

Design, Synthesis and Biological Evaluation of 5-Imidazolone Derivatives as Antimicrobial Agents

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ABSTRACT: In search of less potent antimicrobial agents, a series of 1-[4'-(N-methyl-N-acetyl amino) phenyl]-2'-phenyl-4-(phenyl/substitutedphenyl/heterocyclicphenyl) benzylidene-5-imidazolones (**C₁-C₉**) derivatives were synthesized between the reaction of oxazolones (**A₁-A₉**) and 4-amino-N-methyl acetanilide (**B**). The lead compounds were screened for the antimicrobial activity against *Staphylococcus aureus* [MTCC-96], *Bacillus subtilis* [MTCC-441], *Escherichia coli* [MTCC-443] *Salmonella paratyphi-A* [MTCC-735] as bacterial pathogenic strain and *Fusarium solani* [MTCC-350] as fungal pathogenic strain. Structures of the synthesized compounds were established by IR, ¹H NMR and elemental analysis. The antimicrobial screening studies revealed that 5-imidazolone derivatives carrying 2-furanyl (**C₃**), 3-nitrophenyl (**C₄**), 3-phenoxyphenyl (**C₅**), 4-chlorophenyl (**C₇**) and 2,3-dichlorophenyl (**C₈**) group exhibited excellent antimicrobial activity. The results exposed that the synthesized compounds may be a potential lead for future drug discovery.

KEYWORDS: Oxazolones, 4-Amino-N-methyl acetanilide, 5-Imidazolones, Antibacterial and antifungal activity.

I. INTRODUCTION

The present antimicrobial drugs are losing their effectiveness due to the increase in microbial pathogenic resistance [1]. At present, its impact is major with treatment failures associated with drug-resistant bacteria and it has become a global concern to public health [2]. Moreover, infections with drug resistant organisms remain an important problem in clinical practice. For this reason, finding of new antibiotics is an important objective.

Unsaturated 5-imidazolone is the five membered heterocyclic ring having three carbon and two nitrogen atoms arranged at 1 and 3 positions which are the nitrogen analogues of azalactones. Imidazolones are of many types, e.g. 2-, 4-, or 5-imidazolones. The number indicates the position of the carbonyl group in the ring. Imidazole was first synthesized by Heinrich Debus in 1858 then after various imidazole derivatives have been in the literature [3]. Various methods have been described for the synthesis of imidazolones in literature [4]. Generally imidazolones are prepared by the reaction of azalactones with different type of compounds have been extensively investigated [5]. Literature survey shows that 5-imidazolones and its derivatives have displayed promising biological and pharmacological activities such as anti-inflammatory [6], anti-mycotic [7], antimicrobial [8], analgesic [9], antioxidant [10], anthelmintic [11], antiproliferative [12] etc. Encouraged by the above described findings and in continuation of our investigation [13,14], some new 5-imidazolones (**C₁-C₉**) are synthesized to discover new potentially active microbiologically agents. All the newly synthesized compounds were characterized by spectroscopic techniques and investigated for their *in vitro* antibacterial and antifungal activities.

II. MATERIALS AND METHOD

All reagents and chemicals were of analytical grade. All melting points (uncorrected) were determined in open capillary tubes and are uncorrected. All reactions were monitored by thin-layer chromatography on 0.25 mm silica gel (60GF-254) plates, using toluene : methanol in the ratio of [10:6] as mobile phase and visualized with UV light or keeping the plates in iodine chamber. IR Spectra (ν_{max} in cm^{-1}) were recorded in Perkin-Elmer - 282 instrument (USA) and ¹H-NMR spectra on Bruker Avance II 400 spectrometer at 400 MHz using TMS as internal standard (Chemical Shifts in δ

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ppm). Elemental analyses of the newly synthesized compounds were performed on Perkin-Elmer 2400 series-II elemental analyzer (Perkin-Elmer, USA). The standard reference drugs used for antimicrobial evaluation were Chloramphenicol, Streptomycin and Greseofulvin of commercial grade.

