

Computational Evaluation of a Novel Nitrothiophene-Derived Schiff Base Ligand Against Breast Cancer-Associated Proteins and Andes Hantavirus Nucleoprotein: Molecular Docking and ADMET Analysis

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Abstract The identification of small molecules capable of interacting with multiple therapeutically relevant protein targets is an important strategy in early-stage drug discovery. In the present study, the Schiff base ligand ((*N*¹*E,N*⁸*E*)-*N*¹,*N*⁸-bis((5-nitrothiophen-2-yl)methylene)naphthalene-1,8-diamine; N1) was computationally evaluated against a panel of representative disease-associated proteins to investigate its target-binding profile. The primary focus was the assessment of N1 against breast cancer-associated receptor kinases, including EGFR, HER2, VEGFR2, and PI3K, which play central roles in oncogenic signaling pathways. In addition, the Andes hantavirus nucleoprotein was included as an exploratory antiviral target to examine the broader target recognition capability of the ligand rather than to propose a common therapeutic mechanism. Molecular docking studies were performed using AutoDock Vina with experimentally determined protein structures obtained from the Protein Data Bank. N1 demonstrated favorable binding affinities toward all investigated breast cancer targets, with docking scores of -8.708 kcal/mol for EGFR, -8.836 kcal/mol for HER2, -8.906 kcal/mol for VEGFR2, and -9.066 kcal/mol for PI3K. The ligand also exhibited a docking score of -8.8 kcal/mol against the Andes hantavirus nucleoprotein. Interaction analysis revealed multiple stabilizing hydrogen bonds, hydrophobic contacts, electrostatic interactions, and π -mediated interactions within the respective binding pockets. Drug-likeness assessment indicated compliance with Lipinski's and Ghose's rules, while ADMET prediction suggested favorable absorption and membrane permeability. Nevertheless, the predicted risks of hepatotoxicity, cardiotoxicity, and mutagenicity indicate that further structural optimization and experimental validation are required. Overall, this study demonstrates the potential of N1 as a promising scaffold for breast cancer-associated kinase inhibition while providing preliminary evidence of its broader protein-binding capability across biologically distinct targets.

Keywords: Breast cancer, Hantavirus, Molecular docking, Drug-likeness, ADMET, Schiff base

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1. Introduction

Cancer and viral infections remain among the most serious global health challenges due to their high mortality rates, rapid disease progression, and limited availability of effective therapeutic agents [1,2]. Among different malignancies, breast cancer is one of the most frequently diagnosed cancers and represents a leading cause of cancer-related death among women worldwide [3]. The

development and progression of breast cancer are closely associated with abnormal activation of receptor tyrosine kinases and intracellular signaling proteins, particularly Epidermal Growth Factor Receptor (EGFR), Human Epidermal Growth Factor Receptor 2 (HER2), Vascular Endothelial Growth Factor Receptor 2 (VEGFR2), and phosphoinositide 3-kinase (PI3K) [4,5,6]. These signaling proteins regulate essential cellular processes such as proliferation, angiogenesis, migration, metastasis, survival, and apoptosis. Overexpression or mutation of these targets has been strongly linked with aggressive tumor

progression and poor clinical prognosis [7].

EGFR and HER2 activation initiates downstream signaling cascades, including the RAS/RAF/MEK/ERK and PI3K/AKT/mTOR pathways, which contribute to uncontrolled cancer cell proliferation, enhanced survival, and metastatic progression (Figure 1) [8,9]. VEGFR2 plays a crucial role in tumor angiogenesis by stimulating endothelial cell migration and vascular formation necessary for tumor growth and metastasis [10]. PI3K, a central component of the PI3K/AKT signaling pathway, regulates cellular growth, proliferation, metabolism, and survival and is frequently dysregulated in breast cancer [11]. Collectively, EGFR, HER2, VEGFR2, and PI3K represent interconnected signaling proteins that regulate complementary aspects of breast cancer progression, including cell proliferation, survival, angiogenesis, and metastasis. Since these proteins belong to functionally linked oncogenic signaling networks, their simultaneous computational evaluation provides an opportunity to investigate whether a single chemical scaffold can potentially interact with multiple biologically relevant targets involved in breast cancer. It should be noted that the present study aims to explore the binding characteristics of N1 toward these proteins through molecular docking and does not imply experimentally validated inhibition of these signaling pathways. Therefore, EGFR, HER2, VEGFR2, and PI3K were selected as representative breast cancer-associated targets for an exploratory computational target-profiling study (Figure 1) [8,9,10,11].

In addition to cancer, viral infections caused by emerging and re-emerging viruses continue to pose major public health concerns worldwide. Andes hantavirus, a member of the Hantaviridae family, is responsible for hantavirus cardiopulmonary syndrome (HCPS), a severe respiratory disease associated with high fatality rates [12]. The viral nucleoprotein (N protein) plays an essential role in viral RNA encapsidation, ribonucleoprotein complex formation, genome replication, and viral assembly, making it a biologically relevant target for antiviral drug

discovery (Figure 2) [13]. Unlike viral enzymes, the nucleoprotein does not possess catalytic activity; instead, its RNA-binding region is responsible for recognizing and stabilizing viral genomic RNA during ribonucleoprotein assembly. Accordingly, the molecular docking analysis in the present study focused on this functionally important RNA-binding region to evaluate the potential molecular recognition of N1. Binding at this site may theoretically interfere with RNA recognition or ribonucleoprotein assembly; however, such effects remain computational hypotheses that require experimental validation [13,14]. The inclusion of the Andes hantavirus nucleoprotein was intended as an exploratory assessment of the binding versatility of the N1 scaffold against a structurally unrelated viral target rather than to propose a unified therapeutic strategy linking breast cancer and hantavirus infection. Despite the severe pathogenicity associated with hantavirus infections, currently available antiviral therapies remain limited, emphasizing the continuing need to identify new antiviral scaffolds for future investigation [14].

In the present work, we report the synthesis and computational evaluation of a novel nitrothiophene-derived Schiff base ligand (N1). The primary objective of this study was to investigate its interaction with multiple breast cancer-associated kinase targets, including EGFR, HER2, VEGFR2, and PI3K, which collectively regulate tumor proliferation, survival, and angiogenesis. As an exploratory extension of this computational investigation, the ligand was also docked against the Andes hantavirus nucleoprotein to assess whether this chemical scaffold exhibits potential binding capability toward a structurally unrelated viral protein involved in RNA encapsidation. This exploratory comparison should not be interpreted as evidence of a unified therapeutic strategy but rather as an initial computational assessment of the molecular recognition properties of N1 across biologically distinct protein targets. The ligand (N^1E,N^8E)- N^1,N^8 -bis((5-nitrothiophen-2-yl)methylene)naphthalene-1,8-diamine, and its *in silico* activities are reported here for the first time.

