RASĀYAN *J. Chem.*
Vol. 19 | No. 2 | 877-883| April-June | 2026
ISSN: 0974-1496 | e-ISSN: 0976-0083 | CODEN: RJCABP
http://www.rasayanjournal.com
http://www.rasayanjournal.co.in

MICROWAVE-ASSISTED, ONE-POT SYNTHESIS OF NOVEL HEXA HYDRO IMIDAZO [1,2-a] PYRIDINE: WITH DIVERSE CATALYST SCREENING AND INSILICO-STUDIES

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ABSTRACT

A microwave-assisted, one-pot, three-component synthesis of Imidazo [1,2-a] pyridine using four different catalysts was reported. The authors primarily focused on methodological development rather than synthesis of multiple derivatives, comparing reaction times and yields with those obtained under conventional conditions. Most importantly, in silico studies were conducted on the newly synthesised compound using the crystal structure of the enzyme 1A3 (PDB ID: 6TE5. Imidazo [1,2-a] pyridine derivatives are known inhibitors of aldehyde dehydrogenase 1A3 (ALDH1A3), an enzyme whose overexpression is associated with various cancers, including breast, lung, brain and colon cancers.

Keywords: Imidazo [1,2-a] Pyridines, Microwave Synthesis, Zolpidem, Cinnamaldehyde, Ethylene Diamine, Docking, Aldehyde Dehydrogenase.

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INTRODUCTION

Imidazo[1,2-a] pyridine is one of the familiar bi-nitrogen-containing heterocyclic moieties, and particularly its arylated derivatives are found in many approved drug formulations, such as Zolpidem 1 (used as hypnotics and sedatives to treat anxiety disorders), savolitinib 2 (used for the treatment of metastatic non-small cell lung cancer), Soraprazan 3 (used to treat Stargardt's disease) and Micropren 4 used as an anti-inflammatory and antipyretic. Their structures are shown in Fig.-1. Apart from their biological activities, such as analgesic, anti-pyretic, anti-viral, and anti-bacterial activities, Imidazo[1,2-a] pyridines are effective against hepatocellular carcinoma (HepG2 cells). Particularly, imidazo[1,2-a] pyridines are glioblastoma stem cell inhibitors,[1-3] making them effective in the treatment of brain cancer. Earlier, the synthesis of Imidazo [1,2-a] pyridines by the condensation reaction between 2-aminopyridine and various substrates, especially carbonyl compounds, using catalysts such as perchloric acid, hydrochloric acid, ammonium chloride in ethanol, sodium dodecyl sulfate, and thiamine hydrochloride was reported.[4-7] The syntheses involving microwave irradiation displayed an enhanced rate of reaction, greater selectivity, and maximum yields relative to that of conventional refluxing.[8-23] Among all the synthetic methods, microwave synthesis using acidic resin in PEG was considered the best method, as it provided superior reaction rates and percentage yields. Recognizing the importance of 7-phenyl imidazo[1,2-a] pyridines as glioblastoma (GBM) stem cell inhibitors, and as a part of exploring new methodologies, a microwave-assisted one-pot, three-component synthesis of Imidazo [1,2-a] pyridine with different catalysts was developed and compared with conventional methods, based on duration and yields. Further, conducted in-silico studies against aldehyde dehydrogenase 1A3.

EXPERIMENTAL

Material and Methods

All the chemicals and reagents used for the synthesis were procured from Sigma-Aldrich and used as received. Microwave irradiated synthesis was performed by heating the reaction mixture in a microwave oven with model kmg 2111.

