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Preliminary Investigation of Antifungal Activity of 3-(3-fluoro-4-piperazine-1-phenyl)-1,3-oxazolidin-2-ones

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ABSTRACT: Few analogues of 3-(3-fluoro-4-piperazine-1-phenyl)-1,3-oxazolidin-2-one were synthesized and structurally characterized using physical and spectral data. Current research work is to evaluate the potential of these analogues as antifungal agents. Two fungal strains, *Aspergillus flavus* & *Penicillium chrysogenum* were used in the Kirby bauer agar diffusion assay. Results revealed that 3-(3-fluoro-4-piperazine-1-phenyl)-1,3-oxazolidin-2-ones doesn't have significant antifungal activity against *P. chrysogenum* but Ox 1.3 & Ox 1.5 have shown potential inhibition of *A. flavus* comparable to that of standard oxytetracycline. This antifungal activity can be attribute to the 4-acetylpiperazinyl ring in 3-(3-fluoro-4-piperazine-1-phenyl)-1,3-oxazolidin-2-one. Further tailoring up the structure can augment the drug discovery.

KEYWORDS: 1,3-Oxazolidin-2-one; Antifungal Activity; Medicinal Chemistry; *Aspergillus flavus*; *Penicillium chrysogenum* .

INTRODUCTION

In recent years, it has been observed that life threatening systemic fungal infections have become increasingly common, especially in the immuno-compromised host suffering from tuberculosis, cancer or AIDS and in organ transplant cases[1-3]. 1,3-oxazolidin-2-one, and oxygen and nitrogen comprising heterocyclic structures attracts many researchers all over the world, evidenced to have unique and potential antibacterial activity, with the outcome as scaffold of first ever totally synthetic antimicrobial agent i.e. Linezolid [4,5]. Famoxadone is a new agricultural fungicide recently commercialized by DuPont that demonstrate excellent control on plant pathogens in the ascomycete, basidomycete and oomycete class. Oxazolidin-2-one analogs are the potent inhibitors of mitochondrial ubiquinol: cytochrome c oxidoreductase(cytochrome bc_1) and they bind in the Q_o site of the enzyme near the potential heme of cytochrome b[6,7].

3-Chlorooxazolidin-2-ones were evaluated for their antifungal activity against *Candida albicans*[8], aim of present work was to evaluate the antifungal activity of 3-Fluorooxazolidin-2-ones(against *Aspergillus flavus* & *Penicillium chrysogenum*.

MATERIALS & METHODS

Six 1,3-oxazolidin-2-ones were synthesized and structurally characterized[4]. The general scheme of their synthesis is shown in **Figure 1**.