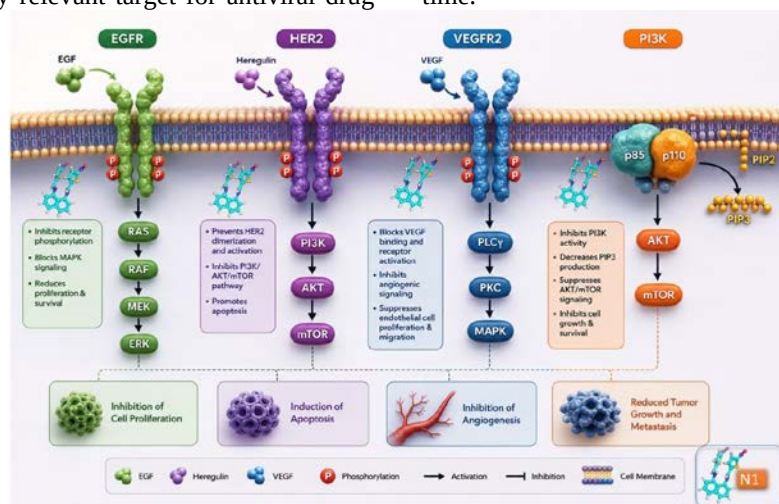


Figure 1. The figure illustrates the proposed mechanism of action of the investigated ligand against major breast cancer-associated signaling proteins, including EGFR, HER2, VEGFR2, and PI3K. Activation of EGFR and HER2 normally initiates downstream signaling cascades such as the RAS/RAF/MEK/ERK and PI3K/AKT/mTOR pathways, which promote cancer cell proliferation, survival, and metastasis. VEGFR2 activation stimulates angiogenic signaling pathways responsible for tumor vascularization and endothelial cell migration. In the proposed mechanism, inhibition of these receptors suppresses phosphorylation-mediated signaling events, thereby reducing tumor growth, angiogenesis, and metastatic progression. PI3K inhibition further decreases AKT/mTOR signaling, leading to apoptosis induction and suppression of cancer cell survival. Overall, the figure demonstrates the multi-target inhibitory action of the ligand against critical pathways involved in breast cancer progression

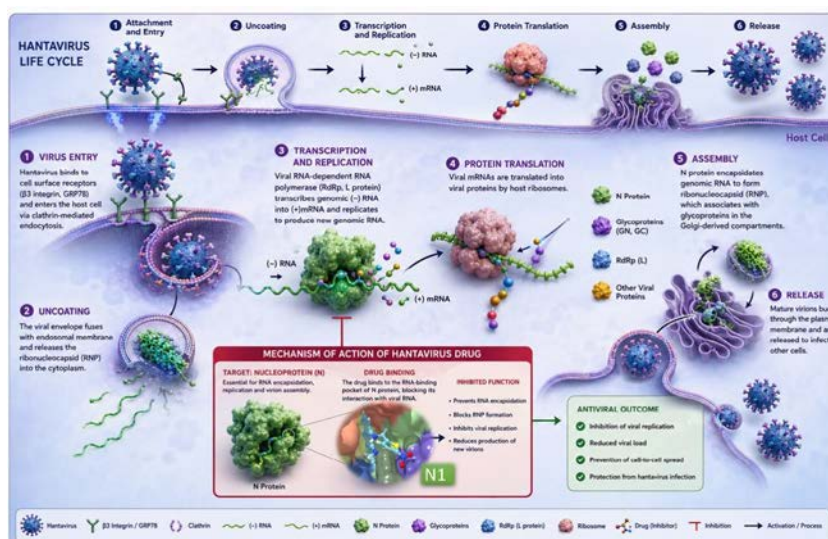


Figure 2. The figure represents the life cycle of Andes hantavirus and the proposed antiviral mechanism of the investigated compound targeting the viral nucleoprotein (N protein). The hantavirus initially enters the host cell through receptor-mediated endocytosis, followed by viral uncoating and release of ribonucleoprotein complexes into the cytoplasm. Viral RNA transcription and replication are subsequently carried out by the viral RNA-dependent RNA polymerase, leading to synthesis of viral proteins and assembly of new virions. The proposed ligand is suggested to bind within the RNA-binding region of the hantavirus nucleoprotein, thereby interfering with viral RNA encapsidation and ribonucleoprotein complex formation. This inhibition may suppress viral replication, reduce formation of mature viral particles, and prevent further viral dissemination within host cells. The overall antiviral outcome includes inhibition of viral replication, reduction of viral load, and prevention of hantavirus propagation

2. Materials and Methods

2.1. Synthesis: Material

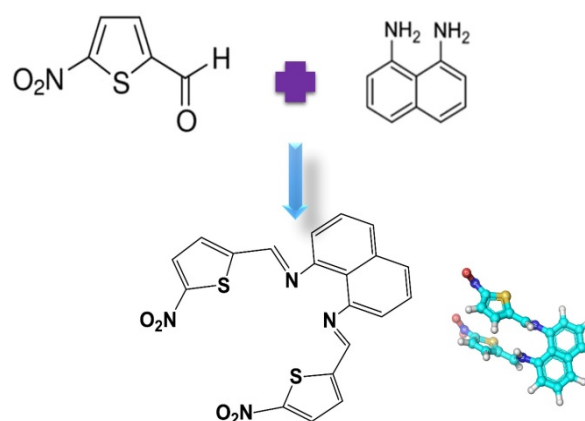
All starting materials and solvents used were purchased from Aldrich and Fluka and were used without further purification. Melting points were determined in an open capillary tube on a Gallenkamp (Variable heater) melting point apparatus. NMR spectrum (^1H) was recorded on an analysis X-685 benchtop NMR spectrophotometer at 60 MHz DMSO- d_6 with TMS as internal standard, at the central science laboratory, Covenant University, Ota. The infrared spectra of all synthesized products were obtained using Agilent Cary 630 FTIR. The electronic spectra, of all the compounds, were obtained in solution, in the wavelength range 400-1000 nm using 1800 Shimadzu ultra-violet spectrophotometer. Both were carried out at the central science laboratory, Obafemi Awolowo University, Ile-Ife.

2.2. Synthesis; Experimental

An ethanolic solution of 1,8-diaminonaphthalene (0.83 g, 5.00 mmol) was introduced to a solution of 5-nitro-2-carboxaldehyde (1.62 g, 10.0 mmol) in absolute ethanol (25 mL) supplemented with glacial acetic acid (3 drops) as a catalyst. The reaction mixture was subjected to reflux conditions for 4 hours under atmospheric pressure. Following thermal treatment, the reaction vessel was allowed to equilibrate to ambient temperature, after which the volatile organic solvent was removed via rotary evaporation under reduced pressure until precipitation of a solid product occurred. The crude material was subsequently triturated with cold ethanol and subjected to recrystallization from a chloroform/ethanol solvent mixture (volume ratio 30:70). A deep orange-colored solid was obtained, collected by vacuum filtration, and dried

under reduced pressure at 60°C until constant mass was achieved, yielding N1 as the isolated product. The compound demonstrated appreciable solubility in chloroform, ethanol, and methanol. The schematic representation for the preparation of N1 is given in Scheme 1.

Yield: 1.49 g, 68.78%; m.p: 165°C - 166°C (d); IR (cm^{-1}): 1608 $\nu(\text{C}=\text{C})$, 1587 $\nu(\text{C}=\text{N})$, 1423 $\nu(\text{C}=\text{C})$, thiophene aromatic ring) 1490 and 1326 $\nu(\text{NO}_2)$, UV-Vis (nm): 299; ^1H NMR (60 MHz): DMSO- d_6 δ 7.95 (s, 1H), 7.21, 7.04 (d, 6H), 6.64, 6.55 (d, 2H).



Scheme 1. Schematic representation of the synthesis pathway of the novel Schiff base ligand N1, (N^1E,N^8E)- N^1,N^8 -bis((5-nitrothiophen-2-yl)methylene)naphthalene-1,8-diamine formed through the condensation reaction between 5-nitrothiophene-2-carbaldehyde and naphthalene-1,8-diamine. The figure also illustrates the optimized three-dimensional molecular structure of the synthesized compound

2.3. Retrieval of Protein Structures

The three-dimensional crystal structures of the selected

therapeutic targets associated with breast cancer and viral infection were retrieved from the Protein Data Bank (PDB). The protein structures used in this study included epidermal growth factor receptor (EGFR, PDB ID: 1M17, human epidermal growth factor receptor 2 (HER2, PDB ID: 3PP0), vascular endothelial growth factor receptor 2 (VEGFR2, PDB ID: 1YWN), phosphoinositide 3-kinase (PI3K, PDB ID: 4JPS), and Andes hantavirus nucleoprotein (PDB ID: 5E04). The biologically relevant protein chain (Chain A) was selected for all docking studies. These structures were chosen based on their high crystallographic resolution and the presence of co-crystallized ligands within the active site, allowing accurate definition of the ligand-binding pocket for molecular docking.

