WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 5.045
Volume 3, Issue 10, 1103-1110. Research Article ISSN 2277– 7105

AN EFFICIENT, OPERATIONALLY SIMPLE AND GREEN METHOD FOR SYNTHESIS OF IMIDAZOLES WITH ANTIBACTERIAL ACTIVITY

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Article Received on
27 September 2014,

Revised on 22 Oct 2014,
Accepted on 17 Nov 2014

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ABSTRACT

We have developed a simple, novel and efficient method for the synthesis of imidazole derivatives (1a-1e) by using microwave irradiation and have been compared with conventional method. The Non conventional method has been found to be superior to conventional method in respect of required reaction time, easy work up, energy saver and high yield. The synthesized compounds have been screened in vitro for their antimicrobial activity against *S. aureus* and *K. pneumoniae*. Some of the compounds displayed pronounced biological activity. The resulting products were characterized by IR, ^{1}H NMR and elemental analysis.

KEYWORDS: Imidazole, Conventional, Non conventional, Antibacterial activity.

INTRODUCTION

Imidazole is a five membered**,** heterocyclic ring which contains two nitrogen atoms and two double bonds. There are so many compounds which contain Imidazole ring and exhibit different types of pharmacological and biological activities such as antibacterial, [1] anticancer, [2] antidepressant, [3] antileishmanial, [4] antiviral, [5] antitubercular, [6] anti-inflammatory [7] and anticonvulsant activity [8] etc. It is also called an important synthon for the preparation of biologically active compounds. [9] Apart of its use for pharmaceutical purpose it also has variety of applications in industries. One of the applications of imidazole is in the purification of His tagged proteins in immobilized metal affinity chromatography (IMAC). [10] Besides these, they are used as synthetic intermediates [11] and ligands for

asymmetric catalysis [12] in various synthetic reactions. , act as α2-adrenoceptor agonist, [13] chiral auxiliaries [14] and chiral catalysts [15] So we have developed simple, efficient, environmental benign protocol for the synthesis of imidazole derivatives with antibacterial activity and its comparative study with conventional method as per Scheme-I and II.

MATERIALS AND METHODS

All chemicals were of synthetic grade (S.D. Fine Chem. Ltd. Mumbai, India). MP was determined by electro-thermal apparatus and is uncorrected. Products were recrystalized from methanol as a solvent. The purity of compounds was checked by the TLC on silica gel G plates and they were purified by column chromatography on silica gel (60-120 mesh). The microwave used for the synthesis is of LG-Little Chef MS-192 W. The compounds were characterized by IR, 1H NMR and mass spectral analysis. IR spectra were recorded on Perkin-Elmer spectrum in the form of KBr Pellet. 1H NMR was recorded in $CDCl_3$ and DMSO on Perkin-Elmer R-32 spectrum using TMS as internal standard. All the compounds were analyzed for C, H and N on Carlo-Erba elemental analyzer.

Experimental Section

Method-I: Conventional Procedure: Synthesis of (Substituted) Benzimidazole (Ia-e)

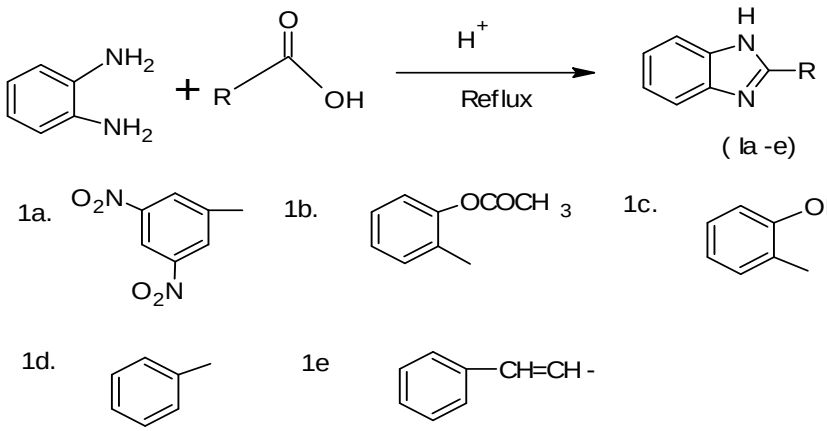
A mixture of o- Phenylenediamine (0.01 mole), different aromatic acid (0.01 mole)at 25 ml and of 4N dilute hydrochloric acid was refluxed for 2 hours at 453-458K. The reaction mixture was cooled and poured on to crushed ice then the product was filtered and washed with water. Product was recrystallized in the boiled water.

Method-II: Non Conventional Procedure:Synthesis of (Substituted)Benzimidazole (Ia-e)

A mixture of o- Phenylenediamine (0.01 mole), different aromatic acid (0.01 mole)at 25 ml and of 4N dilute hydrochloric acid was kept for 2 -3 min. in Micro oven. The reaction mixture was cooled and poured on to crushed ice then the product was filtered and washed with water. Product was recrystallized in the boiled water.

