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

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ABSTRACT

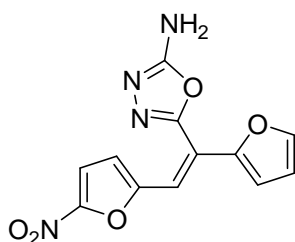
A new series of 1-(substituted)-2-({5-[(naphthalen-1/2-yloxy)methyl]-1,3,4-oxadiazol-2-yl}sulfonyl)ethanone **5** was synthesized by reacting 5-[(naphthalen-1/2-yloxy)methyl]-1,3,4-oxadiazole-2-thiol **4** with appropriate α -haloketones by multistep organic synthesis. The newly synthesized compounds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

Keywords: 1,3,4-oxadiazole, α - and β -Naphthol, Antioxidant.

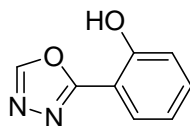
INTRODUCTION

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].

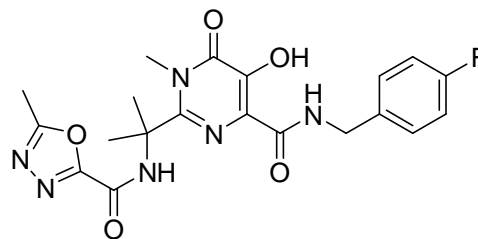
Synthetic organic chemistry has always played a vital role in drug discovery process. Many of the drugs in use in the last fifty years or more have been of synthetic or semi-synthetic origin. Among the several synthesized novel compounds, oxadiazoles draw the attention for their wide applications. The 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, nesapidil, 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.



Furamizole (Antibacterial)



Fenadiazole (Hypnotic)



Raltegravir (Anti-HIV)

In addition, naphthalene containing drugs are also available in the market, such as nafcillin, 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 ^1H 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-III (Elementar Analysensysteme GmbH).

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

To a clear solution of α/β -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 (2×20 mL), saturated brine solution (1×20 mL) and dried over anhydrous Na_2SO_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_2S 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-yloxy)methyl]-1,3,4-oxadiazol-2-yl}sulfanyl)ethanone (5 a-5'h)

Preparation of **5'b**: To a solution of 5-[(naphthalen-2-yloxy)methyl]-1,3,4-oxadiazole-2-thiol (2.58g, 10 mmol) in acetone (25 ml) and triethylamine (1.37mL, 15mmol), 4-chloro phenacyl 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 × 25 mL), saturated brine solution (1 × 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-yloxy)methyl]-1,3,4-oxadiazol-2-yl}sulfanyl)propan-2-one:

Yield 79%, m.p. 76-77°C; IR (KBr) γ/cm^{-1} : 3062 (Ar C-H stretching), 2910 (Aliph C-H stretching), 1720 (C=O), 1662 (C=N oxadiazole ring), 1602, 1581, 1575 (C=C), 1153 (C-O-C); ¹H NMR (300MHz, CDCl₃): δ 2.34 (s, 3H, -CH₃), 4.27 (s, 2H, O-CH₂), 5.41 (s, 2H, S-CH₂), 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- C₁₆H₁₄N₂O₃S).

5'a: 1-({5-[(Naphthalen-2-yloxy)methyl]-1,3,4-oxadiazol-2-yl}sulfanyl)propan-2-one:

Yield 82%, m.p. 111-112°C; IR (KBr) γ/cm^{-1} : 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); ¹H NMR (300MHz, CDCl₃): δ 2.37 (s, 3H, -CH₃), 4.23 (s, 2H, O-CH₂), 5.34 (s, 2H, S-CH₂), 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- C₁₆H₁₄N₂O₃S).

5b: 1-(4-Chlorophenyl)-2-({5-[(naphthalen-1-yloxy)methyl]-1,3,4-oxadiazol-2-yl}sulfanyl)ethanone:

Yield 77%, m.p. 96-97°C; IR (KBr) γ/cm^{-1} : 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); ¹H NMR (400MHz, DMSO-d₆): δ 5.11 (s, 2H, O-CH₂), 5.57 (s, 2H, S-CH₂), 7.12-7.14 (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), 7.62-7.64 (d, 2H, J=9.0 Hz, Ar-H meta to -Cl), 7.87-7.89 (d, 1H, 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- C₂₁H₁₅ClN₂O₃S).

