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Synthesis, Characterization, DFT, In Silico ADMET and Molecular Docking Investigations of a NO2-Donor Tridentate Schiff Base Ligand Against Cancer Targets

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Abstract: The tridentate Schiff base ligand (HPEYAP) from 2,4-pentanedione and 2-aminophenol was synthesised via conventional and grinding method. The ligand was characterized by FT-IR, UV–Vis, ^{1}H NMR, mass spectrometry, and elemental analysis. To give the theoretical evaluation of the quantum calculations and biological activity, computational techniques such Density Functional Theory (DFT), molecule docking, and ADMET investigations have been used. The energy gap (ΔE = 4.8176 eV), bond length, bond angle, and frontier molecular orbitals (HOMO and LUMO) of the optimized geometry of HPEYAP were predicted. The effectiveness of HPEYAP's inhibition against the estrogen receptor (3ERT) and CDK2 (3QTR) was predicted using a molecular docking analysis. The molecular docking results showed that the HPEYAP exhibited -6.4 and -6.7 kcal.mol^{-1} value of binding energy respectively. In-silico ADMET study of HPEYAP was also carried out.

Keywords: *Schiff Base, DFT, HOMO, LUMO, Molecular Docking, In-Silico ADMET Study.*

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I. INTRODUCTION

Millions of individuals worldwide are impacted by the complex and difficult disease known as cancer [1]. Over the last several decades, researchers have been interested in generating novel anticancer medicines with improved action and efficiency. Schiff base ligands and metal complexes are appropriate and useful molecules for anticancer medicines [2]. Schiff base ligands have C=N bond, due to this bond they are very good chelating agents. Additionally, if they have adjacent -OH group significantly enhance their coordination capacity, which allows a metal ion to create a ring with five or six members [3]. transition-metal ions are easily chelated by Schiff base ligands, creating stable mono- or polynuclear complexes with distinct chelate rings. The broad-spectrum antibacterial, anticancer, and antioxidant properties of Schiff base metal complexes make them of great interest for medicinal applications [4]. Schiff bases exhibit biological activity, including antibacterial [5], antifungal [6], antiviral [7,8], anticancer [9], and antidiabetic [10] activities. Schiff bases are still important ligands in the field of metal coordination chemistry, despite being present for more than a century after their discovery [11].

In this paper, we synthesize, and analyse the well-known Schiff-base ligand 2-{(E)-[(3Z)-4-hydroxypent-3-en-2-ylidene]amino}phenol (HPEYAP) [12]. In order to anticipate and investigate the interactions between the synthesized HPEYAP against the MCF-7 estrogen receptor with 4-hydroxytamoxifen (PDB ID: 3ERT) and CDK2 with inhibitor RC-1-148 (PDB ID: 3QTR) this work utilized molecular docking, a popular computational method in drug development.

II. EXPERIMENTAL

➢ *Chemicals and Instruments*

The chemicals and solvents are of AR grade and were purchased from Avra and CDH. and utilized without any additional purification. The IR spectra recorded using NICOLET iS50 FT-IR with diamond ATR was used in the range 4000-400 cm^{-1}. ^{1}H-NMR spectra (Bruker Avance Neo) were recorded at 400 MHz using DMSO-d_6 as solvents, with

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TMS as the internal standard at USIC. HRMS analysis using Waters Xevo G2-XS QTOF instrument was done at IIT Jammu. Elemental analysis for C, H and N was carried out using elemental analyser at IIT Jammu. UV-Visible spectra were recorded using UV1800i spectrophotometer (Shimadzu). The UV-Visible spectra of compounds were measured using DMSO as a solvent. Melting points were determined by using electrical melting point apparatus.

➢ *Preparation of HPEYAP*

- *Conventional Heating Method:*

Hot 2,4-pentanedione (1.00 g in 20 mL ethyl alcohol) was mixed with a hot solution of 2-aminophenol (1.09 g) in 20 mL ethyl alcohol. Small amount of CH3COOH was added in reaction mixture. Reaction mixture reflux for 2hr then reaction mixture cool at room temperature and stay for slow evaporation at room temperature for 24hr (fig 1). Brownish orange colour crystal obtained, filtered and washed with ethyl alcohol, after that filtered and washed with ethyl alcohol. Then dry at room temperature.

- *Grinding Method:*

2,4-pentanedione (1.00 g) was mixed with 2-aminophenol (1.09 g) in mortar and pastel then ground about 15 min. small amount of ethyl alcohol was added in reaction mixture and grind about 15 min then added 5mL ethyl alcohol in reaction mixture and let it stands at room temperature for 24hr. Brownish orange colour crystal obtained, washed with ethyl alcohol and filtered. Then dried at room temperature.

Mp:180° Anal.Calcd for C11H13NO2 (191.23):C,69.47; H, 6.89; N, 7.37. Found: C, 69.31; H, 6.49; N, 7.46. FTIR (ATR, cm^{-1}): 3374 (O-H), 1587 (C=N), 1533 (Ar C=C), 1504 (Ar C=C), 1277 (phenolic C-O).

1H-NMR (400 MHz, DMSO-d6): 12.15 (s, 1H, OH), 9.92 (s, 1H, Ar-OH), 7.17-6.77 (m, 4H, Ar-H), 5.20 (s, 1H, C=CH), 2.33 (s, 3H, -CH3), 1.97 (s, 3H, -CH3) ppm. Mass (ESI-MS, m/z): 192 [M+H] +

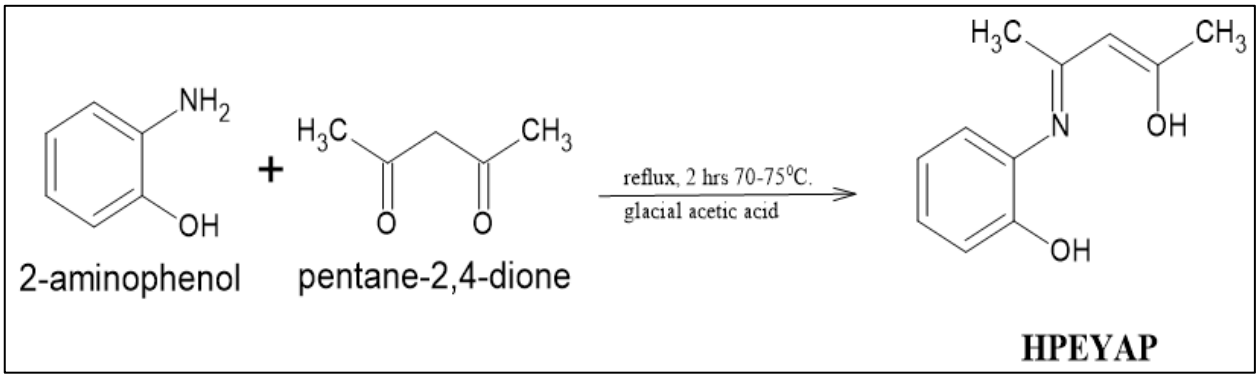


Fig 1 Scheme of Synthesis of HPEYAP

III. RESULTS AND DISCUSSIONS

➢ *Physical and Analytical Data*

The synthesized Schiff base ligand (HPEYAP) was differentiated using various spectrum analyses. Proposed Structures of HPEYAP is given in fig 5. Physical and analytical data of HPEYAP listed in table 1.

