Innovations in Pharmaceuticals and Pharmacotherapy

www.innpharmacotherapy.com

eISSN: 2321–323X
pISSN: 2395-0781

Research Article

Microwave assisted novel synthesis and biological evaluation of 1-(Substituted phenyl)-2-phenyl-4-(Substituted benzylidene)-imidazole-5-ones

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Abstract

A series of 5-substituted imidazolones 1-20 analogs were prepared by the condensation of different substituted 5-oxazolone analogs with various aromatic amines by using microwave irradiations. The structures of all the newly synthesized compounds were elucidated by using IR and ^{1}H-NMR. All the synthesized compounds were evaluated against six bacterial strains *i.e. M. luteus* MTCC 2470, *S. aureus* MTCC 96, *B. subtilus* MTCC 121, *P. aeruginosa* MTCC 2453, *K. planticola* MTCC 530, *E. coli* MTCC 739 and one fungal strain *C. albicans* MTCC 3017. Ampicillin and amphoterecin B was used as standard drug for antibacterial and antifungal activity, respectively. Out of all, compound 7 and 10 were found to possess broad spectrum antibacterial activity. Compound 13 exhibit significant antibacterial activity against Gram-negative bacteria where as 5, 14 and 18 shows good to moderate antibacterial activities against Gram-positive bacteria.

Keywords: Imidazolones, oxazolone, antimicrobial, microwave.

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1. Introduction

The exploitation of a simple molecule with different functionalities for the synthesis of heterocyclic compounds is a worthwhile contribution in the chemistry of heterocycles. 5-imidazolone is a five-membered heterocyclic ring system having three carbon and two nitrogen atoms at 1 and 3 positions with a carbonyl group at 5 position. A large number of imidazolone containing compounds have been in the market from the past decade e.g. clonidine, phentolamine for the treatment of hypertension, cimetidine as antiulcer, dacarbazine as anticancer, metronidazole as antiprotozoal drug, ketoconazole, econazole as antifungal agents [1] and two imidazolines priscol and privine are vasodilating and vasoconstricting drugs [2]. In addition, an array of imidazoles and substituted imidazolones have also been reported to be associated with diverse pharmacological activities including anti-HIV [3-4], antimicrobial [4], antibacterial [5-7], anticonvulsant [8-9], monoamine oxidase inhibitory [9-10], CNS depressant [11-12], anti-inflammatory [13-14], anticancer [3-4], leishmanicidal activity [15], antiparkinsonain [16] and immunomodulatory activities [17]. Previously, the 5-substituted imidazolones have been prepared by heating a mixture of 5-oxazolone analogs with differently substituted aromatic or aliphatic amines in presence of excess of pyridine for 10-15 hours. The yield of the imidazolones was very poor and the reaction required long time to complete [7-9, 12, 13, 18-19].

Literature survey reveals that, recently green technologies such as microwave irradiation are being used for the synthesis of novel 5-substituted

imidazoles analogs [13, 20]. However, in the present article we introduced the synthesis of eighteeen new 5-substituted imidazolones analogs by the condensation of aromatic substituted amines with 5-oxazolone analogs by using microwave irradiations (Scheme 1). The reaction takes place in 10-15 minutes with excellent yield. The products were crystallized from alcohol and the structures of all the synthesized compounds were determined on the basis of spectral data. In view of emerging bacterial resistance to the currently available antibiotics and potent antimicrobial potential of imidazolones, has driven the search for new 5-substituted imidazolones analogs associated with antimicrobial activity. All the synthesized compounds were screened for *in vitro* activities against a panel of Gram-positive and Gram-negative bacteria and the yeast-like pathogenic fungus *Candida albicans*.

