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Synthesis, Anticancer Evaluation and Molecular Docking of Novel Imidazo[1,2-*a*]pyridine Derivatives

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Imidazo[1,2-*a*]pyridine and its derivatives are widely recognized for their antifungal and anti-yeast activities, primarily through ergosterol synthesis inhibition. In this study, an efficient and high-yield synthesis route is presented for three novel imidazo[1,2-*a*]pyridine derivatives based on 1-(4-phenoxyphenyl)ethan-1-one. These compounds were synthesized by reacting 1-(4-phenoxyphenyl)ethan-1-one with pyridin-2-amine in presence of iodine as a cyclizing agent and ethanol. The structures of the synthesized compounds (**A**, **B** and **C**) were confirmed by spectroscopic techniques, including FT-IR, ^{1}H NMR and ^{13}C NMR. The molecular docking studies were conducted to evaluate their binding affinity toward oxidoreductase, a key enzyme in breast cancer progression, Compound **C** exhibited the highest binding energy (-9.207 kcal/mol) and interacted with essential amino acids (His 222, Tyr 216, Lys 270), anticancer activity was assessed against MCF7 (breast cancer) and PC3 (prostate cancer) cell lines using the MTT assay. These findings suggest that structural optimization enhances selectivity toward breast cancer cells, This study highlights the potential of tailored imidazo[1,2-*a*]pyridine derivatives as targeted therapies, particularly for breast cancer, further mechanistic and *in vivo* investigations are warranted to validate their selectivity and safety profiles.

Keywords: Imidazo[1,2-*a*]pyridine, Pyridin-2-amines, 1-(4-Phenoxyphenyl)ethan-1-one, Molecular docking.

INTRODUCTION

The presence of N-bridged heterocyclic systems particularly imidazopyridines is widely observed in various pharmaceutical compounds. Due to their diverse pharmacological properties, imidazo[1,2-*a*]pyridines hold significant importance in the medical field, particularly the substituents at the 2 and 3 positions [1,2]. They have so diverse biological effects, these compounds are important parts of many therapeutic drugs. As an example, alpidem and other 2,3-disubstituted imidazo[1,2-*a*]-pyridines work as anxiety-lowering drugs by changing gamma-aminobutyric acid (GABA) receptors in a way that makes people feel less anxious without making them sleepy [3,4] (Fig. 1).

Their wide range of drug effects is shown by their ability to block aromatase γ-aminobutyric acid (GABA) and benzodiazepine receptors. Moreover, these compounds possess cardioprotective characteristics, inhibit the development of β-amyloid (associated with neurodegenerative disorders) and function as non-peptide bradykinin receptor antagonists suitable for oral administration. This shows that they have a lot of potential for use in different treatment areas [5-11]. In addition to being used in medicine, imidazo[1,2-*a*]pyridine derivatives are also useful in dyes, optoelectronics and sensing materials [12,13].

Due to their versatility, scientists have developed efficient and eco-friendly methods of synthesizing these compounds [14,15]. Common ways to make imidazo[1,2-*a*]pyridines are to cyclocondensate 2-aminopyridines with α-haloketones or similar α,β-unsaturated carbonyl compounds under normal reaction conditions [16,17]. There are also two-step methods that use coupling processes between 2-aminopyridines and other chemicals, such as metal- mediated oxidative addition of alkynes [18-21], tandem methods with nitroalkenes [22]

