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SYNTHESIS OF NEWER MANNICH BASES OF QUINOLINE DERIVATIVE FOR ANTIMICROBIAL ACTIVITY

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ABSTRACT

Antimicrobial agents are widely used in the management of infectious disease but most of them have developed resistance to micro-organism. The cinchophen, which is water insoluble compound, has reported antimicrobial activity. To overcome this problem and to lower the side effects, many approaches can be utilized and Mannich base approach is one of them. In the present study, cinchophen having carboxylic acid (-COOH), group was converted to amide ($-CONH_2$) and it is utilized to synthesize Mannich bases. At first cinchophen **I,** was synthesized by Doebnear synthesis, then it was converted to cinchophen chloride **II,** using oxalyl chloride. Cinchophen chloride was converted to cinchophen amide **III,** using ammonia. The Mannich bases **IVa-e** have been synthesized by reaction of cinchophen amide with formaldehyde and secondary amine. The prepared Mannich bases were subjected to physicochemical studies like melting point determination, TLC and % yield. The structures of Mannich bases were characterized by UV, IR, Mass and NMR spectroscopy. Antibacterial screening of newly synthesized compounds **IVa-e** was carried out against *E. coli, P. aureoginosa, S. aureus* and antifungal activity against *C. albicans* and *A. niger* according to cup-plate method.

Key words : Mannich base, Cinchophen, Antimicrobial

INTRODUCTION

The prevalence of heterocyclic ring among drugs and biological agents of mammalian origin can lead to the erroneous assumption that the presence of such rings in drugs means that this moiety necessarily constitutes a part of pharmacophore. Replacement of the particular ring system in such cases leads to loss of desirable biological activity. Recognition of pharmacophoric functions is still largely an empirical art[1].

The diversity of biological effects is possessed by benzofused six membered

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heterocyclic rings. These range from antimicrobial property, CNS and inflammation influencing agents. It can be inferred that ring system itself is primarily a molecular scaffold, upon which the characteristic pharmacophore for the various receptor is involved. It is also interesting to note that range of bioactivities involved is different substantially from those seen with the benzofused five membered heterocycles[17].

Quinoline is used as a lead compound in which benzene ring is fused with pyridine ring on the 2-3 position. The heterocyclic ring of quinoline is a significant pharmacophore. Replacement of this ring leads to loss of pharmacological activity.

Cinchophen is a derivative of cinchoninic acid in which there is a phenyl ring at second position. The condensation of a compound having one or more active hydrogen atoms with formaldehyde and ammonia or a primary or secondary amine resulting in the formation of β-amino-carbonyl compound is known as Mannich reaction. The essential feature of the reaction is the replacement of the active hydrogen atom by an amino methyl or substituted amino-methyl group. The product obtained is called a 'Mannich base'[15]. The present investigation compares the antimicrobial activity of the cinchophen and its Mannich bases and characterizes the prepared compounds for their purity. The cinchophen is insoluble in water and posses antimicrobial activity. In Mannich base approach, the conjugation is made with secondary amines, which is an impetus approach to make the compound water soluble and also to increase the antimicrobial activity of parent compound.

EXPERIMENTAL

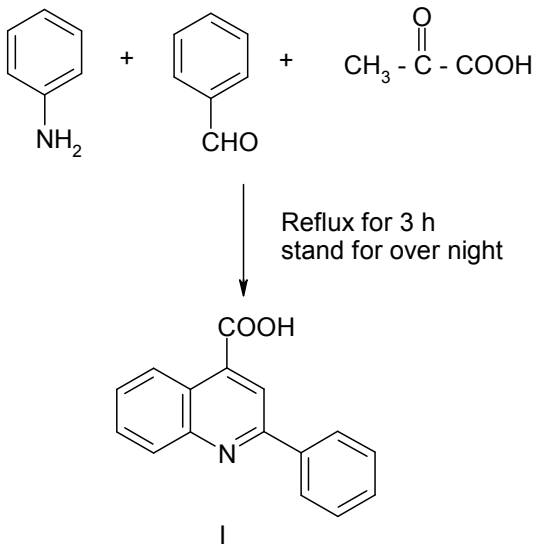
Pyruvic acid and oxalyl chloride were purchased from MERCK Chemicals. All the chemicals used were of A. R. grade. The Mueller-Hinton Agar medium and Saubrod's dextrose agar were purchased from Hi-media India.

