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Novel Chalcone Derivatives as Potent Lyn Tyrosine Kinase Inhibitors: A Promising In Silico Approach for Targeted Therapy in Triple-Negative Breast Cancer †

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Abstract

Triple-negative breast cancer (TNBC) accounts for approximately 10–15% of breast cancer cases and poses a significant clinical challenge due to its aggressive nature and poorer survival outcomes compared to other subtypes. This is primarily attributed to the lack of estrogen, progesterone, and HER2 receptors, which renders conventional hormone-based therapies ineffective. In this study, we employed in silico approaches to design and evaluate novel chalcone derivatives as potential inhibitors of Lyn tyrosine kinase, a critical enzyme implicated in TNBC progression. The designed compounds were screened for drug-likeness and toxicity, all meeting Lipinski's rule of five and demonstrating favorable toxicity profiles. Molecular docking analyses identified five promising ligands; CHCN1, CHCN19, CHCN48, CHCN333, and CHCN94 that exhibited strong binding affinities to key active site residues of Lyn kinase, including Asp385, Phe386, Gly387, Lys275, and Glu290. Among these, CHCN1 showed the highest binding affinity at –8.4 kcal/mol, likely due to interactions with Asp385 and Lys275. These results suggest that the chalcone derivatives may effectively disrupt Lyn-mediated signaling pathways essential for cancer cell survival, potentially inhibiting proliferation, metastasis, and invasion. Overall, this study provides valuable insights into the therapeutic potential of chalcone derivatives for TNBC, offering promising avenues for targeted intervention.

Keywords: triple-negative breast cancer (TNBC); chalcone derivatives; Lyn tyrosine kinase inhibition; molecular docking; drug-likeness; targeted cancer therapy

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1. Introduction

Breast cancer remains the most frequently diagnosed cancer among women worldwide, with a steady increase in incidence since 2020. An estimated 13.1% of women in the U.S. are projected to be diagnosed with the disease in their lifetime [1], with approximately 2.3% of deaths attributed to it [2]. Breast cancer is classified into three primary subtypes based on molecular markers for estrogen (ER), progesterone (PR), and human epidermal growth factor receptor 2 (HER2/ERBB2). Triple-negative breast cancer (TNBC), characterized by the absence of all three receptors, accounts for approximately 15% of all cases [3]. TNBC is particularly aggressive, with a higher likelihood of invasion, metastasis,

and poor prognosis compared to other subtypes [4] making it a focal point for cancer research. Among the members of the Src kinase family, Lyn tyrosine kinase is uniquely implicated in TNBC progression, promoting increased cell migration and metastatic potential [5]. A study by [6] demonstrated that silencing Lyn, but not Src, significantly reduced invasion in mesenchymal breast cancer cell lines. Furthermore, the ratio of Lyn splice isoforms (LYNA to LYNB) has been correlated with TNBC patient outcomes, with a higher ratio associated with reduced overall survival [7]. Chalcones are a class of naturally occurring compounds predominantly found in plants. Their characteristic scaffold structure demonstrated anticancer activity making them promising candidates for cancer treatment, including TNBC [8]. Recent studies, such as [9], have shown that chalcone derivatives, including novel acetamide forms, possess cytotoxic activity against TNBC cell lines. Although chemotherapy, particularly anthracycline- and taxane-based regimens, remains the frontline treatment for TNBC, the limited availability of effective targeted therapies underscores the urgent need for new therapeutic compounds. In this study, we evaluate the potential of newly designed chalcone derivatives to inhibit Lyn tyrosine kinase activity using a comprehensive in silico approach, aiming to identify viable candidates for TNBC therapy.

2. Materials and Methods

2.1. Software, Hardware, and Databases

Auto Dock Vina version 1.5.6 [10], UCSF Chimera [11], ChemDraw ultra.12, Discovery Studio, Spartan 04, SwissAdme (online server), Windows (Intel processor, Corei7).

Protein crystal structure;

The protein structure was retrieved from the Protein Data Bank (http://www.rcsb.org) under the PDB ID; 2ZVA. It was determined using X-ray diffraction at a resolution of 2.60Å, originating from the species *Mus musculus*. The structure was co-crystallized with its native ligand, Dasatinib, and the associated published data is accessible.

2.2. In Silico Evaluation of Anticancer Activity

2.2.1. Creation of Library

A library of five chalcone derivatives were designed using ChemDraw ultra. 12, where the 2D chemical structure and IUPAC names were generated. The corresponding SMILEs were then exported into a separate file for further analysis.

