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Antimicrobial evaluation of 2-azetidinonyl 5-(2-benzoyl-phenoxymethyl)-1,3,4-oxadiazole derivatives

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ABSTRACT

Benzophenone and their derivatives are important and useful compounds with diverse pharmacological properties. In the present study, we have evaluated the in vitro antibacterial activity of new 2-azetidinonyl-5-(2-benzoyl-phenoxymethyl) -1,3,4-oxadiazole derivatives ***6a-j*** *using Gram positive and Gram negative bacterial strains. Minimal inhibitory concentrations (MIC) were determined in order to monitor the efficacy of the synthesized compounds. Certain compounds inhibit bacterial growth with low MIC (μg/mL) value. The most potent antibacterial compounds of this series were compounds* ***6a****,* ***6d*** *and* ***6g*** *which have lower MIC value of 4.68 μg/ml in selected strains.*

Keywords: antimicrobial activity, azetidinonyl, benzophenone, 1,3,4-Oxadiazole, MIC.

INTRODUCTION

Antibiotics have revolutionized mankind's health status, allowing treatment of life threatening infections. However with the increasing occurrence of bacterial resistance against available antibiotics, it has now become essential to look for newer antibiotics. The growing incidence of infection caused by the rapid development of bacterial resistance to most of the known antibiotics is a serious health problem [1-3]. While many factors may be responsible for mutations in microbial genomes, it has been widely demonstrated that the incorrect use of antibiotics can greatly increase the development of resistant genotypes [4-6]. As multidrug-resistant bacterial strains proliferate, the necessity for effective therapy has stimulated research towards the novel antimicrobial molecules.

Benzophenone and substituted benzophenone derivatives have been found to possess diverse biological activities like antimicrobial [7], anti-inflammatory [8], antioxidant [9], anticancer [10] activity. At present situation penicillins and cephalosporins are widely used therapeutic agents against bacterial infection and diseases. The antimicrobial activity of these compounds is mainly associated with the β-lactam ring. They inhibit the cell wall synthesis by binding to membrane-bound bacterial transpeptidase, also known as penicillin binding proteins. 2-Azetidinones possess β-lactamase inhibitory activity and hence became an attractive nucleus for development of new antimicrobial agents. Numerous 2-azetidinone derivatives were reported to exhibit antibacterial and antifungal activity [11-13].

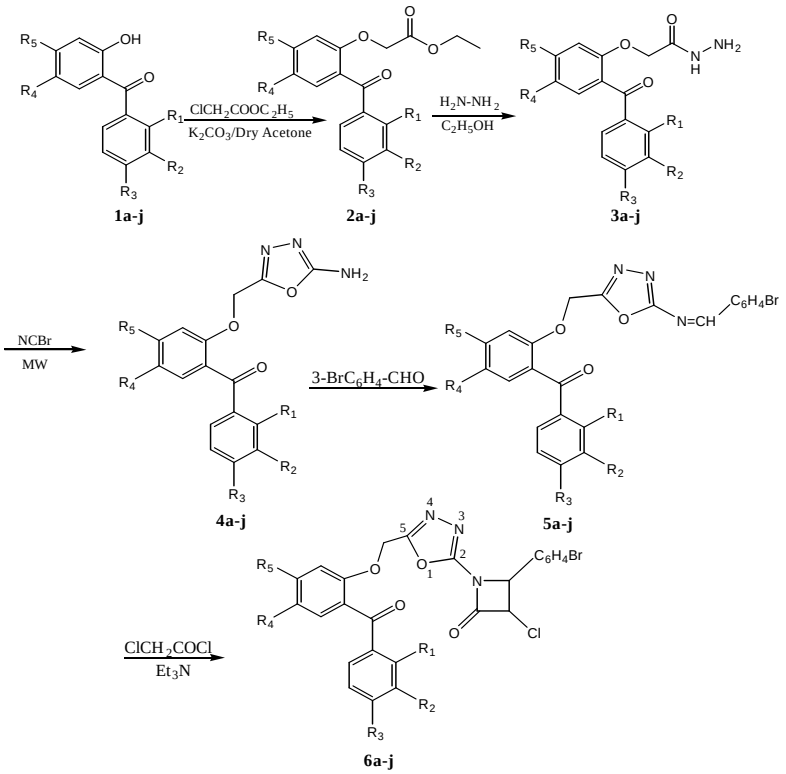
Microbial infections are nowadays more common than during the first half of the century. Observing this, we have previously reported synthesis of 2-azetidinonyl-5-(2-benzoyl-phenoxymethyl)-1,3,4-oxadiazole derivatives [14-15].

