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Synthesis and Antimicrobial Studies on New Substituted 1,3,4-Oxadiazole Derivatives Bearing 6-Bromonaphthalene Moiety

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Abstract

A series of new 1,3,4-oxadiazole derivatives having 6-bromonaphthalene moiety are synthesized. 2-[(6-bromo-2-naphthyl)oxy]acetohydrazide was treated with various substituted aromatic acids in presence of $POCl_3$ to give 2-{[(6-bromo-2-naphthyl)oxy]methyl}-5-aryl-1,3,4-oxadiazole. Also the hydrazide on treating with CS_2/KOH gave 5-{[(6-bromo-2-naphthyl)oxy]methyl}-1,3,4-oxadiazole-2(3*H*)-thione, which was subjected to Mannich reaction to get a series of Mannich bases and with alkyl/aryl halide to give 2-{[(6-bromo-2-naphthyl)oxy]methyl}-5-[(alkyl/aryl)thio]-1,3,4-oxadiazole. The newly synthesized compounds were characterized by analytical and spectral data. Antimicrobial activities of these compounds were carried out and some of them have exhibited good activity.

Keywords: 1,3,4-Oxadiazole-2(3*H*)-thione, Mannich base,
2-{[(6-Bromo-2-naphthyl)oxy]methyl}-5-aryl-1,3,4-oxadiazole,
2-{[(6-Bromo-2-naphthyl)oxy]methyl}-5-[(alkyl/aryl)thio]-1,3,4-oxadiazole, Antimicrobial activity

1. Introduction

1,3,4-Oxadiazoles are heterocyclic compounds, which serve both as biomimetic and reactive pharmacophores and many are the key compounds with potential biological activities (Hokfelt *et al*., 1962; Hashem *et al*., 2007; Boschelli *et al*., 1993; Adelstein *et al*., 1976). For instance, 2-amino-1,3,4-oxadiazole acts as muscle relaxtant (Yale *et al*., 1966) and 1,3,4-oxadiazole having naphthalene nucleus have shown to posses anti-inflammatory activity (Amir *et al*., 1998; Rajak *et al*., 2007). Synthesis, anti-inflammatory and antiproteolytic properties of naphthyl thio semicarbazides and cyclized oxadiazoles derivatives have been reported (Kishore *et al.,* 1975). 1,3,4-oxadiazole derivatives are good monoamine oxidase inhibitors (antidepressants), anti-convulsant agent (Shaoyong *et al*., 2008; Zarghi *et al*., 2008) and potential inhibitors targeting chitin biosynthesis (Shaoyong *et al*., 2009).

In recent years, Mannich bases have gained importance because of their pharmaceutical importance (Dimmock *et al*., 1997; Sridhar *et al*., 2002). The presence of basic Mannich side chain has shown a marked antimalarial activity (Kotecka *et al*., 1997). Studies revealed that Mannich bases showed good anticancer (Aboraia *et al*., 2005) and antimycobacterial activity (Ali *et al*., 2007). Mannich bases are also known to posses remarkable anti-HIV and antitubercular activities (Sriram *et al*., 2009). Also 1,3,4-oxadiazole-5-thioether derivatives have been the object of investigation due to their different properties such as antibacterial (Macaev *et al*., 2005) and antifungal (Chen *et al*., 2000)**.** In continuation of our work on 1,3,4-oxadiazole derivatives bearing naphthalene ring (Narayana *et al*., 2005) it was contemplated to synthesize some new 1,3,4-oxadiazole derivatives bearing 6-bromonaphthalene moiety.

2. Material and Methods

2.1 Experimental

TLC was run on a Merck silica gel 60 F254 coated aluminum plates and melting points were taken in open capillary tubes and are uncorrected. Elemental analysis was carried out using Flash EA 1112 Series, CHNSO Analyzer (Thermo). IR spectra in KBr pellets were recorded on Jasco FT/IR-4100 FTIR spectrophotometer. ^{1}H-NMR spectra were recorded in $CDCl_3$ and in DMSO-d_6 on a Bruker DRX-300 (300 MHz) spectrometer using TMS as internal standard and Mass spectra were recorded on a Jeol SX 102/Da-600 mass spectrometer/Data System using Argon/Xenon (6 kV,10 mA) as FAB gas.

2.1.1 General procedure for the preparation of ethyl (6-bromo-2-naphthyloxy) acetate **(2)**

6-Bromo-2-naphthol **(1)** (10 g, 0.044 mol) was dissolved in 250 ml dry acetone and mixed with anhydrous potassium carbonate (11 g, 0.08 mol). This was treated with ethylchloroacetate (5.4 g, 0.044 mol) and the mixture was refluxed for 5-6 h. After the completion of reaction (monitored by TLC), the reaction mixture was filtered and the filtrate was distilled under reduced pressure. The solid obtained was recrystallized from acetonitrile. Yield 88 %, m.p. 62-65°C.

The structure of the compound was confirmed from single crystal X-ray study **(**Sarojini, Yathirajan *et al*., 2007).

2.1.2 General procedure for the preparation of 2-[(6-bromo-2-naphthyl)oxy]acetohydrazide **(3)**

A mixture of ethyl(6-bromo-2-naphthyloxy)acetate **(2)** (5.0 g, 0.01 mol) and hydrazine hydrate (1.6 g, 0.02 mol) in ethanol (20 ml) was heated under reflux for 5 h. The reaction mixture was cooled to room temperature and the solid separated was collected by filteration. It was washed with ethanol and recrystallized in methanol. The product was obtained as light yellow solid in 92 % yield, m.p 198-200 °C.

Elemental analysis % Calculated (Found) for $C_{12}H_{11}BrN_2O_2$: C- 48.83(48.79), H- 3.75(3.71) and N-9.49(9.43). IR (KBr, γ_{max} cm^{-1}): 3311 (NH_2), 3206 (NH), 1667 (C=O), 1541 (C =C). ^{1}H NMR (DMSO-d_6, δ ppm): 4.35(bs, 2H, NH_2), 4.60(s, 2H, CH_2), 7.28-7.32 (m, 2H, naphthalene ring proton), 7.57 (d, J=6.5 Hz, 1H, naphthalene ring proton), 7.75 (d, J=6.5 Hz, 1H, naphthalene ring proton), 7.84 (d, J= 6.5 Hz, 1H, naphthalene ring proton), 8.11 (s, 1H, naphthalene ring proton), 9.41 (bs, lH, NH). MS FAB$^+$(%)*:* 295(100) M^+, 297(85) $[M+2]^+$.

2.1.3 Procedure for the preparation of 2-{[(6-bromo-2-naphthyl)oxy]methyl}-5-aryl-1,3,4-oxadiazole **(4a-r).**

2-[(6-Bromo-2-naphthyl)oxy]acetohydrazide (1 g, 0.003 mol) was refluxed with (un)substituted aromatic acid (0.003 mol) in $POCl_3$ (5 ml) for 8 h. The reaction mixture was slowly quenched into crushed ice with stirring and neutralized it with solid sodium bicarbonate. The solid which separated after standing overnight was filtered, washed with cold water, dried, and recrystallized from methanol to afford the title compounds. The characterization data are given in **Table-1**. The spectral details are given below.

2-{[(6-Bromo-2-naphthyl)oxy]methyl}-5-(2-methoxyphenyl)-1,3,4-oxadiazole ***(4a)***

IR (KBr, γ_{max} cm^{-1}): 2935 (C-H str), 1640 (C=N), 1234(C-O).

^{1}H NMR ($CDCl_3$, δ ppm): 3.93 (s, 3H, -OCH_3), 5.45 (s, 2H, O-CH_2) 7.06 (t, J=8.8 Hz, 2H, phenyl ring proton), 7.27 (d, J=8.5 Hz, 1H, naphthalene ring proton), 7.32 (s, 1H, naphthalene ring proton), 7.49 (d, J=7.2 Hz, 1H, phenyl ring protons),7.53 (d, J=8.6 Hz, 1H, naphthalene ring proton), 7.64 (d, J= 8.8 Hz, 1H, naphthalene ring proton), 7.69 (d, J=8.9 Hz, 1H, naphthalene ring proton), 7.93 (s, 1H, naphthalene ring proton),7.95 (d, J=7.8 Hz, 1H, phenyl ring protons). MS FAB^+(%): 411(90%) M^+, 413(100%) $[M+2]^+$.

2-{[(6-Bromo-2-naphthyl)oxy]methyl}-5-(2-fluorophenyl)-1,3,4-oxadiazole ***(4b)***

IR (KBr, γ_{max} cm^{-1}): 3035 (C-H str), 1648 (C=N), 1262(C-O).

