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Microwave assisted synthesis and *in vitro* evaluation of some new imidazolin-5-one derivatives

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Abstract
Microwave assisted imidazolin-5-one derivatives have been synthesised at laboratory scale by oxazole condensation followed by reaction with amino N-heterocyclics. The compounds structures were characterized by IR, H^1 NMR and C^{13} NMR. All the compounds have been evaluated for *in-vitro* antimicrobial and antioxidant activity and were compared with their corresponding standards. Of all the synthesised derivatives compounds **5a**, **5b** exhibited good antimicrobial properties.

Keywords: Oxazole, Imidazolin-5-one, amino N-heterocyclics, antimicrobial and antioxidant activity.

1. Introduction
Imidazoline derivatives are of great interest and importance because of their pharmaceutical and synthetic material applications. They exhibit significant biological and pharmacological activities such as antihyperglycemic [1], antidepressive [2], antihypercholesterolemic [3] and anti-inflammatory [4] and antihypertensive [5].These compounds are also used as catalysts [6], synthetic intermediates [7]. Chiral auxiliaries [8], chiral catalysts [9] and ligands for asymmetric catalysis [10]. There are several methods for the synthesis of 2-imidazolines from carboxylic acids [11], esters [12], nitriles [13], orthoesters [14], hydroximoylchlorides [15], hydroxy amides [16], mono- or disubstituted (chlorodicyanovinyl) benzene [17], and N-tert-butoxycarbonyl-protected α-amino acids [18]. However, some of these methods have disadvantages such as long reaction times, low yields, difficulty in preparation of starting materials and tedious workup, due to which, there is still scope to find new methods for the synthesis of imidazolines.
Recently, the organic reactions under microwave irradiation attracted attention of scientists due to their high reaction rate, mild reaction conditions and the formation of clean products [19]. Microwave-assisted reactions are well known to promote the synthesis of a variety of organic compounds, where chemical reactions are accelerated because of selective absorption of microwave by polar molecule [20]. As a part of our programme towards the nontraditional approach to the experimental setup of organic reactions, the concept of "Microwave induced Organic Reaction Enhancement" (MORE) chemistry has been utilized for rapid, sustainable and efficient synthesis. Microwave assisted organic synthesis [21-23] has attracted attention in recent years because of its association with enhanced reaction rates, higher yields, improved purity, and eco-friendly reaction conditions when compared to the conventional methods.
In this work, we report an efficient method of synthesis of imidazoline derivatives by microwave irradiation and their *in-vitro* evaluation due to high pharmacological importance.

2. Materials and Methods
Melting points were determined in open glass capillaries using GallenKamp (MFB-600) melting point apparatus and were uncorrected. IR spectra (KBr discs) Bruker analyzers were confirmed by Shimadzu FT-IR Spectrophotometer using KBr pellets technique, Model No.8400S (Japan). 1H NMR spectra were recorded on Bruker 300 MHz NMR spectrometer (Switzerland) using CDCl3 as solvent. T.L.C. was run on silica gel G plates using ethyl acetate: pet. Ether (10:1) as developing solvent for the purity of the compounds. All other chemicals used in the present studies were either of A.R or G.R quality.

2.1. Drugs and Chemicals
Hippuric acid – (LOBA-B.NO-G228507), Acetic anhydride – (FISHER'S SCIENTIFIC-B.NO-92757004-2), Sodium Acetate – (FINAR-B.NO-19095780), 2-Amino Pyrimidine – (SIGMA ALDRICH-B.NO-STBCOO82V), 4-Amino pyridine – (SD FINE-CHEMLIMITED-

K12A/0112/1904/13), Methanol (SD FINE-CHEMLIMITED- B.NO-IOZA-0502-0409-13), Glacial acetic acid – (LOBA-B.NO-LL13871205), Charcoal – (QUALINGENS-BNO-17335406-S), Ethanol – (CSS-B.NO-110605), N,N-Dimethylformamide (DMF) – (LOBA-B.NO-LIO1571306).

3. Chemical Synthesis

Step 1: Synthesis of 4-benzylidene-2-phenyloxazol-5(4H)-one (1-7)