2.4. Protein Preparation

Protein preparation was performed using AutoDock Tools. Prior to docking, all crystallographic water molecules, co-crystallized ligands, and non-essential heteroatoms were removed while preserving the protein backbone and active-site residues. Polar hydrogen atoms were subsequently added, and Kollman united-atom partial charges were assigned to the protein structures. The prepared receptors were saved in PDBQT format for docking calculations [19].

2.5. Ligand Preparation

The chemical structure of the synthesized ligand was generated using ChemDraw Professional 12.0 and converted into a three-dimensional structure using Avogadro. Geometry optimization was carried out using the MMFF94 force field until convergence to obtain a minimum-energy conformation. Hydrogen atoms were added, appropriate protonation corresponding to physiological pH (approximately 7.4) was assigned, and Gasteiger partial atomic charges were calculated using AutoDock Tools. The optimized ligand was finally converted into PDBQT format for molecular docking [20,21].

2.6. Molecular Docking

Molecular docking studies were performed using AutoDock Vina (version 1.2.7) to evaluate the binding affinity and binding mode of the ligand against the selected protein targets. The docking grid was centered on the active-site region defined by the co-crystallized ligand in each receptor structure. A grid box of $25 \times 25 \times 25$ Å with a grid spacing of 1.0 Å was employed to adequately encompass the entire binding pocket. Docking calculations were carried out using an exhaustiveness value of 8, and 10 binding poses were generated for each protein-ligand complex. The resulting docking conformations were ranked according to their predicted binding free energies (kcal/mol). The optimal binding pose for each complex was selected based on the lowest binding free energy together with a favorable binding orientation and the formation of key interactions with biologically relevant active-site residues identified from the corresponding crystal structures and supported by

previous literature [22,23].

2.7. Drug-Likeness Evaluation

The drug-likeness properties of N1 were evaluated using widely accepted computational pharmacokinetic filters, including Lipinski's Rule of Five and Ghose's filter, to assess its suitability as a potential orally active therapeutic agent. Physicochemical parameters such as molecular weight, hydrogen bond acceptors, hydrogen bond donors, partition coefficient (logP), molar refractivity, and total number of atoms were calculated to determine the drug-like behavior and oral bioavailability of the compound [24,25].

Lipinski's Rule of Five was applied based on the criteria of molecular weight below 500 Da, hydrogen bond acceptors fewer than 10, hydrogen bond donors fewer than 5, and logP value below 5, which are considered favorable for oral drug candidates [24]. In addition, Ghose's filter was employed to further evaluate the compound by considering acceptable ranges of molecular weight, lipophilicity, molar refractivity, and atom count commonly associated with biologically active molecules [25]. All calculations and predictions were performed using an online ADMET and drug-likeness prediction platform. The obtained parameters were analyzed to determine the compliance of N1 with established drug-likeness criteria

2.8. ADMET Prediction Studies

ADMET (Absorption, Distribution, Metabolism, Excretion, and Toxicity) prediction studies are extensively utilized in modern drug discovery to evaluate the pharmacokinetic behavior, bioavailability, and toxicity profile of potential therapeutic molecules prior to experimental and clinical investigations [26,27]. ADMET analysis assists in identifying compounds with favorable absorption, distribution, metabolic stability, elimination characteristics, and reduced toxicity, thereby minimizing the risk of late-stage drug failure and reducing the overall cost and time required for drug development [28].

In the present study, ADMET prediction of N1 was performed using the admetSAR web server. Parameters associated with intestinal absorption, blood-brain barrier permeability, cytochrome P450 metabolism, excretion behavior, and different toxicity endpoints were evaluated to determine the pharmacological suitability and safety profile of N1 as a potential anticancer and antiviral therapeutic candidate [29,30].

3. Results and Discussion

3.1. Characterization

3.1.1. NMR Spectroscopic Characterization of N1

^1H NMR: Proton nuclear magnetic resonance spectroscopy of N1 in dimethyl sulfoxide- d_6 (DMSO- d_6) revealed diagnostic resonances consistent with successful Schiff base formation via aldehyde-amine condensation. The azomethine proton manifested as a singlet at δ 7.95

ppm (1H), characteristic of the iminic C-H moiety [31,32]. The observed chemical shift reflects pronounced electronic effects originating from the thiophene heterocycle. The sulfur atom within the thiophene ring system exerts significant influence on the electronic architecture of the adjacent azomethine functional group through enhanced electron-donating capacity. Thiophene exhibits substantially greater electron-donating character relative to benzene and other common aromatic chromophores, thereby augmenting electron density at the iminic nitrogen atom. Consequentially, this electronic enrichment induces an upfield shift of the iminic proton resonance relative to analogous phenyl-substituted Schiff bases, reflecting the enhanced nucleophilicity imparted by thiophene conjugation.

The naphthalene aromatic protons appeared as two doublets at δ 7.21 and δ 7.04 ppm (6H), consistent with the aromatic proton manifold of the peri-disubstituted naphthalene ring system [31,32]. Additionally, thiophene aromatic protons were observed at δ 6.64 and δ 6.55 ppm (1H), appearing as a doublet. Significantly, the aldehyde proton (ca. δ 10.00 ppm) characteristic of the unsubstituted starting aldehyde was absent from the spectrum, providing definitive confirmation of complete conversion to the Schiff base product and exclusion of residual aldehyde reactant [31,32].

3.1.2. Electronic Spectroscopic Characterization

The ultraviolet-visible (UV-Vis) spectrum revealed the extended conjugation resulting from the integrated aromatic systems, exhibiting absorption maxima at 299 nm.

3.1.3. Infrared Spectroscopic Characterization

The azomethine C=N stretching vibration serves as a characteristic diagnostic feature in the infrared spectrum of Schiff base ligands. In the spectrum of (*N*¹*E*,*N*⁸*E*)-*N*¹,*N*⁸-bis((5-nitrothiophen-2-yl)methylene)naphthalene-1,8-diamine, a strong absorption band was observed at 1587 cm⁻¹, which was assigned to the C=N stretching mode of the imine functionality [33]. This frequency positioning is attributable to the partial double-bond character of the imine functional group, which exhibits electronic properties intermediate between those of typical C=O and isolated C=N bonds [33]. The conjugation of the azomethine moiety with both the naphthalene and thiophene aromatic systems results in a bathochromic shift of the C=N stretching frequency relative to aliphatic imines, a phenomenon arising from extended electronic delocalization across the conjugated π -system. A critical indicator of successful condensation between the diamine and aldehyde precursors is the absence of diagnostic absorption bands characteristic of the reactant species. Specifically, the primary N-H stretching frequencies of naphthalene-1,8-diamine, which appeared as two doublets at 3416, 3388 cm⁻¹ and 3334, 3304 cm⁻¹ in the spectrum of the unreacted diamine, were not observed in the product spectrum [31,33]. Further evidence supporting complete condensation is provided by the absence of the aldehyde C=O stretching band at 1654 cm⁻¹, previously observed in the spectrum of 5-nitro-2-thiophenecarboxaldehyde. The thiophene aromatic ring C=C stretching vibrations were observed at 1423 cm⁻¹ (Thamaraichelvan, 2024), serving

as a diagnostic feature confirming the presence and structural integrity of the heterocyclic system. The in-plane C-H bending vibrations of the thiophene ring appeared at approximately 1032 cm⁻¹, providing additional spectroscopic markers for the ligand characterization [31,32]. The naphthalene core of (*N*¹*E*,*N*⁸*E*)-*N*¹,*N*⁸-bis((5-nitrothiophen-2-yl)methylene)naphthalene-1,8-diamine contributes several characteristic vibrational bands to the overall infrared spectrum. The naphthalene C-H stretching modes appeared at approximately 3150 cm⁻¹, exhibiting spectral overlap with the aromatic C-H stretches of the thiophene rings. An absorption band of weak to moderate intensity was observed at 1608 cm⁻¹, corresponding to naphthalene aromatic C=C stretching vibrations that overlap with the azomethine (C=N) stretching region. The nitro group substituents on the thiophene rings exhibited characteristic asymmetric and symmetric N=O stretching vibrations at 1490 cm⁻¹ and 1326 cm⁻¹, respectively, confirming the presence of the nitro-substituted thiophene moieties in the final product [32,33].