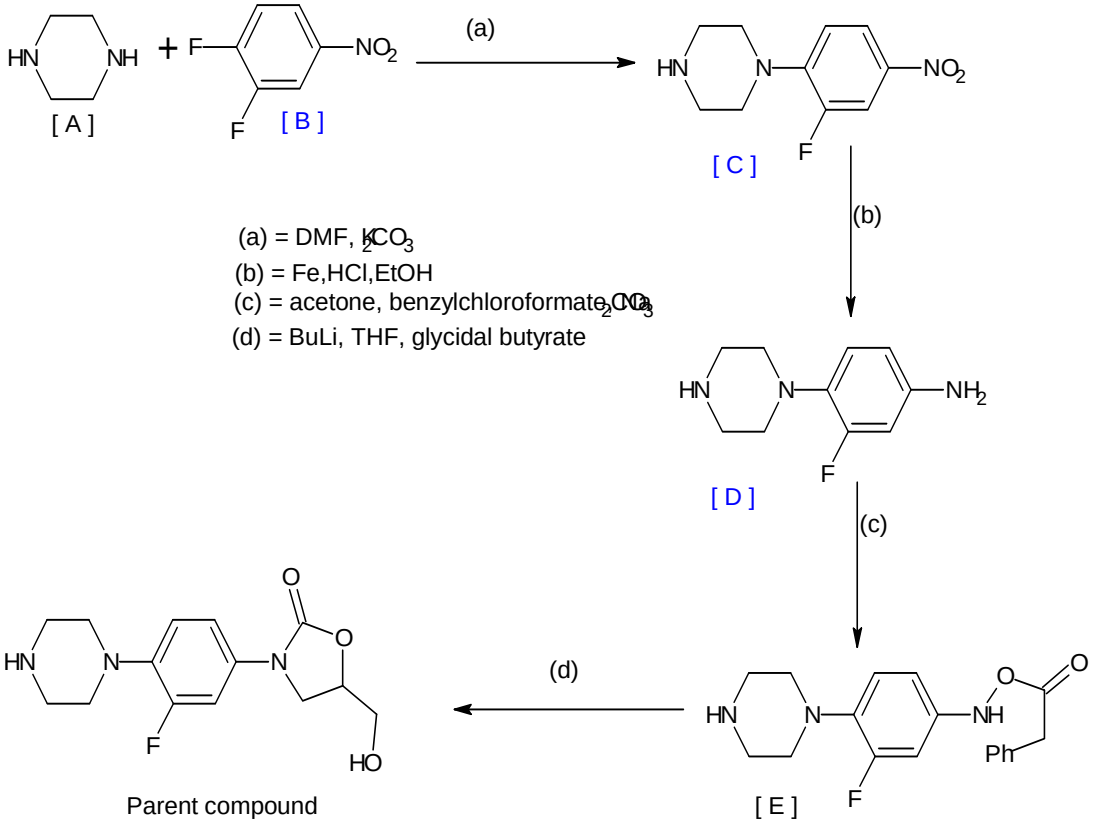

Figure 1 General procedure for the synthesis of parent ring (3-(3-fluoro-4-piperazine-1-phenyl)-5-(hydroxymethyl)-1, 3-oxazolidin-2-one)[4]

Synthesis of [3-(3-fluoro-4-piperazine-1-phenyl)-5-[hydroxyl(pyrimidin-4-yl)methyl]-1,3 oxazolidin-2-one] (**Ox 1.1**) [4] – Refer **Figure 2**.

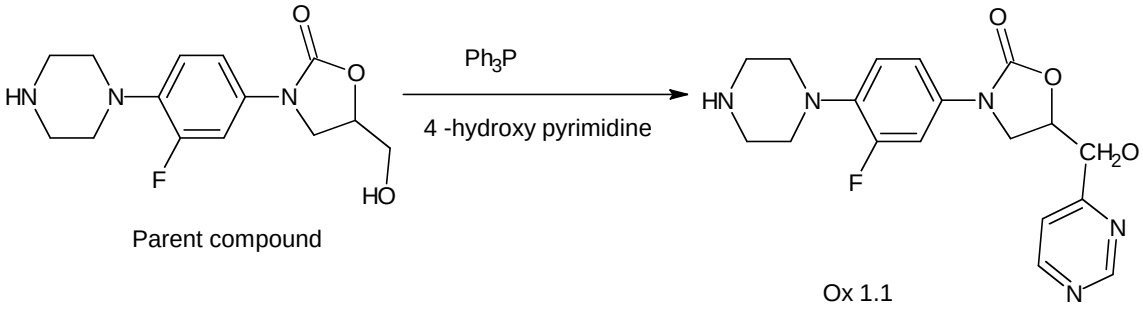

Figure 2 Synthesis of Ox 1.1

*Synthesis of [3-(3-fluoro-4-piperazine-1-phenyl)-5-pyrazine-1,3 oxazolidin-2-one] (**Ox 1.2**)* [4] – Refer **Figure 3**.

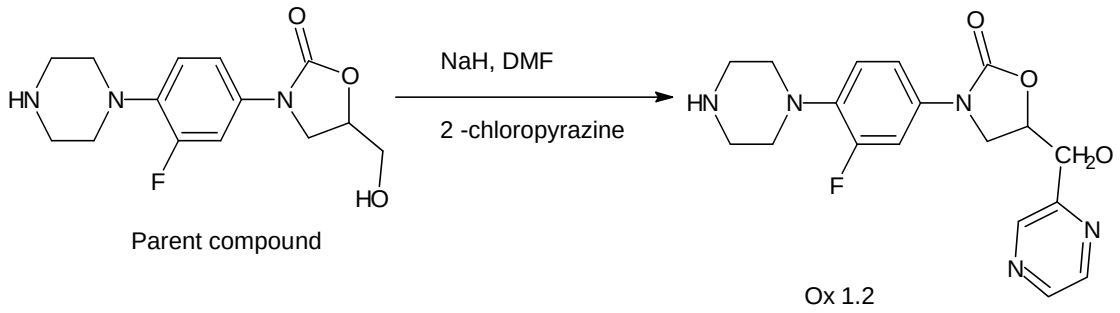

Figure 3 Synthesis of Ox 1.2

*Synthesis of [3-(4acetylpiperazine-1-phenyl)-5-hydroxymethyl-1,3 oxazolidin-2-one] (**Ox 1.3**)* [4] – Refer **Figure 4**.

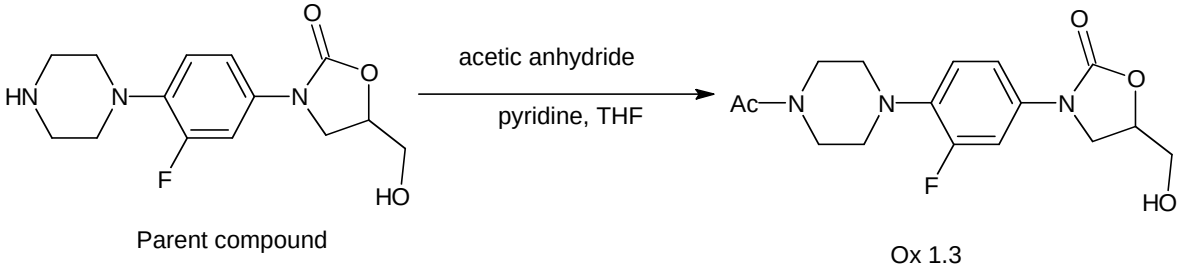

Figure 4 Synthesis of Ox 1.3

*Synthesis of [3-(3-fluoro-4-piperazine-1-phenyl)-5-carbaldehyde-1,3 oxazolidin-2-one] (**Ox 1.4**)* [4] – Refer **Figure 5**.

