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Synthesis and characterization of certain novel azetidinone derivatives as antibacterial and antifungal agents

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ABSTRACT

The development of resistance to current antibacterial therapy continues to drive the search for more effective agents. The chemistry, synt hesis and biology of the 2-azetidinone pharmacophore continues to be fuelled by their wide range of biological properties such as antibacterial [1], anticonvulsant [2], antihyperglycemic, antitumour, anti-HIV, anti-inflammatory and enzyme inhibitory activities. The 2-azetidinone ring is common structural feature of a member of broad spectrum β-lactum antibiotic including Penicillin's, cephalosporin and other monobactum which are widely used as chemotherapeutic agents to treat bacterial infection and microbial diseases. In light of these interesting biological activities, it was our interest to synthesize some novel 2-azetidinone derivatives. 3-bromo-4-methoxybenzoyl hydrazine (1) [3] was prepared from methyl ester of 4-methoxybenzoic acid by bromination and subsequent hydrazinolysis. The acid hydrazide (1) was condensed with different aromatic aldehydes in ethanol as solvent to yield substituted benzal-3-(3'-bromo-4'-methoxybenzoyl) hydrazines 2(a-h). The benzal hydrazines 2(a-h) on cyclization with phenoxyacetyl chloride in presence of triethylamine as catalyst afforded 3-phenoxy-4-(substituted phenyl)-1-(3'-bromo-4'-methoxy benzamide)azetidin-2-ones 3(a-h). The structure of the newly synthesized compounds 2(a-h) and 3(a-h) has been confirmed by IR, ^{1}H NMR. All the compounds have been screened in vitro for their antibacterial and antifungal activity. Among the compounds tested, 3b, 3c and 3h showed good antibacterial activity as compared with standard ciprofloxacin and rest of the compounds showed moderate activity.

Keywords: Azetidinone, aromatic aldehydes, antibacterial, antifungal.

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INTRODUCTION

The treatment of infectious diseases still remains an important and challenging problem because of a combination of factors including emerging infectious diseases and the increasing number of multi-drug resistant microbial pathogens. The therapeutic problem has achieved increasing importance in hospitalised patients, in immuno suppressed patients with AIDS or undergoing anticancer therapy and organ transplants. In spite of a large number of antibiotics and chemotherapeutics available for medical use, the emergence of old and new antibiotic resistance developed in the last decades, has created a substantial medical need for new classes of antibacterial agents. A potential approach to overcome the resistance problem is to design innovative agents with a different mode of action so that no cross resistance with the present therapeuticals can occur [4, 5].

Infectious diseases are one of the leading causes of death worldwide. During the past few decades, new infectious diseases have appeared and old ones previously thought to be controlled have reemerged [6] and thus, despite of many significant developments in the antimicrobial therapy, many problems remain to be solved for most of the antimicrobial drugs available [7]. Hence, discovery of novel antimicrobial agents with better pharmacological profile is still highly desirable.

In recent decades, the problems of multi-drug resistant microorganism have reached on alarming stage in many countries around the world. A number of recent clinical reports describe the increasing occurrence of meticillin-resistant *Staphylococcus aureus* and other antibiotic-resistant human pathogenic microorganisms in United State and European countries. Infections caused by these microorganisms pose a serious challenge to the medical community and need for an effective therapy has led to an escalating search for novel antimicrobial agents. [8]

Small ring heterocycles containing nitrogen, sulfur and oxygen have been under investigation for a long time because of their important medicinal properties [9]. Also, 2-azetidinone have been reported to possess a variety of significant and diverse pharmacological activities such as antibacterial, anticonvulsant, antihyperglycemic, antitumour, anti-HIV, anti-inflammatory and enzyme inhibitory activities. In light of these findings, it was felt worthwhile to synthesize some new 2-azetidinone derivatives and evaluate them for their antimicrobial potential.

On the other hand conventional methods of organic reactions have emerged as a new 'lead' in organic synthesis with important advantages like highly acclerated rate of reaction alongwith improvement in yield and quality of products [10]. Thus keeping in view the advantages of these techniques, and immense biological importance of azetidinones, it was felt worthwhile to study the reaction under conventional methods and to screen the target compounds for antimicrobial activity.

