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COMPUTATIONAL STUDIES AND GREEN SYNTHESIS OF BENZIMIDAZOLES THROUGH SEQUENTIAL OXIDATIVE CYCLISATION OF ARYLDIAMINES IN SOLVENT-FREE CONDITIONS

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ABSTRACT

Benzimidazoles were synthesized under solvent-free conditions using Ionic Liquids (IL), specifically 1-Pentyl-3-methylimidazolium bromide ([pmim]Br), derived from aryl aldehydes and phenylenediamine. A comparative study of yields was conducted by reacting aryl aldehydes with both electron-donating and electron-withdrawing groups with substituted o-phenylenediamines, resulting in the formation of 2-phenylbenzimidazoles via cyclization. The yield of final products, optimum reaction conditions, plausible mechanism of the reaction, and the effect of substitutions at various positions of either of the reactants are presented in this paper. Computational studies have been done to explore the possibility of synthesized compounds for anticancer activity. Molecular docking studies were conducted to explore the inhibitory effects of steroidal derivatives against the estrogen receptor-derived Mutants [PDB ID: 2ITO]. The docking results of all compounds revealed significant inhibitory activity against the estrogen receptor 2ITO, with binding energy (ΔG) values for compounds 3a, 3b, 3c, 3d, 3e, 3f, and 3g against protein 2ITO recorded as -7.1 Kcal/mole, -7.3 Kcal/mole, -7.2 Kcal/mole, -7.8 Kcal/mole, -7.5 Kcal/mole, -7.6 Kcal/mole, and -7.6 Kcal/mole respectively.

Keywords: Aromatic Aldehydes, Phenyl Amine, Benzimidazole, Heterocyclic Compounds, Ionic Liquids
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INTRODUCTION

Benzimidazole, a bicyclic heterocyclic compound, has attracted considerable interest in organic chemistry and medicinal research due to its broad spectrum of biological activities and pharmaceutical uses.[1] Benzimidazole derivatives demonstrate a diverse range of pharmacological properties, encompassing antifungal[2], antibacterial[3], antiviral[4], anticancer[5], and antihelminthic[6] effects. The compound's ability to interact with various biological targets, such as enzymes and receptors, has led to the development of numerous therapeutic agents. The therapeutic value of benzimidazole has been explored through a number of current existing drugs, like Omeprazole(I) is used to treat the symptoms of gastroesophageal reflux disease, Carbendazim(II)[7], a fungicide; Telmisartan(III) for hypertension[8] and Astemizole(IV) is a long-acting, antihistamine used in the treatment of allergy symptoms.[9]The multiple therapeutic potential of benzimidazole is the reason for its exploration as an important drug candidate.[10] Several synthetic pathways have been proposed for the synthesis of benzimidazole. This versatile compound has been synthesized using different catalytic methods including chlorosulfonic acid[11], $Ce(NO_3)_3 \cdot 6H_2O$ as a promoter[12], sodium metabisulfite ($Na_2S_2O_5$)[13], $CuFe_2O_4$[14], iron[15], and a combination of 2-nitropyridine and triflic anhydride.[16] A novel one-pot synthesis strategy has been employed for benzimidazole production. One-pot syntheses are often preferred over multistep routes due to their higher yields and shorter time requirements. This approach is recognized for its environmental friendliness and efficiency in chemistry. Taking this perspective into account, we have developed a more environmentally friendly, one-pot synthetic pathway for benzimidazole, utilizing an ionic liquid as a catalyst.

This synthesis approach draws inspiration from Zare's research[17] on the preparation of 1-amidoalkyl-2-naphthols, emphasizing greener and higher-yielding methods for benzimidazole synthesis. The process involves the reaction of aryl aldehydes and phenylenediamine in the presence of 1-Pentyl-3-methylimidazolium bromide ([pmim]Br). The novelty of this research resides in employing 1-butyl-3-

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methylimidazolium bromide ([Bmim]Br) for the synthesis of benzimidazole derivatives. Additionally, computational and molecular docking studies were conducted to explore the inhibitory effects of steroidal derivatives against estrogen receptor-derived EGFR mutants [PDB ID: 2ITO].