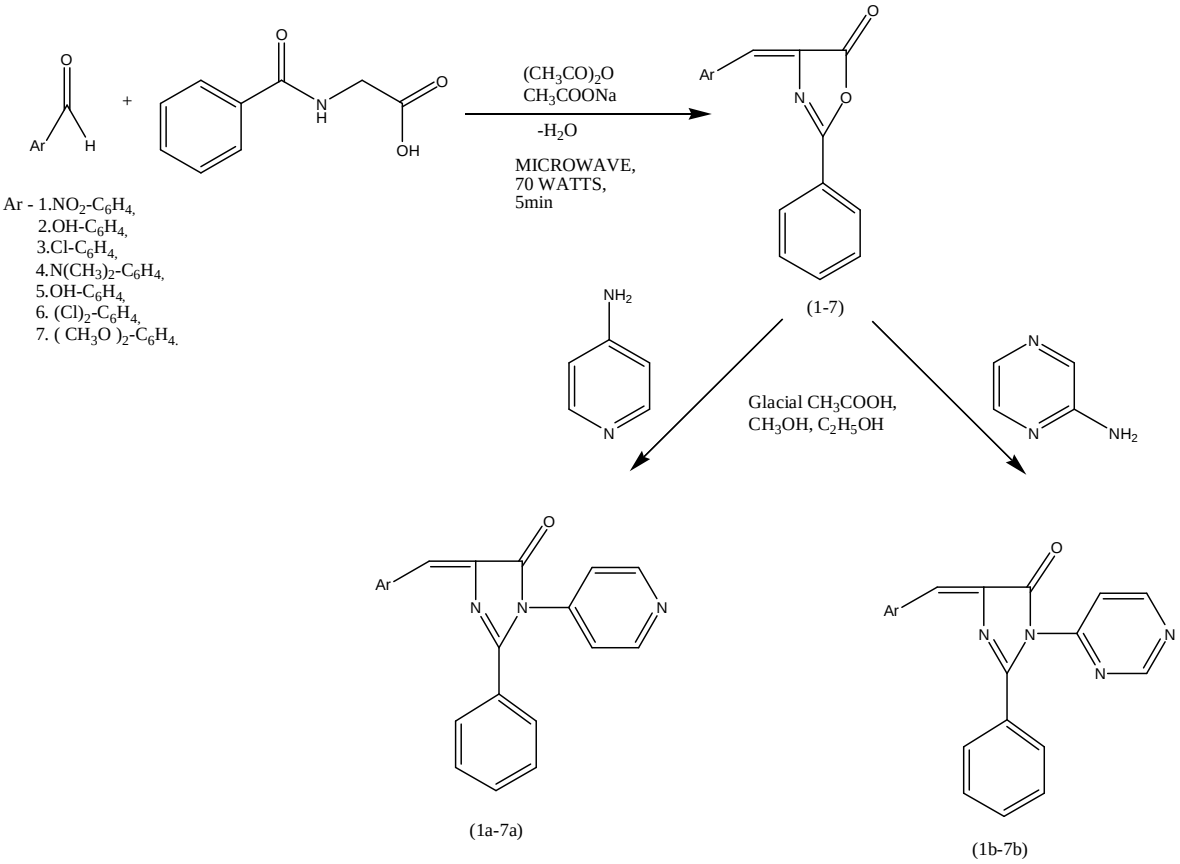
Oxazolin-5-ones were prepared by condensation of 0.01 moles of Hippuric Acid with 0.02 moles of different types of aromatic aldehydes in the presence of 0.075 moles of Acetic Acid and 0.025 moles of Sodium Acetate .To this 2 ml of water was added and the reaction was proceeding in a microwave for 5minutes at 70 watts. The reaction mixture was cooled, the precipitate was filtered, dried, recrystallized from methanol and confirmed by thin layer chromatography and melting point.

Step2: 4-benzylidene-2-phenyl-1-(pyridin-4-yl)-1H-imidazol-5(4H)-one (1a-7a and 1b-7b)

Imidazolin-5-one derivatives were synthesised by amination of equimolar (0.001moles) of step 1 with various amino heterocyclics in presence of ethanol and a few drops of Glacial acetic acid. The reaction mixture was heated, cooled; the product formed was filtered, dried, recrystallized from methanol and conformed by thin layer chromatography and melting point. The procedure was illustrated under Scheme 1 and the physical data were tabulated in Table 1

Table 1: Physical Data

Code	Compound	M.F	M.W	MP(^{0}c)	%Yield	C%	H%	O%	N%	Cl%
1a	4-(4-nitrobenzylidene)-2-phenyl-1-(pyridin-4-yl)-1H-imidazol-5(4H)-one	$C_{21}H_{14}O_3N_4$	370	226	63	68.12	3.78	12.97	15.13	-
2a	4-(4-hydroxybenzylidene)-2-phenyl-1-(pyridin-4-yl)-1H-imidazol-5(4H)-one	$C_{21}H_{15}O_2N_3$	341	253	65	73.92	4.39	9.38	12.31	-
3a	4-(4-chlorobenzylidene)-2-phenyl-1-(pyridin-4-yl)-1H-imidazol-5(4H)-one	$C_{21}H_{14}$ ON_3Cl	359.5	212	66	70.09	3.89	4.45	11.68	12.57
4a	4(4(dimethylamino)benzylidene)-2-phenyl-1-(pyridin-4-yl)-1H-imidazol-5(4H)-one	$C_{23}H_{20}ON_4$	368	211	60	75.2	5.43	4.34	15.21	-
5a	4-(2-hydroxybenzylidene)-2-phenyl-1-(pyridin-4-yl)-1H-imidazol-5(4H)-one	$C_{21}H_{15}O_2N_3$	341	239	65	73.92	4.39	9.38	12.31	-
6a	4-(2,4-dichlorobenzylidene)-2-phenyl-1-(pyridin-4-yl)-1H-imidazol-5(4H)-one	$C_{21}H_{13}ON_3Cl_2$	394	224	60	63.95	3.29	4.09	10.65	18.02
7a	4-(3,4dimethoxybenzylidene)-2-phenyl-1-(pyridin-4-yl)-1H-imidazol-5(4H)-one	$C_{23}H_{19}O_3N_3$	385	196	61	71.68	4.96	12.46	10.90	-
1b	4-(4-nitrobenzylidene)-2-phenyl-1-(pyrimidin-4-yl)-1H-imidazol-5(4H)-one	$C_{20}H_{13}O_3N_5$	371	251	62	64.69	3.52	12.93	18.86	-
2b	4-(4-hydroxybenzylidene)-2-phenyl-1-(pyrimidin-4-yl)-1H-imidazol-5(4H)-one	$C_{20}H_{14}O_2N_4$	342	246	63	70.17	4.09	9.35	16.39	-
3b	4-(4-chlorobenzylidene)-2-phenyl-1-(pyrimidin-4-yl)-1H-imidazol-5(4H)-one	$C_{20}H_{13}ON_4Cl$	358.5	220	67	66.94	3.62	4.46	15.62	9.90
4b	4(4(dimethylamino)benzylidene)-2-phenyl-1-(pyrimidin-4-yl)-1H-imidazol-5(4H)-one	$C_{22}H_{19}ON_5$	369	218	61	71.54	5.16	4.33	18.97	-
5b	4-(2-hydroxybenzylidene)-2-phenyl-1-(pyrimidin-4-yl)-1H-imidazol-5(4H)-one	$C_{20}H_{14}O_2N_4$	342	240	63	70.17	4.09	9.35	16.39	-
6b	4-(2,4-dichlorobenzylidene)-2-phenyl-1-(pyrimidin-4-yl)-1H-imidazol-5(4H)-one	$C_{20}H_{12}ON_4Cl_2$	395	227	61	60.75	3.03	4.25	4.25	14.37
7b	4-(3,4dimethoxybenzylidene)-2-phenyl-1-(pyrimidin-4-yl)-1H-imidazol-5(4H)-one	$C_{22}H_{18}O_3N_4$	386	215	60	68.3	4.62	12.4	14.50	-



