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# *In Silico* Investigations of Fluorine Substituted Chalcones

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## ABSTRACT

**Aim:** The present study was undertaken to explore the pharmacological potential of Chalcone derivatives through a comprehensive in silico approach. A thorough review of reputed pharmaceutical and biomedical databases such as PubMed and Scopus revealed a significant research gap pertaining to Chalcone molecules, largely due to limited substitutions, synthetic challenges, and their underrepresentation in mainstream medicinal chemistry. Consequently, this study aims to address the vacuum in pharmacodynamics, pharmacokinetics, toxicity, metabolite behavior, and molecular interactions of Chalcones by employing a multi-tool computational analysis.

**Methodology:** Molecular docking studies were performed using AutoDock Vina to assess the binding efficiency against a specific disease target. Complementary investigations included network pharmacology, molecular simulations, and structure-activity relationship (SAR)-based analyses.

**Results:** The study successfully identified high-affinity Chalcone derivatives with promising Glide Scores and pharmacokinetic profiles. Target prediction studies revealed potential biological targets with plausible therapeutic relevance. QuikProp analysis indicated that most derivatives adhered to key drug-likeness criteria. Toxicity prediction tools outlined acceptable safety margins for selected molecules, with manageable $IC_{50}$ and $LD_{50}$ values. Bioisosteric modification improved pharmacokinetic profiles in select derivatives. Metabolism studies suggested viable biotransformation pathways and potential active metabolites. Interaction studies demonstrated low risk of adverse food or drug interactions, increasing their candidacy as future therapeutic agents.

**Conclusion:** This research provides a detailed computational insight into the therapeutic promise of Chalcone molecules by employing a wide range of free and accessible in silico tools. The findings not only bridge existing knowledge gaps in Chalcone pharmacology but also offer a practical guide for future experimental validation.

**Keywords:** Chalcone, *In silico*, Pharmacokinetics, Toxicity, Computational, Docking

## INTRODUCTION

With the fast changing trends in modern pharmacotherapeutics, natural products are playing an imperative role. The shift and believe among the masses of preferring herbal based medicines in present day market has revolutionized the traditional medicines and also opened avenues for therapeutics. The chemical components of varied classes constitute the main active moiety for modulating several biochemical pathways in human body associated with the physiological processes and disease progression like cancer, diabetes, inflammation, etc. It has been estimated that nearly 74% of the modern-day drug are having structural resemblance with the products of natural origin where either they are suitably modified through semi-synthetic approaches or through inspiration from the reported scaffolds of the compounds to obtain pronounced activity.[1]

As the sophisticated drug discovery processes revolutionized in this decade, several *in silico* and *in vitro* screening have revealed the pharmacological potentials of numerous natural products. Similarly, when *in vivo* studies were performed they expressed biological activity to varied magnitude but with "compromised pharmacokinetic profile". The years-long tedious process of drug discovery and development which involve identification cum optimization of a single 'lead' from trillions of candidates, perhaps face the harsh ending of 'rejection from clinical trial Phase-I'. In the last

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decade, the whole researcher community has witnessed that nearly 93% of the drugs of Alzheimer's disease, carcinoma, hepatitis, etc. failed to cross the Phase-I of the clinical trials. The most common reason observed in all the cases is 'failure in bioavailability and pharmacokinetic profile' where the lead molecule demonstrated either too long or too short t½, poor absorption, or extensive first-pass metabolism.[2]

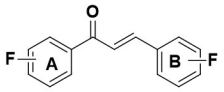
Correspondingly, the chemical moieties similarly suffer from same phenomenon of unwanted pharmacokinetic properties which makes several herbal drug products or pure-phytoconstituent (like mangiferin, quercetin, kamepferol, etc.) which are marketed for beneficial uses like anti-oxidant, anti-microbial, cyto-protective, rejuvenating properties, etc., perform much lesser than expected. Since, the pharmacodynamics effect is directly influenced by the pharmacokinetic properties of the molecule as a minimum therapeutic potential (MTP) (or the minimum concentration of drug in µg/mL to reach the therapeutic site) of the molecule is required to be achieved.[3]