^{1}H NMR ($CDCl_3$, δ ppm): 5.47 (s, 2H, O-CH_2) 7.23-7.33 (m, 3H, phenyl ring proton and 2H, naphthalene ring proton), 7.54 (d, J=8.3 Hz, 1H, naphthalene ring proton), 7.65 (d, J=8.6 Hz, 1H, naphthalene ring proton), 7.70 (d, J=8.8 Hz, 1H, naphthalene ring proton), 7.94 (s, 1H, naphthalene ring proton), 8.0 (t, J=7.8 Hz, 1H, phenyl ring protons). MS FAB^+(%): 399(85%) M^+, 401(100%) $[M+2]^+$.

2-{[(6-Bromo-2-naphthyl)oxy]methyl}-5-phenyl-1,3,4-oxadiazole ***(4c)***

IR (KBr, γ_{max} cm^{-1}): 2931 (C-H str), 1644 (C=N), 1034(C-O).

^{1}H NMR ($CDCl_3$, δ ppm): 5.44 (s, 2H, O-CH_2), 7.24 (d, J=6.4 Hz, 1H, naphthalene ring proton), 7.31 (s, 1H, naphthalene ring proton), 7.58-7.47 (m, 4H, 3 phenyl ring protons and 1 naphthalene ring proton), 7.64 (d, J=8.7 Hz, 1H, naphthalene ring proton), 7.69 (d, J=8.9 Hz, 1H, naphthalene ring proton), 7.93 (s, 1H, naphthalene ring proton), 8.07 (d, J=6.4 Hz, 2H, phenyl ring proton). MS FAB^+(%): 381(90%) M^+, 383(100%) $[M+2]^+$.

2-{[(6-Bromo-2-naphthyl)oxy]methyl}-5-(3-chlorophenyl)-1,3,4-oxadiazole ***(4d)***

IR (KBr, γ_{max} cm^{-1}): 2975 (C-H str), 1640 (C=N), 1224(C-O).

^{1}H NMR ($CDCl_3$, δ ppm): 5.46 (s, 2H, O-CH_2) 7.24 (d, J=6.3 Hz, 1H, phenyl ring proton), 7.31 (s, 1H, naphthalene ring proton), 7.37-7.47 (m, 1H, phenyl ring protons and 2H naphthalene ring proton), 7.51 (d, J=5.1 Hz, 1H, phenyl ring proton), 7.62 (d, J=8.8 Hz, 1H, naphthalene ring proton), 7.67 (d, J=8.9 Hz, 1H, naphthalene ring proton), 7.93 (s, 1H, naphthalene ring proton), 7.99(d, J=7.6 Hz, 1H, phenyl ring proton). MS FAB^+(%): 415(95%) M^+, 417(100%) $[M+2]^+$.

2-{[(6-Bromo-2-naphthyl)oxy]methyl}-5-(4-nitrophenyl)-1,3,4-oxadiazole ***(4e)***

IR (KBr, γ_{max} cm^{-1}): 3035 (C-H str), 1620 (C=N), 1021(C-O).

^{1}H NMR ($CDCl_3$, δ ppm): 5.43 (s, 2H, O-CH_2), 7.24 (d, J=2.4 Hz, 1H, naphthalene ring proton), 7.30 (s, 1H, naphthalene ring proton), 7.48-7.55 (m, 2H, phenyl ring protons and 1H naphthalene ring proton), 7.64 (d, J=8.7 Hz, 1H, naphthalene ring proton), 7.70 (d, J=8.9 Hz, 1H, naphthalene ring proton), 7.94 (s, 1H, naphthalene ring proton), 8.26 (d, J=8.5 Hz, 2H, phenyl ring protons). MS FAB^+(%): 426(90%) M^+, 428(100%) $[M+2]^+$.

2-{[(6-Bromo-2-naphthyl)oxy]methyl}-5-(4-methylphenyl)-1,3,4-oxadiazole ***(4f)***

IR (KBr, γ_{max} cm^{-1}): 2938 (C-H str), 1645 (C=N), 1251(C-O).

^{1}H NMR ($CDCl_3$, δ ppm): 2.42 (s, 3H, CH3), 5.43 (s, 2H, O-CH_2), 7.14 (d, J=7.6 Hz, 1H, naphthalene ring proton), 7.26 (d, J= 6.0 Hz, 2H, phenyl ring protons), 7.32 (s, 1H, naphthalene ring proton), 7.39 (d, J=7.1 Hz, 1H, naphthalene ring proton), 7.53 (d, J=8.7 Hz, 1H, naphthalene ring proton), 7.65 (d, J=8.8 Hz, 1H, naphthalene ring proton), 7.69 (d, J=8.9 Hz, 1H, naphthalene ring proton), 7.85(d, J=6.0 Hz, 2H, phenyl ring protons), 7.97 (s, 1H, naphthalene ring proton). MS FAB^+(%): 395(90%) M^+, 397(100%) $[M+2]^+$.

2-{[(6-Bromo-2-naphthyl)oxy]methyl}-5-(3,5-dinitrophenyl)-1,3,4-oxadiazole ***(4g)***

IR (KBr, γ_{max} cm^{-1}): 3018 (C-H str), 1629 (C=N), 1092(C-O).

^{1}H NMR ($CDCl_3$, δ ppm): 5.52 (s, 2H, O-CH_2), 7.31-7.17 (m, 2H, naphthalene ring proton), 7.55 (d, J=8.6 Hz, 1H, naphthalene ring proton), 7.66 (d, J=8.5 Hz, 1H, naphthalene ring proton), 7.73 (d, J=8.7 Hz, 1H, naphthalene ring proton), 7.95 (s, 1H, naphthalene ring proton), 8.21-8.25 (m, 3H, phenyl ring proton). MS FAB^+(%): 471(80%) M^+, 473(85%) $[M+2]^+$.

4-(5-{[(6-Bromo-2-naphthyl)oxy]methyl}-1,3,4-oxadiazol-2-yl)-2-chloropyridine ***(4h)***

IR (KBr, γ_{max} cm^{-1}): 2968 (C-H str), 1638 (C=N), 1095(C-O).

^{1}H NMR ($CDCl_3$, δ ppm)*:* 5.46 (s, 2H, O-CH_2), 7.23 (d, J=7.2 Hz, 1H, naphthalene ring proton), 7.31 (s, 1H, naphthalene ring proton), 7.37-7.55 (m, 2H, pyridine ring protons and 1H naphthalene ring proton), 7.63 (d, J=8.8 Hz, 1H, naphthalene ring proton), 7.68 (d, J=8.8 Hz, 1H, naphthalene ring proton), 7.91 (s, 1H, naphthalene ring proton), 7.98 (d, J=6.0 Hz, 1H, pyridine ring protons). MS FAB^+(%): 416(80%) M^+, 418(85%) $[M+2]^+$.

2-{[(6-Bromo-2-naphthyl)oxy]methyl}-5-(4-chlorophenyl)-1,3,4-oxadiazole ***(4i)***

IR (KBr, γ_{max} cm^{-1}): 2939 (C-H str), 1642 (C=N), 1244(C-O).

^{1}H NMR ($CDCl_3$, δ ppm): 5.43 (s, 2H, O-CH_2), 7.24 (d, J=2.4 Hz, 1H, naphthalene ring proton), 7.30 (s, 1H, naphthalene ring proton), 7.55-7.48 (m, 2H, phenyl ring protons and 1H naphthalene ring proton), 7.64 (d, J=8.7 Hz, 1H, naphthalene ring proton), 7.70 (d, J=8.9 Hz, 1H, naphthalene ring proton), 7.94 (s, 1H, naphthalene ring proton), 8.02 (d, J=8.5 Hz, 2H, phenyl ring protons). MS FAB$^+$(%): 415(90%) M^+, 417(100%) $[M+2]^+$.

2-{[(6-Bromo-2-naphthyl)oxy]methyl}-5-(2,4-dichlorophenyl)-1,3,4-oxadiazole ***(4j)***

IR (KBr, γ_{max} cm^{-1}): 2935 (C-H str), 1641 (C=N), 1090(C-O).

^{1}H NMR ($CDCl_3$, δ ppm): 5.43 (s, 2H, O-CH_2), 7.16 (d, J=7.4Hz, 1H, naphthalene ring proton), 7.29 (s, 2H, naphthalene ring proton and phenyl ring proton), 7.53 (d, J=8.7 Hz, 1H, naphthalene ring proton), 7.64 (d, J=8.7 Hz, 1H, naphthalene ring proton), 7.70 (d, J=8.7 Hz, 1H, naphthalene ring proton), 7.91 (d, J=8.6 Hz, 1H, phenyl ring protons), 7.94 (s, 1H, naphthalene ring proton), 8.06 (s, 1H, phenyl ring proton). MS FAB$^+$(%): 450(100%) M^+, 452(90%) $[M+2]^+$.