Table 1 Physical and Analytical Data of HPEYAP

Compound	M.Wt.	Color	M.Pt. °C	Molar conductance Ω^{-1} cm^2 Mol^{-1}	Elemental analysis Calculated (found) %		
					C	**H**	**N**
Ligand(HPEYAP) **(C11H13NO2)**	191.23	Brownish-Orange	178-180°	Non- electrolyte	69.47 (69.31)	6.89 (6.49)	7.37 (7.46)

➢ *FT-IR Spectral Studies*

The proposed structural of HPEYAP was established using a combination of FTIR, 1H-NMR, UV-VIS and Mass spectral analyses. Aliphatic C-H stretching is shown by the FTIR spectrum peaks at 2947 and 2862 cm^{-1}. The azomethine (C=N) core system is the very intense peak at 1587cm^{-1}. The modes of the aromatic ring skeleton (vC=C) are observed at 1533 and 1504cm^{-1}.[13] The strong peak at 748cm^{-1}, defining the ortho-disubstituted pattern of the aminophenol ring, and the sharp phenolic and enolic C-O stretching bands at 1277 and 1238cm^{-1} support the structure (fig 2). Table 2 show FT-IR spectrum characteristics.

Table 2 IR Spectral Data Analysis of the HPEYAP.

Compounds	**ν(OH)**	**Aromatic ν(C-H)**	**Aliphatic Asymmetric ν(C-H)**	**ν(C=C) aromatic**	**ν(C=N)**
HPEYAP	3374	3008	2947,2862	1533	1587

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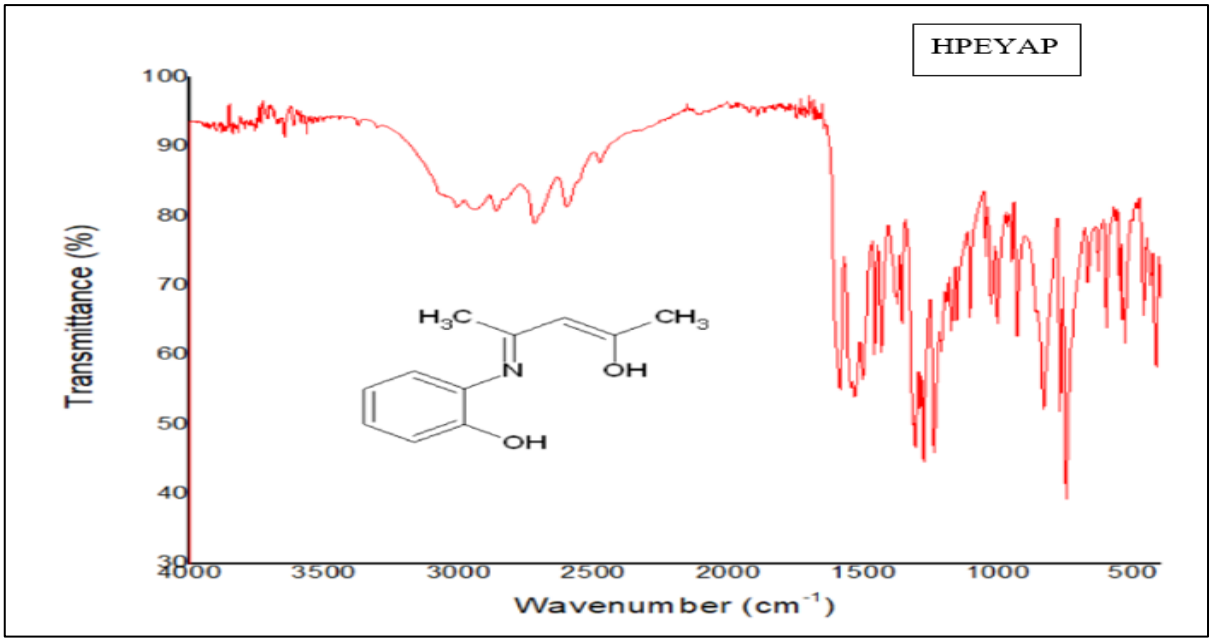


Fig 2 FT-IR Spectrum of the HPEYAP.

➢ *Nuclear Magnetic Resonance Spectroscopy*

The 1H NMR spectrum of the HPEYAP (Fig 3) was obtained on an Avance Neo (400 MHz) spectrometer using DMSO-d_6 as the solvent. The strongly intramolecularly hydrogen-bonded enol proton appears downfield at δ12.15ppm, while the phenolic δOH proton absorbs at δ9.92 ppm. The four aromatic protons (Ar-H) are accounted for by multiplets between δ7.17and 6.77 ppm. Crucially, the central vinylic methine proton (-C=CH-) is confirmed as a sharp singlet at δ5.20 ppm. The two distinct CH3 signals at delta 2.334 ppm and delta 1.970 ppm (figure 3) [14].