Scheme 1

Compound 1a: 4-(4-nitrobenzylidene)-2-phenyl-1-(pyridin-4-yl)-1H-imidazol-5(4H)-one: Yield 63 %, mp. 226 °C; FTIR (γ max, cm^{-1}) 1464(-C=C stretch), 3036(=C-H stretch),746(=C-H bend),1684(-C=O), 1646(-C=N),1305(-C-N), 1510(Asymmetric stretch -NO_2),1338(Symmetric stretch r-NO_2); ^{1}H NMR(400MHZ,$CDCl_3$): ***δ*** 4.195,4.325 (s, 1H, -C**H**=C), ***δ*** 6.196-7.724 (m, 5H**,** ***J*** 2.02, Ar-**H**), ***δ*** 8.245-9.620 (q, 1H, ***J*** 3.03, **H**C=N); ^{13}C NMR (400MHZ,$CDCl_3$): ***δ*** 113.40,114.24,115.23,117.16,127.91,123.96,121.74,132.54,130.61,155.02,157.02,164.09 (Ar-**C**), ***δ*** 115.42, 113.94 (C=**C**), ***δ*** 166.55 (O= **C**-N), ***δ*** 150.01 (**C**=N), ***δ*** 70.8 (Ar-NO_2-**C**).

Compound 2a: 4-(4-hydroxybenzylidene)-2-phenyl-1-(pyridin-4-yl)-1H-imidazol-5(4H)-one
Yield 65 %, mp. 253 °C; FTIR (γ max, cm^{-1}) 1458(-C=C stretch), 3033(=C-H stretch), 852(=C-H bend), 1649(-C=O), 1540(-C=N), 1209(-C-N), 3743(O-H stretch); ^{1}H NMR (400MHZ,$CDCl_3$) : ***δ*** 1.254,1.580 (s, 1H, -C**H**=C), ***δ*** 7.261-7.943 (m, 5H**,** ***J*** 5.10 , Ar-**H**), ***δ*** 8.8(d, 1H, ***J*** 2.02, **H**C=N), ***δ*** 9.3(d, 1H, ***J*** 2,O-**H**); ^{13}C NMR (400MHZ,$CDCl_3$): ***δ*** 123.39, 124.24, 125.22, 127.91, 127.91, 128.96, 129.73, 132.54, 133.62, 150.01, 159.01, 166.08 (Ar-**C**), ***δ*** 116.41, 119.94 (C=**C**), ***δ*** 161.91 (O= **C**-N), ***δ*** 150.02 (**C**=N), ***δ*** 159.01 (Ar-OH-**C**).

Compound 3a: 4-(4-chlorobenzylidene)-2-phenyl-1-(pyridin-4-yl)-1H-imidazol-5(4H)-one
Yield 66 %, mp. 212 °C; FTIR (γ max, cm^{-1}) 1458(-C=C stretch),3033 (=C-H stretch),898(=C-H bend),1649(-C=O),1540 (-C=N), 1230(-C-N), 775(C-Cl) ; ^{1}H NMR (400MHZ,$CDCl_3$): ***δ*** 2.33,3.4 (s, 1H, -C**H**=C), ***δ*** 6.161-8.124 (m, 5H**,** ***J*** 4.02, Ar-**H**), ***δ*** 9.641,9.214 (d, 1H, ***J*** 1.03, **H**C=N); ^{13}C NMR (400MHZ,$CDCl_3$): ***δ*** 121.20, 123.34, 124.23, 126.26, 137.91,
122.76, 123.64, 131.54, 138.61, 160.02, 158.09, 166.08 (Ar-**C**), ***δ*** 111.52,118.94 (C=**C**), ***δ*** 164.95 (O= **C**-N), ***δ*** 157.04 (**C**=N), ***δ*** 70.95 (**C**-Cl).

