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APPLICATION OF OXAZOLONE IN SYNTHESIS OF NEW HETEROCYCLE CONTAINING 5-IMIDAZOLONE MOIETY AS POTENT PHARMACOLOGICALLY ACTIVE SCAFFOLD

***Anjani Solankee**

Department of Chemistry, B. K. M. Science College, Valsad - 396001, Gujarat Veer Narmad South Gujarat University, Surat, Gujarat, India.

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***Corresponding Author**
Dr. Anjani Solankee
Department of Chemistry,
B. K. M. Science College,
Valsad - 396001, Gujarat
Veer Narmad South Gujarat
University, Surat, Gujarat,
India.

ABSTRACT

In a search of new antimicrobial agents, a new series of 1-[4'-(N-methyl-N-acetyl amino) phenyl] -2-phenyl-4- (phenyl/ substitutedphenyl/ heterocyclic) benzylidine-5-imidazolones **(3a-j)** have been prepared with the reaction of oxazolones **(1a-j)** and 4-amino-N-methyl acetanilide **(2)**. The chemical structures of all newly synthesized compounds were established on the basis of their FTIR, ^{1}H NMR as well as elemental analysis. All the compounds were screened for their *in vitro* antimicrobial activity against selected pathogens such as *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. Most of the compounds showed appreciable antimicrobial activity against the all tested strains. Among the synthesized compounds **3b**, **3c**, **3e**, **3h** and **3j** displayed significant antimicrobial activity and said to be the most proficient members of the series.

KEYWORDS: 4-Amino-N-methyl acetanilide, oxazolones, 5-imidazolones, antimicrobial activity.

INTRODUCTION

Infections caused by microorganisms can be prohibited, controlled and treated through anti-bacterial group of compounds known as antibiotics. Antibiotics are natural, semi-synthetic or synthetic compounds that kill or inhibit the growth of microorganisms. Increasing bacterial resistance to antibiotics represents a major health problem. Solving this problem and search

for new sources of antimicrobial agent is a worldwide challenge.[1] Hence, for the purpose of obtaining new and more potent antimicrobial compounds that can improve the current chemotherapeutic antimicrobial treatment, 5-imidazolones have synthesized and tested for antimicrobial activity.

5-Imidazolone is a planner five membered pharmacologically active heterocyclic ring system having nitrogen atoms at 1 and 3 position and a carbonyl group at 5-position. They are found in several natural compounds like histidine, histamine, biotin, nucleic acid and alkaloids.[2] Different methods have been discribed for the synthesis of imidazolines in literature.[3] Generally imidazolones are prepared by the reaction of azalactones with different type of compounds have been extensively investigated.[4] Recently 5-imidazolone has drawn much attention because of their various pharmacological activities such as antimicrobial[5], anthelmintic[6], anti-inflammatory[7], anticonvulsant agents[8], antituberculer[9], immunomodulatory properties[10] etc. In our ongoing research on pharmacologically active compounds[11-12], we synthesized new series of 1-[4-(N-methyl-N-acetyl amino) phenyl]-2-phenyl-4-(phenyl/substitutedphenyl/heterocyclic) benzylidine-5-imidazolones by treating different oxazolones with 4-amino-N-methyl acetanilide.

MATERIALS AND METHODS

All the reagents were used of analytical grade. Melting points were determined in open capillary tubes and are uncorrected. IR Spectra (ν_{max} in cm^{-1}) were recorded in Perkin-Elmer -282 instrument (USA) and ^{1}H-NMR spectra on Bruker Avance II 400 spectrometer at 400 MHz using TMS as internal standard (Chemical Schifts in δ ppm). The purity of the compound was cheeked by TLC on silica gel-G plate using mobile phase toluene: methanol and the spots were visualised by iodine vapour/ultraviolet light as visualizing agent. 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/heterocyclic)-benzylidine-5-oxazolones (1a-j)

2-phenyl-4-(phenyl/substituted/heterocyclicphenyl)-benzylidine-5-oxazolones **(1a-j)** were prepared by well known Erlenmeyer Azalactone synthesis.[13]

General procedure for the preparation of 1-[4'-(N-methyl-N-acetyl amino) phenyl]-2'-phenyl-4-(phenyl/substitutedphenyl/heterocyclicphenyl)-benzylidine-5-imidazolones (3a-j)

A mixture of 2-phenyl-4-(phenyl/substitutedphenyl/heterocyclicphenyl)-benzylidine-5-oxazolones **(1a-j)** (0.01 mol) and 4-Amino-N-methyl acetanilide (0.01 mol) was refluxed in pyridine for 10-12hours. 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 **(3a-j)** thus obtained was filtered, washed with water and recrystallized from methanol. The physical and analytical data are given in **Table1** and their spectral data are given below.

