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Molecular Docking Studies and ADME Predictions on Synthesized Chalcone Compounds Targeting EGFR

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ABSTRACT

In the present study, new chalcone derivatives (5-7) obtained from the condensation reaction of cuminaldehyde and acetophenone compounds containing different substituents were reported. Chemical characterization (^{1}H-NMR and ^{13}C-NMR analysis) and molecular docking studies of the synthesized compounds were performed against the epidermal growth factor receptor (EGFR) and reference drug (metachalcone). Erlotinib was used as the reference ligand. Compound 5 (-7.6 kcal mol-1), compound 6 (-7.38 kcal mol-1), and compound 7 (-7.44 kcal mol-1) were found to be the strongest inhibitors of EGFR when compared to Erlotinib (-7.0 kcal mol-1). In addition, an ADME estimation was made. It was determined that the synthesized compounds could be potent EGFR inhibitors compared to Erlotinib. Compounds 5-7 and the target protein showed a better binding affinity for EGFR than the reference compound (Erlotinib). The synthesized compounds can be potent inhibitors for EGFR-mutated cancers.

Keywords:
Chalcon, Cuminaldehyde, Claissen-Schmidt condensation, Moleculer dockıng, ADME

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This article has been checked for similarity.

INTRODUCTION

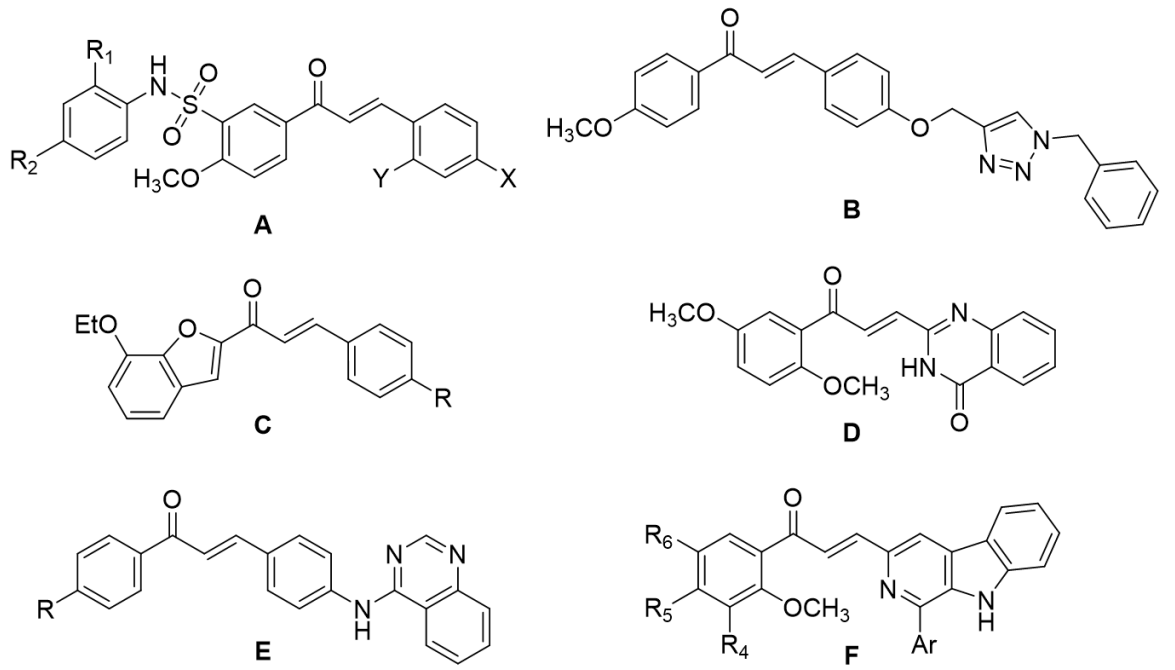
Chalcones are the precursor compounds of flavonoids and they are widely found in plants (1). Chalcones are the most common group of flavonoids, discovered by the German chemist Schmidt in 1880 and later developed by Ludwig Claisen. They are compounds linked by an α,β-unsaturated carbonyl bridge (2-3). In addition to the wide biological, pharmacological and industrial properties that chalcones exhibit, the interest of scientists in chalcones is increasing day by day because they are obtained in natural and synthetic ways (2).

Chalcone and its derivatives are used as drugs in the treatment of cancer, cardiovascular and other diseases. These compounds have biological activities such as antibacterial, anti-malarial, anthelmintic, antiulcer, antiviral, insecticidal, anticancer, anti-inflammatory, cytotoxic, anti-HIV and enzyme inhibitions (4-8). Chalcones are known as substances with anti-cancer capacity and have been the subject of many studies (9-13).

