Int J Adv Life Sci Res. Volume 9(1) 143-156
https://doi.org/10.31632/ijalsr.2026.v09i01.011

International Journal of Advancement in Life Sciences Research

Online ISSN: 2581-4877

Journal homepage http://ijalsr.org

Original Article

Exploration of Mesyl Chalcones as Potent Inhibitor of the Proto Oncogene Erbb-2 Proliferation by Using Computational *In-silico* Approach

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Abstract

The discovery of novel drugs was recognized as a convoluted, costly, time-consuming, and demanding process. It was found that more than 10 years and approximately 4 billion INR are required for the finding of a novel medicine through old-fashioned drug development procedures. In the pharmaceutical industry, figuring out how to lower research costs and accelerate the development process of new drugs has become a difficult and pressing question. Computer-aided drug design has become a potent and capable technique for a quicker, less expensive, and more successful approach. Molecular docking is a useful technique for estimating the structure of ligand-protein complexes. Over the past few years, computational tools for drug discovery, including antitumor therapies, have displayed a significant and exceptional power on the design of antitumor drugs. It has been found that chalcones serve as starting materials for the synthesis of a large number of organic compounds, and this moiety has a variety of pharmacological properties, including anticancer activity. The present study aims to identify a new chemical entity of mesyl chalcone as anticancer agents and analyze their binding capacities, Van der Waals potentials, and drug likeness through the molecular docking process. Physicochemical properties were calculated using Molinspiration and Swiss ADMET. The docking study was done on the crystal structure of receptor tyrosine protein kinase ErbB2. The study shown that all the compounds exposed outstanding binding energies in the active sites of the protein and can be considered potent inhibitors of the proto-oncogene ErbB-2 proliferation.

Keywords: *ADME Properties; Anticancer; HER2, Ligands; Mesyl Chalcones; Protein; Molecular Docking*

Introduction

Molecular docking, a computational modelling technique, predicts the binding alignment of ligands and receptors, facilitating the understanding of intermolecular interactions. It uses scoring functions to estimate binding free energy, stability, and molecular strength, offering insights into molecular structure and the strength of attractive forces between proteins and ligands (Mishra *et al*., 2021; Umar *et al*., 2024). Widely employed in predicting small molecule binding to biochemical targets, it aids in rational drug design, enabling the development of more effective drugs. By optimizing molecular conformations

Received on :28th March 2025; Revised version received on :17th December 2025; Accepted: 29th December 2025

and minimizing energy, it elucidates physical mechanisms governing molecular interactions. Access to a structural database and reliable methodology ensures accurate evaluation of ligand-target interactions, facilitating the prediction of ligand affinity with protein targets. Advanced computational tools aid in identifying optimal ligands, streamlining drug discovery. Molecular docking revolutionizes drug development by predicting molecular interactions, informing molecule optimization, and identifying novel drug candidates, thus saving time and energy in the drug development process (Redhwan *et al*., 2020). Drug discovery and development process were given in Fig. 1. Docking software has an effective scoring function which allows it to accept or reject poses accordingly. This ensures quality control and accuracy in the process. Even in the event of a rejection, new poses are created and the search iteration continues until it reaches an endpoint with one accepted pose. Molecular docking combines searching and scoring together to provide a comprehensive analysis. This process is highly efficient and provides an accurate result. Ranking docked conformers based on their binding affinities and free energies can be more challenging than the searching of the binding orientation (Mishra *et al*., 2021; Kodical *et al*., 2020). There is a great variety of software programs for docking available, yet we have used iGEMDOCK, a structure based virtual screening system. This software is incredibly helpful in providing interfaces to create both binding sites. To date, cancer is still a main worldwide community health concern that needs to be addressed urgently. Researchers estimate that there are around 200 different types of cancer, typically named after the tissue in which it was first discovered. Cancer is one of the most serious reasons for mortality in the modern world, and a major obstacle to increases in life expectancy across the globe. According to statistics, cancer is the second chief cause of death among people who are 70 years old and below in 91 countries. For 22 other nations, it is either the third or fourth leading cause of life loss (Cui *et al*., 2020). According to a study, worldwide cancer cases have skyrocketed by 18.1 million and shockingly 9.6 million deaths attributed to cancer have been reported. It's even more alarming that 70% of the cancer-related deaths occur in low- and middle-income countries (Bray *et al*., 2018). Cancer is spreading rapidly and becoming one of the biggest health concerns across the globe. This has posed an immense challenge in trying to contain its impacts on people's lives. Finding effective and safe solutions to reduce the cancer-related death rate is a priority for governments, societies, medical industries and scientific communities around the globe. This has led to major advances in cancer treatments being developed at an accelerated rate.

