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Synthesis and Computational Evaluation of CoII and CuII Schiff Base Complexes: Synthesis and Computational Evaluation of CoII and CuII Schiff Base Complexes

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Abstract

General Background Schiff base ligands are widely studied in coordination chemistry due to their versatile binding modes and relevance in biological and pharmaceutical research. **Specific Background** Pyrazolone-based Schiff bases derived from 4-aminoantipyrine have demonstrated notable coordination behavior with transition metals and promising computational bioactivity profiles. **Knowledge Gap** However, limited studies integrate microwave-assisted synthesis with combined spectroscopic characterization, theoretical stability analysis, molecular docking, and ADME prediction for such systems. **Aims** This study aimed to synthesize a new Schiff base ligand and its Co(II) and Cu(II) complexes, characterize their structural properties, and evaluate their theoretical stability, docking behavior, and drug-likeness. **Results** Spectroscopic and analytical data confirmed successful complex formation with a 1:2 metal–ligand ratio and octahedral geometry. Computational calculations indicated higher stability of the complexes compared to the free ligand. Docking analysis revealed favorable binding interactions with breast cancer-related protein targets, while ADME prediction showed compliance with Lipinski's rule and acceptable pharmacokinetic parameters. **Novelty** The novelty lies in the integrated experimental–computational approach combined with microwave synthesis for this specific ligand–metal system. **Implications** These findings support the relevance of Schiff base metal complexes as structurally stable candidates for further theoretical and experimental bioactivity investigations.

Keywords: Schiff Base Complexes, Microwave Synthesis, Molecular Docking, ADME Prediction, Transition Metal Coordination

Key Findings Highlights:

1. Stable octahedral cobalt and copper complexes were confirmed by spectroscopic and magnetic data
2. Theoretical calculations demonstrated higher stability of complexes relative to the free ligand
3. Docking and pharmacokinetic analyses indicated suitability for further bioactivity-oriented studies

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Introduction

It has been known that many metal ions on interaction with Schiff bases give chelates [1]. Schiff bases are a special class of ligands with a variety of donor atoms exhibiting interesting coordination modes towards various metals [2], [3], [4] . Many compounds of Schiff base ligands are known and the properties of their metal chelates have been identified. Metal complexes of nitrogen-oxygen chelating agents derived from 4-aminoantipyrine Schiff base have studied widely due to their great applications in biological, clinical, analytical and pharmacological areas [[5][6]].

There are many methods to synthesis Schiff bases and Schiff base complexes, one of these method using microwave technique.Microwave irradiation applications include chemical transformations that are pollution-free, environmentally benign, low-cost, and produce a high-quality product while being simple to manufacture and handle. The essential benefits of the microwave method are reduced reaction times and easy conditions of reaction [[7],[8]].

In the present work, we have synthesized a new bidentate Schiff base ligand (BDP) using 4-aminoantipyrine as a starting material, then it's Co (II), and Cu (II) complexes were formed by the reaction of BDP and appropriate metal salts. All of the synthesized compounds were identified using several analytical and spectroscopic techniques.

EXPERIMENTAL

Instrumentation

Element C.H.N analyzer was carried out on a EM - 017. Mth instrument. The FTIR spectra in the range (4000 - 400) cm^{-1}were recorded as KBr disc on FT-IR-8000, single beam path Laser, Shimadzu Fourier transform infrared spectrophotometer. UV-Visible spectrophotometer in range (250 - 1100) nm. The microwave irradiation were complete using microwave oven - Panasonic. NN - ST300W. The magnetic susceptibility values of the prepared complexes were obtained at room temperature using Magnetic Susceptibility Balance of Johnson matter catalytic system division, England. The metal percentage of the complexes was measured using atomic absorption technique by Shimadzu Atomic Absorption 680 Flam Spectrophotometer for the determination of (Cu^{+2} , and Co^{+2}) metal ions. Using GBS - 933 Flame and Atomic Absorption Spectrophotometer. The conductivity measurements were obtained using Conduct meter WTW at (25˚C) with concentration of 10^{-3} M. The complexes were dissolved in DMSO.

Synthesis of ligand BDP [[9]]

All materials were used further purification. To (0.005mol) (0.203 g) of the 4-aminoantipyrine dissolved in (15 ml) of ethanol, it was added (0.005 mole) (0.924 g) of 4-bromo benzaldehyde in (10 ml) of ethanol with three drops of glacial acetic acid as a catalyst, then left at room temperature extended to (15 minutes), filtered off, and dried and recrystallized by using ethanol the physical data are shown in the table 1.