3.2. Molecular Docking Analysis

The molecular docking study revealed that the ligand (N1) exhibited favorable binding affinity toward all selected breast cancer-associated therapeutic targets. The docking scores obtained against EGFR, HER2, VEGFR2, and PI3K were -8.708, -8.836, -8.906, and -9.066 kcal/mol, respectively. Among the investigated receptors, PI3K demonstrated the highest binding affinity, indicating that the ligand may possess strong inhibitory potential toward the PI3K/AKT signaling pathway.

In addition to the cancer-related targets, the ligand also showed promising interaction with the Andes hantavirus nucleoprotein, with a docking score of -8.8 kcal/mol (Table 1). This result suggests that N1 may have potential antiviral activity alongside its anticancer properties, highlighting its possible role as a multifunctional therapeutic candidate.

Table 1. Docking scores of the ligand against selected breast cancer targets

Target	PDB ID	Docking Score (kcal/mol)
EGFR	1M17	-8.708
HER2	3PP0	-8.836
VEGFR2	1YWN	-8.906
PI3K	4JPS	-9.066

3.3. EGFR–Ligand Interaction Analysis

The ligand demonstrated strong binding affinity toward EGFR with a docking score of -8.708 kcal/mol. The docked complex revealed that the ligand occupied the ATP-binding pocket efficiently through multiple stabilizing interactions (Figure 3). Hydrogen bond interactions were observed with ARG817 and GLY695 residues at bond distances of 2.63 and 2.68 Å, respectively. These interactions contributed significantly to stabilization and proper orientation of the ligand within the kinase cavity.

An electrostatic Pi-anion interaction with ASP831 further enhanced ligand stabilization through electrostatic

Additionally, the ligand exhibited Pi-Pi stacked interaction and Pi-sulfur interaction with PHE699, which may contribute to favorable aromatic stabilization and van der Waals interactions (Table 2). Collectively, the interaction profile suggests stable occupancy of the EGFR catalytic site, which may interfere with receptor phosphorylation and downstream proliferative signaling pathways.

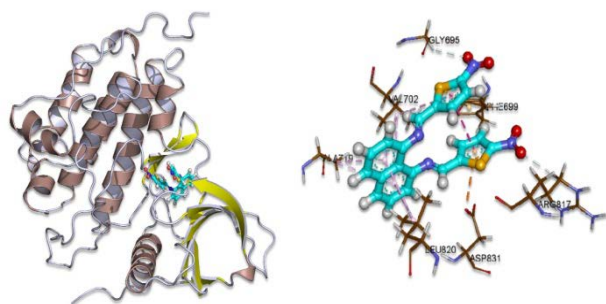


Table 2. Bond distances and type between EGFR receptor and ligand(N1)

Bond Name	Distance (Å)	Bond category	Bond type
A:ARG817:HD2 - A:N1:O	2.63472	Hydrogen Bond	Carbon Hydrogen Bond
A:GLY695:HA1 - A:N1:O	2.68855	Hydrogen Bond	Carbon Hydrogen Bond
A:ASP831:OD2 - A:N1	3.85797	Electrostatic	Pi-Anion
A:N1 - A:N1	4.1088	Hydrophobic	Pi-Pi Stacked
A:N1 - A:LEU820	4.49308	Hydrophobic	Pi-Alkyl
A:N1 - A:ALA719	4.52284	Hydrophobic	Pi-Alkyl
A:N1 - A:LEU820	4.56729	Hydrophobic	Pi-Alkyl
A:N1 - A:ALA719	4.59354	Hydrophobic	Pi-Alkyl
A:N1 - A:VAL702	5.09366	Hydrophobic	Pi-Alkyl
A:N1 - A:VAL702	5.33141	Hydrophobic	Pi-Alkyl
A:N1 - A:VAL702	5.37742	Hydrophobic	Pi-Alkyl
A:N1:S - A:PHE699	5.58999	Other	Pi-Sulfur
A:N1 - A:ALA1048	4.16179	Hydrophobic	
A:N1:S - A:PHE1045	4.46952	Other	
A:N1 - A:ALA864	4.87936	Hydrophobic	
A:N1 - A:LEU1033	5.29068	Hydrophobic	
A:N1 - A:PHE1045	5.4832	Hydrophobic	

The docking study revealed that the ligand strongly interacted with HER2 with a docking score of -8.836 kcal/mol. Multiple conventional hydrogen bonds were observed with MET801, THR862, and ASP863. Among these residues, MET801 belongs to the hinge region of the HER2 kinase domain, and interaction with this residue is considered highly important for kinase inhibition (Figure 4).

The observed Pi-Pi stacked interactions indicate favorable aromatic stabilization of the ligand inside the HER2 active site (Table 3). The combination of hydrogen bonding, electrostatic stabilization, and hydrophobic interactions strongly supports the potential inhibitory activity of the ligand toward HER2-mediated signaling pathways associated with aggressive breast cancer progression.

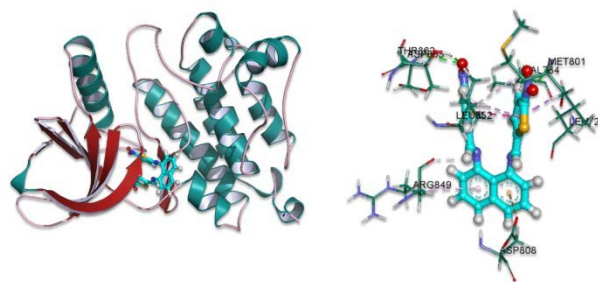


Table 3. Bond distances and type between HER2 receptor and ligand(N1)

Bond Name	Distance (Å)	Bond category	Bond type
A:MET801:HN - A:N1:O	2.25184	Hydrogen Bond	Conventional Hydrogen Bond
A:THR862:HG1 - A:N1:O	2.27182	Hydrogen Bond	Conventional Hydrogen Bond
A:N1:H - A:ARG849:O	2.44311	Hydrogen Bond	Carbon Hydrogen Bond
A:LEU726:HD11 - A:N1	2.63954	Hydrophobic	Pi-Sigma
A:ASP863:HN - A:N1:O	2.90881	Hydrogen Bond	Conventional Hydrogen Bond
A:ASP808:OD2 - A:N1	3.47672	Electrostatic	Pi-Anion
A:N1 - A:N1	4.07456	Hydrophobic	Pi-Pi Stacked
A:N1 - A:VAL734	4.97229	Hydrophobic	Pi-Alkyl
A:N1 - A:LEU852	4.98197	Hydrophobic	Pi-Alkyl
A:N1 - A:LEU852	5.02009	Hydrophobic	Pi-Alkyl
A:N1 - A:ARG849	5.06506	Hydrophobic	Pi-Alkyl
A:N1 - A:VAL734	5.10052	Hydrophobic	Pi-Alkyl

The VEGFR2 complex exhibited highly favorable interactions with the ligand and produced a docking score

of -8.906 kcal/mol. A strong conventional hydrogen bond was observed between ARG1030 and the ligand oxygen atom at a bond distance of 1.75 Å, indicating highly stable interaction (Figure 5). Another conventional hydrogen bond with ASN921 further contributed to stabilization of the complex.

Several hydrophobic interactions involving ALA864, VAL846, ALA1048, and LEU1033 stabilized the aromatic scaffold of the ligand inside the ATP-binding pocket. Aromatic Pi-Pi T-shaped interaction with PHE1045 and Pi-sulfur interactions additionally enhanced the overall stability of the complex (Table 4).

VEGFR2 is an important regulator of tumor angiogenesis and vascularization. Therefore, stable occupation of the VEGFR2 catalytic site by the ligand suggests possible antiangiogenic activity, which may suppress tumor growth and metastatic progression.

