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Article

Innovative Synthesis and Structural Elucidation of Imidazo[1,2-a]pyridines: Incorporating Molecular Docking for Targeted Interactions

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Abstract: A new group of 3-substituted heterocyclic molecules with bridge head nitrogen has been made using several steps of reactions. A well-known method was used to make the first 2-substituted heterocyclic compounds of pyridine. It involves mixing 2-amino pyridine with (2-bromo-1-(4-phenoxyphenyl)ethan-1-one). Using the Vilsmeier-Haack reaction, the carbaldehyde group was added to position-3 of the synthetic 2-substituted imidazo/pyridine rings. It was also found that 3-carbaldehyde reacted with 2-amino pyridine, creating new imidazo/pyridine rings. All of the molecules that were made were characterized using FT-IR, ^{1}H-NMR, and ^{13}C-NMR spectroscopy.The synthesized substances were looked at more closely using molecular docking to see how well they worked in stopping oxidoreductase, an enzyme that is linked to the growth of breast cancer.

Keywords: Imidazo[1,2-A] Pyridine, 4-(4-Chlorophenoxy)Benzoyl Bromide, Molecular Docking, Pyridin-2-Amines.

1. Introduction

In the field of molecular science, heterocycles are the most varied group of molecules. These have become very important, mostly in the biological, chemical, and industrial fields [1–3]. Heterocyclic structures with nitrogen have always gotten a lot of attention because they are so important in medicines, natural things, and basic materials [3–5]. Imidazo[1,2-a]pyridines are a group of nitrogenous heterocyclic molecules that have a pyridine moiety joined to an imidazole ring. These scaffolds have many biological effects, such as anti-inflammatory, anti-protozoal, antibacterial, anticancer, selective anxiolytic, and anti-ulcer qualities [6–8]. There are many medicines on the market that contain imidazo[1,2-a]pyridines derivatives. These include Olprinone (a heart-strengthening drug), Zolpidem (for insomnia), Miroprofen (a painkiller), Zolimidine (for peptic ulcers), Minodronic acid (an anti-osteoporosis drug), and Saripidem (an anxiety-reducing drug). It is also possible to make some rare N-heterocyclic carbenes from imidazo[1,2-a]pyridines. Because of its interesting structure, many synthetic methods have been created to make imidazo[1,2-a]pyridines [11]. The old way of making them involved mixing 2-aminopyridines with different chemicals, like α-halo ketones, arylglyoxal hydrates, and sulfonamides. The steps that 2-aminopyridines and nitroolefins take to react with each other [16]. Many people who have these illnesses are treated with broad-spectrum antifungal drugs. Certain pharmaceuticals employed for this purpose

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include azoles (imidazoles), which inhibit the lanosterol 14-demethylase (CYP51) enzyme, regulated by the CYP51/ERG11 gene. All CYP51 proteins possess heme as their prosthetic group within the active site. This group depends on cytochrome P450, an enzyme that is needed to make sterols. The chemicals we just talked about are very important to the fungus membrane [17]. Previous studies have shown that azoles and their derivatives are effective against a wide range of clinical samples and strains of Candida species. A lot of isolates have shown that they are not sensitive to azoles [18–20], so researchers need to look for other ways to treat fungal diseases. Reports indicate that imidazo[1,2-a]pyrimidine derivatives may serve as antifungal agents; nevertheless, they currently lack an appropriate pharmacological profile. Consequently, it is imperative to discover and synthesize novel compounds with superior pharmacological properties. Tschichibabin came up with the main way to make the imidazo[1,2-a]pyrimidine core, which involves 2-aminopyrimidine reacting with an alpha haloketone [23–26]. Different methods have been used to make imidazo[1,2-a]pyridines, but it is hard to make modified imidazo[1,2-a]pyridines that don't have a substituent at position 2 [27,28].

Experimental

Synthesis of 2-(4-(4-chlorophenoxy)phenyl)imidazo[1,2-a]pyridine (HA)

A solution was prepared by dissolving 0.020 mol of 2-amino pyridine and 0.020 mol of 4-(4-chlorophenoxy)benzoyl bromide in 25 ml of ethanol. The solution underwent reflux for a duration of six hours. The solution was subsequently cooled and adjusted to a basic pH of 10 through the addition of 5% NaOH. The resultant solid underwent purification and recrystallization utilizing ethanol subsequent to being rinsed with water, yellow solid (yield 87%), m.p 193-196 Chemical formal $C_{19}H_{13}ClN_2O$.

Synthesis of 2-(4-(4-chlorophenoxy)phenyl)imidazo[1,2-a]pyridine-3-carbaldehyde (HB)

Phosphorus oxychloride (6.00 ml) was introduced gradually to a round-bottom flask containing DMF (3 ml), while maintaining the temperature below 10 °C. A duration of 15 minutes was allocated for the stirring of the reaction mixture, after which a solution of compound (HA) (0.010 mol) in DMF (30 ml) was introduced. The reaction mixture underwent heating at a temperature of 75 °C for a duration of 14 hours. The amalgamation was subsequently permitted to cool prior to being decanted onto crushed ice. Subsequently, the precipitate underwent extensive washing with water and was refined using a solvent mixture of ethanol and acetone in equal proportions. product HB as brown solid (yield 75%), m.p 118-120, Chemical formal $C_{20}H_{13}ClN_2O_2$

Synthesis of (Z)-1-(2-(4-(4-chlorophenoxy)phenyl)imidazo[1,2-a]pyridin-3-yl)-N-(pyridin-2-yl)methanimine (HC)

In a solution of absolute ethanol (20 ml) combined with 2-3 drops of glacial acetic acid, an equimolar quantity of aldehyde (HB) (0.020 mol) and thiosemicarbazide (0.020 mol) were subjected to reflux for a duration of 4 hours. Upon completion of the reflux, the mixture was allowed to cool to ambient temperature, after which the solid product underwent a washing process with cold water and was subsequently purified using ethanol, resulting in the formation of compounds (HC). product C as yellow solid (yield 76%), m.p 185-187, Chemical formal $C_{25}H_{17}ClN_4O$.