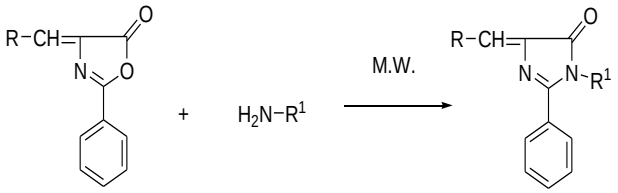
2. Material and Methods

a. Chemistry

Melting points were determined by open capillary tubes and were uncorrected. IR spectra recorded on Perkin Elmer RX1 spectrophotometer using KBr pellets and are expressed in cm^{-1}. The ^1H NMR spectra were recorded on Brucker 300 MHz spectrometer in ($CDCl_3$) using TMS as an internal reference and chemical shifts is measured in δ ppm. The progress of the reaction was monitored by TLC using 0.2 mm thickness aluminium sheet precoated with silica gel Merck 60F 254 and visualization was done using iodine/UV lamp for detection of the spots. The solvent was removed under reduced pressure using Buchi rotary evaporator.

b. General Procedure for the Synthesis of Compounds 1- 20

A mixture of different substituted oxazolones (1 mmol) and substituted aromatic amines (1.1 mmol) in anhydrous pyridine was irradiated in microwave reactor for 10-15 min. The completion of reaction was monitored by TLC and then 5 ml of ice cool 5% HCl in water was added and the mixture was left for overnight. The resultant solids were collected and washed with water. The resultant solid was crystallized by ethanol, filtered and on drying to afford title compounds 1-20.



Scheme 1: Synthesis of 5-imidazolones analogs

The spectral data (IR, ^1H NMR) of known compounds such as 4-(3-nitrobenzylidene)-2-phenyl-1-p-tolyl-1H-imidazol-5(4H)-one (2), 4-(3-nitrobenzylidene)-1-(4-chlorophenyl)-2-phenyl-1H-imidazol-5(4H)-one (3), 4-(2-chlorobenzylidene)-1-(2,6-dimethylphenyl)-2-phenyl-1H-imidazol-5(4H)-one (5), 4-(2-chlorobenzylidene)-1-(4-methoxyphenyl)-2-phenyl-1H-imidazol-5(4H)-one (6), 4-(4-fluorobenzylidene)-1-(4-chlorophenyl)-2-phenyl-1H-imidazol-5(4H)-one (9), 2-(4-(4-hydroxybenzylidene)-4,5-dihydro-5-oxo-2-phenylimidazol-1-yl)benzoic acid (11), 4-(4-hydroxybenzylidene)-2-phenyl-1-p-tolyl-1H-imidazol-5(4H)-one (12), N-(4-(4-methoxybenzylidene)-4,5-dihydro-5-oxo-2-phenylimidazol-1-yl)isonicotin- amide (13), 4-(4-methoxybenzylidene)-1-(3-aminophenyl)-2-phenyl-1H-imidazol-5(4H)-one (15) and 2,3-Diphenyl-5-[(E)-phenylmethylidene]-3,5-dihydro-4H-imidazole-4-one (20) were found to be identical with those reported in the literature [22]. The physical data of twelve new compounds (1, 4, 7-8, 10, 14, 16-19) are provided below.

1.1.1. 4-(3-nitrobenzylidene)-1-(4-aminophenyl)-2-phenyl-1H-imidazol-5(4H)-one (1): Molecular formula $C_{22}H_{16}N_4O_3$, Yield: 76%, mp: 176-177 °C; IR (KBr): 1610 (C=N), 1590 (C=C), 1640 (C=O) cm^{-1}, ^1H NMR (300 MHz, $CDCl_3$) δ 4.1 (s, 2H, NH_2), 7.8 (s, 1H, CH), 6.4-6.6 (s, 2H, Ar-H), 7.2-8.3 (m, 11H, Ar-H).

1.1.2. 4-(4-(3-nitrobenzylidene)-4,5-dihydro-5-oxo-2-phenylimidazol-1-yl)benzoic acid (4): Molecular formula $C_{23}H_{15}N_3O_5$, Yield: 72%, mp: 170-171 °C; IR (KBr): 1620 (C=N), 1595 (C=C), 1650 (C=O) cm^{-1}, ^1H NMR (300 MHz, $CDCl_3$) δ 7.7 (s, 1H, CH), 7.3-8.2 (m, 13H, Ar-H), 11.0 (s, 1H, -COOH).