Mass spectra were recorded with a MICROMASS QUATTO II triple quadrapole mass spectrometer. The proton nuclear magnetic spectra (^{1}H NMR) were recorded on Bruker DRX-300, (300MHz FT MNR) using methanol. UV spectra were taken on U. V. 2401 (PC) S 220V double beam U. V. spectrophotometer, Tokyo, Japan. Infrared spectra were recorded on FTIR spectrophotometer 8400 S, Shimadzu Corporation, Tokyo, Japan.

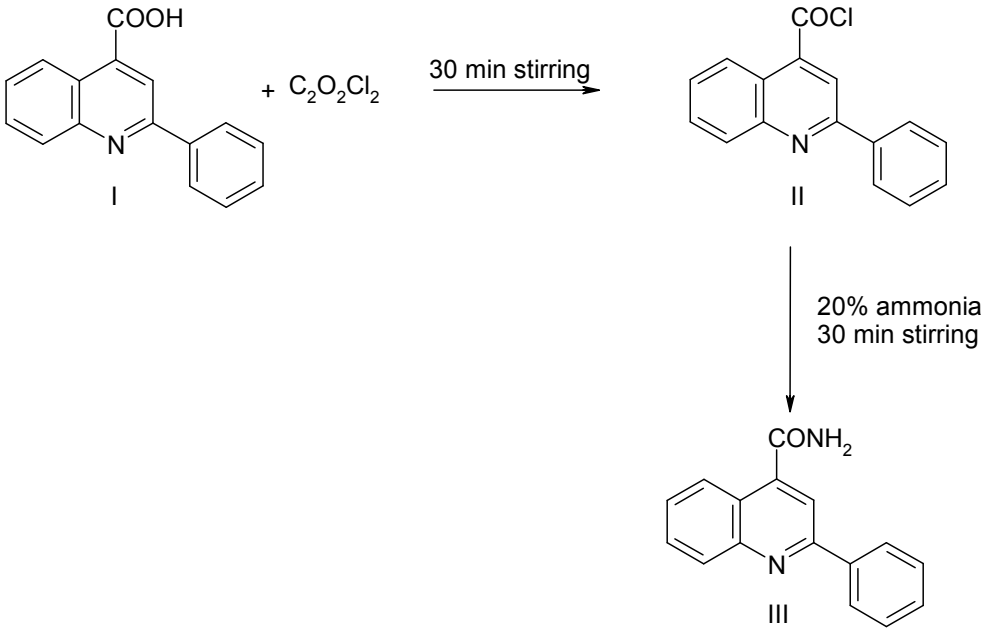
Method for synthesis of 2-phenylquinoline-4-carboxylic acid (I)

Pyruvic acid (22 mL, 0.25 mol) in 200 mL of ethanol and benzaldehyde (24 mL, 0.236 mol) were mixed and heated upto the boiling point. A solution of pure aniline (23

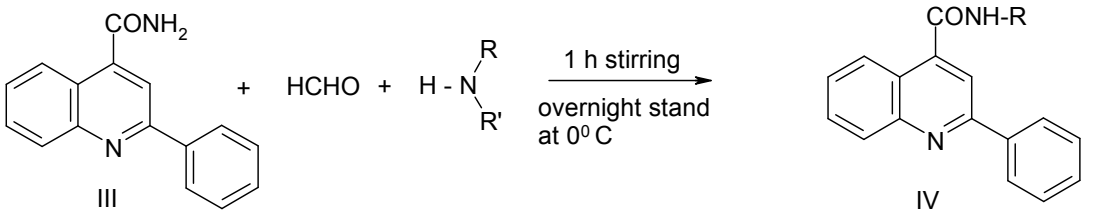
mL, 0.248 mol) in 100 mL of ethanol was added. The addition was done for 1 h. The mixture was refluxed for about 3 h and allowed to stand overnight.