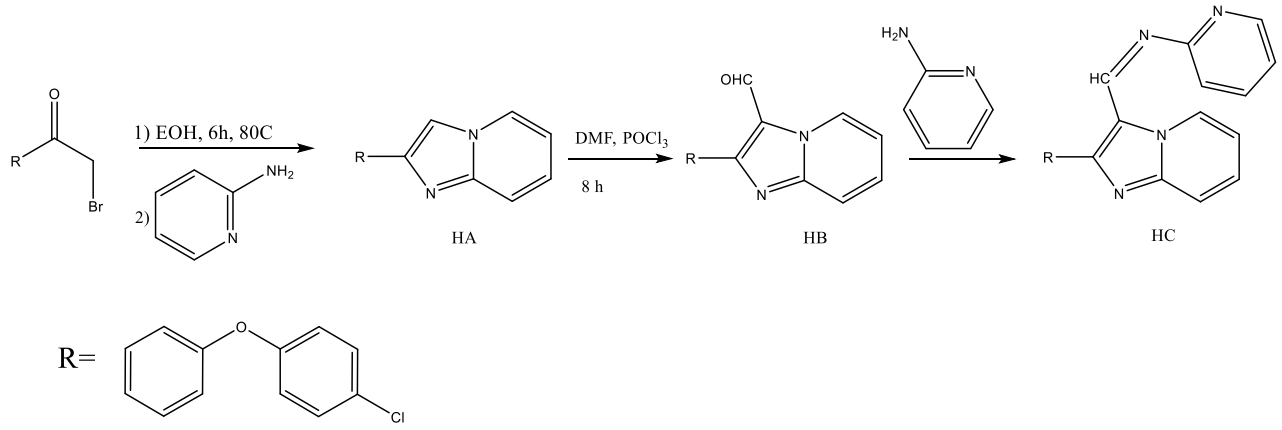
2. Materials and Methods

Molecular docking studies forecast probable chemical binding arrangements at protein active sites, offer critical insights into ligand-enzyme interactions, and facilitate the creation of innovative and effective inhibitors. The Molecular Operating Environment (MOE) tool was employed to conduct molecular docking on the enzyme to attain these objectives. Two pre-existing protein binding sites were individually docked to each ligand. Essential criteria, including binding score (S) and root mean square deviation

(RMSD), were employed to evaluate the docking data, thereby assessing the interaction quality and binding efficacy of each derivative to proteins.

3. Results

A one-pot technique was employed to manufacture novel imidazo[1,2-a]pyridine derivatives by combining two components: 2-aminopyridine, and (2-bromo-1-(4-phenoxyphenyl)ethan-1-one). All synthesized compounds yielded results; the molecular structure is validated by FT-IR, ^{1}H-NMR, ^{13}C-NMR . Scheme (1) illustrates all the produced chemicals.



Scheme 1. Synthesis route of compounds (HA, HB and HC)

In the first step, fused ring imidazo/pyridine were prepared by using one-pot reaction.Elemental analysis was as follows: $C_{19}H_{13}ClN_2O$.:IR (KBr/cm-1): 1633 (C=N) imidazo, 1475 and 1533 (C=C) aromatic, 1249, 1269 (C-O) imidazo pyridine, The NH_2 group bands of 2-amino pyridine are vanishing in the range of 3200-3300 cm^{-1}. ^{1}H-NMR (DMSO,500 MHZ): δ 7.15-8.19 (m,13 Ar-H). ^{13}C-NMR (DMSO, 500 MHZ): δ 114.60-131.57 (24 C- aromatic), 138.07 and 146.69 (C=N Ar), 164.12 and 154.35 (C-O).

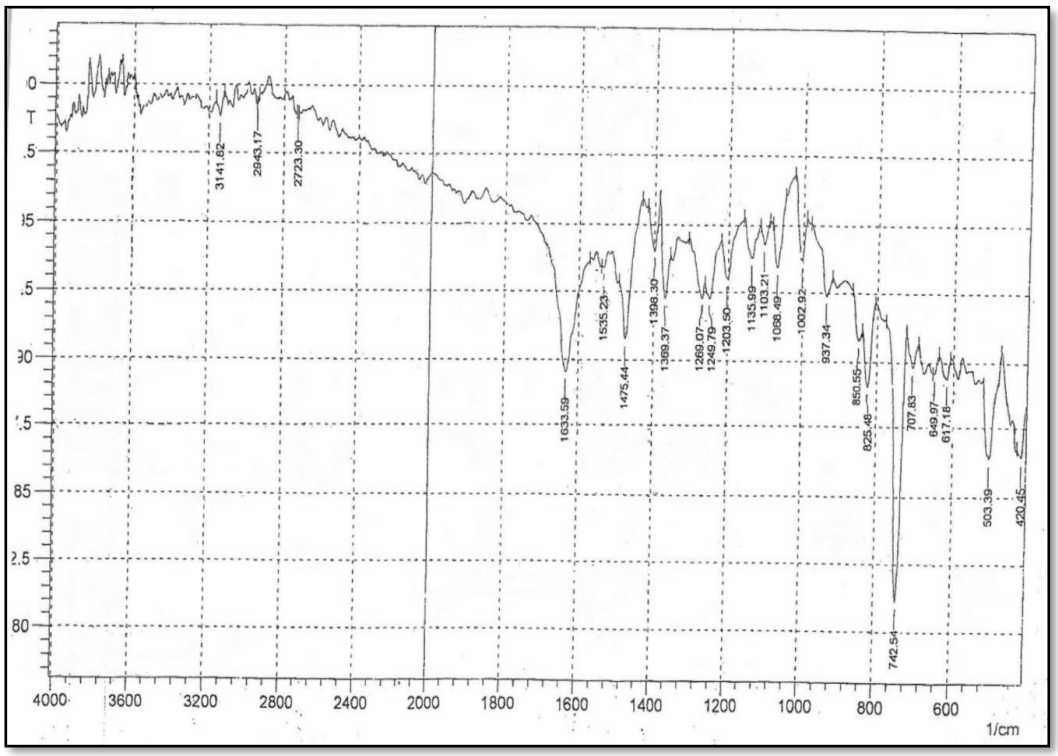


Fig 1. FT-IR spectrum of compound [HA]