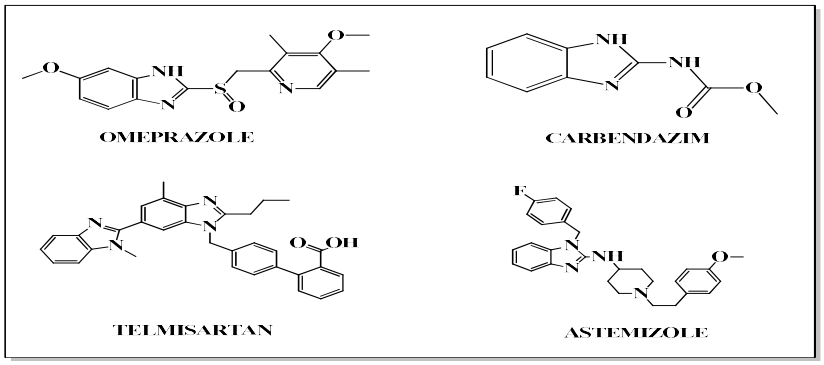


Fig.-1: Potential Therapeutic Compounds Containing Benzimidazole Scaffold

EXPERIMENTAL

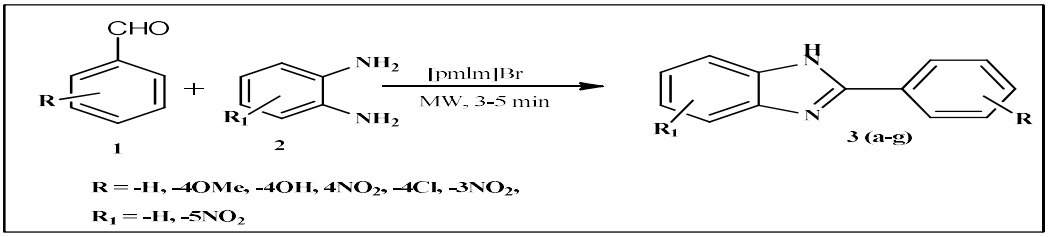
Material and Methods

The research's initial supplies (glassware, laboratory-grade chemicals, etc.) were sourced from commercial vendors (Sigma-Aldrich and Merck) and utilized without additional purification. Infrared spectra (IR) were directly captured using an Agilent Cary 630 spectrophotometer. Mass spectra were acquired using an Agilent 6520 Q-TOF instrument, while NMR spectra were obtained using a Bruker Avance 400 (FT NMR) DPX 300 MHz NMR spectrometer.

General Procedure

Step-1: Preparation Process for Ionic Liquid [pmim]Br

Methylimidazole [1.2 grams, 15 millimoles] and n-pentyl bromide [2.71 grams, 18 millimoles] were mixed in a small round-bottom flask. The mixture underwent heating in a water bath at 80 ℃ for an hour, with a guard tube positioned at the flask's mouth. This procedure resulted in the formation of a transparent, yellow, thick liquid. After cooling, it underwent two washes with a small volume of ether (1 ml each) to remove any unreacted bromide. Lastly, the remaining thick liquid was dried under a vacuum using a pump.



Scheme-1: Model Reaction for the Synthesis of Benzimidazole with the Help of Ionic Liquid

Step-2: General Procedure for Preparations of Benzimidazoles by Ionic Liquid(3a-3g)

An aryl aldehyde (1.0 g) and o-phenyldiamine (1.25 g) were combined and subjected to microwave heating (120 W, 10% power) under the influence of 500 milligrams of ionic liquid [pmlm]Br for a period of 3 minutes. After cooling, the mixture undergoing the reaction was subjected to ether extraction, subsequently, the obtained ether extract was evaporated to acquire the product. The crude product was later recrystallized from a mixture of ethanol and water (4:1) to yield a white solid.

Analytical Data of Synthesized Compounds

2-Phenyl-1H-Benzimidazole:3a

Pale yellow, Yield, 5.0 g, 93%; M.P.- 293-295 (°C); Calculated for $C_{13}H_{10}N_2$: C, 80.38%; H, 5.18%; N, 14.43%. Found: C, 81.41%; H, 5.20%; N, 14.43%. ^{1}H NMR (DMSO-d6, 400 MHz), δ (ppm): 13.12 (doublet, 1H, -NH), 8.34-8.33 (multiplet, 2H, aromatic -H), 7.82 (doublet,1H J = 7.2, aromatic -H), 7.56-

7.53 (multiplet, 3H, aromatic-H), 7.28-7.33 (multiplet, 4H, aromatic-H). ^{13}C NMR (100.6 MHz, DMSO-d6), δ (ppm): 152.00, 141.70, 115.23, 134.72, 131.47, 129.20, 127.52, 123.11. IR (KBr, cm^{-1}): 3544 (-NH), 1610 (C=N), 1450, 1100, 1200, 950. ESI-MS (positive mode): $[M+H]^+$ 240.071.

