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Der Pharma Chemica, 2013, 5(4):269-273
(http://derpharmachemica.com/archive.html)

ISSN 0975-413X
CODEN (USA): PCHHAX

In vitro antibacterial and antifungal evaluation of some benzophenone analogues

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ABSTRACT

Antibacterial and antifungal agents are widely used in the management of infectious disease but most of them have developed resistance to micro-organism. To overcome this problem and to lower the side effects, many approaches can be utilized. Benzophenone derivatives are reported to have the broad spectrum of biological activities. In the present study we have screened benzophenone derivatives ***5a-k*** *against six bacterial species viz gram positive (Bacillus subtilis and Staphylococcus aureus) and gram negative (Pseudomonas aeruginosa, Salmonella typhi, Proteus vulgaris, Shigella flexneri) bacteria. Also compounds* ***5a-k*** *were tested with six fungal species viz (Candida albicans, Aspergillus niger, Fusarium solani, Aspergillus flavus, Botrytis cinerea, Candida krusei). The obtained results showed that the synthesized compounds* ***5a-k*** *exhibited moderate to good activities against all the tested strains. Compounds* ***5a, 5c, 5d, 5f*** *and* ***5g*** *have shown good antibacterial and antifungal activities against selected strains.*

Keywords: Benzophenone, Antibacterial activity, Antifungal activity.

INTRODUCTION

Infections diseases represent a critical issue for health and the major cause of morbidity and mortality worldwide. Despite significant progress in human medicine, infections diseases caused by microorganisms are still a serious threat to public health. The impact is even greater in developing countries due to unavailability of medicine in all the locations, the practice of self-medication and the emergence of microorganism drug resistance[1]. The development of resistance to current antibacterial therapy continues to drive the search for more effective agents. In addition, primary and opportunistic fungal infections continue to increase the number of immune compromised patients, those suffering from such as AIDS or cancer or who have undergone organ transplantation.

In recent years, the incidence of fungal and bacterial infections has increased dramatically. The widespread use of antibacterial and antifungal drugs resulted in resistance to drug therapy against bacterial and fungal infections which led to serious health hazards. The resistance of wide spectrum antibacterial and antifungal agents has initiated discovery and modification of the new antibacterial and antifungal drugs.

Benzophenones are a class of compounds obtained from natural products[2] or by synthetic methods[3]. The structural features of benzophenones have been of tremendous interest in medicinal, chemical and industrial fields. Many

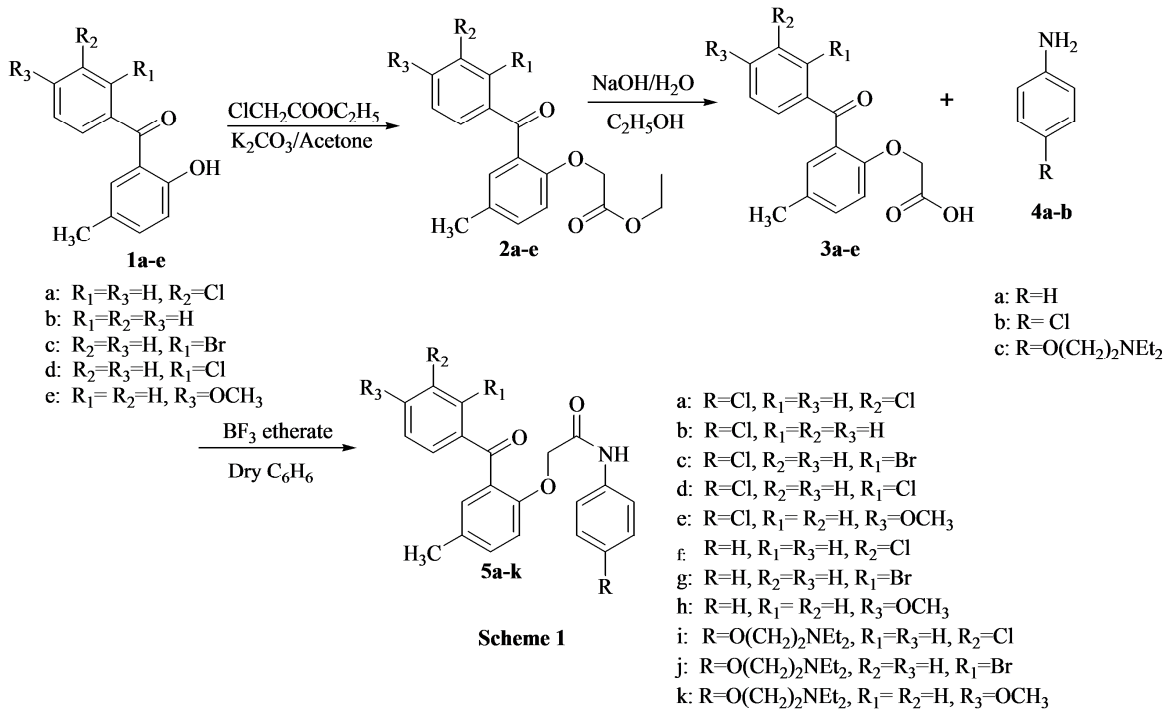
benzophenone derivatives are reported to have the broad spectrum of biological activities, such as CNS depressant[4], antimalarial[5], antimitotic[6], antiprotozoal[7], antiulcer[8], antibacterial[9], antioxidant, spermicidal[10], antitumor[11], and anti-inflammatory[12] activities. The aim of this study was to investigate antibacterial and antifungal effects of benzophenone derivatives against a panel of bacteria and fungi.