Sulfonamide-containing chalcone compounds A against MCF-7 cell line (9), Triazole-containing chalcone compound B against HepG2, MIA-Pa-Ca-2, MCF-7 and A549 cancer cell lines (14), benzofuran-chalcone compounds C against MCF-7, A549 and PC-3 cell lines (15) are known to exhibit anticancer activity. Recently, chalcone analogs containing 4-oxoquinazolin 2-yl scaffolds evaluated for their antitumor effects.

Compound D was shown as the most potent agent exhibiting cytotoxic activity against HCT-116 and MCF-7 cells (16). Also, quinazoline-based chalcone derivatives E show activity against cancer cell lines such as G, A549, HT-29, A375, MCF-7 (17), while tricyclic pyrido(3,4-b) indole (β-carboline)-linked chalcone derivatives F have anticancer activities (A549, B-16, PC-3, HT-29 and HeLa) and DNA binding affinities were evaluated (18).

Various macromolecules are responsible for cancer types. In this regard, a single drug cannot block more than one cancer pathway. Therefore, it is difficult to find cancer-specific drugs. In the literature, it has been reported that 10 million people died from different types of cancer in 2020 (4). In silico virtual screening, approaches are used to identify several molecules involved in the signalling pathway and to find specific cancer treatments. Epidermal growth factor receptor (EGFR), receptor tyrosine kinases (RTKs), are cell signaling effectors responsible for cancer development (10). The EGFR gene has been targeted for the treatment of a variety of cancers, including pancreatic, non-small cell lung car-



Scheme 1. Some chalcone derivatives (A-F) with anticancer activity

cinoma (NSCLC), colorectal, and breast cancer (4). Figure 1 shows the epidermal growth factor receptor (EGFR) structure.

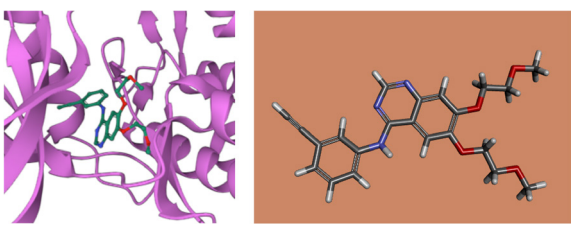
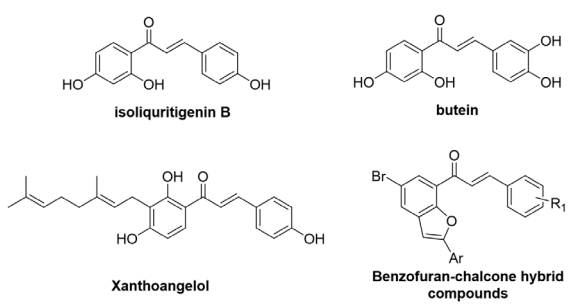


Figure 1. 3D-Structure of EGFR with the Erlotinib (PDB ID:1M17).

It has been reported in the literature that chalcone-derived compounds such as isoliquiritigenin, butein and xanthoangelol can inhibit EGFR (10). Also, benzofuran-chalcone hybrid compounds have been reported to have the potential to exert inhibitory effects against tubulin polymerization and epidermal growth factor receptor tyrosine kinase (EGFR-TK) phosphorylation (15).



Scheme 2. Chalcone derivatives capable of inhibiting EGFR

In this study, it was aimed to synthesize new chalcone derivative compounds with biological activity potential and to determine whether they have an inhibitory effect in EGFR-based cancers in silico. The results were compared with the recoupling of a standard drug, Erlotinib (PDB ID:1M17) and metachalcone, known for its anti-cancer activity.

MATERIAL AND METHODS

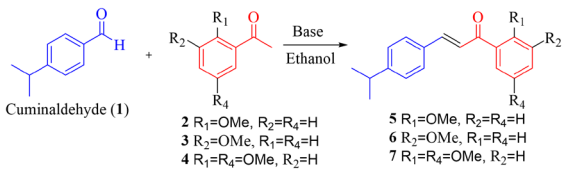
Chemistry

Chemicals were ordered from Sigma Aldrich and Merch and used directly. In the experiments, thin layer chromatography (TLC) was used (made with Merck silica gel 60 F254). UV wave light (254 nm) and phosphomolybdic acid (PMA) solution dissolved in ethanol were used for imaging thin layer chromatography (TLC). The synthesized compounds were purified by crystallization method or column chromatography. Column chromatography (Fluka Silica gel 60 (0.063 - 0.2 mm) ethyl acetate/petroleum ether solvent system was used. Structure analyses were also taken with a Bruker 400 MHz NMR spectrometer (^{1}H-NMR 400 MHz, ^{13}C-NMR 100 MHz) or Varian 400 MHz spectrometer (^{1}H-NMR 400 MHz, ^{13}C-NMR 100 MHz). Elemental analysis results were obtained on a Leco CHNS-932 instrument.