2-(4-Methoxy-phenyl)-1H-benzimidazole: 3b
Yellow solid, Yield, 4.1 g, 96%; M.P. 225-227(°C); Calculation for $C_{14}H_{12}N_2O$: Calculated - C- 74.96%, H- 5.38%, N- 12.48%. Found: C- 74.99%, H: 5.36%, N- 12.50%.; ^{1}H NMR (400 MHz, DMSO-d6) peaks: δ 13.71 (1H, -NH), 8.15 (doublet, 2H, J= 8, aromatic-H), 7.73 (doublet, 2H, J = 7.0, aromatic-H), 7.42-7.39 (multiplet, 2H, aromatic-H), 7.25-7.22 (multiplet, 2H, aromatic-H), 3.64 (singlet, 3H, -CH_3).; +IR (KBr, cm-1): 3439 (-NH), 2965 (C-C), 1613 (C=N). ESI-MS (positive mode): $[M+H]^+$225.069.

3-(1H-benzimidazol-2-yl)phenol: 3c
Orange solid, wt.- 2.0 g, M.P.- 321-323°C; Found: C- 74.30%; H- 4.78%; N- 13.35%. Calculated for $C_{13}H_{10}N_2O$: C- 74.31%, H- 4.76%, N-13.22%. ^{1}H NMR (DMSO-d6, 400 MHz): δ (ppm)- 12.65 (1H, -NH, singlet), 9.96 (b, 1H, OH), 8.01 (doublet, 2H, J = 2.4, aromatic-H), 7.53 (singlet, 2H, aromatic- H), 7.16-6.92 (multiplet, 4H, aromatic-H), 6.92 (doublet, 2H, J = 3.6, aromatic-H). ^{13}C NMR (DMSO-d6, 100.6 MHz) spectrum: δ ppm - 159.59, 152.25, 128.60, 122.00, 121.58, 116.16. IR (KBr, cm-1): 3308 (-NH, OH), 2965 (C-C), 1613 (C=N). ESI-MS (positive mode): $[M+H]^+$ 211.13.

2-(4-nitrophenyl)-1H-benzimidazole: 3d
Dull white, Yield, 3.0 g, 70%; M.P.- 324-326(°C). Found: C-65.28%, H-3.79%, N-17.58%. Calculated for $C_{13}H_9N_3O$: C-65.29%, H-3.78%, N-17.59%. ^{1}H NMR (DMSO-d6, 400 MHz,) spectrum: δ ppm - 13.02 (b, 1H, -NH), 8.31 (doublet, 2H, J = 7.2, aromatic-H), 8.07 (doublet, 2H, J = 7.2, aromatic-H), 7 .17-7.18 (multiplet, 4H, aromatic-H). ^{13}C NMR (DMSO-d_6,100.6 MHz), δ (ppm): 149.48, 144.24, 141.72, 135.50, 127.22, 124.77, 123.02, 115.92, 112.29.

3-(4-Chloro-phenyl)-1H-benzimidazole:3e
Brown solid, Yield, 2.87 g, 75%; M.P. 303-310(°C); Found: C- 68.30, H-3.98, Cl-15.53, N-12.28%; Calculatedfor $C_{13}H_9ClN_2$: C-65.29, H-3.78, N-17.59%; ^{1}H NMR (DMSO-d6, 400 MHz,), δ ppm: 12.88(singlet 1H, -NH), 8.18(doublet, 2H, J = 8.8, aromatic-H), 7.66-7.51(multiplet, 4H, aromatic-H); ^{13}C NMR (100.6 MHz, DMSO-d6), δ (ppm): 150.08, 146.78, 134.24, 129.74, 128.12, 122.34, 121.48, 118.42.IR (KBr, cm-1): 3544(-NH), 1621(C=N), 1450, 1550, 748.ESI-MS (positive mode): $[M+H]^+$ 230.12.