Synthesis of BDP metal complexes [[10]].

The (BDP) ligand (2 mmol) and the metal salt (1mmol) ($CoCI_2.6H_2O$) and ($CuCl_2.2H_2O$) were mixed in a grinder. The reaction mixture was the added in the microwave oven using few drops from solvent. The reaction was completed in (2) minute. The resulting complexes washed several times with absolute ethanol.

Formation Complexes in Solution

The molar ratio plot was obtained in order to calculate the [M: L] ratio of the complexes by adding an increased amount of ligand (0.25 - 5.0 ml) of 10-3M to a constant amount of metal ion (1 ml of 10-3M ($CoCl_2.6H_2O$ and $CuCl_2.2H_2O$) in a volumetric flask of 10 ml methanol. Absorbance measurements were taken against a blank for each chelating agent concentration at the formation complex's λmax.

Theoretical study

Computational Methods Theoretical calculation were performed on hyperchem program version 8.03. The geometries of the BDP ligand and its metal complexes were optimized first at level molecular mechanics force field (MM+) and then at level semi empirical theory (PM3).

Molecular Docking Study

Choosing the antiviral target protein depends on ligand affinities and the competition between docked poses, using appropriate docking parameters. The target is the breast cancer virus (PDB IDs: 3PP0 and 3POZ, with resolutions of 2.25 Å and 1.50 Å, respectively, downloaded in PDB format from the Protein Data Bank (RCSB PDB: Homepage) [11]. The breast cancer virus's site, as a receptor (both 3POZ and 3PP0 used chain A), has been meticulously docked with the synthesized ligand BDP. The reference ligands used for the receptor (3POZ and 3PP0), Control 1 and Control 2, respectively, have been carefully chosen to estimate the strength of the resulting contact and to identify a theoretical association with their breast cancer antiviral activity. The three-dimensional structure of ligand BDP was built using Avogadro software. A molecular docking study was implemented using the AutoDock tools 1.5.6 software [[12][13]]. Initially, the chosen target protein was prepared, ensuring that any water molecules, extra ions, or ligands not specified in the study protocol were removed. Polar

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hydrogens were added to the protein, and Gasteir charges were assigned. The BIOVIA Discovery Studio Visualizer (v.4.5) was used for this purpose.

ADME prediction

According to Lipinski's Rule of Five, a perfect drug Compound is characterized by specific physicochemical properties. This rule proposes the capacity of a chemical compound to function as a potent oral medication [[14]]. RO5 states that for a chemical to be similar to a drug, the Compound being judged must comply with as many of the subsequent rules as possible [[15]]. Firstly, an MW of ≤ 500 g/mol, log P value of ≤ 5, Number of H-bond donors ≤ 5, Number of H-bond acceptors ≤ 10 [[16]]. Polarity: TPSA between ≤ 130 Å^2, and finally, flexibility ≤ 9 rotatable bonds [[17]]. The pharmacokinetics part of the Swiss ADME online site (http://www.swissadme.ch/index.php) describes gastrointestinal (GI) absorption, blood-brain barrier (BBB) permeation, P-glycoprotein (P-gp) substrate, and inhibition of cytochrome P450 enzymes in the compounds. These factors explain the importance of computer-based drug design methods in approximating how the hits will work in the body and whether they will be harmful [[18]]. All predictions were performed using default settings and evaluated for compliance with standard drug-likeness and safety criteria.

Result And Disccusion

The microanalysis results and physical properties for the ligand and its metal complexes are summarized in Table I. The calculated values of C.H.N and metal analysis were in a good agreement with the experimental values.

Found (calc.)%				M.Wt g.mol-1	Yield%	M.p.˚C	Colour	Compound
M	N	H	C					
------	10.45(11.35)	4.70(4.36)	67.44(58.39)	370.24	85	250-252	pale yellow	BDP
5.43(6.02)	7.97(8.59)	4.75(4.53)	34.22(44.19)	978.42	78	110-112	Dark green	CoBDP
7.12(6.98)	8.34(9.23)	4.21(3.98)	46.55(47.46)	910.97	80	188d	Pale green	CuBDP

Table 1. TABLE I. Physical data of Schiff base compounds.

Infrared Spectral Study

The infrared spectra of the relevant metal complexes and the free BDP ligand were contrasted. Table II lists the most significant vibrational bands of the ligand and its metal complexes, along with their respective designations. Every compound in its solid state was measured using a KBr disc in the 4000-400 cm-1 range. Ligand BDP spectra showed a prominent band at (1649.19) cm–1, which may have been caused by interference of the (C=O), while the bands at (1595, 18 -1570.11) cm^{-1} may be referred to as (C=N) and aromatic (C=C) stretching [19].