1-[4'-(N-methyl-N-acetyl amino) phenyl]-2-phenyl-4-phenyl-benzylidine-5-imidazolones (3a)

IR (KBr, $\nu_{max,}$ cm^{-1}): 3010 (aromatic =CH str.), 2920 (C-H str. of alkane) 1700 (C=O str. of imidazolone), 1655 (C=N str. of imidazolone), 1520 (aromatic C=C str.), 1390 (CH_3 str.), 1382 (C-N str.), 1250 (asymmetric C-O-C str. of ether linkage), 815 (C-H bending 1,4 disubstituted benzene ring); ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 2.3 (s, 3H, C-C$\underline{H}_3$), 3.2 (s, 3H, N-C$\underline{H}_3$), 6.2 (s, 1H, Ar-C$\underline{H}$=C), 7.0-8.0 (m, 13H, Ar-H).

1-[4'-(N-methyl-N-acetyl amino) phenyl]-2-phenyl-4-(2'-chlorophenyl)-benzylidine-5-imidazolones (3b)

IR (KBr, $\nu_{max,}$ cm^{-1}): 3025 (aromatic =CH str.), 2936 (C-H str. of alkane) 1712 (C=O str. of imidazolone), 1650 (C=N str. of imidazolone), 1529 (aromatic C=C str.), 1394 (CH_3 str.), 1378 (C-N str.), 1240 (asymmetric C-O-C str. of ether linkage), 721 and 810 (C-H bending 1,2 and 1,4 disubstituted benzene ring), 742 (C-Cl str.); ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 2. 0 (s, 3H, C-C$\underline{H}_3$), 2.9 (s, 3H, N-C$\underline{H}_3$), 6.4 (s, 1H, Ar-C$\underline{H}$=C), 7.5-8.2 (m, 12H, Ar-H).

1-[4'-(N-methyl-N-acetyl amino) phenyl]-2-phenyl-4-(2'-thienyl)-benzylidine-5-imidazolones (3c)

IR (KBr, $\nu_{max,}$ cm^{-1}): 3046 (aromatic =CH str.), 2998 (C-H str. of alkane) 1723 (C=O str. of imidazolone), 1687 (C=N str. of imidazolone), 1554 (aromatic C=C str.), 1383 (CH_3 str.), 1361 (C-N str.), 1221 (asymmetric C-O-C str. of ether linkage), 735 and 826 (C-H bending 1,2 and 1,4 disubstituted benzene ring), 668 (C-S-C linkage); ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 1.9 (s, 3H, C-C$\underline{H}_3$), 2.6 (s, 3H, N-C$\underline{H}_3$), 5.6 (s, 1H, Ar-C$\underline{H}$=C), 6.8-7.9 (m, 11H, Ar-H).

1-[4'-(N-methyl-N-acetyl amino) phenyl]-2-phenyl-4-(3'-chlorophenyl)-benzylidine-5-imidazolones (3d)

IR (KBr, $v_{max,}$ cm^{-1}): 3009 (aromatic =CH str.), 2940 (C-H str. of alkane) 1702 (C=O str. of imidazolone), 1642 (C=N str. of imidazolone), 1519 (aromatic C=C str.), 1402 (CH_3 str.), 1346 (C-N str.), 1232 (asymmetric C-O-C str. of ether linkage), 712 and 856 (C-H bending 1,3 and 1,4 disubstituted benzene ring), 750 (C-Cl str.); ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 2. 4 (s, 3H, C-C$\underline{H}_3$), 3.1 (s, 3H, N-C$\underline{H}_3$), 6.6 (s, 1H, Ar-C$\underline{H}$=C), 7.0-7.8 (m, 12H, Ar-H).