5'b: 1-(4-Chlorophenyl)-2-({5-[(naphthalen-2-yloxy)methyl]-1,3,4-oxadiazol-2-yl}sulfanyl)ethanone:

Yield 91%, m.p. 147-148°C; IR (KBr) γ/cm^{-1} : 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); ¹H NMR (400MHz, DMSO-d₆): δ 5.10 (s, 2H, O-CH₂), 5.49 (s, 2H, S-CH₂), 7.21-7.24 (d, 1H, J=9.0 Hz, naphthyl ring), 7.35-7.40 (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- C₂₁H₁₅ClN₂O₃S).

5c: 1-(4-Fluorophenyl)-2-({5-[(naphthalen-1-yloxy)methyl]-1,3,4-oxadiazol-2-yl}sulfanyl)ethanone :

Yield 93%, m.p. 109-110°C; IR (KBr) γ/cm^{-1} : 3050 (Ar C-H stretching), 2917 (Aliph C-H stretching), 1671 (C=O), 1624 (C=N oxadiazole ring), 1588 (C=C) 1155 (C-O-C); ¹H NMR (400MHz, CDCl₃): δ 4.92 (s, 2H, O-CH₂), 5.45 (s, 2H, S-CH₂), 6.98-7.00 (d, 1H, J=7.6 Hz, naphthyl ring), 7.19-7.23 (m, 2H, naphthyl ring), 7.51-7.54 (m, 1H, naphthyl ring), 7.82-7.85 (m, 3H, naphthyl ring), 8.07-8.10, 8.25-8.28 (m, 4H, Ar-H ortho and meta to -F); LC-MS (m/z): 395 (M+1), (M.F- C₂₁H₁₅FN₂O₃S).

5'c: 1-(4-Fluorophenyl)-2-({5-[(naphthalen-2-yloxy)methyl]-1,3,4-oxadiazol-2-yl}sulfanyl)ethanone:

Yield 87%, m.p. 130-131°C; IR (KBr) γ/cm^{-1} : 3051 (Ar C-H stretching), 2919 (Aliph C-H stretching), 1675 (C=O), 1626 (C=N oxadiazole ring), 1593 (C=C) 1156 (C-O-C); ¹H NMR (400MHz, CDCl₃): δ 4.91 (s, 2H, O-CH₂), 5.36 (s, 2H, S-CH₂), 7.17-7.22 (m, 3H, naphthyl ring), 7.23-7.29 (m, 1H, naphthyl ring), 7.37-7.41 (m, 1H, naphthyl ring), 7.46-7.50 (m, 1H, naphthyl ring), 7.76-7.80 (m, 3H, 1H of naphthyl ring, 2H of Ar-H), 8.05-8.09 (m, 2H, Ar-H); LC-MS (m/z): 395 (M+1), (M.F- C₂₁H₁₅FN₂O₃S).

5d: 1-(4-Nitrophenyl)-2-({5-[(naphthalen-1-yloxy)methyl]-1,3,4-oxadiazol-2-yl}sulfanyl)ethanone:

Yield 92%, m.p. 190-191°C; IR (KBr) γ/cm^{-1} : 3042 (Ar C-H stretching), 2920 (Aliph C-H stretching), 1678 (C=O), 1625 (C=N oxadiazole ring), 1597 (C=C), 1510 (NO₂ asymmetric stretch), 1384 (NO₂ symmetric stretch), 1161 (C-O-C); ¹H NMR (400MHz, DMSO-d₆): δ 5.18 (s, 2H, O-CH₂), 5.57 (s, 2H, S-CH₂), 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, 1H, J=8.8 Hz, naphthyl ring), 8.22-8.25 (d, 2H, J=9.2 Hz, Ar-H meta to -NO₂), 8.33-8.36 (d, 2H, J=9.0 Hz, Ar-H ortho to -NO₂); LC-MS (m/z): 422 (M+1), 423 (M+2), (M.F- C₂₁H₁₅N₃O₅S).