2.2.2. Evaluation of Theoretical Oral Bioavailability and Toxicity

Using ProTox 3.0, the oral toxicity of the compounds was analyzed (CHCN1 CHCN19 CHCN48 CHCN333 CHCN94) where the LD50 in mg/kg was assessed for all five compounds. To ensure that the designed compounds were druglike, further pharmacokinetic profiling was conducted using SwissADME (http://www.swissadme.ch/) where the Lipinski's rule of five was used as a metric to identify drug-like compounds. These included the number of hydrogen bond acceptors, number of hydrogen bond donors, the LogP value, and the molecular weight.

2.2.3. Protein Structure Preparation

The protein structure was obtained from the protein data bank (http:www.rscb.org) PDB ID: 2ZVA. Through X-ray diffraction from the organism *Mus musculus* with a resolution of 2.60 A, co-crystallized with the native ligand Dasatinib and published data available. Before the docking procedure was conducted, all water molecules, ions and bound ligands, were removed from the 3D structure obtained, addition of Gasteiger charges was done and the resulting file was saved as rec.pdb file. The output file from Chimera was

then imported into AutoDockTools (ADT) (https://vina.scripps.edu/), for further conversion to the pdbqt format. After the retrieval of high-resolution protein (2zva) from Protein Data Bank (http://www.rcsb.org), it was then exported into chimera in the pdb format where protein preparation was conducted. All nonstandard amino acids, unbound water molecules and ions were equally eliminated. Finally, Gasteiger charges were added. The final output file was transferred to Autodock Vs 1.5.6 for conversion to the corresponding pdbqt formats for docking.

2.2.4. Ligand Structure Preparation

The newly designed compounds having passed oral bioavailability and toxicity evaluation were exported into Spartan 04 where energy minimization was done and saved in the MOL2 format. This was further processed using UCSF Chimera where Gasteiger charges were included. The corresponding pdb files were then converted in a similar way to pdbqt using Discovery Studio.

2.2.4. Molecular Docking Analysis

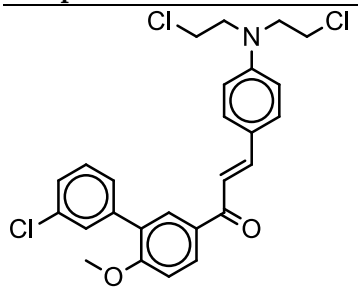
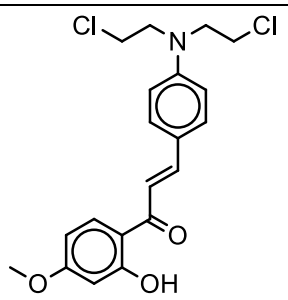
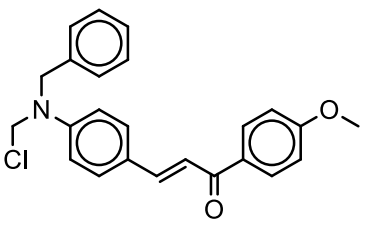
To ensure the reliability of the docking protocol, the co-crystallized ligand (Dasatinib) was first removed from the enzyme's crystal structure and then re-docked using the established docking parameters [12]. Successful validation was confirmed by the close alignment of the re-docked ligand with its original position in the active site, as observed in the crystal structure. The active site was defined using the coordinates from the crystallographic data, and an appropriate grid box was set around this region. The most favorable binding pose was selected for further analysis. Post-docking evaluation and visualization of ligand-protein interactions were conducted using Discovery Studio.

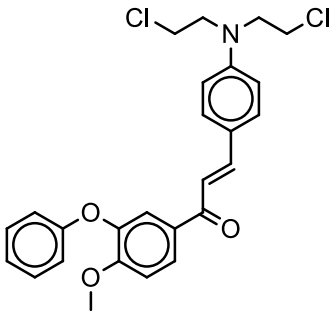
3. Results

3.1. Creation of Library

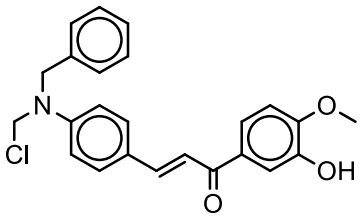
Table 1 represents a library of chalcone derivatives. A total of ten novel nitrogen-based chalcone analogs (CHCN1-CHCN94) were successfully designed in-silico using ChemDraw for structural construction and visualization. The chalcone core was maintained while systematically modified to incorporate diverse nitrogen-containing groups.

Table 1. Represents a library of chalcone derivatives.

