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Design, Synthesis and *in vitro* Antibacterial Evaluation of Naphthalen-2-yloxy based Oxadiazole-2-thione Derivatives

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A series of novel Mannich bases 5-(naphthalen-2-yloxymethyl)-3-(substituted)aminomethyl-3*H*-[1,3,4]oxadiazole-2-thiones **(5a-h)** were synthesized by aminomethylation of substituted-1,3,4-oxadiazole-2(3*H*)-thione by equimolar concentration of primary or secondary amines. Synthesized compounds were characterized by spectrometric techniques (IR, ^{1}H & ^{13}C NMR), and evaluated for antibacterial potential against various Gram-positive and Gram-negative bacterial strains using cup-plate method employing ciprofloxacin as standard drug. Compounds **5a-c** and **5g** exhibited strong antibacterial activity against tested bacterial strains. Compound **5a** was active against *Bacillus pumilus, Shigella dysenteriae* and *Vibrio cholera*; compound **5b** exhibited significant activity against *Bacillus pumilus,* and *Shigella dysenteriae;* compound **5c** was active against *Bacillus pumilus* and *Vibrio cholera* and compound **5g** was active against *Dshigella boydii* and *Acinetobacter aceti* bacterial strains. The SAR study revealed that the synthesized compounds (**5a-h**) having less bulky group exhibited good antibacterial activity.

Keywords: Mannich base, Naphthoxy acetic acid, 1,3,4-Oxadiazole, Antibacterial activity.

INTRODUCTION

Heterocyclic chemistry plays a key role in the development of newer drug molecules. Large number of drug molecules incorporate variety of heterocyclic moieties like oxadiazole, pyrazole, quinoline, pyrazoline, pyrrole, thiazolidine, *etc*. that are being used as pharmacophores for the treatment of various diseases [1-7]. Oxadiazole is one of the most common heterocycles used in drug development. It exists in three isomeric forms, namely: 1,2,4-oxadiazole [8], 1,3,4-oxadiazole [9] and 1,2,5-oxadiazole [10]. All the isomeric forms of oxadiazole possess versatile therapeutic activities such as anti-inflammatory [11], analgesic [12], antimicrobial [13], anticonvulsant [14], antitumor [15], antimalarial [16] and anti-hepatitis B activities [17,18]. Studies suggest compounds containing naphthoxy group in their structure also exhibits significant potential against all spectrum of bacteria [19,20]. Based on the importance of naphthyl and oxadiazole moieties, present study was designed to synthesize the novel oxadiazole derivatives containing oxadiazole and naphthoxy moieties using molecular hybridization strategy to achieve synergistic antibacterial activity of both oxadiazole and naphthoxy groups. For this purpose, aminomethylation of substituted-1,3,4-oxadiazole-2(3*H*)-thione was done using equimolar concentration of primary or secondary amines, that resulted in formation of a new series of Mannich bases [21-23]. For aminomethylation, some less common amines, like as quinoline-5-ylamine, were chosen to maximize the antibacterial potential of resulting Mannich bases [24].

EXPERIMENTAL

All the chemicals and solvents were of synthetic grade and procured from CDH, India. Melting points were determined by using an open capillary melting point apparatus (Lab India) and are uncorrected. Spectroscopic data of newly synthesized compounds were recorded on the following instruments: UV (Shimadzu UV 2100S) spectrophotometer, Perkin-Elmer 1600 FTIR spectrophotometer, ^{1}H NMR (Bruker 300 MHz) and ^{13}C NMR (Bruker Avance II 500MHz) spectrometer. The purity of the compounds was confirmed by thin layer chromatography on silica 160-120 lattice (Merck, India).