Compound 4a: 4-(4-(dimethylamino)benzylidene)-2-phenyl-1-(pyridin-4-yl)-1H-imidazol-5(4H)-one: Yield 60%, mp. 211 °C; FTIR (γ max, cm^{-1}) 1458(-C=C stretch), 3033(=C-H stretch), 846(=C-H bend), 1648(-C=O), 1517(-C=N), 1159(-C-N); ^{1}H NMR (400MHZ,$CDCl_3$): ***δ*** 3.111 (s, 3H, -CH_3), ***δ*** 1.255,1.563 (s, 1H, -C**H**=C), ***δ*** 6.740-7.574 (m, 5H**,** ***J*** 1.02, Ar-**H**), ***δ*** 8.137-8.159 (d, 1H, ***J*** 2.03, **H**C=N); ^{13}C NMR (400MHZ,$CDCl_3$): ***δ*** 127.81, 128.78, 132.28, 133.32, 134.85 (Ar-**C**), ***δ*** 111.82 (C=**C**), ***δ*** 164.21 (O= **C**-N), ***δ*** 151.23 (**C**=N), ***δ*** 40.03 (**C**-N).

Compound 5a: 4-(2-hydroxybenzylidene)-2-phenyl-1-(pyridin-4-yl)-1H-imidazol-5(4H)-one
Yield 65%, mp. 239 °C; FTIR (γ max, cm^{-1}) 1457(-C=C stretch), 3032(=C-H stretch), 851 (=C-H bend), 1650 (-C=O), 1519(-C=N), 1246(-C-N),3742 (O-H stretch); ^{1}H NMR (400MHZ,$CDCl_3$) : ***δ*** 1.254,1.580 (s, 1H, -C**H**=C), ***δ*** 7.261-7.943 (m, 5H**,** ***J*** 5.10 , Ar-**H**), ***δ*** 8.8(d, 1H, ***J*** 2.02, **H**C=N), ***δ*** 9.3(d, 1H, ***J*** 2,O-**H**); ^{13}C NMR (400MHZ,$CDCl_3$): ***δ*** 123.39, 124.24, 125.22, 127.91, 127.91, 128.96, 129.73, 132.54, 133.62, 150.01, 159.01, 166.08 (Ar-**C**), ***δ*** 116.41, 119.94 (C=**C**), ***δ*** 161.91 (O= **C**-N), ***δ*** 150.02 (**C**=N), ***δ*** 159.01 (Ar-

OH-**C**).

Compound 6a: 4-(2,4-dichlorobenzylidene)-2-phenyl-1-(pyridin-4-yl)-1H-imidazol-5(4H)-one: Yield 60 %, mp. 224 °C; FTIR (γ max, cm-1) 1574(-C=C stretch),3099 (=C-H stretch), 851(=C-H bend), 1644(-C=O), 1535(-C=N),1323(-C-N), 756(C-Cl); ^{1}H NMR (400MHZ,$CDCl_3$): ***δ*** 4.188,4.220(s, 1H, -C**H**=C), ***δ*** 6.781-7.217 (m, 5H**,** ***J*** 5.02, Ar-**H**), ***δ***8.117-9.540 (q, 1H, ***J*** 6.03, **H**C=N); ^{13}C NMR (400MHZ,$CDCl_3$): ***δ*** 113.40, 114.24, 123.23, 122.16, 127.91, 128.96, 119.74, 132.54, 233.61, 150.02,119.02, 165.09 (Ar-**C**), ***δ*** 126.42,129.94 (C=**C**), ***δ*** 164.59(O= **C**-N), ***δ*** 159.02 (**C**=N), ***δ*** 69.59 (Ar-**C**-Cl).

Compound 7a: 4-(3,4dimethoxybenzylidene)-2-phenyl-1-(pyridin-4-yl)-1H-imidazol-5(4H)-one: Yield 65%, mp. 239 °C; FTIR (γ max, cm-1) 1541(-C=C stretch), 3062(=C-H stretch),852(=C-H bend),1646(-C=O), 1510(-C=N), 1331(-C-N), 1148(C-O); ^{1}H NMR (400MHZ,$CDCl_3$): ***δ*** 3.094,3.154 (d, 3H, -C**H**$_3$), ***δ*** 4.298,4.450 (s, 1H, -C**H**=C), ***δ*** 6.635-7.907 (m, 5H**,** ***J*** 4.16, Ar-**H**), ***δ*** 8.125-9.745 (q, 1H, ***J*** 2.61, **H**C=N); ^{13}C NMR (400MHZ,$CDCl_3$): ***δ*** 143.41, 164.22,125.13,127.10,128.91,127.94,129.44,138.54,123.61,150.02,159.02,136.09 (Ar-**C**), ***δ*** 126.12,159.34 (C=**C**), ***δ*** 169.55 (O= **C**-N), ***δ*** 155.09 (**C**=N), ***δ*** 65.99 (O-**C**).