General procedure for the preparation of 2-phenyl-4-(phenyl/substitutedphenyl/heterocyclicphenyl)-benzylidene-5-oxazolones (A₁-A₉)

The starting precursors 2-phenyl-4-(phenyl/substitutedphenyl/heterocyclicphenyl)-benzylidene-5-oxazolones (A₁-A₉) were prepared by well known Erlenmeyer Azalactone synthesis [15] in good yield.

General procedure for the preparation of 1-[4'-(N-methyl-N-acetyl amino) phenyl]-2'-phenyl-4-(phenyl/substitutedphenyl/heterocyclicphenyl)-benzylidene-5-imidazolones (C₁-C₉)

A 100 ml round bottom flask, fitted with a reflux condenser, was charged with a mixture of an appropriate 2-phenyl-4-(phenyl/substitutedphenyl/heterocyclicphenyl)-benzylidene-5-oxazolones (A₁-A₉) (0.01 mol) and 4-amino-N-methyl acetanilide (0.01 mol) was refluxed in pyridine for 10-12 hours. The progress of the reaction was monitored by TLC using toluene: methanol (12:8 V/V) eluent as mobile phase. After completion of the reaction, resulting reaction mixture was poured into crushed ice and neutralized with hydrochloric acid. The product (C₁-C₉) thus obtained was filtered, washed with water and recrystallized from methanol. The analytical and their spectral data are given below.

Analytical and Spectral analysis Data

The analytical and spectral data of newly synthesized compounds are given below.

1-[4'-(N-methyl-N-acetyl amino) phenyl]-2-phenyl-4-(3',4',5'-trimethoxyphenyl)-benzylidene-5-imidazolones (C₁):
Yield 67%; M. P. 84 °C; Anal. Calcd. for C₂₈H₂₇N₃O₅: C, 69.27; H, 5.60; N, 8.65%. Found: C, 69.20; H, 5.67; N, 8.60%; IR (KBr, ν_{\max} , cm⁻¹): 3139 (aromatic =CH str.), 2959 (C-H str. of alkane) 1731 (C=O str. of imidazolone), 1696 (C=N str. of imidazolone), 1590 (aromatic C=C str.), 1397 (CH₃ str.), 1376 (C-N str.), 1226 (asymmetric C-O-C str. of ether linkage), 1136 (C-OCH₃ str.), 810 (C-H bending 1,4 disubstituted benzene ring); ¹H NMR (400 MHz, CDCl₃, δ ppm): 1.9 (s, 3H, C-CH₃), 3.2 (s, 3H, N-CH₃), 3.5-3.9 (s, 3H, OCH₃), 5.9 (s, 1H, Ar-CH=C), 7.2-7.8 (m, 10H, Ar-H).

1-[4'-(N-methyl-N-acetyl amino) phenyl]-2-phenyl-4-(cinnamyl)-benzylidene-5-imidazolones (C₂):
Yield 75%; M. P. 115 °C; Anal. Calcd. for C₂₇H₂₃N₃O₂: C, 76.95; H, 5.50; N, 9.97%. Found: C, 76.90; H, 5.59; N, 9.90%; IR (KBr, ν_{\max} , cm⁻¹): 3026 (aromatic =CH str.), 2936 (C-H str. of alkane) 1713 (C=O str. of imidazolone), 1650 (C=N str. of imidazolone), 1529 (aromatic C=C str.), 1384 (CH₃ str.), 1372 (C-N str.), 1248 (asymmetric C-O-C str. of ether linkage), 823 (C-H bending 1,4 disubstituted benzene ring); ¹H NMR (400 MHz, CDCl₃, δ ppm): 2.0 (s, 3H, C-CH₃), 3.8 (s, 3H, N-CH₃), 5.7 (s, 1H, Ar-CH=C), 5.8 (s, 1H, Ar-CH=CH), 7.1 (s, 1H, Ar-CH), 7.2-8.3 (m, 14H, Ar-H).

