Synthesis of new 5-naphthyl substituted 1,3,4-oxadiazole derivatives and their antioxidant activity

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ABSTRACT

A new series of 1-(substituted)-2-\{5-[(naphthalen-1/2-yloxy)methyl]-1,3,4-oxadiazol-2-yl}sulfanyl\}ethanone 5 was synthesized by reacting 5-\{[(naphthalen-1/2-yloxy)methyl]-1,3,4-oxadiazol-2-yl\}sulfonyl\}ethanone 4 with appropriate \(\alpha\)-haloketones by multistep organic synthesis. The newly synthesized compounds were characterised by IR, \(^{1}\)H NMR, mass spectral data and elemental analysis. They were evaluated for antioxidant properties. Few of them exhibited promising activities.

Keywords: 1,3,4-oxadiazole, \(\alpha\)- and \(\beta\)-Naphthol, Antioxidant.

INTRODUCTION

Man has always been fascinated with things that would help him remain youthful and healthy. This desire of mankind is answered through antioxidants. Antioxidants play a key role in achieving optimum health and longevity. The much hype about antioxidants among people is attributed to their ability to combat deadly diseases effectively. They help prevent cancer, prostatitis, heart disease, cataracts, allergies, inflammation and respiratory diseases such as bronchitis and asthma [1]. Hence efforts are going on continuously to discover more efficient antioxidant drugs in order to accomplish our health goals [2-3].

Synthetic organic chemistry has always played a vital role in drug discovery process. Many of the drugs in use in the last fifty years or more have been of synthetic or semi-synthetic origin. Among the several synthesized novel compounds, oxadiazoles draw the attention for their wide applications. The capacity of 1, 3, 4-oxadiazole nucleus to undergo variety of chemical reactions have made it medicinal backbone on which number of potential molecules can be constructed. In fact there are a number of drugs available in the market like raltegravir, an antiretroviral drug, nesapidel, a class IV antiarrhythmic drug, furamizole, a nitro furan derivative possessing a strong antibacterial activity, tiodazosin, an antihypertensive drug, fenadiazole, a hypnotic drug, BB-83698 an antibacterial agent, all of which incorporate the oxadiazole ring [4]. Also documented data suggest that 1, 3, 4 – oxadiazoles possess strong pharmacological properties such as antitumor [5-7], analgesic, anti-inflammatory [8-12], antimitotic [13], antiallergic [14], urease inhibitory [15], cytotoxic [16], antimycobacterial [17], antidiarrheal [18], muscle relaxant[19], photo and electro- luminescence [20], hypotensive [21], hypnotic and sedative [22-23], anti-tubercular, antimalarial [24-25], as well as diuretic [26] property.
In addition, naphthalene containing drugs are also available in the market, such as nafacillin, naftifine, tolnaftate, terbinafine etc, which play vital role in the control of microbial infection. 1,3,4-Oxadiazoles carrying naphthalene moiety have exhibited good antimicrobial [27], anti-inflammatory [28] and antimycobacterial activity [17].

From our laboratory we have reported the synthesis of several new series of bioactive 1, 3, 4 – oxadiazole derivatives [29-33]. α- and β-naphthols and related compounds being identified as active components, we attempted the synthesis of naphthyl substituted 1,3,4-oxadiazole derivatives. The new compounds were evaluated for their antioxidant properties.

MATERIALS AND METHODS

**Chemistry**

Melting points were determined using open capillary method and are uncorrected. The IR spectra (in KBr pellets) were recorded on a Shimadzu FT-IR 157 spectrometer. The $^1$H NMR spectra were recorded on a Bruker AMX–400 (400 MHz) or Bruker AC 300 F (300 MHz) spectrometer using TMS as an internal standard. The chemical shifts are expressed in δ scale downfield from TMS and proton signals are indicated as s= singlet, d= doublet, t= triplet, q= quartet, m = multiplet. The mass spectra were recorded either on a Jeol JMS-D 300 mass spectrometer operating at 70 eV. CHN analysis was carried out on a VARIO EL-I II (Elementar Analysensysteme GmbH).