In the spectra of Co and Cu complexes, the bands of C=O and C=N were shifted, which is characteristic of a bidentate coordination mode.Another weak band appeared at 505.37-450.00, attributed to coordination between M-N and M-O [[20]].

Symb.	ν (C=O)	ν (C=N)	ν (C=C)	v (M-O)	v (M-N)	v (H_2O)
BDP	1649.19 s	1595.18 s	1570.11	-------	--------	------
Co-BDP	1687.72s	1691.33s	1620.20 m	505.37vw	476.43 vw	3450.77 b
Cu-BDP	1737.92 s	1593.25s	1570.11 m	586.00 vw	450.00 vw	3365.90 b

Table 2. TABLE II. Most diagnostic FTIR bands of the BDP ligand and its metal complexes
Where: w=weak, s=strong, sh=sharp, m=medium b=broad

U.V–Vis spectral data for the BDP ligand and its complexes

The electronic spectrum of the ligand shows transitions at 274 and 350 nm, respectively as shown in Table III. The electronic spectrum of Co complex shows transitions at 993.50 and 678.68 nm, respectively. There are three probable d-d transitions for high spin Co II octahedral complexes:$^4T_1g \rightarrow {}^4T_2g$ (ν_1), $^{4T1g} \rightarrow {}^4A_2g$ (ν_2), and $^4T_1g \rightarrow {}^4T_1g$ (ν_3), the last transition may be appear under the envelop of ligand-centered transitions because will be highest in energy [[21]]. Thus, the two bands appear in the spectrum of CoII complex may be due to$^4T_1g \rightarrow {}^4T_2g$ (ν_1) and $^4T_1g \rightarrow {}^4A_2g$ (ν_2) transitions respectively. The spectrum also showed other bands at 343.50 and 272.00 nm might be assigned to charge transfer bands. The magnetic moment value of Co (II) complex found to be (4.51 B. M) indicates that the dark green CoII complex to be paramagnetic and is characteristic of high spin cobalt ion geometry. Conductivity values show the complex to be nonionic. The electronic spectrum of the CuII complex displayed a broad band at 750.00 cm^{-1} due to the $^2Eg \rightarrow {}^2T_2g$ transition, which conforms with the octahedral arrangement around the copper ion [[10]].The spectrum also showed transitions at 402.00 and 302.00 nm can be assigned to charge transfer bands. Conductivity value show the complex to be nonionic. Cu II complex showed magnetic moment 1.78 BM higher than the spin only value 1.73 BM agreement for one unpaired electron monomeric octahedral geometry [[22]].

Compound	BDP	CoBDP	CuBDP
AbsorptionBands(cm^{-1})	350.00274.00	993.50678.68343.50272.00	750.00402.01302.00
Assignments	n→π*π→π*	$^4T_1g \rightarrow {}^4T_2g {}^4T_1g \rightarrow {}^4A_2g {}^4T_1g \rightarrow {}^4T_1$ gL→CoCT	$^2Eg \rightarrow {}^2T_2g$L→CuCT
$\mu_{eff.}$ B.M	--------	4.15	1.78
μscm^{-1}	--------	0.26	0.40
Suggested geometry	---------	O.h	O.h

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Table 3. Table of Complexes in Solution data, Conductivity in DMSO solvent, and magnetic

The Complexes were studied in solution using methanol as a solvent, to determine [M/L] ratio of the complexes using molar ratio method [[23]]. A series of solutions having a concentration (10^{-3} M) were prepared of Cu(II) and Co(II) ion and ligand . The metal: ligand ratio calculated from the relationship between the absorbance and the mole ratio of [M/L] [[24]]. The results of complexes in methanol propose that the metal to ligand ratio was [1:2] for complexes, which was approximately that obtained from the study in the solid state. Figures 1 and 2 show mole ratio plotting of the BDP ligand and its metal complexes.