EXPERIMENTAL

All the melting points were taken in open capillaries and are uncorrected. IR spectra (KBr in cm^{-1}) were recorded on Shimadzu 8201 PC FTIR Spectrophotometer. ^{1}H NMR spectra were recorded on a varian 300 MHz NMR spectrophotometer using DMSO-d6 as solvent and TMS as internal standerd (chemical shifts in δppm). The purity of the compounds was monitored by thin layer chromatography.

Substituted benzal-(3-bromo-4'-methoxybenzoyl) hydrazine's 2(a-h).

3-Bromo-4-methoxybenzoyl hydrazine 1 (2.45g, 0.01 mol) was dissolved in 30 ml of ethanol containing few drops of glacial acetic acid. The appropriate aromatic aldehydes (0.01 mol) were added and the reaction mixture was refluxed for 3 hr, cooled and then poured into crushed ice. The solid obtained was filtered, washed with water and crystallized from ethanol. 2d: IR (KBr) 3440 (N-H str), 3080 (C-H, aromatic), 2840 (C-H str), 1650 (C=O str), 1600 (C=N str), 1560,1500,1370 (C=C, aromatic), 1280 (C-O str), 1090-810 (C-C str), 1050 (C-N str), 680

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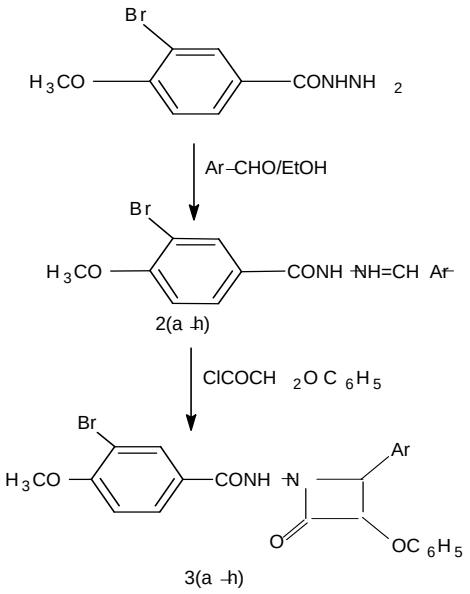
(C-Cl str), 520 (C-Br str); 2f: IR (KBr) : 3440 (N-H str), 3100 (C-H, aromatic), 2840 (C-H str), 1650 (C=O str), 1610 (C=N str), 1560,1520,1500 (C=C, aromatic),1280 (C-O str), 1180-820 (C-C str), 1050 (C-N str), 540 (C-Br str); NMR (DMSO-d_6); δ 1.8 (d, 1H, -N-CH-C), 2.5 (d, 1H, -C-CH-Cl), 3.8 (s, 3H, -OCH_3 of phenyl ring), 3.9 (s, 3H, -OCH_3 of benzamido ring), 7.0-8.4 (m, 7H, ArH), 8.2 (s, 1H, -C-NH-N).

The characterization data of compounds 2(a-h) & 3(a-h) are given in Table-1.

Table1. Physical and analytical data of the synthesized compounds

Compound	Ar	M.P. (^oC)	Yield (%)
2a	Phenyl	140	91
2b	4-Hydroxyphenyl	115	95
2c	4-Hydroxy-3-methoxyphenyl	155	90
2d	4-Chlorophenyl	140	90
2e	2-Hydroxyphenyl	160	97
2f	4-Methoxyphenyl	110	95
2g	2-Thienyl	186	96
2h	2-Furyl	190	95
3a	Phenyl	128	73
3b	4-Hydroxyphenyl	105	60
3c	4-Hydroxy-3-methoxyphenyl	90	55
3d	4-Chlorophenyl	130	71
3e	2-Hydroxyphenyl	158	86
3f	4-Methoxyphenyl	106	95
3g	2-Thienyl	172	75
3h	2-Furyl	184	80

Scheme: 1



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3-phenoxy-4-(substituted phenyl)-1-(3'-bromo-4'-methoxy benzamide) azetidin-2-ones 3(a-h).

