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Short Communication

Antibacterial screening of novel Mannich bases of 5H-dibenzo [b,f]azepine-5-corboxamide

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Abstract

Current work involves antibacterial screening of Mannich bases of 5H-dibenzo[b,f]azepine-5-carboxamide. A series of Mannich bases of 5H-dibenzo[b,f]azepine-5-carboxamide (4a-4j) were synthesized via Mannich reaction of 5H-dibenzo[b,f]azepine-5-carboxamide with primary/secondary amines and formaldehyde. After characterization of Mannich bases by spectroscopic techniques i.e. UV, IR, ^{1}H NMR and ^{13}C NMR, compounds of series (4a-4j) were screened against pathogen K. pneumoniae. Sulfonamides that used as primary amine during synthesis of mannich bases were also screened against pathogen K. pneumonia and results obtained were compared with synthesized mannich bases. Antibacterial activities of synthesized Mannich bases and sulfonamides have been determined in term of 'zone of inhibition'. Result obtained shows some of newly synthesized Mannich bases have potent antibacterial activity against pathogen K. pneumoniae.

Keywords: 5h-dibenzo[b,f]azepine-5-carboxamide, Mannich bases, Antibacterial Activity, *K. pneumoniae*.

Introduction

Chemistry of Mannich bases were 105 year old, where accidently Germen chemist Carl Mannich did amino-alkylation[1]. In this era a number of pharmaceutical chemists derived a variety of Mannich bases those possess remarkable pharmaceutical activity. These Mannich bases work as antibacterial[2], antifungal[3], anticonvulsant[4], anticancer[5] and anti-inflammatory[6] agents Researchers has been shown their interest in synthesis of Mannich bases due to versatile applications of Mannich bases. This aminoalkylation reaction is important for the synthesis and modification of biologically important compounds. 5H-dibenzo[b,f] azepine-5-carboxamide is usually used as anticonvulsant agent[7], to treat post-traumatic stress disorder. Sulfonamides are amine and widly used as antimicrobial agents[8]. Joshi et al[9-10] synthesized a number of Mannich bases in past era and their synthesized Mannich bases shows potent antibacterial activities. Recently we synthesized a seriers of novel Mannich bases derived from 5H-dibenzo[b,f] azepine-5-corboxamide, characterized the novel compounds by physic-chemical and spectral techniques i.e. UV, IR, 1HNMR and 13C NMR spectroscopy. Antibacterial screening of these compounds against pathogenic bacteria *Bacillus subtilis, salemonella typhi, E.coli. and S. aureus* shows some of synthesized compounds are more potent antibacterial agents in compare to their parent sulfonamides[11,12]. *K. pneumoniae* frequently causes urinary tract infections like abscesses, meningitis and septicaemia. In present work we screened the series of Mannich bases derived from 5H-dibenzo[b,f] azepine-5-corboxamide against pathogenic bacteria *K. phenumoniae*.

Materials and methods

The in-vitro screening of series of Mannich bases were carried out on gram negative microorganism i.e. *Klebsiella pneumonia*. Methodology described by Ingraham et al[13] is used as reference for the antimicrobial screening. The quantity needed to produce the specific effect on microorganism is determined to measure activity of the synthesized compounds.

Determination of zone of inhibition (Paper Disk Method): In paper disk method the discs containing various concentrations of test compounds are placed on the surface of a solid nutrient inoculated with the culture of suitable microorganism and the zone of microbial growth inhibition is depends upon the potency of drug to inhibit the growth of microb. The measurement of inhibition produced by the known concentration of drug is compared with known concentration of reference.

Prepration of media: Mullar Hinton Agar, Hi media is used to subcultured the culture of gram negative microorganism *K. pneumoniae*. This media was suspended in doubly distilled water and boiled to dissolve the media completely. It was sterized by autoclaving at 15lbs pressure (121.6°C) for 30 minutes. The pH of media was maintained specifically. The media were transformed asceptically to petri dishesh and to cool.

Prepration of solution: The screening was carried out at varying concentrations. The Mannich bases and the standard compounds (carbamazepine, sulphonamides and secondary amines) were dissolved in solvent (methanol) and the dilutions

were prepared corresponding to 80 µg/ml, 160 µg/ml and 320µg/ml. 0.45 µm Millipore filters are used to filter the solutions.

Inoculums preparation: The decontaminated laminar flow bench is used for innocums preparation, separate pre sterilized applicators were used to transferred inoculums into freshly prepared and sterilized nutrient broth. This nutrient broth is incubated at 37±20 C for 24 hrs.

