s, 2H, OCH_2), 7.05-7.79 (m, 4H, Ar-H); ^{13}C-NMR ($CDCl_3$): δ 25.55, 26.67, 30.25, 50.57, 54.55, 68.50, 75.31, 115.84, 137.05, 154.96, 165.47; LC-MS m/z 365 (M+1). Anal. Calcd. for $C_{16}H_{20}N_4O_4S$: C, 52.73; H, 5.53; N, 15.37. Found: C, 52.68; H, 5.51; N, 15.38%.

2-(3-(3-Nitrophenoxy)propyl)-5-((2-(piperidin-1-yl) ethyl)thio)-1,3,4-oxadiazole (6d) Yield 76%; mp. 85-87°C; IR (cm^{-1}): 1338 (C=N), 1276 (C-O-C); ^1H NMR ($CDCl_3$): δ 1.57 (m, 6H, $2CH_2$ of piperidine ring), 2.32 (m, 2H, CH_2), 2.40 (t, 4H, CH_2NCH_2 of piperidine ring), 2.77 (t, 2H, CH_2N), 2.95 (t, 2H, CH_2), 3.43 (t, 2H, CH_2S), 3.96 (t, 2H, OCH_2), 7.10–7.89 (m, 4H, Ar-H); ^{13}C-NMR ($CDCl_3$): δ 22.46, 24.76, 24.54, 28.64, 53.17, 60.71, 66.92, 77.54,

116.72, 127.62, 130.78, 156.23, 166.53; LC-MS m/z 393 (M+1). Anal. Calcd. for $C_{18}H_{24}N_4O_4S$: C, 55.08; H, 6.16; N, 14.28. Found: C, 54.78; H, 6.11; N, 14.32%.

2-(3-(4-Bromophenoxy)propyl)-5-((2-(piperidin-1-yl) ethyl)thio)-1,3,4-oxadiazole (6e) Yield 79%; mp. 78-80°C; FT-IR (KBr, cm^{-1}): 1336 (C=N), 1276 (C-O-C); ^{1}H NMR ($CDCl_3$): δ 1.54 (m, 6H, $2CH_2$ of piperidine ring), 2.22 (m, 2H, CH_2), 2.39 (t, 4H, CH_2NCH_2 of piperidine ring), 2.83 (t, 2H, CH_2N), 2.97 (t, 2H, CH_2), 3.35 (t, 2H, CH_2S), 3.93 (t, 2H, OCH_2), 7.10-7.89 (m, 4H, Ar-H); ^{13}C-NMR ($CDCl_3$): δ 21.45, 23.12, 26.76, 30.05, 53.40, 57.66, 63.21, 72.83, 76.89, 117.52, 124.08, 156.23; LC-MS m/z 425 (M^+), 227 (M+2). Anal. Calcd. for $C_{18}H_{24}BrN_3O_2S$: C, 50.71; H, 5.67; N, 9.86. Found: C, 50.66; H, 5.53; N, 9.81%.

2-((2-(Piperidin-1-yl)ethyl)thio)-5-((o-tolyloxy) methyl)-1,3,4-oxadiazole (6f) Yield 82%; mp. 74-76°C; FT-IR (KBr, cm^{-1}): 1333 (C=N), 1277 (C-O-C); ^{1}H NMR ($CDCl_3$): δ 1.56 (m, 6H, $2CH_2$ of piperidine ring), 2.16 (s, 3H, CH_3), 2.35 (t, 4H, CH_2NCH_2 of piperidine ring), 2.73 (t, 2H, CH_2N), 3.44 (t, 2H, CH_2S), 5.11 (s, 2H, OCH_2), 6.97-7.54 (m, 4H, Ar-H); ^{13}C-NMR ($CDCl_3$): δ 14.23, 23.53, 26.54, 30.99, 50.72, 53.87, 60.02, 77.53, 77.75, 114.33, 131.88, 153.39, 156.22; LC-MS m/z 334 (M+1). Anal. Calcd. for $C_{17}H_{23}N_3O_2S$: C, 61.23; H, 6.95; N, 12.60 Found: C, 61.27; H, 6.81; N, 12.46%.

2-((4-Methoxyphenoxy)methyl)-5-((2-(piperidin-1-yl) ethyl)thio)-1,3,4-oxadiazole (6g) Yield 75%; mp. 71-73°C; FT-IR (KBr, cm^{-1}): 1330 (C=N), 1265 (C-O-C); ^{1}H NMR ($CDCl_3$): δ 1.56 (m, 6H, $2CH_2$ of piperidine ring), 2.37 (t, 4H, CH_2NCH_2 of piperidine ring), 2.83 (t, 2H, CH_2N), 3.51 (t, 2H, CH_2S), 3.86 (s, 3H, OCH_3), 5.17 (s, 2H, OCH_2), 6.92–7.21 (m, 4H, Ar-H); ^{13}C-NMR ($CDCl_3$): δ 24.51, 26.62, 28.66, 36.89, 56.36, 66.45, 77.35, 77.35, 116.38, 119.04, 151.02, 163.12; LC-MS m/z 350 (M+1). Anal. Calcd. for $C_{17}H_{23}N_3O_3S$: C, 58.43; H, 6.63; N, 12.02. Found: C, 58.27; H, 6.43; N, 11.89%.