Synthesis of (naphthalen-2-yloxy)acetic acid ethyl ester (2): An ethanolic solution of 0.01 mol (10 g) of (naphthalen-2-

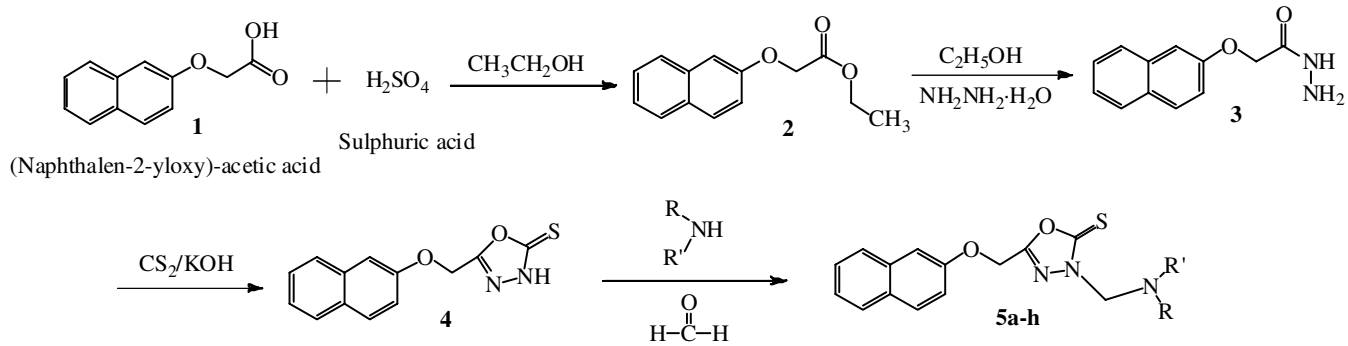
yloxy)acetic acid (**1**) and 1 mL (0.01mol) of sulphuric acid was refluxed for 6-10 h. The resultant reaction mixture was added to the crushed ice and kept undisturbed for two days. The crude precipitates were filtered under vacuum, washed with water and recrystallized using ethanol to obtain pale yellow crystals compound **2**. Yield 68%; m.p.: 80-83 ºC; m.f.: $C_{14}H_{14}O_3$; m.w.: 330.3; IR (KBr, ν_{max}, cm^{-1}): 2850 (C-H, *str.*), 1690 (C=O, *str.*), 1610 (C=C, *str.*), 1225 (C-O, *str.*), and 1210 (C-O-C, *str.*); ^{1}H NMR (DMSO-d_6, 300 MHz), δ in ppm: 1.101-1.222 (t, 3H, -CH_3), 4.654-4.700 (q, 2H, -CH_2), 4.783 (s, 2H, -CH_2), 6.759 (s, 1H, naphthyl), 7.297-7.365 (m, 4H, naphthyl), 7.566-7.666 (t, 2H, naphthyl); ^{13}C NMR (DMSO-d_6, 500 MHz), δ in ppm: 13.007, 57.854, 77.114, 103.996, 121.389, 127.881, 129.005, 129.839, 130.001, 130.505, 131.672, 133.699, 155.008, 173.869.

Synthesis of (naphthalen-2-yloxy)acetic acid hydrazide (3): A mixture of naphthalene-2-yloxyacetic acid ethyl ester (**2**) and hydrazine hydrate were refluxed in the presence of ethanol (10-15 mL) for 6-10 h at 110-120 ºC. After completion of the reaction, the mixture was cooled at room temperature and poured into crushed ice to offer a crude solid mass, which was washed with water and recrystallized from ethanol to yield pale yellow crystals compound **3**. Yield 59%; m.p.: 186-187 ºC; m.f.: $C_{12}H_{12}N_2O_2$; m.w.: 216.2; TLC (R_f value): 0.54; IR (KBr, ν_{max}, cm^{-1}): 3318 (N-H, *str.*), 2800 (C-H, *str.*), 1621 (C=C, *str.*), 1690 (C=O, *str.*), 1210 (N-N, *str.*), 1100 (C-N, *str.*), 1080 (C-O, *str.*), 1050 (C-O-C, *str.*); ^{1}H NMR (DMSO-d_6, 300 MHz) δ in ppm: 4.240-4.258 (brs, 2H, -NH_2), 4.770 (s, 2H, -CH_2), 7.353-7.785 (m, 7H, naphthyl), 8.105 (brs, 1H, -NH); ^{13}C NMR (DMSO-d_6, 500 MHz) δ in ppm: 78.565, 105.386, 122.810, 129.450, 130.561, 131.219, 131.438, 132.545, 132.454, 134.999, 156.505, 171.362.