3-(5-{[(6-Bromo-2-naphthyl)oxy]methyl}-1,3,4-oxadiazol-2-yl)aniline ***(4k)***

IR (KBr, γ_{max} cm^{-1}): 2935 (C-H str), 1629 (C=N), 1214(C-O).

^{1}H NMR ($CDCl_3$, δ ppm): 5.43 (s, 2H, O-CH_2), 6.08 (s, 2H, NH_2), 7.16 (d, J=7.5Hz, 1H, naphthalene ring proton), 7.32 (s, 1H, naphthalene ring protons),7.37-7.41 (m, 3H, phenyl ring proton), 7.48(d, J=8.4 Hz, 1H, phenyl ring proton), 7.53 (d, J=8.7 Hz, 1H, naphthalene ring proton), 7.64 (d, J=8.7 Hz, 1H, naphthalene ring proton), 7.70 (d, J=8.9 Hz, 1H, naphthalene ring proton), 7.92 (s, 1H, naphthalene ring proton). MS FAB$^+$(%): 396(100%) M^+, 398(95%) $[M+2]^+$.

2-{[(6-Bromo-2-naphthyl)oxy]methyl}-5-(3-methylphenyl)-1,3,4-oxadiazole ***(4l)***

IR (KBr, γ_{max} cm^{-1}): 2964 (C-H str), 1630 (C=N), 1084(C-O).

^{1}H NMR ($CDCl_3$, δ ppm): 2.44 (s, 3H, CH3), 5.43 (s, 2H, O-CH_2), 7.14 (d, J=7.5Hz, 1H, naphthalene ring proton), 7.32 (s, 1H, naphthalene ring protons),7.41-7.37 (m, 2H, phenyl ring proton), 7.53 (d, J=8.7 Hz, 1H, naphthalene ring proton), 7.64 (d, J=8.7 Hz, 1H, naphthalene ring proton), 7.70 (d, J=8.9 Hz, 1H, naphthalene ring proton), 7.86 (d, J=6.8 Hz, 1H, phenyl ring protons), 7.90 (s, 1H, phenyl ring protons), 7.94 (s, 1H, naphthalene ring proton). MS FAB$^+$(%): 397(95%) $[M+2]^+$, 395(100%) M^+.

2-{[(6-Bromo-2-naphthyl)oxy]methyl}-5-(3,5-dichlorophenyl)-1,3,4-oxadiazole ***(4m)***

IR (KBr, γ_{max} cm^{-1}): 3029 (C-H str), 1659 (C=N), 1226(C-O)

^{1}H NMR ($CDCl_3$, δ ppm): 5.44 (s, 2H, O-CH_2), 7.16 (d, J=7.4 Hz, 1H, naphthalene ring proton), 7.29 (s, 1H, naphthalene ring protons), 7.53(d, J=8.7 Hz, 1H, naphthalene ring proton), 7.64 (d, J=8.7 Hz, 1H, naphthalene ring proton), 7.70 (d, J=8.7 Hz, 1H, naphthalene ring proton), 7.94 (s, 1H, naphthalene ring proton), 7.97 (s, 2H, phenyl ring protons), 8.02 (s, 1H, phenyl ring proton). MS FAB$^+$(%): 450(100%) M^+, 452(90%) $[M+2]^+$.

2-{[(6-Bromo-2-naphthyl)oxy]methyl}-5-(1-ethoxy-2-naphthyl)-1,3,4-oxadiazole ***(4o)***

IR (KBr, γ_{max} cm^{-1}): 2945 (C-H str), 1641 (C=N), 1234(C-O).

^{1}H NMR (DMSO, δ ppm): 1.12 (t, J=6.9 Hz, 3H, CH_3 ethyl group), 4.18(q, J=7.02 Hz, 2H, CH_2 ethyl group), 5.68 (s, 2H, O-CH_2), 7.31-8.22 (m, 12H two naphthalene ring proton). MS FAB$^+$(%): 477(90%) $[M+2]^+$, 475(100%) M^+.

2-{[(6-Bromo-2-naphthyl)oxy]methyl}-5-(2-chlorophenyl)-1,3,4-oxadiazole ***(4p)***

IR (KBr, γ_{max} cm^{-1}): 2941 (C-H str), 1638 (C=N), 1092(C-O).

^{1}H NMR ($CDCl_3$, δ ppm)*:* 5.47 (s, 2H, O-CH_2), 7.14 (d, J=7.2 Hz, 1H, naphthalene ring proton), 7.32 (s, 1H, naphthalene ring proton), 7.55-7.37 (m, 3H, phenyl ring protons and 1H naphthalene ring proton), 7.64 (d, J=8.8 Hz, 1H, naphthalene ring proton), 7.69 (d, J=8.8 Hz, 1H, naphthalene ring proton), 7.93 (s, 1H, naphthalene ring proton), 8.0 (d, J=6.5 Hz, 1H, phenyl ring protons). MS FAB$^+$(%): 415(80%) M^+, 417(85%) $[M+2]^+$.

2.1.4 General procedure for the preparation of 5-{[(6-bromo-2-naphthyl)oxy]methyl}-1,3,4-oxadiazole-2(3H)-thione **(5)**

2-[(6-Bromo-2-naphthyl)oxy]acetohydrazide (10.0 g, 0.033 mole) was treated with a solution of potassium hydroxide (2.8 g, 0.05 mole) dissolved in methanol (100 ml) under stirring. Carbon disulfide (3.8 g, 0.05 mole) was added slowly to the reaction mixture. The reaction mixture was slowly heated to reflux and refluxed for 8 h.The solvent was distilled under vacuum and the residue was dissolved in water. Acidified the solution and collected the resulting solid by filtration. Yield 86%. m.p 148-150 °C.

Elemental analysis % Calculated (found) for $C_{13}H_9BrN_2O_2S$ C- 46.30(46.31), H- 2.69(2.67) and N- 8.30(8.29).

IR (KBr) cm^{-1}: 3400 (NH), 2950 (CH), 1255 (C=S), 1635 (C=N cyclic).

^{1}H NMR (DMSO-d_6, δ ppm): 5.37 (s, 2H, O-CH_2), 7.29 (d, J=7.1 Hz, 1H, naphthalene ring proton), 7.42 (d, J=7.1 Hz, 1H, naphthalene ring proton), 7.52 (s, 1H, naphthalene ring proton), 7.78 (d, J=8.85 Hz, 1H, naphthalene ring proton), 7.87 (d, J=8.8 Hz, 1H, naphthalene ring proton), 8.15 (s, 1H, naphthalene ring proton), 15.1 (bs, 1H, SH).

FAB MS: 337(100)M^+, 339(40)$[M+2]^+$.

2.1.5 Procedure for the preparation of Mannich bases **(6a-j)**

To a mixture of 5-{[(6-bromo-2-naphthyl)oxy]methyl}-1,3,4-oxadiazole-2(3*H*)-thione**(5)** (1.0 g, 3.0 mmol) in methanol (5ml) was added formaldehyde (0.5 ml, 37%) and appropriate primary or secondary amine (3.0 mmol). The reaction mixture was stirred overnight. After cooling, the precipitate was filtered and crystallized from methanol. The characterization data are given in **Table 2.**

5-{[(6-Bromo-2-naphthyl)oxy]methyl}-3-(morpholin-4-ylmethyl)-1,3,4-oxadiazole-2(3H)-thione **(6a)**

IR (KBr, γ_{max} cm^{-1}): 3035 (C-H str), 1651 (C=N), 1325 (C=S), 1236(C-O).

^{1}H NMR ($CDCl_3$, δ ppm): 2.77 (t, J=4.6 Hz, 4H, morpholine protons), 3.67 (t, J=4.4 Hz, 4H, morpholine protons), 4.99(s, 2H, O-CH_2), 5.15 (s, 2H, N-CH_2), 7.20 (d, J=7.4 Hz, 1H, naphthalene ring proton), 7.23 (s, 1H, naphthalene ring proton) 7.54 (d, J=8.7 Hz, 1H, naphthalene ring proton), 7.62 (d, J=8.7 Hz, 1H, naphthalene ring proton), 7.71 (d, J=9.0 Hz, 1H, naphthalene ring proton), 7.95 (s, 1H, naphthalene ring proton).

FAB MS: 436(100)M^+, 438(85)$[M+2]^+$.

5-{[(6-Bromo-2-naphthyl)oxy]methyl}-3-[(4-methylpiperazin-1-yl)methyl]-1,3,4-oxadiazole-2(3H)-thione **(6b)**

IR (KBr, γ_{max} cm^{-1}): 2935 (C-H str), 1650 (C=N), 1320 (C=S), 1224(C-O).