Screening by paper disk method: Aseptic conditions i.e. sterilized room, decontaminated laminar flow bench, are used to carried out the complete antimicrobial procedure. The 20 ml of sterilized Mullar Hinton Agar was transformed asceptically to each of previously sterilized petri dish and allowed to set uniformaly. 2ml of 24 hours broth culture of respective organism was added to each of the petri dish and was allowed to settle. One each sterile 6 mm paper disc (Hi-media) was socked in solution of sample to be tested and placed on agar plates made out of Mullar Hinton Agar as media for cultivation of bacteria.

A disc soaked in solvent was also placed simultaneously to check if the solvent used shows any inhibition (in most cases it doesn't shows any inhibition). The disk agar plates are kept for incubation for 24 hours at 37+1°C and then the inhibitory effect of the samples and their corresponding sulphonamides were measured against the pathogenic bacteria *K. pneumoniae*. The experiments were run in triplicate and the mean of readings were recorded. Antimicrobial screening is recorded in term of zone of inhibition for synthesized compounds and standard drugs. The zone of inhibition for seies of synthesised compounds is tabulated in Table-1.

Synthesis and characterization of novel Mannich bases: A series of Mannich bases derived from 5H-dibenzo[b,f]azepine-5-carboxamide were synthesized and characterized by spectral techniques as described by Joshi et al[12]. The structure and molecular formulae of synthesized compounds are tabulated in Table-2.

Results and discussion

Paper disc method described in pharmacopeia has been used to analyze the antibacterial activity of series of newly synthesized compounds against pathogen *K. pneumoniae* and the results were statistically analyzed. The results obtained were compared with standard (parent sulfonamides) and showed significant activity against *K. pneumoniae*. The antibacterial activities of the synthesized Mannich bases have been determined in terms of 'zone of inhibition'. Antibacterial screening of series 4a-4j shows all synthesized compounds are potent against pathogenic bacteria *K. pneumoniae*. Compound 4d, 4f, 4g, 4j are more potent in compare to other synthesized compounds of the group. Compound 4g, 4h and 4j are more potent in compare to their parent sulphonamides.

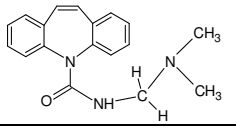
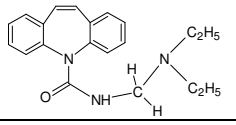
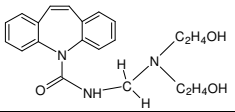
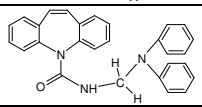
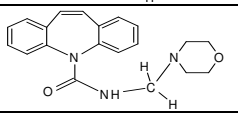
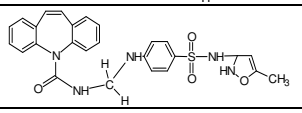
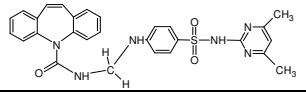
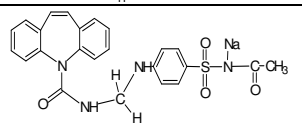
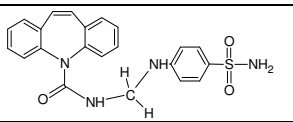
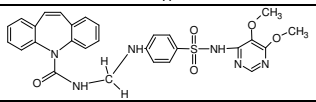
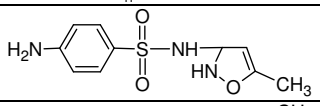
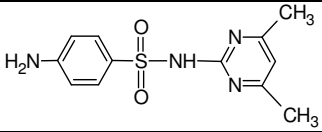
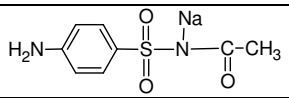
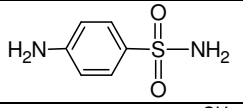
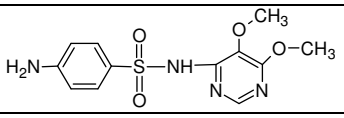
Table-1: Antimicrobial activity of novel synthesized compounds and their parents sulphonamides against *K. pneumoniae.*

Compound No.	Antimicrobial activity against pathogenic microorganism *K. pneumoniae*			
	Concentration in µg/ml			
	80.0	160.0	320.0	Avg.
4a	6.2	8.4	7.6	7.4
4b	-	2.2	2.8	1.7
4c	12.2	13.2	15.2	13.5
4d	14.9	18.7	21.2	18.3
4e	10.2	12.7	14.3	12.4
4f	22.1	25.3	26.7	24.7
4g	14.9	17.2	19.6	17.2
4h	11.2	12.9	13.2	12.4
4i	5.5	6.9	8.6	7.0
4j	12.3	16.9	20.3	16.5
3f	23.5	25.3	28.4	25.7
3g	14.2	15.3	15.9	15.1
3h	13.5	16.8	20.9	17.1
3i	-	-	-	0.0
3j	11.2	14.9	18.1	14.7

Conclusion

Work represent shows novel series (4a-4j) of Mannich bases of 5H-dibenzo[b,f]azepine-5-corboxamide have noticeable and prolonged activity against *K. pneumoniae* and few of them are more potent in compare to their parent sulphonamides. The work could be more investigated to determine the possibility of more potent drug with less side effects.