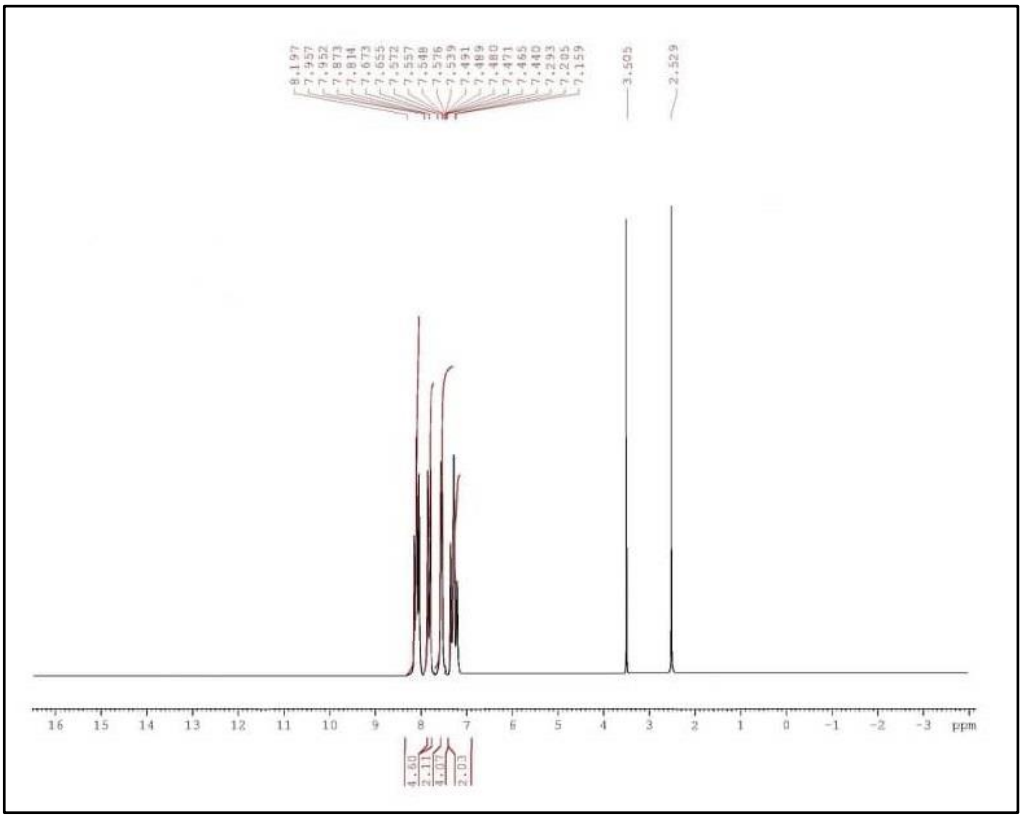


Fig. 2 : ^{1}H-NMR spectral data (ppm) compound [HA].