^{1}H NMR ($CDCl_3$, δ ppm): 2.25 (s, 3H, CH_3 of piperazine), 2.40 (t, J=7.2 Hz, 4H, CH_2 of piperzaine), 2.42 (t, J=7.2Hz, 4H, CH_2 piperzaine), 4.97(s, 2H,O-CH_2), 5.13 (s, 2H, N-CH_2), 7.09 (d, J=7.4Hz, 1H, naphthalene ring proton), 7.21 (s, 1H, naphthalene ring proton), 7.53 (d, J=8.7 Hz, 1H naphthalene ring proton), 7.61 (d, J=8.7 Hz, 1H, naphthalene ring proton), 7.73 (d, J=9.0 Hz, 1H, naphthalene ring proton), 7.96(s, 1H, naphthalene ring proton).

FAB MS: 449(95) M^+, 451(20) $[M+2]^+$.

5-{[(6-Bromo-2-naphthyl)oxy]methyl}-3-(piperidin-1-ylmethyl)-1,3,4-oxadiazole-2(3H)-thione **(6c)**

IR (KBr, γ_{max} cm^{-1}): 3015 (C-H str), 1624 (C=N), 1298 (C=S), 1086(C-O).

^{1}H NMR ($CDCl_3$, δ ppm): 2.10-2.63 (m, 6H, piperidine protons), 2.78 (t, J= 5.2 Hz, 4H, CH_2-N-CH_2 piperidine protons), 4.99 (s, 2H, O-CH_2), 5.15 (s, 2H, N-CH_2), 7.18 (d, J=7.4Hz, 1H, naphthalene ring proton), 7.23 (s, 1H, naphthalene ring proton), 7.54 (d, J=8.7 Hz, 1H naphthalene ring proton), 7.62 (d, J=8.7 Hz, 1H, naphthalene ring proton), 7.71 (d, J=9.0 Hz, 1H, naphthalene ring proton), 7.95 (s, 1H, naphthalene ring proton).

FAB MS: 434 (100)M^+, 436 (60)$[M+2]^+$

5-{[(6-Bromo-2-naphthyl)oxy]methyl}-3-[(diethylamino)methyl]-1,3,4-oxadiazole-2(3H)-thione **(6d)**

IR (KBr, γ_{max} cm^{-1}): 3035 (C-H str), 1650 (C=N), 1324 (C=S), 1216(C-O).

^{1}H NMR ($CDCl_3$, δ ppm): 1.07 (t, 6H, Two CH_3 protons), 2.97 (q, 4H, CH_2-N-CH_2 protons), 4.99 (s, 2H, O-CH_2), 5.15 (s, 2H, N-CH_2), 7.17 (d, J=7.4 Hz, 1H, naphthalene ring proton), 7.23 (s, 1H, naphthalene ring proton), 7.54 (d, J=8.7 Hz, 1H, naphthalene ring proton), 7.62 (d, J=8.7 Hz, 1H, naphthalene ring proton), 7.71(d, J=9.0 Hz, 1H, naphthalene ring proton), 7.95 (s, 1H, naphthalene ring proton).

FAB MS: 422 (95)M^+, 424 (65)$[M+2]^+$.

5-{[(6-Bromo-2-naphthyl)oxy]methyl}-3-(1H-imidazol-1-ylmethyl)-1,3,4-oxadiazole-2(3H)-thione **(6e)**

IR (KBr, γ_{max} cm^{-1}): 3033 (C-H str), 1648 (C=N), 1318 (C=S), 1235(C-O).

^{1}H NMR ($CDCl_3$, δ ppm): 5.02 (s, 2H,O-CH_2), 5.47 (s, 2H, N-CH_2), 7.16 (d, J=7.4 Hz, 1H, naphthalene ring proton), 7.23 (m, 1H, naphthalene ring proton and 2H imidazole ring protons) 7.54 (d, J=8.7 Hz, 1H, naphthalene ring proton), 7.62 (d, J=8.7 Hz, 1H, naphthalene ring proton), 7.71 (d, J=9.0 Hz, 1H, naphthalene ring proton), 7.81 (s, 1H, imidazole ring proton), 7.95 (s, 1H, naphthalene ring proton).

FAB MS: 417 (80)M^+, 419 (30)$[M+2]^+$.

5-{[(6-Bromo-2-naphthyl)oxy]methyl}-3-{[(2-fluorophenyl)amino]methyl}-1,3,4-oxadiazole-2(3H)-thione **(6f)**

IR (KBr, γ_{max} cm^{-1}): 3031 (C-H str), 2966 (NH), 1624 (C=N), 1325 (C=S), 1208(C-O).

^{1}H NMR ($CDCl_3$, δ ppm): 5.37 (s, 2H, O-CH_2), 5.45 (d, J=7.0 Hz, 2H, N-CH_2-NH), 6.97 (bs, NH proton), 7.23-7.33 (m, 3H, phenyl ring proton and 2H, naphthalene ring proton), 7.54 (d, J=8.3 Hz, 1H, naphthalene ring proton), 7.65 (d,

J=8.6 Hz, 1H, naphthalene ring proton), 7.70 (d, J=8.8 Hz, 1H, naphthalene ring proton), 7.94 (s, 1H, naphthalene ring proton), 8.0 (t, J=7.8 Hz, 1H, phenyl ring protons).

FAB MS: 460(80)M^+, 462(20) $[M+2]^+$.

5-{[(6-Bromo-2-naphthyl)oxy]methyl}-3-{[(4-chlorophenyl)amino]methyl}-1,3,4-oxadiazole-2(3H)-thione **(6g)**

IR (KBr, γ_{max} cm^{-1}): 3072 (C-H str), 2978 (NH), 1640 (C=N), 1326 (C=S), 1088(C-O).

^{1}H NMR ($CDCl_3$, δ ppm): 5.43 (s, 2H, O-CH_2), 5.55 (d, J=7.0 Hz, 2H, N-CH_2-NH), 6.96 (bs, NH proton), 7.24 (d, J=8.4 Hz, 1H, naphthalene ring proton), 7.30 (s, 1H, naphthalene ring proton), 7.55-7.48 (m, 2H, phenyl ring protons and 1H naphthalene ring proton), 7.64 (d, J=8.7 Hz, 1H naphthalene ring proton), 7.70 (d, J=8.9 Hz, 1H, naphthalene ring proton), 7.94 (s, 1H, naphthalene ring proton), 8.02 (d, J=8.5 Hz, 2H, phenyl ring protons).

FAB MS: 476(85) M^+, 478(60) $[M+2]^+$.

5-{[(6-Bromo-2-naphthyl)oxy]methyl}-3-{[(2-methylphenyl)amino]methyl}-1,3,4-oxadiazole-2(3H)-thione **(6h)**

IR (KBr, γ_{max} cm^{-1}): 3031 (C-H str), 2986 (NH), 1628 (C=N), 1319 (C=S), 1067(C-O).

^{1}H NMR ($CDCl_3$, δ ppm): 2.28 (s, 3H, -CH_3), 5.07 (s, 2H, O-CH_2), 5.45 (d, J=7.0 Hz, 2H, N-CH_2-NH), 7.12 (bs, NH proton), 7.15 (s, 1H, naphthalene ring proton), 7.33-7.21 (m, 4H phenyl ring protons and 1H naphthalene ring proton), 7.46 (d, J=8.7 Hz, 1H, naphthalene ring proton), 7.55 (d, J=8.7 Hz, 1H, naphthalene ring proton), 7.64 (d, J=9.0 Hz, 1H naphthalene ring proton), 7.89 (s, 1H, naphthalene ring proton).

FAB MS: 456 (90) M^+, 458(65) $[M+2]^+$.

5-{[(6-Bromo-2-naphthyl)oxy]methyl}-3-{[(3-methoxyphenyl)amino]methyl}-1,3,4-oxadiazole-2(3H)-thione **(6j)**

IR (KBr, γ_{max} cm^{-1}): 3021 (C-H str), 2849 (NH), 1640 (C=N), 1327 (C=S), 1092(C-O).

^{1}H NMR ($CDCl_3$, δ ppm): 3.93 (s, 3H, OCH_3), 5.06 (s, 2H, O-CH_2), 5.42 (d, J=6.9 Hz, 2H, N-CH_2-NH), 7.10 (bs, NH proton), 7.15 (s, 1H, naphthalene ring proton), 7.33-7.21 (m, 4H phenyl ring protons and 1H naphthalene ring proton), 7.46 (d, J=8.7 Hz, 1H, naphthalene ring proton), 7.55 (d, J=8.7 Hz, 1H, naphthalene ring proton), 7.64 (d, J=8.9 Hz, 1H, naphthalene ring proton), 7.89 (s, 1H, naphthalene ring proton).