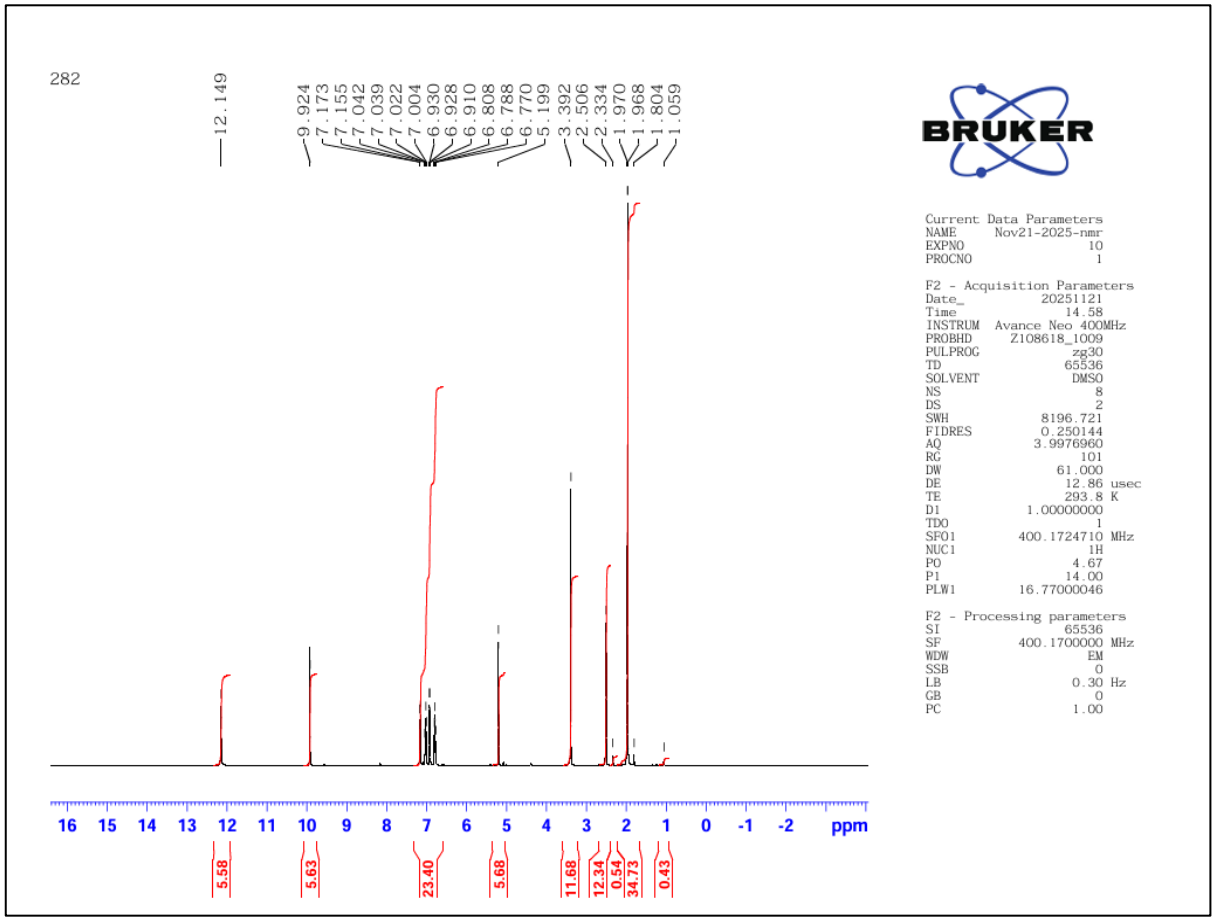


Fig 3 [1]H NMR Spectra of Schiff Base Ligand (HPEYAP)

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➢ *Electronic Spectral Studies*

The UV-vis absorption spectra of HPEYAP were recorded in the range of 200-800 nm using DMSO as solvent [15]. The electronic spectra of HPEYAP exhibit two absorption peaks, at 258 nm and 331 nm, which can be attributed to π-π* and n-π* transitions in the aromatic group of the ligand and azomethine group (CH=N) [16]. Electronic spectral data of the HPEYAP is listed in table 3.

Table 3 Electronic Spectral Data of the HPEYAP

Compound	Absorption (nm)	Band assignment
Ligand (HPEYAP)	258	π-π*
	331	n-π*

➢ *Mass Spectral Studies*

A common and useful method for structural characterization is mass spectrometry. The structure of HPEYAP shown in Scheme 1 closely matches the large peak seen in the mass spectra of the free Schiff base ligand [HPEYAP]. The calculated molecular weight of 292.23 is in good agreement with the large peak in the mass spectrum at 192.1063 m/z [M+H] +. The mass spectrum supports the 1:1 mono-condensation. Fig 4 showed the mass spectra of the HPEYAP.

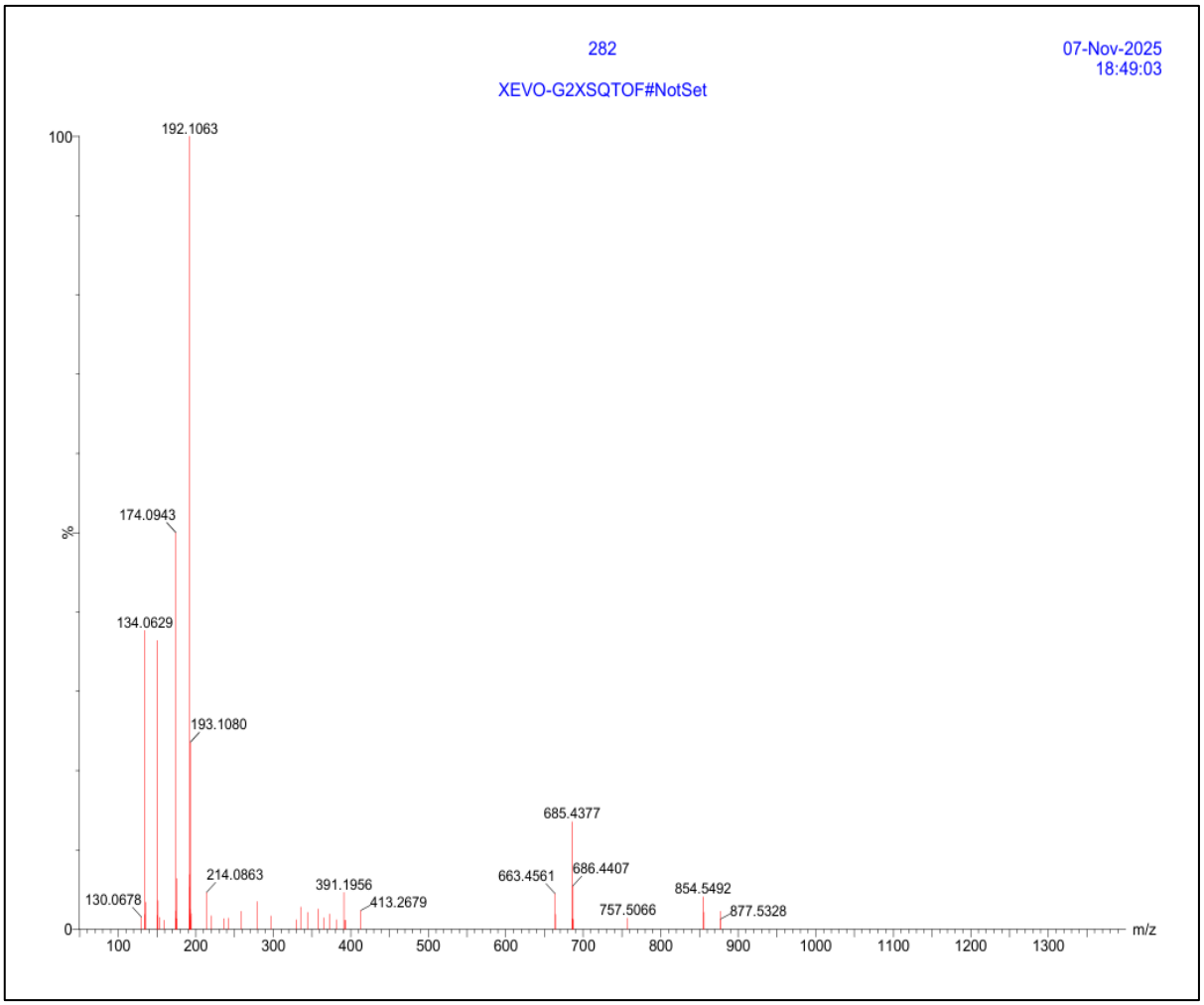


Fig 4 Mass Spectrum of the HPEYAP

IV. COMPUTATIONAL STUDIES

➢ *DFT*

One of the most potent and popular methods for examining the electrical structure of molecular systems is Density Functional Theory (DFT). Molecular geometry, electronic distribution, and spectroscopic characteristics may all be accurately predicted by DFT at comparatively minimal computing costs [17]. The Avogadro (1.2.0) with ORCA software (4.2.1) was used for all quantum chemistry calculations [18,19]. Density Functional Theory (DFT) was first used to fully optimize the molecular geometry of the free Schiff base ligand in the gas phase. Using function B3LYP and basis set def2-SVP based on density functional theory, geometry optimization and frequency was carried out for the Schiff base ligand. The optimization structures match real local minima on the potential energy surface, as shown by the total absence of imaginary frequencies [20].