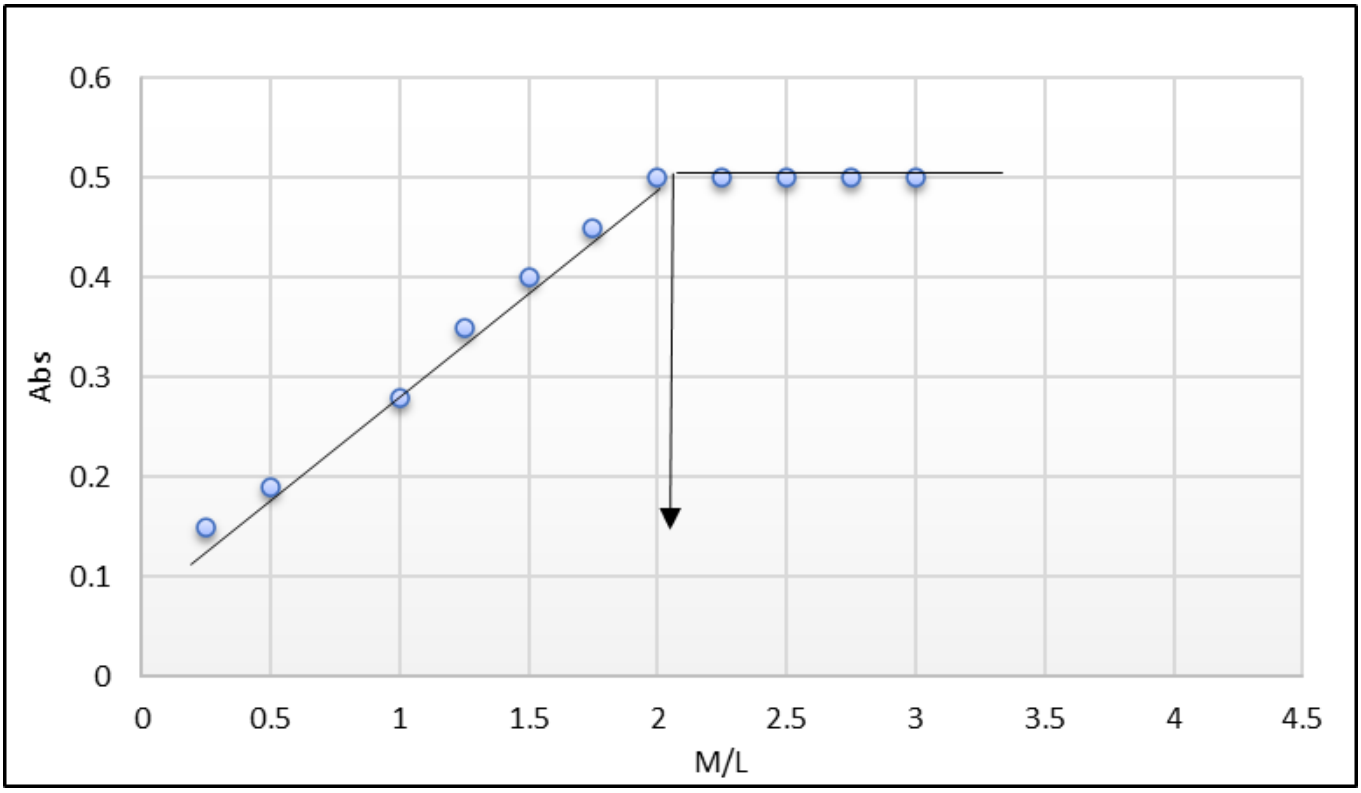

Figure 1. Fig. 1: Mole L\Mole Cu(II)\ λ_{max} 302 nm

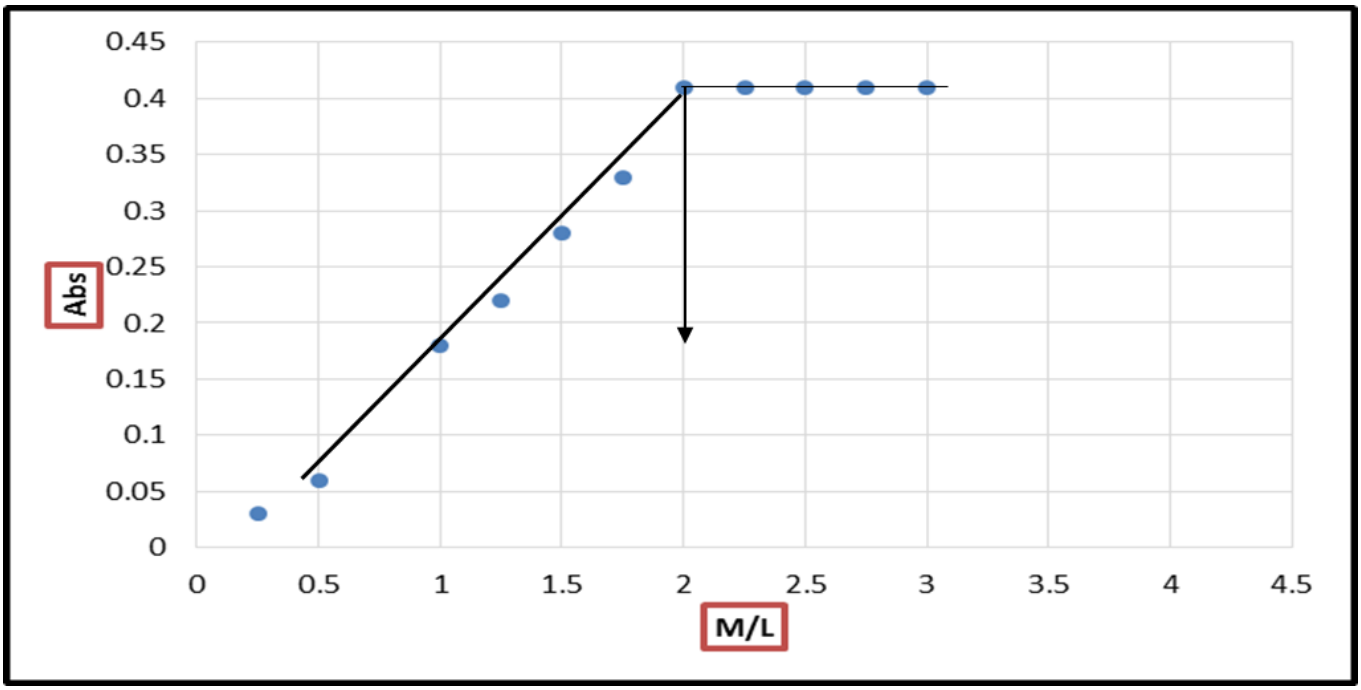

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Figure 2. Fig. 2: Mole L\Mole Co(II)\ λ_{max} 343 nm

Computational Study:

In this research, Hyperchem 8.3 program was used to calculate the heat of formation (ΔHºf), binding energy (ΔEb) and dipole moment (μ) for the BDP ligand and its metal complexes using semi-empirical PM3 at 298K, also The HOMO and LUMO frontier orbital and energy gab of compounds were calculated, and from the result the complexes are more stable than the ligand as illustrate in Table IV.

Comp.	$\Delta H^{\circ}f$	ΔE_b	μ	HOMO	LUMO	ΔE_{gab}
BDP	329.60	-17807.83	5.43	-8.83	-1.12	7.71
CoBDP	-816.450	-37762.35	11.76	-8.85	-1.10	7.75
CuBDP	320.30	-36514.23	11.75	-8.87	-1.11	7.76

Table 4. TABLE IV. Conformation energetic (in $K.J.mol^{-1}$) and dipole moment (in Debye) for Compounds.

Molecular Docking Analysis

The molecular docking process requires predicting the favorable binding affinity between ligands and a rigid/flexible macromolecular target, typically a protein. Table V: Molecular docking visualization showing the binding conformation of the ligand within the active site of the target breast cancer protein (3POZ). The ligand BDP is surrounded by several key amino acid residues through multiple hydrogen bonds, including Leu718, Val726, Lys745, Leu858, Phe859, Asp855, and Met766, with a docking score of -9.00 kcal/mol. At the same time, the control (1) inhibits the docking score (-10.6 kcal/mol) and is surrounded by several key amino acid residues, including Leu718, Val726, Lys745, Phe856, Leu844, Met793, Ala743, Leu788, Thr790, Leu774, Met766, Arg776, Gly775, and Thr790. On the other hand, binding of the receptor