FAB MS: 472 (85)M^+, 474 (35)$[M+2]^+$.

2.1.6 Procedure for the preparation of 2-{[(6-bromo-2-naphthyl)oxy]methyl}-5-(methyl/ethyl thio)-1,3,4-oxadiazole **(7a-b)**

5-{[(6-Bromo-2-naphthyl)oxy]methyl}-1,3,4-oxadiazole-2(3*H*)-thione **(5)** (2.0 g, 5.9 mmol) was dissolved in ethanol (5 ml) and 10% aqueous sodium hydroxide(3.5 ml). Methyl/ethyl iodide (6.2 mmol) was added and sonicated for 20 min. Water was added and the solid obtained was filtered and then crystallized from methanol.

The characterization data are given in **Table 3.**

2-{[(6-Bromo-2-naphthyl)oxy]methyl}-5-(methylthio)-1,3,4-oxadiazole **(7a)**

IR (KBr, γ_{max} cm^{-1}): 2938 (C-H str), 1651 (C=N), 1238(C-O).

^{1}H NMR ($CDCl_3$, δ ppm): 2.73 (s, 3H, SCH_3), 5.33 (s, 2H,O-CH_2), 7.24-7.20 (m, 2H, naphthalene ring proton), 7.52 (d, J=8.7 Hz, 1H, naphthalene ring proton), 7.62 (d, J=8.7 Hz, 1H naphthalene ring proton), 7.67 (d, J=8.9 Hz,1H, naphthalene ring proton), 7.93 (s, 1H, naphthalene ring proton).

FAB MS: 351(100) M^+, 353 (30) $[M+2]^+$.

2-{[(6-Bromo-2-naphthyl)oxy]methyl}-5-(ethylthio)-1,3,4-oxadiazole **(7b)**

IR (KBr, γ_{max} cm^{-1}): 2965 (C-H str), 1640 (C=N), 1254(C-O).

^{1}H NMR ($CDCl_3$, δ ppm): 1.56 (t, J=7.2 Hz, 3H, CH_3), 3.30 (q, J=7.2 Hz, 2H, CH_2), 5.34 (s, 2H, O-CH_2), 7.24-7.27(m, 2H, naphthalene ring proton), 7.56 (d, J=8.7 Hz, 1H, naphthalene ring proton), 7.64 (d, J=8.6 Hz, 1H, naphthalene ring proton), 7.70 (d, J=8.89 Hz, 1H, naphthalene ring proton), 7.95 (s, 1H, naphthalene ring proton)

FAB MS: 365 (100) M^+, 367 (60)$[M+2]^+$.

2.1.7 Procedure for the preparation of 2-{[(6-bromo-2-naphthyl)oxy]methyl}-5-[(aryl)thio]-1,3,4-oxadiazole **(7c-f)**

5-{[(6-Bromo-2-naphthyl)oxy]methyl}-1,3,4-oxadiazole-2(3*H*)-thione **(5)** (1.0 g, 3.0 mmol) in 10 ml DMF was refluxed for 5 h with substituted benzyl chloride (3.0 mmol) in presence of 0.5 g potassium carbonate. After completion of reaction, the mixture was filtered and concentrated the filtrate. The residue was quenched to water. The solid obtained was collected by filtration and recrystallized in methanol

The characterization data are given in **Table 3.**

2-{[(6-Bromo-2-naphthyl)oxy]methyl}-5-[(2,4-dichlorobenzyl)thio]-1,3,4-oxadiazole **(7c)**

IR (KBr, γ_{max} cm^{-1}): 3025 (C-H str), 1594 (C=N), 1184(C-O).

^{1}H NMR ($CDCl_3$, δ ppm): 4.51(s, 2H, SCH_2), 5.30 (s, 2H, O-CH_2), 7.13 (d, J=9.0 Hz, 1H, naphthalene ring proton), 7.18 (s, 1H naphthalene ring proton), 7.23 (d, J=9.0 Hz, 1H, naphthalene ring proton), 7.39 (s, 1H, phenyl ring proton), 7.45 (d, J=6.0 Hz, 1H, phenyl ring proton), 7.52 (d, J=6.0 Hz, 1H, phenyl ring proton), 7.6 (d, J=9.0 Hz, 1H, naphthalene ring proton), 7.67 (d, J=9.0 Hz, 1H, naphthalene ring proton), 7.92(s, 1H, naphthalene ring proton)

FAB MS: 496 (100)M^+, 498 (30)$[M+2]^+$.

2-{[(6-Bromo-2-naphthyl)oxy]methyl}-5-[(2-chlorobenzyl)thio]-1,3,4-oxadiazole **(7d)**

IR (KBr, γ_{max} cm^{-1}): 2969 (C-H str), 1621 (C=N), 1214(C-O).

^{1}H NMR ($CDCl_3$, δ ppm): 4.58(s, 2H, S-CH_2), 5.32 (s, 2H, O-CH_2), 7.17 (s, 1H naphthalene ring proton), 7.26-7.19(m, 2H, phenyl ring proton, 1H naphthalene ring proton), 7.38 (d, J=6.0 Hz, 1H, phenyl ring proton), 7.53 (d, J=9.0 Hz, 1H, naphthalene ring proton), 7.55 (d, J=6.2 Hz, 1H, phenyl ring proton), 7.63 (d, J=9.0 Hz, 1H, naphthalene ring proton), 7.67 (d, J=9.0 Hz,1H, naphthalene ring proton), 7.93 (s, 1H, naphthalene ring proton)

FAB MS: 461(95) M^+, 463(20)$[M+2]^+$.

2-{[(6-Bromo-2-naphthyl)oxy]methyl}-5-[(2-methylbenzyl)thio]-1,3,4-oxadiazole **(7f)**

IR (KBr, γ_{max} cm^{-1}): 2939 (C-H str), 1642 (C=N), 1218(C-O).

^{1}H NMR ($CDCl_3$, δ ppm): 2.31 (s, 3H, CH_3), 4.43 (s, 2H, SCH_2), 5.30(s, 2H, O-CH_2), 7.1 (s, 1H, naphthalene ring proton), 7.25-7.15 (m, 4H, phenyl ring proton and 1H naphthalene ring proton), 7.51 (d, J=9.0 Hz, 1H, naphthalene ring proton), 7.60 (d, J=9.0 Hz, 1H, naphthalene ring proton), 7.65 (d, J=9.0 Hz, 1H naphthalene ring proton), 7.91(s, 1H, naphthalene ring proton). FAB MS:441(100)M^+, 443(60)$[M+2]^+$.

2.2 Pharmacology

2.2.1 Antibacterial studies: The newly synthesized compounds were screened for their antibacterial activity against *Escherichia coli* (ATTC-25922), *Staphylococcus aureus* (ATTC-25923), *Pseudomonas aeruginosa* (ATCC-27853) and *Klebsiella pneumoniae* (recultured) bacterial strains by serial plate dilution method (Barry A L 1991, James D 1970)**.** Serial dilutions of the drug in Mueller-Hinton broth were taken in tubes and their pH was adjusted to 5.0 using phosphate buffer. A standardized suspension of the test bacterium was inoculated and incubated for 16-18 h at 37 °C. The minimum inhibitory concentration (MIC) was noted by seeing the lowest concentration of the drug at which there was no visible growth.

A number of antimicrobial discs were placed on the agar for the sole purpose of producing zones of inhibition in the bacterial lawn. Twenty milliliters of agar media was poured into each Petri dish. Excess of suspension was decanted and plates were dried by placing in an incubator at 37 °C for an hour. Using a punch, wells were made on these seeded agar plates and minimum inhibitory concentrations of the test compounds in dimethylsulfoxide (DMSO) were added into each labeled well. A control was also prepared for the plates in the same way using solvent DMSO. The Petri dishes were prepared in triplicate and maintained at 37 °C for 3-4 days. Antibacterial activity was determined by measuring the diameter of inhibition zone. Activity of each compound was compared with Ciprofloxacin as standard (Felon C H 1986)**.** Zone of inhibition was determined for newly synthesized compounds and the results are summarized in **Table 4**.