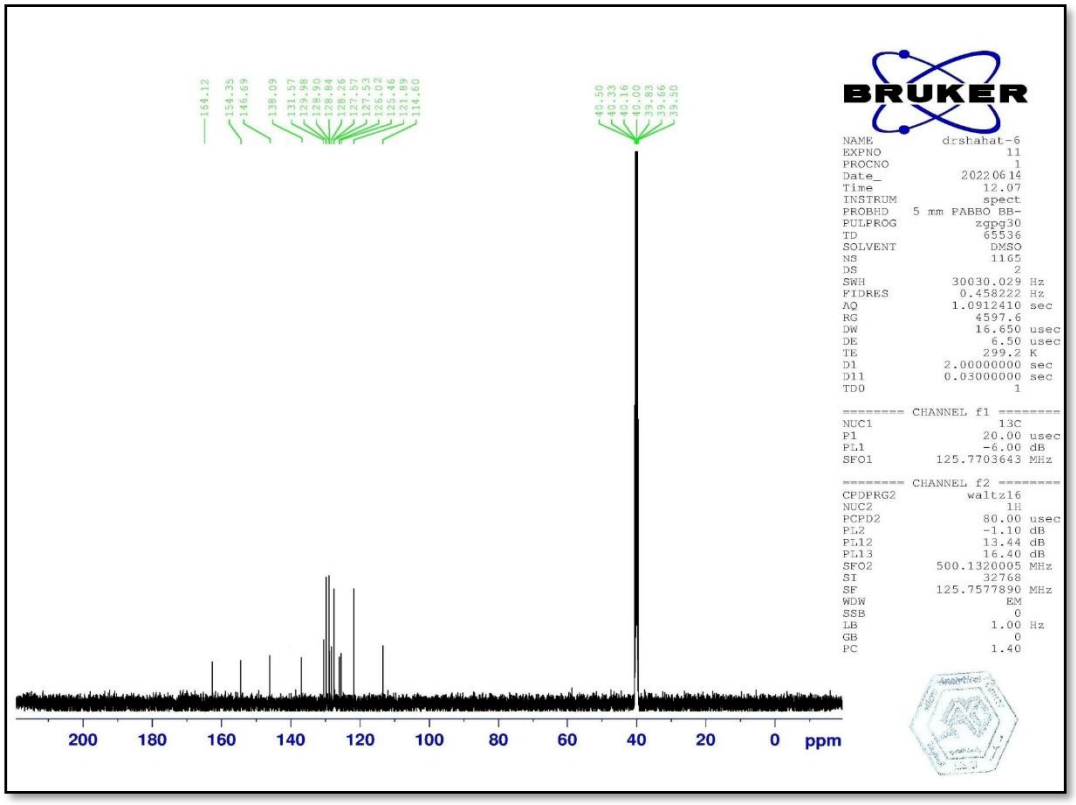
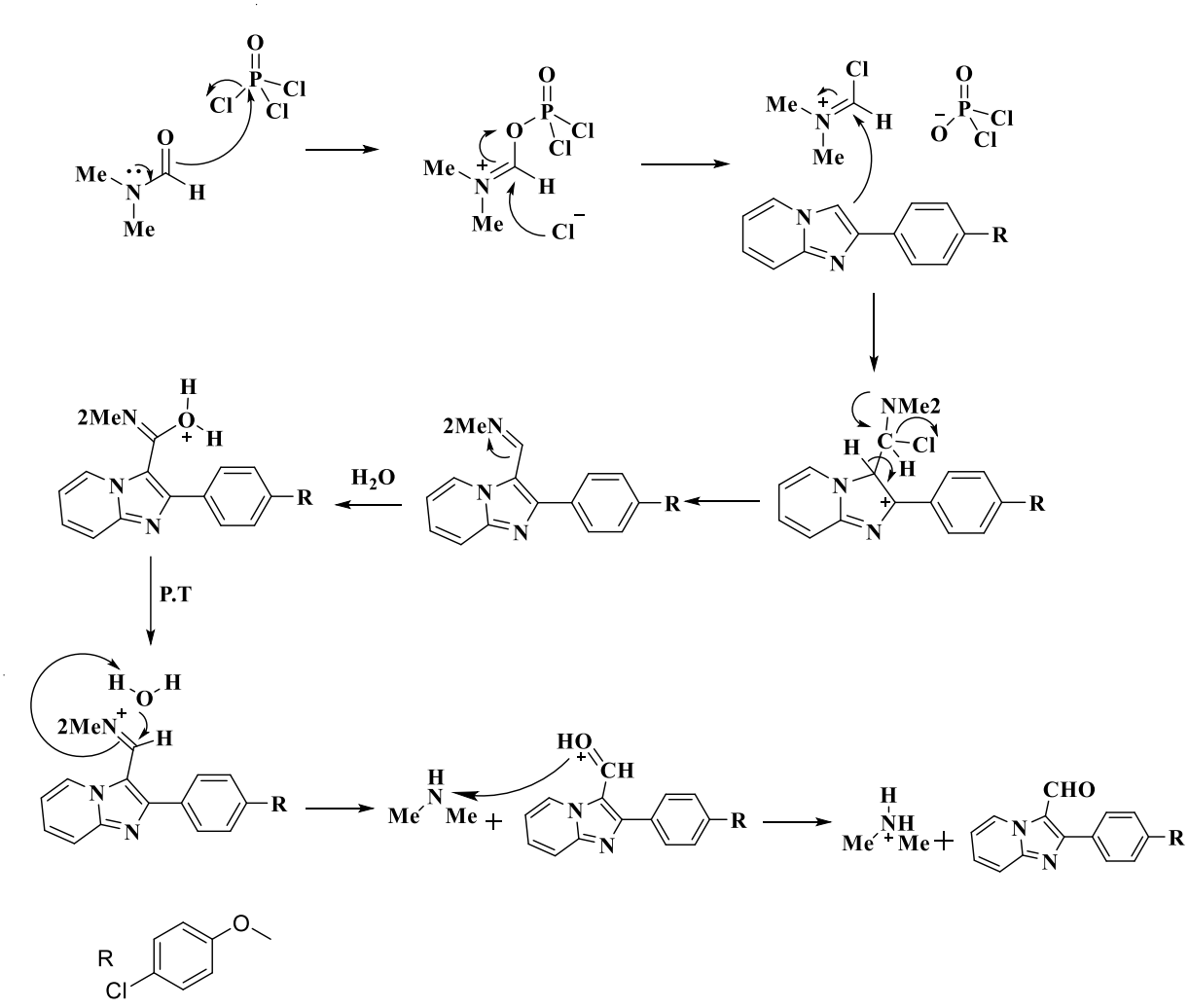


Fig. 3 : ^{13}C-NMR spectral data (ppm) compound [HA].

Compounds [HB] were synthesised by the Vilsmeier-Haack reaction to include the aldehyde group (CHO) at the 3-position. The reaction involved the amalgamation of phosphorus oxychloride ($POCl_3$) and DMF in chloroform ($CHCl_3$) with imidazo[1,2-a]pyridine [HA]. This approach enabled the targeted synthesis of the aldehyde-substituted imidazo[1,2-a]pyridine derivative at the specified location, as shown in the following mechanics Scheme (2).



Scheme 2. Synthesis mechanism of compounds [HB]

Elemental analysis was as follows: $C_{20}H_{13}ClN_2O_2$:IR (KBr/cm-1): 1693 (aldehyde group), 2817 and 2879 C-H stretching). ^{1}H-NMR (DMSO,500 MHZ): δ 10.134 (s, 1H, -CHO). ^{13}C-NMR (DMSO, 500 MHZ): δ 107.31-138.09 (20C- aromatic), 146.69 (C=N Ar), 154.35 (C-O), 184.12 (formyl group).

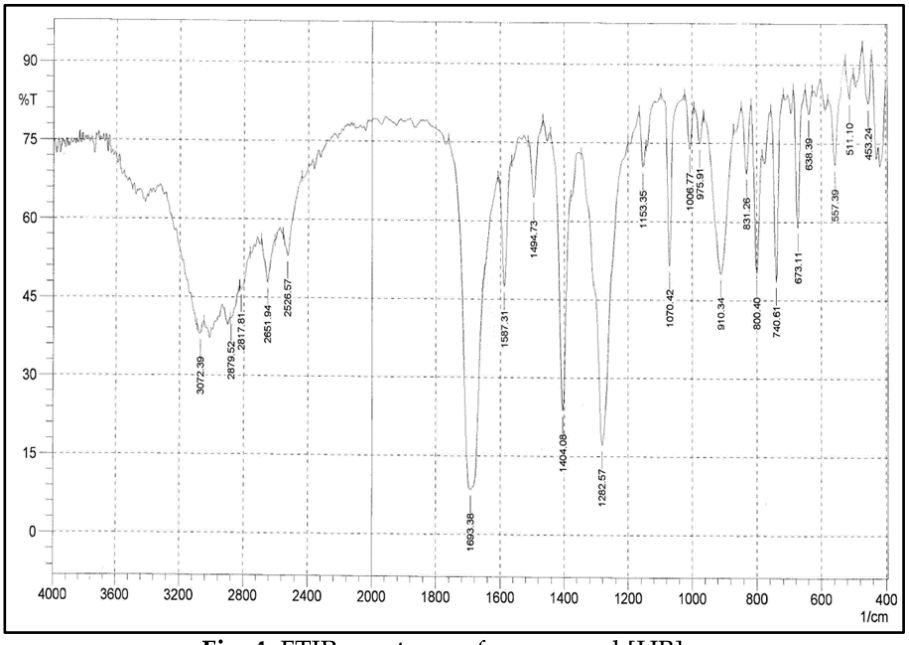


Fig. 4. FTIR spectrum of compound [HB].