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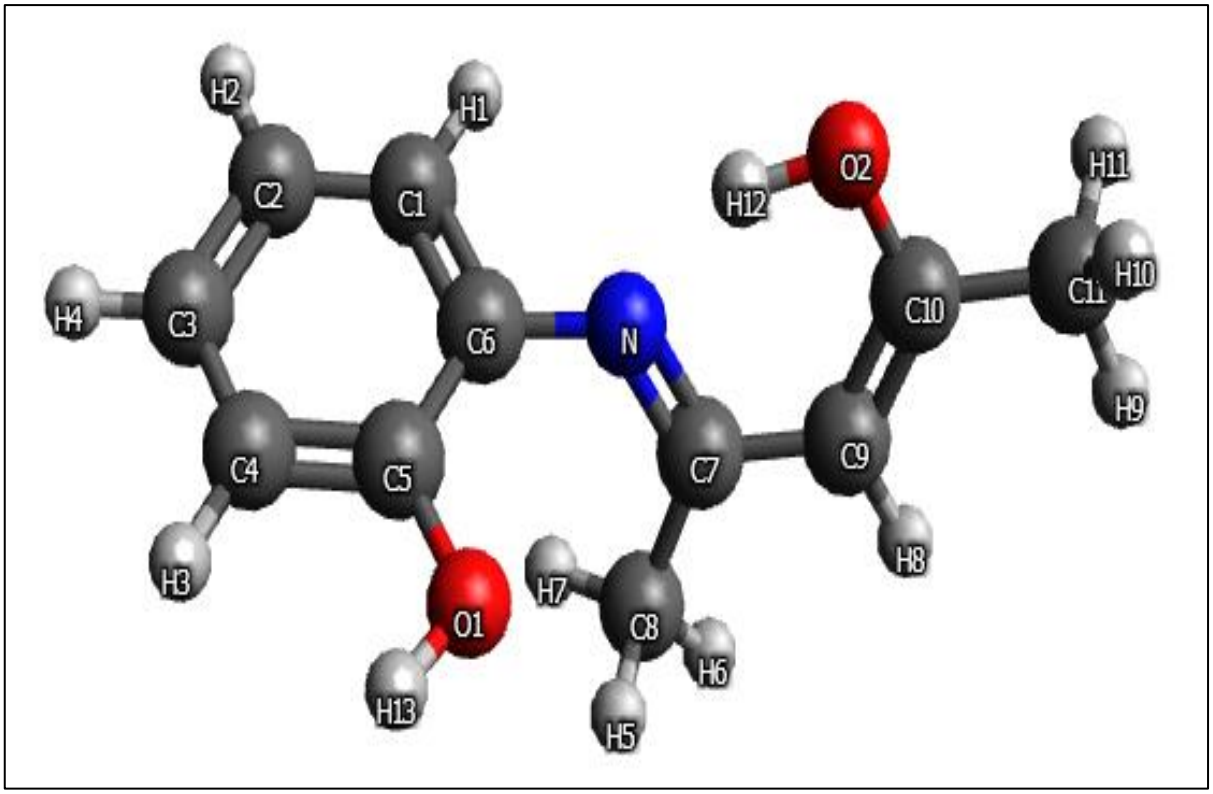


Fig 5 Geometry Optimised Structure of HPEYAP [Colour Code: C-Grey, N-Blue, O-red] (The Ball-Stick Models)]

Table 4 Optimised Geometry of the HPEYAP (Bond Lengths in Angstroms and Bond Angles in Degrees)

Atoms	**Bond length**	**Atoms**	**Bond angle**
C7-N	1.307	C7-N-C6	124.4
C7-C9	1.443	C6-C5-O1	117.8
C9-C10	1.377	N-C7-C8	123.2
C10-O2	1.317	C7-C9-C10	121.9
C6-N	1.400	C9-C10-O2	122.2
C5-O1	1.363	N-C6-C1	119.6
C6-C1	1.404	N-C6-C5	122.1
C6-C5	1.416	C11-C10-O2	114.4
C10-C11	1.498	C9-C10-C11	123.4
C7-C8	1.507	C9-C7-C8	118.3

➢ *Frontier Molecular Orbital Analysis:*

Frontier molecular orbitals (FMOs) are the most important molecular orbitals in a structure. They are categorized as the highest occupied molecular orbitals (HOMO) and the lowest unoccupied molecular orbitals (LUMO) [21]. The HOMO and LUMO energy values can be used to determine a molecule's capacity to donate and receive electrons (fig 6). In addition to providing information about biological mechanisms, these molecular orbitals are essential for electrical and optical characteristics, luminescence, photochemical reactions, UV-VIS, quantum chemistry, and pharmaceutical research [20].

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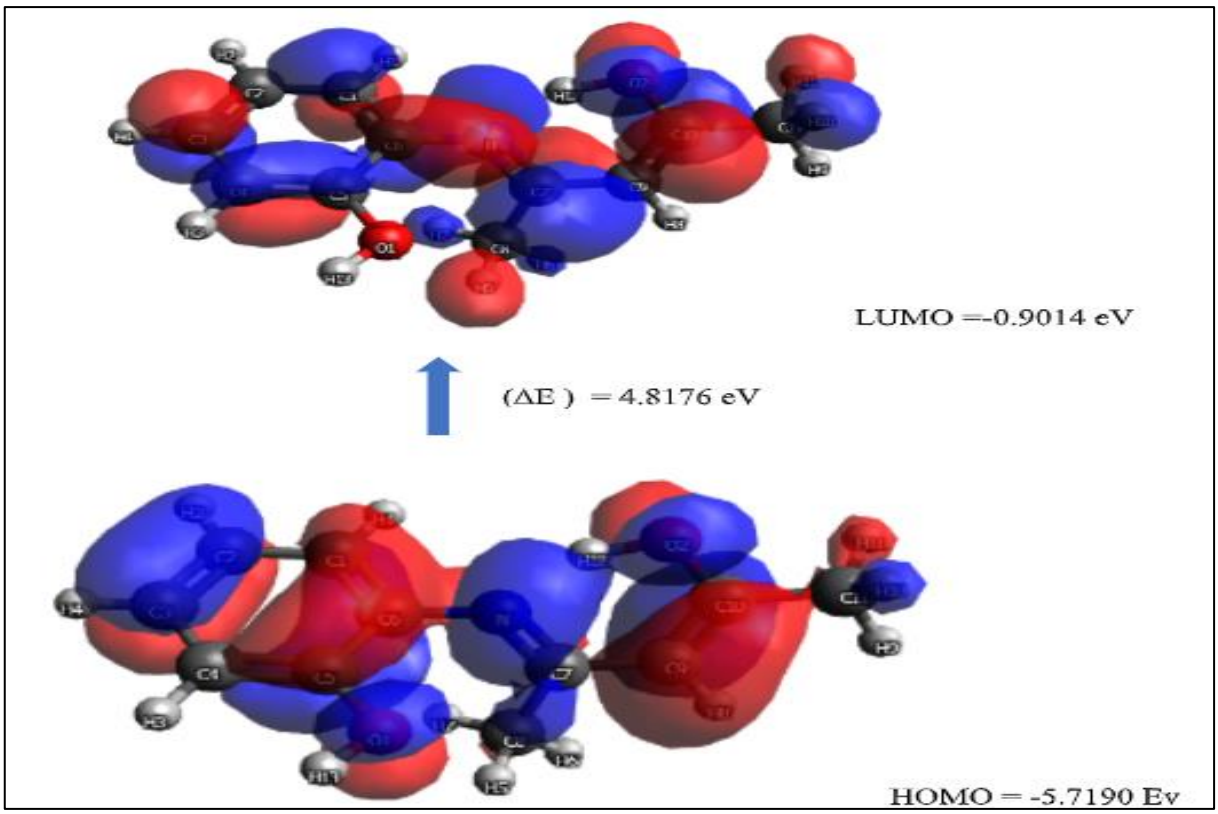