2.2.2 Antifungal studies: Newly prepared compounds were screened for their antifungal activity against *Aspergilus flavus* (NCIM No.524), *Aspergilus fumigates* (NCIM No. 902), *Penicillium* (*S.aurus*) (recultured) and *Trichophyton mentagrophytes* (recultured) in DMSO by serial plate dilution method (Arthington-skaggs 2000, Verma R S. 1998)**.** Sabourands agar media was prepared by dissolving peptone (1 g), D-glucose (4 g) and agar (2 g) in distilled water (100 ml) and adjusting the pH to 5.7. Normal saline was used to make a suspension of spore of fungal strains for lawning. A loopful of particular fungal strain was transferred to 3 ml saline to get a suspension of corresponding species. Twenty milliliters of agar media was poured into each Petri dish. Excess of suspension was decanted and plates were dried by placing in incubator at 37 °C for 1 h. Using a punch, wells were made on these seeded agar plates minimum inhibitory concentrations of the test compounds in DMSO were added into each labeled well. A control was also prepared for the plates in the same way using solvent DMSO. The Petri dishes were prepared in triplicate and maintained at 37 °C for 3-4 days. Antifungal activity was determined by measuring the diameter of inhibition zone. Activity of each compound was compared with Cyclopiroxolamine as standard. Zones of inhibition were determined and the results are summarized in **Table 5**.

3. Result and discussion

3.1 Chemistry

1,3,4-Oxadiazoles were generally prepared by treating carboxylic acid and acid hydrazide through cyclization in presence of chlorinating agent, which performs dehydration. Generally $POCl_3$ is used as chlorinating reagent, which either used as such or in combination with a solvent. The reaction sequences employed for synthesis of title compound

is shown in **scheme-1**. The key intermediate, ethyl (6-bromo-2-naphthyloxy)acetate **(2)** was prepared by treating ethyl chloroacetate with 6-bromonaphthol **(1)** by boiling in dry acetone in presence of potassium carbonate. The ester **(2)** was conveniently converted to 2-[(6-bromo-2-naphthyl)oxy]acetohydrazide **(3)** by refluxing with hydrazine hydrate in ethanol. Condensation of **(3)** with various aromatic carboxylic acids in presence of boiling phosphorous oxychloride yielded 2-{[(6-bromo-2-naphthyl)oxy]methyl}-5-aryl-1,3,4-oxadiazole **(4a-r)** in moderate to good yield. The structure of newly synthesized compounds were established on the basis of elemental analysis and spectral (IR, ^{1}H NMR and FAB mass) data.

The IR spectrum of 2-[(6-bromo-2-naphthyl)oxy]acetohydrazide **(3)** showed absorption band in the region of 3311 cm^{-1} characteristic of NH_2 group and at 3206 cm^{-1} of NH group. The C=O stretching was observed at 1667 cm^{-1}. The ^{1}H NMR spectrum showed a broad singlet at δ 4.35 integrating for two protons were due to NH_2 group. The O-CH_2- proton came into resonance at δ 4.60 as singlet. The 5 protons of naphthalene ring resonated at δ 7.28 – 7.75. The C_5-H proton appeared as singlet at δ 7.84 and a broad singlet at δ 9.41 for NH proton. The mass spectrum of this compound showed molecular ion peak at m/z 295 which is the base peak and M+ 2 peaks at 297.

Condensation of hydrazide with various substituted aromatic carboxylic acid followed by cyclization in presence of phosphorous oxychloride under reflux gave the respective 1,3,4-oxadiazole derivatives **(4a-r) (Table-1)**. The evidence for the formation of 1,3,4-oxadiazole derivatives were obtained by recording the proton NMR and from FAB mass spectra.

The ^{1}H NMR spectrum of **4l**, the methyl protons came into resonance as a singlet at δ 2.44 integrating for three protons while the singlet due to -O-CH_2- came into resonance at δ 5.43 accounting for 2 protons. The signal for naphthalene ring proton appeared as follows C_4-H appeared at δ 7.14 as doublet J=7.5Hz, C_1-H at 7.32 singlet, C_8-H proton at δ 7.53 J=8.7 Hz, C_3 –H at δ 7.64 J=8.7 Hz, C_7 –H at δ 7.70 J=8.9 Hz as doublets respectively and C_5-H as singlet at δ 7.94. The phenyl protons resonated at δ 7.41 – 7.37 as a multiplet accounting 2 protons. The C_4 –H phenyl ring proton resonated at δ 7.86 J=6.8 Hz as a doublet and at δ 7.90 as a singlet is due to C_2-H proton. The FAB mass of this compound showed the molecular ion peak at m/z = 395, which is also the base peak there by indicating the stability of oxadiazole derivative. The other peak was observed at 397 (M+2) indicating the presence of bromine.

Compound 5-{[(6-bromo-2-naphthyl)oxy]methyl}-1,3,4-oxadiazole-2(3*H*)-thione **(5)** was synthesized by the ring closure reaction of hydrazide **(3)** with carbon disulfide in presence of a base. A series of Mannich bases **(6a-j)** were then synthesized by the reaction of **(5)** with suitable primary / secondary amines and formaldehyde in methanol. The compound **(5)** was also treated with alkyl halide in alkaline media to get 2-{[(6-bromo-2-naphthyl)oxy]methyl}-5-(alkylthio)-1,3,4-oxadiazole **(7a-b)** and with substituted benzylchlorides in presence of potassium carbonate to get **(7c-g).** The structure of newly synthesized compounds were established on the basis of elemental analysis and spectral (IR, ^{1}H NMR, and FAB mass) data.

5-{[(6-Bromo-2-naphthyl)oxy]methyl}-1,3,4-oxadiazole-2(3*H*)-thione **(5)** was obtained by reacting hydrazide **(3)** with carbon disulfide in presence of KOH in methanolic medium under reflux condition followed by acidification with HCl. The evidence for the proposed structure was obtained by recording the IR, proton NMR and FAB mass.

The IR spectra showed a band in the region of 3400 cm^{-1} characteristic of NH group and at 2950 cm^{-1} of C-H stretching. The C=S stretching was observed at 1255 cm^{-1} and C=N at 1635 cm^{-1}. In the ^{1}H NMR spectra the O-CH_2- proton came into resonance at δ 5.37 as singlet. The C_4-H proton of naphthalene ring resonated as doublet at δ 7.29 with J=7.1 Hz, C_8-H at δ 7.42 as doublet with J=7.1 Hz, C_1-H as singlet at δ 7.52, C_3-H resonated as doublet at δ 7.78 with J=8.85 Hz, C_7-H at δ 7.87 as doublet with J=8.82 Hz. The C_5-H proton appeared as singlet at δ 8.15 and a broad singlet at δ 15.1 for SH proton. The mass spectrum of this compound showed molecular ion peak at m/z: 337 and M+2 at 339.

Further the Mannich reaction of oxadiazole **(5)** with primary/secondary amine and formaldehyde in methanol medium gave corresponding N-Mannich base **(6a-j)**. The Mannich bases were confirmed by analytical and spectral studies.

The ^{1}H NMR spectrum of Mannich base **6a** ($CDCl_3$), the morpholine ring protons appeared as triplet at δ 2.77 and 3.67 accounting for 4 protons each. The singlet due to O-CH_2- appeared at 4.99 integrating for two protons, while the –N-CH_2- protons resonated as singlet at δ5.15. The C_7-H naphthalene ring proton resonated as doublet at δ 7.7 with J=9.0 Hz and C_5 –H proton resonated at δ 7.95 as singlet. The compound **6a** is also confirmed with single crystal X-ray study, which confirms the formation of N-Mannich (Jasinski, Yathirajan *et al*., 2009)

Condensation of 5-{[(6-bromo-2-naphthyl)oxy]methyl}-1,3,4-oxadiazole-2(3*H*)-thione **(5)** with alkyl halide in ethanol by sonicating in presence of 10% NaOH gave **7a-b**. The ^{1}H NMR spectrum of S-methylated oxadiazole **7a** showed a singlet at δ 2.73 accounting for three protons for SCH_3 and the O-CH_2- protons resonated at δ 5.33 as singlet. The proton C_4-H and C_1-H proton appeared as multiplet at δ 7.20-7.24, C_8-H at δ 7.52 as doublet with J=8.7 Hz, C_3 –H at δ 7.62 as doublet with J=8.7 Hz, C_7 –H at δ 7.67 as doublet J=8.9 Hz and C_5-H at δ 7.93 as singlet. The FAB mass of this compound showed the molecular ion peak at m/z = 351.

Further reacting **(5)** with substituted benzyl chloride in presence of potassium carbonate yielded **7c-g**. In a typical example, the ^{1}H NMR spectrum of **7f,** the methyl protons appeared as singlet at δ 2.31 integrating for three protons. The signal due to S-CH_2 protons appeared at δ 4.43 integrating for two protons while the O-CH_2 protons resonated as singlet at δ 5.30 integrating for two protons. The phenyl ring protons resonated as multiplates at δ 7.15-7.25. The C_3-H, C_8-H, C_7-H protons of naphthalene ring resonated as doublets at δ 7.51, 7.60 and 7.65 respectively with J=9 Hz. The C_5-H proton resonated at δ 7.91 as singlet. Further the mass spectrum of this compound showed molecular ion peak at m/z 441.in agreement with the molecular formula $C_{21}H_{17}BrN_2O_2S$. The peak at m/z 443 (M+2) is due to presence of bromine atom in the molecule.