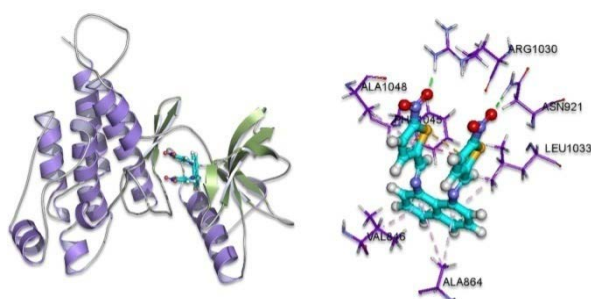


Figure 5. Molecular docking analysis of the ligand within the active site of VEGFR2. The left panel represents the overall binding orientation of the ligand inside the VEGFR2 catalytic pocket, shown in cartoon representation. The right panel illustrates detailed ligand-protein interactions, including hydrogen bonding with ligand surrounding amino acids

Table 4. Bond distances and type between VEGFR2 receptor and ligand (N1)

Bond Name	Distance (Å)	Bond category	Bond type
A:ARG1030:HH21 - A:N1:O	1.75813	Hydrogen Bond	Conventional Hydrogen Bond
A:ASN921:HD22 - A:N1:O	2.44476	Hydrogen Bond	Conventional Hydrogen Bond
A:N1:S - A:N1	3.861	Other	Pi-Sulfur
A:N1 - A:ALA864	3.90161	Hydrophobic	Pi-Alkyl
A:N1 - A:N1	3.99616	Hydrophobic	Pi-Pi Stacked
A:N1 - A:VAL846	4.10243	Hydrophobic	Pi-Alkyl
A:N1 - A:ALA1048	4.16179	Hydrophobic	Pi-Alkyl
A:N1:S - A:PHE1045	4.46952	Other	Pi-Sulfur
A:N1 - A:ALA864	4.87936	Hydrophobic	Pi-Alkyl
A:N1 - A:LEU1033	5.29068	Hydrophobic	Pi-Alkyl
A:N1 - A:PHE1045	5.4832	Hydrophobic	Pi-Pi T-shaped

3.6. PI3K–Ligand Interaction Analysis

Among all studied receptors, PI3K demonstrated the strongest interaction with the ligand, with a docking score of -9.066 kcal/mol. The ligand established multiple hydrogen bonds with SER774, ASP933, and LYS802 residues (Figure 6). These residues are critically involved in catalytic activity and inhibitor recognition within the PI3K active site.

Hydrogen bonding with ASP933 and LYS802 is particularly important because these residues contribute significantly to stabilization of kinase inhibitors within the catalytic region. In addition to hydrogen bonding, multiple hydrophobic interactions involving ILE848, ILE932, VAL850, and MET922 stabilized the aromatic framework of the ligand inside the hydrophobic cavity.

Aromatic Pi-Pi T-shaped interaction with TRP780 and Pi-sulfur interaction with MET922 further enhanced the binding affinity and overall stability of the complex (Table 5). The presence of extensive stabilizing interactions explains the superior docking score observed for PI3K compared to the other targets.

The results strongly suggest that the ligand may effectively inhibit the PI3K/AKT signaling pathway, which is frequently dysregulated in breast cancer and associated with uncontrolled cellular proliferation, survival, metastasis, and drug resistance.

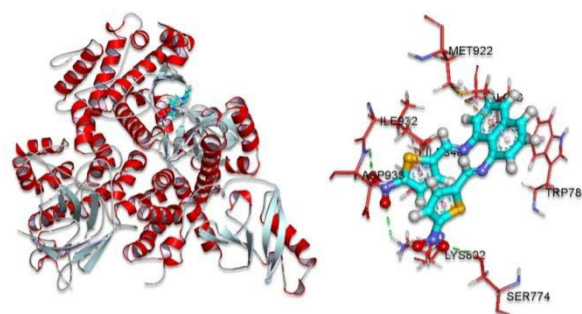


Figure 6. Molecular docking analysis of the ligand within the active site of PI3K. The left panel represents the overall binding orientation of the ligand inside the PI3K catalytic pocket, shown in cartoon representation. The right panel illustrates detailed ligand-protein interactions, including hydrogen bonding with ligand surrounding amino acids

Table 5. Bond distances and type between PI3K receptor and ligand(N1)

Bond Name	Distance (Å)	Bond category	Bond type
A:SER774:HG - A:N1:O	2.27608	Hydrogen Bond	Conventional Hydrogen Bond
A:ASP933:HA - A:N1:O	2.30744	Hydrogen Bond	Carbon Hydrogen Bond
A:LYS802:HZ3 - A:N1:O	2.55324	Hydrogen Bond	Conventional Hydrogen Bond
A:ASP933:HN - A:N1:O	2.73516	Hydrogen Bond	Conventional Hydrogen Bond
A:N1 - A:ILE848	4.12926	Hydrophobic	Pi-Alkyl
A:N1 - A:N1	4.15632	Hydrophobic	Pi-Pi Stacked
A:MET922:SD - A:N1	4.21582	Other	Pi-Sulfur
A:N1 - A:ILE932	5.06517	Hydrophobic	Pi-Alkyl
A:N1 - A:VAL850	5.08159	Hydrophobic	Pi-Alkyl
A:TRP780 - A:N1	5.1968	Hydrophobic	Pi-Pi T-shaped
A:N1 - A:MET922	5.38192	Hydrophobic	Pi-Alkyl

3.7. Andes Hantavirus Nucleoprotein –Ligand Interaction Analysis

Molecular docking analysis revealed that ligand N1 exhibited favorable binding affinity toward the Andes hantavirus nucleoprotein with a docking score of -8.8 kcal/mol, suggesting stable complex formation within the protein binding cavity (Figure 7). The ligand was stabilized through multiple intermolecular interactions

involving hydrogen bonding, electrostatic, hydrophobic, and aromatic contacts. A strong conventional hydrogen bond was observed between the ligand and Ala192 at a bond distance of 1.84 Å, indicating significant stabilization of the docked complex (Table 6). Additional hydrogen bonding interactions with Ser27 and Gly78 further contributed to ligand accommodation within the receptor pocket. Notably, the ligand formed a π -cation interaction with Arg81, an important positively charged residue associated with the RNA-binding region of the nucleoprotein, suggesting possible interference with viral RNA recognition and ribonucleoprotein assembly. Furthermore, hydrophobic π -sigma and π -alkyl interactions involving Val101 and Ala192 enhanced the overall binding stability of the complex. Aromatic interactions including π - π stacked interaction with Tyr246 and π - π T-shaped interaction with Phe242 additionally strengthened ligand binding through favorable aromatic packing. Collectively, these results indicate that ligand N1 possesses strong binding capability toward the Andes hantavirus nucleoprotein and may potentially inhibit viral replication by disrupting nucleoprotein-mediated RNA packaging and assembly processes.