3-2-(3-Nitrophenyl)-1h-benzimidazole: 3f
Yellow solid, wt.- 2.02g, Yield- 78%, M.P.- 205-213°C. Found: C-65.30%, H-3.79%, N-17.58%. Calculatedfor $C_{13}H_9N_3O_2$: C-65.28%, H-3.76%, N-17.57%. ^{1}H NMR (400 MHz, DMSO-d6): δ ppm - 13.30 (b, 1H, -NH), 8.40-8.37 (multiplet, 4H, aromatic-H), 7.67 (singlet, 2H, aromatic-H), 7.23 (singlet, 2H, aromatic-H). ^{13}C NMR (DMSO-d6, 100.6 MHz): δ ppm - 150.01, 149.26, 147.67, 136.55, 134.23, 127.35, 124.17, 124.10, 122.98, 115.68. IR (KBr, cm-1): 3435 (-NH), 1625 (C=N), 1513 (NO_2), 1336. ESI-MS (positive mode): $[M+H]^+$ 230.119.

6-Nitro-2-phenyl-1H-benzimidazole: 3g
Yellow crystals, wt.- 2.36 g, Yield - 85%, M.P.- 300-312(°C); Found: C, 60.98%; H, 3.12%; N, 16.26%. Calculated for $C_{13}H_9N_3O_2$: C, 61.10%; H, 3.55%; N, 16.46%. ^{1}H NMR (DMSO-d6, 400MHz): δ ppm - 13.64 (1H, -NH, singlet), 9.39 (b, 1H, -OH), 8.53 (singlet, 1H, aromatic-H), 8.25-8.17 (multiplet, 2H, aromatic-H), 7.78 (doublet, 3H, J=6.6, aromatic-H). ^{13}C NMR (DMSO-d6, 100.6 MHz): δ (ppm) - 154.18, 144.18, 131.43, 129.62, 129.51, 127.46, 118.44. IR (KBr, cm-1): 3428 (-NH, OH), 1624 (C=N), 1512 (NO2), 1334. ESI-MS (positive mode): $[M+H]^+$ 257.319.

RESULTS AND DISCUSSION

Continuing our exploration of the effectiveness of straightforward one-pot, solvent-free techniques, we opted to examine the synthesis of biologically active benzimidazole derivatives. The reaction of

substituted aryl benzaldehydes with o-phenylenediamine resulted in the formation of benzimidazoles in an ionic liquid ([pmIm]Br). The reaction afforded products 3a-g with yields and purity as shown in Table-1.

Table-1: Displays the Completion Time and Discrete Yields of Each Compound

S. No.	Aryl aldehydes (R)	O-Phenylenediamine (R1)	In Ionic liquid		M.P(℃) Exp.	M.P(℃) Reported
			Time (min)	Yield[b] %		
3a	-H	-H	3min	85	293	295
3b	-4OMe	-H	3min	67	225	226
3c	-4OH	-H	3min	70	321	328
3d	-4NO2	-H	3min	95	324	326
3e	-4Cl	-H	3min	75	303	304
3f	-3NO2	-H	3min	73	205-207	207-208
3g	-H	-5NO2	3min	78	208	207-208

[a]Reaction condition: aromatic benzaldehyde (1 mmol), 2aminoaniline (1 mmol), [b] isolated yields, [c] Reported melting point

Molecular Docking

Docking analysis was employed to assess the pharmaceutical potential of the synthesized steroidal compounds. To conduct the molecular docking study, the three-dimensional molecular structure of the estrogen receptor target (PDB ID: 2ITO) was obtained via the Protein Data Bank. Table-2 presents bonding energy values resulting from molecular docking. The protocol docking validated by removing the inhibitor co-crystallized with the target receptor (PDB ID: 2ITO). Results of compounds 3a, 3b, 3c, 3d, 3e, 3f, and 3g demonstrated significant inhibitory activity against the estrogen receptor, with binding energy (ΔG) values of -7.1 kcal/mole, -7.3 kcal/mole, -7.2 kcal/mole, -7.8 kcal/mole, -7.5 kcal/mole, -7.5 kcal/mole, and -7.6 kcal/mole respectively (Table-2). Figures-2 to 8 illustrate the energetically most favorable docked structures obtained from the rigid molecular docking of compounds 3a, 3b, 3c, 3d, 3e, 3f, and 3g with 2ITO. A comprehensive examination of the binding interaction between compound 3a (Fig.-2) and the protein 2ITO indicated that 3a binds to the protein with a binding energy (ΔG) of -7.1 Kcal/mole. Compound 3a forms a π-cation bond with the protein 2ITO, The NH_2 group of the Lys745 amino acid residue interacts with the phenyl ring of the imidazole in 3a, maintaining a distance of 4.11 Å. Additionally, other interactions between the ligand and the protein were also observed.