Fig 6 The Frontier Molecular Orbitals of HPEYAP Calculated from DFT Approach.

Table 5 Energies of HOMO - LUMO and Other Quantum Parameters of Schiff Base Ligand

Compound	HOMO eV	LUMO eV	ΔE eV	I Ev	A Ev	χ eV	η eV	S $(eV)^{-1}$
HPEYAP	-5.7190	-0.9014	4.8176	5.7190	0.9014	3.3102	2.4088	0.4151

➢ *Molecular Docking Study*

Enzyme crystal structures were obtained from the Protein Data Bank (http://www.rcsb.org/pdb/) [23]. The structure of HPEYAP is optimized in Avogadro and Orca. AutoDockTools-1.5.7 was used for protein preparation. The docking findings were visualized using PyMOL 4.6 and Discovery Studio Visualizer 2025 [24]. The proposed docking techniques in this work were self-docked using native ligands of 3ERT and 3QTR. Root mean square deviation (RMSD) values are 1.73 and 1.38 A˚. The grid spacing measurements were 0.375 Å. Binding energies are listed in table 6. As energy decreases, the ligand's affinity for the receptor binding site is increased [25]. Lowest energy docking pose of the HPEYAP docked with the cancer targets show in fig 7,8,9 and 10.

The HPEYAP showed hydrophobic interactions with LEU346 (Alkyl, 5.07), MET421 (Alkyl,4.57), LEU384 (Alkyl, 4.61), LEU525 (Alkyl, 3.98), PHE404 (Pi-Alkyl, 5.17), LEU346 (Pi-Alkyl, 4.93), LEU387 (Pi-Alkyl, 5.44), LEU391 (Pi-Alkyl, 4.77) and PHE404 (Pi-Pi T-shaped, 5.43) against 3ERT and it showed only hydrophobic interactions with ILE10 (Pi-sigma, 3.81), LEU134 (Pi-sigma, 3.96), LEU134 (Pi-sigma, 3.88), PHE82 (Pi-Pi Stacked, 5.84), ALA144 (Alkyl, 4.04), LEU134 (Alkyl, 4.34), VAL18 (Alkyl, 4.07), LYS33 (Alkyl, 4.36) and ALA31 (Pi-Alkyl, 4.58) against 3QTR., where the type of hydrophobic interaction and distance in Å are given in brackets.

Table 6 Molecular Docking Binding Energies of HPEYAP Ligand.

Target	Binding energy (kcal.mol-1)	Interactions					
		H-Bond	Hydrophobic				
			Alkyl	π -Alkyl	π -π T-shaped	Pi-sigma	Pi-Pi Stacked
3ERT	-6.4	LEU387	LEU346 MET421 LEU384 LEU525	PHE404 LEU346 LEU387 LEU391	PHE404	-	-
3QTR	-6.7	-	ALA144 LEU134 VAL18 LYS33	ALA31	-	ILE10 LEU134 LEU134	PHE82

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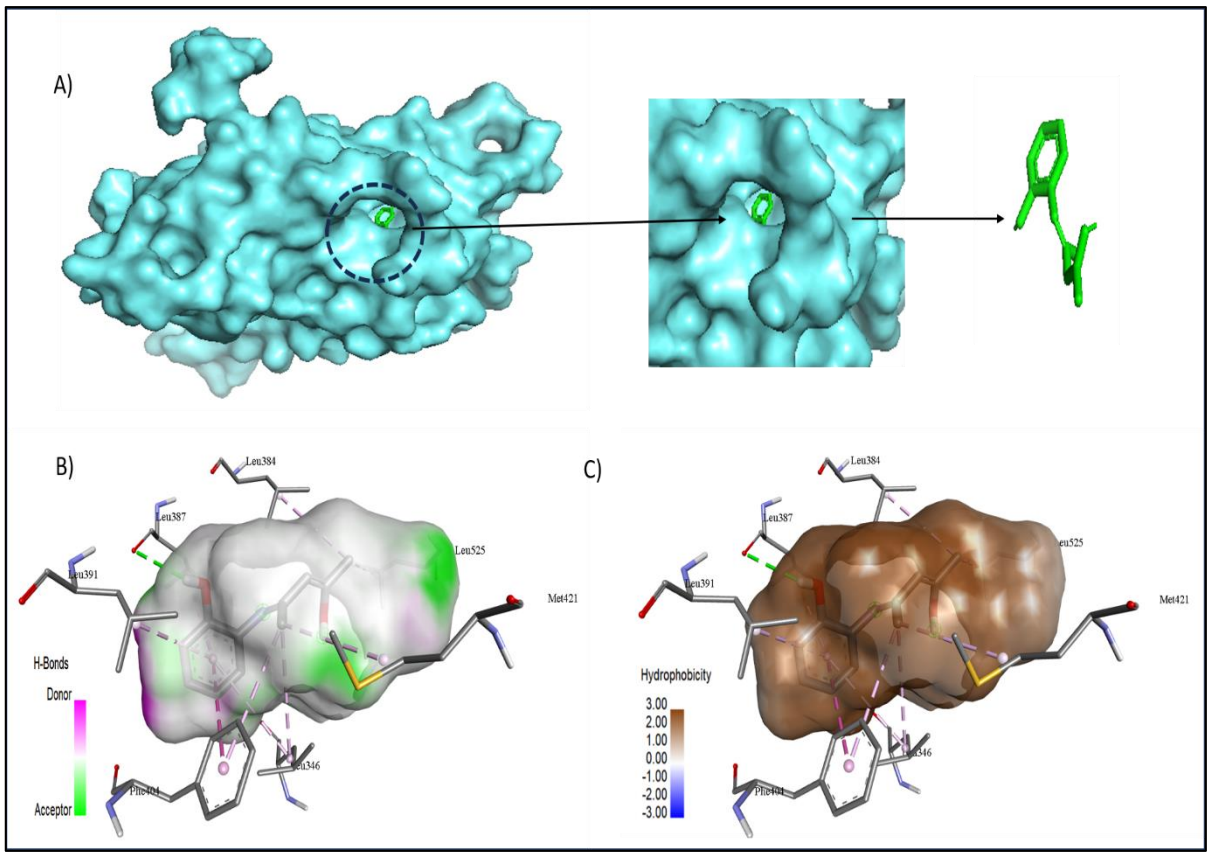


Fig 7 3D Docking Interactions (A) Surface (B) Hydrogen Bond (C) Hydrophobic Interaction of Schiff Base (HPEYAP) with 3ERT.