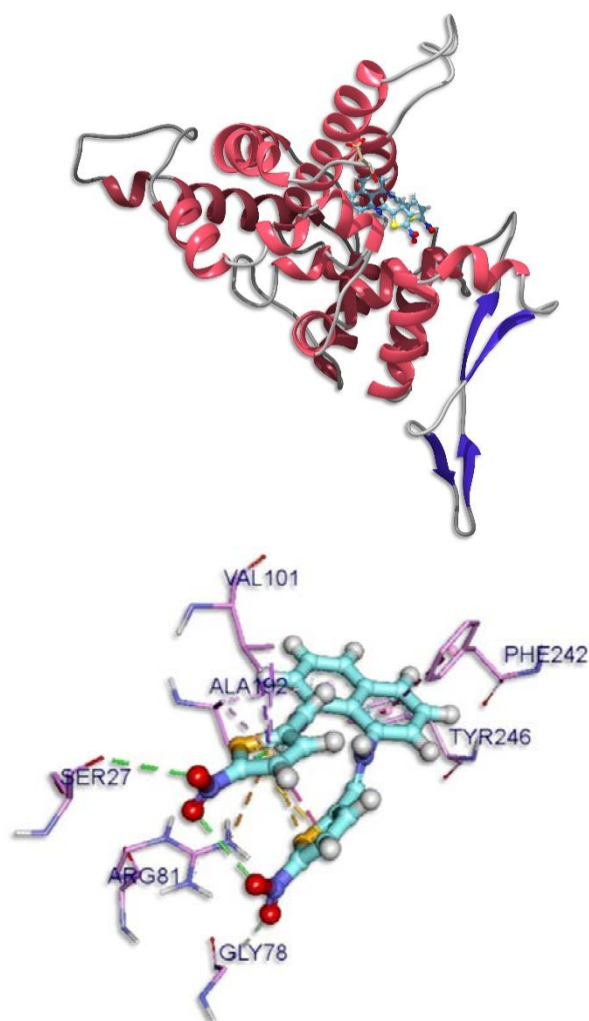


Figure 7. Molecular docking analysis of the ligand within the active site of hantavirus nucleoprotein. The left panel represents the overall binding orientation of the ligand inside the hantavirus nucleoprotein RNA-binding groove, shown in cartoon representation. The right panel illustrates detailed ligand-protein interactions, including hydrogen bonding with ligand surrounding amino acids

Table 6. Bond distances and types between Andes hantavirus nucleoprotein receptor and ligand (N1)

Bond Name	Distance (Å)	Bond category	Bond type
P:N1:H4 - A:ALA192:O	1.84042	Hydrogen Bond	Conventional Hydrogen Bond
P:N1:O2 - P:N1:O3	3.35107	Hydrogen Bond	Conventional Hydrogen Bond
P:N1:O4 - A:SER27:O	3.36542	Hydrogen Bond	Conventional Hydrogen Bond
A:VAL101:CG2 - P:N1	3.4586	Hydrophobic	Pi-Sigma
A:GLY78:CA - P:N1:O1	3.69134	Hydrogen Bond	Carbon Hydrogen Bond
A:VAL101:CG1 - P:N1	3.73459	Hydrophobic	Pi-Sigma
P:N1 - A:ALA192	3.75398	Hydrophobic	Pi-Alkyl
P:N1 - P:N1	3.76032	Hydrophobic	Pi-Pi Stacked
A:ARG81:NH2 - P:N1	4.10255	Electrostatic	Pi-Cation
P:N1:S1 - P:N1	4.35024	Other	Pi-Sulfur
P:N1:S2 - P:N1	4.35695	Other	Pi-Sulfur
P:N1 - A:ALA192	4.82387	Hydrophobic	Pi-Alkyl
A:TYR246 - P:N1	5.44358	Hydrophobic	Pi-Pi Stacked
A:PHE242 - P:N1	5.70563	Hydrophobic	Pi-Pi T-shaped

3.8. Biological Significance of Multi-Target Inhibition

The present docking study suggests that the investigated ligand may function as a multi-target inhibitor against several major breast cancer-associated signaling pathways. Simultaneous inhibition of EGFR, HER2, VEGFR2, and PI3K may provide synergistic therapeutic benefits by suppressing tumor proliferation, angiogenesis, survival signaling, and metastatic progression.

Among the studied targets, PI3K and HER2 exhibited particularly favorable interactions, indicating that these pathways may represent the primary therapeutic mechanisms of the ligand. The strong interaction with VEGFR2 additionally supports potential antiangiogenic properties of the compound.

The ability of a single molecule to interact efficiently with multiple therapeutic targets is highly advantageous because it may reduce drug resistance associated with single-target therapies and improve overall therapeutic efficacy.

3.9. Drug-likeness properties

The drug-likeness properties of N1 were evaluated using Lipinski's Rule of Five and Ghose's rule to assess its suitability as a potential orally active therapeutic candidate (Table 8). The results revealed that N1 satisfied all the criteria of Lipinski's Rule of Five without any violations, indicating favorable pharmacokinetic characteristics. The molecular weight of the compound was found to be 436.4637 Da, which is within the acceptable limit (<500 Da) for efficient membrane permeability and oral bioavailability. The compound possessed six hydrogen bond acceptors and no hydrogen bond donors, both of which fall within the recommended ranges, suggesting balanced hydrogen-bonding capacity and suitable interaction potential with biological targets.

Furthermore, the calculated virtual logP value of 2.090 indicated moderate lipophilicity, which is advantageous for maintaining an appropriate balance between aqueous solubility and membrane permeability.

In addition to Lipinski's parameters, N1 also fulfilled Ghose's rule, further supporting its drug-like nature. The compound contained 30 atoms, which lies within the acceptable range defined by the Ghose filter, while the molar refractivity value of 110.7864 also satisfied the recommended criteria. These observations collectively suggest that N1 possesses favorable physicochemical properties for drug development. The absence of any rule violations indicates that the compound may exhibit good absorption and permeability characteristics, making it a promising candidate for further biological and pharmacological investigations.

Table 7. Drug-likeness evaluation of N1 based on Lipinski's Rule of Five and Ghose's rule, demonstrating favorable physicochemical properties and compliance with standard criteria for orally active drug candidates

Parameter	N1	Status
Lipinski's Rule of Five		OK
Molecular weight	436.4637 Da	OK
H-Bond Acceptors	6	OK
H-Bond Donors	0	OK
logP (Virtual)	2.090	OK
Lipinski's Rule of Five		OK
Ghose's Rule		OK
Molecular weight	436.4637 Da	OK
Number of atoms	30	OK
logP (Virtual)	2.090	OK
Molar Refractivity	110.7864	OK
Ghose's rule.		OK

3.10. ADMET Analysis

The ADMET profile of N1 was evaluated to investigate its pharmacokinetic behavior, drug-likeness, toxicity profile, and environmental impact (Table 8). The absorption analysis revealed a logS value of -5.85 , indicating moderate aqueous solubility of the compound, while the logP value of 5.07 suggested relatively high lipophilicity, which may facilitate membrane permeability and hydrophobic interactions with biological targets [30]. The predicted pKa values indicated that N1 possesses weak acidic and basic characteristics, which may influence its ionization state and absorption behavior under physiological conditions. Positive Caco-2 permeability and MDCK permeability predictions suggested favorable membrane transport properties, while the positive Human Intestinal Absorption (HIA) prediction with a high probability (97.2%) indicated potentially efficient intestinal uptake and oral absorption [34]. Furthermore, positive F20%, F30%, and F50% oral bioavailability predictions suggest that N1 possesses computationally favorable characteristics for oral administration. However, these pharmacokinetic predictions should be interpreted cautiously, as they represent *in silico* estimates and do not establish satisfactory oral bioavailability under physiological conditions.

Distribution studies predicted positive blood-brain barrier (BBB) permeability, suggesting that N1 may

penetrate the central nervous system. Plasma protein binding (PPB) was predicted to be high (97.7%), indicating strong interaction with plasma proteins, which may influence systemic distribution and drug half-life [35]. The compound was also predicted to inhibit OATP1B1 and OATP1B3 transporters while showing no inhibition toward OCT1, OCT2, and MATE1 transporters. Additionally, N1 was predicted to act as a P-glycoprotein (P-gp) inhibitor but not as a P-gp substrate, suggesting that the compound may exhibit reduced efflux-mediated transport and increased intracellular retention. Nevertheless, the biological significance of these transporter interactions requires experimental verification [36].

Metabolism prediction suggested that N1 may undergo biotransformation through several cytochrome P450 enzymes. The compound was predicted to act as a substrate for CYP1A2, CYP3A4, CYP2B6, CYP2C9, and CYP2C19, indicating that these enzymes may contribute to its metabolic clearance. Moreover, N1 exhibited inhibitory effects toward CYP1A2, CYP2B6, CYP2C9, and CYP2C19, while no inhibition was predicted for CYP3A4 and CYP2D6. Such inhibitory behavior may increase the possibility of drug-drug interactions during co-administration with therapeutics metabolized through the same enzymatic pathways [37]. The predicted lack of human liver microsome stability further suggested that N1 may undergo relatively rapid hepatic metabolism.