5'd: 1-(4-Nitrophenyl)-2-({5-[(naphthalen-2-yloxy)methyl]-1,3,4-oxadiazol-2-yl}sulfanyl)ethanone:

Yield 91%, m.p. 155-156°C; IR (KBr) γ/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-CH₂), 5.49 (s, 2H, S-CH₂), 7.21-7.24 (d, 1H, J=8.8 Hz, naphthyl ring), 7.35-7.39 (t, 1H, J=8.0 Hz, naphthyl ring), 7.44-7.49 (t, 2H, J=8.2 Hz, naphthyl ring), 7.77-7.79 (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.F- C₂₁H₁₅N₃O₅S).

5e: 2-({5-[(Naphthalen-1-yloxy)methyl]-1,3,4-oxadiazol-2-yl}sulfanyl)-1-phenylethanone:

Yield 83%, m.p. 105-106°C; IR (KBr) γ/cm^{-1} : 3055 (Ar C-H stretching), 2920 (Aliph 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-CH₂), 5.44 (s, 2H, S-CH₂), 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), 7.83-7.86 (m, 1H, 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.F- C₂₁H₁₆N₂O₃S).

5'e: 2-({5-[(Naphthalen-2-yloxy)methyl]-1,3,4-oxadiazol-2-yl}sulfanyl)-1-phenylethanone:

Yield 69%, m.p. 124-125°C; IR (KBr) γ/cm^{-1} : 3055 (Ar C-H stretching), 2922 (Aliph C-H stretching), 1680 (C=O), 1631 (C=N oxadiazole ring), 1585 (C=C), 1170 (C-O-C); ¹H NMR (300MHz, CDCl₃): δ 4.97 (s, 2H, O-CH₂), 5.37 (s, 2H, S-CH₂), 7.21-8.01 (m, 12H, 7H of naphthyl ring & 5H of Ar-H); LC-MS (m/z): 377 (M+1), (M.F- C₂₁H₁₆N₂O₃S).

5f: 1-(4-Methoxyphenyl)-2-({5-[(naphthalen-1-yloxy)methyl]-1,3,4-oxadiazol-2-yl}sulfanyl)ethanone:

Yield 84%, m.p. 144-145°C; IR (KBr) γ/cm^{-1} : 3056 (Ar C-H stretching), 2925 (Aliph 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, -OCH₃), 4.94 (s, 2H, O-CH₂), 5.44 (s, 2H, S-CH₂), 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), 7.84-7.86 (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.F- C₂₂H₁₈N₂O₄S).

5'f: 1-(4-Methoxyphenyl)-2-({5-[(naphthalen-2-yloxy)methyl]-1,3,4-oxadiazol-2-yl}sulfanyl)ethanone:

Yield 70%, m.p. 126-127°C; IR (KBr) γ/cm^{-1} : 3057 (Ar C-H stretching), 2913 (Aliph C-H stretching), 1656 (C=O), 1629 (C=N oxadiazole ring), 1594 (C=C), 1160 (C-O-C); ¹H NMR (300MHz, CDCl₃): δ 3.94 (s, 3H, -OCH₃), 4.95 (s, 2H, O-CH₂), 5.43 (s, 2H, S-CH₂), 6.95-7.04 (m, 3H, naphthyl ring), 7.36-7.42 (t, 1H, J=9.0 Hz, naphthyl ring), 7.54-7.61 (m, 3H, 1H of naphthyl ring, 2H Ar-H meta to -OCH₃), 7.85-7.88 (m, 1H, naphthyl ring), 8.02-8.07 (d, 2H, J=9.0 Hz, Ar-H ortho to -OCH₃), 8.27-8.31 (m, 1H, naphthyl ring); LC-MS (m/z): 407 (M+1), (M.F- C₂₂H₁₈N₂O₄S).