1-[4'-(N-methyl-N-acetyl amino) phenyl]-2-phenyl-4-(3'-bromophenyl)-benzylidine-5-imidazolones (3e)

IR (KBr, $v_{max,}$ cm^{-1}): 3123 (aromatic =CH str.), 2992 (C-H str. of alkane) 1689 (C=O str. of imidazolone), 1676 (C=N str. of imidazolone), 1535 (aromatic C=C str.), 1390 (CH_3 str.), 1369 (C-N str.), 1212 (asymmetric C-O-C str. of ether linkage), 689 and 826 (C-H bending 1,3 and 1,4 disubstituted benzene ring), 589 (C-Cl str.); ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 2. 8 (s, 3H, C-C$\underline{H}_3$), 3.6 (s, 3H, N-C$\underline{H}_3$), 5.9 (s, 1H, Ar-C$\underline{H}$=C), 6.7-7.6 (m, 12H, Ar-H).

1-[4'-(N-methyl-N-acetyl amino) phenyl]-2-phenyl-4-(3'-methoxyphenyl)-benzylidine-5-imidazolones (3f)

IR (KBr, $v_{max,}$ cm^{-1}): 3106 (aromatic =CH str.), 2949 (C-H str. of alkane) 1732 (C=O str. of imidazolone), 1698 (C=N str. of imidazolone), 1586 (aromatic C=C str.), 1390 (CH_3 str.), 1353 (C-N str.), 1225 (asymmetric C-O-C str. of ether linkage), 1126 (C-OCH_3 str.), 680 and 818 (C-H bending 1,3 and 1,4 disubstituted benzene ring); ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 2. 5 (s, 3H, C-C$\underline{H}_3$), 3.1 (s, 3H, N-C$\underline{H}_3$), 3.9 (s, 3H, OC$\underline{H}_3$), 6.0 (s, 1H, Ar-C$\underline{H}$=C), 6.9-7.8 (m, 12H, Ar-H).

1-[4'-(N-methyl-N-acetyl amino) phenyl]-2-phenyl-4-(4'-fluorophenyl)-benzylidine-5-imidazolones (3g)

IR (KBr, $v_{max,}$ cm^{-1}): 3156 (aromatic =CH str.), 3015 (C-H str. of alkane) 1726 (C=O str. of imidazolone), 1660 (C=N str. of imidazolone), 1543 (aromatic C=C str.), 1364 (CH_3 str.), 1338 (C-N str.), 1220 (asymmetric C-O-C str. of ether linkage), 1070 (C-F str.), 842 (C-H bending 1,4 disubstituted benzene ring); ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 1.7 (s, 3H, C-C$\underline{H}_3$), 2.4 (s, 3H, N-C$\underline{H}_3$), 6.8 (s, 1H, Ar-C$\underline{H}$=C), 7.2-8.0 (m, 12H, Ar-H).

1-[4'-(N-methyl-N-acetyl amino) phenyl]-2-phenyl-4-(4'-methylphenyl)-benzylidine-5-imidazolones (3h)

IR (KBr, $v_{max,}$ cm^{-1}): 3202 (aromatic =CH str.), 3026 (C-H str. of alkane) 1703 (C=O str. of imidazolone), 1692 (C=N str. of imidazolone), 1575 (aromatic C=C str.), 1398 (CH_3 str.), 1352 (C-N str.), 1248 (asymmetric C-O-C str. of ether linkage), 819 (C-H bending 1,4 disubstituted benzene ring); ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 1.5 (s, 3H, C-CH_3), 1.8 (s, 3H, CH_3), 2.9 (s, 3H, N-CH_3), 6.7 (s, 1H, Ar-CH=C), 6.8-7.5 (m, 12H, Ar-H).

1-[4'-(N-methyl-N-acetyl amino) phenyl]-2-phenyl-4-(4'-N-N-dimethylamino phenyl)-benzylidine-5-imidazolones (3i)

IR (KBr, $v_{max,}$ cm^{-1}): 3212 (aromatic =CH str.), 3026 (C-H str. of alkane) 1716 (C=O str. of imidazolone), 1688 (C=N str. of imidazolone), 1570 (aromatic C=C str.), 1401 (CH_3 str.), 1364 (C-N str.), 1250 (asymmetric C-O-C str. of ether linkage), 816 (C-H bending 1,4 disubstituted benzene ring); ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 1.4 (s, 3H, C-CH_3), 1.6 (s, 3H, CH_3), 1.9 (s, 3H, CH_3), 2.7 (s, 3H, N-CH_3), 5.9 (s, 1H, Ar-CH=C), 7.1-8.0 (m, 12H, Ar-H).