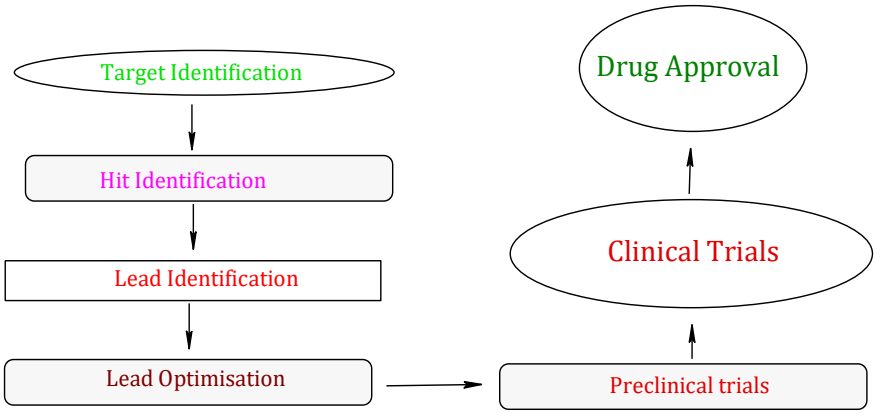


Figure 1: *Drug Discovery and Development Process*

Materials and Methods

Tools and materials used

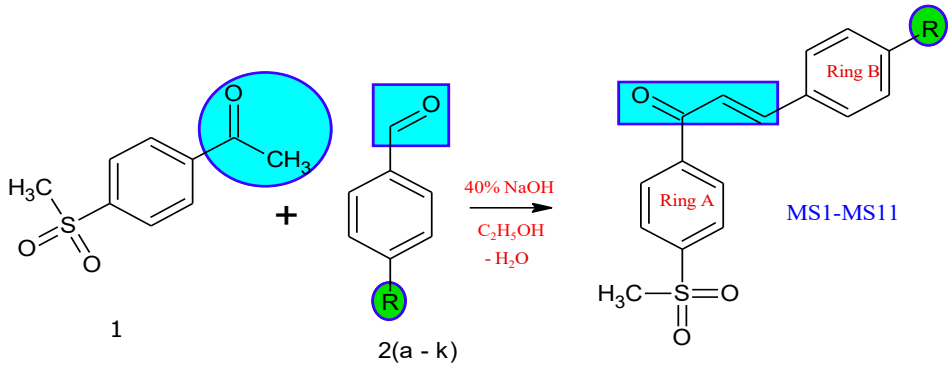
In our study, we're exploring novel chalcones with methanesulfonyl end derivatives for potent anticancer activity. We utilized databases like PDB, Drug Bank, and software such as ChemSketch, ChemDraw, iGEMDOCK, Molinspiration, and Swiss ADMET. iGEMDOCK, a docking software, serves as a valuable tool for understanding pharmacological interactions, aiding in the discovery of potentially active molecules. The drug's ability to bind strongly to target molecules is crucial, with higher binding energy

may indicating better suitability. Negative binding energy may correlates with drug potential, suggesting higher likelihood of approval (Parameswari & Devika, 2019).

Chemistry of Mesyl Chalcones

Aromatic aldehydes with different para substitution 2(a-k) (0.01 mol) were stirred with 4-(methylsulfonyl) acetophenone (1) (0.01 mol) in water (40 ml) and ethanol (25 ml) in presence of alkali (0.01 mol) for 5-6 h. The reaction mixture was kept overnight in a refrigerator, then add excess ice cold water. The precipitated product (MS1 to MS11) was filtered, washed with water and recrystallized from ethanol (Lakshminarayanan *et al*., 2020; Ahsan *et al*., 2025). The synthetic route is given in Scheme 1.

Pharmacokinetics (ADME) properties like lipophilicity, water solubility, druglikeness, Physicochemical and medicinal properties of the mesyl chalcones were determined by using Swiss ADMET server. Binding interactions of the synthesized mesyl chalcones with protein were determined by docking (In-silico approaches) by using iGEMDOCKv2.1 software (Kumar *et al*., 2016). A personal computer HP Compaq (Presario CQ61) running on Intel Pentium core 2 duo processor was used for the computational work.



R	R
MS1: H	MS7: 4-Cl
MS2: 4-OCH_3	MS8: 4-F
MS3: 4-CH_3	MS9: 4-Br
MS4: 4-CH_2CH_3	MS10: 4-CF_3
MS5: 4-$N(CH_3)_2$	MS11: 4-OH
MS6: 4-NO_2	

Scheme 1: *Synthetic Route for Mesyl Chalcones*

Protein Selection

Humans possess approximately 30,000 genes, with 6,000 to 8,000 offering potential for pharmacological targeting in drug development. However, only about 400 encoded proteins have been validated for this purpose (Chen *et al*., 2016). Traditional drug discovery often overlooks drug-protein interactions, focusing on a "one molecule - one target - one disease" approach, despite many diseases involving multiple target proteins (Mishra *et al*., 2022). Notably, over expression of the epidermal growth factor receptor 2 (HER2) is associated with certain aggressive breast cancers. Blocking HER2 binding is crucial in such cases. Protein 7JXH, a structural chain of HER2, was selected as the receptor for docking mesyl chalcones in this study.

Preparation and purification of the target protein

The 3D crystal structure of HER2 protein (7JXH) was retrieved from data bank of protein by giving the protein ID (PDB code: 7JXH, http://www.rcsb.org) in the data base. Longest chain was selected; water molecules and other undesired portions were removed from the structure of protein. Polar hydrogens were added to the protein and the energy of the protein was minimised. The protein saved as a (.pdb) format in desired place in the PC. Now the protein was ready to bind with ligands. Structure of the protein, 7JXH and its 3D view were given in Fig. 2 and Fig. 3.