Compound 1b: 4-(4-nitrobenzylidene)-2-phenyl-1-(pyridimin-4-yl)-1H-imidazol-5(4H)-one
Yield 61%, mp. 196 °C; FTIR (γ max, cm^{-1}) 1460(-C=C stretch), 3031(=C-H stretch),845(=C-H bend),1684(-C=O), 1513(-C=N),1255(-C-N), 1540(Asymmetric stretch-NO_2),1340(Symmetric stretch- NO_2); ^{1}H NMR (400MHZ,$CDCl_3$)***:*** ***δ*** 4.298,4.310 (s, 1H, -C**H**=C), ***δ*** 6.694-7.834 (m, 5H**,** ***J*** 5.02, Ar-**H**), ***δ*** 8.127-9.740 (q, 1H, ***J*** 9.03, **H**C=N). ^{13}C NMR (400MHZ,$CDCl_3$): ***δ*** 125.45, 144.24,122.13,128.17,137.41,129.76,129.74,132.54,133.61,150.02,159.02,166.09 (Ar-**C**), ***δ*** 115.52,118.93 (C=**C**), ***δ*** 161.05 (O= **C**-N), ***δ*** 140.02 (**C**=N), ***δ*** 70.8 (Ar-NO_2-**C**).

Compound 2b: 4-(4-hydroxybenzylidene)-2-phenyl-1-(pyrimidin-4-yl)-1H-imidazol-5(4H)-one: Yield 63%, mp. 246 °C; FTIR (γ max, cm^{-1}) 1459 (-C=C stretch), 3032(=C-H stretch), 849(=C-H bend), 1649(-C=O), 1540(-C=N), 1338(-C-N), 3742(O-H stretch); ^{1}H NMR (400MHZ,$CDCl_3$): ***δ*** 1.566 (s, 1H, -C**H**=C), ***δ*** 7.261-7.943 (m, 5H**,** ***J*** 4.14 , Ar-**H**), ***δ*** 8.8(d, 1H, ***J*** 2, **H**C=N), ***δ*** 9.3(d, 1H, ***J*** 1.01,O-**H**); ^{13}C NMR (400MHZ,$CDCl_3$): ***δ*** 123.40, 124.24, 125.23, 127.91, 128.52, 128.96, 129.74, 132.54, 133.61 (Ar-**C**), ***δ*** 116.41, 119.94 (C=**C**), ***δ*** 161.95 (O= **C**-N), ***δ*** 150.01 (**C**=N), ***δ*** 159.01 (Ar-OH-**C**).

Compound 3b: 4-(4-chlorobenzylidene)-2-phenyl-1-(pyrimidin-4-yl)-1H-imidazol-5(4H)-one Yield 67 %, mp. 220 °C; FTIR (γ max, cm^{-1}) 1458(-C=C stretch), 3032(=C-H stretch), 871(=C-H bend), 1649(-C=O), 1540 (-C=N), 1339(-C-N), 776(C-Cl) ; ^{1}H NMR (400MHZ,$CDCl_3$): ***δ*** 1.254,1.580 (s, 1H, -C**H**=C), ***δ*** 7.261-7.943 (m, 5H**,** ***J*** 1.52, Ar-**H**), ***δ*** 8.853,8.876 (d, 1H, ***J*** 2.93, **H**C=N); ^{13}C NMR (400MHZ,$CDCl_3$): ***δ*** 123.40, 124.24, 125.23, 127.16, 127.91,128.96,129.74,132.54,133.61,150.02,159.02,166.09 (Ar-**C**), ***δ*** 116.42,119.94 (C=**C**), ***δ*** 165.90 (O= **C**-N), ***δ*** 150.02 (**C**=N), ***δ*** 75.95 (**C**-Cl).

Compound 4b: 4-(4-(dimethylamino)benzylidene)-2-phenyl-1-(pyrimidin-4-yl)-1H-imidazol-5(4H)-one: Yield 61 %, mp. 218 °C; FTIR (γ max, cm^{-1}) 1457(-C=C stretch), 3032(=C-H stretch),891(=C-H bend), 1648(-C=O), 1519(-C=N), 1288(-C-N); ^{1}H NMR (400MHZ,$CDCl_3$): ***δ*** 3.109(s, 3H, -C**H**$_3$) ***δ*** 1.255,1.563 (s, 1H, -C**H**=C), ***δ*** 6.739-7.573(m, 5H**,** ***J*** 3.10, Ar-**H**), ***δ*** 8.132-8.158 (d, 1H, ***J*** 4.02, **H**C=N); ^{13}C NMR (400MHZ,$CDCl_3$): ***δ*** 121.90, 126.48, 127.83, 128.48, 128.80, 132.29, 133.34, 134.87, 152.34, (Ar-**C**), ***δ*** 111.84 (C=**C**), ***δ*** 166.34 (O= **C**-N), ***δ*** 152.34 (**C**=N), ***δ*** 40.05 (**C**-N).

Compound 5b: 4-(2-hydroxybenzylidene)-2-phenyl-1-(pyrimidin-4-yl)-1H-imidazol-5(4H)-one: Yield 63%, mp. 240 °C; FTIR (γ max, cm^{-1}) 1456 (-C=C stretch), 3205(=C-H stretch), 854(=C-H bend), 1651(-C=O), 1522(-C=N), 1352(-C-N), 3742 (O-H stretch); ^{1}H NMR (400MHZ,$CDCl_3$): ***δ*** 1.566 (s, 1H, -C**H**=C), ***δ*** 7.261-7.943 (m, 5H**,** ***J*** 4.14 , Ar-**H**), ***δ*** 8.8(d, 1H, ***J*** 2, **H**C=N), ***δ*** 9.3(d, 1H, ***J*** 1.01,O-**H**); ^{13}C NMR (400MHZ,$CDCl_3$): ***δ*** 123.40, 124.24, 125.23, 127.91, 128.52, 128.96, 129.74, 132.54, 133.61 (Ar-**C**), ***δ*** 116.41, 119.94 (C=**C**), ***δ*** 161.95 (O= **C**-N), ***δ*** 150.01 (**C**=N), ***δ*** 159.01 (Ar-OH-**C**).