General Synthesis of Chalcones

A solution of acetophenone (1 mmol) in 10 ml of etha-

nol was added to a 30% solution of NaOH and stirred at room temperature for 5 minutes. Cuminaldehyde (1) (1 mmol) dissolved in 5 ml of ethanol was then added to the mixture. The reaction was followed by TLC. After the reaction was completed, HCl solution was added to the reaction medium and allowed to solidify. The reaction flask was then placed in the refrigerator and precipitation was allowed to complete. The resulting solid was filtered off (19). If there is no solidification after the addition of HCl, the mixture was extracted with 3x20 ml DCM, the solvent was removed on a rotary evaporator (20-21). The crude product obtained was purified by chromatographic methods. Structure analyses were performed by ^{1}H NMR and ^{13}C NMR spectroscopy.



Scheme 3. The synthesis of chalcone compounds (5-7)

Molecular docking analysis

Molecular docking studies are of great importance in drug design and pharmacology. This analysis method is a widely used and reliable method to detect protein-ligand interactions and binding sites in a short time (22-23). The in silico molecular docking interactions of 5-7 within the EGFR receptors (PDB: 1M17) were investigated by the AutoDock Tolls. Molecules (5-7) and ligand was optimized in Avagadro, their structures were determined and pdb forms of the ligands were then recorded (Fig. 2).

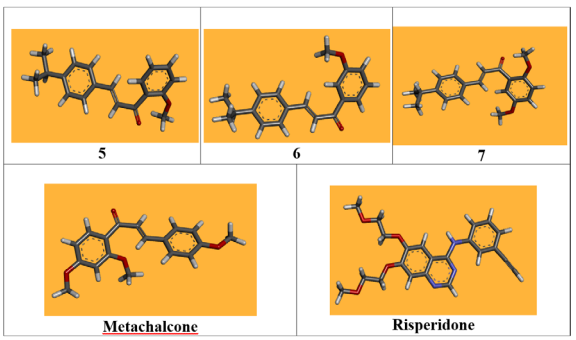


Figure 2. The optimized structures of 5-7, metachalcone and risperidone with Avagodro

EGFR/PDB: 1M17 (24) was selected as the target protein and was taken from Protein Data Bank (https://www.rcsb.org/). MGLTools was used to prepare proteins and ligands for molecular docking. Water molecules were removed and polar hydrogen charges were added. Torsion angles were verified and re-recorded in pdb form by adding Kollman loads. The active sites of the proteins were identified to complete the docking process more. Therefore, the grid parameters were selected as 60*60*60, Å 3 x, y, z dimensions, 0.553 Å space and 22.014, 0.253, 52.794 x, y, z centres for EGFR/PDB: 1M17. These preparations were converted to PDBQT format using Discover Studio Visualizer 4.0 (http://www.3dsbiovia.com/). For molecular docking, the Lamarckian Genetic Algorithm (LA) protocol was used. The automated loading calculation approach was used to predict pole contacts, Van der Waals forces, and interactions between other non-covalent proteins and bound ligands.

3D structures of molecules were obtained by drawing 2D structures of the molecules. With the Avagadro program, the energies of the molecules were reduced to a minimum and converted into PDB format. Ligands and protein molecules were converted to pdbqt file formats using AutoDock tools 1.5.7. Files converted to the protein-ligand complex were analyzed using BioVia Discovery Studio Software. In Table 8 and Figs. 3-8, the obtained molecular docking scores were given.

ADMET properties

The Swiss ADME web server was used to calculate the drug similarity parameters and ADME values (www.swissadme.ch) (25). Pharmacokinetic parameters, physicochemical, and lipophilicity of the virtual screening candidates, such as TPSA, ADMET, blood-brain barrier (BBB) permeant, gastrointestinal (GI) absorption, Lipinski etc. were predicted. SMILES data was obtained from PubChem for each phytochemical (8).

RESULTS

Chemistry

(E)-3-(4-isopropylphenyl)-1-(2-methoxyphenyl)prop-2-en-1-one (5):

It was obtained in 85-90% yield. ^{1}H NMR (400 MHz, CDCl3) δ 7.67 – 7.61 (m, 2H), 7.56 (t, J = 7.1 Hz, 2H), 7.52 -7.46 (m, 1H), 7.39- 7.33 (m, 1H), 7.29 (dd, J = 9.9, 5.8 Hz, 2H), 7.10-6.99 (m, 2H), 3.91 (s, 3H), 3.09-2.85 (m, 1H), 1.30 (s, 3H), 1.28 (s, 3H). ^{13}C NMR (100 MHz, CDCl3) δ 193.19, 158.07, 151.64, 143.49, 132.80, 132.70, 130.28, 129.50, 128.56, 127.02, 126.31, 120.73, 111.68, 55.76, 34.12, 23.78. Elemental Analysis for C19H20O2 Calcd. C, 81.40; H, 7.19; O, 11.41 Found C, 81.46; H, 7.12; O, 11.44.