1-[4'-(N-methyl-N-acetyl amino) phenyl]-2-phenyl-4-(2'-furanyl)-benzylidene-5-imidazolones (C₃):
Yield 71%; M. P. 158 °C; Anal. Calcd. for C₂₃H₂₃N₃O₃: C, 70.95; H, 5.95; N, 10.79%. Found: C, 70.90; H, 5.88; N, 10.70%; IR (KBr, ν_{\max} , cm⁻¹): 3050 (aromatic =CH str.), 2992 (C-H str. of alkane) 1720 (C=O str. of imidazolone), 1680 (C=N str. of imidazolone), 1550 (aromatic C=C str.), 1389 (CH₃ str.), 1368 (C-N str.), 1236 (asymmetric C-O-C str. of ether linkage), 731 and 840 (C-H bending 1,2 and 1,4 disubstituted benzene ring); ¹H NMR (400 MHz, CDCl₃, δ ppm): 1.7 (s, 3H, C-CH₃), 2.5 (s, 3H, N-CH₃), 4.6 (s, 1H, Ar-CH=C), 6.6-7.5 (m, 11H, Ar-H).

1-[4'-(N-methyl-N-acetyl amino) phenyl]-2-phenyl-4-(3'-nitrophenyl)-benzylidene-5-imidazolones (C₄):
Yield 80%; M. P. 98 °C; Anal. Calcd. for C₂₅H₂₀N₄O₄: C, 68.18; H, 4.57; N, 12.72%. Found: C, 68.10; H, 4.62; N, 12.65%; IR (KBr, ν_{\max} , cm⁻¹): 3012 (aromatic =CH str.), 2938 (C-H str. of alkane) 1698 (C=O str. of imidazolone), 1659 (C=N str. of imidazolone), 1554 (aromatic C=C str.), 1489 (C-NO₂ str.), 1401 (CH₃ str.), 1389 (C-N str.), 1231 (asymmetric C-O-C str. of ether linkage), 710 and 852 (C-H bending 1,3 and 1,4 disubstituted benzene ring); ¹H NMR (400 MHz, CDCl₃, δ ppm): 2.4 (s, 3H, C-CH₃), 3.1 (s, 3H, N-CH₃), 6.6 (s, 1H, Ar-CH=C), 7.0-7.8 (m, 12H, Ar-H).

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1-[4'-(N-methyl-N-acetyl amino) phenyl]-2-phenyl-4-(3'-phenoxyphenyl)-benzylidene-5-imidazolones (**C₅**):
Yield 64%; M. P. 187 °C; Anal. Calcd. for C₃₁H₂₅N₃O₃: C, 76.38; H, 5.16; N, 8.62%. Found: C, 76.30; H, 5.07; N, 8.55%; IR (KBr, ν_{\max} , cm⁻¹): 3123 (aromatic =CH str.), 2978 (C-H str. of alkane) 1740 (C=O str. of imidazolone), 1648 (C=N str. of imidazolone), 1589 (aromatic C=C str.), 1380 (CH₃ str.), 1356 (C-N str.), 1210 (asymmetric C-O-C str. of ether linkage), 729 and 842 (C-H bending 1,3 and 1,4 disubstituted benzene ring); ¹H NMR (400 MHz, CDCl₃, δ ppm): 2.9 (s, 3H, C-CH₃), 3.3 (s, 3H, N-CH₃), 6.8 (s, 1H, Ar-CH=C), 7.6-9.2 (m, 17H, Ar-H).