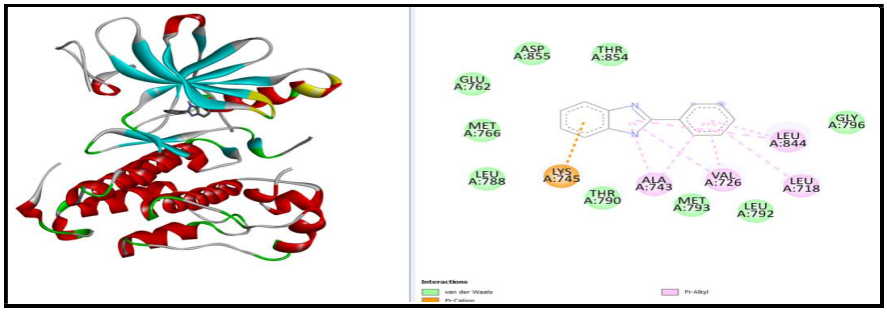


Fig.-2: A) Depiction of Docking Outcomes Showcasing the Integration of 3a within the Estrogen Receptor (PDB ID: 2ITO). B) Illustration of the 2D Interactions of 3a

Docking analysis of ligand 3b (Fig.-3) with the protein 2ITO indicated that 3b binds to the protein with a binding energy (ΔG) of -7.3 kcal/mole. Ligand 3b forms an π-cation bond with protein 2ITO, where the NH_2 group of the Lys745 amino acid residue interacts with the phenyl ring of the imidazole in 3b, positioned at a distance of 4.09 Å. Additionally, other interactions between the ligand and the protein were also observed. The docking analysis of ligand 3c (Fig.-4) with the protein 2ITO demonstrated that 3c binds to the protein with a binding energy (ΔG) of -7.2 kcal/mole. Ligand 3c forms an π-cation bond with protein 2ITO, where the NH_2 group of the Lys745 amino acid residue engages with the imidazole phenyl ring in 3c, positioned at a distance of 4.13 Å. Docking analysis of ligand 3d (Fig.-5) with the

protein 2ITO indicated that 3d binds to the protein with a binding energy (ΔG) of -7.8 kcal/mole. Ligand 3d forms one hydrogen bond with protein 2ITO, in this scenario, the -NH group of the Asp855 amino acid residue interacts with the oxygen atom of the nitro group in ligand 3d, maintaining a distance of 2.33 Å.

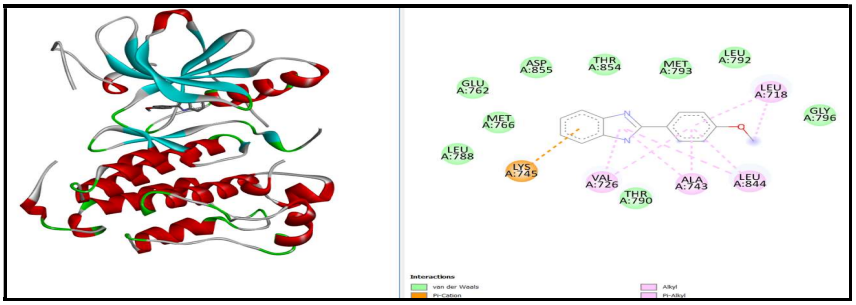


Fig.-3: (A) Visualization of Docking Outcomes Showcasing the Integration of 3b within the Estrogen Receptor (PDB ID: 2ITO), (B) Visualization of the 2D Interaction Pattern of 3b

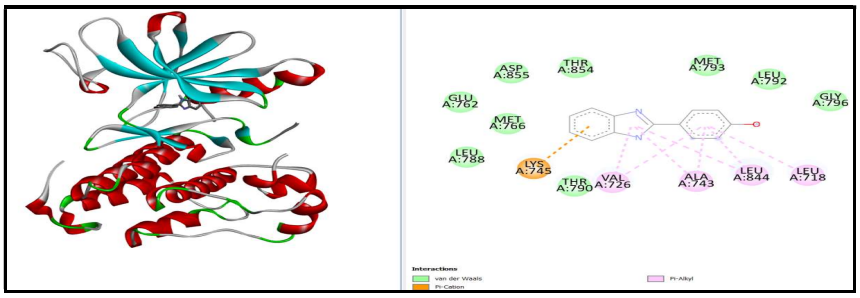


Fig.-4: (A) Visualization of Docking Outcomes Illustrating the Integration of 3c within the Estrogen Receptor (PDB ID2ITO), (B) Illustration of the 2D Interaction Pattern of 3c