Scheme

I: Conventional



II: Non conventional

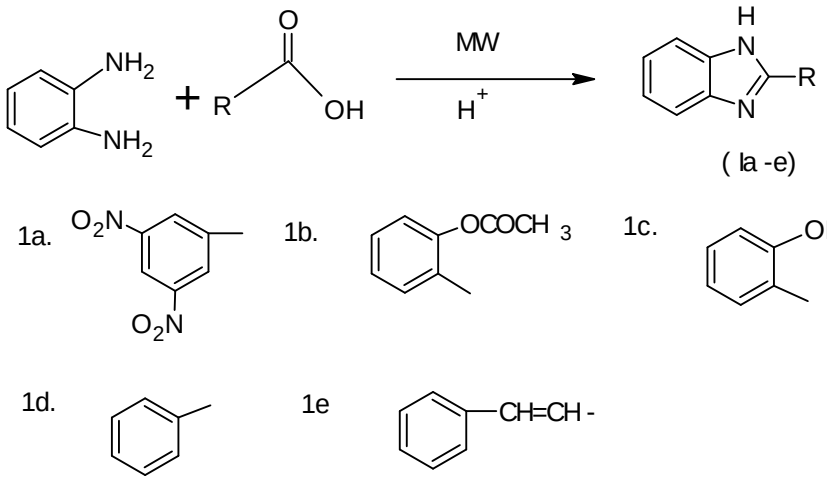


Table-I:-Physical data of synthesized compound (Conventional)

Compound No.	M.P. °C	Yield %	Molecular formula	Time required (Min.)	Elemental Analysis Calc./(Found) %		
					C	H	N
Ia	140	45	$C_{14}H_{11}N_4O_4$	180	56.19 (56.20)	3.68 (3.64)	18.73 (18.70)
Ib	137	55	$C_{14}H_{13}N_2O$	180	74.67 (74.60)	5.78 (5.76)	12.44 (12.45)
Ic	89-91	39	$C_{14}H_{13}N_2O$	180	74.67 (74.65)	5.78 5.79)	12.44 12.40)
Id	170-172	43	$C_{14}H_{13}N_2$	180	80.38 (80.40)	6.22 (6.20)	13.39 (13.30)
Ie	227-228	50	$C_{15}H_{15}N_2$	180	80.72 (80.70)	6.73 (6.71)	12.56 (12.51)

Table-II:-Physical data of synthesized compound (Non conventional)

Compound No.	M.P.°C	Yield %	Molecular formula	Time required (Min.)	Elemental Analysis Calc./(Found) %		
					C	H	N
Ia	140	85	$C_{14}H_{11}N_4O_4$	10	56.19 (56.20)	3.68 (3.64)	18.73 (18.70)
Ib	137	76	$C_{14}H_{13}N_2O$	8	74.67 (74.60)	5.78 (5.76)	12.44 (12.45)
Ic	89-91	69	$C_{14}H_{13}N_2O$	2	74.67 (74.65)	5.78 5.79)	12.44 12.40)
Id	170-172	74	$C_{14}H_{13}N_2$	1	80.38 (80.40)	6.22 (6.20)	13.39 (13.30)
Ie	227-228	80	$C_{15}H_{15}N_2$	2	80.72 (80.70)	6.73 (6.71)	12.56 (12.51)

Table- III: Spectral Characteristics of Synthesized compounds (1a-1e)

Compound No.	Spectral Characteristics
Ia	IR(KBr):√max, 3263(-NH),1640(>C=N-), 1620(>C=C<),1580(Ar -NO_2) Cm^{-1}; NMR ($CDCl_3$):δ, 3.6 (1H, s, -NH) ,7.1-7.9(7H,m,Ar-H) ppm.
Ib	IR(KBr):√max, 3270(-NH), 1737(>C=O, ester), 1635(>C=N-),1620 (>C=C<) $cm^{-1.}$; NMR ($CDCl_3$):δ,3.6 (1H,s,-NH),2.45(3H,s,-$COCH_3$), 7.1-7.9 (8H,m,Ar-H) ppm.
Ic	IR(KBr):√max, 3450(-OH),3260 (-NH), 1640(>C=N-),1620 (>C=C<) $cm^{-1.}$; NMR ($CDCl_3$):δ, 2.31(1H,s,-OH),3.6 (1H, s, -NH) ,7.1-7.9(7H,m,Ar-H) ,ppm.
Id	IR(KBr):√max, 3250(-NH), 1634(>C=N-),1620(>C=C<) $cm^{-1.;}$NMR ($CDCl_3$):δ, 7.0-7.9 (9H,m,Ar-H) ppm.
Ie	IR (KBr):√max, 3267(-NH), 1640(C=N-),1611(>C=C<) $cm^{-1.}$ NMR ($CDCl_3$): δ, 6.4(2H,dd,=CH) ,7.1-7.9 (9H,m,Ar-H) ppm.