protein 3pp0 to the ligand BDP engages in hydrogen-bond interactions with multiple amino acid residues in the receptor's active site, notably Lys753, Arg868, Ala751, Leu726, Leu852, Leu796, Thr862, and Asp863, and its binding energy is -10.6 kcal/mol compared with the control (2), which has a docking score of -11.1 kcal/mol. Furthermore, the ligand shows several stabilizing interactions, involving π–π T-shaped interactions, van der Waals contacts, attractive charge interactions, and π–sigma addition to π–alkyl interactions. These collective non-covalent interactions contribute to enhancing the ligand's stability and proper orientation within the active site, thereby supporting its overall binding affinity toward the breast cancer target protein, as illustrated in Figures 3 and 4, respectively." The arrangement suggests that the ligand is stabilized primarily through van der Waals forces and hydrophobic stacking, which may contribute significantly to its binding affinity and specificity toward the receptor. Based on the overhead and the results obtained, it appears that the synthesized ligand (BDP) shows high anti-breast cancer properties, as the bioactivity is typically affected by the substituents attached to the pyrazole ring. Furthermore, previous studies have reported that coordination of ligands with transition metals often enhances their docking scores and binding interactions, likely due to increased structural rigidity, altered electronic distribution, and additional coordination sites [[25]]. In light of these findings, it is reasonable to hypothesize that complexation of the present ligand with metals such as cobalt and copper could further improve its docking performance and overall biological activity, a premise that merits further investigation in future research.