**General procedure for the preparation of ethyl (naphthalen-1/2-yloxy)acetate (2)**

To a clear solution of αβ-naphthol (0.144g, 1mmol) in dry acetone (10ml) and potassium carbonate (0.152g, 1.1mmol), ethyl chloroacetate (0.134g, 1.1mmol) was added. The reaction mixture was stirred for 36 hrs. The contents were filtered and the filtrate was successively washed with water ($2 \times 20$ mL), saturted brine solution ($1 \times 20$ mL) and dried over anhydrous Na$_2$SO$_4$. Organic layer was evaporated to dryness. Crude product was recrystallized using a mixture of ethyl acetate and hexane.

Ethyl (naphthalen-1-yloxy) acetate; Yield= 95%, M. Pt= 52°C.

Ethyl (naphthalen-2-yloxy) acetate; yield= 94%, M. Pt= 44°C.

**General procedure for the preparation of 2-(naphthalen-1/2-yloxy)acetohydrazide (3)**

To a clear solution of ethyl (naphthalen-1/2-yloxy)acetate 2 (1 eq) in ethanol (10 vol), hydrazine hydrate (1.5 eq) was added slowly. The contents were refluxed on a water bath for 4 hrs. The reaction mixture was concentrated under vacuum. On cooling, hydrazide began to separate. The solid obtained was filtered and recrystallized using ethanol.

2-(Naphthalen-1-yloxy)acetohydrazide; Yield= 96%, M.Pt= 150°C.

2-(Naphthalen-2-yloxy)acetohydrazide; Yield= 96%, M.Pt= 154°C.

**General procedure for the preparation of 5-[(naphthalen-1/2-yloxy)methyl]-1,3,4-oxadiazole-2-thiol (4)**

To a stirred solution of 2-(naphthalen-1/2-yloxy)acetohydrazide 3 (1 eq) in ethanol was added KOH (1.5 eq). To this mixture carbon disulphide (1.5 eq) was added drop wise at room temperature with continuous stirring. Stirring was continued for two more hours to ensure the complete conversion of hydrazide in to its potassium salt. The white precipitate obtained was heated under reflux until the evolution of H$_2$S was completely ceased. It was further heated until an almost pale yellow solution was seen. The solvent was removed under reduced pressure and the residue was dissolved in water, acidified with dil HCl. The resulting product was filtered, washed with water and dried. It was recrystallized from ethanol.

5-[(Naphthalen-1-yloxy)methyl]-1,3,4-oxadiazole-2-thiol; Yield=88%, M.Pt=111°C.

5-[(Naphthalen-2-yloxy)methyl]-1,3,4-oxadiazole-2-thiol; Yield=90%, M.Pt=161°C.
General procedure for the preparation of 1-(substituted)-2-\{5-[(naphthalen-1/-2-yl oxy)methyl]-1,3,4-oxadiazol-2-yl\}sulfanyl)ethanone (5a-5b)

Preparation of 5b: To a solution of 5-[(naphthalen-2-yl oxy)methyl]-1,3,4-oxadiazole-2-thiol (2.58g,10 mmol) in acetonitrile (25 ml) and triethylamine (1.37mL,15mmol), 4-chlorophenyl bromide (2.56g, 11mmol) was added and heated to reflux for 2 hrs. The reaction mixture was concentrated and the residue was dissolved in 50 mL of ethyl acetate and successively washed with water (2 x 25 mL), saturated brine solution (1 x 25 mL) and dried over anhydrous Na₂SO₄. Organic layer was evaporated to dryness. Crude product was recrystallized using a mixture of ethyl acetate and hexane.

5a: 1-\{5-[(Naphthalen-1-yl oxy)methyl]-1,3,4-oxadiazol-2-yl\}sulfanyl)propan-2-one:
Yield 79%, m.p. 76-77°C; IR (KBr) \(\nu/cm\): 3062 (Ar C-H stretching), 2910 (Aliph C-H stretching), 1720 (C=O), 1662 (C=N oxadiazole ring), 1602, 1518, 1575 (C=C), 1153 (C-O-C); \(^1\)H NMR (300MHz, CDCl\(_3\)): \(\delta\) 2.34 (s, 3H, -CH\(_3\)), 4.27 (s, 2H, O-CH\(_3\)), 5.41 (s, 2H, S-CH\(_2\)), 7.21-7.26 (dd, 1H, J=9.0 Hz, naphthyl ring), 7.41-7.58 (m, 3H, naphthyl ring), 7.79-7.85 (m, 3H, naphthyl ring); LC-MS (m/z): 315 (M+1), (M.F.-C\(_{16}\)H\(_{14}\)N\(_2\)O\(_3\)).