All the newly synthesized compounds were screened for their antimicrobial activity. The investigation of antibacterial and antifungal screening data revealed that all the tested compounds **(4a-r)** and **(6a-j)** showed moderate to good inhibition at μg ml^{-1} in DMSO. The compounds **4p** and **4r** showed comparatively good activity against all the bacterial strains. The good activity is attributed to the presence of pharmacologically active group attached to phenyl group at position **5** of the oxadiazole ring. Introduction of aryl moiety carrying chloro and dichloro group enhanced activity compared to the standard against *T. mentagrophytes*, *A. flavus* and *A. fumigatus*. The presence of N-Mannich base has shown good antibacterial and antifungal activity. Among the tested compounds, Mannich bases **6a, 6b, 6f, 6g**, and **6h** have shown remarkable activity against all tested microorganisms. This may be attributed to the presence of pharmacologically active morpholine, 4-methylpiperazine, 2-fluorophenyl, 4-chlorophenyl and 2-methylphenyl groups associated with oxadiazole ring, while S-methylation caused decrease in activity against most of the strains. The compounds **7c-g** were inactive compared to that of standard against all the bacterial and fungal strains. Results of antibacterial and antifungal screening are discussed in **Table-4** and **Table-5** respectively.

4. Conclusion

The research study reports the successful synthesis and antimicrobial activity of new 1,3,4 oxadiazole derivatives bearing 6-bromonaphthalene moiety. The antimicrobial activity study revealed that all the compounds tested showed moderate to good antibacterial and antifungal activities against tested pathogenic strains. Compounds with phenyl ring substituted with chloro and dichloro showed good activity. Mannich base with morpholine, 4-methylpiperazine, phenyl ring substituted with 2-fluro, 4-chloro and 2-methyl group showed good activity where as (aryl)thio groups were inactive.

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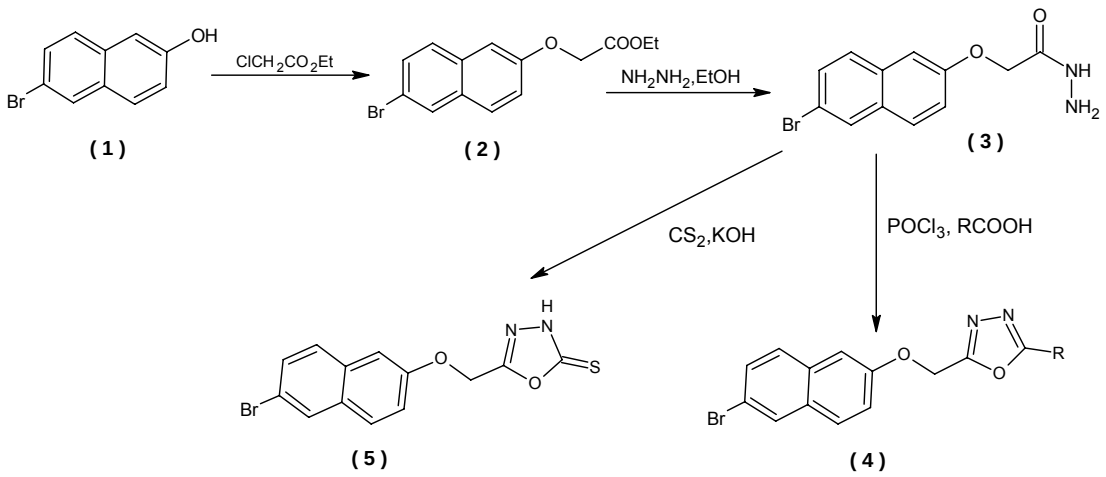
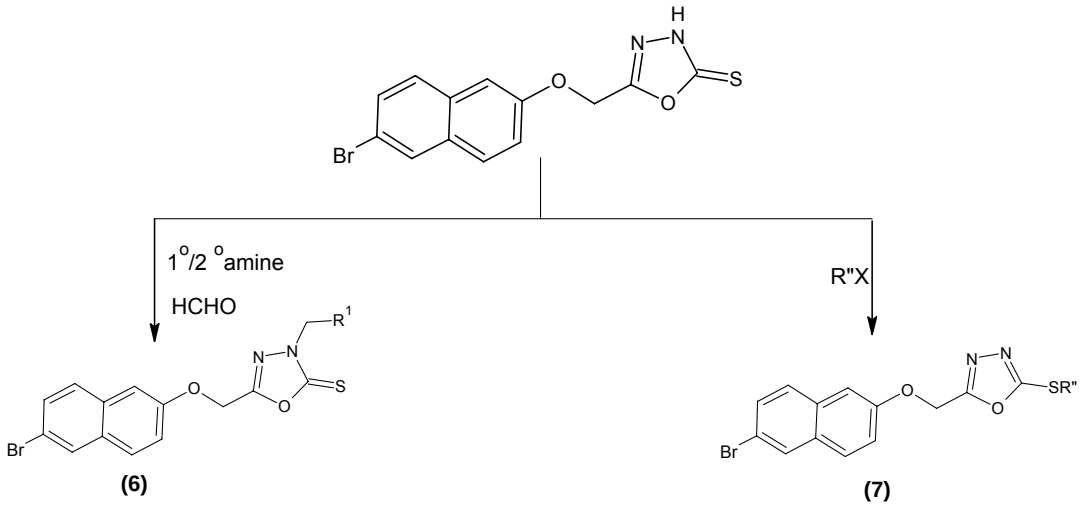


Scheme 1. Synthesis of 2-{[(6-bromo-2-naphthyl)oxy]methyl}-5-aryl-1,3,4-oxadiazole

R = aryl group

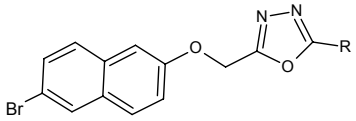


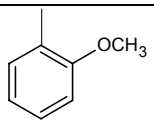
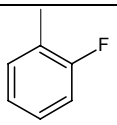
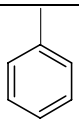
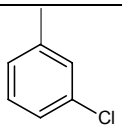
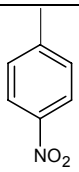
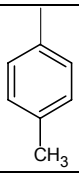
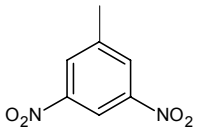
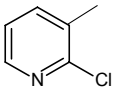
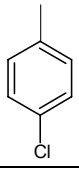
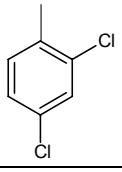
Scheme 2. Synthesis of Mannich bases and 2-{[(6-bromo-2-naphthyl)oxy]methyl}-5-[(alkyl/aryl)thio]-1,3,4-oxadiazole

R^1 = primary/secondary amine

R^{11} = CH_3, C_2H_5, substituted benzyl

Table 1. Characterization data of compounds (4a-r)



Compd.	R	m.p (°C)	Yield %	Elemental analysis % found (calculated)		
				C	H	N
4a		108-110	58	58.40 (58.41)	3.65 (3.67)	6.79 (6.81)
4b		136-138	46	57.14 (57.16)	3.02 (3.03)	7.03 (7.01)
4c		134-136	60	59.84 (59.86)	3.40 (3.43)	7.31 (7.34)
4d		142-144	59	54.89 (54.91)	2.90 (2.91)	6.74 (6.74)
4e		160-162	54	53.52 (53.54)	2.82 (2.83)	9.86 (9.85)
4f		158-160	62	60.77 (60.78)	3.80 (3.82)	7.06 (7.08)
4g		216-218	52	48.42 (48.43)	2.31 (2.35)	11.87 (11.89)
4h		180-182	48	51.86 (51.89)	2.64 (2.66)	10.05 (10.08)
4i		178-180	58	54.92 (54.91)	2.89 (2.91)	6.73 (6.74)
4j		160-162	54	50.69 (50.70)	2.46 (2.46)	6.20 (6.22)