(E)-3-(4-isopropylphenyl)-1-(3-methoxyphenyl)prop-2-en-1-one (6):

It was obtained in %90-95 yield. ^{1}H NMR (400 MHz, CDCl3) δ 7.67 – 7.61 (m, 2H), 7.59-7.53 (m, 2H), 7.52 – 7.48 (m, 1H), 7.42 – 7.34 (m, 1H), 7.29 (dd, J = 9.9, 5.8 Hz,

2H), 7.10 – 6.99 (m, 2H), 3.91 (s, 3H), 3.09 – 2.85 (m, 1H), 1.30 (s, 3H), 1.28 (s, 3H). ^{13}C NMR (100 MHz, CDCl3) δ 193.19, 158.07, 151.64, 143.49, 132.80, 132.70, 130.28, 129.50, 128.56, 127.02, 126.31, 120.73, 111.68, 55.76, 34.12, 23.78. Elemental Analysis for C19H20O2 Calcd. C, 81.40; H, 7.19; O, 11.41 Found C, 81.45; H, 7.13; O, 11.46.

(E)-1-(2,5-dimethoxyphenyl)-3-(4-isopropylphenyl)prop-2-en-1-one (7):

It was obtained in %85-90 yield. ^{1}H NMR (400 MHz, CDCl3) δ 7.66 (d, J = 15.9 Hz, 1H), 7.55 (d, J = 8.2 Hz, 2H), 7.44 – 7.37 (m, 1H), 7.27 (t, J = 7.0 Hz, 2H), 7.23 – 7.19 (m, 1H), 7.07 – 7.02 (m, 1H), 6.95 (dd, J = 8.2, 3.6 Hz, 1H), 3.86 (s, 3H), 3.82 (s, 3H), 3.03 – 2.85 (m, 1H), 1.30 (s, 3H), 1.28 (s, 3H). ^{13}C NMR (100 MHz, CDCl3) δ 192.60, 153.66, 152.53, 151.67, 143.51, 132.81, 129.91, 128.58, 127.02, 126.10, 118.94, 114.48, 113.47, 56.53, 55.84, 34.12, 23.77. Elemental Analysis for C20H22O3 Calcd. C, 77.39; H, 7.14; O, 15.46 Found C, 77.44; H, 7.17; O, 15.40.

ADME analysis

For a compound to be a drug candidate, it must have good pharmacological activity as well as comply with the adsorption, distribution, metabolism and elimination (ADME) and Lipinski value ranges (24,26). The synthesized compounds and reference molecules followed Lipinski's five rules (Table 1). As a result, it can be said that the synthesized compounds are suitable candidates for drug development.

in Table 2.

BOILED-Egg model

The Brain Or IntestinaL EstimateD permeation method used to predict gastrointestinal absorption (GI) and brain access of small molecules (23). The yellow part contains molecules with high BBB permeability, while the white part indicates molecules with high human intestinal absorption. All compounds remained in the yolk of the boiled egg. Figure 3 and Table 2 showed that all of the compounds in the yellow part were all likely to have brain penetration as well as absorption from the human gut. According to this study, all of these compounds are likely to cross the brain barrier.

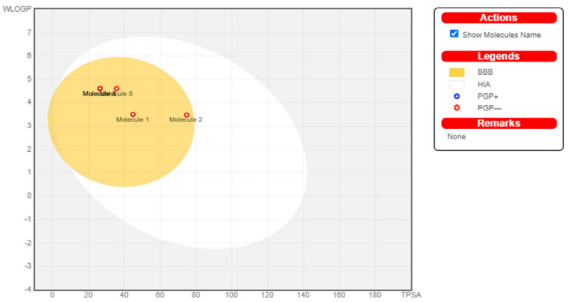


Figure 3. Brain Or IntestinaL EstimateD permeation method (BOILED-Egg) model of 5-7, metochalcone and Erlotinib.

The optimum range for physicochemical properties (saturation, size, lipophilicity, polarity, flexibility, and solubility) are shown in the pink area on Bioavailability radars. Scheme 2 depicts the bioavailability radar for all compounds.

Table 1. Chemical and physical properties of the Erlotinib and the chalcones compounds (5-8).

Molecules	Formula	MW (g/mol)	TPSA Å²	Num. rotatable bonds	Num. H-bond acceptors	Num. H-bond donors	Lipinski violations
5	$C_{19}H_{20}O_2$	280.36	26.30	5	2	0	0
6	$C_{19}H_{20}O_2$	280.36	26.30	5	2	0	0
7	$C_{20}H_{22}O_3$	310.39	35.53	6	3	0	0
Metachalcone	$C_{18}H_{18}O_4$	298.33	44.76	6	4	0	0
Erlotinib	$C_{22}H_{23}N_3O_4$	393.44	74.73	10	6	1	0

* MW: Molecular weight, TPSA topological polar surface area, Lipinski: Lipinski (Pfizer) filter.