Table-2: Compound name, compound nuber, molecular formula and structure of compounds (4a-4j and 3f-3j).

Compound No.	Compound Name	Molecular Formula	Structure
4a	5H-dibenzo[b,f]azepine-5-carboxamide methyl dimethyl amine	$C_{18}H_{19}N_3O$	
4b	5H-dibenzo[b,f]azepine-5-carboxamide methyl diethyl amine	$C_{20}H_{23}N_3O$	
4c	5H-dibenzo[b,f]azepine-5-carboxamide methyl diethanol amine	$C_{20}H_{23}N_3O_3$	
4d	5H-dibenzo[b,f]azepine-5-carboxamide methyl diphenyl amine	$C_{28}H_{23}N_3O$	
4e	5H-dibenzo[b,f]azepine-5-carboxamide methyl morpholine	$C_{20}H_{21}N_3O_2$	
4f	5H-dibenzo[b,f]azepine-5-carboxamide methyl sulphamethoxazole	$C_{26}H_{25}N_5O_4S$	
4g	5H-dibenzo[b,f]azepine-5-carboxamide methyl sulfadimidine	$C_{28}H_{26}N_6O_3S$	
4h	5H-dibenzo[b,f]azepine-5-carboxamide methyl sulphaacetamide sodium	$C_{24}H_{21}N_4NaO_4S$	
4i	5H-dibenzo[b,f]azepine-5-carboxamide methyl sulphanilamide	$C_{22}H_{20}N_4O_3S$	
4j	5H-dibenzo[b,f]azepine-5-carboxamide methyl sulfadoxine	$C_{28}H_{26}N_6O_5S$	
3f	Sulphamethoxazole	$C_{10}H_{11}N_3O_3S$	
3g	Sulfadimidine	$C_{12}H_{14}N_4O_2S$	
3h	Sulphaacetamide sodium	$C_8H_9N_2NaO_3S$	
3i	Sulphanilamide	$C_6H_8N_2O_2S$	
3j	Sulfadoxine	$C_{12}H_{14}N_4O_4S$	

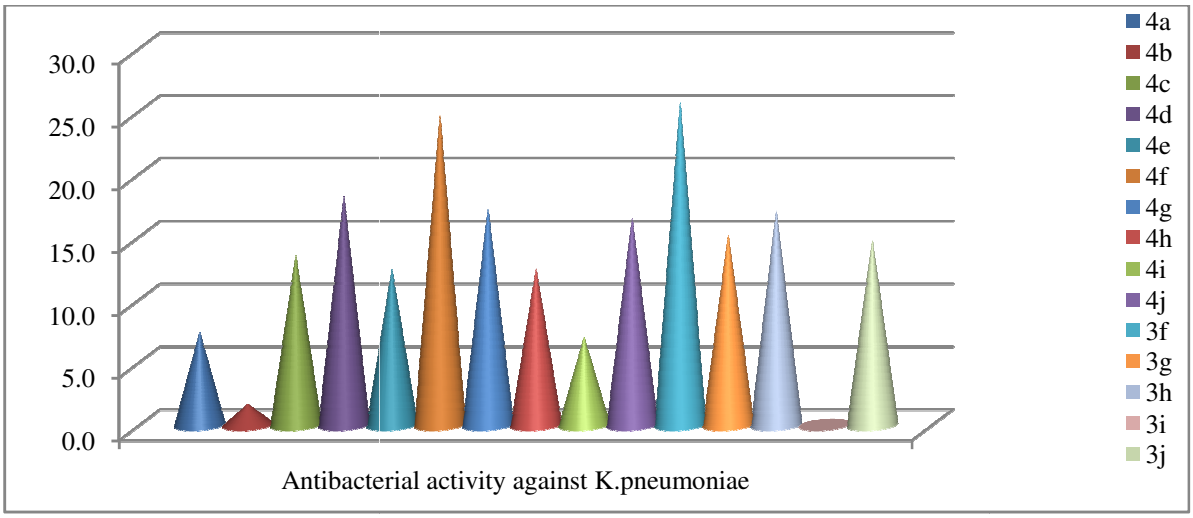


Figure-1: Antibacterial activity of compound (4a-4j) and sulfonamides (3f-3j) against *K. pneumoniae.*

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