Excretion analysis indicated low plasma clearance (CL_p) and renal clearance (CL_r), suggesting relatively slow elimination of the compound from systemic circulation. The predicted half-life (T_{1/2}) and mean residence time (MRT) values imply moderate systemic retention; however, the pharmacological significance of these predictions remains to be established experimentally.

Organ toxicity prediction identified several potential safety liabilities. N1 was predicted to exhibit a positive Drug-Induced Liver Injury (DILI) profile, suggesting a possible risk of hepatotoxicity. Positive nephrotoxicity prediction and concentration-dependent hERG inhibition, which was negative at 1 μ M but positive at 10 and 30 μ M, further indicate potential cardiotoxicity at higher exposure levels [38]. These findings warrant careful consideration because N1 contains a nitrothiophene moiety, which belongs to the broader class of nitroheteroaromatic compounds. Such compounds may undergo metabolic activation by cellular reductases to generate reactive intermediates capable of inducing oxidative stress and covalent interactions with cellular macromolecules, effects that have been associated with hepatotoxicity and other toxicological liabilities. Although these predictions do not confirm actual toxicity, they highlight important structural concerns that require further investigation through experimental toxicological studies. In contrast, respiratory toxicity and skin sensitization were predicted to be negative, suggesting comparatively lower risks in these specific toxicological categories.

Toxicity endpoint analysis predicted positive Ames mutagenicity, rodent carcinogenicity, micronucleus toxicity, and mitochondrial toxicity, indicating potential genotoxic and cellular toxicity concerns. Although these endpoints represent computational predictions rather than experimentally verified toxicities, they emphasize the necessity for comprehensive *in vitro* and *in vivo*

toxicological evaluation before further pharmacological development. Conversely, negative predictions for reproductive toxicity, hemolytic toxicity, and acute oral toxicity suggest comparatively lower risks in these specific toxicological categories.

Endocrine disruption analysis predicted positive interaction with estrogen receptor (ER), ER ligand-binding domain (ER-LBD), thyroid receptor (TR), glucocorticoid receptor (GR), and PPAR γ pathways. These findings suggest that N1 may interfere with endocrine signaling pathways, which could potentially influence both pharmacological activity and toxicity profiles [39]. Positive activation of the p53 and antioxidant response element (ARE) pathways may further indicate possible involvement in oxidative stress responses and apoptosis-related cellular pathways.

Ecological risk assessment predicted high toxicity toward aquatic organisms, including *P. subcapitata*, *Daphnia magna*, fish species, rainbow trout, bluegill sunfish, and *Tetrahymena pyriformis*. In contrast, low honey bee toxicity was predicted, suggesting comparatively lower environmental risk toward pollinating insects. The

compound was also predicted to be non-biodegradable, indicating the potential for environmental persistence following release into aquatic ecosystems.

Overall, the ADMET analysis suggests that N1 possesses several favorable predicted pharmacokinetic characteristics, including acceptable intestinal absorption, membrane permeability, and oral bioavailability. Nevertheless, these favorable properties should be interpreted together with the predicted toxicity liabilities. In particular, the positive predictions for hepatotoxicity, nephrotoxicity, concentration-dependent cardiotoxicity, mutagenicity, and ecological toxicity indicate that the current scaffold requires further optimization before therapeutic development. The presence of the nitrothiophene pharmacophore may contribute to these toxicity alerts through metabolic activation, although this hypothesis requires experimental confirmation. Therefore, the computational ADMET results should be regarded as preliminary predictions useful for compound prioritization rather than evidence of therapeutic suitability, and comprehensive experimental pharmacokinetic and toxicological investigations will be essential in future studies.

Table 8. Predicted physicochemical, pharmacokinetic, metabolic, and toxicity properties of the compound obtained using admetSAR 3.0

Category	Parameter	Predicted Value	Probability (%)
Absorption	logS	-5.85	28.55
	pKa	6.78	55.81
	Acidic pKa	6.66	45.5
	Basic pKa	5.78	56.81
	Caco-2 Permeability	Positive	73.0
	Caco-2 Value	-4.98	73.89
	Human Intestinal Absorption (HIA)	Positive	97.2
	MDCK Permeability	Positive	59.5
	Oral Bioavailability (F50%)	Positive	71.6
	Oral Bioavailability (F30%)	Positive	82.3
	Oral Bioavailability (F20%)	Positive	88.3
Distribution	Blood-Brain Barrier (BBB)	Positive	71.4
	OATP1B1 Inhibitor	Yes	78.2
	OATP1B3 Inhibitor	Yes	79.7
	OATP2B1 Inhibitor	No	43.3
	OCT1 Inhibitor	No	50.2
	OCT2 Inhibitor	No	13.3
	BCRP Inhibitor	Yes	61.1
	BSEP Inhibitor	Yes	91.2
	MATE1 Inhibitor	No	21.2
	P-gp Inhibitor	Yes	76.0
	P-gp Substrate	No	8.59
	Plasma Protein Binding (PPB)	Positive	97.7
Metabolism	VDss	0.21	47.65
	CYP1A2 Inhibitor	Yes	84.0
	CYP3A4 Inhibitor	No	16.9
	CYP2B6 Inhibitor	Yes	75.2
	CYP2C9 Inhibitor	Yes	72.8
	CYP2C19 Inhibitor	Yes	75.5
	CYP2D6 Inhibitor	No	9.8
	CYP1A2 Substrate	Yes	75.8
	CYP3A4 Substrate	Yes	76.7
	CYP2B6 Substrate	Yes	66.4
	CYP2C9 Substrate	Yes	74.4
	CYP2C19 Substrate	Yes	70.1
	CYP2D6 Substrate	No	35.1
	Human Liver Microsome Stability	No	34.69

Category	Parameter	Predicted Value	Probability (%)
Excretion	Rat Liver Microsome Stability	Yes	56.1
	UGT Substrate	No	36.9
	Plasma Clearance (CLp)	No	39.3
	Renal Clearance (CLr)	No	31.7
	Half-life (T1/2)	-1.89	12.56
Organ Toxicity	Mean Residence Time (MRT)	-1.9	13.47
	Neurotoxicity	-2.78	31.84
	Drug-Induced Liver Injury (DILI)	Positive	89.2
	hERG (1 μ M)	Negative	26.5
	hERG (10 μ M)	Positive	66.6
Toxicity Endpoints	hERG (30 μ M)	Positive	93.1
	Respiratory Toxicity	Negative	10.7
	Nephrotoxicity	Positive	73.1
	Eye Irritation	Positive	95.6
	Skin Sensitization	Negative	47.4
	Acute Dermal Toxicity	Positive	72.1
	Ames Mutagenicity	Positive	82.6
	Mouse Carcinogenicity	Positive	58.1
	Rat Carcinogenicity	Negative	50.3
	Rodent Carcinogenicity	Positive	61.9
	Micronucleus Toxicity	Positive	68.7
	Reproductive Toxicity	Negative	35.4
	Mitochondrial Toxicity	Positive	98.4
	Hemolytic Toxicity	Negative	8.9
	Repeated Dose Toxicity	Positive	66.3
Endocrine Disruption	Acute Oral Toxicity	Negative	45.4
	Estrogen Receptor (ER)	Positive	60.9
	ER-LBD	Positive	69.49
	ARE	Positive	87.2
	p53	Positive	65.7
Ecological Risk Assessment	PPAR γ	Positive	52.9
	MMP	Positive	98.6
	Thyroid Receptor (TR)	Positive	58.1
	Glucocorticoid Receptor (GR)	Positive	59.2
	P. subcapitata Toxicity	Positive	83.4
	Crustacean Toxicity	Positive	96.1
	D. magna Toxicity	Positive	96.3
	Fish Toxicity	Positive	94.5
	Fathead Minnow Toxicity	Positive	92.4
	Bluegill Sunfish Toxicity	Positive	93.8
	Rainbow Trout Toxicity	Positive	96.4
	Sheepshead Minnow Toxicity	Positive	95.0
	T. pyriformis Toxicity	Positive	99.8
	Honey Bee Toxicity	Negative	16.9
	Biodegradability	Negative	2.5