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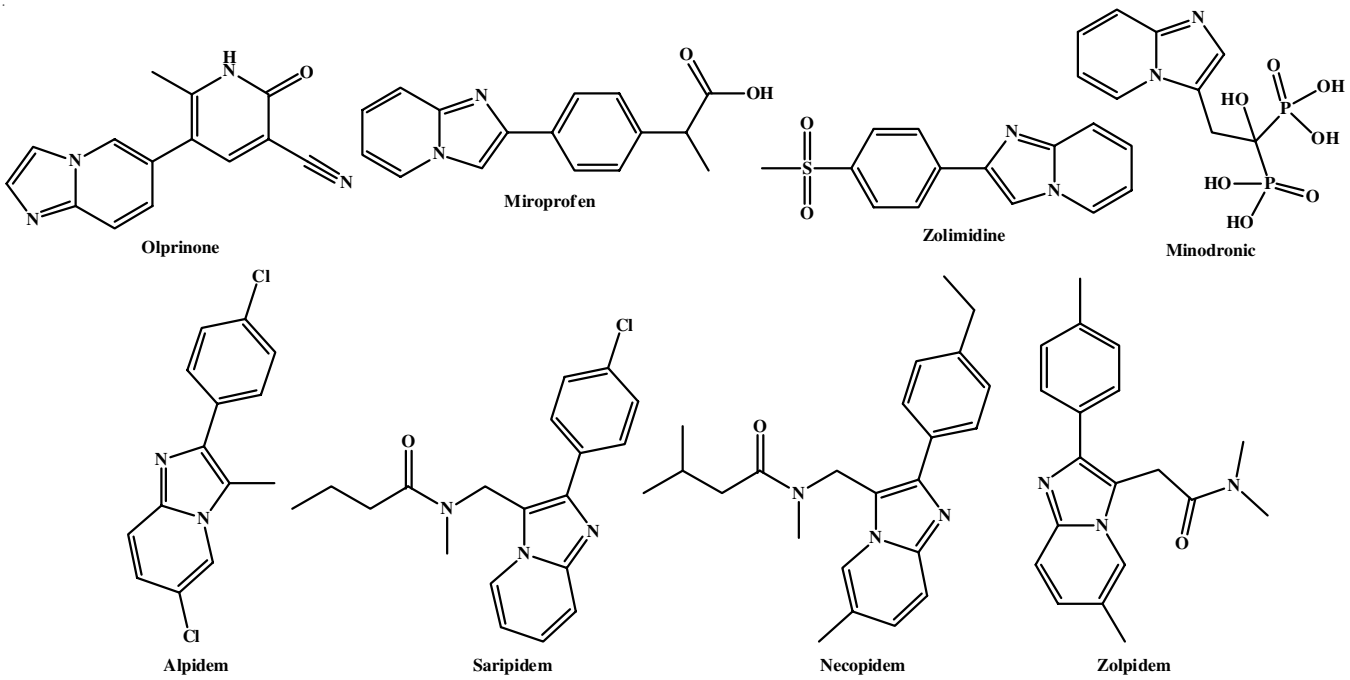


Fig. 1. Structure of some drugs based on imidazo[1,2-*a*]pyridine

and oxidative coupling of 1,3-dicarbonyl compounds [23-25]. These ways make it possible to synthesize imidazo[1,2-*a*]-pyridines with different functional groups, which makes them more useful in biology. Multicomponent reactions such as the Groebke-Blackburn-Bienaymé reaction and metal-catalyzed coupling have also proven particularly efficient for constructing imidazo[1,2-*a*]pyridines [26]. In this work, we present an improved synthetic approach for imidazo[1,2-*a*]pyridines using iodine in ethanol replacing the conventional DMSO solvent. This method eliminates the need for external metals or bases simplifying the reaction setup and reducing environmental impact. Enhanced efficiency is achieved through streamlined purification and higher yield compared to previous methods [27]. Furthermore, this study addresses these challenges by introducing an eco-friendly ethanol-based synthesis the scalability and cost of this strategy highlight its potential for industrial applications in pharmaceutical and chemical synthesis.