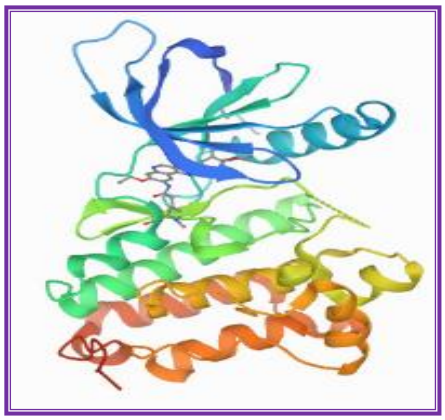


Figure 2: *Structure of 7JXH*

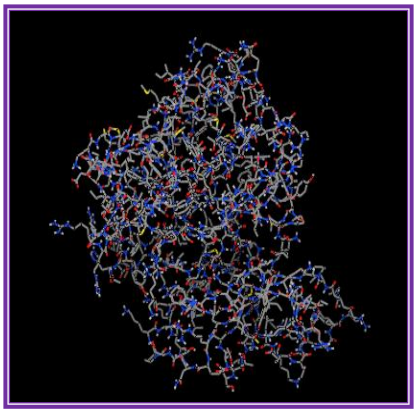
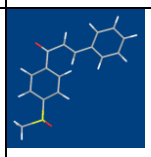
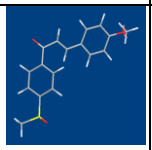
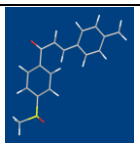
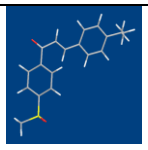
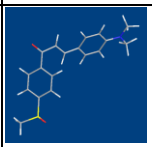
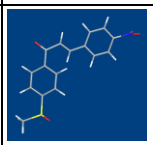
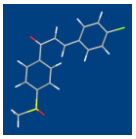
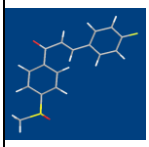
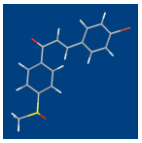
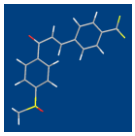
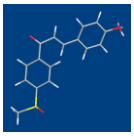
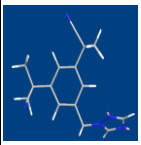
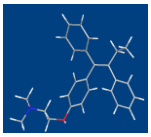


Figure 3: *3D view of 7JXH*

Preparation of the ligand structures

Chemical formula of eleven mesyl chalcones (MS1 to MS11) and standard drugs, Anastrozole and tamoxifen were drawn using ChemDraw Ultra 8.0 software. All the structures were transformed as ligand structures and each molecule energy was minimized by using Chem3D Pro software, then it was saved as (.pdb) format. Molecular structures of methanesulfonyl (mesyl) chalcones were drawn by ChemSketch software, Ligand view of all the mesyl chalcones and standards are given in Table 1.

Table 1: *Ligand View of Mesyl Chalcones and Standards*

Code	MS1	MS2	MS3	MS4	MS5	MS6	MS7
Ligand							
Code	MS8	MS9	MS10	MS11	STD1	STD2	
As a ligand and STD							STD 1 – Anastrozole STD 2 – Tamoxifen

Molecular docking study on receptor tyrosine protein kinase ErbB2

To find out the attractions between the mesyl chalcones (ligands) and the protein, docking was performed by using the software, iGEMDOCKv2.1 (Leite *et al.,* 2023; Askarzade *et al.,* 2025). Upload the protein and all the ligands in the suitable place in the software iGemdock.exe. Then perform standard docking by click “start docking” with 70 generations in the population size of 200. Once the docking was finished, view the docked poses, energy released, VDW and H Bond, then analyze and interpret the results of each enzyme-ligand complex. All the results were compared with Anastrozole and tamoxifen as positive standards for docking process.

Anastrozole and tamoxifen were selected as docking standards because of their well-established clinical relevance in hormone-dependent breast cancer and their extensively characterized molecular interactions, despite not being direct HER2 tyrosine kinase inhibitors. Breast cancer progression is frequently driven by significant cross-talk between estrogen receptor (ER) signalling and the HER2 pathway, where activation of one pathway can influence or compensate for the other. Literature reports indicate that ER-modulating agents such as tamoxifen and estrogen-synthesis inhibitors like anastrozole can indirectly affect HER2-mediated signalling cascades by altering downstream proliferative and survival pathways. Therefore, using these compounds as docking standards provides

a biologically meaningful reference to compare ligand–protein interactions in the context of breast cancer–related targets. Their inclusion helps to benchmark binding behaviour against clinically validated agents involved in interconnected signalling networks, even though their primary mechanism of action is not direct inhibition of HER2 tyrosine kinase activity.

Results

Physicochemical properties like molecular formula, molecular weight, number of aromatic atoms present, molecular orbital character (Fraction sp^3) and properties of polar atoms were calculated by the Swiss ADMET server and given in Table 2 Characters of synthesized compounds like Lipophilicity, Pharmacokinetics properties, Druglikeness and Medicinal Chemistry characters were also calculated by Swiss ADMET server and given Table 3 to 6 respectively.