Compounds		
 CHCN1	 CHCN19	 CHCN48



CHCN333



CHCN94

3.2. Evaluation of Theoretical Oral Bioavailability and toxicity

The theoretical oral bioavailability of all compounds was assessed and presented in Table 2. This includes the molecular weight, number of hydrogen bond acceptors, number of hydrogen bond donors, MlogP, Topological Surface Area, Molar refractivity, amongst others. These parameters are in congruence with Lipinski's requirements for characterizing the drug-likeness property of drug molecules [13]. Where all compounds had their violations within acceptable range. The Veber violation, Ghose violation, Egan violation and Muegge violations which also use the physicochemical properties of compounds to access drug likeness were included in this study.

Table 2. Drug-likeness and oral bioavailability analysis of test compounds.

Compound Name	**CHCN1**	**CHCN19**	**CHCN48**	**CHCN333**	**CHCN94**
Formula	C26H24Cl3NO2	C20H21Cl2NO3	C24H22ClNO2	C26H25Cl2NO3	C24H22ClNO3
Molecular weight	488.83 g/mol	394.29 g/mol	391.89 g/mol	470.39 g/mol	407.89 g/mol
Num. heavy atoms	32	26	28	32	29
Num. arom. heavy atoms	18	12	18	18	18
Fraction Csp3	0.19	0.255	0.12	0.19	0.12
Num. rotatable bonds	10	9	8	11	8
Num. H-bond acceptors	2	3	2	3	3
Num. H-bond donors	0	1	0	0	1
Molar Refractivity	136.60	108.18	116.23	132.67	118.25
TPSA	29.54 Å^2	49.77 Å^2	29.54 Å^2	38.77 Å^2	49.77 Å^2
Log $P_{o/w}$ (MLOGP)	5.28	3.22	4.21	4.50	3.61
Inference	Yes	Yes	Yes	Yes	Yes
Lipinski's Violation	1	0	0	0	0
Veber Violation	0	0	0	1	0
Ghose violations	3	0	0	2	0
Egan Violation	1	0	0	1	0
Muegge Violation	1	1	1	1	1

Bioavailability Score	0.55	0.55	0.55	0.55	0.55
Synthetic accessibility	3.38	2.94	2.90	3.45	3.01

3.2.1. ADMET Analysis

Further ADMET profiling results in Table 3 represents the pharmacokinetic profiling of the drug molecules. These includes the Log Sw implying oral solubility at a range of (−6.54 to −10.23) solubility, blood brain permeation ability, substrate specificity and possible metabolic pathway. Toxicity profiling Table 4, highlights the LD50 values of test compounds. Also highlights the mutagenic, carcinogenic and hepatoxic tendencies as well.

Table 3. Pharmacokinetics prediction output of the test compounds.

Compound Name	**CHCN1**	**CHCN19**	**CHCN48**	**CHCN333**	**CHCN94**
Silicos-IT LogSw	−10.23	−6.62	−8.29	−6.54	−7.70
Silicos-class	Insoluble	Poorly Soluble	Poorly soluble	Poorly soluble	Poorly soluble
Log Kp (cm/s)	−4.16 cm/s	−5.04 cm/s	−4.45 cm/s	−4.56 cm/s	−4.81 cm/s
GI Absorption	Low	High	High	High	High
BBB Permeant	No	Yes	Yes	No	Yes
Pgp substrate	Yes	No	Yes	Yes	Yes
CYP1A2 inhibitor	Yes	Yes	Yes	Yes	Yes
CYP2C19 inhibitor	No	Yes	Yes	No	Yes
CYP2C9 inhibitor	No	Yes	Yes	Yes	Yes
yCYP2D6 inhibitor	No	Yes	Yes	Yes	Yes
CYP3A4 inhibitor	Yes	Yes	Yes	Yes	Yes

Table 4. Toxicity profile of test compounds.

Properties	**CHCN1**	**CHCN19**	**CHCN48**	**CHCN333**	**CHCN94**
Oral Acute Toxicity	V	V	IV	IV	IV
Carcinogenicity	+	−	−	−	−
Hepatotoxicity	-	+	+	+	−
Androgen receptor binding	−	−	−	−	−
Thyroid Receptor Binding	−	−	−	−	−
Estrogen Receptor Binding	−	+	+	+	+
Aromatase Binding	−	+	+	+	+

− = Inactive; + = active; Class IV = LD50 ≤ 2000 mg/kg; Class V = LD50 ≤ 5000 mg/kg.

3.2.2. Molecular Docking Analysis

3.3. Title

3.3.1. Grid Point

Mapping of native ligand to the active site enzyme generated grid box parameters which formed the basis for generating the (config. txt) file used in the docking process. Autodock vina generated results in pdbqt file format and complexes of the respective compounds and the protein. The specific grid box position used in this study is represented below in Table 5.