1-[4'-(N-methyl-N-acetyl amino) phenyl]-2-phenyl-4-(3'- methoxy, 4'-hydroxyphenyl)-benzylidine-5-imidazolones (3j)

IR (KBr, $v_{max,}$ cm^{-1}): 3013 (aromatic =CH str.), 2909 (C-H str. of alkane) 1706 (C=O str. of imidazolone), 1684 (C=N str. of imidazolone), 1572 (aromatic C=C str.), 1368 (CH_3 str.), 1332 (C-N str.), 1205 (asymmetric C-O-C str. of ether linkage), 1245 (C-OH str.), 669 and 808 (C-H bending 1,3 and 1,4 disubstituted benzene ring); ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 1.6 (s, 3H, C-CH_3), 3.7 (s, 3H, N-CH_3), 3.8 (s, 3H, OCH_3), 6.2 (s, 1H, OH), 6.7 (s, 1H, Ar-CH=C), 7.2-8.2 (m, 11H, Ar-H).

Table 1. The physical and analytical data of the synthesized compounds (4a-f) and (5a-f)

Compd	R	Molecular Formula	Yield (%)	M. P. ^{0}C	Elemental analysis Calculated (Found) %		
					C	H	N
3a	Phenyl	$C_{25}H_{21}N_3O_2$	79	219	75.94 (75.85)	5.35 (5.30)	10.63 (10.55)
3b	2-Chlorophenyl	$C_{25}H_{20}N_3O_2Cl$	81	Limpid	69.84 (69.80)	4.69 (4.75)	9.77 (9.70)
3c	2-Thienyl	$C_{23}H_{23}N_3O_2S$	68	238	68.14 (68.10)	5.71 (5.78)	10.37 (10.30)
3d	3-Chlorophenyl	$C_{25}H_{20}N_3O_2Cl$	75	108	69.84	4.69	9.77

					(69.82)	(4.64)	(9.74)
3e	3-Bromophenyl	$C_{25}H_{20}N_3O_2Br$	72	193	63.29 (63.20)	4.25 (4.21)	8.86 (8.78)
3f	3-Methoxyphenyl	$C_{26}H_{23}N_3O_3$	80	177	73.41 (73.32)	5.44 (5.40)	9.88 (9.80)
3g	4-Fluorophenyl	$C_{25}H_{20}N_3O_2F$	78	148	72.63 (72.55)	4.87 (4.81)	10.16 (10.10)
3h	4-Methylphenyl	$C_{26}H_{23}N_3O_2$	74	172	76.28 (76.20)	5.66 (5.70)	10.26 (10.15)
3i	4-N-N-dimethyl amino phenyl	$C_{27}H_{26}N_3O_3$	82	244	73.63 (73.55)	5.94 (5.90)	9.54 (9.45)
3j	3-Methoxy, 4-hydroxylphenyl	$C_{26}H_{23}N_3O_4$	65	122	70.74 (70.66)	5.25 (5.21)	9.52 (9.42)

Methodology for antibacterial activity

All the newly synthesized compounds were screened for their antimicrobial activity by applying cup-plate agar diffusion method[14] against Gram positive and Gram negative bacteria such as *Staphylococcus aureus* [MTCC-96], *Bacillus subtilis* [MTCC-441], *Escherichia coli* [MTCC-443] and *Salmonella paratyphi-A* [MTCC-735]. The compounds were tested at 40 µg/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 (40 µg/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 37^0C 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 1)**. The standard known antibiotics like Chloramphenicol and Streptomycin were used.