Synthesis of 5-(naphthalen-2-yloxymethyl)-3*H*-[1,3,4]-oxadiazole-2-thione (4): A mixture of naphthalene-2-yloxy-acetic acid hydrazide (**3**) (0.0025 mol), KOH (0.0025 mol) and 10 mL of carbon disulphide was refluxed in 95% ethanol (50 mL) for 6-12 h at 110-120 ºC. After completion of the reaction, the mixture was cooled at room temperature and poured into crushed ice and acidified with dil. HCl to offer a solid mass which was washed with water and recrystallized from ethanol to yield pale yellow compound **4**. Yield 63%; m.p.: 184-186 ºC; m.f.: $C_{13}H_{10}N_2O_2S$; m.w.: 258.3; TLC (R_f value) in TEF (5:4:1): 0.52; IR (KBr, ν_{max}, cm^{-1}): 3310 (N-H, *str.*), 2810 (C-H, *str.*), 1750 (C=O, *str.*), 1620 (C=N, *str.*), 1600 (C=C, *str.*), 1220 (N-N, *str.*), 1210 (C-O, *str.*), 1200 (C-N, *str.*), 1150 (C-O-C, *str.*), 1105 (C=S, *str.*); ^{1}H NMR (DMSO-d_6, 300 MHz) δ in ppm: 4.715 (s, 2H, -CH_2), 6.551 (s, 1H, naphthyl), 6.882 (s, 1H, -NH), 7.592-7.617 (d, 2H, naphthyl), 7.690-7.715 (m, 2H, naphthyl), 7.908-7.934 (m, 2H, naphthyl); ^{13}C NMR (DMSO-d_6, 500 MHz) δ in ppm: 77.219, 108.136, 133.310, 133.850, 134.261, 134.779, 135.030, 135.265, 135.858, 135.999, 154.961, 155.795, 156.269.

General procedure for synthesis of 5-(naphthalen-2-yloxymethyl)-3-(substituted)aminomethyl-3*H*-[1,3,4]-oxadiazole-2-thiones (5a-h): To a mixture of 5-(naphthalen-2-yloxymethyl)-3*H*-[1,3,4]oxadiazole-2-thione (**4**) (3.0 mol) in methanol (5 mL), formaldehyde (0.5 mL, 37%) and various primary or secondary amines (3.0 mmol) were added. The reaction mixture was stirred overnight. After cooling, the precipitate was filtered and recrystallized from ethanol to yield pure compounds **5a-h** (**Scheme-I**).

5-(Naphthalen-2-yloxymethyl)-3-phenylaminomethyl-3*H*-[1,3,4]oxadiazole-2-thione (5a): Pale yellow crystals, yield: 65%; m.p.: 211-214 ºC; m.f.: $C_{20}H_{17}N_3O_2S$; m.w.: 363.26; TLC (R_f value) in TEF (5:4:1): 0.49; IR (KBr, ν_{max}, cm^{-1}): 3320 (N-H, *str.*), 3150 (C-H, *str.*), 1630 (C=C, *str.*), 1580 (C=N, *str.*), 1235 (N-N, *str.*), 1150 (C-O, *str.*), 1120 (C=S, *str.*), 1035 (C-O-C, *str.*), 1040 (C-N, *str.*); ^{1}H NMR (DMSO-d_6, 300 MHz) δ in ppm: 4.242 (brs, 1H, -NH), 4.282 (d, 2H, -CH_2), 4.647 (s, 2H, -CH_2), 6.810 (s, 1H, naphthyl), 7.261-7.380 (m, 5H, -Ar), 7.653-7.776 (m, 6H, naphthyl); ^{13}C NMR (DMSO-



Compounds	R	R'
5a	C_6H_5	H
5b	C_2H_5	H
5c	Piperazinyl	H
5d	C_6H_5	C_6H_5
5e	$C_6H_4CH_3$	H
5f	Quinolinyl	H
5g	$C_6H_4C_2H_5$	H
5h	$C_6H_3(CH_3)_2$	H

Scheme-I

d_6, 500 MHz) δ in ppm: 69.720, 80.101, 114.509, 115.101, 116.285, 117.162, 124.917, 125.737, 128.881, 129.005, 129.505, 129.839, 130.261, 130.425, 130.907, 131.099, 131.272, 156.907, 157.760, 158.426.