5g: 2-({5-[(Naphthalen-1-yloxy)methyl]-1,3,4-oxadiazol-2-yl}sulfanyl)-1-[4-(trifluoromethyl)phenyl]ethanone:

Yield 83%, m.p. 93-94°C; IR (KBr) γ/cm^{-1} : 3058 (Ar C-H stretching), 2916 (Aliph C-H stretching), 1680 (C=O), 1624 (C=N oxadiazole ring), 1597 (C=C), 1325 (C-F of CF₃), 1161 (C-O-C); ¹H NMR (300MHz, CDCl₃): δ 4.92 (s, 2H, O-CH₂), 5.43 (s, 2H, S-CH₂), 6.96-6.99 (d, 1H, J=7.2 Hz, naphthyl ring), 7.36-7.41 (t, 1H, J=8.1 Hz, naphthyl ring), 7.50-7.53 (m, 3H, naphthyl ring), 7.78-7.80 (m, 3H, 1H of naphthyl ring and 2H of Ar-H meta to -CF₃), 8.13-8.16 (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.F- C₂₂H₁₅F₃N₂O₃S).

5'g: 2-({5-[(Naphthalen-2-yloxy)methyl]-1,3,4-oxadiazol-2-yl}sulfanyl)-1-[4-(trifluoromethyl)phenyl]ethanone:

Yield 85.9%, m.p. 145-147°C; IR (KBr) γ/cm^{-1} : 3057 (Ar C-H stretching), 2914 (Aliph C-H stretching), 1680 (C=O), 1627 (C=N oxadiazole ring), 1597 (C=C), 1322 (C-F of CF₃), 1166 (C-O-C); ¹H NMR (300MHz, CDCl₃): δ 4.92 (s, 2H, O-CH₂), 5.36 (s, 2H, S-CH₂), 7.18-7.19 (dd, 1H, J=9.03 Hz, naphthyl ring), 7.26-7.29 (t, 1H, J=7.83 Hz, naphthyl ring), 7.36-7.41 (t, 1H, J=8.1 Hz, naphthyl ring), 7.45-7.50 (t, 1H, J=7.98 Hz, naphthyl ring), 7.75-7.80 (m, 5H, 3H of naphthyl ring and 2H of Ar-H meta to -CF₃), 8.12-8.15 (d, 2H, J=8.28 Hz, 2H of Ar-H ortho to -CF₃); LC-MS (m/z): 445 (M+1), (M.F- C₂₂H₁₅F₃N₂O₃S).

5h: 1-({5-[(Naphthalen-1-yloxy)methyl]-1,3,4-oxadiazol-2-yl}sulfanyl)butan-2-one:

Yield 77% m.p. 80-81°C; IR (KBr) γ/cm^{-1} : 3062 (Ar C-H stretching), 2941 (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-CH₂), 7.01-8.12 (m, 7H, naphthyl ring); LC-MS (m/z): 329 (M+1), (M.F- C₁₇H₁₆N₂O₃S).

5'h: 1-({5-[(Naphthalen-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), 4.19 (s, 2H, O-CH₂), 5.20 (s, 2H, S-CH₂), 6.85-7.79 (m, 7H, naphthyl ring); LC-MS (m/z): 329 (M+1), (M.F- C₁₇H₁₆N₂O₃S).

DPPH radical scavenging assay

The DPPH assay was based on the reported method [34]. Briefly, the DMSO sample of compounds at 100 $\mu\text{g}/\text{mL}$ 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:

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

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 $\mu\text{g}/\text{mL}$ and all experiments were carried out in triplicate and the % RSC is shown in **Fig 1**.