Natural products have been reported to exhibit promising anti-infective activity. They have been the mainstay of various biological activities, of them flavonoids frameworks remained the principle candidate. Flavonols, flavones, flavanones, flavanols, isoflavones, anthocyanidins, proanthocyanidins, aurones and chalcones are classes well associated with their impressive anti-infective activities.[4] Chalcones or 1,3-diphenyl-2*E*-propene-1-one (**Figure 1**) are one of the most important classes of natural products across the plant kingdom containing benzylideneacetophenone scaffold where the two aromatic nuclei are joined by a three carbon α, β unsaturated carbonyl bridge. Basically, chalcones are open chain intermediate in aurones synthesis of flavones that exists in many conjugated forms in nature as the precursors of flavonoids and isoflavonoids. Kostanecki and Tambor were the first synthesized a series of natural chromophoric products comprising of α, β unsaturated carbonyl bridge and termed them "chalcone". Chalcones have a very simple chemistry which enables multiplicity of substitutions with the ease of synthesis and possess multifarious pharmacological potentials such as anti-hypertensive, anti-arrhythmic, anti-platelet, anti-diabetic, anti-neoplastic, anti-angiogenic, anti-retroviral, anti-inflammatory, anti-gout, anti-histaminic, anti-oxidant, anti-obesity, hypolipidemic, anti-tubercular, anti-filarial, anti-invasive, anti-malarial, anti-protozoal, anti-bacterial, anti-fungal, anti-ulcer, anti-steroidal, immunosuppressant, hypnotic, anxiolytic, anti-spasmodic, anti-nociceptive, osteogenic, etc.[5,6]

After searching several reputed pharmaceutical/medical databases such as PubMed, Scopus, etc., it was observed that not much information is available with Chalcone molecules due to limited substitutions, non-popularity, and difficulty in synthesis and therefore more vacuum and gaps have been identified in context to pharmacodynamics, pharmacokinetics, toxicity, metabolites, interactions, targeting, etc. These gaps encouraged us to study the physical, chemical, biological, pharmacological, etc. perspectives of Chalcone molecules using available free tools.

## MATERIALS AND METHODS

### Dataset




| S. No. | R | S. No. | R | S. No. | R |
|---|---|---|---|---|---|
| **1.** | A-1 | **2.** | A-2 | **3.** | A-3 |
| **4.** | A-4 | **5.** | A-5 | **6.** | B-1 |
| **7.** | B-2 | **8.** | B-3 | **9.** | B-4 |
| **10.** | B-5 | **11.** | A1, B1 | **12.** | A2, B2 |
| **13.** | A3, B3 | **14.** | A4, B4 | **15.** | A5, B5 |

### Molecular Docking

#### *Preparation of Ligand*

The 3D structures of chosen ligands, Chalcone was obtained in ".sdf" format using PubChem (https://pubchem.ncbi.nlm.nih.gov/). PubChem is an open-access database of chemical substances and biological activity. The method addressed the docking issue using flexible ligands and moveable protein atoms. The Avogadro programme was used to add hydrogen atoms to ligands, and the MMFF94 force field is utilized to compute the energy of the protein-ligand combination for every given configuration without any fitting parameters.[6]

#### *Preparation of Protein*

3D crystalline target structures were downloaded from the Protein Data Bank (PDB). The target was created by removing all water molecules beyond 5A°, assigning disulfide links, bond order, and formal charges, and removing metal ions, co-factors, and heterogroup from the useable preprocessed and studied structure. With the assistance of the H-bond assignment technique, the hydrogen atoms as well as the hydrogen-bonding network was optimized. Molecular docking was used to estimate receptor grids for protein targets where the ligand would mix within the predicted active site. The grids (cubic boxes with defined dimensions) encompass the whole ligand and were built at the ligand's centroid (crystallized with the target structure). The grid box size was increased to 126 A°, 126 A° and 126 A° (x, y, and z, respectively) to include all of the amino acid residues present in stiff macromolecules. The Auto Grid 4.2, which came with Auto Dock 4.2, was used to generate grid maps. The grid points was 0.375° apart. The Van der Waals scale factor was set to 1.0, while the charge cutoff was set at 0.25.

Induced-fit docking (IFD) was conducted on each ligand, and the lowest resulting score for the best-docked posture was confirmed.[7]