3-Ethylaminomethyl-5-(naphthalen-2-yloxymethyl)-3*H*-[1,3,4]oxadiazole-2-thione (5b): Pale yellow crystals, yield: 70%; m.p.: 236-240 ºC; m.f.: $C_{16}H_{17}N_3O_2S$; m.w.: 315.22; TLC (R_f value) in TEF (5:4:1): 0.46; IR (KBr, ν_{max}, cm^{-1}): 3265 (N-H, *str.*), 2800 (C-H, *str.*), 1665 (C=C, *str.*), 1610 (C=N, *str.*), 1250 (N-N, *str.*), 1150 (C-O, *str.*), 1025 (C-O-C, *str.*), 1015 (C-N, *str.*), 1105 (C=S, *str.*). ^{1}H NMR (DMSO-d_6, 300 MHz), δ in ppm: 1.610-1.731 (s, 3H, -CH_3), 4.161 (d, 2H, -CH_2), 4.705 (s, 2H, -CH_2), 4.254 (brs, 1H, -NH), 4.669 (d, 2H, -CH_2), 7.111-7.353 (m, 3H, -naphthyl), 7.71-7.893 (m, 4H, -naphthyl); ^{13}C NMR (DMSO-d_6, 500 MHz) δ in ppm: 16.004, 40.994, 64.003, 79.421, 121.980, 122.931, 123.505, 124.330, 124.701, 125.325, 125.832, 126.908, 127.706, 156.208, 157.639, 158.960.

5-(Naphthalen-2-yloxymethyl)-3-piperazin-1-ylmethyl-3*H*-[1,3,4]oxadiazole-2-thione (5c): Pale yellow crystals, yield: 68%; m.p.: 180-183 ºC; m.f.: $C_{18}H_{20}N_4O_2S$; m.w.: 356.24; TLC (R_f value) in TEF (5:4:1): 0.55; IR (KBr, ν_{max}, cm^{-1}): 3375 (N-H, *str.*), 2765 (C-H, *str.*), 1650 (C=C, *str.*), 1580 (C=N, *str.*), 1215 (N-N, *str.*), 1145 (C=S, *str.*), 1135 (C-O, *str.*), 1120 (C-N, *str.*), 1095 (C-O-C, *str.*); ^{1}H NMR (DMSO-d_6, 300 MHz) δ in ppm: 2.240-2.809 (m, 8H, -piperazinyl), 4.164 (d, 2H, -CH_2), 4.290 (brs, 1H, -NH), 4.777 (s, 2H, -CH_2), 6.683-7.786 (m, 7H, naphthyl); ^{13}C NMR (DMSO-d_6, 500 MHz) δ in ppm: 42.744, 51.681, 52.535, 53.204, 66.103, 81.020, 126.305, 127.356, 127.989, 128.220, 129.473, 130.002, 130.702, 131.001, 132.135, 148.628, 157.939, 153.162.

3-[(Diphenylamino)methyl]-5-(naphthalen-2-yloxymethyl)-3*H*-[1,3,4]oxadiazole-2-thione (5d): Pale yellow crystals, yield: 61%; m.p.: 170-171 ºC; m.f.: $C_{26}H_{21}N_3O_2S$; m.w.: 439.32; TLC (R_f value) in TEF (5:4:1): 0.48; IR (KBr, ν_{max}, cm^{-1}): 3304 (N-H, *str.*), 2846 (C-H, *str.*), 1633 (C=C, *str.*), 1583 (C=N, *str.*), 1244 (N-N, *str.*), 1129 (C=S, *str.*), 1218 (C-O, *str.*), 1155 (C-O-C, *str.*), 1070 (C-N, *str.*); ^{1}H NMR (DMSO-d_6, 300 MHz), δ in ppm: 4.255 (s, 2H, -CH_2); 4.605 (s, 2H, -CH_2), 6.941-6.966 (t, 2H, -Ar), 6.995-7.581 (m, 8H, -Ar), 7.609-7.710 (m, 4H, naphthyl), 7.755-7.896 (m, 3H, naphthyl); ^{13}C NMR (DMSO-d_6, 500 MHz) δ in ppm: 70.989, 75.835, 120.230, 121.895, 122.182, 123.002, 123.410, 124.175, 124.781, 125.006, 125.310, 125.726, 125.899, 126.192, 126.735, 127.402, 128.110, 128.489, 129.004, 129.825, 130.285, 131.128, 145.529, 147.350, 155.930, 156.001.