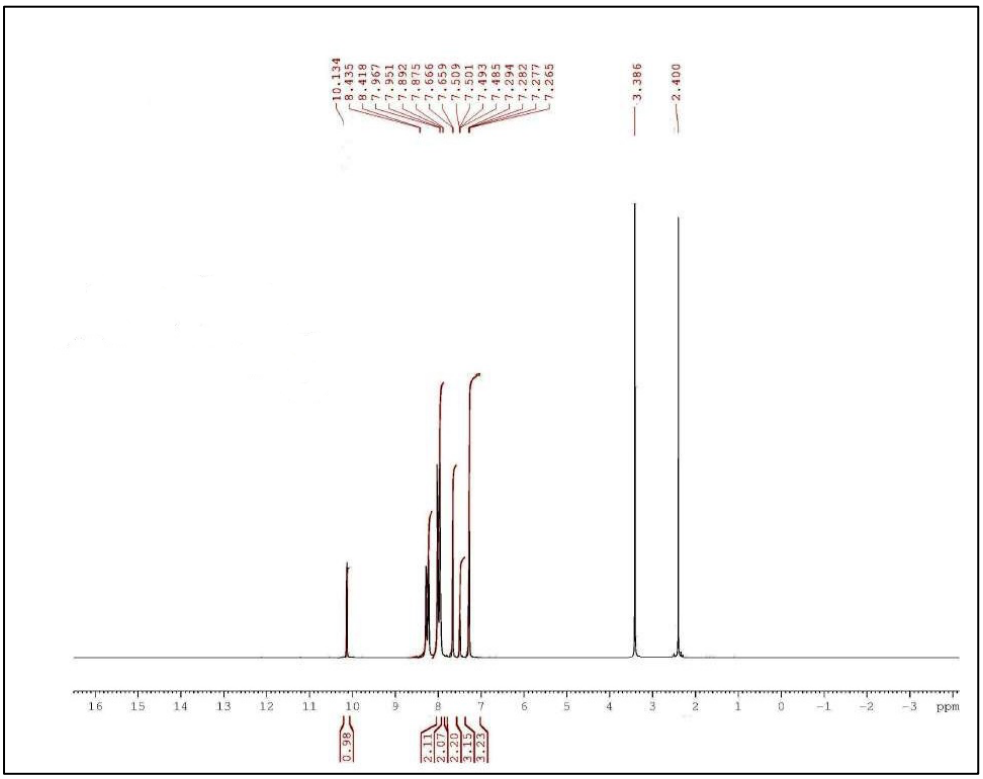


Fig. 5. ^{1}H-NMR spectral data (ppm) compound [HB]

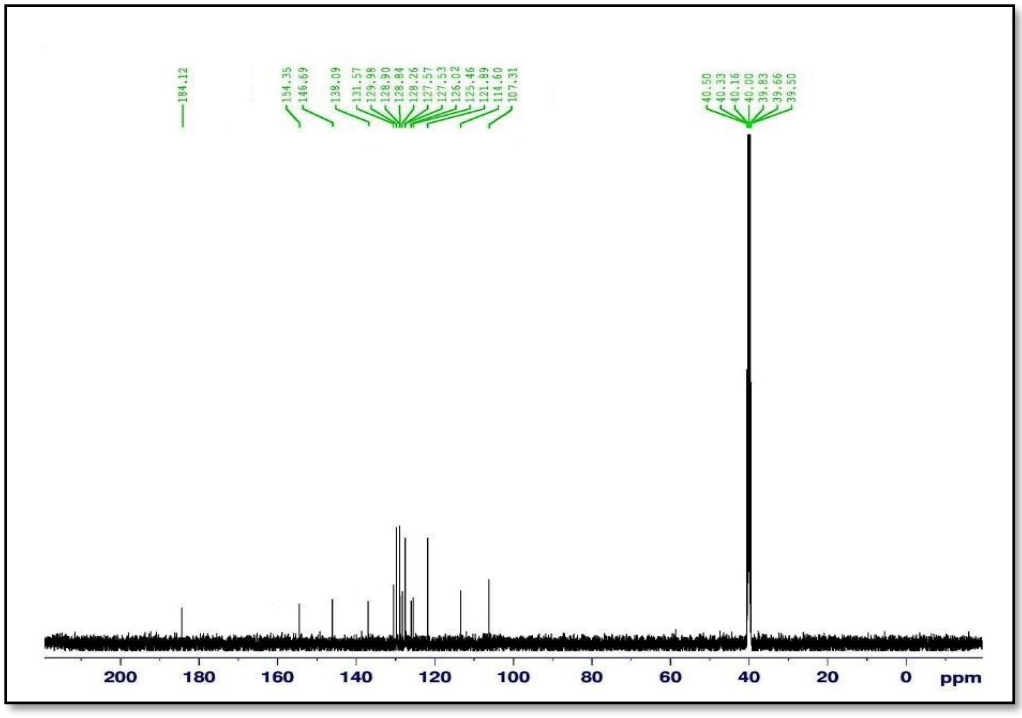
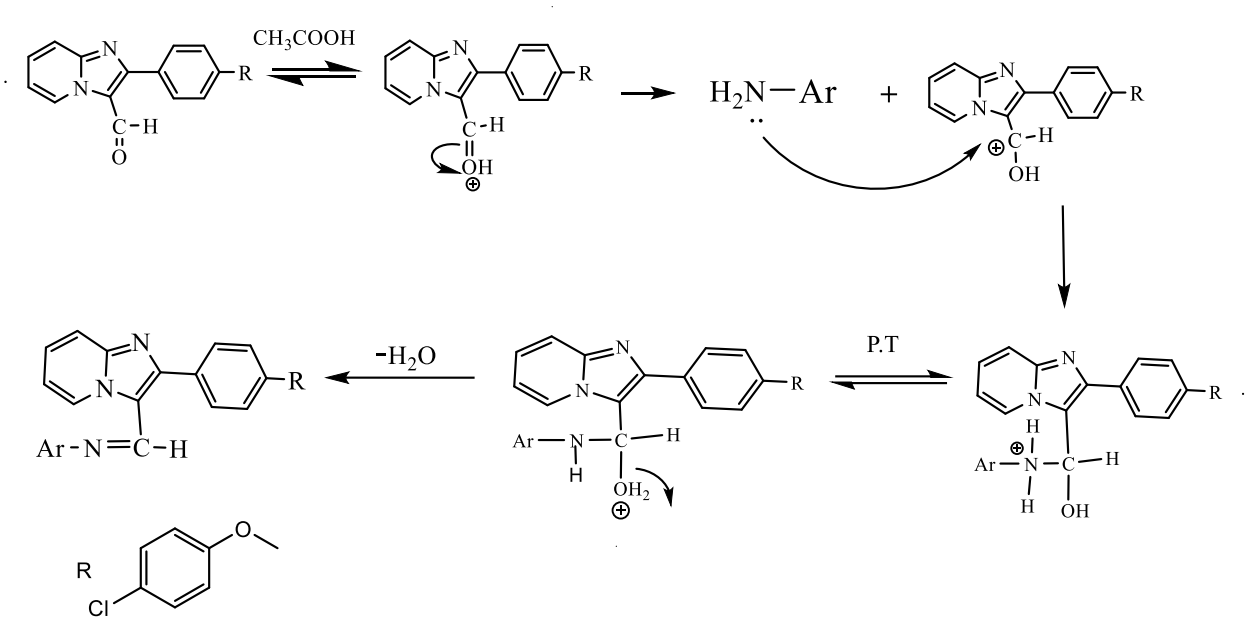