5a: 1-\{5-[(Naphthalen-2-yl oxy)methyl]-1,3,4-oxadiazol-2-yl\}sulfanyl)propan-2-one:
Yield 72%, m.p. 111-112°C; IR (KBr) \(\nu/cm\): 3059 (Ar C-H stretching), 2914 (Aliph C-H stretching), 1718 (C=O), 1624 (C=N oxadiazole ring), 1595 (C=C), 1155 (C-O-C); \(^1\)H NMR (300MHz, CDCl\(_3\)): \(\delta\) 2.37 (s, 3H, -CH\(_3\)), 4.23 (s, 2H, O-CH\(_3\)), 5.34 (s, 2H, S-CH\(_2\)), 7.19-7.23 (dd, 1H, J=9.0 Hz, naphthyl ring), 7.37-7.54 (m, 3H, naphthyl ring), 7.76-7.81 (m, 3H, Naphthyl ring); LC-MS (m/z): 315 (M+1), (M.F.-C\(_{16}\)H\(_{14}\)N\(_2\)O\(_3\)).

5b: 1-(4-Chlorophenyl)-2-\{5-[(naphthalen-1-yl oxy)methyl]-1,3,4-oxadiazol-2-yl\}sulfanyl)ethanone:
Yield 77%, m.p. 96-97°C; IR (KBr) \(\nu/cm\): 3049 (Ar C-H stretching), 2912 (Aliph C-H stretching), 1689 (C=O), 1624 (C=N oxadiazole ring), 1597, 1521 (C=C) 1188 (C-O-C); \(^1\)H NMR (400MHz, DMSO-d\(_6\)): \(\delta\) 5.11 (s, 2H, O-CH\(_3\)), 5.57 (s, 2H, S-CH\(_2\)), 7.19-7.24 (d, 1H, J=7.2 Hz, naphthyl ring), 7.40-7.44 (t, 1H, J=8.0 Hz, naphthyl ring), 7.46-7.55 (m, 2H, naphthyl ring), 7.62-7.76 (m, 2H, J=8.8 Hz, naphthyl ring), 8.01-8.05 (d, 2H, J=9.0 Hz, Ar-H ortho to -Cl), 8.77-8.99 (d, 2H, J=8.8 Hz, naphthyl ring), 8.01-8.05 (d, 2H, J=9.0 Hz, Ar-H ortho to -Cl), 8.07-8.09 (d, 2H, J=8.8 Hz, naphthyl ring); LC-MS (m/z): 411 (M+1), 413 (M+2), (M.F.-C\(_{16}\)H\(_{14}\)N\(_2\)O\(_3\)).

5c: 1-(4-Fluorophenyl)-2-\{5-[(naphthalen-1-yl oxy)methyl]-1,3,4-oxadiazol-2-yl\}sulfanyl)ethanone:
Yield 93%, m.p. 147-148°C; IR (KBr) \(\nu/cm\): 3055 (Ar C-H stretching), 2918 (Aliph C-H stretching), 1683 (C=O), 1631 (C=N oxadiazole ring), 1591 (C=C) 1172 (C-O-C); \(^1\)H NMR (400MHz, DMSO-d\(_6\)): \(\delta\) 5.10 (s, 2H, O-CH\(_3\)), 5.49 (s, 2H, S-CH\(_2\)), 7.21-7.24 (d, 1H, J=9.0 Hz, naphthyl ring), 7.37-7.40 (t, 1H, J=7.2 Hz, naphthyl ring), 7.45-7.49 (t, 2H, J=7.8 Hz, naphthyl ring), 7.61-7.64 (d, 2H, J=8.8 Hz, Ar-H meta to -Cl), 7.77-7.79 (d, 1H, J=8.0 Hz, naphthyl ring), 7.84-7.86 (d, 2H, J=9.2 Hz, naphthyl ring), 8.00-8.04 (d, 2H, J=8.8 Hz, Ar-H ortho to -Cl); LC-MS (m/z): 411 (M+1), 413 (M+2), (M.F.-C\(_{16}\)H\(_{14}\)N\(_2\)O\(_3\)).