5-(Naphthalen-2-yloxymethyl)-3-(*o*-tolylaminomethyl)-3*H*-[1,3,4]oxadiazole-2-thione (5e): Pale yellow crystals, yield: 55%; m.p.: 217-220 ºC; m.f.: $C_{21}H_{19}N_3O_2S$; m.w.: 377.27; TLC (R_f value) in TEF (5:4:1): 0.48; IR (KBr, ν_{max}, cm^{-1}): 3312 (N-H, *str.*), 2907 (C-H, *str.*), 1623 (C=C, *str.*), 1522 (C=N, *str.*), 1219 (C-N, *str.*), 1218 (N-N, *str.*), 1127 (C=S, *str.*), 1112 (C-O-C, *str.*), 1098 (C-O, Str.); ^{1}H NMR (DMSO-d_6, 300 MHz) δ in ppm: 2.281 (s, 3H, -CH_3), 4.013 (brs, 1H, -NH), 4.182 (d, 2H, -CH_2); 4.642 (s, 2H, -CH_2); 6.810-6.871 (m, 4H, -Ar), 7.284-7.702 (m, 5H, naphthyl), 7.750-7.776 (t, 2H, naphthyl); ^{13}C NMR (DMSO-d_6, 500 MHz) δ in ppm: 13.306, 69.012, 74.125, 115.310, 116.658, 122.410, 123.989, 128.999, 129.825, 130.950, 131.107, 132.002, 132.201, 133.105, 133.632, 134.986, 140.876, 144.365, 154.001, 154,801, 155.117.

5-(Naphthalen-2-yloxymethyl)-3-(quinolin-5-ylaminomethyl)-3*H*-[1,3,4]oxadiazole-2-thione (5f): Pale yellow crystals, yield: 67%; m.p.: 214-216 ºC; m.f.: $C_{23}H_{18}N_4O_2S$; m.w.: 414.29; TLC (R_f value) in TEF (5:4:1): 0.48; IR (KBr, ν_{max}, cm^{-1}): 3200 (N-H, *str.*), 3145 (C-H, *str.*), 1646 (C=N, *str.*), 1635 (C=C, *str.*), 1254 (N-N, *str.*), 1215 (C-N, *str.*), 1151 (C=S, *str.*), 1150 (C-O, *str.*), 1124 (C-O-C, *str.*); ^{1}H NMR (DMSO-*d*6, 300 MHz) δ in ppm: 4.267 (d, 2H, -CH_2), 4.400 (brs, 1H, -NH), 4.642 (s, 2H, -CH_2), 7.201 (s, 1H, naphthyl), 7.271-7.487 (m, 6H, naphthyl), 7.690-7.786 (m, 4H, -Ar), 8.628-8.916 (m, 2H, -Ar); ^{13}C NMR (DMSO-d_6, 500 MHz) δ in ppm: 66.021, 80.080, 108.601, 108.721, 111.002, 111.416, 111.608, 111.895, 112.004, 112.406, 113.210, 115.121, 117.010, 119.702, 120.101, 120.222, 120.314, 121.235, 123.001, 123.418, 158.150, 159.901, 160.995.