1-[4'-(N-methyl-N-acetyl amino) phenyl]-2-phenyl-4-(4'-methoxyphenyl)-benzylidene-5-imidazolones (**C₆**):
Yield 78%; M. P. 118 °C; Anal. Calcd. for C₂₆H₂₃N₃O₃: C, 73.41; H, 5.44; N, 9.88%. Found: C, 73.32; H, 5.49; N, 9.80%; IR (KBr, ν_{\max} , cm⁻¹): 3108 (aromatic =CH str.), 2952 (C-H str. of alkane) 1730 (C=O str. of imidazolone), 1690 (C=N str. of imidazolone), 1589 (aromatic C=C str.), 1394 (CH₃ str.), 1353 (C-N str.), 1223 (asymmetric C-O-C str. of ether linkage), 1125 (C-OCH₃ str.), 812 (C-H bending 1,4 disubstituted benzene ring); ¹H NMR (400 MHz, CDCl₃, δ ppm): 2.4 (s, 3H, C-CH₃), 3.8 (s, 3H, N-CH₃), 3.9 (s, 3H, OCH₃), 6.2 (s, 1H, Ar-CH=C), 7.0-8.0 (m, 12H, Ar-H).

1-[4'-(N-methyl-N-acetyl amino) phenyl]-2-phenyl-4-(4'-chlorophenyl)-benzylidene-5-imidazolones (**C₇**):
Yield 82%; M. P. 102 °C; Anal. Calcd. for C₂₅H₂₀N₃O₂Cl: C, 69.84; H, 4.69; N, 9.77%. Found: C, 69.80; H, 4.73; N, 9.70%; IR (KBr, ν_{\max} , cm⁻¹): 3012 (aromatic =CH str.), 2946 (C-H str. of alkane) 1706 (C=O str. of imidazolone), 1645 (C=N str. of imidazolone), 1520 (aromatic C=C str.), 1408 (CH₃ str.), 1349 (C-N str.), 1238 (asymmetric C-O-C str. of ether linkage), 847 (C-H bending 1,4 disubstituted benzene ring), 754 (C-Cl str.); ¹H NMR (400 MHz, CDCl₃, δ ppm): 2.1 (s, 3H, C-CH₃), 2.8 (s, 3H, N-CH₃), 5.6 (s, 1H, Ar-CH=C), 6.7-7.8 (m, 12H, Ar-H).

1-[4'-(N-methyl-N-acetyl amino) phenyl]-2-phenyl-4-(2',4'-dichlorophenyl)-benzylidene-5-imidazolones (**C₈**):
Yield 71%; M. P. 92 °C; Anal. Calcd. for C₂₅H₁₉N₃O₂Cl₂: C, 64.65; H, 4.12; N, 9.05%. Found: C, 64.55; H, 4.16; N, 8.95%; IR (KBr, ν_{\max} , cm⁻¹): 3024 (aromatic =CH str.), 2967 (C-H str. of alkane) 1717 (C=O str. of imidazolone), 1678 (C=N str. of imidazolone), 1532 (aromatic C=C str.), 1410 (CH₃ str.), 1364 (C-N str.), 1214 (asymmetric C-O-C str. of ether linkage), 728 and 838 (C-H bending 1,2 and 1,4 disubstituted benzene ring); 721 (C-Cl str.); ¹H NMR (400 MHz, CDCl₃, δ ppm): 2.9 (s, 3H, C-CH₃), 3.4 (s, 3H, N-CH₃), 6.5 (s, 1H, Ar-CH=C), 6.9-7.6 (m, 11H, Ar-H).

1-[4'-(N-methyl-N-acetyl amino) phenyl]-2-phenyl-4-(3'-ethoxy-4'-hydroxyphenyl)-benzylidene-5-imidazolones (**C₉**):
Yield 79%; M. P. 110 °C; Anal. Calcd. for C₂₇H₂₅N₃O₄: C, 71.20; H, 5.53; N, 9.23%. Found: C, 71.15; H, 5.47; N, 9.15%; IR (KBr, ν_{\max} , cm⁻¹): 3010 (aromatic =CH str.), 2913 (C-H str. of alkane) 1705 (C=O str. of imidazolone), 1685 (C=N str. of imidazolone), 1570 (aromatic C=C str.), 1367 (CH₃ str.), 1336 (C-N str.), 1221 (asymmetric C-O-C str. of ether linkage), 1240 (C-OH str.), 664 and 832 (C-H bending 1,3 and 1,4 disubstituted benzene ring); ¹H NMR (400 MHz, CDCl₃, δ ppm): 1.9 (s, 3H, C-CH₃), 2.5 (t, 3H, OCH₂CH₃), 3.4 (s, 3H, N-CH₃), 3.7 (q, 2H, OCH₂CH₃), 6.1 (s, 1H, OH), 6.9 (s, 1H, Ar-CH=C), 7.1-8.0 (m, 11H, Ar-H).