RESULTS AND DISCUSSION

MW may be considered as efficient source of heating superior to conventional one, as it offers reduced chemical reaction time from hours to minutes, reduced side reactions and increased yields and it is 'in situ' mode of energy conversion .We have carried out comparative synthesis of imidazole derivatives by using conventional and non conventional method. In Conventional method, Synthesis of (Substituted) Benzimidazole (1a-1e) has been carried out by the reaction of o- Phenylenediamine with different aromatic acid in presence of dilute hydrochloric acid was refluxed for 3 hours and the yield which has been obtained 39-55%. While same procedure has been applied in Non conventional method i.e. use of Micro-oven (LG-Little Chef MS-192 W). It has been found that Non conventional method requires short reaction time, easy work up, high yield (69-85%) as compare with conventional method and operationally simple method. The synthesized compounds were

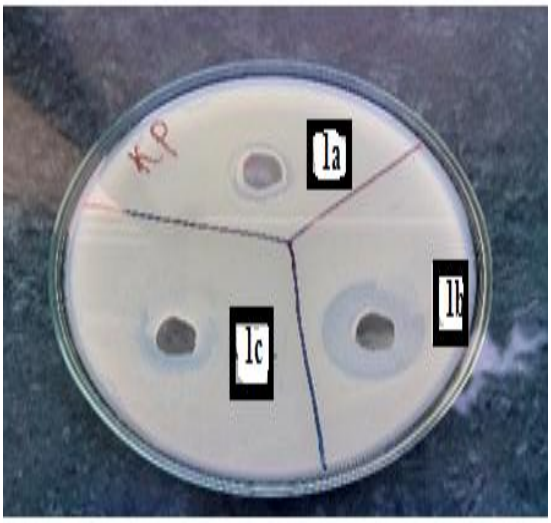
characterized on the basis of IR, NMR and Elemental analysis.IR shows Presence of –NH band at 3250 cm^{-1} while ^{1}H NMR shows peak at δ, 3.3-3.6 ppm due to –NH which conform formation of imidazole and Aromatic protons were found their respected position.

Antibacterial Activity

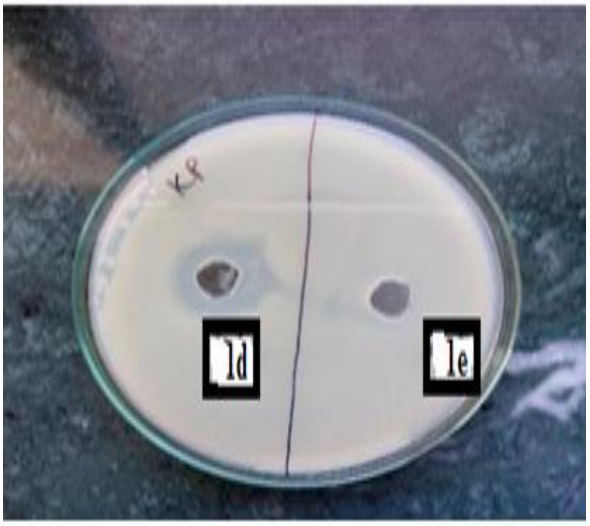
All the synthesized compounds (1a-1e) were screened for *in vitro* antimicrobial by crowded plate method. The bacterial strains Gram positive (Staphylococcus aureus), Gram negative (Klepsiella pneumoniae) were used .The standard used for comparison was streptomycin. DMSO was used as a solvent. The compounds 1a, 1b, 1d and 1e exhibited strong activity comparable to the standard against Gram negative bacterial strain. While the compounds 1b, 1d and 1e exhibited pronounced activity comparable to the standard against Gram positive bacterial strain and rest of the compounds shows moderate to good activity against standard drug and both bacterial strain.

Table No.-III: Antibacterial activity of Synthesized compounds(1a-1e):