EXPERIMENTAL

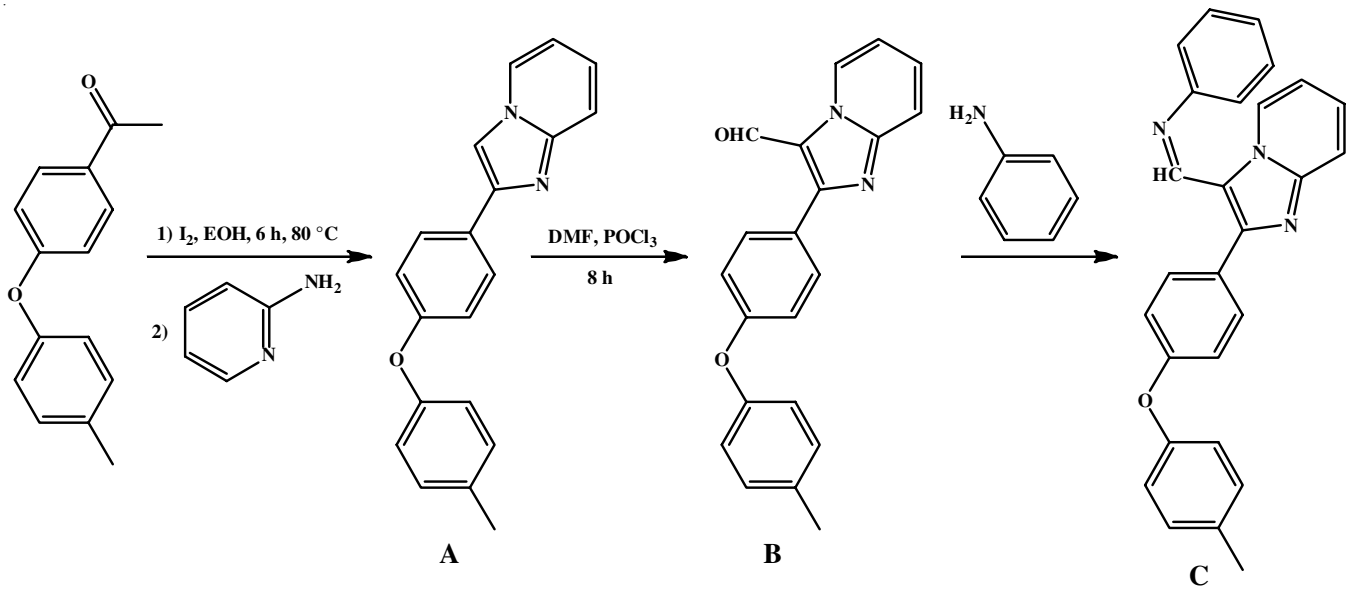
The chemicals and solvents were procured from Sigma-Aldrich, USA and used without further purification. The reaction was confirmed to be complete by TLC utilizing solvent solutions and iodine vapour. Using the Perkin FT-IR spectrometer, the infrared spectra were measured within the range of 4000-400 cm^{-1}. The ^{1}H and ^{13}C NMR spectra were measured in DMSO-d_6 solvent using TMS as internal standard. At 70 eV, spectra were acquired using Shimadzu GCMS-QP 1000 EX mass spectrometer. The melting points were measured with open capillaries and are uncorrected.

Synthesis of 2-(4-phenoxyphenyl)imidazo[1,2-*a*]pyridine (A): Iodine (0.02 mol) mixed with 1-(4- phenoxyphenyl)ethan-1-one (0.01 mol) in 20 mL of ethanol was heated up to 80 ºC for 3 h and then 2-aminopyridine (0.01 mol) was added. Once the heating process was over and then cooled down, the solution was made alkaline with NaOH (5%) until it reached pH 10. After the removal of solvent and purification of the residue by column chromatography, the desired product **A** was obtained as white solid (yield: 83%, m.f.: $C_{19}H_{14}N_2O$, m.p. 194-196 ºC).

Synthesis of 2-(4-phenoxyphenyl)imidazo[1,2-*a*]pyridine-3-carbaldehyde (B): Phosphorus oxychloride ($POCl_3$) (5 mL) was gradually introduced to a round-bottom flask containing DMF (3 mL), while maintaining the temperature below 10 ºC. The reaction mixture was agitated for 10 min, subsequent to which a solution of compound **A** (0.02 mol) in DMF (25 mL) was added. The reaction mixture was subsequently heated to 70 ºC and sustained for 12 h. Upon completion, the reaction mixture was permitted to cool prior to being poured upon crushed ice. Subsequent to aqueous washing, the product underwent recrystallization utilizing ethanol, gave the desired product **B** as brown solid (yield 78%, m.f.: $C_{20}H_{14}N_2O_2$, m.p. 116-118 ºC).

Synthesis of (*Z*)-1-(2-(4-phenoxyphenyl)imidazo[1,2-*a*]-pyridin-3-yl)-*N*-phenylmethanimine (C): Carbaldehyde (**B**) (0.01 mol) was dissolved in absolute ethanol (20 mL), then 2-3 drops of glacial acetic acid and aniline (0.01 mol) were added and heated under reflux in water bath for 6 h. The resulting mixture was cooled until the solid separated (**Scheme-I**). This solid was washed with water, filtered and purified by recrystallization from ethanol, gave the desired product **C** as white solid (yield 86%, m.f. $C_{26}H_{19}N_3O$, m.p. 180-182 ºC).