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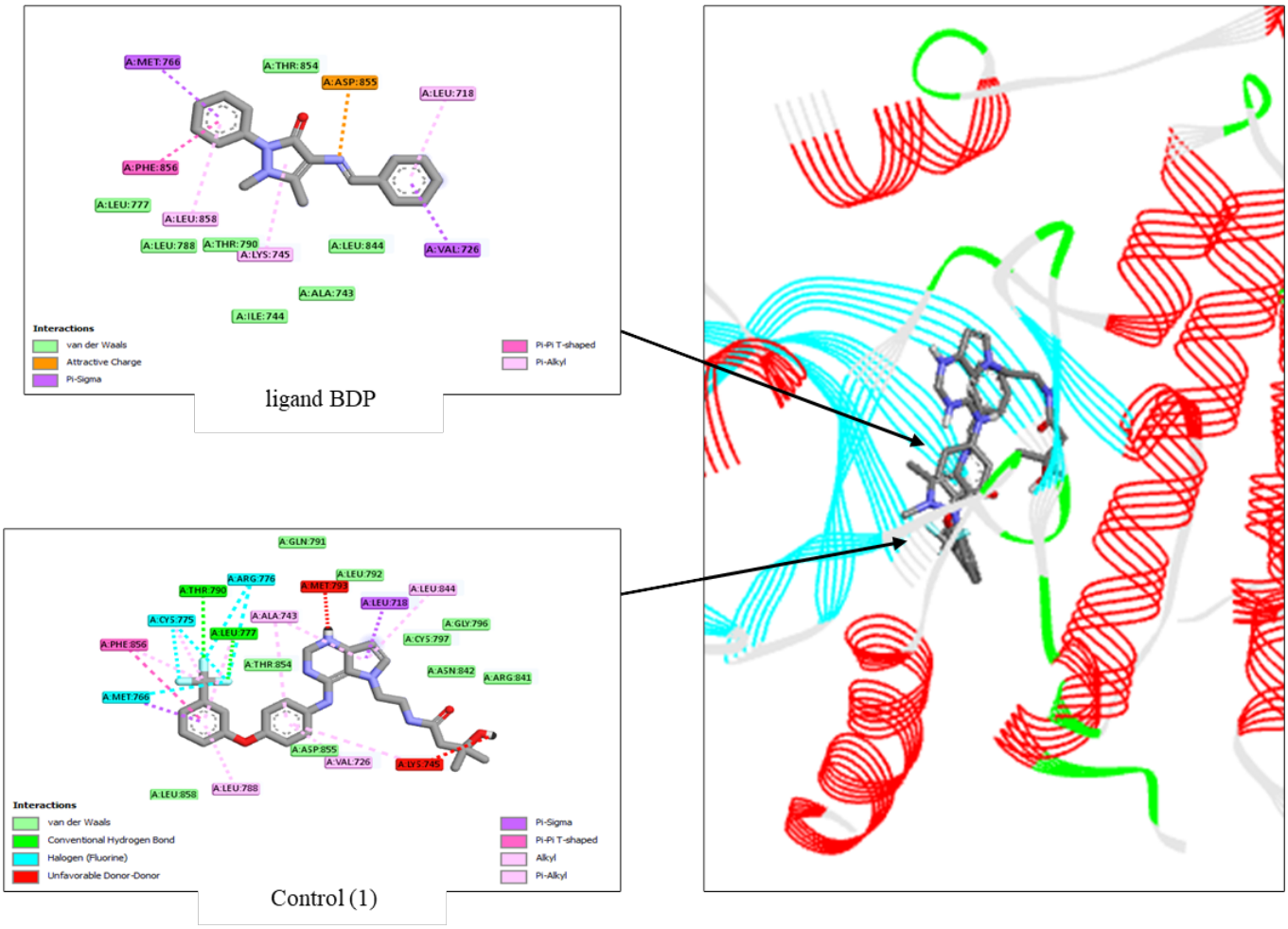