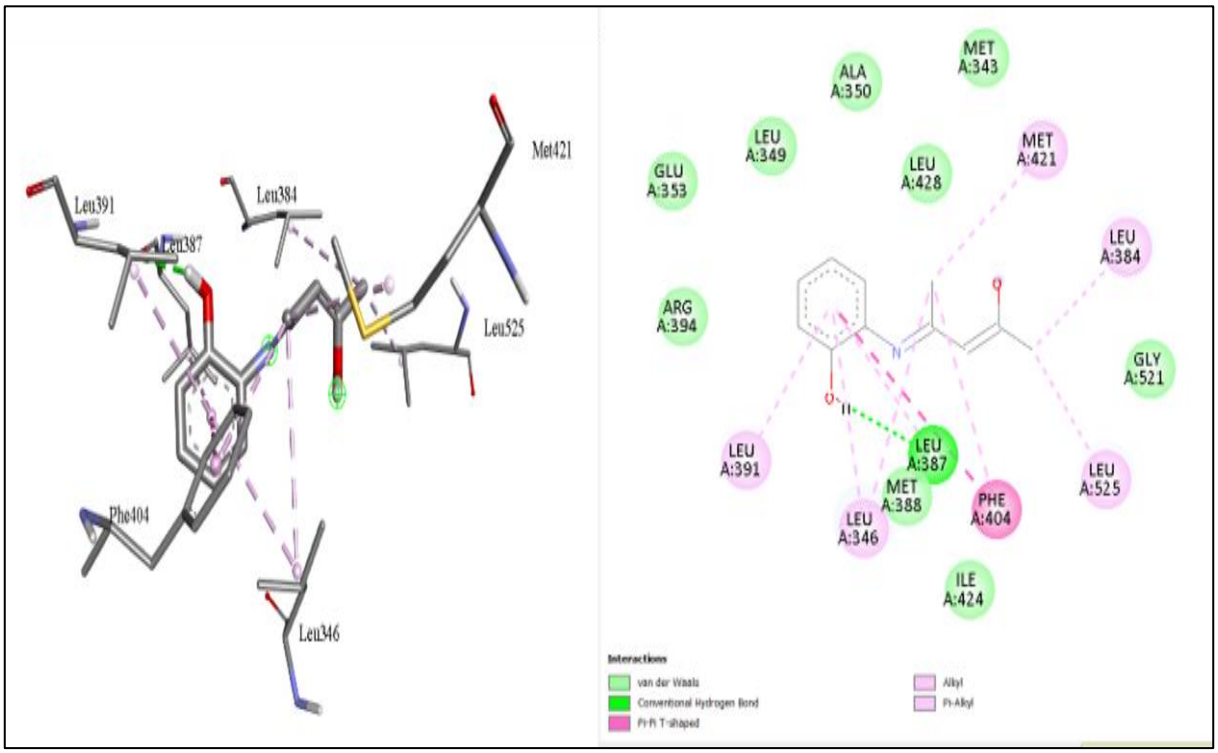


Fig 8 3D and 2D Interaction of Schiff Base Ligand (HPEYAP) with 3ERT Receptor

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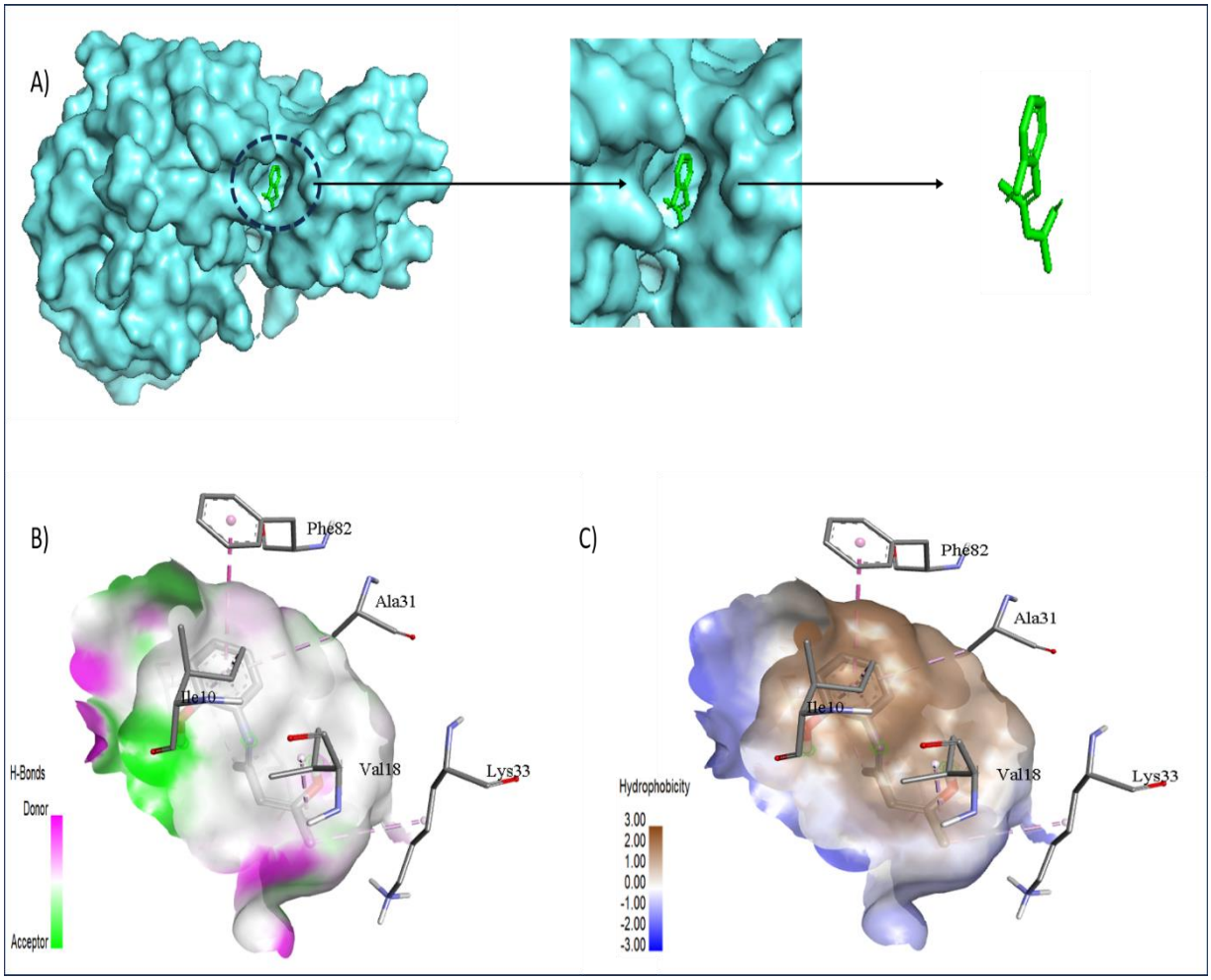


Fig 9. 3D Docking Interactions (A) Surface (B) Hydrogen Bond (C) Hydrophobic Interaction of Schiff Base (HPEYAP) with 3QTR.