Fig. 6 : ^{13}C-NMR spectral data (ppm) compound [HB].



Scheme 3: Synthesis mechanism of compounds [HC]

Elemental analysis was as follows: $C_{25}H_{17}ClN_4O$:IR (KBr/cm-1): 1608-1633(C=N) Schiff base, 1087-1247 (C=N) imidazo/pyridine , disappearing bands of carbonyl group at (1693) cm^{-1} of aldehyde. ^{1}H-NMR (DMSO,500 MHZ): δ 9.39 (s,H,CH=N), 7.41-8.07(m, 20H, Ar-H). ^{13}C-NMR (DMSO, 500 MHZ): δ 114.25-139.67(25 C-Ar), 143.87 (C=N Ar), 151.59 (C=N Schiff base) and 155.16 (C-O).

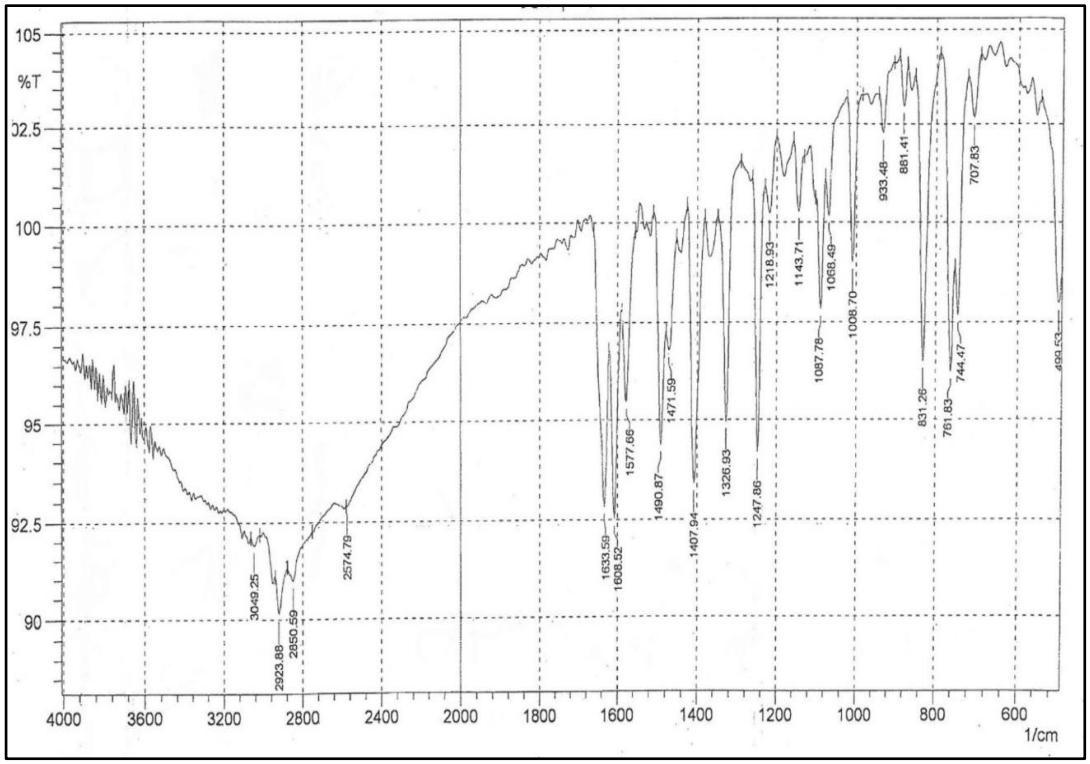


Fig. 7 : FTIR spectrum of compound [HC]