3-[(4-Ethyl-phenylamino)methyl]-5-(naphthalen-2-yloxymethyl)-3*H*-[1,3,4]oxadiazole-2-thione (5g): Pale yellow crystals, yield: 52%; m.p.: 221-224 ºC; m.f.: $C_{22}H_{21}N_3O_2S$; m.w.: 391.28; TLC (R_f value) in TEF (5:4:1): 0.52; IR (KBr, ν_{max}, cm^{-1}): 3348 (N-H, *str.*), 3026 (C-H, *str.*), 1660 (C=C, *str.*), 1633 (C=N, *str.*), 1240 (N-N, *str.*), 1146 (C-O, *str.*), 1127 (C=S, *str.*), 1120 (C-N, *str.*), 1069 (C-O-C, *str.*); ^{1}H NMR (DMSO-d_6, 300 MHz) δ in ppm: 1.631 (t, 3H, -CH_3), 1.922 (q, 2H, -CH_2), 4.237 (d, 2H, -CH_2), 4.412 (brs, 1H, -NH), 4.605 (s, 2H, -CH_2), 6.785-6.862 (m, 4H, -Ar), 7.322-7.416 (m, 3H, naphthyl), 7.666-7.895 (m, 4H, naphthyl); ^{13}C NMR (DMSO-d_6, 500 MHz) δ in ppm: 13.614, 28.951, 65.855, 77.374, 113.739, 114.841, 123.215, 123.430, 124.007, 125.285, 125.771, 127.123, 127.709, 129.225, 129.769, 131.419, 132.205, 133.194, 134.522, 135.915, 155.602, 159.185.

3-[(3,5-Dimethyl-phenylamino)methyl]-5-(naphthalen-2-yloxymethyl)-3*H*-[1,3,4] oxadiazole-2-thione (5h): Pale yellow crystals, yield: 58%; m.p.: 221-224 ºC; m.f.: $C_{22}H_{21}N_3O_2S$; m.w.: 391.14; TLC (R_f value) in TEF (5:4:1): 0.49; IR (KBr, ν_{max}, cm^{-1}): 3362 (N-H, *str.*), 2896 (C-H, *str.*), 1657 (C=C, *str.*), 1585 (C=N, *str.*), 1239 (N-N, *str.*), 1155 (C-O, *str.*), 1143 (C=S, *str.*), 1122 (C-O-C, *str.*), 1086 (C-N, *str.*); ^{1}H NMR (DMSO-d_6, 300 MHz) δ in ppm: 2.393-2.894 (s, 6H, -CH_3), 4.448 (brs, 1H, -NH), 4.276 (d, 2H, -CH_2), 4.750 (s, 2H, -CH_2), 6.759-6.809 (s, 3H, -Ar), 7.263-7.788 (m, 7H, naphthyl); ^{13}C NMR (DMSO-d_6, 500 MHz) δ in ppm: 21.981, 23.704, 65.913, 73.850, 101.705, 102.830, 105.005, 115.836, 121,884, 122.501, 123.330, 124.001, 124.878, 125.885, 126.724, 127.516, 139.312, 142.460, 143.902, 154.753, 155.829, 156.908.

Antibacterial activity: The synthesized compounds **(5a-h)** were evaluated for their antibacterial potential against the Gram (+) and Gram (-) strains of bacteria namely *Acinetobacter aceti* AP586, *Bacillus cereus* MTCC1305, *Bacillus pumilus*, *E. coli* 35B, *Klebsella pneumoniae* NCTC 7447, *Proteus vulgaris*, *Mongonella morganii* ATCC2580, *Shigella dysenteriae, Shigella boydii* ML12BCH937 and *Vibrio cholera.* The antibacterial activity was evaluated using cup-plate method, wherein the solutions of synthesized compounds **5a-h** and standard drug at a concentration of 200 µg/mL were added to the solidified

agar medium in petri dishes containing bacterial growth; and the zone of inhibition (ZOI) of bacterial growth was determined in preferable condition.

The MIC of antibacterial agent is the lowest concentration that inhibits the growth of test bacteria. For its determination, the stock solution of synthesized compounds was prepared in DMSO. The stock solution was further diluted in 5, 10, 25, 50, 100, 200 µg/mL. Various concentrations of synthesized compounds were poured in petri dishes containing molten agar media (70 mm) and refrigerated at 4 ºC for 24 h to ensure uniform diffusion in the agar medium. Before inoculation, the plates were maintained at the optimum temperature of 37 ºC and then inoculated by test organism using smear loop. The petri dishes were incubated for 24 h at room temperature [19]. Ciprofloxacin was used as a standard drug. Each plate was observed for ZOI and MIC values were determined for all synthesized compounds (**5a-h**).