5d: 1-(4-Nitrophenyl)-2-\{5-[(naphthalen-1-yl oxy)methyl]-1,3,4-oxadiazol-2-yl\}sulfanyl)ethanone:
Yield 92%, m.p. 190-191°C; IR (KBr) \(\nu/cm\): 3042 (Ar C-H stretching), 2920 (Aliph C-H stretching), 1678 (C=O), 1625 (C=N oxadiazole ring), 1597 (C=C), 1510 (NO\(_2\) asymmetric stretch), 1384 (NO\(_2\) symmetric stretch), 1161 (C-O-C); \(^1\)H NMR (400MHz, DMSO-d\(_6\)): \(\delta\) 5.18 (s, 2H, O-CH\(_3\)), 5.57 (s, 2H, S-CH\(_2\)), 7.12-7.14 (d, 1H, J=7.2 Hz, naphthyl ring), 7.39-7.43 (t, 1H, J=8.0 Hz, naphthyl ring), 7.47-7.54 (m, 3H, naphthyl ring), 7.86-7.89 (d, 1H, J=8.8 Hz, naphthyl ring), 8.07-8.09 (d, 2H, J=8.8 Hz, naphthyl ring), 8.22-8.25 (d, 2H, J=9.2 Hz, Ar-H meta to -NO\(_2\)), 8.33-8.36 (d, 2H, J=9.0 Hz, Ar-H ortho to -NO\(_2\)); LC-MS (m/z): 422 (M+1), 423 (M+2), (M.F.-C\(_{16}\)H\(_{14}\)N\(_2\)O\(_3\)).
5d: 1-(4-Nitrophenyl)-2-[[5-([naphthalen-2-yl-oxy)methyl]-1,3,4-oxadiazol-2-yl)sulfanyl]ethanone:
Yield 91%, m.p. 155-156°C; IR (KBr) ν/cm⁻¹: 3045 (Ar C-H stretching), 2918 (Aliph C-H stretching), 1691 (C=O), 1627 (C=N oxadiazole ring), 1597 (C=C), 1521 (NO₂ asymmetric stretch), 1400 (NO₂ symmetric stretch), 1165 (C-O-C); ¹H NMR (400MHz, DMSO-d₆): δ 5.17 (s, 2H, O-CH₃), 5.43 (s, 2H, S-CH₃), 7.35-7.39 (t, 1H, J=8.0 Hz, naphthyl ring), 7.47-7.49 (t, 2H, J=8.2 Hz, naphthyl ring), 7.71-7.77 (d, 1H, J=8.0 Hz, naphthyl ring), 7.82-7.86 (dd, 2H, J=8.4 Hz, naphthyl ring), 8.22-8.24 (d, 2H, J=8.8 Hz, Ar-H meta to –NO₂), 8.33-8.35 (d, 2H, J=8.8 Hz, Ar-H ortho to –NO₂); LC-MS (m/z): 422 (M+1), 423 (M+2), (M-F₂C₇H₁₅N₂O₅S).

5e: 2-[[5-([Naphthalen-1-yl-oxy)methyl]-1,3,4-oxadiazol-2-yl)sulfanyl]-1-phenylethanone:
Yield 83%, m.p. 105-106°C; IR (KBr) ν/cm⁻¹: 3055 (Ar C-H stretching), 1685 (C=O), 1631 (C=N oxadiazole ring), 1587 (C=C), 1179 (C-O-C); ¹H NMR (300MHz, CDCl₃): δ 4.97 (s, 2H, O-CH₃), 4.44 (s, 2H, S-CH₃), 6.98-7.01 (d, 1H, J=9.0 Hz, naphthyl ring), 7.37-7.43 (t, 1H, J=9.0 Hz, naphthyl ring), 7.51-7.56 (m, 5H, 2H of naphthyl ring & 3H of Ar-H), 7.64-7.69 (m, 1H, naphthyl ring), 7.83-8.06 (m, 1H, 3H of naphthyl ring), 8.03-8.06 (d, 2H, J=9.0 Hz, Ar-H), 8.25-8.29 (m, 1H, naphthyl ring); LC-MS (m/z): 377 (M+1), (M-F₂C₇H₁₅N₂O₅S).