http://doi.org/10.31788/RJC.2026.1929652

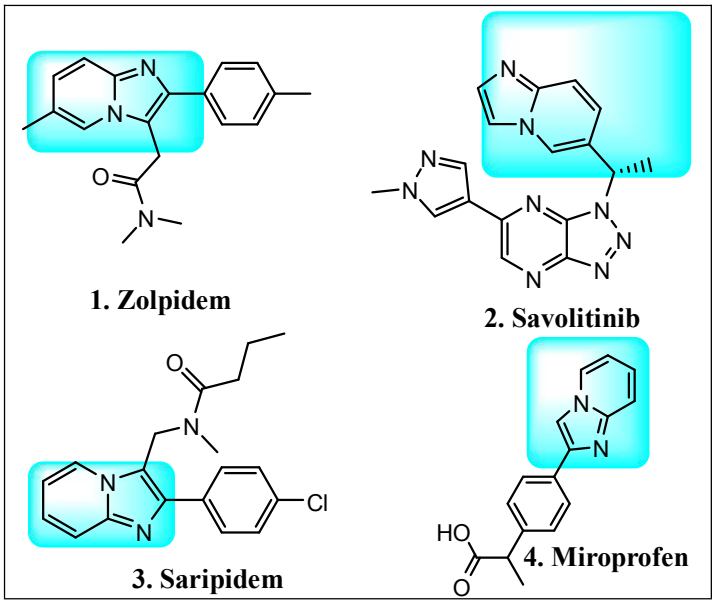


Fig.-1: Structures of Aryl Imidazo [1,2-a] Pyridines as Drugs

Thin Layer Chromatography (TLC) was performed on Merck Kiesel gel 60 F524 plates to monitor the status of reactions, and spots were visualised under UV light. Infrared spectra were measured on a Shimadzu FTIR 8400s spectrophotometer (KBr pellet technique), while mass spectra were recorded on a Shimadzu mass spectrometer.

General Procedure

Synthesis of 7, 8a) -5-Methyl -6 -(pent-1-en-2-yl) -7-phenyl -1, 2, 3,7, 8, 8a -hexa hydro Imidazo[1,2-a] pyridine (7)

A mixture of cinnamaldehyde (1mmol; 1.5ml), ethylene diamine (1mmol; 0.6ml), and ethyl acetoacetate (1.3 mmol; 1.5 ml) was heated in the presence of four different catalysts. The reaction was further tried using microwave irradiation. (Scheme-1).

Method-1

A mixture of cinnamaldehyde (1mmol; 1.5ml), ethylene diamine (1mmol; 0.6ml), and ethyl acetoacetate (1.3 mmol; 1.5 ml) was heated in the presence of 1.5 ml of PEG and heated for 2h at 50- 60^0C. The mixture was filtered, the solvent was removed under reduced pressure and dried.

Method-2

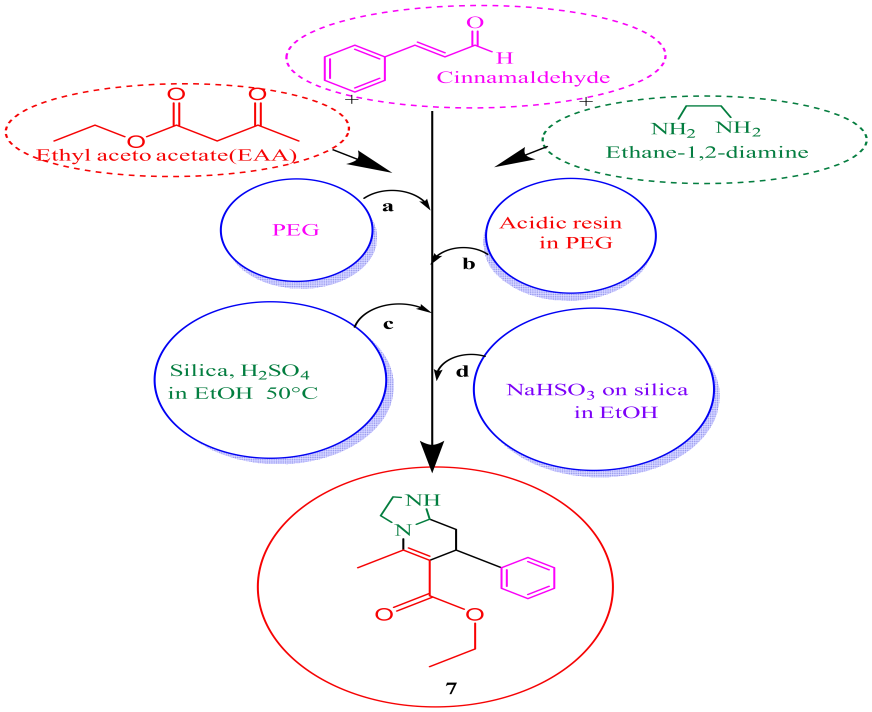
I. Preparation of catalyst: The catalyst was prepared by dissolving 1ml of conc. H_2SO_4 in 5 ml of ethanol, and added 5 gm of silica gel to the same, and made it into a paste. Again, 5 ml of ethanol was added to the paste and filtered.

