Synthesis And Anti Bacterial Activity Of 5-((Naphthylene 2-Yloxy) Methyl)-1,3,4-Oxadiazole-2(3h)-Thione Mannich Bases

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Abstract: In the present study napthol was treated with ethylchloro acetate to get ethyl 2-(naphthalene-2-yloxy)acetate (1), which on reaction with hydrazine hydrate gave 2(naphthalene-2-yloxy)acetohydrazide (2). This on further reaction with potassium hydroxide and Carbon disulfide in methanol yielded 5-((naphthalene-2-yloxy)methyl)-1,3,4-Oxadiazole-2(3H)- thione (3). The compound 3 was treated with formaldehyde and various secondary amines to form 5-((naphthalene-2-yloxy)methyl)-1,3,4-Oxadiazole-2(3H)-thione mannich bases (4a-4f). The structures of all the synthesized compounds were confirmed by spectral data (IR, H1NMR) and were tested for their antibacterial activity by agar cup plate method. The compound 4f showed relatively good antibacterial activity compared to standard used.

Key words: Antibacterial, napthol, secondary amines, hydrazides, cup-plate method.

Introduction

Bacterial infections are increasing worldwide and antibacterial agents are used for the treatment of these infectious diseases. These agents have been widely misused and widespread use of antibacterial agents resulted in increased emergence of resistant bacteria. Hence the existing anti-bacterials are not much effective in the treatment of bacterial infections. 1,3,4 oxadiazoles have attracted in medicine due to their wide range of pharmacological and biological activities. Also mannich bases have proven therapeutic activities. Literature review revealed less documentation on antibacterial 1,3,4 Oxadiazole mannich bases. In view of the above, in the present study a series of 1,3,4 Oxadiazoles mannich bases of naphthalene were synthesized. These synthesized compounds were characterized and screened them for their possible anti-bacterial activity by using cup plate method.

Experimental

The melting points of the synthesized compounds were determined in open capillary using LABHOSP melting point apparatus and recorded in °C without correction. The progress of the reaction and the purity of the compounds were checked using precoated silica gel plates (60 GF, 254 MERCK). The IR spectra of the synthesized compounds were recorded on SHIMADZU FTIR 8400 spectrometer by KBr pellet technique. The H1 NMR Spectra of the synthesized compounds were taken using BRUKER SPECTROSPIN -400MHz spectrometer using CDCl3/ CD3OD as solvents and TMS as internal standard. The chemical shift data were expressed as δ value relative to TMS in ppm. The Mass spectral data of the compounds were recorded by HRMS—QP5050SHIMADZU instrument.
General procedure:

Synthesis of ethyl 2-(naphthalene-2yl oxy) acetate.(1)

In a 1000ml round bottom flask 2-naphthol (24.49 gm, 0.17 mol) was dissolved in 500ml of acetone. 34ml of ethyl chloro acetate(0.17 mol) and 23.4 gm(0.17 mol) of potassium carbonate was added and refluxed for 8 hrs. The solution was evaporated to half its volume and cooled to room temperature. The reaction mixture was then poured into ice cold water, the precipitate thus obtained was filtered, washed with cold water and recrystallized from ethanol. mol.formula: C_{14} H_{15} O_{3}; mol.weight: 213.26 ;%yield 58; m.p 97-99 0°C; IR (cm^{-1}, KBr) : 1747.57 (C=O), 1608.69(C=C ring), 1201.69 (COC),2983.98 (C-H aliphatic), 3095.12 (C-H aromatic).

Synthesis of 2-(naphthalene-2-yl oxy)acetoxy hydrazide.(2)

In a 500ml round bottom flask ethyl 2-(naphthalene-2yl oxy) acetate (1) (23.03gm , 0.1 mol) was dissolved in 200ml of ethanol, hydrazine hydrate (5.0ml , 0.1 mol) was added, the mixture was refluxed for four hours & cooled to room temperature. The solid thus separated was filtered, washed with cold ethanol and recrystallized from ethanol. mol.formula: C_{12} H_{15} N_{2} O ; mol.weight: 216.24 ;%yield 55; m.p 150-152 0°C; IR (cm^{-1}, KBr) : 1662.69 (C=O , amide ) , 1217.12 (COC) , 3051.49 (CH aromatic ) , 3313.82(NH stretch ).