Scheme I

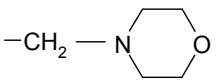
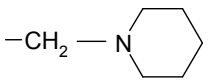
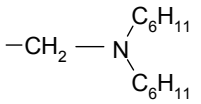
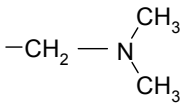
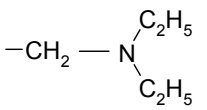


Scheme II



Scheme III

Table 1: Various substitutions used

Compound	R
IVa	
IVb	
IVc	
IVd	
IVe	

Method for synthesis of cinchophen acid chloride (II)

2-Phenylquinoline-4-carboxylic acid, (2.49 g, 0.01 mole) was taken and dichloromethane (6.5 mL) was added to it, to form a suspension. To this suspension, oxalylchloride (0.01 mole) in 10 mL dichloromethane was added to form a clear solution. The solution was concentrated to give yellow solid of acid chloride of cinchophen, which was used for further reaction without purification.

Yield = 95 % M. P. = 146 ºC to 148 ºC R_f value = 0.79

Method for synthesis of cinchophen amide (III)

The acid chloride obtained was treated with solution of ammonia (20 % v/v) and stirred for 30 min. The addition of ammonia was made, part by part.

General procedure for Mannich bases derived from secondary amines and cinchophen amide (IVa-e)

Appropriate secondary amine (0.01 mole) was gradually added to a solution of cinchophen amide, (2.48 g, 0.01 mole) in dried methanol (12 mL), followed by addition of formaldehyde solution (38 %, 0.8 mL, 0.015 mol). The reaction mixture was stirred for 1 h at room temperature and allowed to stand overnight at 0 ºC. Then precipitate was filtered, dried and recrystallised using hot ethanol. The title compounds **IVa-e** were prepared as per the procedure described by Rajesh and Bahekar[3].

Table 2: Physiochemical data of synthesized Mannich bases

Comp.		Spectral data	M. P. (ºC)	% Yield	R_f Value
I	λ max	262 nm	211-216	50	0.83
	IR (KBr, cm^{-1})	1704 (C = O, COOH), 3034 (Ar C-H str), 3360 (O-H str, COOH), 1203, 760, 731, 699			
	MS (m/z)	251, 250, 233, 205, 173, 127, 114, 100, 87, 75, 60.			
	^{1}H NMR (δ ppm)	7.528-7.502 (m, Ar-H), 7.537 (s, 1H, Ar-H) 7.549 (s, 1H, Ar-H), 7.700 -8.094 (s, Ar-H), 8.177 (s, Ar-H), 9.646 (s, 1H, COOH).			
III	λ_{max}	174.6 nm	190–195	90	0.75
	IR (KBr, cm^{-1})	1651 (C=O, Ar-$CONH_2$), 3035 (Ar-CH str.), 3383 (NH str.), 1446, 236, 798, 768, 742, 699, 650			

Cont…

Comp.		Spectral data	M. P. (°C)	% Yield	R_f Value
	MS (m/z)	250, 249, 233, 205, 172, 127, 114, 100, 87, 75, 60.			
	^{1}H NMR (δ ppm)	3.321-3.335 (s, 1H, Ar-NH_2), 7.491-7.805 (m, Ar-H), 7.810- 7.856 (m, Ar-H), 8.100-8.296 (m, Ar-H), 8.536-8.564 (d, 1H, Ar- H).			
IVa	λ_{max}	259 nm			
	IR (KBr, cm^{-1})	1662 (C=O, Ar-CONHR), 3029.96 (Ar-CH str), 3120.61 (N-H str.), 1447, 1103, 1494 (N-H def.), 1234, 769, 698			
	MS (m/z)	349, 348, 305, 291, 249, 233, 206, 172, 127, 114, 100, 87, 75, 60.	145–150	68	0.7
	^{1}H NMR (δ ppm)	3.217-3.333 (m, -N-CH_2), 3.634 (s, 1H, -CH_2), 3.808 (s, 1H, Ar-NH), 3.823-3.935 (m, -O-CH_2), 7.511-7.811 (m, Ar-H), 7.817-7.844 (m, Ar-H), 8.091-8.288 (m, Ar-H), 8.541-8.568 (d, 1H, Ar-H).			
IVb	λ_{max}	264 nm	130–135	53	0.82
	IR (KBr, cm^{-1})	1659.81 (C=O, Ar-CONHR), 3025 (Ar-C-H str.), 3129.60 (NH str.), 1439.51, 1489.73 (N-H def.), 1235.36, 766.62, 696.18			
	MS (m/z)	346, 320, 292, 248, 233, 205, 172, 141, 127, 114, 100, 98, 87, 75, 60.			