1.1.3. 4-(4-(2-chlorobenzylidene)-5-oxo-2-phenyl-4,5-dihydroimidazol-1-yl)benzene sulphonamide (7): Molecular formula $C_{22}H_{16}ClN_3O_3S$, Yield: 76%, mp: 167-168 °C; IR (KBr): 1610 (C=N), 1594 (C=C), 1645 (C=O) cm^{-1}, ^1H NMR (300 MHz, $CDCl_3$) δ 2.10 (s, 2H, NH_2), 7.6 (s, 1H, CH), 7.2-8.0 (m, 13H, Ar-H).

1.1.4. 2-(4-(4-fluorobenzylidene)-4,5-dihydro-5-oxo-2-phenylimidazol-1-yl)benzoic acid (8): Molecular formula $C_{23}H_{15}FN_2O_3$, Yield: 67%, mp: 160-161 °C; IR (KBr): 1605 (C=N), 1590 (C=C), 1660 (C=O) cm^{-1}, ^1H NMR (300 MHz, $CDCl_3$) δ 7.6 (s, 1H, CH), 6.8-8.2 (m, 13H, Ar-H), 11 (s, 1H, -COOH).

1.1.5. 1-(2,4-dinitrophenylamino)-4-(4-hydroxybenzylidene)-2-phenyl-1H-imidazol-5(4H)-one (**10**): Molecular formula $C_{22}H_{15}N_5O_6$, Yield: 77%; mp: 172-173 °C, ^1H NMR (300 MHz, $CDCl_3$) δ 4.2 (s, 1H, -NH), 5.0 (s, 1H, -OH), 7.5 (s, 1H, CH), 7.1-8.9 (m, 12H, Ar-H).

1.1.6. 4-(4-methoxybenzylidene)-2-phenyl-1-(thiazol-2-yl)-1H-imidazol-5(4H)-one (14): Molecular formula $C_{20}H_{15}N_3O_2S$, Yield: 80%; mp: 185-186 °C; IR (KBr): 3100 (Ar C-H), 1615 (C=N), 1590 (C=C), 1660 (C=O) cm^{-1}, ^1H NMR (300 MHz, $CDCl_3$) δ 3.7 (s, 3H, $-OCH_3$), 7.6 (s, 1H, CH), 6.7-7.6 (m, 11H, Ar-H).

1.1.7. 4-(4-methoxybenzylidene)-1-(3-nitrophenyl)-2-phenyl-1H-imidazol-5(4H)-one (16): Molecular formula $C_{23}H_{17}N_3O_4$, Yield: 65%; mp: 184-185 °C; IR (KBr): 3105 (Ar C-H), 1620 (C=N), 1594 (C=C), 1645 (C=O) cm^{-1}, ^1H NMR (300 MHz, $CDCl_3$) δ 3.6 (s, 3H, $-OCH_3$), 7.4 (s, 1H, CH), 6.8-7.5 (m, 11H, Ar-H), 8.1-8.4 (d, 2H, Ar-H).

1.1.8. 4-benzylidene-2-phenyl-1H-imidazol-5(4H)-one (**17**): Molecular formula $C_{16}H_{12}N_2O$, Yield: 74%; mp: 178-179 °C; IR (KBr): 1610 (C=N), 1596 (C=C), 1645 (C=O) cm^{-1}. ^1HNMR (300 MHz, $CDCl_3$) δ: 7.5 (s, 1H, CH), 7.10-7.60 (m, 10H, Ar-H), 7.9 (s, 1H, NH).

1.1.9. 4-benzylidene-4,5-dihydro-5-oxo-2-phenylimidazole-1-carboxamide (18): Molecular formula $C_{17}H_{14}N_4O_2$, Yield: 65%; mp: 195-196 °C, ^1H NMR (300 MHz, $CDCl_3$) δ 5.4-5.8 (s, 3H, -NH and $-NH_2$), 7.4 (s, 1H, CH), 7.1-7.8 (m, 10H, Ar-H).

1.1.10. 4-benzylidene-4,5-dihydro-5-oxo-2-phenylimidazole-1-carbothioamide (19): Molecular formula $C_{17}H_{14}N_4OS$, Yield: 70%; mp: 174-175 °C, IR (KBr): 1610 (C=N), 1594 (C=C), 1655 (C=O) cm^{-1}, ^1H NMR (300 MHz, $CDCl_3$) δ 2.4-2.8 (s, 3H, -NH and $-NH_2$), 7.4 (s, 1H, CH), 7.1-7.8 (m, 10H, Ar-H).