In silico ADMET prediction was made for the synthesized compounds. Preventing a possible precursor chemical from failing in clinical trials is an important step. A medicine should be quickly absorbed, evenly distributed throughout the body, efficiently digested, and eliminated with no negative side effects. Table 2 shows that all compounds had high GI absorption. All of the compounds have excellent BBB permeability and may have pharmacological effects on the brain. That is, these compounds can cause central nervous system depression and drowsiness when crossing the blood-brain barrier. Estimated ADME properties are given

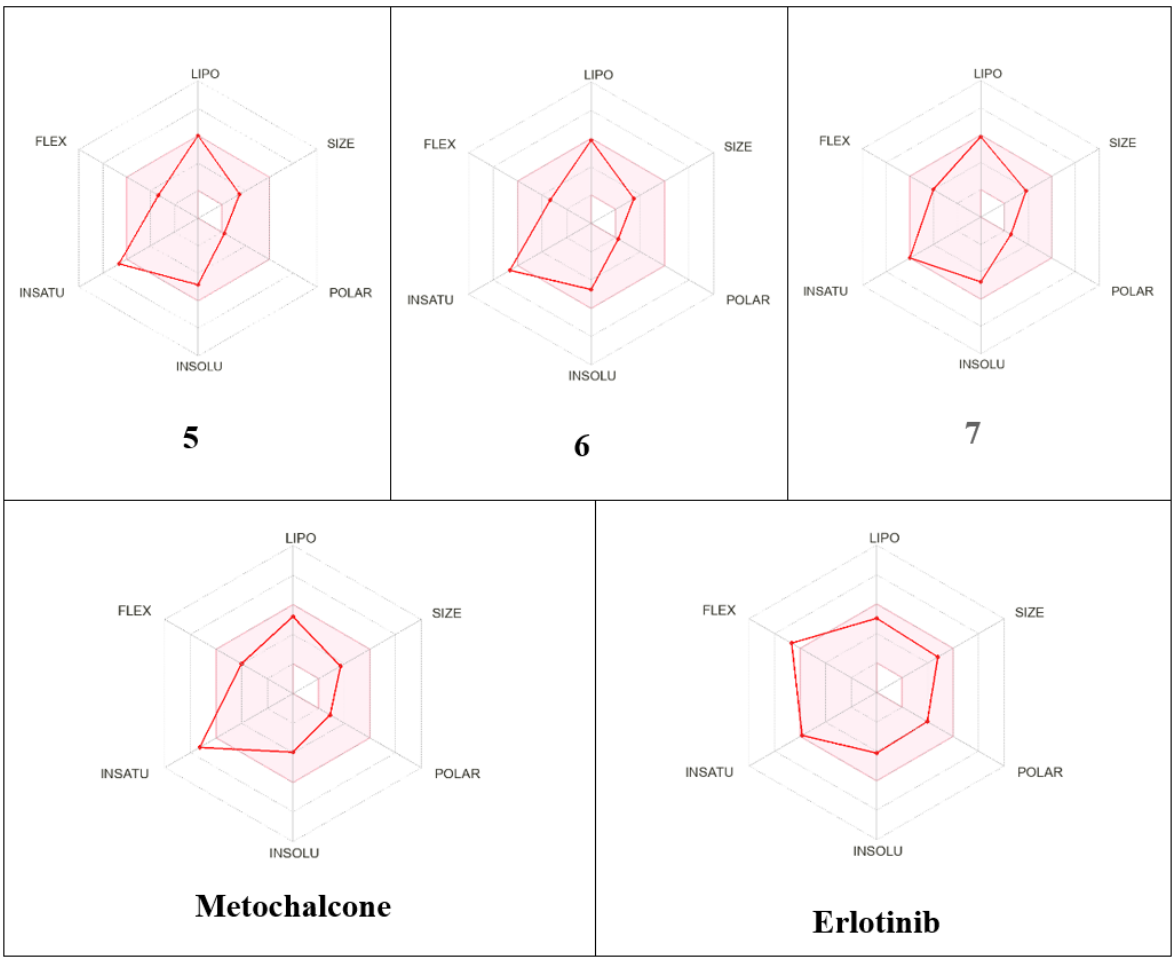
Results of Molecular Docking Studies

Cancer is one of the factors that negatively affect human health. The world is engaged in developing anticancer drugs that will be effective against cancer. In this study, the potential of the synthesized chalcone compounds to be anti-cancer compounds against the target EGFR was investigated. In silico molecular docking, various interactions between EGFR and chalcones were studied and bond energies were calculated. Table 8 shows the binding affinity of chalcones for EGFR ranging from -6.78 to -7.60 kcal mol-1. These values were compared with data ob-

Table 2. Pharmacokinetic properties of compounds 5-7, metachalcone and positive control (Erlotinib) calculated with the SwissADME program