Comp.		Spectral data	M. P. (°C)	% Yield	R_f Value
	^{1}H NMR (δ ppm)	1.671–1.829 (m, -CH_2), 3.113-3.150 (m, -CH_2), 3.623 (s, 1H, -CH_2), 3.925 (s, 1H, Ar-NH), 7.509-, 635 (m, Ar-H). (NH str.), 1439.51, 1489.73 (N-H def.), 1235.36, 766.62, 696.18			
IVc	λ_{max}	265 nm	120–125	62	0.61
	IR (KBr, cm–1)	1652 (C=O, Ar-CONHR), 3031.89 (Ar-CHstr.), 3123.76 (N-H str.), 1441.48, 1491 (N-H def.), 1232.74, 769.40, 699,			
	MS (m/z)	442, 414, 359, 331, 247, 233, 205, 194, 182, 172, 127, 114, 100, 87, 83, 75, 60.			
	^{1}H NMR (δ ppm)	1.196–1.305 (m, -CH_2), 3.619 (s, 1H, -CH_2), 3.943 (s, 1H, Ar-NH), 7.525-8.734 (m, Ar-H).			
IVd	λ_{max}	258 nm	147–150	72	0.92
	IR (KBr, cm^{-1})	1660 (C=O, Ar-CONHR), 3030 (Ar-CH str.), 3127 (NH str.), 1444, 1463 (NH def.), 1234, 768, 698			
	MS (m/z)	306, 248, 233, 205, 172, 127, 114, 100, 87, 75, 60, 58.			
	^{1}H NMR (δ ppm)	3.036 - 3.084 (m, -CH_3), 3.620 (s, 1H, -CH_2), 3.93 (s, 1H, Ar-NH), 7.517-8.594 (m, Ar-H).			

Comp.		Spectral data	M. P. (ºC)	% Yield	R_f Value
IVe	λ_{max}	257 nm	152–155	70	0.86
	IR (KBr, cm^{-1})	1647 (C=O, Ar-CONHR), 3028 (Ar-CH str.), 3178 (NH str.), 1433, 1458 (NH def.), 1237, 760, 684			
	MS (m/z)	334, 248, 233, 205, 172, 127, 114, 100, 87, 86, 75, 60.			
	^{1}H NMR (δ ppm)	1.289–1.338 (m, $-CH_3$), 3.011-3.060 (m, $-CH_2$), 3.620 (s, 1H, $-CH_2$), 3.94 (s, 1H, Ar-NH), 7.517-8.594 (m, Ar-H).			

Antibacterial and antifungal screening

For antibacterial activity norfloxacin was used as standard and fluconazole for antifungal activity. The cup-plate method was performed using Mueller-Hinton agar (Hi-Media) medium for antibacterial activity and Saburoud's dextrose agar (Hi-Media) medium for antifungal activity. The medium was sterilized by autoclaving at 15 lb pressure for 30 min. One loop-ful of the stock culture was inoculated at 10 mL of agar slant previously in sterilized test tubes and incubated at 37 ºC for 24 h and 48 h to 7 days for bacteria and fungi, respectively. About 3 mL of sterile water for injection was added to the test tube and a suspension of the culture was obtained by shaking for few min.

Stock solution

The test compounds (250 mg) were dissolved in DMSO (10 mL) and volume was made up to 100 mL with distilled water and further dilutions were made to produce a concentration of 250 µg/mL, on which concentration, cinchophen shows near about equal zone of inhibition to that of standard. Similarly, the dilutions were prepared for standard drug i. e., norfloxacin and fluconazole in a concentration of 100 µg/mL as reported.

Control parameters

Media control: Sterilized medium was kept for growth (approx 48 hr) so as to assure the sterility of the medium. If this control showed growth of any type, then the

media was discarded.

Culture control: The culture of the organism was inoculated in sterilized medium. If no growth was observed, then the culture was considered to be faulty.

Procedure

Sterile medium was melted on water bath and kept at 45 ºC in constant temperature water bath. In each sterile petri-dish, molten medium was added so that thickness was approximately 4-5 mm and subcultured organism under study was inoculated. The inoculated dishes were allowed to set for 30 min at room temperature. Cups of 6 mm diameter were then made with the help of sterile stainless steel borer and 100 µL of prepared test compounds was added to each cup. Petri-dishes were kept in refrigerator for 30 min so as to allow diffusion of the solutions in the medium and then incubated for approximately 24 hr at 37 ºC for antibacterial activity and 72 hr for antifungal activity. Zone of inhibition produced by test compounds were measured in mm in various axis and average reading was considered and the activity index was calculated against the standard. The results are shown in Table 3.