1.2. Antibacterial Bioassay

The *in vitro* antimicrobial potential of all the prepared analogs **1-20** was carried out at Institute of Microbial Technology (CSIR), Chandigarh-160036 (India) by applying the agar plate diffusion antimicrobial bioassay. The compounds were tested at 5000 µg/ml concentration (DMSO) and the activity was determined by measuring the zone of inhibition. The positive control strength is specified *i.e.* 50 µg/ml of the stock solution was used in well for bioassay. The antibacterial and antifungal potential of the prepared analogs l-20 were compared with standard drug ampicillin (200 µg/ml) and amphoterecin B (500 µg/ml) respectively as depicted in Table 1. Activity was determined by measuring the diameter of zones showing complete inhibition (mm). Growth inhibition was calculated with reference to positive control.

2. Results and Discussion

2.1. Chemistry

A variety of novel 5-substituted imidazolones 1-20 were synthesized from different substituted oxazolones treated with different substituted aromatic amines in the presence of anhydrous pyridine under microwave irradiation. The synthesis pathway leading to the title compounds is given in Scheme 1. The reactions were complete with 10-15 minutes to afforded 5-substituted imidazolones 1-20 in very high yields. The structures of the synthesized compounds have been elucidated on the basis of their spectral data including IR, ^1H NMR and Mass Spectroscopy. All spectral data were in accordance with assumed structures.

2.2. Antibacterial activity

All the synthesized compounds 1-20 were tested against three Gram positive bacterial strains *i.e. M. luteus* MTCC 2470, *S. aureus* MTCC 96, *B. subtilus* MTCC 121, three Gram negative strains *i.e. P. aeruginosa* MTCC 2453, *K. planticola* MTCC 530, *E. coli* MTCC 739 and one fungal strain *Candida albicans* MTCC 3017 according to literature protocol [21a-21b]. Observation made for two days and the sign **"-"** signifies no Zone of Inhibition (ZOI). In many cases, on first day ZOI observed which was disappearing on the next day. The results for antibacterial activity were compared with standard drug ampiciline where as antifungal potential was compared with standard drug amphoterecin B depicted in Table 1.

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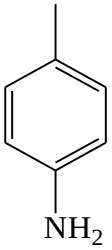
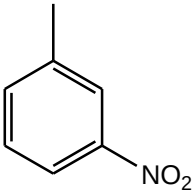
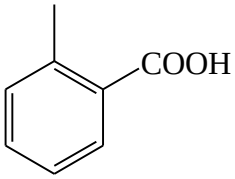
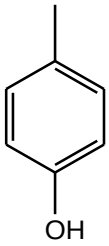
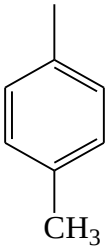
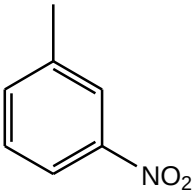
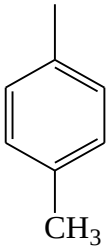
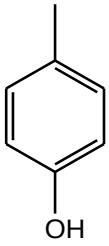
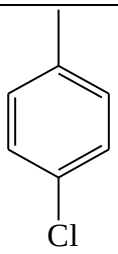
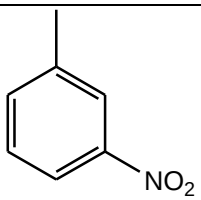
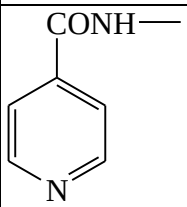
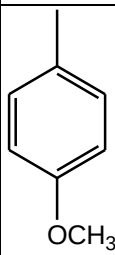
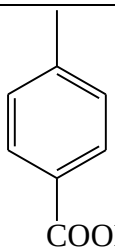
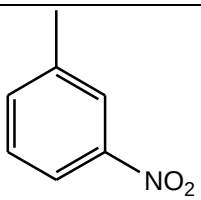
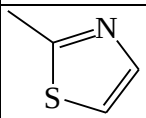
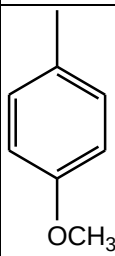
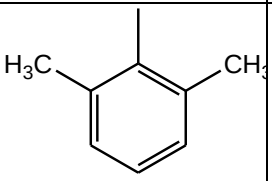
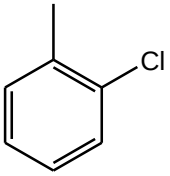
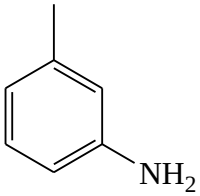
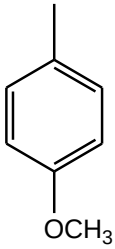
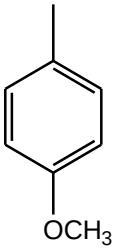
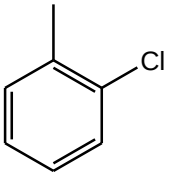
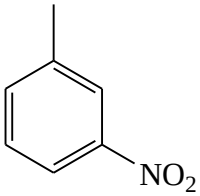
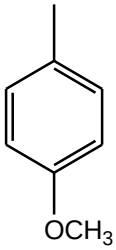
1			11		
2			12		
3			13		
4			14		
5			15		
6			16		