Cell viability in PC3 and MCF7 cells: The MTT assay was employed to assess cellular alterations and evaluate cellular viability. To breakdown the cells, trypsin was used. The cells were then analyzed and set to a density of 1.40×10^4 cells per well. A 86-well plates with 200 µL of new media were used to plant cells. They were left there for 72 h. Once a monolayer



Scheme-I: Synthesis route of compounds **A**, **B** and **C**

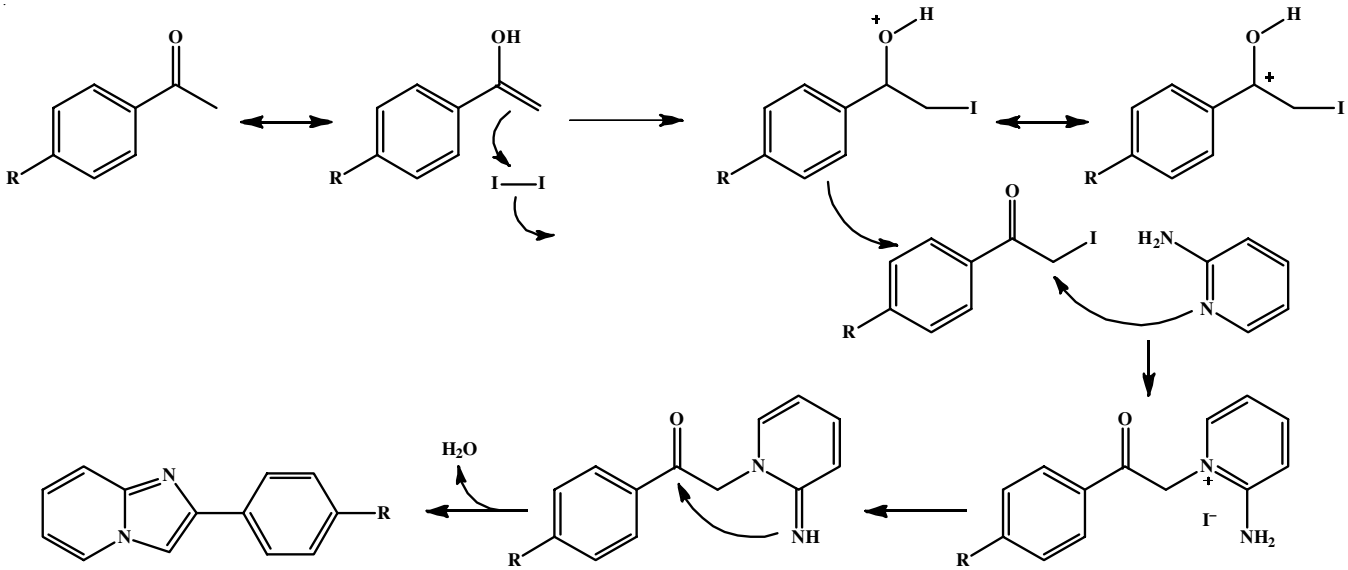
was formed, drugs (100 µg/mL) were added and left on the cells for 1 day at 37 ºC and 5% CO_2. After treating for 72 h, the top fluid was taken off and 200 µL of MTT solution (0.5 mg/mL in PBS) was added to each well. After that, the plate was kept in an incubator at 37 ºC for another 4 h to keep the monolayer culture in the original plate. After getting the cell fluid on top, 100 µL of DMSO was put into each well to make the MTT solution. Shaking the cells and keeping them at 37 ºC until all the crystals were gone was what was done. An ELISA device (Model wave xs2, BioTek, USA) and absorbance at 570 nm were used to test the survival of the cells. Using the right dose-response graphs, the IC_{50} value for chemicals was found to be the amount that killed 50% of the cells.

Molecular docking study: Molecular docking on the enzyme was carried out using the molecular operating environment (MOE) tool. Each ligand was docked to one of two possible protein binding sites on its own. We used important measurements like binding score (S) and root mean square deviation (RMSD) to look at the docking results and judge the quality of the interactions and how well each variation bound to proteins.

RESULTS AND DISCUSSION

One-pot procedure was used to synthesize new imidazo-[1,2-*a*]pyridine derivatives by mixing three components *viz.* 1-(4-phenoxyphenyl)ethan-1-one, 2-aminopyridine and iodine. In the first step, fused ring imidazo/pyridine were prepared by using one-pot reaction, where elemental iodine helps to form a compound α-iodoketone in the presence of EOH as a solvent (low toxicity), as shown in the following mechanics (**Scheme-II**).