Table 2: *Physicochemical Properties of the Mesyl Chalcones and Standards*

Sl. No.	Code	Physicochemical Properties									
		MFa	MWb (g/mol)	nAtomc	nAro. Atomd	FCsp3e	nRBf	nHBAg	nHBDh	MRi	TPSAj
1	MS1	C16H14O3S	286.35	20	12	0.06	4	3	0	79.34	59.59 Ao
2	MS2	C17H16O4S	316.37	22	12	0.12	5	4	0	85.83	68.82 Ao
3	MS3	C17H16O3S	300.37	21	12	0.12	4	3	0	84.31	59.59 Ao
4	MS4	C18H18O3S	314.39	22	12	0.17	5	3	0	89.12	59.59 Ao
5	MS5	C18H19NO3S	329.41	23	12	0.17	5	3	0	93.55	62.83 Ao
6	MS6	C16H13NO5S	331.34	23	12	0.06	5	5	0	88.16	105.41 Ao
7	MS7	C16H13ClO3S	320.79	21	12	0.06	4	3	0	84.35	59.59 Ao
8	MS8	C16H13FO3S	304.34	21	12	0.06	4	4	0	79.30	59.59 Ao
9	MS9	C16H13BrO3S	365.24	21	12	0.06	4	3	0	87.04	59.59 Ao
10	MS10	C17H13F3O3S	354.34	24	12	0.12	5	6	0	84.34	59.59 Ao
11	MS11	C16H14O4S	302.34	21	12	0.06	4	4	1	81.37	79.82 Ao
12	STD1	C17H19N5	293.37	22	11	0.41	4	4	0	83.81	78.29 Ao
13	STD2	C26H29NO	371.51	28	18	0.23	8	2	0	119.71	12.47 Ao

Table 3: *Lipophilicity of The Mesyl Chalcones and Standards*

Sl. No.	Code	Lipophilicity Character logPo/w					
		iLOGP	XLOGP3	WLOGP	MLOGP	SILICOS-IT	Consensus (Average)
1	MS1	2.13	2.32	3.96	2.81	3.26	2.90
2	MS2	2.48	2.90	3.97	2.47	3.32	3.03
3	MS3	2.56	3.29	4.27	3.05	3.77	3.39
4	MS4	2.70	3.73	4.52	3.29	4.16	3.68
5	MS5	2.46	3.05	4.02	2.71	2.94	3.04
6	MS6	1.83	2.76	4.39	1.73	1.51	2.44
7	MS7	2.43	3.56	4.61	3.32	3.90	3.56
8	MS8	2.33	3.03	4.52	3.20	3.68	3.35
9	MS9	2.60	3.62	4.72	3.44	3.94	3.66
10	MS10	2.49	4.81	4.13	4.68	4.35	4.09
11	MS11	1.88	2.57	3.66	2.28	2.78	2.63
12	STD1	2.25	2.03	2.93	1.71	2.85	2.35
13	STD2	4.64	4.14	4.90	4.1	4.99	4.55

Table 4**:** *Pharmacokinetics Properties of the Mesyl Chalcones and Standards*

Sl.No	Code	Pharmacokinetics Properties							
				Cytochrome P450 inhibitor					
		GI absorption	BBB permeant	CYP1A2	CYP2C19	CYP2C9	CYP2D6	CYP3A4	Log Kp
1	MS1	High	+	-	+	-	-	-	-6.40 cm/s
2	MS2	High	+	+	+	+	-	+	-6.17 cm/s
3	MS3	High	+	+	+	-	-	-	-5.80 cm/s
4	MS4	High	+	+	+	+	-	+	-5.57 cm/s
5	MS5	High	+	+	+	+	-	+	-6.14 cm/s
6	MS6	High	-	-	+	+	-	-	-6.36 cm/s
7	MS7	High	+	+	+	+	-	+	-5.73 cm/s
8	MS8	High	+	+	+	-	-	+	-6.01 cm/s
9	MS9	High	+	+	+	+	-	+	-5.96 cm/s
10	MS10	High	-	+	+	-	-	+	-5.76 cm/s
11	MS11	High	-	-	-	-	-	+	-6.32 cm/s
12	STD1	High	+	-	-	+	-	-	-6.65 cm/s
13	STD2	Low	-	-	+	-	+	-	-3.50 cm/s

Table 5: *Druglikeness of The Mesyl Chalcones and Standards*

Sl. No.	Code	Druglikeness Character					
		Lipinski	Ghose	Veber	Egan	Muegge	Bioavailability Score
1	MS1	+	+	+	+	+	0.55
2	MS2	+	+	+	+	+	0.55
3	MS3	+	+	+	+	+	0.55
4	MS4	+	+	+	+	+	0.55
5	MS5	+	+	+	+	+	0.55
6	MS6	+	+	+	+	+	0.55
7	MS7	+	+	+	+	+	0.55
8	MS8	+	+	+	+	+	0.55
9	MS9	+	+	+	+	+	0.55
10	MS10	+	-	+	-	+	0.55
11	MS11	+	+	+	+	+	0.55
12	STD1	+	+	+	+	+	0.55
13	STD2	+	-	+	-	-	0.55