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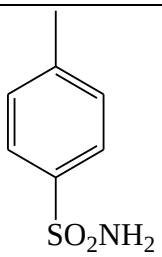
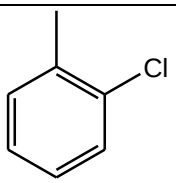
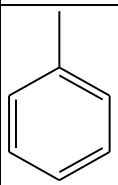
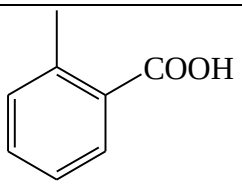
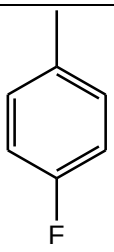
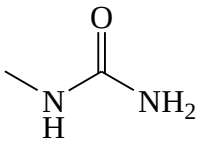
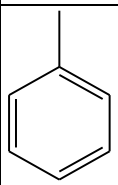
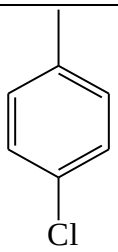
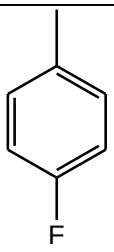
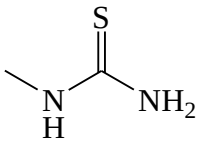
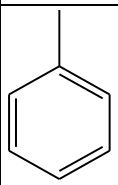
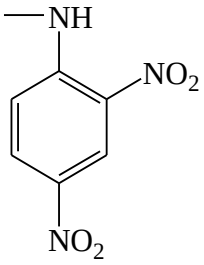
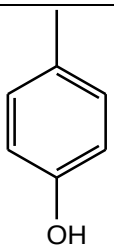
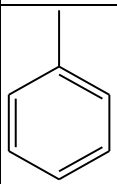
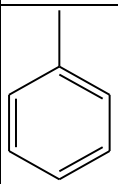
7			17		
8			18		
9			19		
10			20		

Several compounds in this series 1-3, 6, 8-9, 11-12, 15-17, 19-20 showed no activity against all bacteria. Compounds 5 shows moderate antibacterial activities against *M. luteus* MTCC 2470 and good against *B. subtilus* MTCC 121 where as compounds 13 exhibits good antibacterial activities against *P. aeruginosa* MTCC 2453. Compound 7, was found to be posses broad spectrum activity as it shows good activity against both Gram positive (i.e. *M. luteus* MTCC 2470 and *B. subtilus* MTCC 121) and Gram negative (*P. aeruginosa* MTCC 2453) bacterial strain. The most active antibacterial agent which shows wide spectrum of antibacterial activity against *S. aureus* MTCC 96, *B. subtilus* MTCC 121, *P. aeruginosa* MTCC 2453, *K. planticola* MTCC 530 found to be compound 10. Compound 14 was found to exhibited good activity against *B. subtilus* MTCC 121 whereas compound 18, shows moderate activity against *S. aureus* MTCC 96. Although ampicillin is broad spectrum antibiotic but does not showing any activity against *P. aeruginosa* MTCC 2453 and *K. planticola* MTCC 530, it may be due to some mutation or needing higher concentration. Only two compounds (*i.e.* 4 and 10) were found to posse's good antifungal activity against *C. albicans* MTCC 3017.