The characteristic FT-IR peaks of compound **A** were observed at 1616, 1614 cm^{-1} attributed to (C=N) pyridine; the peaks at 1562, 1519 cm^{-1} are associated with (C=C) aromatic and 1479, 1498 cm^{-1} correspond to (C=N) imidazopyridine. The



Scheme-II: The plausible mechanism of compound **A**

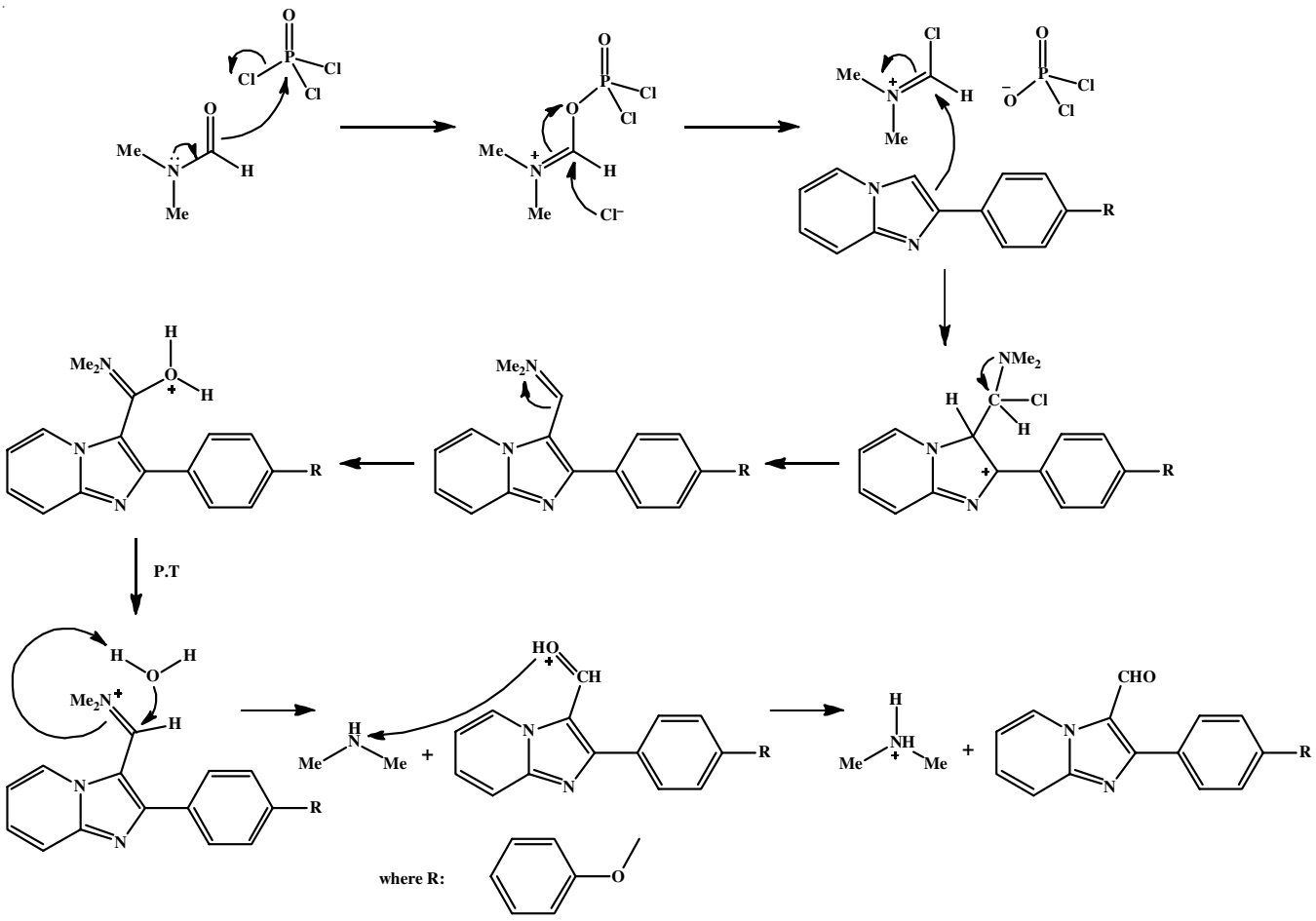
-NH_2 group of 2-aminopyridine is disappeared in the range of 3300-3200 cm^{-1}. ^1H NMR spectrum of compound **A** showed multiplate signals at δ 7.46-8.14 ppm for 2-substituted imidazo-[1,2-*a*]pyridine. It is key to observed that all compounds showed up in the downfiled signals, which is due to the aromaticity of the bridge head nitrogen fused rings removed the shielding effect, while ^{13}C NMR spectrum of compound **A** showed characteristic signals at 16.86 (CH_3), 113.44-134.53 (24 C-Ar), 141.07-148.93 (C=N Ar) and 154.91 (C-O).