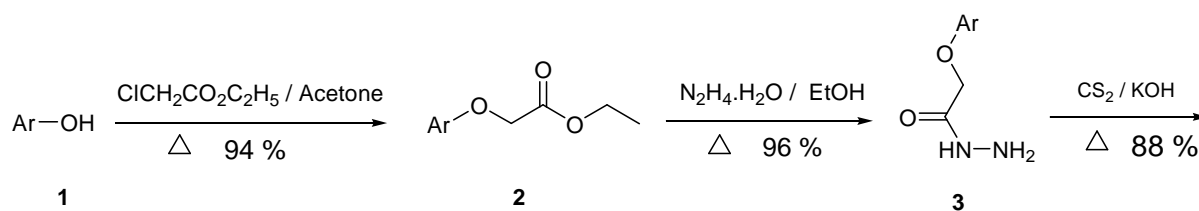
RESULTS AND DISCUSSION

Chemistry

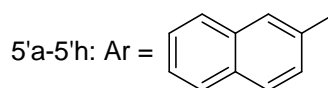
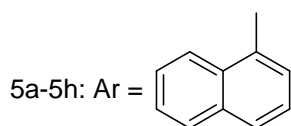
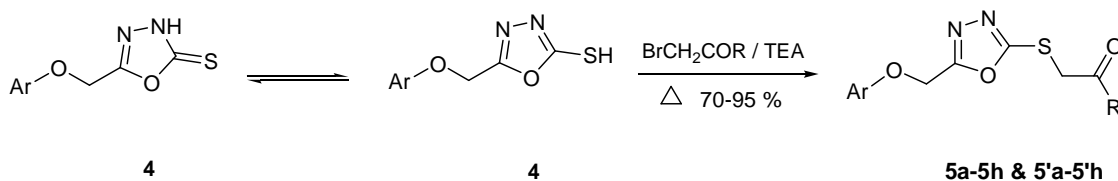
The synthesis of hitherto unreported title compounds was done as per Schemes 1.1 and 1.2. The key intermediate, ethyl (naphthalen-1/2-yloxy)acetate **2**, was prepared in excellent yield by treating α/β -naphthol with ethyl chloroacetate in dry acetone in the presence of anhydrous potassium carbonate under reflux [35-36]. The 2-(naphthalen-1/2-yloxy)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 thio ethers **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 $\sim 1620\text{ cm}^{-1}$ (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-yloxy)acetohydrazide **3** have amide C=O and NH₂ stretching bands at ~ 1670 and $\sim 3220\text{ cm}^{-1}$, 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 $\sim 1632\text{ cm}^{-1}$ 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) from δ 4.9 ppm in hydrazide to δ 5.37ppm further supported the formation of oxadiazole. The IR spectral data of compounds **5a-5'h** lacked a peak at $\sim 3315\text{ cm}^{-1}$ indicating the involvement of -NH/S_H proton of oxadiazole ring in the reaction and S-substitution was reasserted with the presence of a strong peak at $\sim 1715\text{ cm}^{-1}$ characteristic of carbonyl group. Further evidence is seen in ^1H NMR with the downfield shift of -O-CH₂- peak upto 5.2 ppm and appearance of another singlet integrating for 2 protons at $\delta \sim 5.5$ 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

Sl. No.	Ar	R	Mol. Formula (Mol. wt)	Melting point (°C)	Yield (%)	CHN Analysis Found (calculated)		
						C	H	N
5a		-CH ₃	C ₁₆ H ₁₄ N ₂ O ₃ S (314.35)	76-77	79.00	61.19 (61.13)	4.55 (4.49)	8.76 (8.91)
5'a		-CH ₃	C ₁₆ H ₁₄ N ₂ O ₃ S (314.35)	111-112	82.00	61.14 (61.13)	4.52 (4.49)	8.75 (8.91)
5b			C ₂₁ H ₁₅ ClN ₂ O ₃ S (410.87)	96-97	76.96	61.33 (61.39)	3.72 (3.68)	6.78 (6.82)
5'b			C ₂₁ H ₁₅ ClN ₂ O ₃ S (410.87)	147-148	90.95	61.36 (61.39)	3.70 (3.68)	6.81 (6.82)
5c			C ₂₁ H ₁₅ FN ₂ O ₃ S (394.41)	109-110	93.24	63.93 (63.95)	3.95 (3.83)	7.16 (7.10)
5'c			C ₂₁ H ₁₅ FN ₂ O ₃ S (394.41)	130-131	87.10	63.91 (63.95)	3.85 (3.83)	7.08 (7.10)
5d			C ₂₁ H ₁₅ N ₃ O ₅ S (421.42)	190-191	91.80	59.93 (59.85)	3.57 (3.59)	10.01 (9.97)