Table 6: *Medicinal Chemistry Character of The Mesyl Chalcones and Standards*

Sl.No	Code	Medicinal Chemistry Character			
		Pains	Brenk (Alert)	Leadlikeness	Synthetic Accessibility
1	MS1	0	1	+	2.66
2	MS2	0	1	+	2.64
3	MS3	0	1	+	2.73
4	MS4	0	1	-	2.87
5	MS5	1	1	+	2.77
6	MS6	0	2	+	2.68
7	MS7	0	1	-	2.66
8	MS8	0	1	+	2.65
9	MS9	0	1	-	2.70
10	MS10	0	1	-	2.80
11	MS11	0	1	+	2.53
12	STD1	0	0	+	2.21
13	STD2	0	1	-	3.01

Molecular Docking

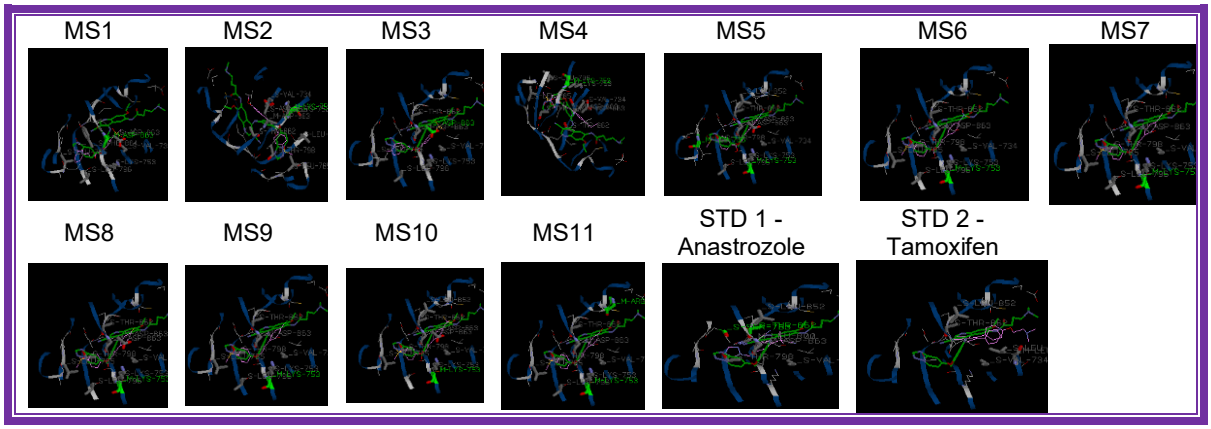
The software tool used is an effective instrument that can provide the better beginning place for perceptive pharmacological interactions, which facilitates outcomes in perceiving additional innovative and possibly active molecules for a particular protein, which is accountable for illnesses. Fitting of drug to the goal molecules have the highest requisite energy of receptor – ligand connections. The drug's

capacity to fit to the target molecules is supported by the binding energy with the maximum value. The more binding energy that is negative, the more probable it is that a chemical may be approved as a drug (Halfar *et al*., 2025; Varghese *et al.,* 2025). Mesyl chalcones and the target protein were docked by iGEMDOCK and hereditary algorithm restrictions were located as two hundred population size, seventy generations in two number of solution. This docking method recognises numerous bond dynamisms, like hydrogen bond, Van Der Walls and electrostatic interface which occur between compounds and the protein. Results were given in Table 7 & Fig 4 and best docking pose were given in Table 8.

Table 7: *Docking Results of Mesyl Chalcones and Standards*

Code	Energy (kcal/mole)	VDW	H-Bond
MS1	-84.21	-74.84	-9.37
MS2	-88.01	-84.55	-3.46
MS3	-86.20	-82.83	-3.37
MS4	-77.77	-68.30	-9.48
MS5	-86.80	-84.30	-2.50
MS6	-86.53	-74.81	-10.82
MS7	-79.24	-76.74	-2.49
MS8	-87.23	-83.73	-3.50
MS9	-78.37	-75.94	2.43
MS10	-90.40	-88.06	-2.34
MS11	-86.82	-75.82	-11.00
STD1	-73.59	-67.33	-06.26
STD2	-91.97	-91.92	-00.00