The mechanism of synthesized compound **B** is shown in **Scheme-III**. Compound **B** was synthesized by the Vilsmeier-Haack reaction to introduce the aldehydic group (CHO) at the 3-position [28]. The reaction involved the amalgamation of $POCl_3$ and DMF in chloroform with imidazo[1,2-*a*]pyridine (**A**). This approach enabled the targeted synthesis of the aldehyde-substituted imidazo[1,2-*a*]pyridine derivative at the specified location.

The FT-IR spectrum of compound **B** shows the absorption bands at 1664 cm^{-1} and 1693 cm^{-1}, indicative of the carbonyl stretch of the aldehyde group in the fused imidazo pyridine-3-carbaldehyde.Moreover, the bands within the 2850-2870 cm^{-1} region were attributed to the C-H stretching of aldehyde group, providing the substantial evidence that the aldehyde had been introduced. The ^1H NMR spectrum of compound **B** exhibited a prominent signal at δ 10.1 ppm (s, 1H, -CHO), indicative of the aldehyde proton in the imidazo pyridine-3-carbaldehyde rings, hence affirming the existence of the aldehyde group inside the fused heterocyclic framework. The ^{13}C NMR spectrum showed the characteristic signals at 14.61 (CH_3), 113.41-137.59 (24 C-Ar), 146.09 (C=N Ar), 154.33 (C-O), 182.55 (formyl group).

Schiff base compound **C** were synthesized through the condensation of compound **B** with aniline in the presence of glacial acetic acid as catalyst. The FT-IR spectrum of Schiff base showed the characteristic band at 1637-1629 cm^{-1} belong to (C=N) Schiff base in fused rings of imidazo/pyridine. Another characteristic bands at 1618-1556 cm^{-1} is due to the stretching of (C=N) imidazo/pyridine and disappearance bands of carbonyl group at 1693-1664 cm^{-1}. ^1H NMR spectrum of compound **C**, displayed the characteristic signals atδ 9.31 ppm (s, H, CH=N), δ 2.19 (3H, s, CH_3), δ 6.80-7.94 (m, 17H, Ar-H). The ^{13}C NMR spectrum showed the characteristic signals at 17.46 (CH_3), 102.34-139.67 (24 C-Ar), 141.17-143.67 (C=N Ar), 151.07-155.16 (C=N Schiff base), 158.90-168.11 (C-O).

Cell viability assay: Using a 72 h IC_{50} assay and cisplatin as the reference drug, the anticancer activity of the synthesized compounds **A**, **B** and **C** against breast (MCF7) and prostate (PC3) cancer cell lines was assessed. Compound **C** demonstrated the strongest anticancer activity against MCF7 cells (IC_{50} = 50.56 μM), surpassing cisplatin (IC_{50} = 53.25 μM), which positions it as a promising candidate for breast cancer therapy. Compound **C** exhibited comparable efficacy to cisplatin against PC3 cells (56.16 μM *vs.* 55.44 μM). Compound **B** had signifi-



Scheme-III: Synthesis mechanism of compounds **B**

cantly lower activity in PC3 (58.32 μM) but nearly equal potency to cisplatin in MCF7 (54.09 μM), suggesting that the structural factors have a minor impact on cell-type selectivity. The higher IC_{50} values of compound **A** (MCF7 62.95 μM, PC3 60.78 μM) highlight the necessity of structural modification to improve efficacy (Table-1).