Figure 3. Fig. 3.Two-dimensional interaction diagrams of ligandBDPand control (1) with the target breast cancer virus 3poz

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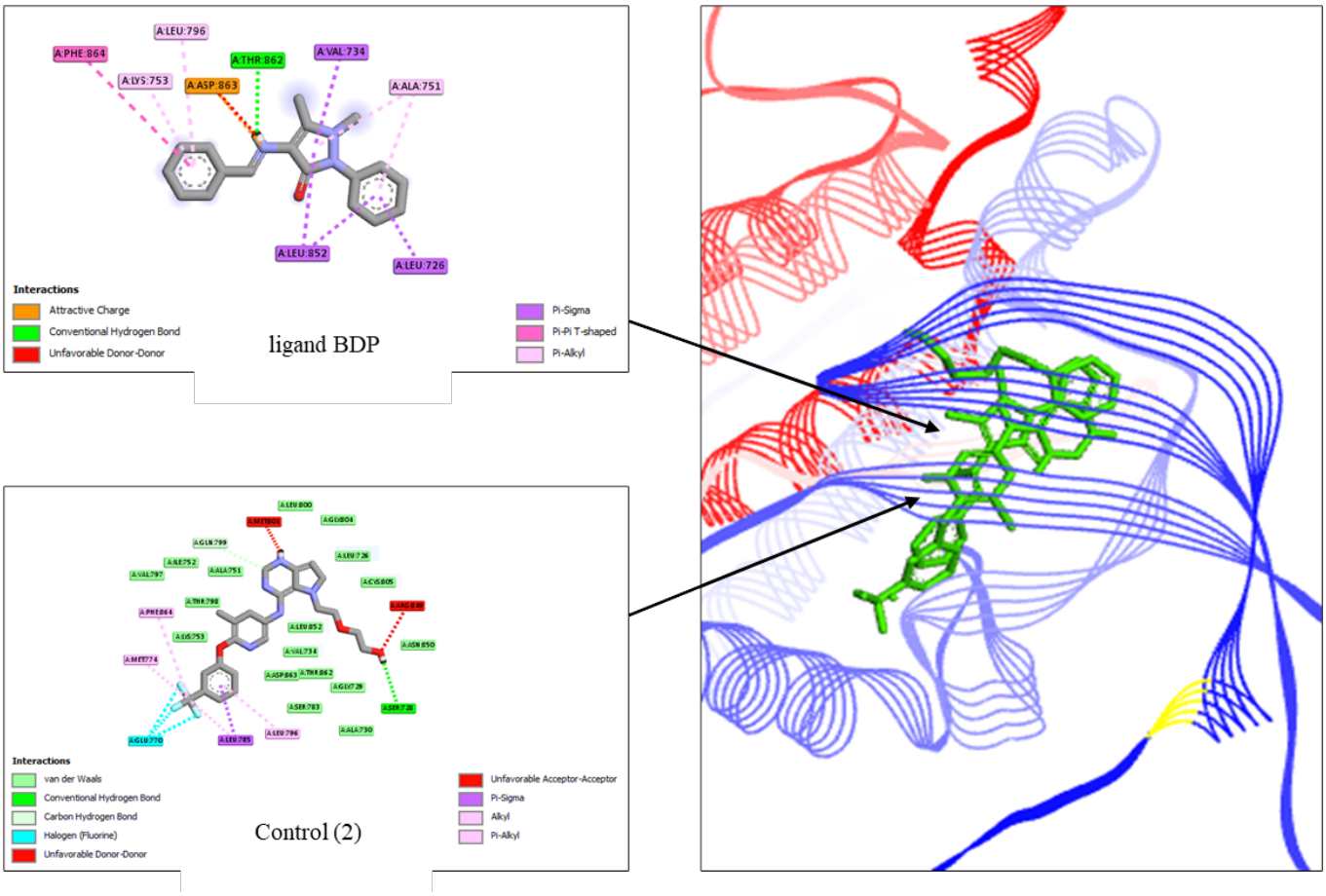

Figure 4. Fig. 4.Two-dimensional interaction diagrams of ligand BDPand control (2) with the target breast cancer virus 3pp0.