The benzal hydrazine 2 (0.01 mol) was dissolved in N, N-dimethylformamide (40 ml) and triethylamine (2.80 ml, 0.02 mol) was added to it. Phenoxyacetyl chloride (1.60 ml, 0.02 mol) was added dropwise over a period of 30 min. The reaction mixture was refluxed for 5 hr and filtered to separate rhe salt formed. The filtrate was concentrated to half its initial volume and then poured onto crushed ice. The product 3 obtained was filtered, washed with water and recrystallized from ethanol. Other azetidine-2-ones were obtained in a similar manner : 3f: IR (KBr) 3450 (N-H str), 3079 (C-H, aromatic), 2840 (C-H str), 1651 (C=O str), 1563,1515,1495 (C=C, aromatic), 1270 (C-O str), 1181-819 (C-C str), 1050 (C-N str), 683 (C-Cl str), 535 (C-Br str) ; NMR (DMSO-d_6); δ 1.8 (d, 1H, -N-CH-C), 2.5 (d, 1H, -C-CH-Cl), 3.8 (s, 3H, -OCH_3 of phenyl ring), 3.9 (s, 3H, -OCH_3 of benzamido ring), 7.0-8.4 (m, 7H, ArH), 8.2 (s, 1H, -C-NH-N).
The characterization and data of compounds (3a-h) are given in Table-1.

Table 2. Antimicrobial activity-sensitivity testing of compounds 2(a-h) and 3(a-h)

Compound No.	Zone of inhition in mm					
	Antibacterial activity				Antifungal activity	
	S.aureus	*B.subtilis*	*E.Coli*	*P.aeruginosa*	*C.albicans*	*A.niger*
2a	10	11	08	08	12	14
2b	13	15	09	09	13	16
2c	10	12	08	09	09	12
2d	12	13	09	09	16	12
2e	11	10	09	09	07	12
2f	10	09	08	08	17	12
2g	10	09	11	08	09	11
2h	10	11	09	08	10	11
3a	09	11	09	09	19	12
3b	24	22	20	19	17	12
3c	22	20	23	24	16	09
3d	11	10	08	08	15	08
3e	10	10	09	09	14	07
3f	09	10	09	09	16	09
3g	10	09	08	10	11	10
3h	24	22	21	20	09	08
Ciprofloxacin	26	26	28	25	-	-
Fluconazole	-	-	-	-	26	25

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Biological activity

The all compounds 2(a-h) and 3(a-h) were screened in vitro for their antibacterial activity against *Staphylococcus aureus*, *Escherichia coli*, *bacillus subtilis* and *Pseudomonash aeruginosa* by the ditch-plate technique and for antifungal activity against *Aspergilus niger* and *Candida albicans* by paper disc diffusion method using concentration of 500 mg/ml. Ciprofloxin (10 µg/disc) was used as a standard drug for antibacterial screening and fluconazole (10 µg/disc) was used as a standard for antifungal screening. Each experiment was done in triplicate and the average reading was taken. Nutrient agar was employed as culture media and DMF was used as solvent for both antibacterial and antifungal activity. Among the compounds tested, 3b, 3c and 3h showed good antibacterial activity as compared with standard ciprofloxacin and rest of the compounds showed moderate activity. The results are tabulated in Table 2.

RESULTS

Substituted benzal-3-(3'-bromo-4'-methoxybenzoyl) hydrazines 2(a-h) were prepared by following the standard protocol. These substituted benzal-3-(3'-bromo-4'-methoxybenzoyl) hydrazines 2(a-h) were reacted to yeild 3-phenoxy-4-(substituted phenyl)-1-(3'-bromo-4'-methoxy benzamide)azetidin-2-ones 3(a-h) by reacting with phenoxyacetyl chloride in presence of triethylamine as catalyst. The synthetic procedure for preparation of title compounds is given in Scheme 1. The assigned structure and molecular formula of the newly synthesized compounds 2(a-h) and 3(a-h) were confirmed and supported by ^{1}H-NMR, IR data which was in full agreement with proposed structures. The compounds were screened *in vitro* for their antibacterial and antifungal potential by disc diffusion assay against selected pathogenic bacteria and human pathogenic fungi. The results of antibacterial and antifungal activities expressed in terms of zone of inhibition are reported in Table 2.

DISCUSSION AND CONCLUSION

Some novel benzal hydrazines and 2-azetidinone derivatives 2(a-h) and 3(a-h) have been synthesized and evaluated for antimicrobial activities. The results of antimicrobial studies of newly synthesized compounds reveal that compounds possess antibacterial activities to certain extent and significant antifungal activities. Among the compounds tested, 3b, 3c and 3h showed good antibacterial activity as compared with standard ciprofloxacin and rest of the compounds showed moderate activity. Even though, the synthesized compounds did not exhibit appreciable antibacterial activity, the data reported in this article may be helpful guide for the medicinal chemists who are working in this area.

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