MATERIALS AND METHODS

Chemicals were purchased from Aldrich Chemical Co. TLC was performed on aluminium-backed silica plated with visualization by UV-light. Melting points were determined on a Thomas Hoover capillary melting point apparatus with a digital thermometer. IR spectra were recorded in Nujol on FT-IR Shimadzu 8300 spectrometer and ^{1}H NMR spectra were recorded on a Bruker (300 MHz) spectrometer in $CDCl_3$. Chemical shifts were recorded in parts per million downfield from tetramethylsilane. Mass spectra were obtained with a VG70-70H mass spectrometer and elemental analysis results are within 0.4% of the calculated value.

Chemistry

The synthesis of the hitherto reported title compounds **5a-k** is as outlined in scheme 1. Hydroxybenzophenones **1a-e** on reaction with ethyl chloroacetate affords ethyl (2-aroyl-4-methylphenoxy) acetates **2a-e** in excellent yield, which on alkaline hydrolysis afforded (2-aroyl-4-methylphenoxy)ethanoic acid **3a-e**. Compounds **3a-e** on condensation with substituted aromatic amines **4a-c** in presence of boron trifluoride etherate and dry benzene furnished benzophenone analogues, (2-aroyl-4-methylphenoxy) acetamides(5a-k)[11].



Scheme 1

Antimicrobial activity

The *in-vitro* antimicrobial activity of all the synthesized compounds **5a-k** at different concentrations (20,40,60 and 80 µg/ml) were studied by agar well diffusion method[13-15] against six bacterial species *viz* gram positive *(Bacillus subtilis* and *Staphylococcus aureus)* and gram negative *(Pseudomonas aeruginosa, Salmonella typhi, Proteus vulgaris* and *Shigella flexneri)* bacteria. Also compounds **5a-k** were tested with six fungal species *viz* (*Candida albicans, Aspergillus niger, Fusarium solani, Aspergillus flavus, Botrytis cinerea* and *Candida krusei).* All the organisms were obtained from stock cultures which were maintained on nutrient agar medium and Sabouraud's dextrose agar medium at 40^{o}C, then subcultures in nutrient broth at 37^{o}C, prior to each antimicrobial test. The antibacterial activities of all the synthesized compounds were compared with standard drug streptomycin and

antifungal activity with fluconazole. The zone of inhibitions was determined by measuring scale as per standard procedure[14]. The experiment was repeated thrice, the mean values were tabulated.

RESULTS AND DISCUSSION

Antimicrobial and antifungal activity

The antibacterial activity of the synthesized compounds **5a-k** was assessed in comparison with streptomycin and antifungal activity with fluconazole as standard drugs against the Gram-positive, Gram-negative bacteria and fungal pathogens using agar well diffusion method and the results are summarized in (**Table 1, 2)**. The obtained results showed that the synthesized compounds **5a–k** exhibited moderate to good activities against all tested strains. Compounds **5a, 5c, 5d, 5f** and **5g** have shown good antibacterial and antifungal activities while compounds **5b, 5h-k** exhibit moderate activities against selected organisms at the concentration 80 µg/ml compared to the standards (20 µg/ml).