Molecules	GI absorption	BBB	PGP substrate	CYP1A2 inhibitor	CYP2C19 inhibitor	CYP2C9 inhibitor	CYP2D6 inhibitor	CYP3A4 inhibitor	log Kp (cm/s)	Log $P_{o/w}$ (iLOGP)
5	High	Yes	No	Yes	Yes	Yes	Yes	Yes	-4.44 cm/s	3.47
6	High	Yes	No	Yes	Yes	Yes	Yes	Yes	-4.61 cm/s	3.51
7	High	Yes	No	Yes	Yes	Yes	Yes	Yes	-4.81 cm/s	3.61
Metochalcone	High	Yes	No	Yes	Yes	Yes	Yes	Yes	-5.56 cm/s	3.22
Erlotinib	High	Yes	No	Yes	Yes	Yes	Yes	Yes	-6.35 cm/s	3.67

*GI ab: Gastrointestinal absorption; BBB:BBB permeation, log Kp: Skin permeability.



Scheme 4. Evaluation of drug properties of compounds by bioavailability radar
*LIPO: Lipophilicity, SIZE: Molecular weight, POLAR: Total Polar Surface Area, INSOLU: insolubility in water according to log S scale, INSATU: in sp^3 hybridization unsaturation concerning carbon fraction, FLEX: flexibility concerning rotatable bonds.

tained by re-docking molecules with the EGFR inhibitor Erlotinib (-7.0 kcal mol-1). The docking results of the Erlotinib and the interactions with the enzyme were given Figure 4 and Table 3. According to docking results, it was seen that the order of activity of the molecules was 5 > 6 > 7 (Figure 5-7).

Fig. 4 shows the structure of EGFR (1M17) with re-docked ligand Erlotinib. Erlotinib showed good binding interactions with EGFR. MET769 and CYS773 had conventional hydrogen bond to Erlotinib with binding lengths of 3.93 and 3.64Å. C-H bond interactions with GLN767, MET769 residues with 5.92, 6.68 Å bond length. π-cation interaction was observed with LYS721 (4.98 Å) residue, π-sigma interactions were with LEU820 (5.61 Å), LEU694 (5.98 Å). π-Alkyl interactions were with ALA719 (5.39Å), ALA719 (4.74 Å), ALA719 (5.12 Å), LEU820 (5.68 Å), VAL702 (5.68 Å), MET769 (5.90 Å), LEU768 (5.66 Å) residues, alkyl interactions was with MET742 (5.08 Å) residues of EGFR. Van der Waals interactions were observed between LEU764, THR830, PHE832, GLU738, ASP831, GLY772, PHE771, PRO770, LEU768 and GLN767. All interactions are shown in detail in Table 3.

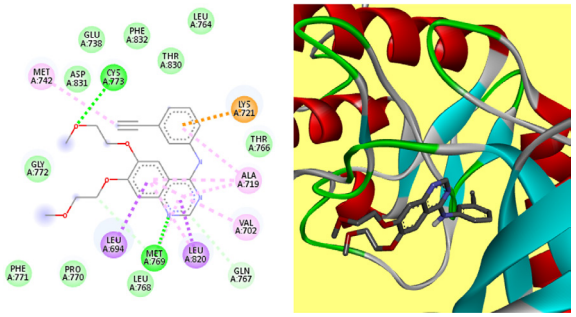
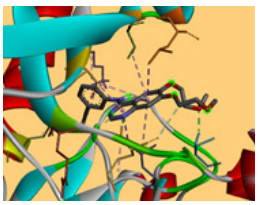


Figure 4. 2D and 3D binding interactions of Erlotinib within active site of EGFR (PDB:1M17).

Table 3. Ligand-protein interactions

Molecule	Hydrogen-bonding	Hydrophobic interactions	Electrostatic	Distances	TYPE
	MET769	-		3.93	Conventional Hydrogen Bond
	CYS773			3.64	
	GLN767	-		5.92	Carbon Hydrogen Bond
	MET769			6.68	
			LYS721	4.98	π-cation
	-	LEU820		5.61	π-sigma
		LEU694		5.98	
	-	ALA719		5.39	π-Alkyl
		ALA719		5.12	
		ALA719		4.74	
		LEU820		5.68	
		VAL702		5.68	
		MET769		5.90	
		LEU768		5.66	
	-	MET742		5.08	Alkyl

It was calculated that 5-7 molecules interact with EGFR /PDB: 1M17 with energies of -7.60, -7.44, and -7.38 kcal/mol. The entire docking mechanism made is given in Figure 5-8.

The amino acid MET769 has conventional hydrogen bond to compound 5 with the binding lengths of 4.33 Å (Fig. 5). LEU694 amino acid had π-sigma interaction between the centre of the phenyl ring with 5.04 Å bond length. π-alkyl interactions existed between amino acids ALA719 (4.96 Å), and LYS721 (6.46 Å). The alkyl interactions were observed between MET742, LYS721, LEU694, and LEU768 residues with 6.60 Å, 4.40 Å, 5.46 Å and 4.42 Å bond lengths, respectively. Also, π-sulfur interactions were observed between CYS751 (7.47 Å), C-H bond interactions were observed with PRO770 (4.26 Å), Van der Waals interactions were observed between VAL 702, CYS 773, GLY 772, LYS704, LEU820, THR776, THR830, PHE832, ASP831, GLU738, LEU764. All interactions are shown in detail in Table 4.