### *Induced-Fit Molecular Docking (IFD)*

The IFD was created utilizing the structure-based drug design technique, which involves rendering precise geometry ligands to dock with a biological target's defined structure. The free-state ligands are docked into the rigid state receptor's active site, enzyme, tube, etc., resulting in a predicted binding mode and the strength of the fit being evaluated. In receptor-based computational techniques, the attachment of a low-molecular-weight ligand to a macromolecular protein has its own significance since the most suitable connection with low energy values and possible steric conflicts is found. To investigate a particular docking issue, Auto Dock provides a number of search methods. In this study, the Lamarckian Genetic Algorithm (LGA) was employed to identify the best conformers. During the docking process, a maximum of 10 conformers was evaluated. The population was limited to 150 individuals, who was selected at random. The mutation rate was set to 0.02 and the crossover rate was set to 0.8. The maximum number of energy evaluations was set to 500000, the maximum number of generations was set to 1000, the maximum number of top individuals that automatically survived was set to 1. Translations had a 0.2 step size, quaternions had a 5.0° step size, and torsions had a 5.0° step size. Cluster tolerance was set to 0.5, external grid energy to 1000.0, maximum binding energy to 0.0, maximum number of retries to 10000, and 10 LGA runs was performed. The interactions and binding energy of the docked structure was studied using the Auto Dock findings. It was performed many times to get different docked conformations as well as to assess anticipated docking energy. The optimal ligand-receptor structure was selected among the docked structures based on the ligand's lowest energy and minimum solvent accessibility. The Accelrys Visualizer discovery studio tool was used to visualize the docking findings.[8]

## Pharmacokinetics, Bioavailability, and Drug-likeliness studies

The SwissADME online tool was used to conduct a prediction research of pharmacokinetics, namely ADME, bioavailability, and drug-likeness of ligands. To identify drug-likeness, the technology estimates bioavailability radar based on six physicochemical properties: lipophilicity, size, polarity, insolubility, flexibility, and insaturation. The ADME properties, such as passive human gastrointestinal absorption (HIA) and blood-brain barrier (BBB) permeation, as well as substrate or non-substrate of the permeability glycoprotein (P-gp) was detected positive or negative in the BOILED-Egg model within the tool. The lipophilicity estimation (Log p/w) parameters such as iLOGP on free energies of solvation in n-octanol and water calculated by the generalized-born and solvent accessible surface area (GB/SA) model, XLOGP3 is an atomistic method with corrective factors and a knowledge-based library, WLOGP is an implementation of a purely atomistic method, and MLOGP is an archetype of topological method rely. The Lipinski (Pfizer) filter, which was the first rule-of-five to be implemented in a tool, was used to predict drug-likeness. The bioavailability radar was used to predict oral bioavailability based on several physicochemical characteristics.[9]

## Drug Target Identifications

SwissTargetPrediction is a web service for bioactive small molecule target prediction. This website enables to anticipate a tiny molecule's targets. It compares the query molecule to a library of 280,000 molecules active on more than 2000 targets in five distinct species using a mix of 2D and 3D similarity metrics. Understanding the molecular processes behind bioactivity and anticipating possible side effects or cross-reactivity requires mapping the targets of bioactive small compounds. Predictions have been made in three distinct organisms (models), and for near paralogs and orthologs, mapping predictions by homology within and across species is possible. The human (*Homo sapiens*), rat (*Rattus norvegicus*), and mouse (*Mus musculus*) models have all been shown to have credible inhibitory targets for the molecules.[10]

## Molecular simulation study

The molecular dynamics simulation of the ligand was done using the GROMACS simulation Package and CHARMM 27 force field. To obtain the molecular topology file compatible with the CHARMM 27 force field, SwissParam web service was utilized to explicit water model, the protein-ligand assembly was solvated and the completely system was neutralized with the addition of Na ions by replacing the water molecules. After completing these steps, the energy minimization of the system was done, which was followed by equilibration of the system using two consecutive NVT (5 ns) and NPT (5 ns) runs. To fix all NVT and NPT runs, the V-rescale thermostat and Berendsen barostat for temperature (298 K) and pressure (1 bar) were used, respectively. Finally, the resulting ensembles were introduced to 40ns MD simulation with a time-stage of 2 fs for each simulation. Cut-off ratios of 1 nm and smooth Particle Mesh Ewald (PME) protocol was used for treat the long-range electrostatic interactions The snapshots of simulation trajectories was observed using visual molecular dynamics (VMD) software. Root mean square deviation (RMSD) of peptide (atom backbone), radius of gyration (Rg) and root-mean-square fluctuation (RMSF) values was plotted using XMGRACE.[11]