Table 8: *Best Docking Pose of Mesyl Chalcones and Standards*



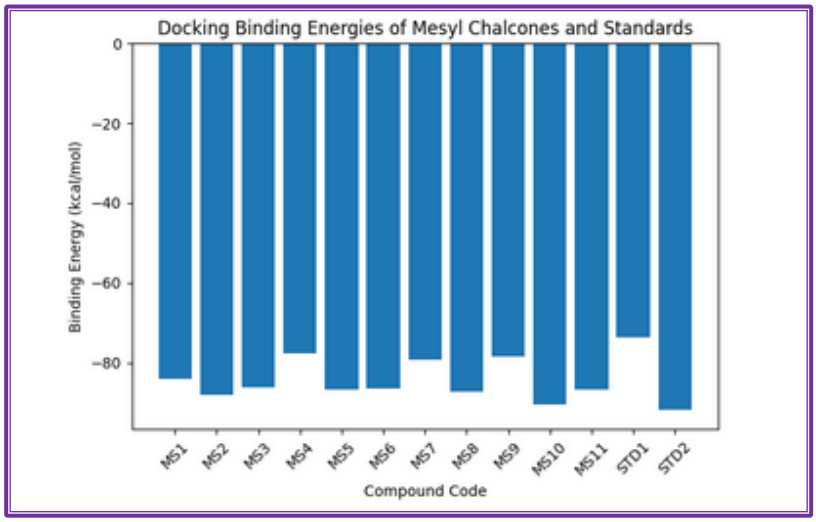


Figure 4: *Docking Results of Mesyl Chalcones and Standards*

Discussion

Physicochemical properties of the mesyl chalcones and standards

Fraction Csp3

Determining the fraction Csp3 is vital for analysing carbon saturation in molecules. Enhancing sp3 character can improve various molecular properties crucial for clinical efficacy. Modifying molecular shape facilitates constructing in-plane and out-of-plane substituents, enhancing receptor-ligand complementarily. This enables additional protein-ligand interactions, enhancing specificity to a target while reducing off-target effects (Thomas *et al*., 2006). Comparison of commercially available medications with drug-like compounds highlights changes. Descriptor analysis using aryl, double, and single bonds helps calculate complexity and saturation (Badertscher *et al*., 2001). About 40% of pharmaceuticals lack sp3 carbons in their ring structures. The FCsp3 value for each scaffold, including -CH2 linkers and chiral carbons (Taylor *et al*., 2014), is determined to assess saturation. Utilizing a saturation index, all compounds exhibit FCsp3 values below 0.25, indicating good molecular planarity.

Topological molecular Polar Surface Area (TPSA)

The transport properties of a drug are characterised by the topological molecular polar surface area, or TPSA. The assets are determined by polar atoms, and it is predicted using various techniques, including tabulated surface contributions from polar fragments and traditional 3D PSA. The TPSA is predicted by Swiss ADMET server using the total of polar fragments surface contributions (Balakrishnan *et al*., 2014). Drug molecules TPSA should ideally be < 160 Ao. In the present study, TPSA value of all the compounds and standards were found to be within the range (12.47 – 105.41 Ao).

ADME properties of the mesyl chalcones - Pharmacokinetic studies

The process of finding new drugs is expensive and time-consuming. It is now simpler to forecast the factors that determine a compound's therapeutic potential thanks to computational approaches. The hydrophobicity of drug molecules is indicated by the cLogP, i,e partition coefficient between n-octanol and water, which affects a medication's absorption, bioavailability, metabolism, and toxicity concerns (Mukadam & Jagdale, 2024). Low permeation or poor absorption is caused by high logP values. The value of cLogP cannot be higher than 5.0. The LogP values of all the mesyl chalcones and standards were found less than five. Because a drug's molecular weight and absorption are correlated, an increase in molecular weight results in a decrease in absorption. In the process of developing new drugs, maintaining lower molecular weight is crucial. It was noted that all the compounds and standards have < 450 molecular weight and cLogP value less than 5. Drug likeliness of the compounds was premeditated based on Lipinshi’s rule, Veber’s, Ghose’s PAINs and other lead likeliness limits and the results were likened with standard drug Anastrozole and tamoxifen.

Lipinski’s rule of five

Pharmaceutical researchers frequently apply Lipinski's Rule of Five to predict the oral bioavailability of potential lead compounds during drug design and development. According to this rule, a drug molecule is likely to be orally active if it meets the following criteria: (i) a molecular weight below 500, (ii) a calculated Log P value of less than 5, (iii) fewer than 5 hydrogen bond donors (OH and NH groups), (iv) fewer than 10 hydrogen bond acceptors (primarily N and O), and (v) no more than one violation. The analysed chalcones exhibited molecular weights under 500, Log P values below 5, fewer than 5 hydrogen bond donors, and fewer than 10 hydrogen bond acceptors. Notably, all mesyl chalcones complied with Lipinski’s Rule of Five without any violations (Lipinski *et al*., 2012).

Veber Rules

Veber Rules states that a potential drug may have good oral bioavailability if it contains 10 or less than 10 rotatable bonds and below 140 Ao Polar surface areas (Veber *et al*., 2002). Rotatable bond in the molecule represents molecular flexibility and Polar surface area was inversely propositional to

permeation rate than lipophilicity (ClogP). Rotatable bonds present in the proposed compounds were found to be between 4 to 8. Hence all the compounds obeyed the Veber rule.

Ghose Filter

This approach was used to reveal the information about quantitative and qualitative characters of a drug molecule. These character of a drug based on Physicochemical properties of a drug like molecular weight, number of atoms, logP and molar refractivity (Ghose & Crippen, 1987). As per Ghose filter, a drug molecule may fulfil the following criteria: cLogP should be between -0.4 – 5.6, Molecular weight between 160 – 480, Molar refractivity between 40 – 130, Total no. of heavy atoms between 20 to 70. Report of all the compounds revealed that cLogP value was found between 2.35 – 4.55, molecular weight between 286 – 371, molar refractivity value between 79.3 – 119.71 and total no. of heavy atoms between 20 – 28. Hence all the compounds fulfil the above Ghose filter criteria.

Egan Filter

The Druglikeness Egan (Pharmacia) filter can give an indication of the absorption rate of a small molecule based on the physical factors that influence it passing through cell membranes. Egan's computational model for predicting the absorption of drugs into the human body takes into account active transport and efflux mechanisms, making it a robust and reliable system. This means that it is extremely useful for accurately estimating passive intestinal absorption of small molecules. After being assessed, all of the compounds passed the Egan filter primarily due to their polar surface area and the numeral of H donors that controlled their hydrophilicity and hydrophobicity (Egan *et al*., 2000).