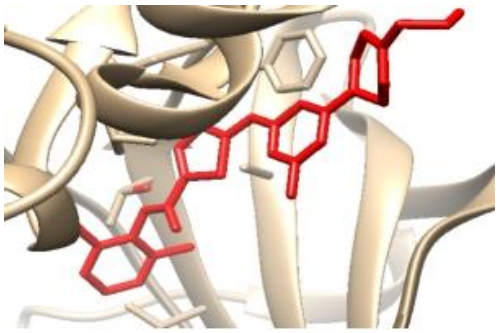
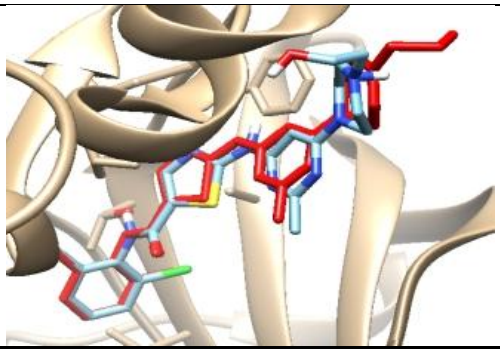
Table 5. Enzyme Grid-box Size Center.

Enzyme	Grid-Box Size			Center		
	X	Y	Z	X	Y	Z
Lyn-kinase	48	44	60	19.669	−9.388	23.998

3.3.2. Validation of Docking Procedures

Dock validation of the docking procedure (Table 6) was carried out by re-docking the co crystallized ligand on the protein active site. This showed perfect superimposition reflecting high accuracy prediction. The co-crystallized ligand was re-docked onto its corresponding protein, aligning well with its original Protein Data Bank (PDB) structure.

Table 6. Dock Validation of ligand against enzyme structure.

Enzyme	Crystal Structure Complex (Enzyme and Ligand)	Crystal Structure Complex with Re-Docked Ligand (Validation)
2zva		

3.3.3. Binding Affinity of Ligands to Protease Enzymes

Table 7 showcases the binding energies of both the co-crystallized ligands and the five isolated compounds in their interactions with the enzymes.

Table 7. Docking scores of the designed chalcone derivatives against Lyn tyrosin kinase enzyme.

Compound Name	SMILE	Dock Scores (kcal/mol)
Lig 0	Dasatinib	−9.8
CHCN1	c1ccc(Cl)cc1c(c(cc2)OC)cc2C(=O)C=Cc3ccc(cc3)N(CCCl)CCCl	−8.6
CHCN19	COc(cc1)cc(O)c1C(=O)C=Cc2ccc(cc2)N(CCCl)CCCl	−7.1
CHCN48	COc(cc1)ccc1C(=O)C=Cc2ccc(cc2)N(CCl)Cc3ccccc3	−8.3
CHCN333	ClCCN(CCCl)c(cc1)ccc1C=CC(=O)c2cc(c(cc2)OC)Oc3ccccc3	−8.1
CHCN94	COc(cc1)c(O)cc1C(=O)C=Cc2ccc(cc2)N(CCl)Cc3ccccc3	−8.0

Lig 0 is the co-crystallized native ligand (Dasatinib).

3.3.4. Binding Poses and Binding Interaction Analysis of Isolated Compounds Against

The binding conformation and interaction of the isolated compounds (CHCN1-CHCN94) with residues on the active site of Lyn tyrosin kinase was elucidated and presented in Figures 1–5. The binding interaction mode and amino acid interaction was also presented in Table 8.