RESULTS AND DISCUSSION

An ethanolic solution of naphthoxy acetic acid (**1**) was esterified in the presence of sulphuric acid to form (naphthalene-2-yloxy)acetic acid ethyl ester (**2**), which was converted to (naphthalene-2-yloxy)acetic acid hydrazide (**3**) by reaction with hydrazine hydrate. (Naphthalene-2-yloxy)acetic acid hydrazide (**3**) when treated with KOH in presence of CS_2 cyclized to form 5-[(naphthalene-2-yloxy)methyl]-1,3,4-oxadiazole-2(3*H*)-thione (**4**). Aminomethylation of 5-[(naphthalene-2-yloxy)methyl]-1,3,4-oxadiazole-2(3*H*)-thione (**4**) by addition of calculated quantity of formaldehyde and equimolar concentration of 1º or 2º amines at room temperature lead to the formation of a new series of Mannich bases **5a-h** *via* reaction sequence described in **Scheme-I**.

The IR spectra of all the synthesized compounds exhibited the peaks for N-H, C-H, C=C, C=N, N-N, C-O and C=S groups in the range of 3465-3200, 3150-2765, 1665-1623, 1646-1522, 1254-1215, 1218-1098 and 1151-1105 cm^{-1}, respectively. The ^1H NMR spectrum exhibited signals for naphthyl proton in the range of δ 6.6 to 7.8 ppm. Other aromatic protons appeared in the range of δ 2.2 to 8.9 ppm. The appearance of singlet between δ 3.6 to 4.7 ppm confirms the presence of methylene (CH_2) protons. The appearance of ^1H NMR signal near δ 4.4 ppm revealed presence of NH protons. The ^{13}C NMR spectrum shows peak for naphthyl carbons at δ 108-158 ppm. While peaks for aromatic and methylene carbons appeared at δ 127-139 and δ 64-81 ppm, respectively. The strong signal observed near δ 155 and 160 ppm were due to presence of C-2 and C-5 carbon of oxadiazole moiety in the compounds.

Antibacterial activity: The antibacterial potential was determined by calculating ZOI and MIC of the active compounds against Gram (-ve) and Gram (+ve) bacterial strains. Among all the synthesized compounds **5a**, **5b**, **5c** and **5g** were found to possess strong antibacterial activity in terms of ZOI and MIC. Compound **5a** was highly effective against *Bacillus pumilus*, *Shigella dysenteriae* and *Vibrio cholera* with ZOI of 12-13.5 mm and MIC of about 25 µg/mL, while it was moderately effective against *Acinetobacter aceti* AP586, *Escherichia coli* 35B, *pneumoniae* NCTC 7447, *Mongonella morganii* ATCC2580 and *Proteus vulgaris* with ZOI from 6.0-8.3 mm and MIC of about 50 to 100 µg/mL and less effective against *B. cereus* MTCC1305 and *Shigella boydii* ML12BCH937 with ZOI of 9 mm and MIC of about 200 µg/mL. Compound **5b** is highly active against *Bacillus pumilus* and *Shigella dysenteriae* 9 with ZOI of 10-11 mm and MIC of about 25 µg/mL while it is moderately effective against *Acinetobacter aceti* AP586, *Proteus vulgaris* and *Vibrio cholera* 1002 with ZOI of 6-8 mm and MIC of about 50 to 100 µg/mL and inactive against *Bacillus cereus* MTCC1305, *Escherichia coli 35B, Klebsella pneumoniae* NCTC 7447, *Mongonella morganii* ATCC2580 and *Shigella boydii* ML12BCH937 with ZOI of 8-9 mm and MIC of about 200 to > 200 µg/mL. Compound **5c** was strongly active against *Bacillus pumilus* and *Vibrio cholera* 1002 with ZOI of 10-12 mm and MIC of about 25 µg/mL, while it is moderately effective against *Bacillus cereus* MTCC1305, *Escherichia coli* 35B, *Klebsella pneumoniae* NCTC 7447, *Proteus vulgaris*, *Vibrio cholera* 1002, *Shigella boydii* ML12BCH937 and *Shigella dysenteriae* 9 with ZOI of 6-8 mm and MIC of about 50 to 100 µg/mL and inactive against *Acinetobacter aceti* AP586 and *Mongonella morganii* ATCC2580 with showed ZOI of 8 mm and MIC of about 200 to > 200 µg/mL. Compound **5g** is also highly effective against *Dshigella boydii* and *Acinetobacter aceti* AP586 with ZOI of 11.6-12 mm and MIC of about 25 µg/mL, while it is moderately effective against *Bacillus cereus* MTCC1305, *Bacillus pumilus*, *Klebsella pneumoniae* NCTC 7447, *Mongonella morganii* ATCC2580, *Proteus vulgaris* and *Shigella boydii* ML12BCH937 with ZOI from 6-8 mm and MIC of about 50 to 100 µg/mL and inactive against *Escherichia coli* 35B with ZOI from 0 mm and MIC of about > 200 µg/mL. Remaining