Pharmacological assay

Antibacterial activity of all the newly synthesized compounds were carried out by applying cup-plate agar diffusion method [16] against two gram positive bacterial pathogens *Staphylococcus aureus* [MTCC-96], *Bacillus subtilis* [MTCC-441] and two gram negative bacterial pathogens *Escherichia coli* [MTCC-443] and *Salmonella paratyphi-A* [MTCC-735]. The compounds were tested at 40 μ g/ml concentration and DMF was used as solvent. The sterilized nutrient agar media [2.4% (w/v) agar-agar, 5% (w/v) NaCl, peptone, pH (6.8 to 7.0)] was poured into a Petridish (9.0 cm in diameter) and allowed to set for 2 hours. On the surface of the media microbial suspension was spread over the agar plates to solidify. A stainless steel cylinder (pre-sterilized) was used to bore the cavities. All the synthesized compounds (100 μ g/ml) in DMF were placed serially in the cavities with the help of micropipette. It is then allowed to diffuse for 10 minutes in refrigerator. The plates were incubated at 37 °C for 24 hours. The control was also maintained with 0.1 ml of DMF in similar manner and the zone of inhibition of the growth was measured in mm (**Table 2**). The standard known antibiotics like Chloramphenicol and Streptomycin were used.

The antifungal activity of the synthesized compounds was carried out by applying poisoned food technique. Fungus which has been selected for inclusion in the test is *Furasium solani* [MTCC-350]. Seven days old cultures are used for

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collecting spores. Standard potato dextrose agar medium is used. Density of spore suspension can be determined in blood counting cell (Haemocytometer) and the final concentration is adjusted to 50,000 spores/ml. This gives about 35 spores in low power field (15× 16 mm). Spores are applied to slides by means of one to two ml pipette. Two pairs of drops are kept on each slide, four drops being in a staged position. Each drop is approximately 0.05 ml on a plain glass, such a drop would spread to a diameter of about 10 mm. For both spore production in test fungus cultures and for germination, the temperature is kept between 20-25 °C. Spores are examined 20-24 hrs. The standard known antifungal drug Griseofulvin was used.

III. RESULT AND DISCUSSION

Chemistry

1-[4'-(N-methyl-N-acetylamino)phenyl]-2'-phenyl-4-arylidine-5-imidazolones (**C₁-C₉**) are achieved from the reaction of oxazolones as systematic path given in **scheme 1**. Structures of all the newly synthesized compounds were confirmed with ¹H-NMR, FT-IR as well as elemental analyses. The spectral data of the isolated product were in complete agreement with the assigned structure. For example, the IR spectrum of compound **C₁** displayed a sharp absorption band at 1731 cm⁻¹ for C=O group along with a band at 1696 cm⁻¹ for C=N stretching of 5-imidazolone ring. A broad stretching band for the C-N functionality and CH₃ group of 4-amino-N-methyl acetanilide ring is observed at 1376 cm⁻¹ and 1397 cm⁻¹ respectively. The asymmetric C-O-C stretching ether linkage, C-H bending vibrations for 1, 4 disubstituted benzene ring and =CH functionality of aromatic ring were observed at 1226, 810 and 3139 cm⁻¹ respectively. The ¹H NMR spectrum of compound **C₁** showed a signal as singlet at δ 5.9 ppm due to Ar-CH proton attached with 5-imidazolone unit. The additional remaining thirteen aromatic protons resonated as a multiplet signal at between δ 7.0-8.0 ppm. C-CH₃ and N-CH₃ protons are appeared as singlet at δ 1.9 and 3.2 ppm. The other remaining ten aromatic protons resonate as a multiplet signal at δ 7.2-7.8 ppm. Moreover, distinctive singlet around δ 3.5 - 3.9 ppm stands for methoxy group of aryl ring attached to 5-imidazolone unit. Finally, the obtained elemental analysis values are also in good agreement with their theoretical data.