2-(3-(4-Methoxyphenoxy)propyl)-5-((2-(piperidin-1-yl)ethyl)thio)-1,3,4-oxadiazole (6h) Yield 72%; mp. 90–92°C; FT-IR (KBr, cm^{-1}): 1330 (C=N), 1265 (C-O-C); ^{1}H NMR ($CDCl_3$): δ 1.58 (m, 6H, $2CH_2$ of piperidine ring), 2.32 (m, 2H, CH_2), 2.37 (t, 4H, CH_2NCH_2 of piperidine ring), 2.75 (t, 2H, CH_2N), 2.95 (t, 2H, CH_2), 3.43 (t, 2H, CH_2S), 3.83 (s, 3H, OCH_3), 4.16 (t, 2H, OCH_2), 6.58–7.13 (m, 4H, Ar-H); ^{13}C-NMR ($CDCl_3$): δ 25.54, 26.32, 28.87, 30.52, 51.26, 58.43, 64.36, 76.90, 78.57, 114.66, 124.76, 132.35, 152.14, 164.17; LC-MS m/z 378 (M+1). Anal. Calcd. for $C_{19}H_{27}N_3O_3S$: C, 60.45; H, 7.21, N, 11.13. Found: C, 60.36; H, 7.06, N, 11.11%.

Biology; antioxidant activity assay

Compounds **6a-h** were tested for antioxidant property by DPPH, NO, and H_2O_2 radical scavenging methods.

DPPH radical scavenging activity

The scavenging effect of 2,2′diphenyl-1-picrylhydrazyl (DPPH) radical was assessed according to earlier method.[17] 0.1 µM solution of DPPH in methanol was prepared, and 1 mL of various concentrations of the test compounds (50, 75, and 100 µg/mL) in methanol was added. The mixture was shaken vigorously and allowed to stand at room temperature for 30 min, and the absorbance was read against blank at 517 nm. Ascorbic acid was used as the standard. The difference between the test and the control experiments was taken and expressed as the percentage scavenging of the DPPH radical as the following equation:

$$I\% = [(A_{control} - A_{sample})/A_{blank}] \times 100$$

Where I% is the percentage of inhibition, $A_{control}$ is the absorbance of the control reaction, A_{sample} is the absorbance of the test compound, and A_{blank} is the absorbance of the blank.

NO scavenging activity

NO was generated from sodium nitroprusside and measured by the Griess reaction as described previously[18] with slight modification. Sodium nitroprusside (2M) in phosphate-buffered saline was mixed with different concentrations of the of the test compounds (50, 75, and 100 µg/mL) and incubated at 25°C for 150 min. 1 mL of the reaction mixture was treated with 1 mL of Griess reagent (1% sulfanilamide, 2% H_3PO_4, and 0.1% naphthylethylenediamine dihydrochloride). The absorbance of the chromophore formed during the diazotization of nitrite with sulfanilamide and its subsequent coupling with naphthylethylenediamine was read at 546 nm, relative to the absorbance of standard solutions of potassium nitrite treated in the same way with Griess reagent. Ascorbic acid was used as the standard. NO scavenging activity was calculated by the following equation:

$$I\% = [(A_{control} - A_{sample})/A_{blank}] \times 100$$

H_2O_2 scavenging activity

The H_2O_2 radical scavenging effect of the test compound was determined according to the pervious method[19] with slight modifications. 2 mL (800 µmol/L) of H_2O_2 was prepared in phosphate buffer (pH 7.4) and mixed with 2 mL of the test compounds (50, 75, and 100 µg/mL), and the solution was incubated at room temperature for 15 min. The absorbance value of the reaction mixture was recorded at 230 nm against a blank. Ascorbic acid was used as the standard. The capability of scavenging effect on H_2O_2 was calculated as follows:

$$I\% = [(A_{control} - A_{sample})/A_{blank}] \times 100$$

CONCLUSION

The oxadiazole–piperidine derivatives **6a-h** were synthesized and screened for *in vitro* antioxidant activities. Compounds **6a** and **6b** having chloro substituent in the benzene ring displayed greater radical scavenging activity while the others compounds showed moderate-to-poor radical scavenging abilities in comparison with the standard antioxidant ascorbic acid.

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Received: 16 Feb 2018; Accepted: 13 Jun 2018