TABLE-1
ANTIBACTERIAL ACTIVITIES (MIC, µg/mL) OF SYNTHESIZED COMPOUNDS **5a-h**

Compounds	Strains									
	Acinetobacter aceti AP586	*Bacillus cereus* MTCC1305	*Bacillus pumilus*	*Escherichia coli* 35B	*Klebsella pneumoniae* NCTC7447	*Mongonella morganii* ATCC2580	*Proteus vulgaris*	*Shigella boydii* ML12BCH937	*Shigella dysenteriae* 9	*Vibrio cholera* 1002
5a	100	200	25	100	50	50	100	200	25	25
5b	50	200	25	200	200	>200	50	200	25	100
5c	200	50	25	100	50	>200	50	50	100	25
5d	100	200	100	100	200	50	100	100	100	>200
5e	200	50	>200	100	100	100	>200	200	100	200
5f	>200	100	100	50	>200	200	>200	50	>200	50
5g	25	100	50	>200	50	50	100	100	25	100
5h	100	100	200	200	100	100	100	>200	200	100
Ciprofloxacin	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5

TABLE-2
ZONE OF INHIBITION (DISK DIFFUSION STUDY) OF SYNTHESIZED COMPOUNDS **5a-h** (200 µg/mL)

Compounds	Strains									
	Acinetobacter aceti AP586	*Bacillus cereus* MTCC1305	*Bacillus pumilus*	*Escherichia coli* 35B	*Klebsella pneumoniae* NCTC7447	*Mongonella morganii* ATCC2580	*Proteus vulgaris*	*Shigella boydii* 12BCH937	*Shigella dysenteriae* 9	*Vibrio cholera* 1002
5a	7.2	8.3	12	7	6	7	8	9	13.5	12.2
5b	6	9	10	9	8	-	7	8	11	8
5c	8	6	10	8	6.5	-	7	6	7	12
5d	7.2	9	8	7	9	6	7.5	8	7	-
5e	8.5	6.6	-	7.3	8	8	-	8.3	8	9
5f	-	8	7	6	-	9	-	7	-	6
5g	12	7	6.2	-	6	6.4	8	8	11.6	7
5h	7.7	7	8.4	9	8	7.1	7	-	9	8
Ciprofloxacin	18	17	16.5	17	15	17	14	15	18	17

compounds were shown to be inactive compared to the standard drug ciprfloxacin (Tables 1 and 2).

It was observed that –H substituent at R′ position favors antibacterial activity. R can be substituted by lower aliphatic, aromatic or heteroaromatic substituent. The synthesized compounds **5e** and **5f** both were found to be moderately active in comparison to the above said active compounds. It may be because of the steric crowding of bulky substituents in these compounds. The inactivity of compounds **5d** and **5h** can also be attributed to the bulky structures of these compounds in comparisons to others.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this article.

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