The amino acid THR766, CYS751, and LYS721 have conventional hydrogen bond to compound 6 with the binding lengths of 4.15 Å, 5.89 Å and 4.43 Å (Fig. 6). π-alkyl interactions existed between LYS721, LEU820, and ALA719 amino acids and the centre of the phenyl ring with 5.94 Å, 5.24 Å and 5.61 Å bond lengths, respectively. The alkyl interactions were observed between LYS721 (4.85 Å), and LEU694 (4.32 Å) residues. The π-sigma interaction was found in LEU694 and the phenyl ring with a 6.12 Å bond length. Additionally, Also, π-sulfur interactions were observed between MET742 (7.83 Å), the amide-pi bond was observed with MET769 (4.81 Å), Van der Waals interactions were observed between PRO770, LEU768, GLN767, THR830, GLU738, ASP831, VAL702, GLY772. All interactions are shown in detail in Table 5.

The amino acid MET769 has conventional hydrogen

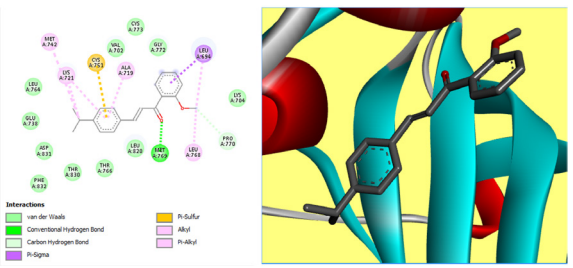


Figure 5. 2D and 3D binding interactions of compound 5 inside 1M17 active site.

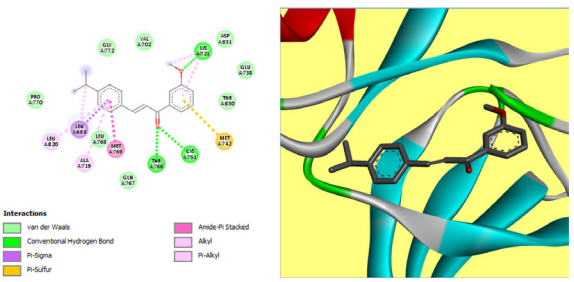


Figure 6. 2D and 3D binding interactions of compound 6 inside 1M17 active site.

bond to compound 7 with the binding lengths of 4.51 Å (Fig. 7). π-alkyl interactions existed between LEU694 (5.34 Å), ALA719 (5.11 Å) amino acids and the centre of the phenyl ring. Alkyl interactions were observed between MET742, LEU694, LEU768, CYS773 and LEU820 residues with 5.66,

Table 4. Ligand-protein interactions

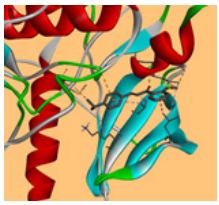
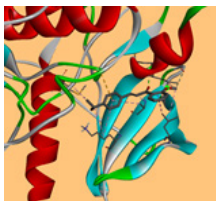
Molecule	Hydrogen-bonding	Hydrophobic interactions	Electrostatic	Distances	TYPE
	MET769	-		4.33	Conventional Hydrogen Bond
	PRO770	-		4.26	Carbon Hydrogen Bond
			CYS751	7.47	π-sulfur
	-	LEU694		5.04	π-sigma
	-	ALA719 LYS721		4.96 6.46	π-Alkyl
	-	MET742 LYS721 LEU694 LEU768		6.60 4.40 5.46 4.42	Alkyl

Table 5. Ligand-protein interactions

Molecule	Hydrogen-bonding	Hydrophobic interactions	Distances	TYPE
	THR766 CYS751 LYS721	-	4.15 5.89 4.43	Convention-al Hydrogen Bond
	-	MET769	4.81	Amide-π
	-	MET742	7.83	π-sulfur
	-	LEU694	6.12	π-sigma
	-	LYS721 LEU820 ALA719	5.94 5.24 5.61	π-Alkyl
	-	LYS721 LEU694	4.85 4.32	Alkyl

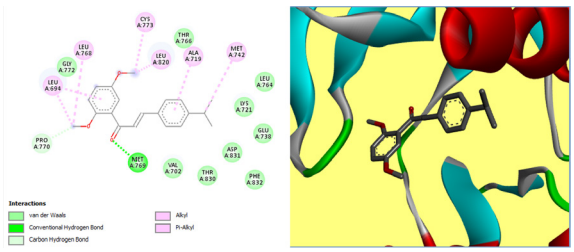
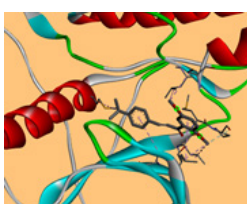