5'd			C ₂₁ H ₁₅ N ₃ O ₅ S (421.42)	155-156	91.03	59.81 (59.85)	3.52 (3.59)	9.98 (9.97)
5e			C ₂₁ H ₁₆ N ₂ O ₃ S (376.42)	105-106	82.56	67.09 (67.00)	4.32 (4.28)	7.39 (7.44)
5'e			C ₂₁ H ₁₆ N ₂ O ₃ S (376.42)	124-125	68.80	67.02 (67.00)	4.31 (4.28)	7.41 (7.44)
5f			C ₂₂ H ₁₈ N ₂ O ₄ S (406.45)	144-145	84.09	65.03 (65.01)	4.45 (4.46)	6.97 (6.89)
5'f			C ₂₂ H ₁₈ N ₂ O ₄ S (406.45)	126-127	68.32	65.06 (65.01)	4.39 (4.46)	6.94 (6.89)
5g			C ₂₂ H ₁₅ F ₃ N ₂ OS (444.42)	93-94	83.04	59.43 (59.46)	3.42 (3.40)	6.41 (6.30)
5'g			C ₂₂ H ₁₅ F ₃ N ₂ OS (444.42)	145-147	85.94	59.39 (59.46)	3.37 (3.40)	6.32 (6.30)
5h		-C ₂ H ₅	C ₁₇ H ₁₆ N ₂ O ₃ S (328.38)	80-81	77.21	62.23 (62.18)	4.89 (4.91)	8.45 (8.53)
5'h		-C ₂ H ₅	C ₁₇ H ₁₆ N ₂ O ₃ S (328.38)	78-79	71.63	62.21 (62.18)	4.89 (4.91)	8.55 (8.53)

Table 1: Characterisation data of thio ethers of 5-(α/β -naphthoxy-methyl)-1,3,4-oxadiazole

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.

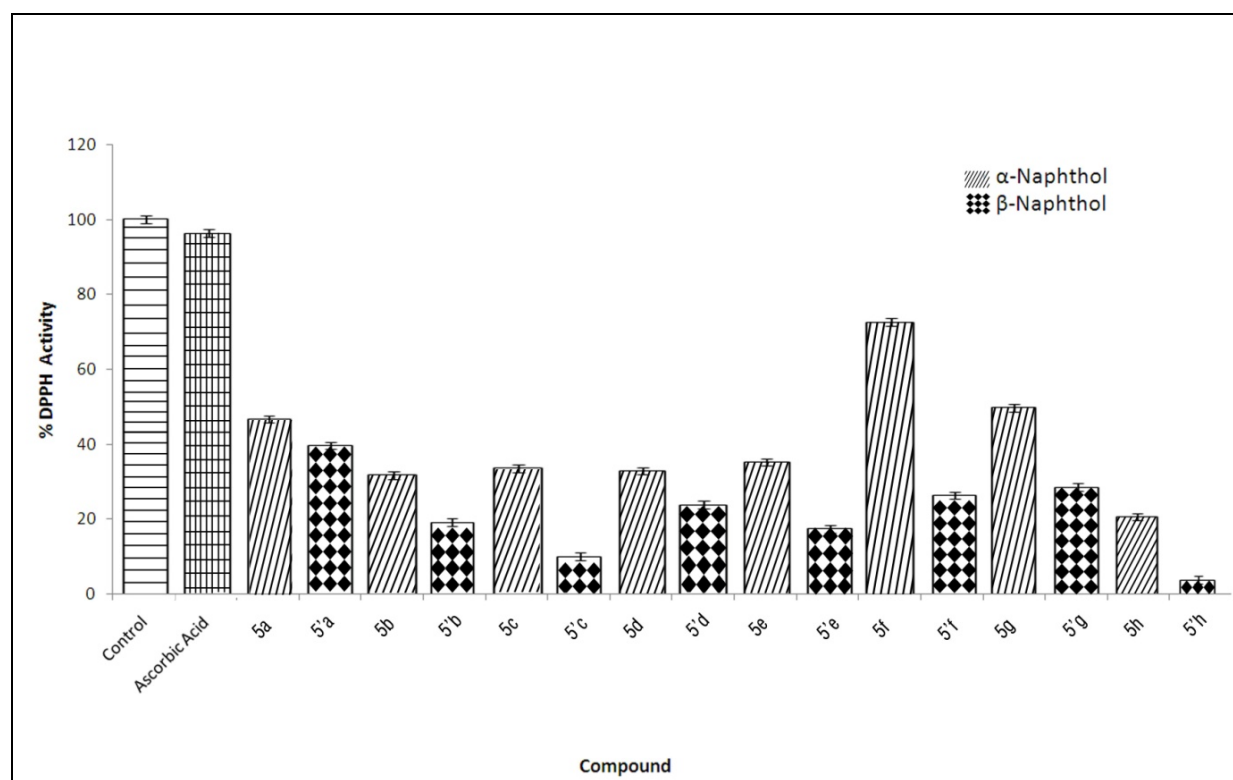


Fig 1: % DPPH radical scavenging activity of synthesized compounds (Avg±SEM) at a concentration of 100µg/ml