Table 3 : Antimicrobial activity index

Comp.	Concentration (µg/mL)	Zone of inhibition in mm diameter against bacteria and fungi				
		S. aureus	***P. aeruginosa***	***E. coli***	***C. albicans***	***A. niger***
I	250	16.0	17.5	17.1	16.2	16.0
III	250	18.4	19.0	18.0	17.4	16.5
IVa	250	22.0	24.0	20.0	19.5	19.0
IVb	250	20.0	21.2	18.4	20.2	21.4
IVc	250	16.0	17.0	16.5	18.4	15.4
IVd	250	16.5	16.4	16.0	-	-
IVe	250	16.2	17.2	17.0	-	-
Std. 1	100	16.2	17.4	16.8	-	-
Std. 2	100	-	-	-	15.7	16.3

S. aureus = *Staphylococcus aureus*

E. Coli	=	*Escherichia coli*
P. aeruginosa	=	*Pseudomonas aeruginosa*
C. albicans	=	*Candida albicans*
A. Niger	=	*Aspergillus niger*
I	=	Cinchophen
III	=	Cinchophen amide
IVa	=	Mannich base of morpholine
IVb	=	Mannich base of piperidine
IVc	=	Mannich base of dicyclohexyl amine
IVd	=	Mannich base of dimethylamine
IVe	=	Mannich base of diethylamine
Std.1	=	Norfloxacin
Std.2	=	Fluconazole

RESULTS AND DISCUSSION

Cinchophen is a quinoline derivative, which is synthesised from cinchoninic acid. Cinchophen **(I)** was synthesised from pyruvic acid, aniline and benzaldehyde by Doebner synthesis. The overall yield was 50 %. The structure was confirmed by IR spectra. The IR spectra showed characteristic peak at 1704 (C = O), 3034 (C-H str), 3360 (O-H str) and appropriate peaks at 1203, 760, 731 and 699 cm^{-1}. Mass spectra showed the appropriate m/z values at 251, 250, 233, 205, 173, 127, 114, 100, 87, 75 and 60. Confirmation of the compound was done by ^{1}H NMR spectra showing the characteristic signals at 7.528-7.502 (m, ArH), 7.537 (s, 1H, ArH), 7.549 (s, 1H, ArH), 7.700- 8.094 (s, ArH) and 8.177 (s, ArH) and 9.646 (s, 1H, COOH).

Cinchophen acid chloride **(II)** was synthesised from cinchophen and oxalyl chloride by acylation reaction. The overall yield was 95 %. The structure was confirmed by IR spectra. The IR spectra showed characteristic peaks at 1716 (CO-Cl), 3046 (C-H str) and appropriate peak at 1754, 244, 767, 731 and 699 cm^{-1}. Mass spectra showed the appropriate m/z values at 250, 249, 233, 205, 172, 127, 114, 100, 87, 75 and 60.

The 2-phenylquinoline-4-carboxylic acid amide **(III)** was synthesized from acid chloride and ammonia by simple reaction. The overall yield ranges from 85 to 90 %. The structure was confirmed by IR spectra. The IR spectra showed characteristic peak at 1651

($CONH_2$), 3035 (CH str.), 3383 (NH str) and appropriate peaks at, 1236, 798, 768, 742, 699 and 650 cm^{-1}. Mass spectra showed the appropriate m/z values at 250, 249, 233, 205, 172, 127, 114, 100, 87, 75 and 60.Confirmation of the compound was done by ^1H NMR spectra showing the characteristic signals at 3.321-3.335 (s, 1H, Ar-NH_2), 7.491-7.805 (m, Ar-H), 7.810- 7.856 (m, Ar-H), 8.100-8.296 (m, Ar-H) and 8.536-8.564 (d, 1H, Ar-H).