5f: 1-(4-Methoxyphenyl)-2-[[5-([naphthalen-1-yl-oxy)methyl]-1,3,4-oxadiazol-2-yl)sulfanyl]ethanone:
Yield 84%, m.p. 144-145°C; IR (KBr) ν/cm⁻¹: 3056 (Ar C-H stretching), 1675 (C=O), 1630 (C=N oxadiazole ring), 1590 (C=C), 1165 (C-O-C); ¹H NMR (300MHz, CDCl₃): δ 3.91 (s, 3H, O-CH₃), 4.94 (s, 2H, O-CH₃), 5.44 (s, 2H, S-CH₃), 6.93-7.01 (m, 3H, naphthyl ring), 7.37-7.43 (t, 1H, J=9.0 Hz, naphthyl ring), 7.51-7.57 (m, 3H, 1H of naphthyl ring, 2H Ar-H meta to –OCH₃), 7.84-8.76 (m, 1H, naphthyl ring), 8.0-8.05 (d, 2H, J=9.0 Hz, Ar-H ortho to –OCH₃), 8.26-8.29 (m, 1H, naphthyl ring); LC-MS (m/z): 407 (M+1), (M-F₂C₇H₁₅N₂O₅S).

5g: 2-[[5-([Naphthalen-2-yl-oxy)methyl]-1,3,4-oxadiazol-2-yl)sulfanyl]-1-[4-(trifluoromethyl)phenyl]ethanone:
Yield 83%, m.p. 93-94°C; IR (KBr) ν/cm⁻¹: 3058 (Ar C-H stretching), 2918 (Aliph C-H stretching), 1680 (C=O), 1629 (C=N oxadiazole ring), 1594 (C=C), 1160 (C-O-C); ¹H NMR (300MHz, CDCl₃): δ 4.92(s, 2H, O-CH₃), 5.43 (s, 2H, S-CH₃), 6.96-6.99 (d, 1H, J=7.2 Hz, naphthyl ring), 7.36-7.42 (t, 1H, J=9.0 Hz, naphthyl ring), 7.53-7.61 (m, 3H, naphthyl ring), 7.78-8.00 (m, 3H, 1H of naphthyl ring and 2H of Ar-H meta to –CF₃), 8.16-8.17 (d, 2H, J=9.0 Hz, 2H of Ar-H ortho to –CF₃), 8.23-8.26 (d, 1H, J=9.0 Hz, naphthyl ring); LC-MS (m/z): 445 (M+1), (M-F₂C₇H₁₅F₃N₂O₅S).

5h: 1-[[5-([Naphthalen-1-yl-oxy)methyl]-1,3,4-oxadiazol-2-yl)sulfanyl]butan-2-one:
Yield 77% m.p. 80-81°C; IR (KBr) ν/cm⁻¹: 3062 (Ar C-H stretching), 2914 (Aliph C-H stretching), 1716 (C=O), 1630 (C=N oxadiazole ring), 1598, 1571 (C=C), 1157 (C-O-C); ¹H NMR (400MHz, MeOD): δ 1.25-1.28 (t, 3H, J=7.5 Hz, -CH₂-CH₃), 2.72-2.77 (q, 2H, J=7.54 Hz, -CH₂-CH₃), 4.21 (s, 2H, O-CH₂), 5.36 (s, 2H, S-CH₃), 7.01-8.12 (m, 7H, naphthyl ring); LC-MS (m/z): 329 (M+1), (M-F₂C₇H₁₅N₂O₅S).
5h: 1-[(5-[(Naphthal-2-yloxy)methyl]-1,3,4-oxadiazol-2-yl)sulfanyl]butan-2-one: Yield 71%, m.p. 78-79°C; IR (KBr) γ/cm⁻¹: 3061 (Ar C–H stretching), 2914 (Aliph C–H stretching), 1714 (C=O), 1627 (C=N oxadiazole ring), 1595 (C=C), 1166 (C-O-C); 1H NMR (400MHz, MeOD); 1.24-1.27 (t, 3H, J=7.5 Hz, -CH₂–CH₃), 2.70-2.75 (q, 2H, J=7.54 Hz, -CH₂–CH₃), 5.20 (s, 2H, S-CH₂–CH₃), 4.19 (s, 2H, O-CH₂–CH₃), 5.20 (s, 2H, S-CH₂–CH₃), 6.85-7.79 (m, 7H, naphthyl ring); LC-MS (m/z): 329 (M+1), (M+H–C=N oxadiazole ring), 1595 (C=C), 1166 (C-O-C); LC-MS (m/z): 329 (M+1), (M+H–C=N oxadiazole ring), 1595 (C=C), 1166 (C-O-C); 1H NMR, IR, mass spectral and elemental analysis. The appearance of peaks at ~1620 cm⁻¹ indicating the involvement of –NH/–NH₂ and ~3220 cm⁻¹ confirmed the cyclization of hydrazide into oxadiazole. The IR spectral data of compounds 5a-5h supported the formation of oxadiazole.