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 $-\text{CH}_3$ and $-\text{CF}_3$ as substituent to the phenyl ring also exhibited good DPPH scavenging, whereas **5'a** ($-\text{CH}_3$), **5c** ($-\text{F}$) and **5e** ($-\text{C}_6\text{H}_5$) 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-yloxy)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.

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REFERENCES

- [1] Prithviraj Chakraborty, Suresh Kumar, Debarupa Dutta, and Vikas Gupta, *Research J. Pharm. and Tech.*, **2009**, 2(2), 238-244.
- [2] María Pilar López-Gresa, Cristina Torres, Laura Campos, Purificación Lisón, Ismael Rodrigo, José María Bellés, Vicente Conejero, *Environ. Exp. Bot.*, **2011**, 74, 216-228.

- [3] Seranthimata Samshuddin, Badiadka Narayana, Balladka Kunhanna Sarojini, Leelavathi Narayana Madhu, *Med Chem Res.*, Nov **2012**, DOI 10.1007/s00044-012-0304-7.
- [4] R. Rakesh Somani, Y. Prabhakar Shirodkar, *Der Pharma Chemica.*, **2009**, 1, 130-140.
- [5] Mohd Rashid, Asif Husain, Ravinesh Mishra, *Eur J. Med. Chem.*, **2012**, 54, 855-866.
- [6] Han-Zhong Zhang, Shailaja Kasibhatla, Jared Kuemmerle, William Kemnitzer, Kristin Ollis-Mason, Ling Qiu, Candace Crogan-Grundy, Ben Tseng, John Drewe, and Sui Xiong Cai, *J. Med. Chem.*, **2005**, 48(16), 5215-5223.
- [7] Jonas Boström, Anders Hogner, Antonio Llinàs, Eric Wellner, and Alleyn T. Plowright, *J. Med. Chem.*, **2012**, 55(5), 1817-1830.
- [8] Nimavat Bhargab, Mohan Shamanna, Saravanan Janardhan, Deka Satyendra, Talukdar Apurba, Sahariah Bhargab Jyoti, Dey Biplab Kumar, Sarma Rama Kanta, *International Journal of Research in Pharmacy and Chemistry*, **2012**, 2(3), 594-602.
- [9] A. Adnan Kadi, R. Nasser El-Brollosy, A. Omar Al-Deeb, E. Elsayed Habib, M. Tarek Ibrahim, A. Ali El-Emam, *Eur. J. Med. Chem.*, **2007**, 42(2), 235-242.
- [10] Mymoona Akhter, Asif Husain, Bismillah Azad, Mohd. Ajmal, *Eur. J. Med. Chem.*, **2009**, 44(6), 2372-2778.
- [11] L. Sawant Ramesh, D. Lanke Prashant, *International Journal of Drug Design and Discovery*, **2010**, 1(4), 336-344.
- [12] V. Shashikant Bhandari, G. Kailash Bothara, K. Mayuresh Raut, A. Ajit Patil, P. Aniket Sarkate and J. Vinod Mokale, *Bioorg. Med. Chem.*, **2008**, 16(4), 1822-1831.
- [13] D.Ghiran, I.Schwartz, Simiti, *Farmacia*, **1974**, 22(3), 141-146.
- [14] Reddy Guda Dinneswara, Park Sae-Jin, Cho Hyeon Mo, Kim Tack-Joong, Lee Myong Euy, *J. Med. Chem.*, **2012**, 55(14), 6438-6444.
- [15] Sohail Anjum Shahzad, Muhammad Yar, Zulfiqar Ali Khan, Islam Ullah Khan, Syed Ali Raza Naqvi, Nasir Mahmood, Khalid Mohammed Khan, *Eur. J. Chem.*, **2012**, 3(2), 143-146.