4. Conclusion

The present study describes the synthesis and computational evaluation of the nitrothiophene-derived Schiff base ligand N1 against selected breast cancer-associated proteins (EGFR, HER2, VEGFR2, and PI3K) together with the Andes hantavirus nucleoprotein. Molecular docking predicted favorable binding poses and interaction patterns across the investigated targets, with PI3K exhibiting the most favorable docking score among the breast cancer-associated proteins. Drug-likeness and

ADMET analyses suggest that N1 possesses several physicochemical properties compatible with further investigation, although predicted hepatotoxicity, cardiotoxicity, nephrotoxicity, and mutagenicity highlight the need for structural optimization. Overall, these computational findings identify N1 as a promising scaffold as a potential lead compound for future medicinal chemistry studies and experimental validation. The docking results should be regarded as preliminary computational hypotheses rather than evidence of biological inhibition or therapeutic efficacy.

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Conflict of Interest

The authors declare no conflict of interest.

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Supplementary Information

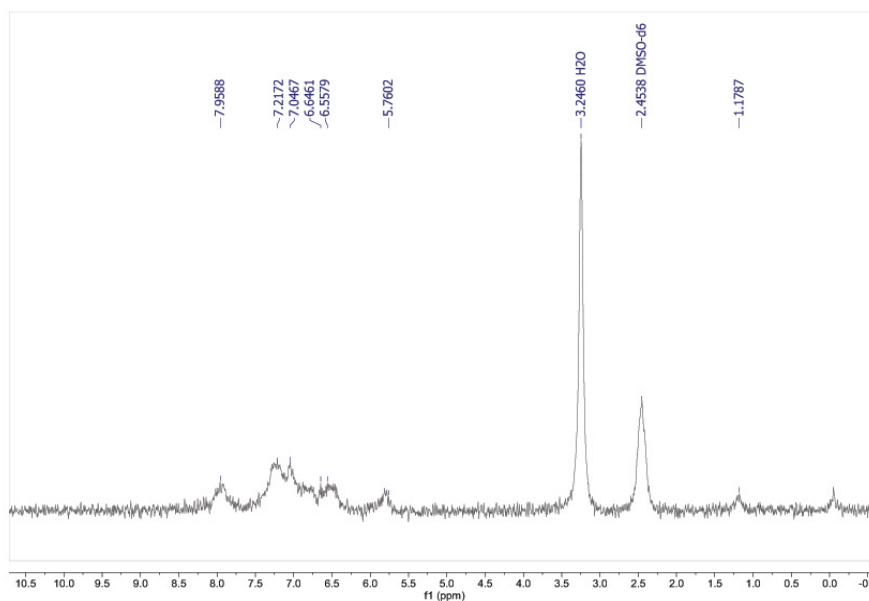


Figure 1. ^1H NMR spectrum of Schiff base ligand N1 recorded in DMSO-d_6 , showing the characteristic azomethine proton resonance at δ 7.95 ppm along with aromatic resonances corresponding to the naphthalene and thiophene moieties

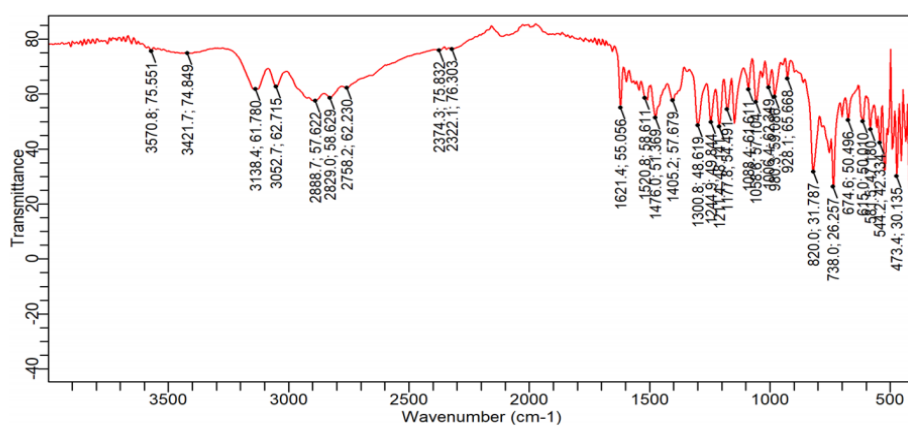


Figure 2. Infrared spectrum of Schiff base ligand N1

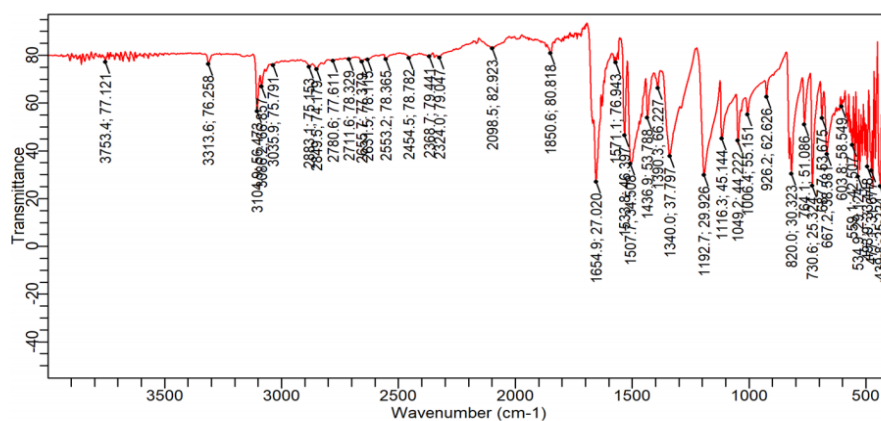


Figure 3. Infrared spectrum of 5-nitro-2-thiophenecarboxaldehyde, starting material

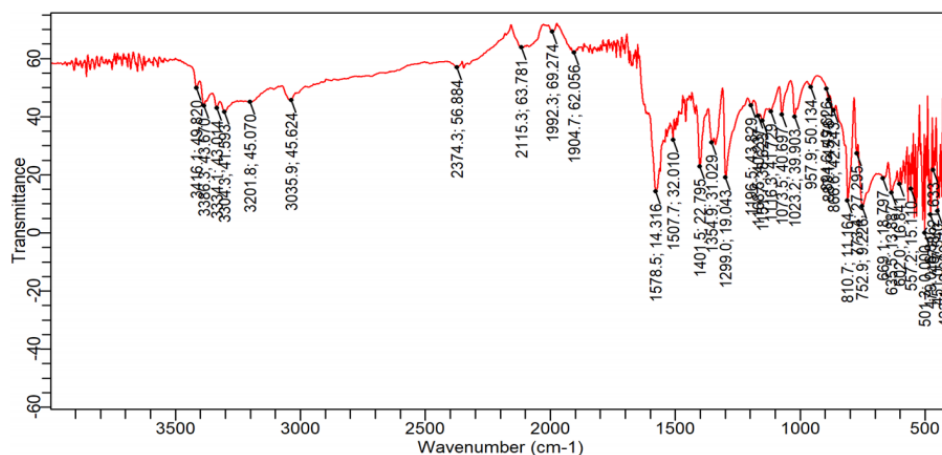


Figure 4. Infrared spectrum of 1,8-diaminonaphthalene, starting material

Computational Evaluation of a Novel Nitrothiophene-Derived Schiff Base Ligand Against Breast Cancer-Associated Proteins and Andes Hantavirus Nucleoprotein: Molecular Docking and ADMET Analysis