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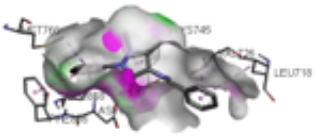
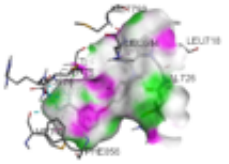
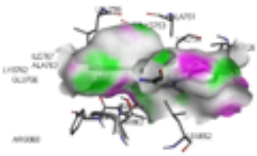
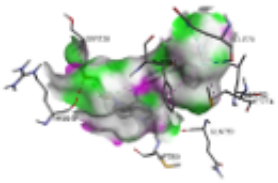
Rank	3D Visualization of Ligand–Receptor Interactions Showing Hydrogen Bonding and Receptor Surface	Binding Energy (kcal/mol)	Amino acid residue
	H-bonds: Acceptor / Donor		
ligand BDP +3poz		-9	Leu718, Val726, Lys745, Leu858, Phe859, Asp855, Met766
Control (1) +3poz		-10.6	Leu718, Val726, Lys745, Phe856, Leu844, Met793, Ala743, Leu788, Thr790, Leu774, Met766, Arg776, Gly775, Thr790
ligand BDP +3pp0		-10.6	Lys753, Arg868, Ala751, Leu726, Leu852, Leu796, Thr862, Asp863
Control (2) +3pp0		-11.1	Met801, Ser728, Leu796, Leu785, Arg849, Leu785, Leu796, Ser728, Phe864

Figure 5. TABLE V: Docking score (ΔG) kcal/mol of ligand **BDP** and references against breast cancer viral target proteins (**3PP0** and **3POZ**)

ADME prediction

The pharmacokinetics analysis of the synthesized ligand (BDP) showed that the ligand fulfills classical oral drug-likeness criteria. Table VI explains the SwissADME result, which reported that the ligand has a molecular weight of 370.24 g/mol, three rotatable bonds, and a TPSA value of 39.29 Å², indicating high membrane permeability and potential to cross the blood–brain barrier [[26]]. The lipophilicity profile (Consensus LogP= 3.64) designates a balanced hydrophilic–lipophilic character, while predicted aqueous solubility is moderate. At the same time, Pharmacokinetic predictions indicate high gastrointestinal absorption, BBB permeation, and the absence of P-gp substrate properties, although the ligand is predicted to inhibit CYP1A2, CYP2C19, and CYP2C9. Druglikeness analysis designates compliance with Lipinski's and other major medicinal chemistry rules, with a bioavailability score of 0.55. No PAINS alerts were detected, but a single Brenk alert was associated with the presence of an imine group. The synthetic accessibility score of 3.01 suggests the ligand can be synthesized with relative ease.

Physicochemical Properties

Property	Value	Interpretation
Molecular weight	370.24 g/mol	<500, compliant with Lipinski's rule
TPSA	39.29 Å²	Low, good BBB permeation
Rotatable bonds	3	Low flexibility, stable conformation
H-bond donors / acceptors	0 / 2	Favorable for permeability
Consensus LogP	3.64	Balanced lipophilicity
Solubility (ESOL)	Moderately soluble	Suitable for oral use

Pharmacokinetics

Parameter	Prediction
GI absorption	High
BBB permeation	Yes
P-gp substrate	No
CYP1A2 inhibitor	Yes
CYP2C19 inhibitor	Yes
CYP2C9 inhibitor	Yes
CYP2D6 inhibitor	No
CYP3A4 inhibitor	No

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Druglikeness & Medicinal Chemistry

Rule/Alert	Result
Lipinski	Yes (0 violations)
Ghose	Yes
Veber	Yes
Egan	Yes
Muegge	Yes
Bioavailability score	0.55
PAINS alerts	0
Brenk alerts	1 (imine group)
Synthetic accessibility	3.01

Table 5. TABLE VI. ADME profile of the synthesized ligand (BDP).

Conclusion

In this research, we synthesized new complexes by microwave technique. The complexes were identified by infrared, UV-Vis., C. H. N, Atomic absorption, Magnetic susceptibility as well as conductivity measurement. The complex formation was studied in solution and the result obtained which were approximately as that obtained from solid state study. The BDP ligand and its metal complexes were studied in gas phase by using PM3 method to calculate the energies and the result showed that the complexes were more stable than the ligand.

The molecular docking results indicate that the synthesized ligand (BDP) demonstrates strong binding affinity toward the target protein, primarily through hydrophobic and van der Waals interactions. Its docking scores suggest significant potential as an anti-breast cancer agent, influenced by substituents on the pyrazole ring. Moreover, previous findings support that coordination with transition metals like cobalt or copper could further enhance its structural stability and bioactivity, warranting future investigation.

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