II. Preparation of target compound: A mixture of cinnamaldehyde (1mmol;1.5ml), ethylene diamine (1mmol; 0.6ml), and ethyl acetoacetate (1.3 mmol; 1.5 ml) was heated in the presence of 2 ml of the above-prepared catalyst and heated for 1.5 h at 50- 60^0C.

Method-3

I. Preparation of catalyst: The catalyst was prepared by taking 1 g of $NaHSO_4$ and 1 gm of silica gel in a mortar. The fine powdered solid, obtained after grinding, was dissolved in 5ml of ethanol.

II. Preparation of target compound: A mixture of cinnamaldehyde (1mmol;1.5ml), ethylene diamine (1mmol; 0.6ml), and ethyl acetoacetate (1.3 mmol; 1.5 ml) was heated in the presence of 2 ml of the above-prepared catalyst and heated for 2.40 hrs at 50 -60^0C.



Scheme-1

Method-4

A mixture of cinnamaldehyde (1mmol; 1.5ml), ethylene diamine (1mmol; 0.6ml), and ethyl acetoacetate (1.3 mmol; 1.5 ml) was heated in the presence of 2ml of PEG and 1 ml of Conc. H_2SO_4 and heated for 2.35 hrs at 40-500 °C. In all the above four methods, the reaction status was checked by TLC and the contents were transferred into ice-cold water after the completion of the reaction. It was then extracted with ethyl acetate. The organic layer was subjected to a brine wash and then dried over anhydrous sodium sulphate. The solvent was removed from the filtered mixture under reduced pressure.

Procedure for the Microwave Method

Method-1

A mixture of three compounds (cinnamaldehyde, ethylene diamine and ethyl acetoacetate) in the same proportion as in the conventional method was heated in the presence of a catalyst, PEG (1.5ml), in a microwave oven for 25 minutes at a low to medium mode to achieve a yield of 1.94 g.

Method-2 The reaction mixture (Cinnamaldehyde, Ethylene diamine and ethyl acetoacetate) in the same proportion as in the conventional method was heated in the presence of 2 ml of catalyst, prepared using conc.H_2SO_4, ethanol and silica gel as in the conventional method) In a microwave oven for 15 minutes on medium mode. The yield of 2.25 g was obtained.

Method-3

The reaction mixture (Cinnamaldehyde, Ethylene diamine and ethyl acetoacetate) in the same proportion as in the conventional method was heated in the presence of 2 ml of catalyst, prepared using $NaHSO_4$, ethanol and silica gel (as in the conventional method) in a microwave oven for 25 minutes by keeping the medium mode to get the yield of 3.16 g.

Method-4

The reaction mixture (Cinnamaldehyde, Ethylene diamine and ethyl acetoacetate) in the same proportion as in the conventional method was heated in the presence of 2 ml of catalyst, PEG and conc.H_2SO_4 (as in the conventional method) in a microwave oven for 10 minutes by keeping the medium mode. A high yield of 3.55 g was obtained. IR(KBR) (cm^{-1}): 3396 5NH), 3080 (C-H), 1719 (C=O) 1532 (C-N); ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.1-7.36 (m, 6H, Ar-H, NH), 4.75 (d, J = 2.4 Hz, 1H, CH), 4.62 (d, J = 2.4

Hz, 1H, -CH), 3.88-3.82 (m, 2H, -CH_2-), 3.52-3.48 (m, 2H, -CH_2-), 2.45-2.35 (m, 2H, CH_2), 2.62 (s, 3H, CH_3), 2.16-2.05 (m, 2H, CH_2-C=O), 1.86 (s, 3H, CH_3). ESI-MS: m/z 287 $(M+1)^+$. Anal. Calcd for $C_{17}H_{22}N_2O_2$: C, 71.42; H, 7.64; N, 9.52, found: C, 70.84; H, 7.21; N, 8.86.