Compound 6b: 4-(2,4-dichlorobenzylidene)-2-phenyl-1-(pyrimidin-4-yl)-1H-imidazol-5(4H)-one: Yield 61 %, mp. 227 °C; FTIR (γ max, cm-1) 1574(-C=C stretch), 3065 (=C-H stretch), 854(=C-H bend), 1646(-C=O), 1542(-C=N), 1324(C-N),757(C-Cl); ^{1}H NMR (400MHZ,$CDCl_3$): ***δ*** 1.275,1.663 (s, 1H, -C**H**=C), ***δ*** 6.739-7.573 (m, 5H**,** ***J*** 9.52, Ar-**H**), ***δ*** 8.102-9.158 (a, 1H, ***J*** 5.93, **H**C=N); ^{13}C NMR (400MHZ,$CDCl_3$): ***δ*** 103.40, 114.24, 125.23, 107.16, 117.91, 118.96, 119.74, 132.54,123.61,110.02,159.02,166.09 (Ar-**C**), ***δ*** 115.22,109.94 (C=**C**), ***δ*** 160.90 (O= **C**-N), ***δ*** 169.05 (**C**=N), ***δ*** 65.99 (Ar-**C**-Cl).

Compound 7b:4-(3,4dimethoxybenzylidene)-2-phenyl-1-(pyrimidin-4-yl)-1H-imidazol-5(4H)-one: yield 60%, mp. 215 °C; FTIR (γ max, cm-1) 1457(-C=C stretch), 3059(=C-H stretch), 861(=C-H bend), 1646(-C=O), 1510(-C=N), 1329(-C-N), 1138(C-O); ^{1}HNMR(400MHZ,$CDCl_3$): ***δ*** 3.534 (s, 3H, -C**H**$_3$), ***δ*** 1.955,1.963 (s, 1H, -C**H**=C), ***δ*** 6.739-7.573 (m, 5H**,** ***J*** 1.02, Ar-**H**), ***δ*** 8.112-9.298 (d, 1H, ***J*** 2.03, **H**C=N); ^{13}C NMR (400MHZ,$CDCl_3$): ***δ***125.31,126.45,127.12,127.80,128.66,128.78,132.00,132.27,133.33,134.85 (Ar-**C**), ***δ*** 111.05,111.82 (C=**C**), ***δ*** 162.68 (O= **C**-N), ***δ*** 154.43 (**C**=N), ***δ*** 69.59 (O-**C**).

4. Experiments

4.1. Ferric reducing antioxidant power (FRAP Assay) [24]:

In ferric reducing antioxidant power assay,1ml of a test sample of DMF(N,N-Dimethylformamide) extract in different concentrations were mixed with 1 ml of 0.2M sodium phosphate buffer (p^H-6.6) and 1 ml of 1% potassium ferricyanide (FINAR- B.NO-18042046) in separate test tubes. The reaction mixtures were incubated at a temperature-controlled water bath at 50 ^{0}C for 20 min followed by addition of 1 ml of 10% trichloroacetic acid (MERCK- B.NO-MD9M590220). The mixtures were then centrifuged for 10 min at room temperature. To the supernatant 1ml of deionized water 200 µl of 0.1%$FeCl_3$ (LOBA-B.NO-SL26831111) was added. The blank was prepared in the same manner as the samples except that 1% potassium ferricyanide was replaced with distilled water. The absorbance of the reaction mixture was measured at 700 nm. The reducing power was expressed as an increase in A_{700} after blank subtraction [25].

Standard drug: Ascorbic acid (LOBA- B.NO-SL44911205) was taken as a reference standard and the concentration of the standard drugs were prepared by making the concentration of 2, 4, 6, 8, 10 µg/ml with DMF. The results were tabulated in Table 2

Table 2: Ic_{50} Values

Compound	Ic_{50}	% Inhibition
1a	7.91	10.30
2a	5.77	29.049
3a	6.53	19.877
4a	5.77	29.202
5a	5.59	31.411
6a	6.99	14.233
7a	5.62	31.042
1b	7.37	9.57
2b	6.19	24.049
3b	6.01	26.258
4b	5.83	28.466
5b	5.25	35.58
6b	6.51	24.54
7b	6.22	23.681
Ascorbic acid	**8.15**	**100**

4.2. Antibacterial activity [26]

All the synthesized compounds **1a-7a** and **1b-7b** to be examined for antibacterial activity were evaluated *in vitro* against an assortment of two gram-positive bacteria *Staphylococcus aureus NCIM 2901* and *Bacillus subtilis MTCC 441* and two Gram-negative bacteria *Escherichia coli NCIM 2563* and *Proteus vulgaris MTCC 1771* by two fold serial broth dilution method. Tetracycline and Chloramphenicol were used as an internal standard. The medium used to be double strength nutrient broth. This method depends upon the inhibition of growth of a microbial culture in a uniform solution of the antibiotic in a liquid medium that is favorable to its rapid growth in the absence of the antibiotic. Minimum Inhibitory Concentration (MIC) of the synthesized compounds was determined. MIC was defined as the lowest concentration of the tested compound able to inhibit visible growth of the microorganism after 24 hr of incubation at 37 °C. Controls with DMF and uninoculated media were run parallel to the tested compounds under the same conditions. Each experiment was repeated thrice and the average of the three independent determinations was recorded. Screening results were summarized in Table 3.