DPPH radical scavenging assay

The DPPH assay was based on the reported method [34]. Briefly, the DMSO sample of compounds at 100 μg/mL was diluted to 4 mL using methanol. To this 1mL of 1,1-diphenyl-2-picryl-hydrazyl (DPPH) solution in methanol was added. The mixed solution was incubated at room temperature for 30 min. The absorbance of stable DPPH was read at 517 nm using UV-Visible spectrophotometer and the remaining DPPH was calculated. Ascorbic acid was taken as standard. The free radical scavenging activity was expressed as follows:

DPPH scavenging activity (%) = \[ \frac{[Ac–As]}{[Ac–Ab]} \times 100 \]

Where Ac was the absorbance of the control, As for the sample and Ab for the blank (MeOH+DMSO). Each sample was assayed at 100 μg/mL and all experiments were carried out in triplicate and the % RSC is shown in Fig 1.

RESULTS AND DISCUSSION

Chemistry

The synthesis of hitherto unreported title compounds was done as per Schemes 1.1 and 1.2. The key intermediate, ethyl (naphthalen-1/2-ylloxy)acetate 2, was prepared in excellent yield by treating α/β-naphthol with ethyl chloroacetate in dry acetone in the presence of anhydrous potassium carbonate under reflux [35-36]. The 2-(naphthalen-1/2-ylloxy)acetohydrazide 3 was prepared by hydrazinolysis of ester 2 with hydrazine hydrate [37]. 5-[(α/β-Naphthoxy-methyl)-1,3,4-oxadiazole-2-thiols 4 were prepared by the nucleophilic addition of carbon disulfide in alcoholic KOH followed by cyclization of resultant potassium salt of carbodithioic acid in con.HCl at 0°C [38-39]. Reaction of 4 with appropriate α-haloketones in the presence of triethylamine yielded thioc compounds 5.

The structures of the newly synthesized compounds have been established on the basis of 1H NMR, IR, mass spectral and elemental analysis. The appearance of peaks at ~1620 cm⁻¹ (C=N), 1510, 1319, 1218 cm⁻¹ (N=C=S) and 1155 cm⁻¹ (cyclic C-O-C) confirmed the cyclization of hydrazide 3 into oxadiazole 4. Also a broad singlet at 14.63 ppm for SH proton and downfield shift of methylene protons from δ 4.9 ppm in hydrazide to δ 5.37ppm further supported the formation of oxadiazole.

The IR spectra of 2-(naphthalen-1/2-ylloxy)acetohydrazide 3 have amide C=O and NH₂ stretching bands at ~1670 and ~3220 cm⁻¹, respectively. The disappearance of amide C=O and NH₂ stretching bands of 3 and detection of strong C–O–C, C=S, and C=N stretching bands at about ~1150, ~1235 and ~1632 cm⁻¹, respectively, are evidences for ring closure of 1,3,4-oxadiazoles-2(3H) thiones 4. NH proton of oxadiazole resonated as a broad singlet at 14.63 ppm and downfield shift of methylene protons (-O-CH₂–CH₃) from δ 4.9 ppm in hydrazide to δ 5.37ppm further supported the formation of oxadiazole. The IR spectral data of compounds 5a-5h lacked a peak at ~3315cm⁻¹ indicating the involvement of –NH/–NH₂ peak up to 5.2 ppm and appearance of another singlet integrating for 2 protons at δ ~ 5.5 ppm for –S-CH₂ further proves it. 7 protons of the naphthyl ring appeared as a multiplet in the region 7.05 to 8.1 ppm. Two more sets of protons, ortho and meta to the substituent group in the phenyl ring showed a pair of doublets which experienced a downfield shift each time the electronegativity of the substituent in phenacyl bromide derivatives increased. Ortho protons resonated at δ 8.01 ppm for 5a (R=CH₃) and at δ 8.36 ppm for 5d (R=NO₂). Similarly for the same compounds meta protons resonated in the range δ 7.62 ppm to δ 8.25 ppm.