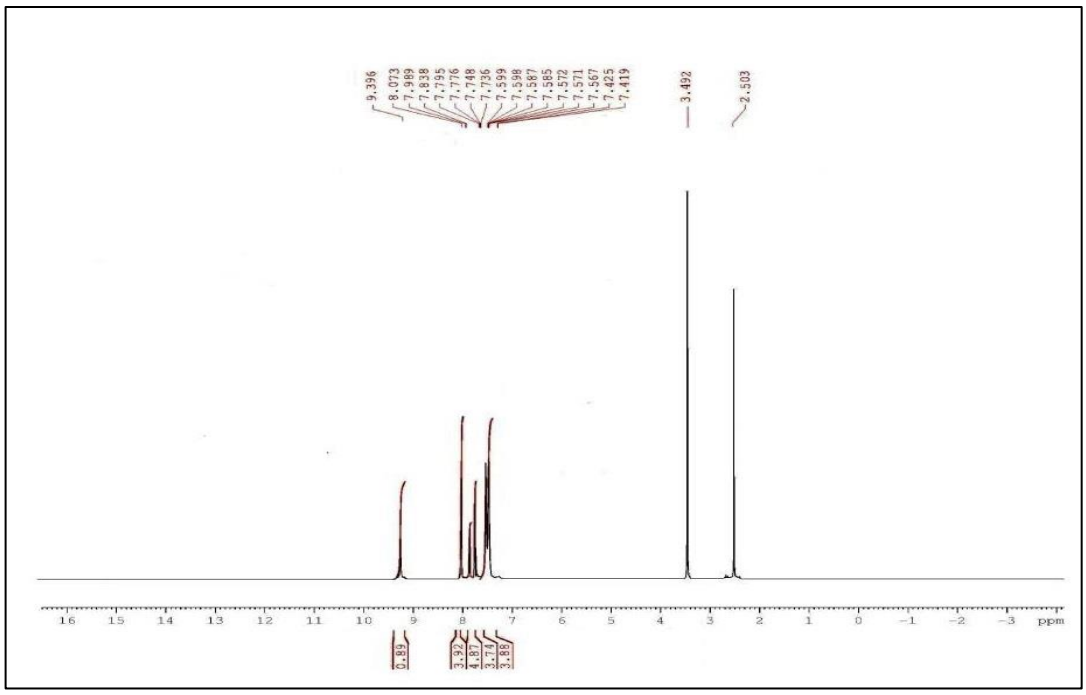


Fig. 8: [1]H-NMR spectral data (ppm) compound [HC].

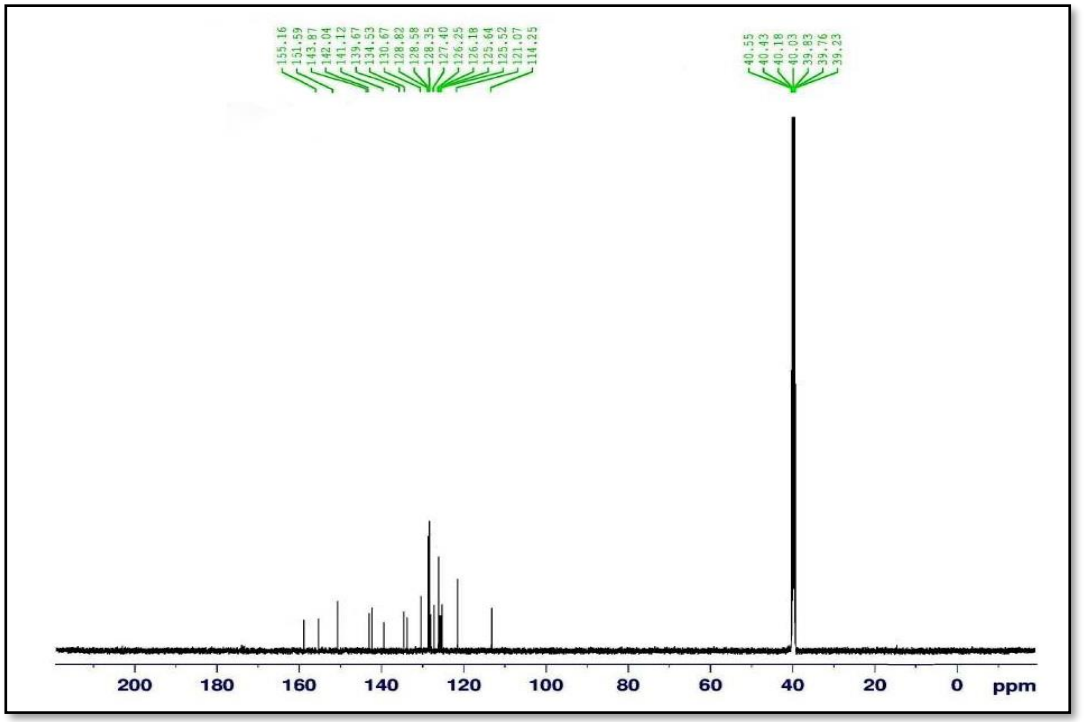


Fig. 9. [13]C-NMR spectral data (ppm) compound [HC].

The docking results

The molecular docking of compounds into the binding sites of the (human Leukotriene A4 hydrolase in complex with inhibitor sc57461A) showed that the compound HA, HB and HC gave the highest docking scores of (-9.995, -12.529 and -11.598) kcal/mol, respectively. Comparing the enzyme active site to the original ligand binding energy of -6.908 Kcal/mol and an RMSD value of 1.493. Figures 10-13. demonstrate that the compounds closely adhered to the original ligand position. The reduced RMSD of the synthesized compounds relative to the original ligand signifies that the compound's design enhances its binding stability to the protein. This suggests that the newly synthesized ligand exhibits a greater diversity and precision in its overlap with the target site compared to the original ligand. Consequently, the new ligand is likely to

demonstrate enhanced steric and chemical compatibility with the site, potentially indicating an improvement in the strength or specificity of the interaction. This is preferable for medicinal efficacy and provides a more precise structural representation than the reference ligand, as illustrated in Table 1.

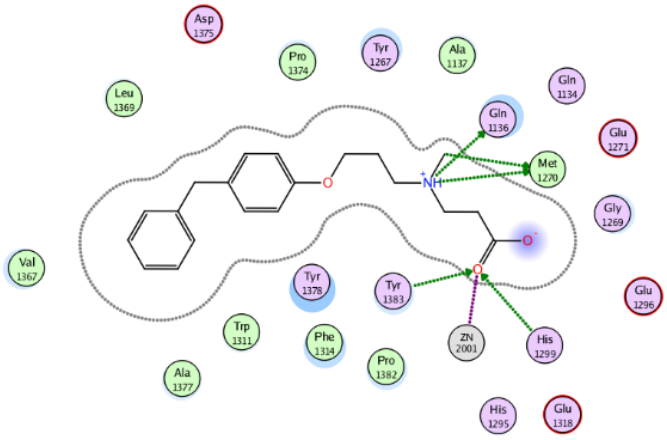


Fig. 10. The interactions of original ligand with with PDB: 3U9W.