Methodology for antifungal activity

The antifungal activity of the all the synthesized compounds were 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 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

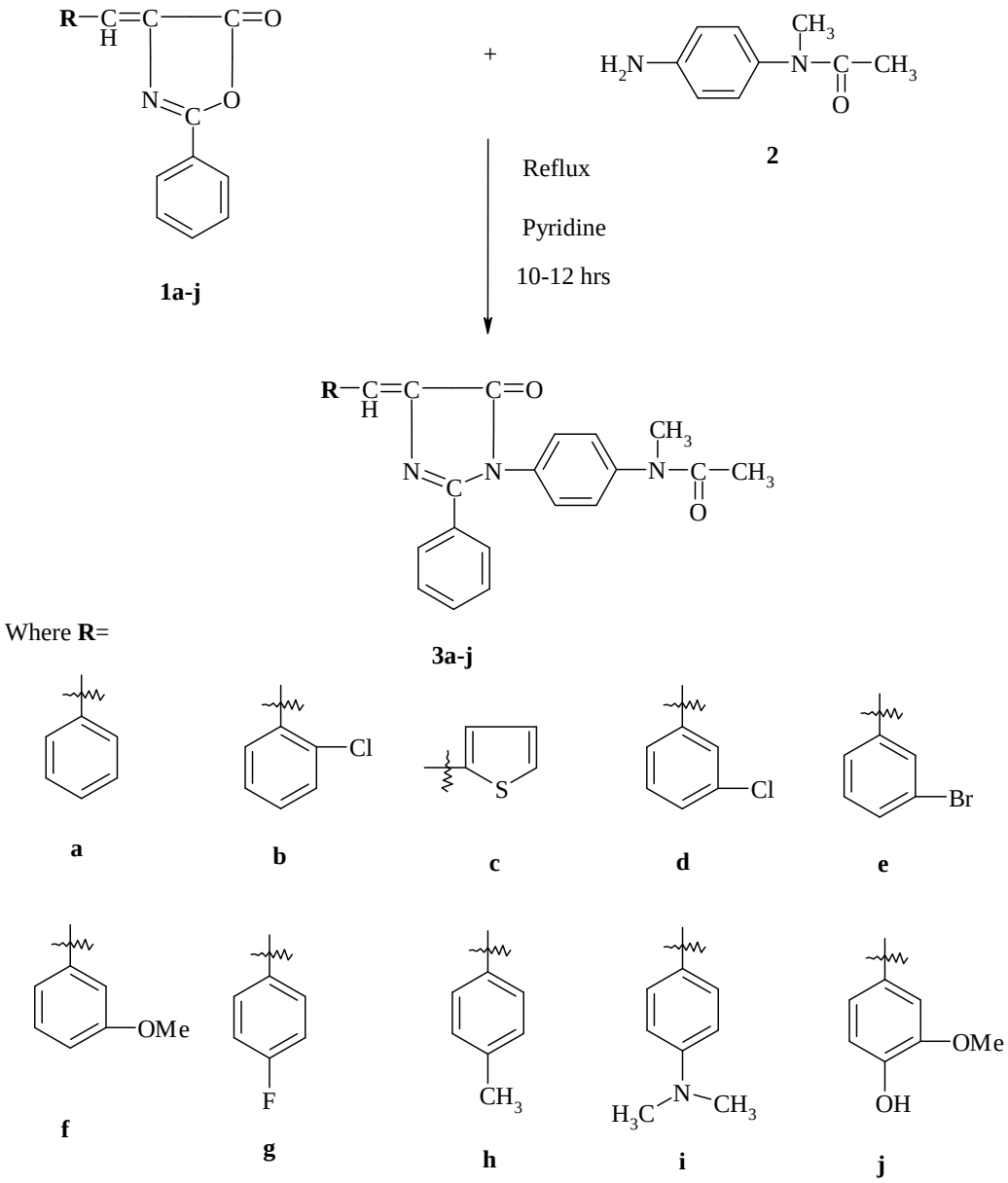
slide, four drops being in a staged position. Each drop is approximately 0.05 ml on a plain glass, such a drop would spread to a diameter of about 10 mm. For both spore production in test fungus cultures and for germination, the temperature is kept between 20-25^{o}C. Spores are examined 20-24 hrs. The standard known antifungal drug Griseofulvin was used.