Synthesis of 5-(naphthalene-2-yl oxy)methyl-1,3,4-oxadiazole -2(3H)-thione (3)

In a 500ml round bottom flask 2-(naphthalene-2-yl oxy)acetoxy hydrazide. (2) (11.61 gm, 0.05mol) was treated with a solution of potassium hydroxide (2.8 gm, 0.05 mol) dissolved in 100ml methanol under stirring. Carbon disulphide (3.8 ml, 0.05 mol) was added slowly to the reaction mixture and reflux for 8 hrs. The solvent distilled under vacuum and residue was dissolved in water, acidified. The solid thus separated was filtered, washed with cold ethanol and purified by recrystallisation from ethanol. mol.formula: C_{13} H_{10} N_{2} S O_{2}; mol.weight: 258.3 ;%yield 62; m.p 148-150 0°C; IR (cm^{-1}, KBr) : 1180.47 (C=S ), 3051.49 (CH aromatic ) , 3311.89(NH stretch ), 1629.90(CN cyclic); H^1 NMR (δ , ppm) : 5.24 (s,2H,NH) , 4.78 (s,2H,CH2 ), 6.9-7.7 (m,7H, Naphtalene ), 8.33(s,1H,NH).

Synthesis of 5-(naphthalene-2-yl oxy)methyl-1,3,4-oxadiazole -2(3H)-thione(3) Mannich bases(4 a – 4 f).

In a 50 ml round bottom flask, to 5-(naphthalene-2-yl oxy) methyl-1,3,4-oxadiazole -2(3H)-thione(3) (0.01 mol, 2.58 gms) in methanol was added formaldehyde (0.5ml,37%) and secondary amines(0.01 mol) – pyrrolidine/piperidine /morpholine/indole/n-methyl piperazine/imidazole. The mixture was stirred overnight and kept at 0-10°C for 3 hrs. The precipitate obtained was collected and recrystallized from methanol (scheme1).

4a: 5-[(naphthalen-2-yl oxy)methyl]-3-(pyrrolidin-3-ylmethyl)-1,3,4-oxadiazole-2(3H)-thione : mol.formula: C_{14} H_{16} N_{2} S O ; mol.weight: 341 ;%yield 45; m.p 160-162°C; IR (cm^{-1}, KBr) : 1087.89 (C=S ) , 3051.49 (CH aromatic), 3000.89(NH stretch), 1660.77(CN cyclic); H^1 NMR (δ , ppm) : 1.6 (t,4H,CH_3piperidine), 2.2 (t,4H,NCH_3pyridine), 3.7 (s,2H,methylene),4.0(s,2H,methylene), 6.9-7.6 (m,7H, naphtalene ).

4b:5-[(naphthalen-2-yl oxy)methyl]-3-(piperidin-4-ylmethyl)-1,3,4-oxadiazole-2(3H)-thione
mol.formula: C_{18}H_{23} N_{2} O _2 S; mol.weight: 355.45;%yield 40; m.p 156-158 0°C; IR (cm^{-1}, KBr):3000.89(NH stretch), 1095.60 (C=S stretch), 1647.26(CN cyclic), 1209.41 (C-N stretch) 3051.49 (CH aromatic); H^1 NMR (δ , ppm) : 1.5 (t,6H,CH_3piperidine), 2.2 (t,4H,NCH_3piperidine), 3.7 (s,2H,methylene),4.0(s,2H,methylene), 6.9-7.6 (m,7H, naphtalene ).

4c:3-(morpholino-4-ylmethyl)-5-[(naphthalen-2-yl oxy)methyl]-1,3,4-oxadiazole-2(3H)-thione
mol.formula: C_{18}H_{19} N_{3} O _3 S; mol.weight: 357.43;%yield 42; m.p 132-134 0°C; IR (cm^{-1}, KBr):3000.89(NH stretch), 1093.67 (C=S stretch) , 1653.06(CN cyclic) , 1209.41 (C-N stretch) 3051.49 (CH aromatic); H^1 NMR (δ , ppm) : 1.9-2.77 (t,4H,NCH_3morpholine), 3.66 (t,4H,OCH_3morpholine), 3.7 (s,2H,methylene), 4.0(s,2H, methylene), 6.9-7.6 (m,7H, naphtalene ).

4d: 3-(1H-indol-5-ylmethyl)-5-[(naphthalen-2-yl oxy)methyl]-1,3,4-oxadiazole-2(3H)-thione
mol. formula: $C_{22}H_{17}N_3O_2S$; mol. weight: 387.45; % yield 39; m.p 80-82 °C; IR (cm$^{-1}$, KBr): 3000.89 (NH stretch) 1060.62 (C=S stretch), 1274.63 (C-N stretch), 3051.49 (CH aromatic); H$^1$ NMR ($\delta$, ppm): 4.0 (s, 2H, methylene), 5.1-5.2 (s, 2H, methylene), 6.9-7.6 (m, 13H, naphthalene and indole).