Muegge Filter

The Muegge Rule (Muegge *et al*., 2001) is a powerful tool for chemists and pharmaceutical researchers to quickly identify drug-like molecules from non-drug-like compounds. Using a pharmacophore point filter, the Muegge Rule determines if a compound has the structural characteristics of a drug by examining several simple structural guidelines. This rule can save time and energy for researchers, as it can quickly sieve out compounds that are structurally improbable to be drugs. Non-drugs have long been underutilized and underestimated in the field of pharmacology. To counter this, a filtering system has been developed to ensure that only molecules with a least amount count of distinct pharmacophore points are allowed to pass through. This system helps to ensure that the drugs used are effective and safe for use, allowing for more efficient and targeted treatments.

Bioavailability Score

Bioavailability is a term used to describe how much and how quickly a drug is absorbed into the body. This can be dependent on the design and manufacturing process of the dosage form, which affects its efficacy. Furthermore, this determines how accessible the active moiety is to reach systemic circulation and ultimately affect its site of action. The Bioavailability Score (BAS) is calculating of the comparative potency of a drug. This rule provides an easy way to determine the therapeutic potential of any drug and how it will interact with other substances in the body. The BAS rule states that drugs with a score greater than 0.0 are physiologically active, drugs with scores in between -5.0 and 0.0 are reasonably active, drugs with scores below -5.0 are inactive. This simple system allows pharmacologists to quickly assess the care and effectiveness of new medications and make informed decisions about their use in medical treatments (Martin, 2005). BAS of all the compounds was found to be 0.55 indicates that all are physiologically active.

PAINs and Brenk

The PAINs (Pan Assay Interference Compounds) and Brenk filters were designed to help identify molecules that are expected to have a response in biological assays. They also target compounds with acceptable toxic levels, as well as chemical reactivity and metabolism stability. PAINs are chemical entities that can trick high-throughput screening tests and give misleading results. They have the impending to interrelate with several living targets moderately, eventually zeroing-in on one preferred target and causing disruption. There are many groups of compounds that cause disruption in enzyme

assays, phenotypic screens, and produce unwanted biological activity due to their presence. These PAINs which need to be taken into consideration when conducting research with these types of assays (Dahlin & Walters, 2014). High Throughput Screening (HTS) is a critical portion of the preparation finding method. However, it can lead to false positives when trying to determine hits. To ensure an accurate result, it is important to be conscious of these impending false positives during the HTS operations (Baell & Walters, 2010). Compounds may be mistakenly identified as false positives for a range of causes such as forming aggregates that interact with proteins, being reactive to proteins, or having a direct effect on assay signalling (Baell & Holloway, 2014).

Lead likeness

Lead likeness analysis is a great way to identify potential sources of drug discovery leads. It allows you to quickly and accurately evaluate complex datasets in order to identify the best lead candidates. Teague *et al* (1999) in their research to discover potential leads for drug development, suggested that lead compounds should have an affinity greater than 0.1μM (Teague *et al*., 1999). The ED50 is typically used as a measure of the affinity of a ligand in situations where the molecule is an agonist. In order to determine this value, the lead must fulfil certain criteria such as having a molecular weight lower than 350 and cLogP value less than 3. All the compounds have significant Leadlikeness character except MS4, MS7, MS9, MS10 and STD2, since they have more than 3 cLogP values.

Synthetic Accessibility

The synthetic accessibility (SA) of compounds plays a crucial role in drug design, as certain compounds cannot be synthesized solely through computer-aided drug design (CADD) (Schneider & Fechner, 2005). If the target compounds are challenging to synthesize, additional time and resources will be required for their production. Lead candidates are typically assessed based on factors such as drug-likeness, natural product potential, and predicted activity. However, the in silico design of a lead compound does not guarantee its feasibility for synthesis, making SA an essential parameter in predicting a compound's synthetic viability.

Estimating the overall accessibility of a large number of compounds is a complex task. To address this, certain computational methods have been developed to perform these predictions more efficiently. One such method estimates the synthetic accessibility of drug-like molecules. The SA score, which ranges from 1 to 10, indicates the ease or difficulty of synthesizing a drug molecule, with lower scores representing easier synthesis and higher scores indicating greater difficulty. The synthetic accessibility score is determined based on a combination of fragmentation contributions and complexity penalties. These fragment contributions are derived from the analysis of one million representative molecules from the PubChem database, effectively capturing the cumulative synthetic knowledge stored in this extensive dataset. From the result analysis of synthetic accessibility, all the mesyl chalcones were found to be good synthetically accessibility (2.53 – 2.87). The order of synthetic accessibility from easy to difficult as follows:

