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Research Article

## SYNTHESIS AND ANTIMICROBIAL ACTIVITY OF 1,4-DIHYDROPYRIDINE DERIVATIVE

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### ABSTRACT

A series of substituted 1,4-dihydropyridine derivatives (SC1-SC10) was synthesized via condensation of acetoacetanilide /4-chloro acetoacetanilide and substituted benzaldehyde in methanol with excess amount of ammonia. The synthesized compounds were characterized using FT-IR, NMR and Mass spectroscopic techniques. The anti-bacterial and anti-fungal activity of title compounds was evaluated utilizing paper disc diffusion method. The anti-bacterial activity was determined by using *S. aureus* and *E. coli* as the gram-positive and gram negative strains, while *Candida albicans* was used to evaluate the anti-fungal activity of synthesized compounds. 1,4-dihydropyridine derivative (SC8) with bromo group at para position of phenyl ring attached to dihydropyridine ring and chloro group linked to para position of carbamoyl phenyl ring was found to be the most active anti-bacterial agent, with its activity observed more on gram negative strain (81.76%) as compared to gram positive strain (75.94%). The most active anti-fungal agent was found to be SC1 (86.85%); 1,4-dihydropyridine derivative with hydroxy group at 2<sup>nd</sup> position and bromo group at 5<sup>th</sup> position of phenyl ring attached to dihydropyridine ring while chloro group linked to para position of carbamoyl phenyl ring. This suggests the requirement of electron withdrawing group at 3<sup>rd</sup> and 5<sup>th</sup> position of dihydropyridine ring for anti-bacterial and anti-fungal activity.

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### INTRODUCTION:

1, 4 Dihydropyridines are nitrogen containing heterocyclic compounds with nitrogen as the heteroatom. This nucleus is associated with varied pharmacological activities, viz. anti-microbial, anti-tubercular, anti-cancer, antioxidant, vasodilator, calcium channel blocker, analgesic, anticonvulsant, anti-inflammatory, anti-ulcer activities<sup>1</sup>. Extensive literature survey revealed its potential for antimicrobial activity. The present work was thus focused to explore the anti-microbial activity of this nucleus. In this regard, it was planned to synthesize a series of 1,4dihydropyridine derivatives (Table 1) by utilizing different substituted aromatic aldehydes group with acetoacetanilide in presence of ammonia and methanol.

### MATERIAL AND METHODS:

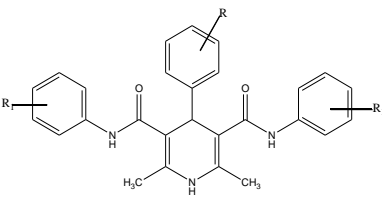
**Synthesis** A mixture of acetoacetanilide /4-chloro acetoacetanilide (0.02 mol) and substituted benzaldehyde (0.01 mol) was dissolved in methanol. 5-7 ml of ammonia (25%) solution was added, followed by refluxing for 5–6 h (Scheme 1). 2-3 ml ammonia was added at an interval of 3-4 h and the refluxing was continued for 24 h<sup>2-3</sup>. The reaction mixture was kept

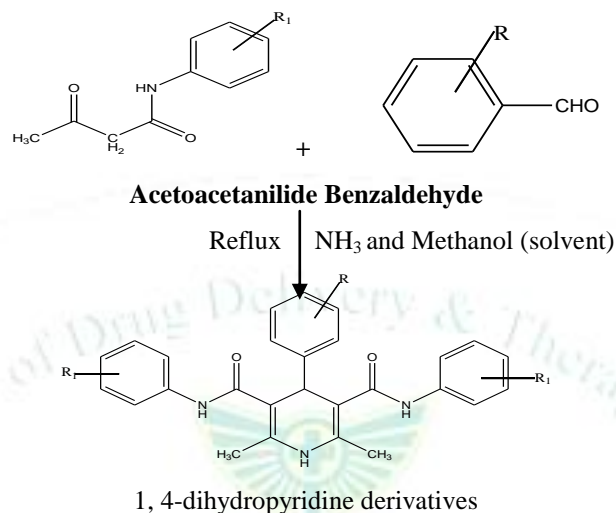
overnight and the crystalline product was separated out. It was then filtered, washed 2–3 times with chilled methanol, dried and recrystallized using methanol. The synthesized compounds were characterized using FT-IR, NMR and Mass spectroscopic techniques.

**Anti-bacterial activity assay** The cultures of gram positive and gram negative strains were obtained in Mueller–Hinton Broth after incubating them at  $37 \pm 1^\circ\text{C}$  for 18–24 h. The anti-bacterial activity was performed on Mueller–Hinton Broth at pH 7.4 and twofold dilution technique was applied. The growth of microorganism was recorded to inhibition zone diameter expressed in percent of relative inhibition zone diameter after incubation for 18–24 h at  $37 \pm 1^\circ\text{C}$ . Ciprofloxacin was used as standard.