TABLE-1
THE IC_{50} VALUES OF THE SYNTHESIZED COMPOUNDS AGAINST DIFFERENT CANCER CELL LINES

Molecule	MCF7\72 h IC_{50} (μM)	PC3\72 h IC_{50} (μM)
A	62.95	60.78
B	54.09	58.32
C	50.56	56.16
Cisplatin (std.)	53.25	55.44

Based on the findings of a structure-activity relationship (SAR) investigation, molecular design is crucial. Compound **C** may have improved performance due to modifications to its functional groups that increase target binding affinity, membrane permeability or metabolic stability. Its superior selectivity for MCF7 over PC3 may be due to variances in drug-efflux processes or biological pathways, such as interactions between estrogen receptors in breast cancer cells. Although the precise mechanisms remain unclear, preliminary data suggest potential pathways such as oxidative stress induction, DNA crosslinking, or apoptosis activation *via* cisplatin-like mechanisms. Among the drawbacks include the lack of mechanistic research and toxicity data on the healthy cells. Future research should concentrate on exploring synergistic effects with cisplatin and *in vivo* validation structural improvements to increase PC3 activity. These findings highlight the importance of molecular design in the development of anticancer drugs and compound **C** is an excellent candidate for further preclinical studies, particularly in the area of breast cancer treatment.

Molecular docking results: Molecular docking technique was employed to predict the optimal binding mode of the ligands to the active site of 3-α-hydroxysteroid dehydrogenase (Fig. 2). Using the molecular operating environment (MOE), protein-ligand interactions were visualized and analyzed. The synthesized compounds **A**, **B** and **C** exhibited strong binding affinity to the active site of enzyme, akin to the native ligand, with additional interactions in the conserved binding pocket.

With the enzyme active site, the synthesized compounds **A**, **B** and **C** exhibited low RMSD (root mean square deviation) values ranging from 0.583 to 1.686 and improved binding energy (S.score) ranging from -7.315 to -9.207 kcal/mol. These values were calculated. With the enzyme active site when compared to original ligand binding energy of -9.0711 kcal/mol and RMSD value of 13.7123.

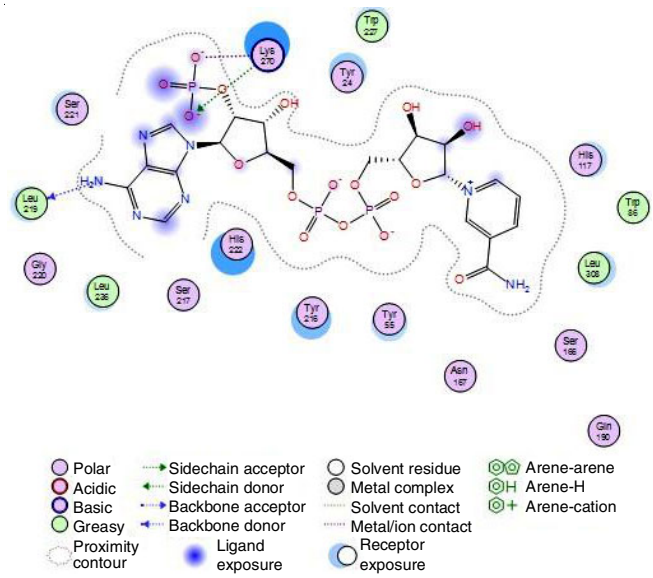


Fig. 2. 2D image of interaction of ligand with enzyme 3α-hydroxysteroid dehydrogenase (PDB code: 4XO7)

As illustrated in Fig. 3, all compounds adopted the binding poses similar to the original ligand, with compound **C** showing the most precise overlap. The lower RMSD values suggest enhanced structural compatibility, while the improved S-scores reflect stronger binding interactions [29]. These results imply that structural modifications in compound **C** enhance both steric and chemical complementarity, potentially increasing therapeutic efficacy (Table-2).

Conclusion

In conclusion, we have successfully synthesized and characterized three novel imidazo[1,2-*a*]pyridine derivatives based on 1-(4-phenoxyphenyl)ethan-1-one and studied their anticancer activity. Amongst the synthesized compounds, Schiff base compound **C** showed excellent anti-proliferative activity on all the tested cell lines, particularly in MCF7 cells (IC_{50} = 50.56 μM). The docking data showed that that compound **C** exhibited promising binding affinity against the targeted proteins compared to known references.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this article.