Figure 7. 2D and 3D binding interactions of compound 7 inside 1M17 active site.

synthesized as a reference drug and whose cancer activity is known, was re-docked for comparison. Metochalcone, as seen in Fig. 7, has conventional hydrogen bond to MET769 with the binding lengths 4.48 Å. The π-alkyl interactions existed between VAL702, ALA719, LYS721, and LEU820 amino acids and phenyl ring with 6.04 Å, 5.22 Å, 6.38 Å and 5.70 Å bond lengths, respectively. Alkyl interactions were observed between LYS721 (5.23 Å), and LEU820 (5.18 Å). Also, C-H bond interactions were observed between

Table 6. Ligand-protein interactions

Molecule	Hydrogen-bonding	Hydrophobic interactions	Distances	TYPE
	MET769	-	4.51	Conventional Hydrogen Bond
	PRO770	-	4.89	C-H
	-	LEU694 ALA719	5.34 5.11	π-Alkyl
	-	MET742 LEU694 LEU768 CYS773 LEU820	5.66 4.87 5.10 4.62 5.44	Alkyl

4.87, 5.10, 4.62 and 5.44 Å bond lengths, respectively. Also, C-H bond interactions were observed between PRO770 (4.89 Å), and Van der Waals interactions were observed between GLY 772, THR776, LEU764, LYS721, GLU738, ASP831, PHE832, THR830, VAL 702. All interactions are shown in detail in Table 6.

In addition, metachalcone, which was previously GLU738 (6.26 Å), PRO770 (6.46 Å), π-sigma interaction was observed between LEU694 (4.90 Å), π-anion interaction was observed between ASP831 (7.64 Å), π-sulfur interaction was observed between CYS751 (7.52 Å), Van der Waals interactions were observed between CYS 773, GLY 772, PHE771, LEU768, THR776 THR830, PHE832. All intereactions are shown in detail in Table 7.

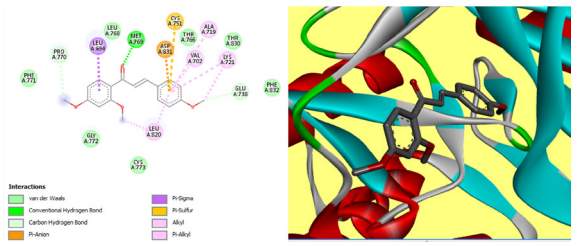


Figure 8. 2D and 3D binding interactions of Metochalcone inside 1M17 active site.

CONCLUSION

In this study, the binding affinities of chalcone derivative (5-7) compounds were evaluated according to the calculated free binding energy for EGFR. For this purpose, the molecular mapping method known in the literature was applied using metachalcone and the reference drug Erlonitib. According to the results of the analysis, the synthesized compounds (5-7) showed better binding affinity towards the target protein EGFR than the reference compound. In addition, these compounds showed pharmacokinetic compatibility according to ADME analysis. The synthesized compounds may be potent inhibitors for EGFR-mutated cancers.

Table 7. Ligand-protein interactions

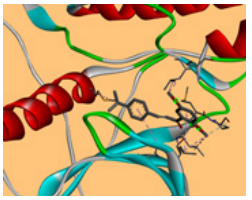
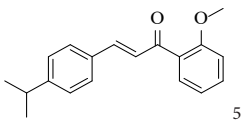
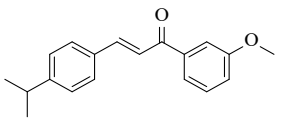
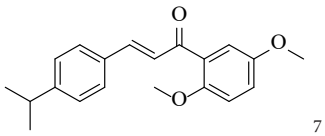
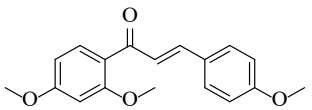
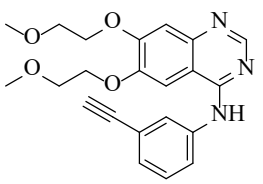
Molecule	Hydrogen-bonding	Hydrophobic interactions	Distances	TYPE
	MET769	-	4.48	Convention-al Hydrogen Bond
	GLU 738 PRO770	-	6.26 6.46	C-H
	-	LEU694	4.90	π-Sigma
	-	ASP831	7.64	π-Anion
	-	CYS751	7.52	π-Sulfur
	-	LEU820 ALA719 VAL702 LYS721	5.70 5.22 6.04 6.38	π-Alkyl
	-	LEU820 LYS721	5.18 5.23	Alkyl

Table 8. Docking scores of the tested compounds 5-7, metochalcone and reference drug (Erlotinib) with EFGR

Entry	2D structures of ligands	Docking score (Kcal/Mol)
1	 5	-7.6
2	 6	-7.38
3	 7	-7.44
4	 Metochalcone	-6.78
5	 Erlotinib	-7.0

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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