**Anti-fungal activity assay** The yeasts were maintained in Sabouraud Dextrose Broth pH 7.4 after incubation for 48 h at  $25 \pm 1^\circ\text{C}$ . Controls tubes contained only inoculated broth. The growth of microorganism was recorded to inhibition zone diameter expressed in percent of relative inhibition zone diameter after incubation for 48 h at  $37 \pm 1^\circ\text{C}$ . Fluconazole was used as standard drug.

**Table 1:** Substituted 1, 4 dihydropyridine derivatives

	Comp. Code	R	R <sub>1</sub>
	SC1	2-OH, 5-Br	4-Cl
	SC2	4-OH	H
	SC3	3,4,5-trimethoxy	H
	SC4	2-NO <sub>2</sub>	4-Cl
	SC5	3,4-dimethoxy	4-Cl
	SC6	2-NO <sub>2</sub>	H
	SC7	3,4-dimethoxy	H
	SC8	4-Br	4-Cl
	SC9	4-NO <sub>2</sub>	4-Cl
	SC10	4-NO <sub>2</sub>	H

**Scheme 1:** Synthesis of 1, 4-dihydropyridines derivatives

**Calculation of percent of relative inhibition zone diameter** The percent of relative inhibition zone diameter (% RIZD) is the calculation of percentage of relative inhibition zone obtained for control as compared to zone of inhibition obtained from standard drug at same concentration. The antimicrobial activity was calculated by applying the expression:

$$\% \text{ RIZD} = \frac{(\text{IZD sample} - \text{IZD negative control})}{(\text{IZD standard} - \text{IZD negative control})} \times 100\%$$

where RIZD is the percent of relative inhibition zone and IZD is the inhibition zone diameter (mm).

## RESULTS AND DISCUSSION:

The title compounds were synthesized via condensation of acetoacetanilide /4-chloro acetoacetanilide and substituted benzaldehyde in methanol. These newly synthesized compounds were assayed for their antimicrobial activity against *Staphylococcus aureus* (Gram-positive bacteria) and *Escherichia coli* (Gram negative bacteria) and the fungal strain *Candida albicans*. The antibacterial activity of compounds was determined by the paper disc diffusion method using Mueller-Hinton agar. Ciprofloxacin was used as the reference antibacterial agent. The antifungal activity of compounds was determined by the paper disc diffusion method using Sabouraud dextrose agar growth medium. Fluconazole was used as the reference antifungal agent. All synthesized compounds exhibited higher inhibitory activity against gram negative bacteria than gram positive bacteria (Table 2, Fig.1).

**Staphylococcus aureus (gram positive)** All the compounds were inactive towards *S. aureus* at minimum concentration of 6.25 µg/ml whereas the compounds showed a significant inhibitory activity towards *S. aureus* at concentration ranging from 12.5-50 µg/ml. Compound SC8 exhibited highest inhibitory activity. Following is the antibacterial efficacy of synthesized compounds against *S.aureus* in decreasing order –

SC8 > SC1 > SC7 > SC10 > SC6 > SC3 > SC4 > SC9 > SC2 > SC5

**E. coli (gram negative)** All the compounds were inactive towards *E. coli* at minimum concentration of 6.25 µg/ml whereas the compounds showed a significant inhibitory activity towards *E. coli* at concentration range 12.5, 25, 50, 100 µg/ml, amongst all these compounds, SC8 (81.76%) showed highest percentage of relative zone of inhibition. Following is the antibacterial efficacy of synthesized compounds against *E. coli* in decreasing order

SC8 > SC3 > SC4 > SC10 > SC9 > SC5 > SC1 > SC2 > SC6 > SC7

**Candida albicans (fungi)** all the compounds were inactive towards *C. albicans* at minimum concentration of 6.25 µg/ml and 12.5 µg/ml. Whereas the compounds showed a significant inhibitory activity towards *C. albicans* at concentration range 25, 50, 100 µg/ml. Amongst all these compounds, SC1 (86.85%) exhibited highest percentage of relative zone of inhibition (Table 3, Figure 1).