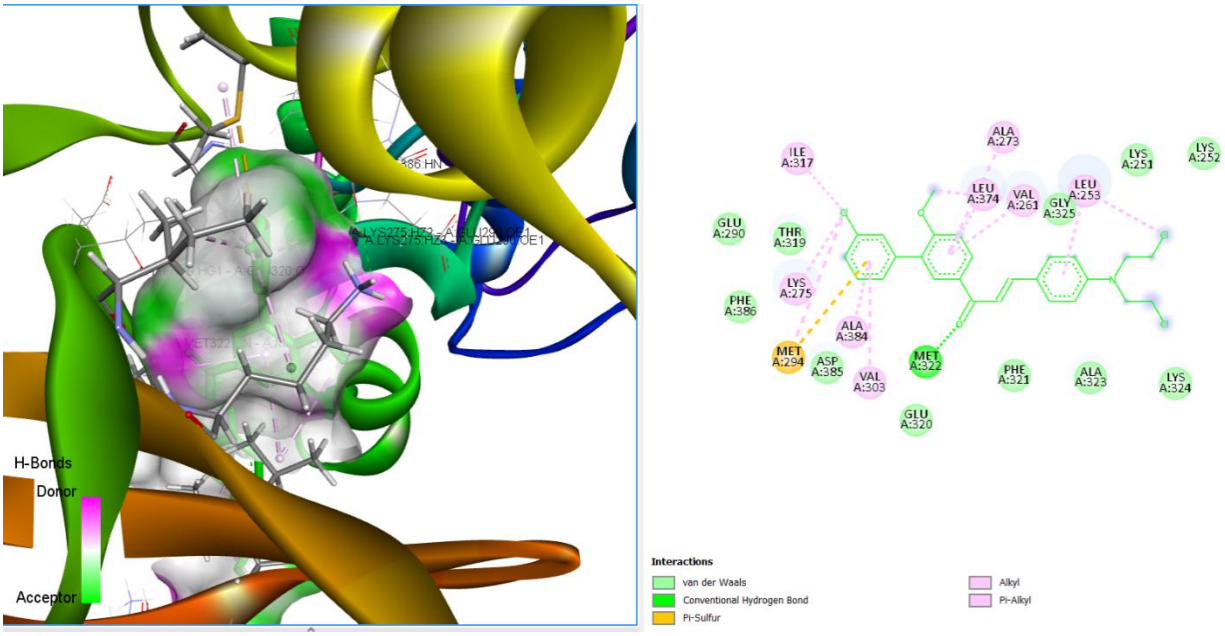


Figure 1. Three-dimensional molecular pose (**left**) and 2D (**right**) interactions of CHCN1 on binding cavity of Lyn tyrosine kinase.

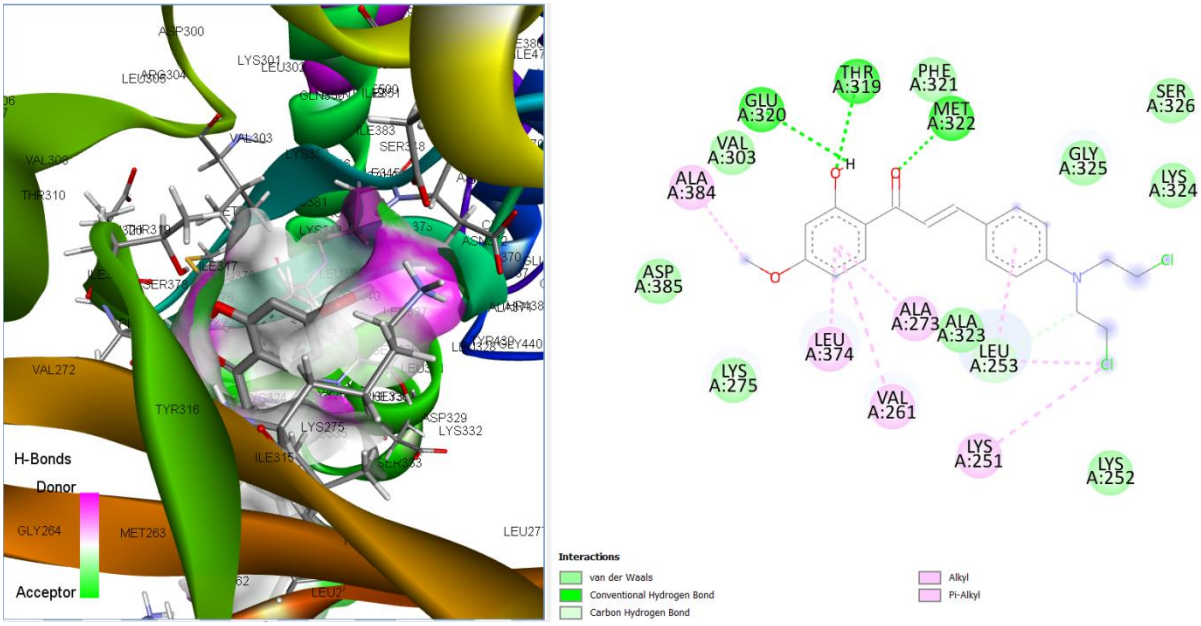


Figure 2. Three-dimensional molecular pose (**left**) and 2D (**right**) interactions of CHCN19 on binding cavity of Lyn tyrosine kinase.