Although, a number of different classes of antibacterial and antifungal agents have been discovered during the last two decades the use is limited due to the development of microbial resistance. This situation highlights the need for development of novel, potent, and safe antimicrobial agents. Therefore, in continuation of our synthesis [14], we have studied the antimicrobial efficacy of 2-amino and 2-azetidinonyl-5-(2-benzoyl-phenoxymethyl) 1,3,4-oxadiazoles derivatives.

MATERIALS AND METHODS

Chemistry

Melting points were determined with Thomas Hoover capillary melting point apparatus and are uncorrected. IR spectra were recorded in Nujol on a FT-IR Shimadzu 8300 spectrophotometer and NMR spectra were recorded on a Bruker spectrophotometer in $CDCl_3$ solution. The ^1H NMR and ^{13}C NMR spectra were measured at 300 and 90 MHz, respectively. The chemical shifts are reported as parts per million relative to internal TMS. Elemental analysis results are within 0.4% of the calculated value. Chemicals were purchased from Aldrich Chemical Co. TLC was performed on preactivated (110˚C) silica gel plates using ethyl acetate:chloroform (7:2) as eluent and the plates were visualized with UV light. Synthesis of the title compounds was clearly discussed earlier. Briefly, the synthetic route is depicted in Scheme **1**. Condensation of substituted 2-hydroxybenzophenones **1a-j** with ethyl chloroacetate yielded substitutedethyl-2-benzoyl-phenoxy acetates **2a-j**, which on treatment with 80% hydrazine hydrate in ethanol afforded the respective 2-benzoyl-phenoxy acethydrazides **3a-j**. The cyclization of **3a-d** with cyanogens bromide furnished the corresponding 2-amino-5-(2-benzoyl-phenoxymethyl) 1,3,4-oxadiazoles **4a-j**. Condensation of **4a-j** with 3-bromo benzaldehyde with a drop of glacial acetic acid furnished Schiff bases, 2-(3-bromobenzylidene)amino-5-(2-benzoyl-phenoxymethyl) 1,3,4-oxadiazoles **5a-j**. The azetidin-2-one moiety in the compounds **5a-j** was introduced by the cycloaddition of chloroacetyl chloride in the presence of triethylamine to give **6a-j** [14, 15].



a: $R_1=R_2=R_3=R_5=H$, $R_4=CH_3$ b: $R_1=R_2=R_3=R_5=H$, $R_4=Cl$
c: $R_1=R_2=R_5=H$, $R_3=R_4=CH_3$ d: $R_1=R_2=R_5=H$, $R_3=Cl$, $R_4=CH_3$
e: $R_1=R_3=R_5=H$, $R_2=Cl$, $R_4=CH_3$ f: $R_1=R_2=R_3=R_4=H$, $R_5=Br$
g: $R_1=R_2=R_5=H$, $R_3=OCH_3$, $R_4=CH_3$ h: $R_1=R_3=R_5=H$, $R_2=R_4=Cl$
i: $R_1=R_2=R_3=H$, $R_4=Cl$, $R_5=CH_3$ j: $R_1=Cl$, $R_2=R_3=R_5=H$, $R_4=CH_3$

Scheme 1

Biology

The microbial strains were procured from the National Chemical Laboratory (NCL), Pune, India. The synthesized compounds were screened against the following Gram positive bacterial strains like B. cereus (*MTCC1303*), S. aureus (*MTCC 7443)*, B. subtilis (*MTCC 121)*, S. aureus (MRSA) *(MTCC 84)*, E. aerogens *(MTCC 111)*, M. luteus *(MTCC 1538)*, and Gram negative bacterial strains like K. pneumonia *(MTCC 109)*, P. aeruginosa *(MTCC 2453)*, S. typhimurium *(MTCC 2488)*, E. coli (*MTCC 7410)*, S. Paratyphi-B *(MTCC 733)* and P. vulgaris *(MTCC 321)*. The minimum inhibitory concentration was done by broth dilution method [16, 17], using Streptomycin as standard control and the results are presented in Table 1.