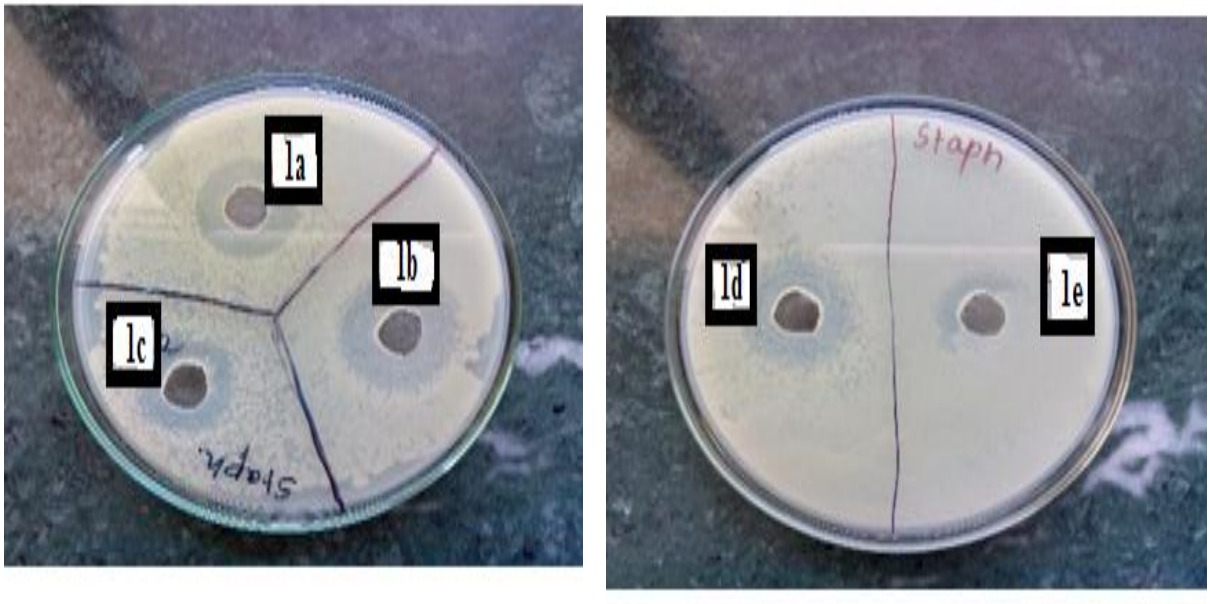
Compound No.	Gram negative	Gram positive
	K. pneumoniae	S. aureus
1a	18	17
1b	24	24
1c	17	18
1d	22	25
1e	25	23
Streptomycin (Standard Drug)	18	25



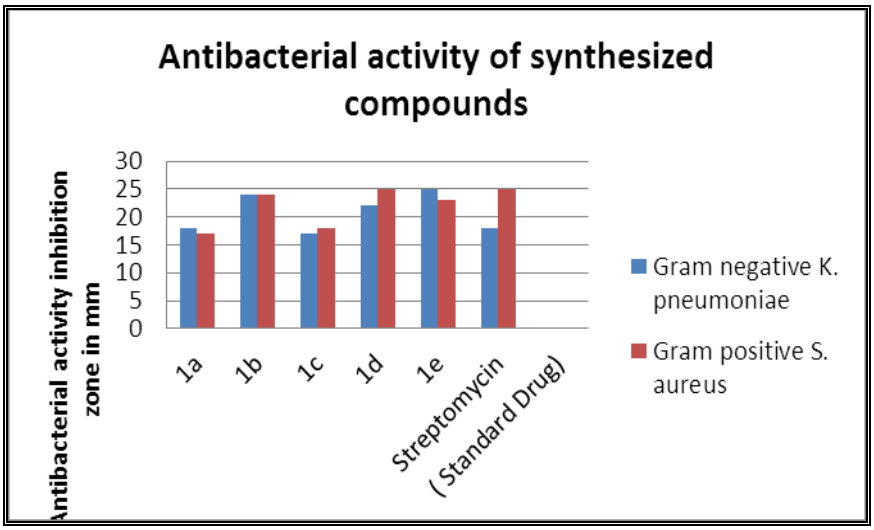
Antibacterial zone against *Klepsiella*



***pneumoniae* (Gram negative bacteria)**



Antibacterial activity against ***Staphylococcus aureus***



Comparative chart of antibacterial activity of synthesized compounds and standard drug

The proposed imidazole substituted derivatives 1a-1e were synthesized and evaluated for their Antimicrobial activity. All of the synthesized compounds were found to be active as Antimicrobial agents and among all the titled compounds, 1b, 1c and 1d showed very high antimicrobial activity as compared to standard result. The significant findings of the present research work in this manuscript may be utilized by the researchers for development of better antimicrobial agents for future.

CONCLUSION

We have demonstrated microwave assisted eco-friendly, operationally simple and time efficient protocol for the synthesis of Imidazole derivatives from o-phenylenediamine. Reaction procedures are very simple and yield of products are also excellent as compare with Conventional method. All synthesized compounds were screened for antimicrobial activities and found to be excellent activity as compare to standard drug.

ACKNOWLEDGEMENT

We are very much thankful to Department of Chemistry, Shivaji University Kolhapur and Dahiwadi College, Dahiwadi (Dist.:- Satara) for spectral interpretation and to Department of Chemistry and Biotechnology, Y. C. Institute of Science, Satara for providing antibacterial screening facilities.

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