RESULT AND DISCUSSION

Chemistry

1-[4'-(N-methyl-N-acetylamino)phenyl]-2'-phenyl-4-arylidine-5-imidazolones as promising molecular target to develop novel antimicrobial agents have been achieved from oxazolones as described in **scheme 1**. The structures of all the newly synthesized compounds were elucidated with ^{1}H-NMR, FT-IR and elemental analyses. The spectral data of the isolated product were in complete agreement with the assigned structure. For example, the IR spectrum of compound **3a** showed a sharp absorption band at 1700 cm^{-1} for C=O group along with a band at 1655 cm^{-1} for C=N stretching of 5-imidazolone ring. A broad stretching band for the C-N functionality and CH_3 group of 4-amino-N-methyl acetanilide ring is observed at 1382 cm^{-1} and 1390 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 1250, 815 and 2920 cm^{-1} respectively.

The ^{1}H NMR spectrum of compound **3a** exerting a signal as multiplet at δ 6.2 ppm and 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. Moreover, the obtained elemental analysis values are also in good agreement with their theoretical data.



Scheme 1. Systematic path to synthesize design compounds 3a-j

Evaluation of antimicrobial activity

The antibacterial activity of all the synthesized compounds were tested *in-vitro* against pathogenic *Staphylococcus aureus [MTCC-96]*, *Bacillus subtilis [MTCC-441]*, *Escherichia coli [MTCC-443] Salmonella paratyphi-A [MTCC-735]*. The obtained scrineening results were compared with standard drugs (Chloramphenicol and Streptomycin) and tabulated in **Table 2**. In case of Gram positive bacteria, compounds **3c** (8 mm), **3b** and **3h** (9 mm), **3j** (10 mm), **3e** and **3i** (12 mm) displayed an significant zone of diameter whereas compounds **3a**, **3d**, **3f** and **3g** exerted no zone of diameter against *Staphylococcus aureus* as compared to Chloramphenicol and Streptomycin. Against *Bacillus subtilis*, compounds **3b** (9 mm) and **3h** (10 mm) found to posses promising activity while the remaining compounds **3a**, **3c**, **3d**, **3e**,

3f, **3g**, **3i** and **3j** found to posses poor activity as compared to standard antibiotics Chloramphenicol and Streptomycin. In the case of Gram negative bacteria, compounds **3j** (9 mm), **3e**, **3f**, and **3g** (11 mm), **3a**, **3b**, **3c**, **3d** and **3h** (12 mm) exerted appreciable activity whereas the compound **3i** exerted moderate activity as compared to Chloramphenicol and Streptomycin. Against *Salmonella paratyphi-A* only one compound **3h** (9 mm) showed a zone of diameter while the remaining compounds did not showed 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 *Furasium solani*. Griseofulvin was used as standard antifungal drug. Scrutinize the data of antifungal activity reveals that compounds **3b** (50), **3i** (54) and **3e** (61) found good inhibition as compared to Griseofulvin while other compounds showed good to mild inhibition.

Table 2. *In Vitro* antimicrobial activity of synthesized compounds 3a-j

Compd	Anti bacterial activity (Diameter of zone inhibition at 40 µg/ml)				Anti Fungal activity % Inhibition
	Gram positive		Gram negative		
	S. aureus **MTCC 96**	***B. subtilis*** **MTCC 441**	***E. coli*** **MTCC 443**	***S. paratyphi-A*** **MTCC 735**	***F. solani*** **MTCC 350**
3a	-	-	12	-	20
3b	9	9	12	-	50
3c	8	-	12	-	25
3d	-	-	12	-	42
3e	12	-	11	-	61
3f	-	-	11	-	25
3g	-	-	11	-	44
3h	9	10	12	9	33
3i	12	-	-	-	54
3j	10	-	9	-	26

CONCLUSION

In the present study, an easy and useful method to synthesize pharmacologically active 5-imidazolone derivatives as an expected pharmacophore has been presented. *In vitro* antibacterial and antifungal ability of these compounds were evaluated. Compounds **3b**, **3c**, **3e**, **3h** and **3j** were the best bioactive desired antimicrobial agents and most proficient member of the series. Moreover, from the antimicrobial screening result it is clear that most of the prepared compounds showed improved activity against the Gram-negative bacteria rather than Gram-positive bacteria. Further biochemical and pharmacological studies are undergoing to optimize their pharmacological profile.

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