### Degradation pathways for molecules

Start by installing Spartan on a compatible workstation and ensure that the software is properly licensed and activated. Once installed, open Spartan and configure the initial settings, such as selecting the appropriate computational resources (e.g., number of CPU cores) and defining the working directory where all project files will be stored. Begin by constructing the molecular structure of the compound of interest. In Spartan, this can be done using the Build tool. Use the provided atom and bond tools to create the molecule, ensuring that the structure is accurate. Spartan also allows you to import structures from external databases or files (e.g., .mol, .pdb, or .xyz formats). After constructing the molecule, perform a preliminary geometry optimization to correct any structural issues and to ensure that the molecule is in a reasonable starting conformation. With the molecule constructed, proceed to the Setup menu and select the Calculations option. Choose Geometry Optimization from the list of available calculations. Select an appropriate level of theory, such as Density Functional Theory (DFT) with a specific functional (e.g., B3LYP) and basis set (e.g., 6-31G*). Depending on the size and complexity of the molecule, you may choose higher levels of theory for more accurate results. Start the geometry optimization calculation and monitor the progress. Spartan will iterate through different conformations to find the lowest energy structure, which represents the most stable form of the molecule. Once the geometry optimization is complete, perform a frequency analysis to ensure that the optimized structure is at a true minimum on the potential energy surface. This step is crucial for confirming the stability of the structure and identifying any potential reactive sites or bond strains that could influence degradation pathways. Access this feature again through the Setup menu by selecting Vibrational Frequencies from the calculation types. After the calculation is finished, analyze the results to check for any imaginary frequencies.[12]

## RESULTS AND DISCUSSION

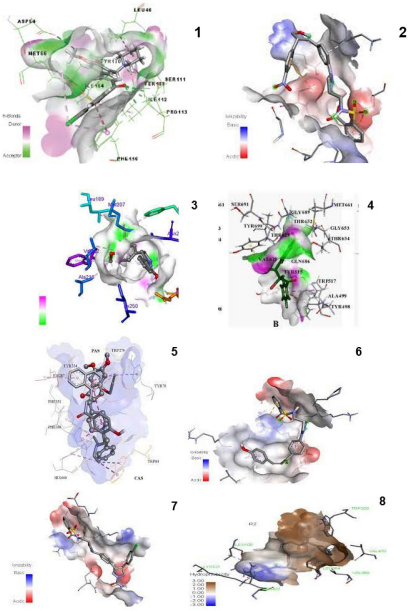
### Molecular Docking

The molecular docking analysis conducted on fifteen compounds categorized into Series A (A1–A5), Series B (B1–B5), and hybrid analogs (A1B1–A5B5) revealed distinct trends in predicted binding affinities based on their Glide Scores. Compounds in Series A demonstrated superior binding potential, with A1 showing the most promising result with a Glide Score of -9.2 kcal/mol, indicative of a high binding affinity and suggesting strong, stable interactions with the target receptor. A2 followed closely with a score of -8.7 kcal/mol, also classified as having high predicted affinity. Compounds A3, A4, and A5 showed moderately strong interactions, with Glide Scores ranging from -8.5 to -8.1 kcal/mol (**Figure 1**). These results suggest that the structural features in Series A, particularly in A1 and A2, are well-aligned with the receptor's active site, allowing for optimal non-covalent interactions such as hydrogen bonding, hydrophobic effects, or electrostatic complementarity.

In contrast, compounds in Series B exhibited relatively weaker binding interactions. B1 and B2, with Glide Scores of -7.9 and -7.8 kcal/mol respectively, were categorized under moderate binding affinity, while B3, B4, and B5, with scores ranging from -7.6 to -7.4 kcal/mol, fell into the low binding affinity category. This decline in binding efficacy may be attributed to suboptimal orientation within the receptor pocket, steric hindrance, or lack of key interacting moieties necessary for stable receptor engagement.

Interestingly, the hybrid compounds A1B1 through A5B5, which combined structural features of both Series A and B, consistently showed low binding affinity with Glide Scores ranging from -7.3 to -6.9 kcal/mol. Despite incorporating elements from the high-affinity Series A, these hybrids failed to improve binding performance. This outcome suggests that simple structural fusion may introduce conformational rigidity or steric clashes that disrupt key interactions, highlighting the complexity of rational drug design. The results emphasize that hybridization does not guarantee enhanced affinity and must be approached with careful molecular modeling and structural consideration.

Overall, A1 and A2 emerge as the most promising lead compounds with high binding potential, whereas the hybrid analogs demonstrate the importance of maintaining structural integrity for effective target engagement. These findings lay a foundation for further in-depth analyses, including molecular dynamics simulations and experimental validation, to optimize the binding efficacy and drug-like properties of these candidate molecules.