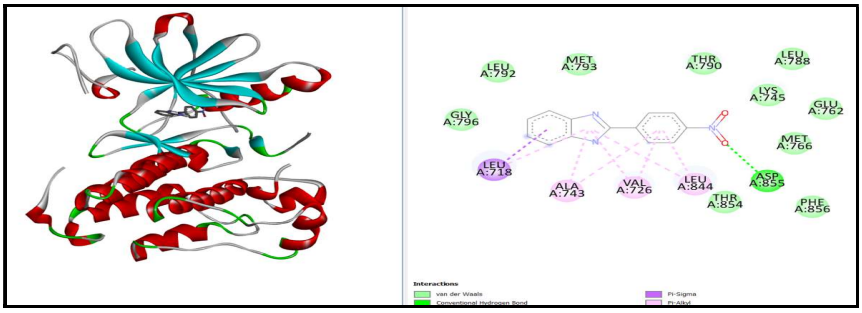


Fig.-5: (A) Docking Results Representation of 3d Incorporated into the Lung Estrogen Receptor (PDB ID: 2ITO), (B) Depiction of 2D Interaction of 3d

The docking analysis of ligand 3e (Fig.-6) with the protein 2ITO indicated that it attaches to the protein with a binding energy (ΔG) of -7.5 kcal/mole. Ligand 3e establishes a π-cation bond with protein 2ITO. This bond is formed by the NH_2 group of the amino acid residue Lys745 with the phenyl ring of the imidazole in 3e, at a distance of 4.12 Å.

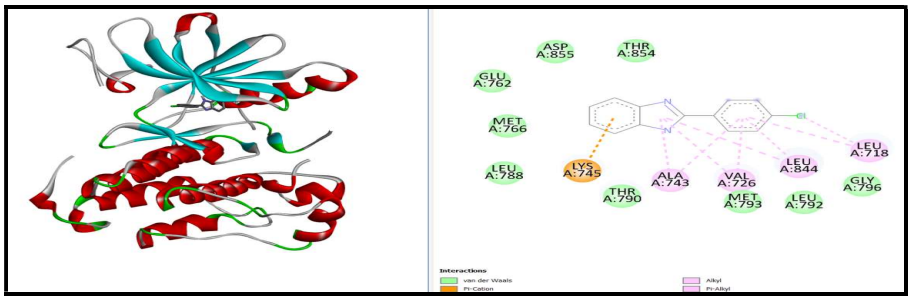


Fig.-6: (A) Visual Depiction of the Docking Outcomes Illustrating the Integration of 3e within the Lung Estrogen Receptor (PDB ID: 2ITO), (B) Illustration of the 2D Interaction Pattern of 3e

The docking analysis of Ligand 3f (Fig.-7) the interaction study involving the protein 2ITO indicated that 3f forms a bond with the protein, exhibiting a binding energy (ΔG) of -7.5 kcal/mole. Ligand 3f forms one hydrogen bond and π-sigma interactions with protein 2ITO.The NH group of the amino acid residue Lys745 forms a hydrogen bond interaction with the oxygen atom of the nitro group of the phenyl ring of 3f, spanning a distance of 2.31 Å. Additionally, pi-sigma interactions are formed between the CH group of the amino acid residues Val726 and Lue718 with the imidazole and phenyl ring of 3f at distances of 3.86Å and 3.68Å respectively.