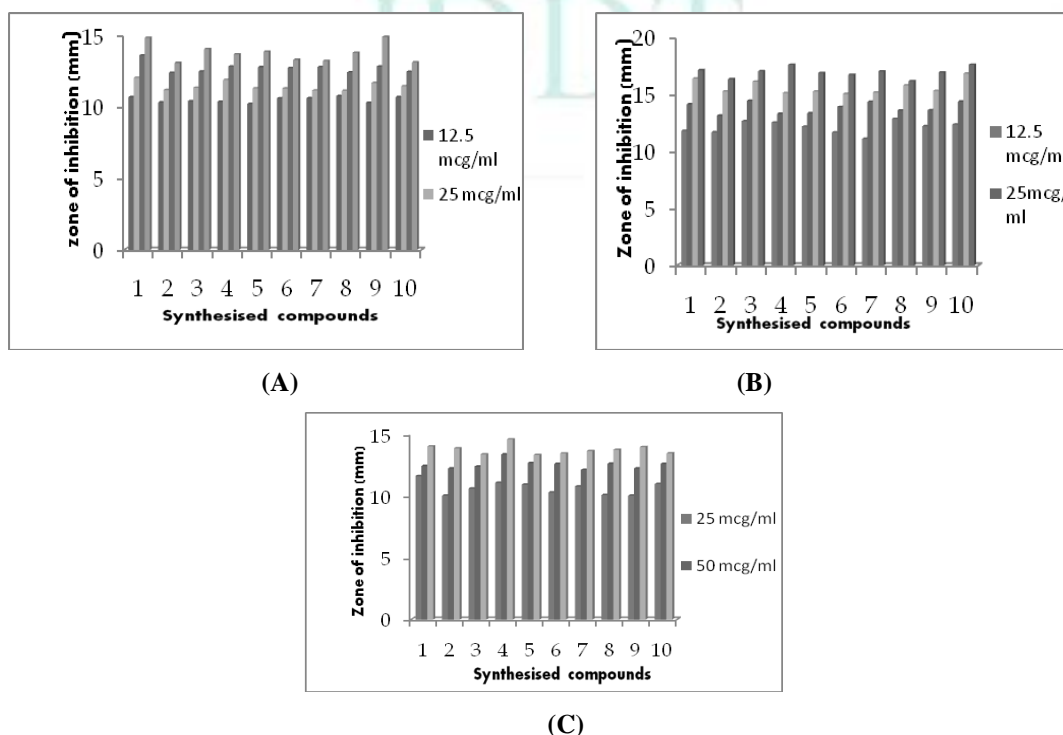
**Table 2:** Anti-bacterial activity of synthesized 1,4-dihydropyridine derivatives in terms of RIZD

Bact.strain	<i>Escherichia coli</i>					<i>Staphylococcus aureus</i>				
	6.25	12.5	25	50	100	6.25	12.5	25	50	100
Conc. in (µg/ml)										
Comp. no.	Relative inhibition zone diameter in percentage									
SC1	-	75.15	79.37	80.05	75.45	-	75.00	71.76	71.85	73.04
SC2	-	74.33	73.76	75.79	71.97	-	71.81	66.64	65.45	64.38
SC3	-	80.49	81.05	80.51	75.05	-	72.44	67.59	65.94	69.15
SC4	-	79.73	74.66	75.09	77.51	-	72.16	70.87	67.79	67.33
SC5	-	77.44	74.94	75.79	74.35	-	71.12	67.36	67.52	68.22
SC6	-	74.20	78.02	74.70	73.69	-	73.83	67.30	67.21	65.46
SC7	-	70.64	80.54	75.34	75.00	-	74.93	66.46	68.79	65.07
SC8	-	81.76	76.34	78.42	71.22	-	75.94	66.34	65.62	67.87
SC9	-	77.70	76.45	76.04	74.57	-	71.88	69.62	67.74	73.33
SC10	-	78.65	80.66	83.58	77.51	-	74.39	68.25	65.83	64.58

**Table 3:** Anti-fungal activity of synthesized 1,4-dihydropyridine derivatives in terms of RIZD

Fungal strain	<i>Candida albicans</i>				
Conc. in (µg/ml)	6.25	12.5	25	50	100
Comp. No.	Relative inhibition zone diameter in percentage				
SC1	-	-	86.85	78.63	79.53
SC2	-	-	74.98	77.27	78.62
SC3	-	-	79.31	78.38	75.85
SC4	-	-	82.82	84.57	82.76
SC5	-	-	81.70	80.15	75.56
SC6	-	-	76.92	79.77	76.30
SC7	-	-	80.58	76.61	77.38
SC8	-	-	75.35	79.73	78.00
SC9	-	-	74.98	77.37	78.62
SC10	-	-	82.00	79.77	76.36

Following is the antimicrobial efficacy of synthesized compounds against *C. albicans* in decreasing order: SC1 > SC4 > SC10 > SC5 > SC7 > SC3 > SC8 > SC2, SC9

**Figure 1:** Antimicrobial activity of synthesized compounds against (A) *S. aureus* (B) *E. coli* (C) *C. albicans*

**CONCLUSION:**

1,4-dihydropyridine derivative (SC8) with bromo group at para position of phenyl ring attached to dihydropyridine ring and chloro group linked to para position of carbamoyl phenyl ring was found to be the most active anti-bacterial agent, with its activity observed more on gram negative strain (81.76%) as compared to gram positive strain (75.94%). The most

active anti-fungal agent was found to be SC1 (86.85%); 1,4-dihydropyridine derivative with hydroxy group at 2<sup>nd</sup> position and bromo group at 5<sup>th</sup> position of phenyl ring attached to dihydropyridine ring while chloro group linked to para position of carbamoyl phenyl ring. This suggests the requirement of electron withdrawing group at 3<sup>rd</sup> and 5<sup>th</sup> position of dihydropyridine ring for anti-bacterial and anti-fungal activity.

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