STD1 > MS11 > MS2 > MS8 > MS7 = MS1 > MS6 > MS9 > MS3 > MS5 > MS10 > MS4 > STD2

Molecular Docking

The docking results presented in Table 7 demonstrate clear variation in the predicted binding affinities of the mesyl chalcone derivatives (MS1–MS11) compared with the standard compounds (STD1 and STD2). Generally, a more negative total binding energy indicates a stronger and more stable interaction between the ligand and the target protein, reflecting higher predicted affinity in silico. This trend is widely recognized in contemporary docking studies, where negative docking scores are interpreted as favourable binding and increased stability of the ligand–protein complex due to stronger intermolecular forces (e.g., hydrogen bonding and van der Waals interactions) contributing to complex stabilization in the binding site. Negative values therefore suggest a potentially higher likelihood of biological activity, whereas less negative or positive values are interpreted as comparatively weaker binding affinity. For example, MS10 exhibits one of the most negative total energy values (−90.40 kcal/mol), outperforming STD1 (−73.59 kcal/mol) and nearing the highly negative score of STD2 (−91.97 kcal/mol). This suggests

that MS10 could form stronger non-covalent interactions and may be a promising candidate for further exploration. Similarly, other mesyl chalcones such as MS2 (−88.01 kcal/mol), MS8 (−87.23 kcal/mol), and MS5 (−86.80 kcal/mol) also show more negative binding energies than STD1, indicating comparatively stronger predicted binding interactions.

The van der Waals (VDW) contributions in many of these ligands (e.g., MS2: −84.55 kcal/mol; MS8: −83.73 kcal/mol) reinforce the importance of hydrophobic contacts and steric complementarity in stabilizing the ligand within the binding pocket. Hydrogen bonding contributions, reflected in the H-bond energy terms, also significantly influence binding affinity, as observed with MS6 (−10.82 kcal/mol) and MS11 (−11.00 kcal/mol), where stronger H-bond energies correlate with increased total affinity. Conversely, MS9 shows a positive H-bond energy term (+2.43 kcal/mol), which may reflect a lack of favorable hydrogen bonds or potential steric clashes, resulting in a comparatively weaker total binding energy (−78.37 kcal/mol). These interpretations align with 2025 docking analyses that emphasize the relationship between lower (more negative) docking scores and enhanced complex stability through non-covalent interactions, including hydrogen bonds and VDW contacts, as key determinants in ranking compounds for further investigation. In molecular docking studies, more negative binding energies are widely accepted as indicative of stronger and more favorable ligand–receptor interactions, enabling the ranking of compounds by predicted affinity (Nivatya *et al*., 2025; McNutt *et al*., 2025). Further, practical docking studies on biologically relevant targets show that compounds with more negative docking energies tend to be prioritized for subsequent analysis and design (Boora *et al*., 2025). The Fig 4 clearly shows that most mesyl chalcones exhibit more negative binding energies than STD1, indicating stronger predicted binding. MS10 and STD2 stand out with the most negative energies, supporting their higher docking affinity. Compounds such as MS2, MS5, MS8 and MS11 also cluster close to the top performers, visually reinforcing the discussion points.

Limitation of the Study

Despite the promising outcomes of this study, certain limitations exist. The molecular docking approach provides theoretical insights into ligand-protein interactions but does not fully account for dynamic physiological conditions, such as metabolic stability and in vivo bioavailability. Experimental validation through in vitro and in vivo studies is essential to confirm the anticancer potential of mesyl chalcones. Additionally, the specificity and off-target effects of these compounds need to be thoroughly investigated to ensure their safety and efficacy.

Future Scope of the Study

Future research should focus on advanced computational techniques, such as molecular dynamics simulations and AI-driven drug design, to enhance predictive accuracy. Furthermore, extensive biological assays and clinical evaluations will be crucial in translating these findings into viable therapeutic agents for cancer treatment.

Conclusion

Cancer is a major health concern, affecting millions of people around the world. Approximately 9.6 million deaths are attributed to cancer annually, as reported in numerous studies. Cancer is now the 2nd biggest source of death in humans. Coming up with an innovative drug molecule for cancer treatment, take 12 years, costs, on average more than 200 billion Indian rupees. What makes the cancer treatment more strenuous is that molecular pharmacology isn't completely understood yet. Developing effective drugs is an unrestrained and time-consuming procedure, so computational approaches can help to lessen the costs and speediness up the process. Such methods are useful for tasks like drug-target prediction, binding site identification, protein interaction network analysis and virtual screening. There are several computational techniques that can dramatically reduce the time spent on discovering new anti-cancer treatments. Computational models could work together to generate reliable predictions and accelerate the process of forming new drugs to combat cancer. Fewer mesyl chalcones were taken into account to analyse their anticancer activities by computational methods. Compound with

trifluoromethyl group (MS10), methoxy group (MS2) fluoro group (MS8) were exactly bind with protein and release high energy they can be considered as potential inhibitor against ErB2 oncogene.

Abbreviations

ADME: Absorption, distribution, metabolism, and excretion; BAS: Bioavailability Score; CADD: Computer aided drug design; ER: Estrogen receptor; ErbB2: Erythroblastic oncogene B; HTS: High throughput screening; HER2: Human epidermal growth factor receptor 2; MF: Molecular Formula; MW: Molecular Weight; PAINs: Pan-Assay INterference compounds; PDB: Protein data bank; SA: Synthetic accessibility; STD: Standard; TPSA: Topological molecular polar surface area; VDW: Van der walls.

Conflicts of Interest

Authors are not having any Conflicts of interests in the subject matter included in this manuscript.

Acknowledgement

Authors are thankful to Madin College of Pharmacy, Vellalar College of Pharmacy, Grace College of Pharmacy, Acharya BM Reddy College of Pharmacy and Annamalai University for academic support.

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