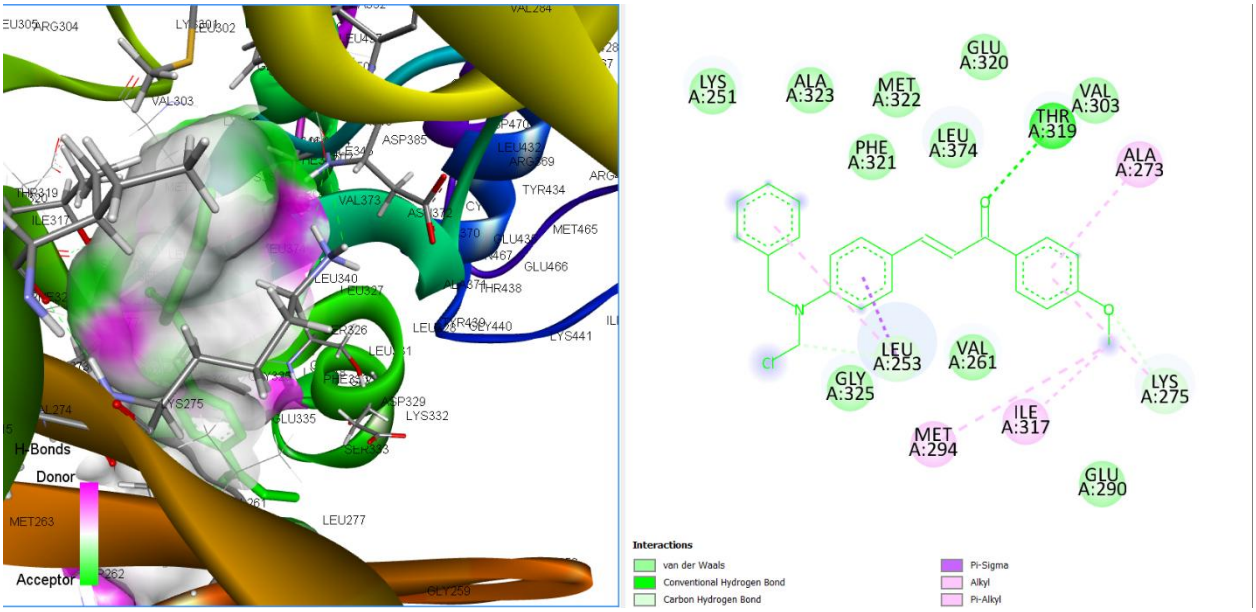


Figure 3. Three-dimensional molecular pose (**left**) and 2D (**right**) interactions of CHCN48 on binding cavity of Lyn tyrosine kinase.

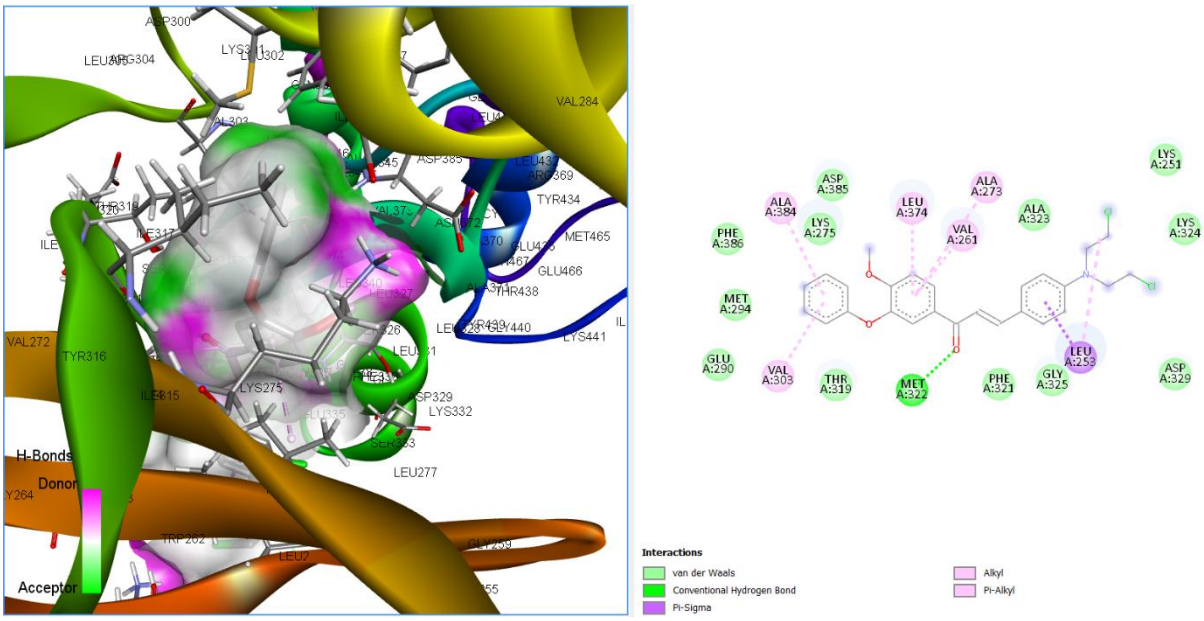


Figure 4. Three-dimensional molecular pose (**left**) and 2D (**right**) interactions of CHCN333 on binding cavity of Lyn tyrosine kinase.