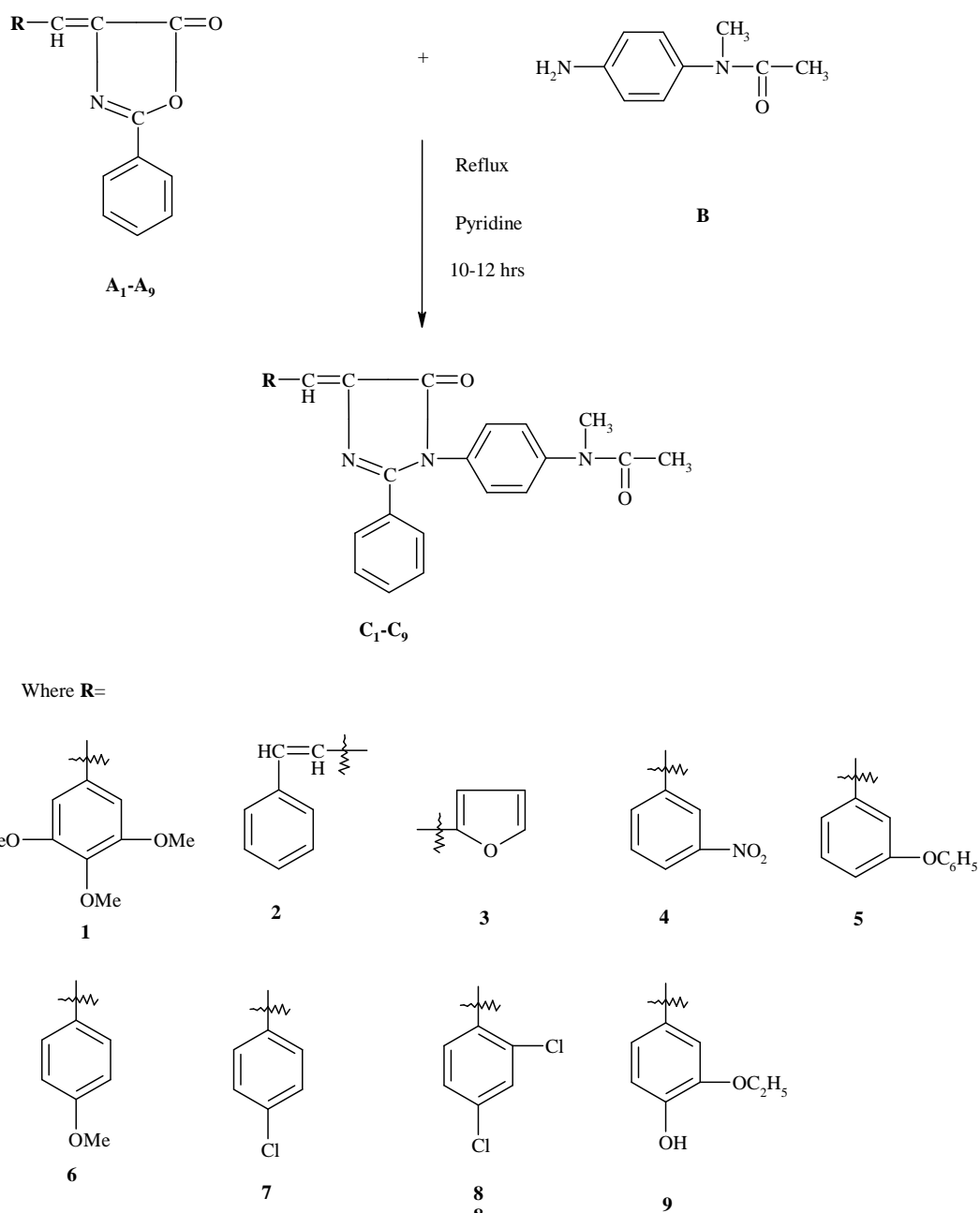
Evaluation of antibacterial activity

The antibacterial evaluation data revealed that, most of the compounds displayed a considerable level of activity in comparison with standard drugs Chloramphenicol and Streptomycin. In case of Gram positive bacteria, compounds **C₃** and **C₄** (10 mm), **C₅**, **C₇** and **C₈** (09 mm) exerted appreciable zone of diameter whereas compounds **C₁**, **C₂** and **C₆** found no zone of diameter against *Staphylococcus aureus* as compared to Chloramphenicol and Streptomycin. Against *Bacillus subtilis*, compounds **C₈** (10 mm), **C₇** and **C₈** (09 mm) and **C₅** (08 mm) found to possess significant activity while the remaining compounds **C₂**, **C₆**, **C₇** and **C₉** found to possess poor activity as compared to standard antibiotics Chloramphenicol and Streptomycin. In the case of Gram negative bacteria *Escherichia coli*, most of compounds found good activity. Compounds **C₇** (14 mm), **C₈** (13 mm), **C₃** and **C₄** (12 mm), **C₆** (11 mm), **C₅** and **C₉** (10 mm) exerted considerable activity whereas the compound **C₁** and **C₂** exerted moderate activity as compared to Chloramphenicol and Streptomycin against *Escherichia coli*. Against *Salmonella paratyphi-A* only two compounds **C₇** (10 mm) and **C₃** (08 mm) showed a zone of diameter while the remaining compounds did not show zone of diameter as compared to Chloramphenicol and Streptomycin. The antifungal activity of all the synthesized compounds was tested *in vitro* against pathogenic fungal strain *Fusarium solani*. Griseofulvin was used as standard antifungal drug. Scrutinize the data of antifungal activity reveals that compounds **C₇** (56 mm) found good inhibition as compared to Griseofulvin while other compounds showed good to mild inhibition.

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Scheme 1. Systematic path to synthesize design compounds C₁-C₉