TABLE-2
DOCKING INTERACTION VALUES OF SYNTHESIZED COMPOUNDS WITH 4XO7 ENZYME

Compound	S score (K cal/mol)	RMSD	Number of binding sites	Binding amino acids
A	-7.315	0.583	5	His 217, Ser 217, Leu 268, Lys 270, Ser 217
B	-8.120	0.600	4	His 117, Lys 270, Ser 217, Lys 270
C	-9.207	1.686	4	His 222, Tyr 216, Lys 270, Tyr 216
Original ligand 4XO7	-9.0711	13.7123	3	Lys 270, Leu217, Lys 270

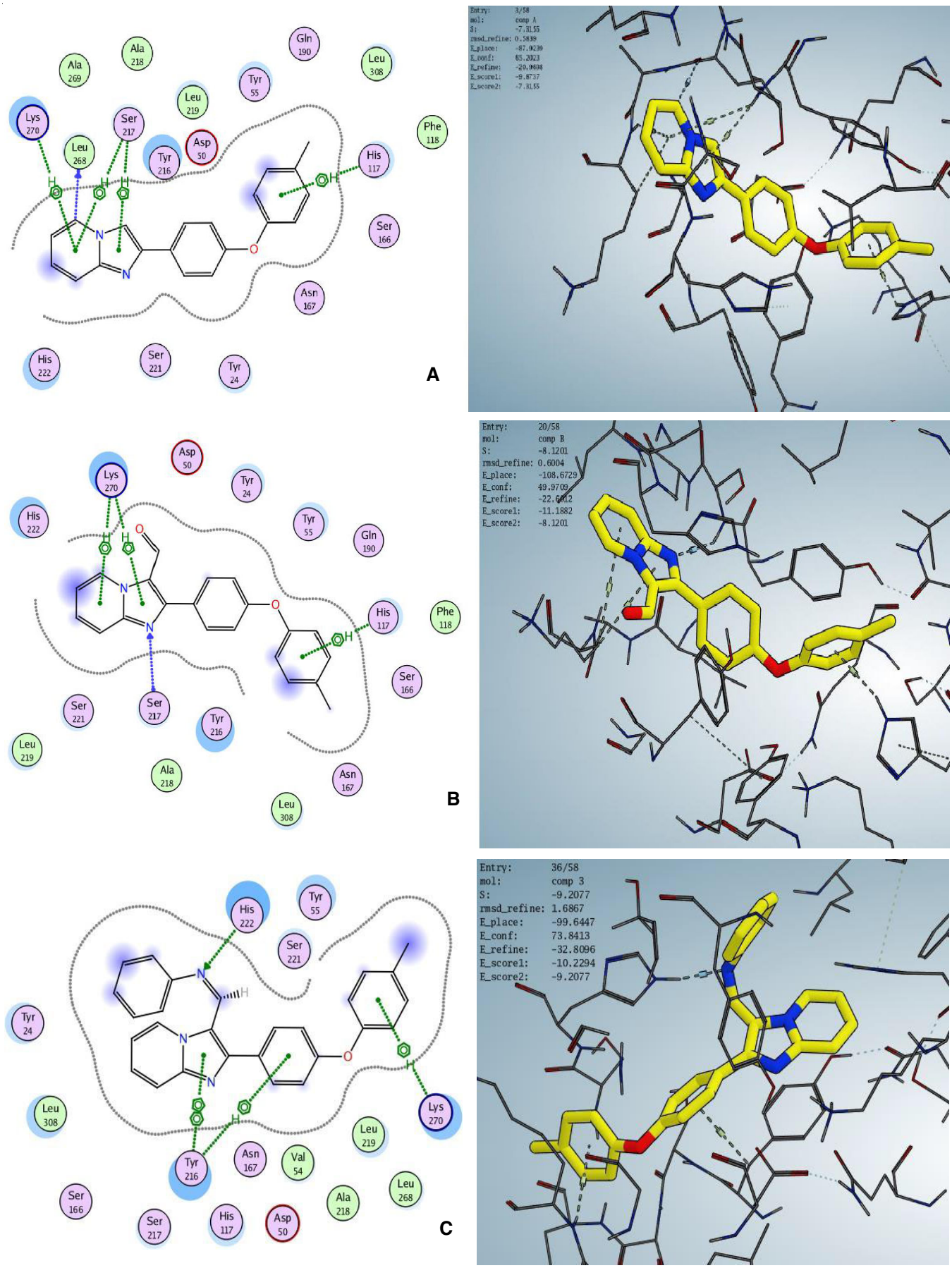

Fig. 3. 2D and 3D interactions of **A**, **B** and **C** with enzyme 3α-hydroxysteroid dehydrogenase (PDB code: 4XO7)

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