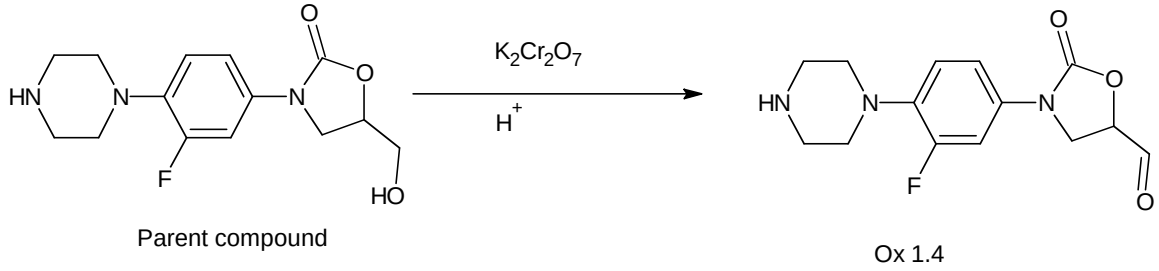

Figure 5 Synthesis of Ox 1.4

*Synthesis of [3-(3-fluoro-4-piperazine-1-phenyl)-5-oxime-1,3 oxazolidin-2-one] (**Ox 1.5**)* [4] – Refer **Figure 6**.

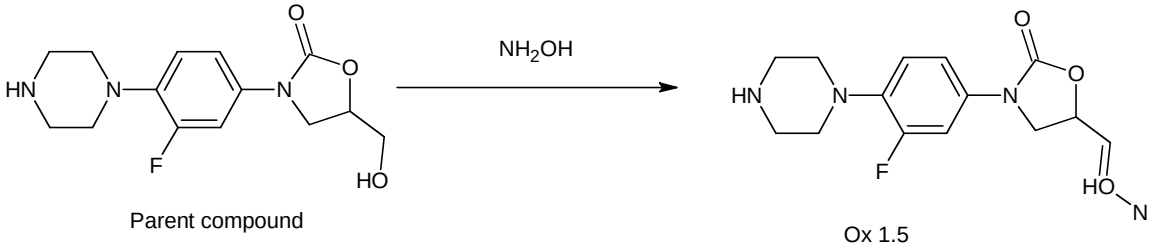

Figure 6 Synthesis of Ox 1.5

Antifungal Activity- Kirby Bauer Agar Diffusion Assay

1,3-Oxazolidiones and standard Oxytetracycline were taken in concentration of 200 mg/ml[9]. Standard Kirby bauer agar diffusion assay method was adopted to screen antifungal activity against *Aspergillus flavus* & *Penicillium chrysogenum*[4, 10].

RESULTS & DISCUSSION

Table 1 Antifungal Activity of 1,3-Oxazolidin-2-ones

Compound (200 mg/ml)	**Zone of inhibition (mm)**	
	Aspergillus flavus	***Penicillium chrysogenum***
Parent	8	4
Ox1.1	-	-
Ox1.2	-	-
Ox1.3	23	9
Ox1.4	4	-
Ox1.5	11	4
Oxytetracycline	27	12

Parent oxazolidinone i.e. 3-(3-fluoro-4-piperazine-1-phenyl)-5-(hyroxymethyl)-1,3-oxazolidin-2-one were synthesized by the four step nucleophillic substitution reactions as explained above(**Figure 1**). Five derivatives of oxazolidinones (**Ox 1.1 – Ox 1.5**) were prepared from the parent oxazolidin-2-one by single step nucleophillic attack(**Figure 2-6**). Structure of all the compounds was characterized by physical data as well as spectral analysis. To evaluate the test compounds for possible antifungal activity, they were tested with the strains of *A. flavus* & *P. chrysogenum* at concentration of 200 mg/ml and compared it with the standard oxytetracycline(200 mg/ml)(**Table 1**)[4]. It has been observed in case of anti-*A. flavus* screening that the acetylation at 4^{th} position of piperazine is essential for activity, as the non-acetyl derivatives of 1,3-oxazolidin-2-one have insignificant growth inhibitory effect against *A. Flavus*. Similarily, 5-oxime 1,3-oxazolidin-2-one derivative(Ox 1.5) have better activity than parent, Ox 1.1, Ox 1.2 & Ox 1.4 compounds. So possibly a derivative where acetyl group will be at 4^{th} position of piperazine and oxime at 5^{th} position of 1,3-oxazolidin-2-one ring could potentially inhibit the growth of *A. Flavus*(A human pathogen which is associated with aspergillosis of

the lungs and sometimes causing corneal, otomycotic, and nasoorbital infections)[11]. So it is highly recommended to further tailored up the structure to optimally design novel 1,3-oxazolidin-2-one derivative with potential anti-*A. flavus* activity.

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