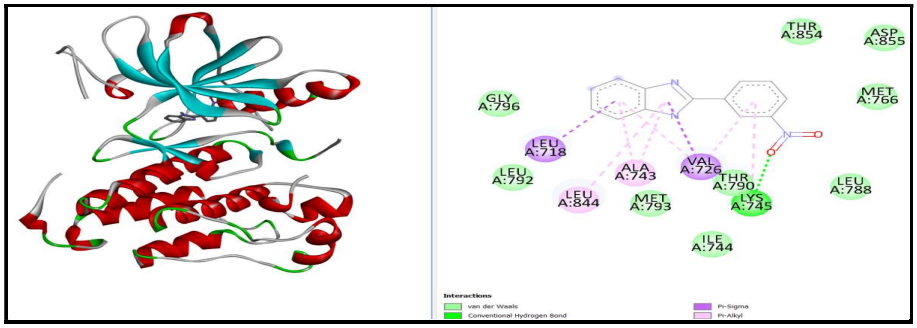


Fig.-7: (A) Visual Representation of the Docking Results Depicting the Integration of 3f within the Lung Estrogen Receptor (PDB ID: 2ITO), (B) Illustration of the 2D Interaction Pattern of 3F

The docking analysis involving ligand 3g (Fig.-8) and the protein 2ITO demonstrated that 3g attaches to the protein with a binding energy (ΔG) of -7.6 Kcal/mole. Ligand 3g establishes a π-sigma interaction with protein 2ITO, facilitated by the CH group of the amino acid residue Leu844 and the phenyl ring of the imidazole in 3g, at distances of 3.72 Å and 3.97 Å. Additionally, another π-sigma interaction is formed between the CH group of the amino acid residue Leu718 with the phenyl ring other than the imidazole of 3g at a distance of 3.72 Å.

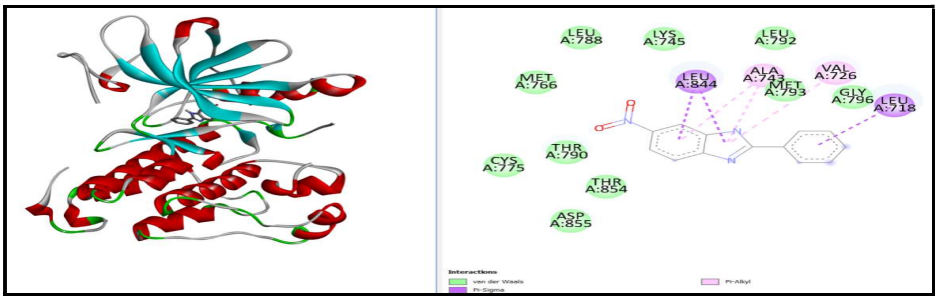


Fig.-8: (A) Visual Depiction of the Docking Results Illustrating the Integration of 3g within the Lung Estrogen Receptor (PDB ID: 2ITO), (B) Illustration of the 2D Interaction Pattern of 3g

The preceding analysis indicates that the synthesized benzimidazole derivatives may demonstrate inhibitory activity against protein inhibitors, yet further biological experiments are necessary to substantiate the computational predictions.

Table-2: Molecular Docking Results of Benzimidazole Derivatives 3a, 3b, 3c, 3d, 3e, 3f, and 3g (ligands) with the Target Protein (2ITO)

S. No.	Ligands	Binding energy (Kcal/mol)	H-Bonding
1	3a	-7.1	No hydrogen bond
2	3b	-7.3	No hydrogen bond
3	3c	-7.2	No hydrogen bond
4	3d	-7.8	Asp-A855
5	3e	-7.5	No hydrogen bond
6	3f	-7.5	Lys-A745
7	3g	-7.6	No hydrogen bond

Lipinski's Rule of Five

Lipinski's Rule of Five was employed via the Molinspiration server (http://www.molinspiration.com) to evaluate the oral bioavailability of the drug molecules. Lipinski's rule, established on five criteria, aids in predicting a compound's potential to serve as an orally active drug. As depicted in Table-3, the Total Polar Surface Area (TPSA) was calculated to determine the drug molecule's bioavailability, which is closely linked to the hydrogen bonding affinity of the synthesized compounds. TPSA values for all compounds 3a, 3b, 3c, 3d, 3e, 3f, and 3g ranged from 28.68 to 94.73. The number of rotatable bonds (nRot) indicates the conformational stability of the compounds. All the compounds exhibit nRot values falling within the range of 1-2, indicating that they are conformationally stable. Moreover, owing to the low molecular weight of the derivatives, they adhere to Lipinski's Rule of Five. Moreover, they adhere to Veber's Rules, indicating that active drugs with total hydrogen bonds of 12 or fewer, rotatable bonds of 10 or fewer, and a Polar Surface Area (PSA) of 140 or less are prone to have oral bioavailability of at least 20%. Hence, according to Veber's rule, it can be inferred that all the compounds are unlikely to encounter issues with oral bioavailability.