RESULTS AND DISCUSSION

The synthesis of Imidazo[1,2-a] pyridine (7**)** was achieved by a three-component reaction involving compounds, cinnamaldehyde, ethylene diamine, and ethyl acetate (Scheme-1). The four different catalysts used in the reaction were PEG, silica /sulphuric acid in ethanol, $NaHSO_4$/silica gel, and acidic resin in PEG, presented as methods 1-4 in Table-1.

Table-1: Comparison between Conventional and Microwave Synthetic Methods

	Name of the Catalyst	Conventional Method		Microwave Method	
		Time (in hours)	% Yield	Time (in min.)	% Yield
Method 1	PEG	2.0	49.7	25	53.8
Method 2	Silica /Sulphuric acid in ethanol	1.50	50.7	15	62.5
Method 3	$NaHSO_4$/Silica gel	2.40	71.9	25	87.7
Method 4	Acidic resin in PEG	2.35	54.4	10	98.6

PEG provides a mild reaction environment, reducing side reactions. It is biodegradable, nontoxic, and a green catalyst. It can be easily recovered and reused, enhancing sustainability. It works more efficiently in the presence of acidic resin. Silica/Sulphuric Acid in Ethanol facilitates easy filtration and recovery of the catalyst. $NaHSO_4$/Silica gel is a mild acidic catalyst with an inert medium (silica gel). All the catalysts used in this reaction are of low cost, mildness, ease of preparation, and insensitivity to moisture. The use of four different catalysts in the synthesis highlights the importance of catalyst selection in organic synthesis. The same synthetic protocols were also performed in a microwave oven with model kmg 2111, and the yields of products in both methods were compared as shown in Table-1. It shows that the yield is high in the presence of acidic resin in PEG. The achieved product was characterized by NMR and mass spectroscopic methods. It was observed that all the products from different catalysts have shown the same peaks.

Molecular Docking Study Against Aldehyde Dehydrogenase 1A3

Glioblastoma multiforme (GBM), an aggressive brain tumour, shows resistance to conventional therapies due to the presence of stem-like cancer cells that promote tumour growth. These cells overexpress aldehyde dehydrogenase 1A3, an enzyme essential for their survival, making it a probable target for effective treatment of GBM. The results were confirmed by redocking the co-crystalised ligand (7,8a) -5-methyl -6- (pent-1-en-2-yl) -7- phenyl -1,2,3,7, 8, 8a-hexahydroimidazo [1,2-a] pyridine (Ligand A) into the active site pocket of 1A3, which has presented an RMSD of 1.16 Å. The docking score of ligand A was found to be -8.5 kcal/mol, and reference ligand NQ4 was reported as -7.6 kcal/mol. The ligand A demonstrated a significant interaction with active site Leu471 with a bond length of 2.80 Å, indicating moderate strength (Fig.-2). Further, a hydrophobic interaction has been observed with the same Leu471 by ligand A. Whereas the reference ligand NQ4 displayed only hydrophobic interactions with active sites Ile132, Thr140, Leu471 and Leu 489 of 1A3 (Fig.-3 and Fig.-4). Dock pose image generated by ligand A and NQ4 in the cavity of 1A3 suggested that they best fit into the active site pocket of aldehyde dehydrogenase 1A3. [24-28]

Molecular Docking Procedure

Molecular docking simulations were performed using Auto Dock Vina integrated within the PyRx platform. The crystal structure of aldehyde dehydrogenase 1A3 (PDB ID: 6TE5) was obtained from the Protein Data Bank (www.rcsb.org). Before docking, heteroatoms and water molecules were removed from the protein structure, and polar hydrogens were added.