4.3. Antifungal activity

The antifungal activity of compounds was assayed against four different strains of *Saccharomyces cerevisiae MTCC 1766, Aspergillus niger MTCC 282, Penicillium chrysogenum MTCC 5108 and Penicillium notatum NCIM 742.* Potato dextrose agar[27] (Hi- media) was dissolved and distributed in 25 ml quantities in 100ml conical flasks and were sterilized in an autoclave at 121 ^{0}C (15lbs/sq.in) for 20 minutes. The medium was inoculated at one percent level using 18hr old cultures of organisms mentioned above aseptically in to sterile petridish and allowed to set at room temperature for about 30 minutes. . At a size of 4 inches petridish 5 cups of 8mm diameter at equal distance were made in a Petri plate with a sterile borer. The solutions of test and standard at concentrations (250µg/ml, 200µg/ml, 150µg/ml, and 100µg/ml) were added to respective cup aseptically and labeled accordingly. DMF as control did not show any inhibition. The plates were left for 90 minutes in refrigerator for diffusion. After incubation for 24 hrs at $37^0 \pm 1^0$ c. The plates were examined for incubation inhibition zones. The experiments were performed in duplicate and the average diameters of the zones of inhibition were summarized in Table 4.

Table 3: Minimum Inhibitory Concentration

	MIC (µg/ml)			
Compound	**Staphylococcus Aureus**	**Bacillus Subtilis**	**Proteus Vulgaris**	**E. Coli**
1a	50	45	40	45
2a	25	20	30	35
3a	50	45	35	40
4a	40	35	45	50
5a	15	20	15	20
6a	20	15	20	25
7a	50	45	25	30
1b	50	45	40	45
2b	25	20	30	35
3b	50	45	35	40
4b	40	35	45	50
5b	15	20	20	25
6b	20	15	25	30
7b	50	45	45	50
Tetracycline	15	20	15	20
Chloramphenicol	25	30	20	25

Table 4: Antifungal Activity

Compound	Zone Of Inhibition (Diameter In Mm)															
	Saccharomyces cerevisiae				Aspergilus niger				Pencillium chrysogenum				Pencillium notatum			
	100 µg/ml	150 µg/ml	200 µg/ml	250 µg/ml	100 µg/ml	150 µg/ml	200 µg/ml	250 µg/ml	100 µg/ml	150 µg/ml	200 µg/ml	250 µg/ml	100 µg/ml	150 µg/ml	200 µg/ml	250 µg/ml
1a	0.8	0.8	0.9	0.9	0.5	0.7	0.8	0.9	0.5	0.7	0.7	0.9	0.6	0.7	0.8	0.9
2a	1	1.1	1.2	1.3	0.6	0..7	0.8	0.9	0.6	0.7	0.8	0.8	0.7	0.7	0.8	0.9
3a	0.7	0.8	0.9	1	0.7	8.0	8.0	1	0.7	8.0	0.9	1.1	0.6	0.7	0.9	1
4a	0.8	0.9	1	1.3	1	1.2	1.2	1.3	1	1.3	1.4	1.5	1.1	1.2	1.2	1.3
5a	1.1	1.3	1.6	1.8	1.1	1.2	1.4	1.5	1.6	1.7	1.8	1.9	1.7	1.8	1.9	2
6a	1.3	1.4	1.5	1.6	1.3	1.4	1.4	1.6	1.5	1.6	1.7	1.8	1.6	1.7	1.8	1.9
7a	0.6	0.9	1	1.3	1	1.1	1.2	1.3	1.1	1.2	1.3	1.4	1.1	1.1	1.2	1.3
1b	1	0.8	0.9	0.9	0.5	0.7	0.8	0.9	0.6	0.7	0.8	0.9	0.5	0.7	0.7	0.9
2b	0.9	1.1	1.2	1.3	0.6	0.7	0.8	0.9	0.7	0.7	0.8	0.9	0.6	0.7	0.8	0.8
3b	0.8	0.8	0.9	1	0.6	0.7	0.8	0.9	0.6	0.7	0.9	1	0.7	8.0	0.9	1.1
4b	0.8	0.9	1	1.3	1.1	1.2	1.2	1.3	1.1	1.2	1.2	1.3	1	1.3	1.4	1.5
5b	1	1.2	1.6	1.8	1.3	1.5	1.6	1.7	1.7	1.8	1.9	2	1.6	1.7	1.8	1.9
6b	1.1	1.4	1.6	1.7	1.2	1.3	1.4	1.5	1.6	1.7	1.8	1.9	1.5	1.6	1.7	1.8
7b	0.9	1	1.1	1.2	1.1	1.1	1.2	1.3	1.1	1.1	1.2	1.3	1.1	1.2	1.3	1.4
Fluconazole	1.6	1.7	1.8	1.9	1.7	1.8	1.9	2	1.6	1.8	1.9	2	1.8	1.9	2	2.1

4.4. *In silico* drug-likeness and toxicity predictions

Currently, several approaches have been developed to assess drug-likeness of bioactive compounds based on topological descriptors, fingerprints of molecular structure or other properties such as molecular weight, water solubility and cLogP [28]. In this work, open-source program OSIRIS Property Explorer [29] was used to predict the fragment-based drug-likeness of title compounds and comparing them with Fluconazole and tetracycline. OSIRIS program involves the database of trading drugs and commercially available compounds (Flukas) assumable as non-drug-like dataset to assess the occurrence frequency of each fragment in the individual structure. The program estimated the risks of side effects, such as mutagenic, tumorigenic, irritant and reproductive effects, as well as drug-relevant properties including cLogP, LogS (solubility), MW and drug-likeness. Moreover, the overall drug-score was estimated by combining outcome of cLogP, LogS, MW, toxicity risks and drug-likeness. Drug-score is a measure of compound's potential to meet the criteria of a possible drug candidate [30].