Table-3: Forecasted Molecular Characteristics of the Synthesized Compounds

Compounds	Mi LogP	TPSA	MW	n ON	NOHNH	N Violations	nRot	Volume
3a	3.54	28.68	194.24	2	1	0	1	180.27
3b	3.60	37.92	224.26	3	1	0	2	205.82
3c	3.07	48.51	210.24	3	2	0	1	188.29
3d	3.50	74.51	239.23	5	1	0	2	203.61
3e	4.22	28.68	228.68	2	1	0	1	193.81
3f	3.48	74.51	239.23	5	1	0	2	203.61
3g	3.48	74.51	239.23	5	1	0	2	203.61

Table-4 Prediction of molecular properties descriptors for compounds 3a, 3b, 3c, 3d, 3e, 3f, and 3g, This comprises LogP (Partition Coefficient), Total Polar Surface Area [TPSA], Molecular Weight [MW], Number of Hydrogen Bond Acceptor [nON], Number of Hydrogen Bond Donors[nOHNH] and Number of Rotatable Bonds[nRot]. Additionally, the table includes various bioactivities and drug-likeness scores of the synthesized molecules.

Table-4: Predicted Bioactivity Scores of the Synthesized Compounds.

Compounds	Gpcr Ligand	Ion channel modulator	Kinase inhibitor	Nuclear receptor	Protease inhibitor	Enzyme inhibitor
3a	-0.18	0.12	0.06	-0.46	-0..55	0.07
3b	-0.11	0.03	0.12	-0.29	-0.45	0.06
3c	-0.04	0.21	0.18	-0.14	-0.43	0.19
3d	-0.20	0.07	0.02	-0.34	-0.50	-0.01
3e	-0.11	0.13	0.09	-0.39	-0.52	0.05
3f	-0.20	0.06	0.06	-0.34	-0.50	0.01
3g	-0.20	0.10	0.05	-0.31	-0.52	-0.00

Plausible Mechanism

The aldehyde group initially undergoes a reaction with one of the amine groups of o-phenylenediamine, forming an electrophilic imine linkage. This is followed by an intra-molecular nucleophilic substitution by the remaining amine group in the ortho-position. Aromatic aldehydes containing both electron-donating and electron-withdrawing groups exhibited satisfactory reactivity. The structures of the products were determined based on their spectroscopic data. Subsequently, various benzimidazoles were synthesized using substituted phenylenediamines following the same protocol. The potential of incorporating electron-donating/withdrawing groups at para and meta positions was explored.

CONCLUSION

We've developed a novel and streamlined synthetic pathway for producing substituted benzimidazole. Incorporating ionic liquids, straightforward work-up and isolation procedures, one-pot synthesis, and yielding high quantities, this method emerges as the favored route for benzimidazole synthesis. Moreover,

docking results indicate promisingly high binding energies (ΔG) for the synthesized pregnenolone derivative, suggesting its potential utility against estrogen receptor-derived Egfr Mutants (PDB ID: 2ITO2ITO).

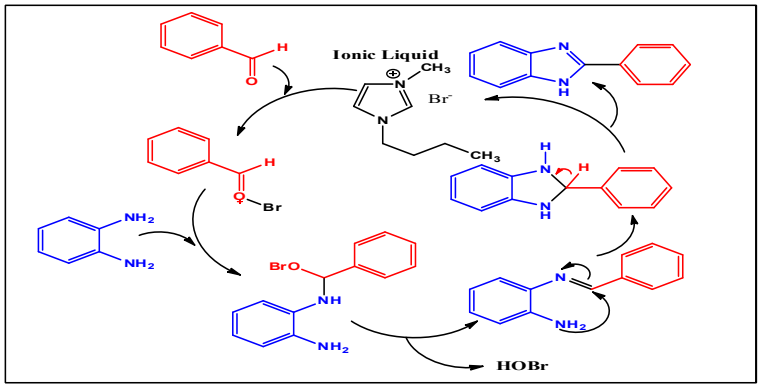


Fig.-9: Plausible Reaction Mechanism with Ionic Liquid

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CONFLICT OF INTERESTS

The authors declare that there is no conflict of interest.

AUTHOR CONTRIBUTIONS

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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