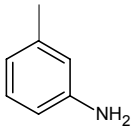
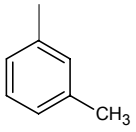
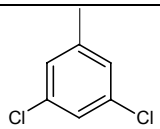
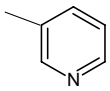
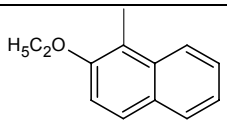
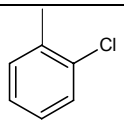
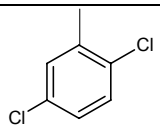
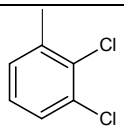
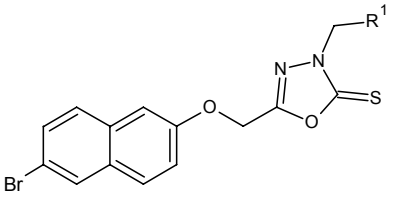
4k		106-108	50	57.56 (57.59)	3.54 (3.56)	10.61 (10.60)
4l		110-112	63	57.71 (57.73)	3.04 (3.06)	7.06 (7.08)
4m		180-182	56	50.71 (50.70)	2.44 (2.46)	6.20 (6.22)
4n		164-166	52	56.53 (56.56)	3.14 (3.16)	10.97 (10.99)
4o		150-152	60	63.15 (63.17)	4.01 (4.02)	5.87 (5.89)
4p		150-152	54	54.90 (54.91)	2.92 (2.91)	6.72 (6.74)
4q		146-148	56	50.69 (50.70)	2.45 (2.46)	6.20 (6.22)
4r		134-136	50	50.71 (50.70)	2.46 (2.46)	6.21 (6.22)

Table 2. Characterization data of compounds 6a-j



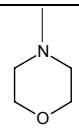
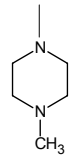
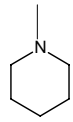
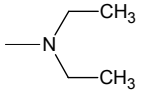
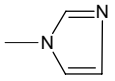
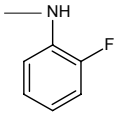
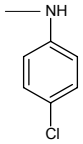
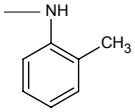
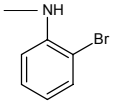
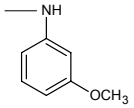
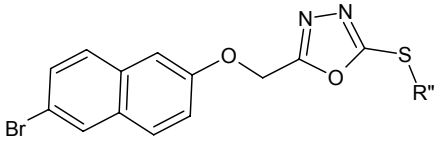
Compd.	R^1	m.p (°C)	Yield %	Elemental analysis % found (calculated)		
				C	H	N
6a		110-112	73	49.50 (49.55)	4.13 (4.16)	9.59 (9.63)
6b		182-184	56	50.70 (50.78)	4.69 (4.71)	12.41 (12.46)
6c		110-112	42	52.51 (52.54)	4.61 (4.64)	9.63 (9.67)
6d		150-152	50	51.16 (51.19)	4.72 (4.77)	9.90 (9.94)
6e		162-164	51	48.61 (48.93)	3.11 (3.14)	13.39 (13.42)
6f		152-154	58	52.16 (52.18)	3.29 (3.28)	9.09 (9.12)
6g		146-148	48	50.36 (50.38)	3.17 (3.17)	8.80 (8.81)
6h		162-164	50	55.23 (55.27)	3.91 (3.97)	9.18 (9.20)
6i		180-182	58	46.04 (46.08)	2.88 (2.90)	8.01 (8.06)
6j		152-154	51	53.31 (53.39)	3.80 (3.84)	8.81 (8.89)

Table 3. Characterization data of compounds 7a-g



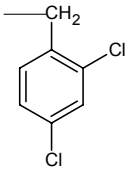
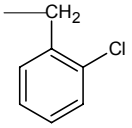
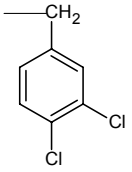
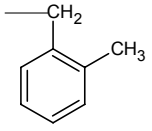
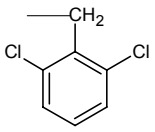
Compd.	R^{11}	m.p (°C)	Yield %	Elemental analysis		
				% found (calculated)		
				C	H	N
7a	CH_3	100-102	60	47.80 (47.87)	3.11 (3.15)	7.93 (7.97)
7b	C_2H_5	118-120	56	50.51 (50.57)	3.51 (3.58)	7.66 (7.67)
7c		92-94	48	48.39 (48.41)	2.59 (2.64)	5.61 (5.64)
7d		154-156	50	52.01 (52.02)	3.04 (3.05)	6.01 (6.06)
7e		184-186	46	48.38 (48.41)	2.60 (2.64)	5.61 (5.64)
7f		128-130	51	57.11 (57.15)	3.82 (3.88)	6.31 (6.34)
7g		110-112	53	48.38 (48.41)	2.61 (2.64)	5.61 (5.64)

Table 4. Antibacterial activity of the compounds. MIC in μgml^{-1}(Zone of inhibition in mm)

Compounds	*E.Coli*	*Staphylococcus*	*Klebsiella*	*Pseudomonas*
4a	-	-	-	-
4b	12.5(11)	-	-	-
4c	-	-	-	-
4d	12.5(15)	6.25(16)	-	6.25(16)
4e	12.5(10)	6.25(12)	-	6.25(12)
4f	12.5(11)	-	-	12.5(15)
4g	12.5(10)		-	-
4h	12.5(10)	-	6.25(12)	-
4i	12.5(10)	-	-	-
4j	12.5(11)	6.25(12)	-	-
4k	12.5(10)	-	-	-
4l	-	-	-	-
4m	12.5(10)		-	-
4n	-	-	-	-
4o	12.5(10)		-	-
4p	6.25(20)	6.25(15)	6.25(18)	6.25(12)
4q	-	-	-	-
4r	6.25(18)	6.25(18)	6.25(15)	6.25(18)
6a	6.25(18)	6.25(20)	6.25(18)	6.25(18)
6b	12.5(15)	12.5(15)	12.5(18)	12.5(15)
6c	12.5(10)	-	-	-
6d	12.5(14)	-	6.25(12)	-
6e	12.5(15)	-	6.25(11)	-
6f	6.25(18)	6.25(16)	6.25(18)	6.25(15)
6g	12.5(15)	12.5(15)	12.5(12)	12.5(12)
6h	12.5(18)	12.5(15)	12.5(15)	12.5(15)
6i	12.5(11)	12.5(14)	12.5(12)	12.5(12)
6j	12.5(10)	6.25(8)	-	-
7a	12.5(8)	12.5(10)	12.5(10)	12.5(10)
7b	12.5(10)	12.5(10)	12.5(12)	12.5(12)
7c	-	-	-	-
7d	-	-	-	-
7e	-	-	-	-
7f	-	-	-	-
7g	-	-	-	-
Ciprofloxacin	6.25(30)	6.25(30)	6.25(27)	6.25(28)

Note: The MIC values were evaluated at concentration range, 1.5-12.5 µg /ml. The figures in the table show the MIC values in µg/ml and the corresponding zone of inhibition in mm.

Table 5. Antifungal activity of the compounds. MIC in μgml^{-1} (Zone of inhibition in mm)

Compounds	*Penicillium*	*Trichophton*	*AS Flavus*	*AS fumigatus*
4a	-	-	-	-
4b	-	12.5(11)	-	-
4c	-	-	-	-
4d	6.25(12)	12.5(15)	6.25(15)	-
4e	6.25(16)	12.5(15)	6.25(16)	-
4f	-	12.5(18)	12.5(18)	-
4g	-	12.5(16)	12.5(15)	-
4h	-	12.5(16)	-	6.25(15)
4i	-	12.5(18)	-	-
4j	6.25(16)	12.5(18)	-	-
4k	-	12.5(18)	-	-
4l	-	-	-	-
4m	-	12.5(15)	-	-
4n	-	-	-	-
4o	-	12.5(15)	-	-
4p	6.25(18)	6.25(18)	6.25(15)	6.25(18)
4q	-	-	-	-
4r	6.25(18)	6.25(15)	6.25(18)	6.25(15)
6a	6.25(18)	6.25(18)	6.25(20)	6.25(20)
6b	12.5(15)	12.5(11)	12.5(15)	12.5(10)
6c	12.5(10)	-	-	-
6d	12.5(15)	-	12.5(16)	
6e	12.5(12)	-	12.5(16)	
6f	6.25(16)	6.25(18)	6.25(16)	6.25(16)
6g	12.5(18)	12.5(15)	12.5(20)	12.5(18)
6h	6.25(20)	6.25(15)	6.25(15)	6.25(18)
6i	6.25(16)	12.5(18)	12.5(11)	12.5(15)
6j	6.25(16)	12.5(15)	12.5(15)	12.5(15)
7a	12.5(10)	12.5(9)	12.5(10)	12.5(10)
7b	12.5(10)	12.5(10)	12.5(10)	12.5(10)
7c	-	-	-	-
7d	-	-	-	-
7e	-	-	-	-
7f	-	-	-	-
7g	-	-	-	-
Cyclopiroxolamine	6.25(27)	3.12(30)	3.125(28)	6.25(28)

Note: The MIC values were evaluated at concentration range, 1.5-12.5 μg /ml. The figures in the table show the MIC values in μg/ml and the corresponding zone of inhibition in mm.