The Synthesis of Acid Derived Compounds Bearing 1,3,4-oxadiazole-2-thion Ring as Potential Antimicrobial Agents

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Abstract

Aromatic heterocycles are very important motifs in medicinal chemistry field. 1,3,4-oxadiazole exhibits a wide range of biological especially antifungal, activities [1]. 1,3,4-oxadiazole and their fused heterocyclic derivatives has gained notable attention due to their effective bio-synthetic importance[2-5].

In this work, various new compounds including ring 1,3,4-Oxadiazole were synthesized from the reactions of hydradizide compounds with carbon sulphur in basic medium. Acid derivatives were prepared by thiol tautomer form of 1,3,4-Oxadiazole (Scheme 1). Furthermore, structure-activity relationship was evaluated in respect to effect of different substitutions in newly synthesized 1,3,4-oxadiazole series. Then these compounds were characterized by performing of melting point, FT-IR, $^1$H-NMR (400 MHz), and $^{13}$C-NMR(100 MHz).

Keywords: 1,3,4-Oxadiazole, Mannich Bases, Thiol-Thione Tautomerism.

Intraduction

Nowadays, the synthesis of polyfunctional and heteroatom bearing cyclic compounds in which possess wide range of antimicrobial and biological activity is an important field in synthetic organic chemistry.

Plenty of information can be found about the ring closure reaction of carbohydrazide compounds. In this type of reaction, three heteroatom bearing five-membered heterocyclic compounds such as 1,3,4-oxadiazole, 1,3,4-thiodiazole, and 1,3,4-thiazole are formed [6]. Carboxylic acid hydrazides react with CS2 in ethanolic KOH to form potassium-3-arylthiocarbazide salts in good yiled. This formed salt converted to 5-aryl-2-mercapto-1,3,4-oxadiazole via ring closure reaction in the presence of pyridine or anhydrous NaOH [7, 8]. Magnetic properties of metal complexes of proper oxadiazole and thiodiazole is another investigating subject [9]. 1-acylthiosemicarbazide, 1,3,4-oxadiaze, 1,3,4-thiodiazole and 1,2,4- triazole-3-thione derivatives were detected as pain releiver and therapeutic effect on stomach diseases such as ulcer, gastritis by Palaska et al. Furthermore, no side effect of these synthesized compunds has been detected [10].
**Experimental**

**The synthesis of 5-Pyridin-4-yl-1,3,4-oxadiazole-2-thiol (2a)**

0.05 mol (6.86 g) isonicotinohydrazide was dissolved in 50 mL of ethanol, sodium hydroxide 0.05 mol, 2 g. and carbon disulfide (0.05 mol, 3.3 mL) were added. the mixture was refluxed for 3 hours. The solvent was evaporated under reduced pressure. The residue was dissolved in water and filtered, the filtrate was acidified and filtered. The precipitate was crystallized from mixture of ethanol-dioksan (5:1). Yield: %54, m.p: 279-280°C.

**The synthesis of 2-(5-Mercapto-1,3,4-oksadiazol-2-yl)phenol (2b)**

7.60 g (0.05 mole) 2-hydroksibenzo-hydrazide was dissolved in 50 ml of ethanol, 2 g of sodium hydroxide (0.05 mole), and 3.3 ml of carbon disulfide (0.05 mole) were added. the mixture was refluxed for 3 hours. The solvent was evaporated under reduced pressure. The residue was dissolved in water and filtered, the filtrate was acidified and filtered. The precipitate was crystallized from mixture of ethanol-dioksan (5:1) 8.74 g, (90%), m.p. 207-208°C;

**The synthesis of 2-((5-Pyridin-4-yl-1,3,4-oxadiazol-2-yl)thio)acetic acid (3a)**

The 5-pyridin-4-yl-1,3,4-oxadiazolee-2-thiol (0.01 mole, 1.79 g), (0.01 mole, 0.4 g.) NaOH in ethanol (40 mL ) was refluxed for 1 h. Ethyl-bromoacetate (0.01 mol, 1.65 g) was added to this solution, and the mixture refluxed for 4 hour. After a slow cooling process, the solution was poured into ice and recrystallization was performed with a mixture of ethanol-water(4:1). Yield: %62, m.p: >375°C.

**The synthesis of 2-((5-(2-hydroxyphenyl)-1,3,4-oxadiazol-2-yl)thio)acetic acid (3b)**

A solution of the 2-(5-mercapto-1,3,4-oxadiazol-2-yl)phenol, 1.94 g (0.01 mole) 2b, and 0.40 g (0.01 mole) of sodium hydroxide in 40 ml ethanol was refluxed for 1 hour. Ethyl bromoacetate (1.65 g, 0.01 mole) was added, and the resulting mixture refluxed for 4 hours. The solution was transferred to ice after cooling and the solid mass recrystallized from a mixture of ethanol-water (4:1). Yield: 1.21 g. (48%), m.p.>375 °C;
Result and discussion

FT-IR, $^1$H-NMR and $^{13}$C-NMR spectrums of compound 2a,b and 3a,b are listed sequentially.