- [16] K. Ilango, C. R Biju, *Journal of pharmacy research*, **2012**, 5(3), 1514-1517.
- [17] Mohamed Ashraf Ali, Mohammad Shaharyar, *Bioorg. Med. Chem. Lett.*, **2007**, 17(12), 3314-3316.
- [18] G.W. Adelstien, C.H. Yen, E.Z. Dajani, R.G. Binachi, *J. Med. Chem.*, **1976**, 19(10), 1221-1225.
- [19] H. Yale, K. Losee, *J. Med. Chem.*, **1966**, 9(4), 478-83.
- [20] Li Yingkui, *Synth. Met.*, **2011**, 161(13-14), 1424-1429.
- [21] Mishra Pradeep, K. Joshi Gopal, K. Shakya Ashok, R.K. Agrawal, G.K. Patnaik, *Indian J. Physiol. Pharmacol.*, **1992**, 36, 247-250.
- [22] R.R. Somani, G. Kadam, R. Vohra, S. Vijayaraghavan, P.Y. Shirodkar, *Indian J Pharmacol*, **2010**, 6, 696-670.
- [23] K. Kashaw Sushil, Gupta Vivek, Kashaw Varsha, P. Mishra, J.P. Stables, N.K. Jain, *Med. Chem. Res.*, **2010**, 19(3), 250-261.
- [24] Akhaja Tarunkumar Nanjibhai, Raval Jignesh Priyakant, *Chin. Chem. Lett.*, **2012**, 23(7), 785-788.
- [25] Macaev Fliur, Ribkovskaa Zinaida, Pogrebnoi Serghei, *Mold. Exam. Pat. Appl.*, **2011**, MD 4118 B1 20110731.
- [26] W.H. Watthey Jeffrey, Desai Mahesh, Rutledge Richard, Dotson Ronald, *J. Med. Chem.*, **1980**, 23(6), 690-692.
- [27] Sahin Gulay, Palaska Erhan, Ekizoglu Melike, Ozalp, Meral, *Farmaco*, **2002**, 57(7), 539-542.
- [28] Palaska Erhan, Sahin Gulay, Kelicen Pelin, N. Durlu Tugba, Altinok, Gulcin, *Farmaco*, **2002**, 57(7), 101-107.
- [29] G.C. Ramaprasad, Kalluraya Balakrishna, B. Kumar Sunil, K. Hunnur Ravindra, *Eur. J. Med. Chem.*, **2010**, 45(10), 4587-4593.
- [30] K. Sujatha, A.M A.Khadar, Kalluraya Balakrishna, M. Babu, *Indian J. Heterocycl. Chem.*, **2009**, 19(1), 33-36.
- [31] B. Holla Shivarama, K. Poojary Narayana, Kalluraya Balakrishna, P. Gowda Venkatramana, *Indian J. Heterocycl. Chem.*, **1996**, 5(4), 273-276.
- [32] Kalluraya Balakrishna, Chimbalkar Ramesh, B. Holla Shivarama, *Indian J. Heterocycl. Chem.*, **1995**, 5(1), 37-40.
- [33] N. Shetty Suresh, Kalluraya Balakrishna, *Chim. Acta Turc.*, **1992**, 19(2), 135-139.
- [34] M.S. Blois, *Nature*, **1958**, 26, 1199-1200.
- [35] M.R. Friedman, K.J. Toyne, J.W. Goodby, M. Hird, *J. Mater. Chem.*, **2001**, 11(11), 2759-2772.
- [36] E. Palaska, G. Sahin, P. Kelicen, N.T. Durlu, G. Altinok, *Farmaco*, **2002**, 57(2), 101-107.
- [37] G. Sahin, E. Palaska, P. Kelicen, R. Demirdamar, G. Altinok, *Arzneim.-Forsch.*, **2001**, 51(6), 478-484.
- [38] M.D. Mullican, M.W. Wilson, D.T. Connor, C.R. Kostlan, D.J. Schrier, R.D. Dyer, *J. Med. Chem.*, **1993**, 36(8), 1090-1099.
- [39] G. Sahin, E. Palaska, M. Ekizoglu, M. Ozalp, *Farmaco*, **2002**, 57(7), 539-542.
- [40] A.K. Tiwari, *Curr. Sci.*, **2004**, 86(8), 1092-1102.