The in silico drug-relevant properties obtained by OSIRIS Property Explorer given in Table 5.

Table 5: Osiris Calculations of Compounds

Compound	Toxicity Risks				Molecular Properties Calculation			
	MUT	TUMO	IRRI	REP	CLP	logS	DL	DS
1a					2.27	-4.93	-6.26	0.34
2a					2.85	-4.18	4.17	0.45
3a					3.8	-5.21	4.75	0.59
4a					3.09	-4.51	-0.45	0.17
5a					2.85	-4.18	4.13	0.75
6a					4.41	-5.94	5.03	0.47
7a					3.06	-4.51	5.98	0.68
1b					2.06	-5.25	-6.21	0.32
2b					2.64	-4.49	4.21	0.43
3b					3.59	-5.52	4.81	0.57
4b					2.88	-4.82	-0.41	0.17
5b					2.64	-4.49	4.17	0.72
6b					4.2	-6.26	5.08	0.46
7b					2.84	-4.82	6.02	0.66
Tetracycline					-1.33	-1.83	5.43	0.81
Fluconazole					-0.11	-2.17	1.99	0.87

MUT: Mutagenic; TUMO: Tumorigenic; IRRI: Irritant; REP: Reproductive Effective; CLP: ClogP; Log s: Solubility mol/lit; DL: Drug-Likeness; DS: Drug-Score.

Interestingly, the potential drug-likeness values of compounds **7a** and **7b** were significantly higher than that of tetracycline and compounds **2a, 3a, 5a, 6a, 7a, 2b, 3b, 5b, 6b, 7b** were higher when compared with a drug likeness score of fluconazole. As shown in Table 5, compounds **4a, 4b** had high in silico tumorigenic and medium mutagenic toxicity risks due to tertiary amine substituent on the benzene ring. However, the in silico prediction by OSIRIS Property Explorer showed that the introduction of electron withdrawing groups can reduce the risk of toxicities. Generally, the drug-score values of compounds **1a-7a** (0.15-0.7) were less than that of standards tetracycline (0.81) and Fluconazole (0.87). Among the final compounds **7a**, **7b** showed the highest values of drug-likeness and compounds **5a**, **5b** showed the highest values of the drug-score.

5. Results and Discussion

5.1. Antibacterial Activity

To further explore the biological activities of these compounds, they were screened for *in-vitro* antibacterial activity against an assortment of two gram-positive bacteria *Staphylococcus aureus NCIM 2901*, *Bacillus subtilis MTCC 441* and two gram-negative bacteria *Escherichia coli NCIM 2563*, *Proteus vulgaris MTCC 1771* by twofold serial broth dilution method. Tetracycline and Chloramphenicol were used as standards. Minimum Inhibitory Concentration (µg/ml) of the test compounds in Table 3 inferred that all the test compounds exhibited promising antibacterial activity, however with a degree of variation. Compounds **5b** and **5a** demonstrated significant antibacterial activity with MIC in the range of 15-20µg/ml. Compound **6a**,**6b** showed potential antibacterial activity against with MIC in the range 15-25 µg/ml. Compounds showed remarkable activity against Gram positive bacteria when compare to gram negative bacteria..

5.2. Antifungal Activity

The results of the compounds represented in Table 4 showed a wide range of anti-fungal activity. Compounds **5a**, **5b**, **6a**, **6b** were found to exhibit the most potent *in vitro* anti-fungal activity against *Penicillium notatum NCIM 742, Penicillium chrysogenum MTCC 5108 and* found to be equally potent with that of standard Fluconazole. Compounds **1a**,**2a**,**3a**,**4a**,**7a**,**1b**,**2b**,**3b**,**4b**,**7b** also exhibited significant antifungal activity.

The structure-activity relationship studies based on the above *in vitro* results clearly indicate that compounds with electron donating groups on the aromatic ring showed increased potency. The intense activity of the compounds is also greatly influenced by the amount of activation or deactivation and position of the groups on the ring. The hydroxyl substitution at ortho position **5a** and **5b** has higher significant activity when compared to the hydroxyl at para position which clearly indicates that ortho substitution is responsible for increased activity. The results also indicate the rise in activity with the increase in the number nitrogens in the heterocyclic ring.

5.3. Conclusion

A series of new imidazolin-5-one derivatives were prepared by novel method and evaluated for their *In-vitro* antimicrobial, ferric oxide reducing properties for which the mechanisms underlying this process remain to be fully elucidated. Detailed mechanistic studies and lead optimization of these imidazolin-5-one derivatives are under investigation. It is intended that the results from these studies will assist in elucidating their precise mechanism of action and provide an approach for further optimization and development to get new leads in the treatment of microbial infections.

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7. References

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