5-Pyridin-4-yl-1,3,4-oxadiazole-2-thiol (2a)

Scheme 2: FT-IR Spectrum of 2a

FT-IR (KBr, $\nu_{\text{max}}$/cm$^{-1}$): 3443-3220 (N-H), 3131-3000 (Ar.C-H), 3000-2883 (Al.C-H), 1252 (C=S), 1621 (C=N)

Scheme 3: $^1$H-NMR Spectrum of 2a

$^1$H-NMR (400 MHz, DMSO-d6, ppm) : $\delta$ 7.78 (dd, J=6.23, 1.83, 2H, Ar. C-CH), 8.78 (d, J=5.83, 2H, Ar. N-CH)
Scheme 4: $^{13}$C-NMR Spectrum of 2a

$^{13}$C-NMR (100 MHz, DMSO-d6, ppm): $\delta$ C$_5$: 182.05, C$_4$: 159.88, C$_2$: 151.47, C$_3$: 132.44, C$_1$: 119.291.

2-(5-Mercapto-1,3,4-oksadiazol-2-yl)phenol (2b)

Scheme 5: FT-IR Spectrum of 2b

FT-IR (KBr, $\nu_{\text{max}}$/cm$^{-1}$): 3503-3180 (O-H), 3131-2830 (C-H), 2976-2777-2554 (S-H), 1622 (C=N)

Scheme 6: $^1$H-NMR Spectrum of 2b

$^1$H-NMR (400 MHz, DMSO-d6, ppm): $\delta$ 6.94 (t, J=8.43, 1H, H$_3$), 7.02 (d, J=8.43, 1H, H$_1$), 7.40 (t, J=8.80, 1H, H$_2$), 7.61 (d, J=8.06, 1H, H$_4$), 10.47 (s, 1H, OH).

Scheme 7: $^{13}$C-NMR Spectrum of 2b

$^{13}$C-NMR (100 MHz, DMSO-d6, ppm): $\delta$ C$_8$: 177.74, C$_1$: 160.52, C$_7$: 156.96, C$_3$: 134.13, C$_5$: 129.73, C$_4$: 120.13, C$_2$: 117.70, C$_6$: 110.05.
2-((5-Pyridin-4-yl-1,3,4-oxadiazol-2-yl)-thio)acetic acid (3a)

FT-IR (KBr, $\nu_{\text{max}}$/cm$^{-1}$): 3516-3246 (O-H), 3131-2925 (Ar/AlC-H), 1740 (C=O), 1610 (C=N)

$^1$H-NMR (400 MHz, DMSO-d6, ppm): $\delta$ 3.79 (s, 2H, S-CH$_2$CO), 7.28 (dd, J=6.23, 1.83, 2H, Ar. C-CH), 8.78 (d, J=5.83, 2H, Ar. N-CH).

2-((5-(2-hydroxyphenyl)-1,3,4-oxadiazol-2-yl)thio)acetic acid (3b)

FT-IR (KBr, $\nu_{\text{max}}$/cm$^{-1}$): 3600-3120 (O-H), 3115-2915 (Ar/AlC-H), 1735 (C=O), 1608 (C=N)


Scheme 11: $^1$H-NMR Spectrum of 3b

$^1$H-NMR (400 MHz, DMSO-d6, ppm) : δ 3.81 (s, 2H, S-CH$_2$-CO), 6.48 (t, J=7.33, 1H, H$_5$), 6.68 (d, J=8.43, 1H, H$_1$), 7.12 (t, J=8.43, 1H, H$_2$), 7.51 (dd, J=7.70, 1.46, 1H, H$_4$).

Antibacterial and antifungal activity

<table>
<thead>
<tr>
<th>Compounds</th>
<th>E.Coli (Conc.)</th>
<th>S. Aureus(Conc.)</th>
<th>B. Subtilis(Conc.)</th>
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<tr>
<td></td>
<td>10 µg/ml</td>
<td>50 µg/ml</td>
<td>100 µg/ml</td>
</tr>
<tr>
<td>2a</td>
<td>-</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>2b</td>
<td>+</td>
<td>+++</td>
<td>++</td>
</tr>
<tr>
<td>3a</td>
<td>-</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>3b</td>
<td>+</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>++</td>
<td>+++</td>
<td>+++</td>
</tr>
</tbody>
</table>

Symbols: (-): < 10% inhibition, (+): 10-30% inhibition, (++): 30-60% inhibition, (+++): 60-90% inhibition, Ciprofloxacin ≥ 90% inhibition

Table 1 The degree of inhibition of antibacterial activity of the synthesized compounds

<table>
<thead>
<tr>
<th>Compounds</th>
<th>C. Albicans (Conc.)</th>
<th>A. Niger (Conc.)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>50 µg/ml</td>
<td>100 µg/ml</td>
</tr>
<tr>
<td>2a</td>
<td>+</td>
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<tr>
<td>2b</td>
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<tr>
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<td>++</td>
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<tr>
<td>Flucanazole</td>
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<td>+++</td>
</tr>
</tbody>
</table>

Symbols: (-) no inhibition, (+) weakly active, (++) moderately active, (+++) highly active

Table 2 Antifungal activity of compounds against C. Albicans, and A. Niger

The compounds (2a–b, 3a,b) were examined for antibacterial activity against E. Coli, S. Aureus and B. Subtilis by agar diffusion technique using ciprofloxacin as the reference (50 µg/ml), antifungal activity against A. Niger and C. Albicans by agar diffusion technique using fluconazole as reference (50 µg/ml). The results and observations are outlined in Table 1 and Table 2.
References