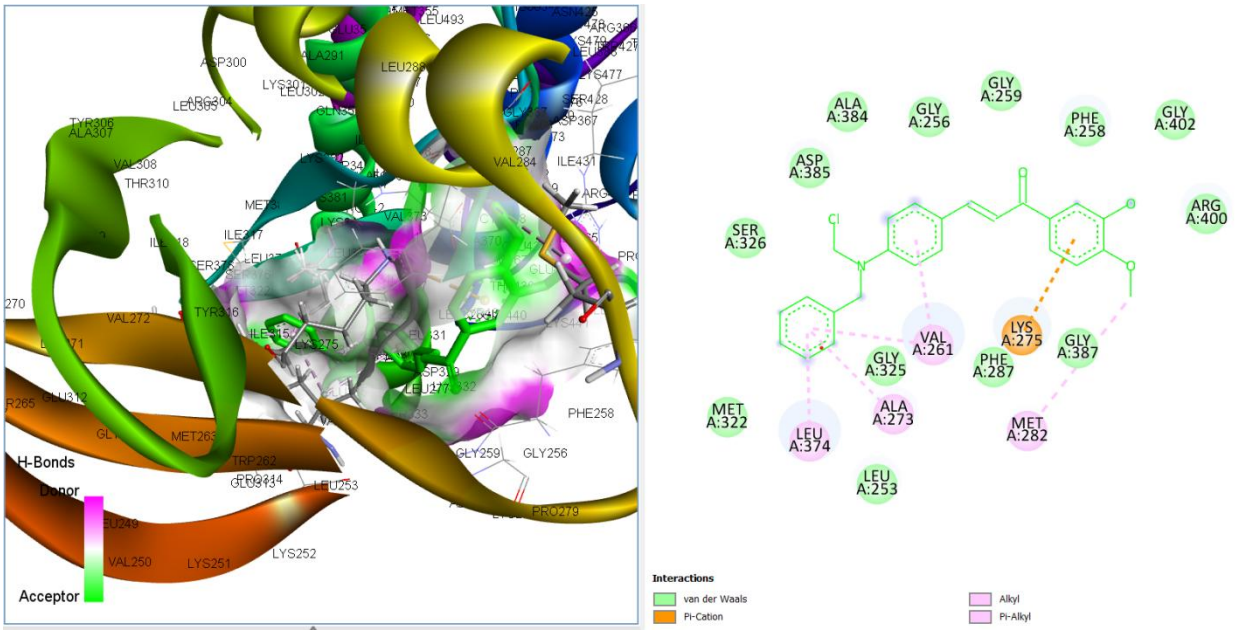


Figure 5. Three-dimensional molecular pose (**left**) and 2D (**right**) interactions of CHCN94 on binding cavity of Lyn tyrosine kinase.

Table 8. Molecular interactions of amino acid residues of compounds from Chalcone derivatives with Protein tyrosin kinase.

Compounds	Hydrogen Bond Interaction	Hydrophobic Interaction
CHCN1	THR319 MET322 GLU320 LEU253	ALA384 LYS251 LEU253 VAL261 ALA273 LEU374 LEU253
CHCN19	THR319 LYS275 LEU253 LEU253	LEU253 MET294 ILE317 ALA273 LYS275 LEU253
CHCN48	THR319 LYS275 LEU253	LEU253 MET294 ILE317 ALA273 LYS275 LEU253
CHCN333	MET322	LEU253 LEU253 VAL261 ALA273 LEU374 VAL303 ALA384
CHCN94		MET282 VAL261 VAL261 ALA273

4. Discussion

According to Lipinski's rules for oral absorptivity [13], the analyzed compounds had molecular weights ranging from 391.89 to 488.83 g/mol. Across all compounds, the maximum number of hydrogen bond acceptors was 3, and the maximum number of hydrogen bond donors was 1. Although the partition coefficient (logP) of CHCN1 was 5.28, slightly exceeding the ideal threshold for oral bioavailability, all compounds generally remained within acceptable limits, indicating favorable oral absorption potential. Vebers' rule, which sets strict criteria for topological polar surface area (TPSA) and the number of rotatable bonds, was met by all compounds except CHCN 4, which exceeded the permissible number of rotatable hydrogen bonds with a score of 11. TPSA values for the compounds ranged from 29.54 to 49.77 Å^2 further buttressing their drug likeness. According to Ghose's criteria, which consider molar refractivity and the total number of atoms, all compounds except CHCN1 and CHCN333 fell within the acceptable range for molar refractivity, and all compounds had a total atom count between 47 and 57. Furthermore, the compounds exhibited an oral bioavailability score of 0.55 and a synthetic accessibility score ranging from 3.45 to 3.94, supporting their suitability for oral formulation and ease of synthesis (Table 2). CHCN333 was identified as a non-P-glycoprotein substrates suggesting good