4e: 3-[(4-methylpiperazin-1-yl)methyl]-5-[(naphthalen-2-yl)oxy]methyl]-1,3,4-oxadiazole-2(3H)-thione; mol. formula: $C_{19}H_{22}N_4O_2S$; mol. weight: 370.47; % yield 35; m.p 140-142 °C; IR (cm$^{-1}$, KBr): 3030.85 (NH stretch), 1093.67 (C=S stretch), 1629.90 (CN cyclic), 1217.12 (C-N stretch), 3051.49 (CH aromatic); H$^1$ NMR ($\delta$, ppm): 2.2 (s, 3H, NCH$_3$ piperazine), 2.4 (t, 8H, NCH$_2$ piperazine), 3.7 (s, 2H, methylene), 4.0 (s, 2H, methylene), 6.9-7.6 (m, 7H, naphthalene).

4f: 3-(1H-imidazol-1-ylmethyl)-5-[(naphthalen-2-yl)oxy]methyl]-1,3,4-oxadiazole-2(3H)-thione; mol. formula: $C_{17}H_{14}N_4O_2S$; mol. weight: 338.38; % yield 44; m.p 60-62 °C; IR (cm$^{-1}$, KBr): 3000.89 (NH stretch), 1168.90 (C=S stretch), 1656.91 (CN cyclic), 1033.68 (C-N stretch), 3001.34 (CH aromatic); H$^1$ NMR ($\delta$, ppm): 4.0 (s, 2H, methylene), 5.1-5.2 (s, 2H, methylene), 6.9-7.6 (m, 10H, naphthalene and imidazole).

Scheme 1: Synthesis of compounds 4a – 4f

Where R= Pyrolidine in 4a; R= piperidine in 4b; R= Morpholine in 4c; R= Indole in 4d; R= N-methyl piperazine in 4e; R= Imidazole in 4f.

Antibacterial activity:

All the synthesized compounds 4a-4f were screened for their antibacterial activity by agar cupplate diffusion method. They were tested against two gram positive bacteria Staphylococcus aureus (ATCC 6632) and Bacillus subtilis (ATCC 6633) and two gram negative bacteria Escherichia coli (ATCC 25923) and Pseudomonas aeruginosa (ATCC 25922). Ciprofloxacin was used as standard and the effectiveness of compounds were determined by comparing zone of inhibition. (Table 1)
Table 1: Antibacterial activity of compounds 4a to 4f:

<table>
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<th>Compound</th>
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<tr>
<td>4b</td>
<td>6.0</td>
<td>7.0</td>
<td>5.0</td>
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</tr>
<tr>
<td>4c</td>
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<td>6.0</td>
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Results and Discussion:

β- napthol was used as starting material to synthesize 5-(naphthalene-2-yloxy)methyl)-1,3,4-oxadiazole-2(3H)-thione mannich bases(4a-4f). The structures of the newly synthesized compounds were characterized by the spectral data. The presence of NH₂ in compound 2-(naphthalene-2-yloxy)acetohydrazide(2) showed the absorption band in the region 3313 cm⁻¹ and NH group at 3203.87 cm⁻¹. The C=O stretching was observed at 1662.69 cm⁻¹. The presence of NH₂ and OCH₂ at 1.58 and 4.78 ppm in the ¹H NMR confirmed the formation of the same. Compound 5-(naphthalene-2-yloxy)methyl)-1,3,4-oxadiazole-2(3H)-thione(3) was used to synthesize the mannich bases(4a-4f). The compound 4c showed morpholine ring protons as triplet at δ 1.9-2.77 accounting for 4 NCH₂ protons & at δ3.66 accounting for 4 OCH₂ protons. The singlet due to naphthalene OCH₂ appeared at δ 4.0 integrating for 2 protons, mannich CH₂ protons resonated as singlet at δ 3.7. The Naphthalene ring protons appeared between δ 6.9-7.6 ppm. The rest of all mannich bases synthesized were in full agreement with the proposed structures. All the compounds were screened for their possible antibacterial activity by agar cupplate diffusion method and the results are tabulated (table1). The compound 4f showed relatively good activity compared to standard ciprofloxacin (100µg/ml) and the rest of the compounds showed poor antibacterial activity.

References:

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