Table 1: Antibacterial activity of compounds 5a-k

Zones of Inhibition of bacteria in mm							
Compd	Conc in µg/ ml	***Bacillus subtilis***	***Pseudomonas aeruginosa***	***Salmonella typhi***	***Proteus vulgaris***	***Shigella flexneri***	S. aureus
5a	20	14	9	16	10	12	11
	40	21	13	21	13	14	19
	60	23	19	25	18	18	22
	80	28	22	28	28	25	24
5b	20	6	6	7	9	5	9
	40	7	8	9	10	9	10
	60	9	12	12	10	9	11
	80	12	15	14	12	12	15
5c	20	13	9	8	8	8	8
	40	21	13	11	8	12	10
	60	23	18	13	9	15	13
	80	27	22	22	12	18	19
5d	20	12	8	10	7	8	8
	40	20	11	12	14	12	11
	60	23	17	13	15	18	15
	80	28	22	23	22	25	21
5e	20	9	7	9	6	9	9
	40	10	7	11	10	14	11
	60	13	10	11	12	16	12
	80	17	13	14	17	20	16
5f	20	10	10	18	8	11	10
	40	19	14	21	13	17	13
	60	21	17	25	19	19	17
	80	25	20	28	26	26	20
5g	20	10	14	9	7	11	8
	40	18	19	14	11	13	10
	60	20	21	19	14	19	16
	80	24	22	23	18	24	19
5h	20	6	7	8	8	6	9
	40	7	9	9	9	7	14
	60	7	13	12	11	10	18
	80	12	16	15	18	15	21
5i	20	7	9	9	8	5	8
	40	7	11	11	13	9	9
	60	9	13	12	15	11	13
	80	10	17	14	19	16	16
5j	20	8	7	9	6	7	9
	40	11	11	9	7	7	11
	60	12	12	10	9	10	11
	80	15	17	15	14	14	15
5k	20	9	6	8	6	8	8
	40	8	10	11	7	9	11
	60	11	13	13	8	9	13
	80	13	16	16	13	12	18
Streptomycin	20	35	23	30	33	29	25
Control	-	-	-	-	-	-	-

Table 2: Antifungal activity of compounds 5a-k

Zones of Inhibition of bacteria in mm							
Compd	Conc in µg/ ml	*C. albicans*	*A. niger*	*F. solani*	*A. flavus*	*B. cinerea*	*C. krusei*
5a	20	15	9	8	13	16	16
	40	22	12	14	18	18	18
	60	25	19	19	21	18	20
	80	28	29	23	27	21	24
5b	20	7	9	7	7	12	10
	40	10	10	9	9	14	14
	60	12	11	13	9	16	16
	80	14	13	19	13	20	23
5c	20	9	8	10	12	18	10
	40	11	9	14	19	20	11
	60	14	11	20	22	22	14
	80	22	15	24	25	24	19
5d	20	10	6	7	11	10	18
	40	11	12	12	18	14	20
	60	13	15	17	21	18	24
	80	23	20	21	27	21	28
5e	20	9	6	7	9	10	10
	40	10	11	9	10	12	14
	60	12	14	10	16	14	16
	80	16	18	17	19	14	22
5f	20	18	8	11	9	10	10
	40	21	14	15	11	16	14
	60	25	21	19	17	20	19
	80	28	27	23	23	20	25
5g	20	9	7	13	9	9	14
	40	14	11	16	13	12	18
	60	19	14	19	19	18	20
	80	23	18	22	23	24	24
5h	20	8	8	6	6	10	9
	40	9	9	9	9	14	11
	60	12	11	14	9	18	13
	80	15	18	18	13	21	18
5i	20	9	8	9	7	9	11
	40	11	13	12	8	11	14
	60	12	15	16	10	16	19
	80	16	19	18	12	18	23
5j	20	8	6	7	8	10	9
	40	9	7	7	11	10	11
	60	10	9	12	13	12	13
	80	15	14	19	17	14	18
5k	20	7	6	6	8	8	9
	40	11	9	11	9	10	12
	60	12	11	14	11	12	15
	80	16	17	18	14	15	20
Fluconazole	20	29	32	27	33	35	39
Control	-	-	-	-	-	-	-

The investigation on the structure-activity relationship shows that, in general the presence of halo groups at the phenyl rings enhanced the antibacterial and antifungal action of the synthesized compounds.

It is worthwhile to note that compound **5a** exhibits significant antibacterial and antifungal activities, possibly due to the presence of chloro group at the *para* position of the phenyl rings. Besides compound **5d** has less activity than **5a** may be due to the presence of chloro group at *ortho* position, also bromo substituted compounds **5c** and **5g** exhibited good activity. Further, the presence of methoxy groups in compound **5e** and **5h** and butoxy groups in compounds **5i-k** may be responsible for their lesser activity.

CONCLUSION

In conclusion, a series of eleven compounds were screened *in vitro* against six bacteria and six fungi. The synthesized compounds have a great interest because there have been few reports on the synthesis and antimicrobial

studies of benzophenone derivatives cited in the literature. In the present study, *in vitro* antimicrobial activity of compounds **5a, 5c, 5d, 5f** and **5g** have shown good antibacterial and antifungal activities against all the bacteria and fungi tested.

Acknowledgements
Lakshmi Ranganatha V. acknowledges the financial support provided by the Department of Science and Technology, New Delhi, under INSPIRE-Fellowship scheme [IF110555]. Shaukath Ara Khanum gratefully acknowledges financial support provided by the UGC, New Delhi, under the Major Research Project Scheme. And all authors thankful to the principal, Yuvaraja's College, University of Mysore, Mysore for their support and encouragement throughout the execution of this work.

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