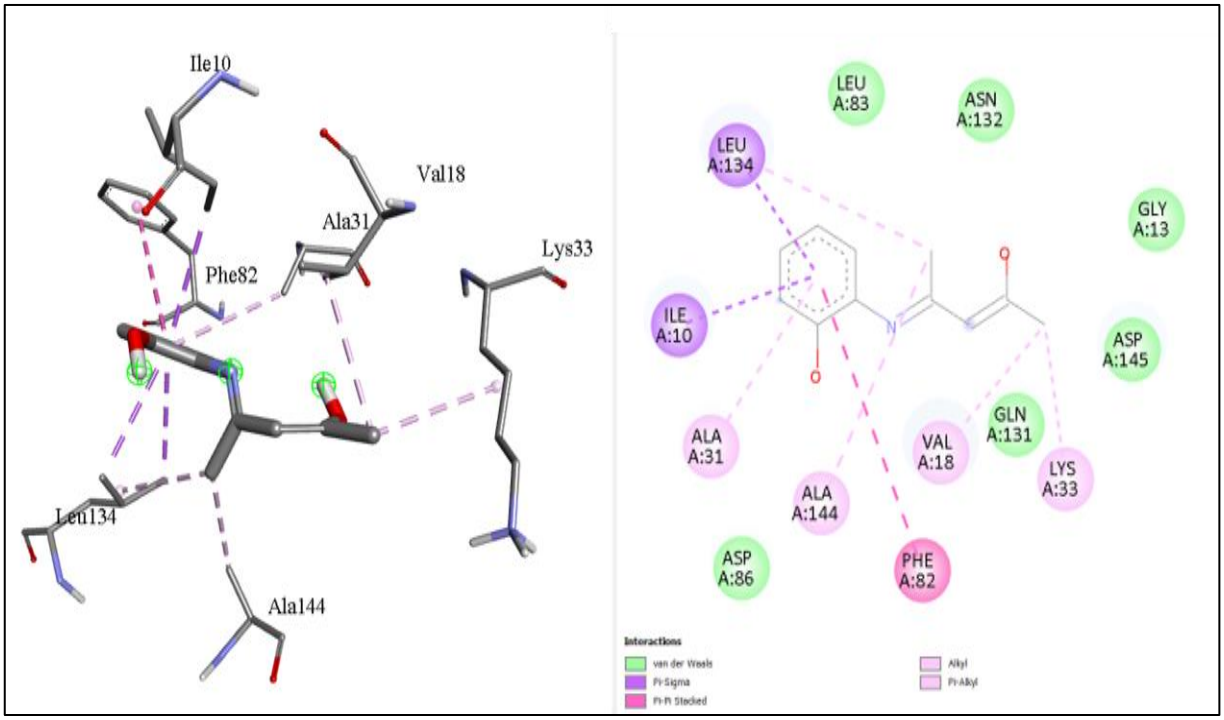


Fig 10 3D and 2D Interaction of Schiff Base Ligand (HPEYAP) with 3QTR Receptor

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➢ *In-Silico Drug-Likeness and ADMET Prediction*

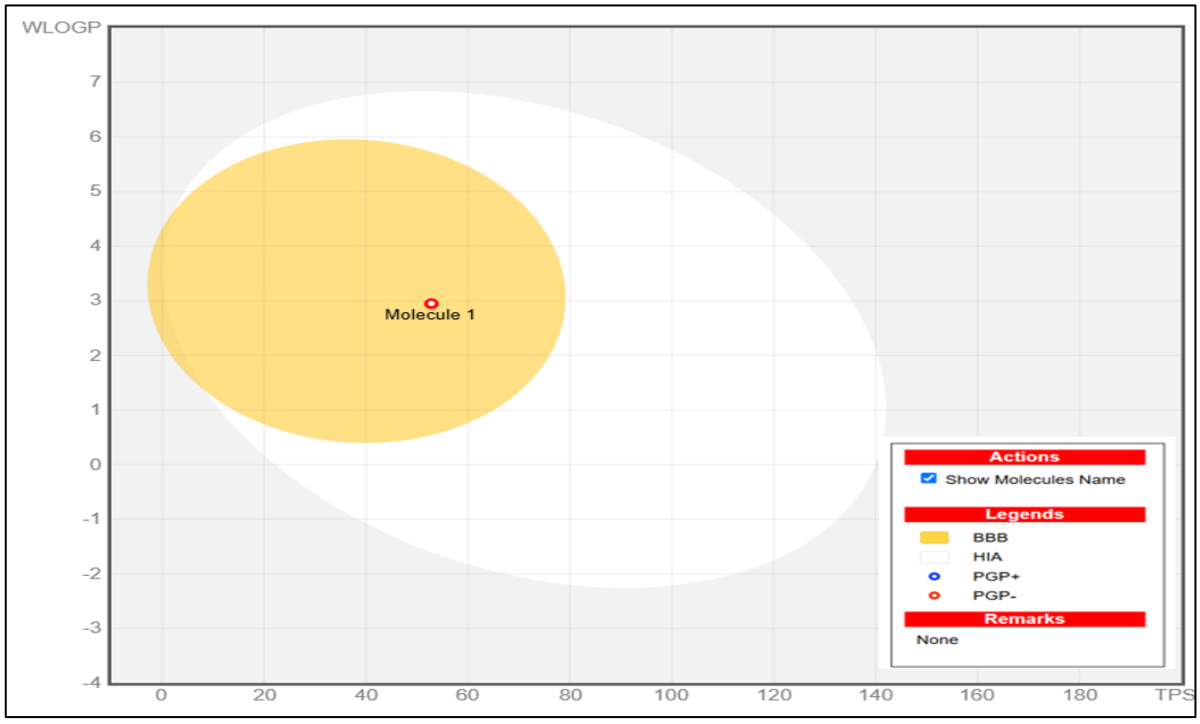


Fig 11 BOILED-Egg Model of HPEYAP Calculated by SwissADME.