RESULTS AND DISCUSSION

The chemistry of the synthesized compounds was clearly discussed earlier [14-15]. The possible antimicrobial activities of compounds **6a-j** were evaluated in vitro by determining MIC values in µg/mL against some gram positive and gram negative bacterial strains such as B. cereus, S. aureus, B. subtilis, S. aureus (MRSA), E. aerogens, M. luteus, K. pneumonia, P. aeruginosa, S. typhimurium, E. coli, S. Paratyphi-B and P. vulgaris. The MIC values were determined by broth dilution method using Streptomycin as standard control and the results are presented in table **1**. Among all the compounds in the series some of them are shown good, moderate and poor antimicrobial activity. The difference in bacterial activity is mainly due to the presence of different substituent's at different positions of 2-azetidinonyl-5-(2-benzoyl-phenoxymethyl) 1,3,4-oxadiazoles **6a-j**. For instance, compounds **6a** with methyl group at para position of phenyl ring have shown significant inhibition towards B. cereus and M. luteus, **6d** with methyl and chloro groups at para position of phenyl and benzoyl rings respectively also shown significant inhibition towards S. aureus. In addition, compound **6g** with methyl and methoxy groups at para position of phenyl and benzoyl rings respectively shown significant inhibition towards E. coli. Further, compounds **6c**, **6e**, **6f**, **6i** and **6j** have shown incredibly moderate inhibition towards all the tested strains. Compounds **6b** with chloro group at para position of phenyl ring and **6h** with two chloro groups one at para position of phenyl ring and another at meta position of benzoyl ring have shown very poor inhibition towards all the tested strains. Finally we can conclude that compounds **6a-j** were having broad range of anti bacterial activity.

Table 1.Antibacterial activity of the compounds: 6a-j: MIC in µg /ml

Compounds	Name of microorganism (MIC in µg /ml)											
	Gram positive bacteria						Gram negative bacteria					
	B. cereus	*S. aureus*	*B. subtilis*	*S. aureus (MRSA)*	*E. aerogens*	*M. luteus*	*K. pneumonia*	*P. aeruginosa*	*S. typhimurium*	*E. coli*	*S. Paratyphi-B*	*P. vulgaris*
6a	4.68	9.37	9.37	9.37	18.75	4.68	9.37	18.75	18.75	9.37	18.75	18.75
6b	300	300	150	150	300	75	300	300	150	300	150	300
6c	9.73	9.73	18.75	9.73	18.75	18.75	9.73	9.73	18.75	18.75	37.5	37.5
6d	18.75	4.68	9.73	18.75	18.75	9.73	18.75	37.5	9.73	9.73	18.75	18.75
6e	37.5	18.75	37.5	9.73	18.75	9.37	18.75	18.75	18.75	9.73	18.75	18.75
6f	75	18.75	9.37	9.37	9.37	37.5	18.75	9.37	18.75	18.75	9.37	18.75
6g	9.37	9.37	18.75	18.75	150	18.75	18.75	9.37	75	4.68	9.37	75
6h	150	300	300	300	150	300	300	150	300	300	75	150
6i	9.37	37	18.75	4.68	9.37	9.37	18.75	37	18.75	9.37	18.75	9.37
6j	37	18.75	9.37	37	9.37	9.37	18.75	18.75	9.37	18.75	18.75	9.37
Streptomycin	2.34	2.34	4.68	1.17	2.34	2.34	4.68	4.68	2.34	2.34	4.68	4.68

CONCLUSION

In conclusion, the present observations confirm the presence of antimicrobial activity in all examined compounds. Among the series compounds **6a**, **6d** and **6g** shown good bacterial growth inhibition compared to other compounds in the series with the MIC value of 4.68 µg/ml in selected strains. Further investigations may help to develop novel antimicrobial drugs for future chemotherapy.

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