Ligand structures were drawn using ChemDraw Professional 16.0 in MDL file format. All ligands were imported into PyRx, where energy minimization was carried out, followed by conversion to PDBQT format. The 3D grid box was configured, and docking simulations were performed after assigning the

exhaustiveness value of 8. The resulting docking poses were analyzed and visualised using PyMOL and BIOVIA Discovery Studio Visualizer.[25-29]

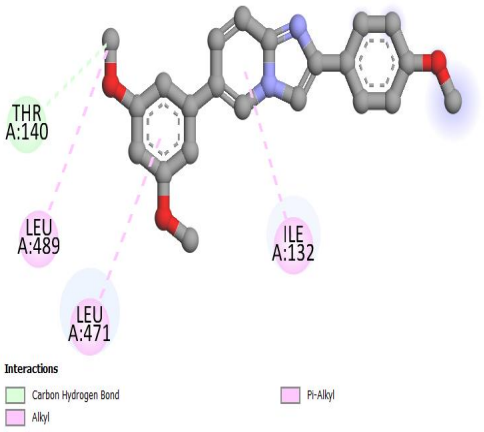


Fig.-2: Ligand A in the cavity of 1A3

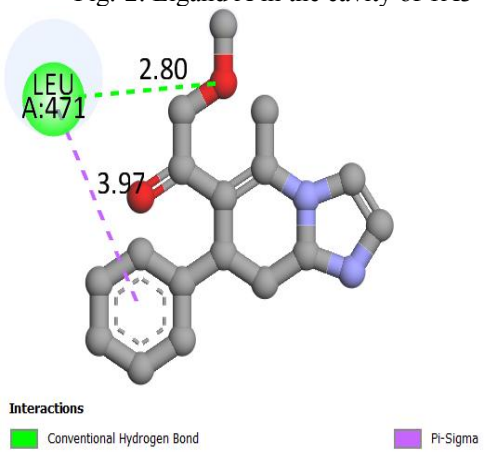


Fig.-3: Ligand NQ4 in Cavity of 1A3

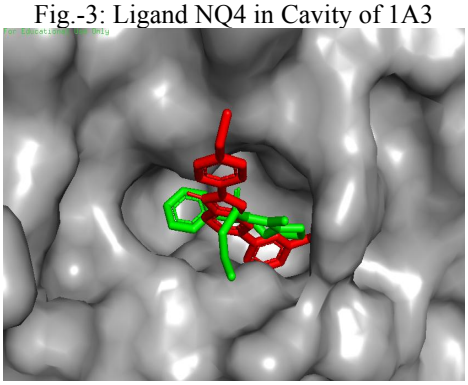


Fig.-4: Dock Pose Image of Ligand A (green) and NQ4 (red) in Cavity of 1A3

CONCLUSION

To conclude, we reported microwave-assisted synthesis of the title compound with four different catalysts. Four distinct methodologies were developed using different catalysts. Microwave irradiated methodologies with catalysts, $NaHSO_4$/Silica gel, and Acidic resin in PEG offered maximum yields as compared to the other two catalysts. Molecular docking studies were performed with an enzyme, aldehyde dehydrogenase 1A3. The docking score of ligand A was found to be -8.5 kcal/mol. The results indicated that the synthesized compound exhibited greater affinity for aldehyde dehydrogenase 1A3;

therefore, it may serve as an effective inhibitor for the treatment of various cancers such as glioblastoma (brain cancer), colorectal carcinoma (colon and rectal cancer), and hepatocellular carcinoma (liver cancer).

ACKNOWLEDGMENTS

The authors are thankful to the management of Geethanjali College of Engineering and Technology and Anurag University for providing the necessary facilities.

CONFLICT OF INTERESTS

The authors declare that there is no conflict of interest.

AUTHOR CONTRIBUTIONS

The present work is related to *SDG-9: Industry, Innovation and Infrastructure*. All the authors contributed significantly to this manuscript, participated in reviewing/editing and approved the final draft for publication. The research profile of the authors can be verified from their ORCID ids, given below:

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Cite this article as: M. Malleli *et al.*, *Rasayan J. Chem.*, 19(2), 877-883(2026), https://doi.org/10.31788/RJC.2026.1929652.

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