Scheme 1 showed the systematic path to synthesize 1-[4'-(N-methyl-N-acetylamino)phenyl]-2'-phenyl-4-arylidine-5-imidazolones (C₁-C₉) with the reaction of oxazolones with 4-amino-N-methyl acetanilide.

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Table 2: *In vitro* antimicrobial activity of synthesized compounds C₁-C₉

Compd	Anti bacterial activity (Diameter of zone inhibition at 40 µg/ml)				Anti Fungal activity % Inhibition
	Gram positive		Gram negative		
	<i>S. aureus</i> MTCC 96	<i>B. subtilis</i> MTCC 441	<i>E. coli</i> MTCC 443	<i>S. paratyphi-A</i> MTCC 735	
C ₁	-	-	-	-	23
C ₂	-	-	-	-	26
C ₃	10	09	12	08	37
C ₄	10	09	12	-	34
C ₅	09	08	10	-	36
C ₆	-	-	11	-	23
C ₇	09	-	14	10	56
C ₈	09	10	13	-	37
C ₉	-	-	10	-	23

Table 1 represent the *in vitro* antimicrobial activity data of newly synthesized 5-imidazolone derivatives which found a changeable pattern of antibacterial activities.

IV. CONCLUSION

In conclusion, some biologically potent 5-imidazolones were synthesised from oxazolones with 4-amino-N-methyl acetanilide (B). The synthetic method is simple because no special apparatus is required, and the compound formed is filtered and purified by simple crystallization. *In vitro* antibacterial and antifungal ability of these compounds were investigated. The inhibitory activity depends on the substitution pattern on the aromatic rings. Moreover, from the antimicrobial screening result it is clear that most of the prepared compounds showed improved activity against both Gram-negative bacteria and Gram-positive bacteria. Compounds C₃, C₄, C₅, C₇ and C₈ were the best bioactive desired antimicrobial agents and most proficient member of the series. Further biochemical and pharmacological studies are undergoing to optimize their pharmacological profile.

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