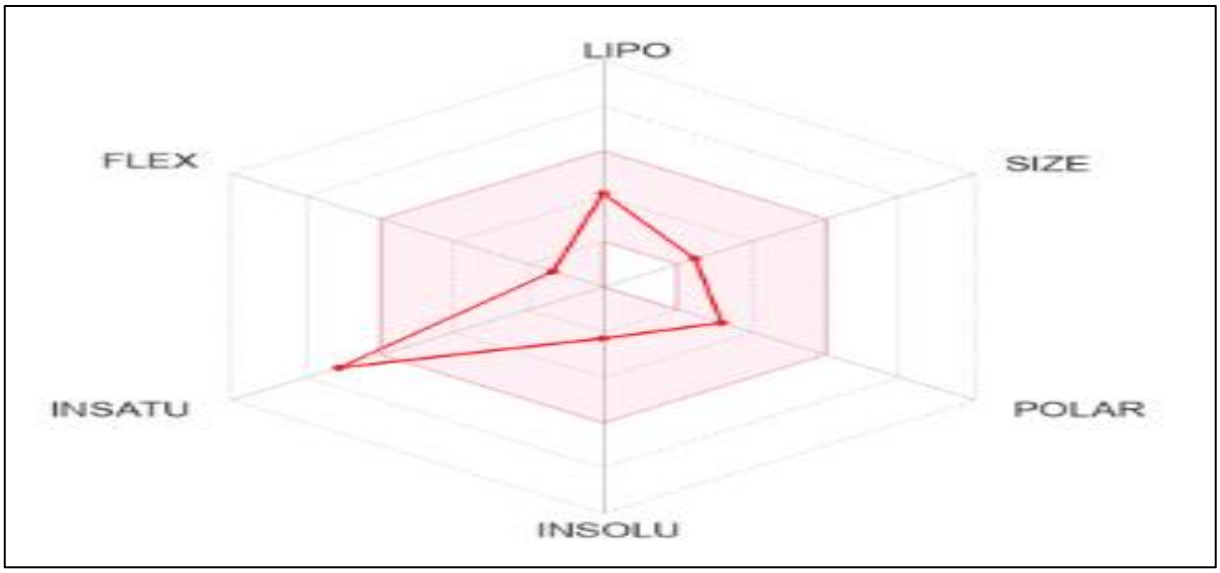


Fig 12 Bioavailability Radar Reflects of HPEYAP Calculated by SwissADME.

In this work, we used SwissADME to predict the ADME characteristics of the HPEYAP using computational models. The HPEYAP had lipophilicity LogPo/w, (XLOGP3) values of 1.69, which satisfied the requirement for acceptable human oral bioavailability [26]. The topological polar surface area (TPSA) is crucial factor in drug bioavailability. Therefore, it is suggested that passively absorbed compounds with a TPSA > 140 Å have poor oral bioavailability. According the analysis results, HPEYAP have TPSA values below 140. Additionally, HPEYAP have bioavailability values of 0.55, showing that ligand reach the systemic circulation [27]. Molecules in the white section (BOILED Egg's white) are expected to be primarily absorbed by the gastrointestinal system, whereas molecules in the yellow region (BOILED-Egg's yolk) are expected to primarily pass through the blood-brain barrier. blue dots (PGP+) signify chemicals that P-glycoprotein actively removes from the central nervous system. Red dots (PGP−) represent molecules that weren't removed [28]. HPEYAP have a positive BBB penetration property (fig 11) Drug-likeness was initially visualized using the bioavailability radar structure, where an optimal physicochemical space is shown by the shaded pink area. (fig 12) [29] The synthesized HPEYAP may have potential for therapeutic development, with possibilities for future optimization and investigation in medicinal chemistry. The physicochemical properties of HPEYAP listed in table 7.

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Table 7 The Physicochemical Properties of HPEYAP

Compounds	Molecular weight	No. of H-bond acceptors	No. of H-bond donor	TPSA	BBB Permeant	GI absorption	Bioavailability Score	Lipinski
Schiff base (HPEYAP)	191.23 g/mol	3	2	52.82 Å²	Yes	High	0.55	Yes; 0 violation

➢ *Toxicity and Metabolism Prediction Analysis*

The metabolic properties of Schiff base ligand (HPEYAP) were simultaneously calculated using the pkCSM-pharmacokinetics website [30]. The synthesised ligand cannot be absorbed via human skin, as indicated by the permeability value of -2.603. One of the most crucial considerations is a pharmaceutical molecule's intestinal absorption in humans. Good absorption in the human intestines can be determined by an intestinal absorption score of between 70 and 100%; for synthesised Schiff base ligand (HPEYAP), it is 91.631% [31]. Table 8 is a summary of AMDET properties.

Table 8 The Adsorption, Distribution, Metabolism, Excretion and Toxicity Prediction of HPEYAP (Predicted Value).

Property	Model name	HPEYAP
Absorption	Water solubility	-2.508
	Caco2 permeability	1.321
	Intestinal absorption (human)	91.631
	Skin Permeability	-2.603
	P-glycoprotein substrate	Yes
	P-glycoprotein I inhibitor	No
	P-glycoprotein II inhibitor	No
Distribution	VDss (human)	-0.134
	Fraction unbound (human)	0.359
	BBB permeability	0.113
	CNS permeability	-2.047
Metabolism	CYP2D6 substrate	No
	CYP3A4 substrate	No
	CYP1A2 inhibitior	Yes
	CYP2C19 inhibitior	No
	CYP2C9 inhibitior	No
	CYP2D6 inhibitior	No
	CYP3A4 inhibitior	No
Excretion	Total Clearance	0.543
	Renal OCT2 substrate	No
Toxicity	AMES toxicity	No
	Max. tolerated dose (human)	1.512
	hERG I inhibitor	No
	hERG II inhibitor	No
	Oral Rat Acute Toxicity (LD50)	2.356
	Oral Rat Chronic Toxicity (LOAEL)	2.279
	Hepatotoxicity	No
	Skin Sensitisation	No
	T.Pyriformis toxicity	0.956
	Minnow toxicity	1.473

V. CONCLUSION

The NO2-type tridentate Schiff base ligand was synthesised from 2,4-pentanedione and 2-aminophenol via conventional and grinding method. The ligand was characterized by FT-IR, UV–Vis, ^{1}H NMR, mass spectrometry, and elemental analysis. The synthesised HPEYAP have an energy gap (ΔE) of is 4.8176 eV with HOMO = -5.7190 eV, LUMO= -0.9014 eV. Using a molecular docking approach, the interaction of HPEYAP against the estrogen receptor (3ERT) and CDK2 (3QTR) was anticipated. The HPEYAP's binding energies against the 3ERT and 3QTR have been found to be −6.4 and −6.7, respectively. The synthesized Schiff base (HPEYAP) has been computationally predicted its anticancer properties; however, this prediction has to be verified experimentally. Therefore, these findings will be helpful in the development of potent medications to treat cancer. further, In-silico ADMET study of Schiff base ligand (HPEYAP) was carried out.

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➢ *Authors' Contributions*

Seema nagar: Conceptualization, Methodology, Investigation, Software, Data Curation, Validation, writing-orignal draft, Writing-review& editing Smriti Raizada: Conceptualization, Formal analysis, Resources, Validation, Visualization, Supervision, Writing-review& editing Neha Tripathee: Formal analysis, Validation, Visualization, Writing-review& editing.

➢ *Ethics Approval and Consent to Participate*

Not applicable.

➢ *Conflict of Interest*

The authors declare no conflict of interest, financial or otherwise.

➢ *Availability of Data and Materials*

All original data use during this study are included in this article.

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