bioavailability and consequent interaction in the active site. All compounds were substrates of either CYP1A2 or CYP3A4 suggesting the possible excretion pathway and drug interaction. The Silicos-IT LogSw values, reflecting molar solubility, ranged from −6.54 to −10.23. Solubility results showed that only CHCN1 is insoluble. This points that the other compounds have some relative potential for oral solubility or other suitable formulation strategy that can deliver the drug equally adequately. Toxicity profiling revealed a good oral toxicity profile [14], with all compounds classified between class IV and V with LD50 values from ≤ 2000 mg/kg to LD50 ≤ 5000 mg/kg (Table 3) Only CHCN1 showed potential carcinogenicity. Compounds CHCN1 and CHCN94 were not hepatotoxic, and none of the compounds exhibited androgen or thyroid receptor binding. Additionally, only CHCN1 lacked estrogen and aromatase receptor binding activity. This reflects relative safety of the drug molecules. Molecular docking results was comparable to that of the native ligand dasatinib (−9.8 kcal/mol). Dock scores of the compound library was −9.8, −8. 6, −7.1, −8.3, −8.1, −8.0 kcal/mol respectively. CHCN19 had the best dock score suggesting it can be taken further for its potential in chemotherapy. The DFG motif (Asp385, Phe386, Gly387) acts like a switch that helps turn the kinase on or off.

When the kinase is active, Lys275 and Glu290 form a bond (a salt bridge) that holds the protein in the right shape so it can grab and use ATP for its activity [15]. CHCN1 reflected Vanderwal interaction with Asp385, Phe386, Glu290 and Pi-alkyl interaction with Lys275. CHCN19 exhibited Vanderwal interaction with Lys275 and Asp385. CHCN48 interacted via pi-alkyl with Lys275 and Vanderwal interaction with Glu290. In CHCN333 Vanderwal interaction was seen with Lys275, Asp385, Glu290, Phe386 (Table 8). Lastly, Vanderwal interaction was recorded between CHCN94 and Asp385. CHCN48 had a docking score of −8.3 kcal/mol which is comparably higher than the others. This could be as a result of the hydrogen and hydrophobic interactions formed with Lys275 which is absent in others. These results highlight the potential of these compounds in inhibiting Lyn tyrosin kinase to modulate cancer proliferation.

Although mustard-type chalcones contain electrophilic centers that could, in principle, undergo covalent interactions with nucleophilic residues or nucleic acids, the present docking study evaluates only non-covalent interactions with Lyn kinase. This approach was chosen to predict initial binding conformations and affinity trends. The reactive centers of the ligands were not positioned close to any nucleophilic residues within the binding pocket, suggesting that reversible binding may still occur prior to any potential covalent modification. Nonetheless, further covalent docking and experimental validation are required to confirm the nature of binding Although mustard-type chalcones contain electrophilic centers that could, in principle, undergo covalent interactions with nucleophilic residues or nucleic acids, the present docking study evaluates only non-covalent interactions with Lyn kinase. This approach was chosen to predict initial binding conformations and affinity trends. The reactive centers of the ligands were not positioned close to any nucleophilic residues within the binding pocket, suggesting that reversible binding may still occur prior to any potential covalent modification. Nonetheless, further covalent docking and experimental validation are required to confirm the nature of binding

5. Conclusions

The chalcone derivatives showed favorable ADME profiles (MW 391.89–488.83 g/mol, TPSA 29.54–49.77 Å^2, bioavailability score 0.55) with low predicted toxicity (LD50 ≤ 2000–5000 mg/kg). Docking scores ranged from –7.1 to –9.8 kcal/mol, with CHCN1 as the most promising candidate. Key interactions were observed with Lys275, Glu290, Asp385, and Phe386, underscoring their potential as Lyn kinase enzmye inhibiton.

Author Contributions: E.O. and Y.J.: Conceptualization, Methodology, Investigation, Data curation, Formal analysis, Writing—original draft. A.N.H. and M.A.: Supervision, Validation, Writing—review & editing. All authors have read and agreed to the published version of the manuscript.

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Conflicts of Interest: The authors declare no conflict of interest.

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