Table 1. The docking of molecules (HA, HB and HC) are the overall energy value for the molecule under study.

Compound	S score (K cal/mol)	Rmsd	Binding amino acids
Original ligand 3U9W	-6.908	1.493	**Gln 1136, Met 1290, His 1299**
HA	-9.995	2.773	**Lys A1565, Gly A1268**
HB	-12.529	0.875	**HIS 1295 (H-acceptor), HIS 1299 (H-acceptor)**
HC	-11.598	2.268	**LYS 1565 (H-acceptor), TYR 1383 (pi-H)**

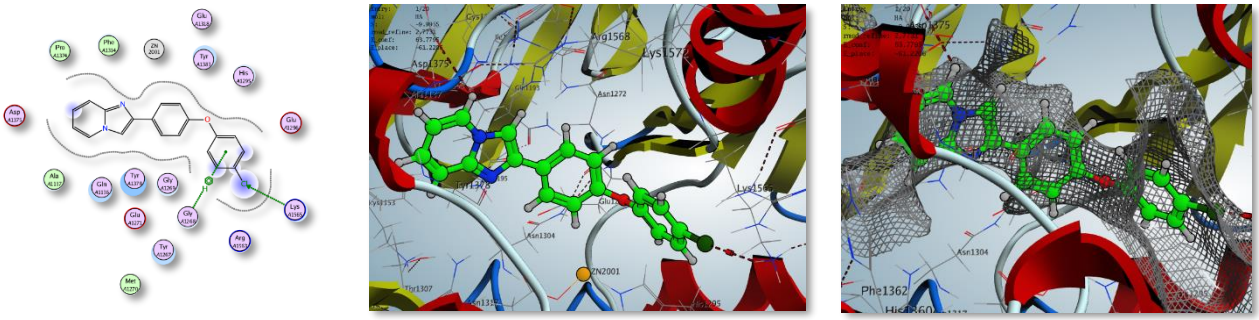


Fig. 11. Docking images of H**A** with PDB: 3U9W.

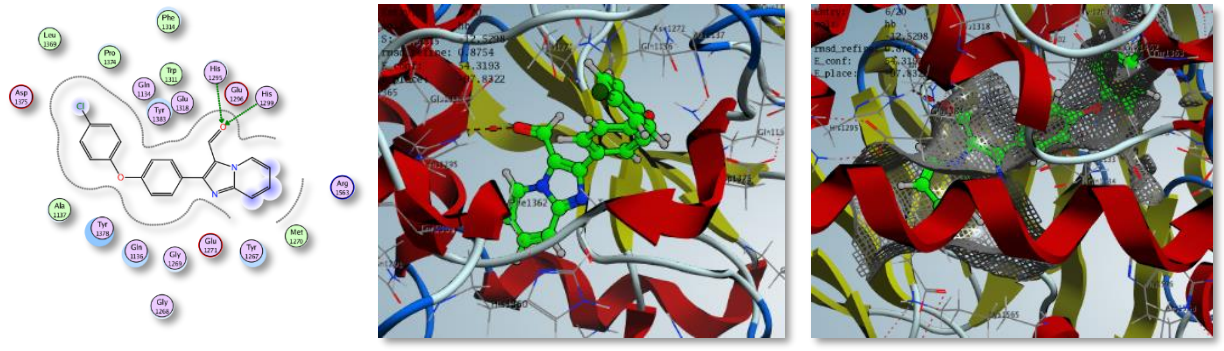


Fig. 12. Docking images of H**B** with PDB: 3U9W.

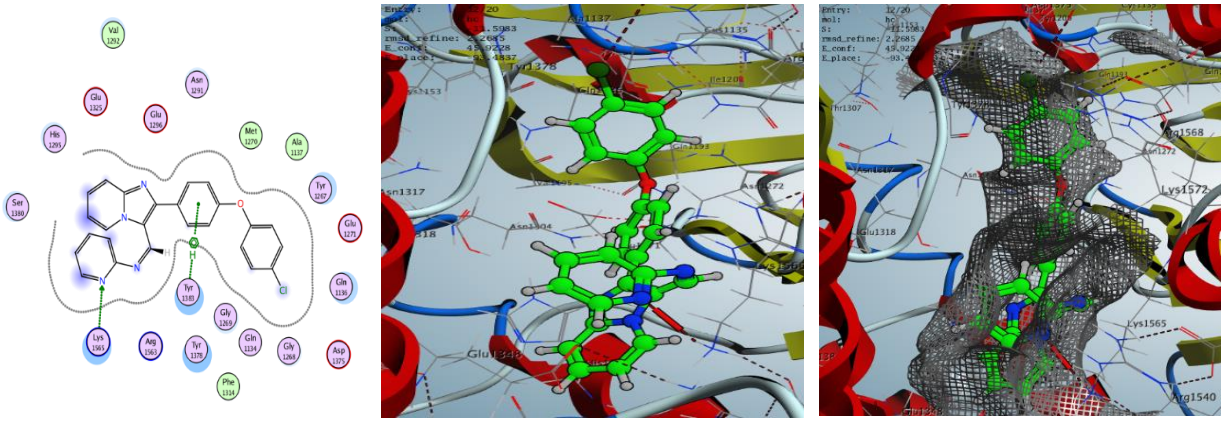


Fig. 13. Docking images of H**C** with PDB: 3U9W.

4. Conclusion

In conclusion, we developed an effective environmentally friendly technique for synthesizing imidazo[1,2-a]pyridine from 2-aminopyridines and aryl ketones, utilizing iodine as a catalyst. The current methodology eliminates the need for anaerobic conditions, metal catalysts, bases, and ligands, in contrast to prior methods. This study presents multiple practical benefits, including gentle reaction conditions, brief reaction times, compatibility with various functional groups, and effective performance under ambient atmospheric settings. Furthermore, this approach is operationally straightforward, devoid of additives, and can be utilized for the effective synthesis of several structurally significant motifs.

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