Table 1: Result of antimicrobial bioassay of Compounds 1-18 (Concentration used 5 mg/ml DMSO)

Sample No	*M. luteus* MTCC 2470 24h 48h	*S. aureus* MTCC 96 24h 48h	*B. subtilus* MTCC 121 24h 48h	*P. aeruginosa* MTCC 2453 24h 48h	*K. planticola* MTCC 530 24h 48h	*E. coli* MTCC 739 24h 48h	*C. albicans* MTCC 3017 24h 48h
1	- -	- -	- -	- -	- -	- -	- -
2	- -	- -	- -	- -	- -	- -	- -
3	- -	- -	- -	- -	- -	- -	- -
4	- -	- -	**6mm** -	- -	- -	- -	**9mm** -
5	**12mm 10mm**	- -	**6mm 6mm**	- -	- -	- -	- -
6	- -	- -	- -	- -	- -	- -	- -
7	**10mm 8mm**	- -	**9mm 7mm**	**10mm 10mm**	- -	- -	- -
8	- -	- -	- -	- -	- -	- -	- -
9	- -	- -	- -	- -	- -	- -	- -
10	- -	**16mm 15mm**	**15mm 15mm**	**19mm** -	**20mm 20mm**	- -	**13mm** -
11	- -	- -	- -	- -	- -	- -	- -
12	- -	- -	- -	- -	- -	- -	- -
13	- -	- -	- -	**9mm** -	- -	- -	- -
14	- -	- -	**11mm 10mm**	- -	- -	- -	- -
15	- -	- -	- -	- -	- -	- -	- -
16	- -	- -	- -	- -	- -	- -	- -
17	- -	- -	- -	- -	- -	- -	- -
18	- -	**12mm** -	- -	- -	- -	- -	- -

19	- -	- -	- -	- -	- -	- -	- -
20	- -	- -	- -	- -	- -	- -	- -
Positive control	**42mm 40mm** (Ampicillin 200 µg/ml)	**44mm 45mm** (Ampicillin 200 µg/ml)	**27mm 22mm** (Ampicillin 200 µg/ml)	- - (Ampicillin 200 µg/ml)	- - (Ampicillin 200 µg/ml)	**15mm 17mm** (Ampicillin 200 µg/ml)	**16mm 15mm** (Amphoterecin B, 500 µg/ml)
DMSO (Vehicle control)	- -	- -	- -	- -	- -	- -	- -

Conclusion

A practical and efficient synthesis of a series of novel 5-substituted imidazolones has been reported by us using microwave assisted technology in good yields (80% - 92%). The structures of the target molecules were characterized by using spectroscopic data *v.i.z.*, IR, and ^{1}H NMR. All spectral data were in accordance with assumed structures. Some compounds 5, 14 and 18 shows good to moderate antibacterial activities against Gram-positive bacteria whereas compound 13 exhibits good antibacterial activities against Gram-negative bacteria. Both compound 7 and 10 were found to possess broad spectrum antibacterial activity. Compound 4 show good antibacterial activity against *B. subtilus* MTCC 121 along with antifungal activity against *C. albicans* MTCC 3017. The promising activity of these compounds along with the other activity data obtained during the study can also be useful for establishing the structure activity relationship studies and for the development of newer and potent 5-substituted imidazolone compounds.

Acknowledgement

The authors extend their heartful thanks to Dr. Hemraj Nandanwar, Scientist at Institute of Microbial Technology, (CSIR), Chandigarh and Dr. Rohit Dutt, Associate Professor at Guru Gobind Singh College of Pharmacy, Yamuna Nagar for providing the facilities necessary for the present study.

Conflict of Interest

There is no conflict of interest.

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