Scheme 1.1

Scheme 1.2

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<th>Sl. No.</th>
<th>Ar</th>
<th>R</th>
<th>Mol. Formula (Mol. wt)</th>
<th>Melting point (°C)</th>
<th>Yield (%)</th>
<th>CHN Analysis Found (calculated)</th>
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<td>5a</td>
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<td>-CH₃</td>
<td>C₁₆H₁₄N₂O₃S (314.35)</td>
<td>76-77</td>
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<td>111-112</td>
<td>82.00</td>
<td>61.14 (61.13)</td>
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<td>5b</td>
<td></td>
<td></td>
<td>C₁₂H₁₀ClN₂O₅S (410.87)</td>
<td>96-97</td>
<td>76.96</td>
<td>61.33 (61.39)</td>
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<tr>
<td>5'b</td>
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<td></td>
<td>C₁₂H₁₀ClN₂O₅S (410.87)</td>
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<td>90.95</td>
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<tr>
<td>5c</td>
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<td>93.24</td>
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<td>63.91 (63.95)</td>
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<td>5d</td>
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<td>190-191</td>
<td>91.80</td>
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### Table 1: Characterisation data of thio ethers of 5-(α/β-napthoxy-methyl)-1,3,4-oxadiazole

<table>
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<th>Molecular Formula</th>
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<th>% C</th>
<th>% H</th>
<th>% N</th>
<th>% S</th>
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**Antioxidant Activity**

**DPPH Radical Scavenging Assay**

The DPPH antioxidant assay, a rapid, simple and inexpensive method to measure antioxidant capacity of substances, is based on the ability of DPPH, a stable free radical to decolorize in the presence of antioxidants. The DPPH radical contains an odd electron which is responsible for the absorbance at 517 nm and also for visible deep purple colour. When DPPH accepts an electron donated by an antioxidant compound the DPPH is decolorized which can be quantitatively measured from the changes in absorbance. Antioxidants tested on DPPH were also found extremely effective in cell systems. This simple test provides information on the ability of a compound to donate electrons during antioxidant action [40]. The radical scavenging mechanism is based on the transfer of acidic H-atom from the compound to DPPH radical to form DPPH-H.
Results based on DPPH radical scavenging assay indicated that, few of the tested compounds are significant in their antioxidant properties. Compound 5f was the most efficient of them with its %DPPH assay value almost comparable with the standard drug ascorbic acid. Its property could be attributed to the methoxy group attached to the phenyl ring in the molecule, as the rest of the molecule is the same in all the compounds. Apart from this, compounds 5a and 5g with –CH₃ and –CF₃ as substituent to the phenyl ring also exhibited good DPPH scavenging, whereas 5′a (-CH₃), 5c (-F) and 5e (-C₆H₅) showed moderate activities in comparison with the standard drug ascorbic acid. One of the most striking observations is that, out of the six compounds mentioned above, five of them (5f, 5c, 5e, 5f & 5g) are derivatives of α-naphthol. It is interesting to note that α-naphthol derivatives are better in their antioxidant property than their corresponding β-derivatives.

CONCLUSION

To summarize, we have synthesized a new class of 1,3,4-oxadiazoles as potent antioxidant agents. The newly synthesized heterocycles exhibited noteworthy DPPH radical scavenging. Compound 1-(4-methoxyphenyl)-2-{5-[(naphthalen-1-yl-oxy)methyl]-1,3,4-oxadiazol-2-yl}sulfanyl)ethanone (5f) could be a compound of great interest with its good antioxidant activity. These results make novel oxadiazoles interesting lead molecules for more synthetic and biological evaluation. It can be concluded that this class of compounds in particular α-naphthol derivatives certainly hold great promise towards pursuit to discover novel class of antioxidant agents. Further work is in progress to screen these compounds for some more activity.

Acknowledgements

One of the authors (P.P) is thankful to UGC for providing financial help for the research work through UGC-BSR scheme, the Head, IISc, Bangalore, for spectral data and also thanks to the Department of Applied Botany, Mangalore University for the antioxidant studies.

REFERENCES