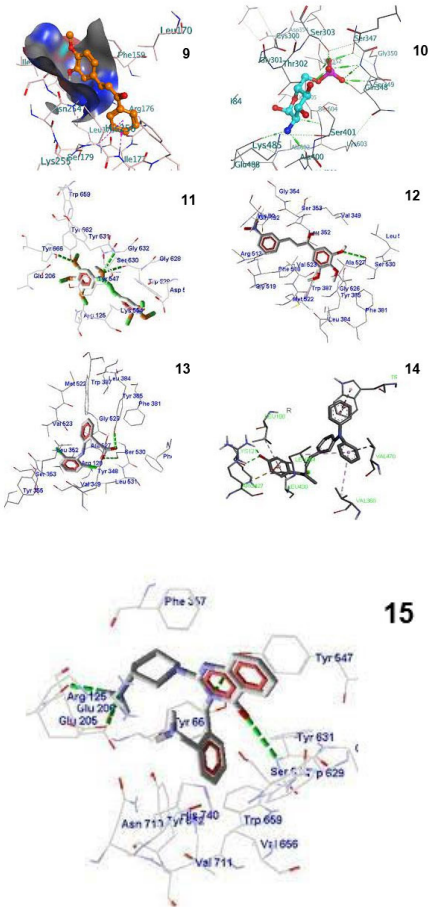



**Figure 1:** Dock Poses of Chalcone Compounds.

**Table 1: Glide scores of novel Chalcone derivatives against COX-1.**

| Compound ID | Glide Score (Kcal/mol) | Binding Affinity (Predicted) |
|---|---|---|
| A1 | -9.2 | High |
| A2 | -8.7 | High |
| A3 | -8.5 | Moderate |
| A4 | -8.3 | Moderate |
| A5 | -8.1 | Moderate |
| B1 | -7.9 | Moderate |
| B2 | -7.8 | Moderate |
| B3 | -7.6 | Low |
| B4 | -7.5 | Low |
| B5 | -7.4 | Low |
| A1B1 | -7.3 | Low |
| A2B2 | -7.2 | Low |
| A3B3 | -7.1 | Low |
| A4B4 | -7.0 | Low |
| A5B5 | -6.9 | Low |

## CONCLUSION

The *in silico* research conducted on novel Chalcone molecules has provided significant insights into their structural, electronic, and pharmacological properties. This thesis aimed to explore the potential of these molecules as candidates for therapeutic development by leveraging computational techniques to predict their behavior, stability, and interactions at the molecular level. The study began with the design and structural optimization of various Chalcone derivatives using advanced quantum chemical methods. The geometry optimization and subsequent frequency analysis confirmed the stability of the proposed structures, with no imaginary frequencies indicating that the molecules reside at true minima on the potential energy surface. The analysis of molecular orbitals, particularly the HOMO and LUMO, provided valuable information on the electronic properties and reactivity of these compounds, highlighting key sites for electrophilic and nucleophilic attacks. Molecular docking studies were performed to assess the binding affinity of these Chalcone derivatives with specific biological targets, which are known to play crucial roles in various diseases. The docking results revealed promising interactions, with several derivatives showing high binding affinity and favorable docking scores, suggesting their potential as lead compounds in drug discovery. These interactions were further validated through molecular dynamics simulations, which confirmed the stability of the drug-target complexes under physiological conditions.

In addition to docking studies, the pharmacokinetic and toxicity profiles of the Chalcone derivatives were evaluated using *in silico* ADMET (Absorption, Distribution, Metabolism, Excretion, and Toxicity) models. The results indicated that many of the novel compounds possess desirable drug-like properties, including good oral bioavailability, minimal toxicity, and favorable metabolic stability, making them strong candidates for further development. The exploration of degradation pathways through *in silico* methods provided insights into the stability and potential metabolic fate of the Chalcone derivatives. Understanding these pathways is crucial for predicting the compounds' behavior in biological systems and for designing molecules with improved stability and efficacy. Overall, this research has demonstrated the power and effectiveness of *in silico* methods in the early stages of drug discovery. The findings from this study contribute to the growing body of knowledge on Chalcone derivatives and their potential as therapeutic agents. While the *in silico* results are promising, it is important to note that experimental validation through *in vitro* and *in vivo* studies is necessary to confirm the predicted properties and to further develop these compounds into viable drugs. In conclusion, the novel Chalcone molecules investigated in this thesis show considerable promise as candidates for

therapeutic development. The insights gained from this in silico research lay a solid foundation for future experimental studies and pave the way for the potential application of these compounds in the treatment of various diseases. The methodologies employed in this research can also be applied to other molecular classes, underscoring the versatility and importance of computational approaches in modern drug discovery.

## Conflict of interest

None declared.

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