Then the compounds **IVa-e** were prepared according to **Scheme III** by the use of secondary amines and formaldehyde. The yield of the compounds prepared was in the range 50 – 85 %. The **IVa** show the characteristic IR peaks at 1662 (C=O, Ar-CONHR), 3029.96 (Ar-CH str) and 3120.61 (NH str) cm^{-1}. Mass spectra showed the appropriate m/z values at 349, 348, 305, 291, 249, 233, 206, 172, 127, 114, 100, 87, 75 and 60. Confirmation of the compound was done by ^1H NMR spectra showing the characteristic signals at 3.217-3.333 (m, -NCH_2), 3.634 (s, 1H, -CH_2), 3.808 (s, 1H, Ar-NH), 3.823-3.935 (m, -O-CH_2), 7.511-7.811 (m, Ar-H), 7.817-7.844 (m, Ar-H), 8.091-8.288 (m, Ar-H) and 8.541-8.568 (d, 1H, Ar-H). The **IVb** show the characteristic IR peaks at 1659.81 (C=O, Ar-CONHR), 3025 (Ar-C-H str.), 3129.60 (N-H str.), 1439.51, 1489.73 (N-H def.), 1235.36 and 766.62 cm^{-1}. Mass spectra showed the appropriate m/z values at 346, 320, 292, 248, 233, 205, 172, 141, 127, 114, 100, 98, 87, 75 and 60. Confirmation of the compound was done by ^1H NMR spectra showing the characteristic signals at 1.671–1.829 (m, -CH_2), 3.113-3.150 (m, -CH_2), 3.623 (s, 1H, - CH_2), 3.925 (s, 1H, Ar-NH), 7.509-8 and 635 (m, Ar-H). Compound **IVc** show the characteristic IR peaks at 1652 (C=O, Ar-CONHR), 3031.89 (Ar-CH str.) 3123.76 (N-H str.), 1441.48, 1491 (N-H def.), 1232.74, 769.40 and 699 cm^{-1}. Mass spectra showed the appropriate m/z values at 442, 414, 359, 331, 247, 233, 205, 194, 182, 172, 127, 114, 100, 87, 83, 75 and 60. Confirmation of the compound was done by ^1H NMR spectra showing the characteristic signals at 1.196–1.305 (m, -CH_2), 3.619 (s, 1H, -CH_2), 3.943 (s, 1H, Ar-NH) and 7.525-8.734 (m, Ar-H). **IVd** show the characteristic IR peaks at 1660 (C=O, Ar-CONHR), 3030 (Ar-CH str.), 3127 (NH str.), 1444, 1463 (NH def.), 1234, 768 and 698 cm^{-1}. Mass spectra showed the appropriate m/z values at 306, 248, 233, 205, 172, 127, 114, 100, 87, 75, 60 and 58. Confirmation of the compound was done by ^1H NMR spectra showing the characteristic signals at 3.036 - 3.084 (m, -CH_3), 3.620 (s, 1H, -CH_2), 3.93 (s, 1H, Ar-NH) and 7.517-8.594 (m, Ar-H). **IVe** show the characteristic IR peaks at 1647 (C=O, Ar-CONHR), 3028 (Ar-CH str.), 3178 (N-H str.), 1433, 1458 (N-H def.), 1237, 760 and 684 cm^{-1}. Mass spectra showed the appropriate m/z values at 334, 248, 233, 205, 172, 127, 114, 100, 87, 86, 75, 60. Confirmation of the compound was done by ^1H NMR spectra showing the characteristic signals at 1.289–1.338 (m, -CH_3), 3.011-3.060 (m, -CH_2), 3.620 (s, 1H, -CH_2), 3.94 (s, 1H, Ar-NH) and 7.517-8.594 (m, Ar-H).

CONCLUSION

In the present study, cinchophen having carboxylic acid (-COOH) group was converted to amide (-$CONH_2$), which is utilized to synthesize Mannich bases. The lead compound cinchophen **I** was synthesised by the Doebnear synthesis. The acid chloride **II** and amide **III** was then prepared by reported methods with good yield. The Mannich bases of the amide of cinchophen **IVa-e** were prepared by condensation with secondary amines and formaldehyde by Mannich reaction with satisfactory yield and purity. The structures of synthesised compounds were confirmed by spectral analysis.

Synthesized compounds **IVa-e** were subjected for their antimicrobial activity. All the synthesized compounds have shown mild to good activity against the pathogenic bacteria and fungi. Three synthesized compounds, **IVa, IVb** and **IVc**, have been shown to be more potent than cinchophen. Two synthesized compounds **IVd** and **IVe** were almost equipotent as cinchophen but failed to show activity against fungi.

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