Molecular Docking Analyses of Few Chalcone Analogues In To the Ligand Binding Domain of EGFR in Search of Anticancer Agents

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Abstract:

Cancer is one of the leading cause mortality across the globe and it is public health and economic issue. Further existing agents used in treatment of cancer are known for serious undesirable effects. Hence there is urgent need of agents which will take care of cancerous pain and will exhibit minimal undesirable effects. In the present work molecular docking analyses of few chalcones in to the ligand binding domain of epidermal growth factor receptor in search of anticancer agent is reported. The 3D structures of all the 15 designed chalcone derivatives were sketched using chemsketch and geometric optimization with 1000 iteration was carried out using universal force field in Argus Lab until each ligand converged to lowest energy state and saved in .pdb format for docking process. Receptor, (Epidermal Growth Factor Receptor tyrosine kinase domain with 4-anilinoquinazoline inhibitor Erlotinib), Pdb-id: 1M17 was undertaken for the analyses. Molecular modeling and docking approaches have been implemented to compare the binding efficiency between the indigenous inhibitor Erlotinib, designed 15 chalcone derivatives with EGFR kinase.

Structure:

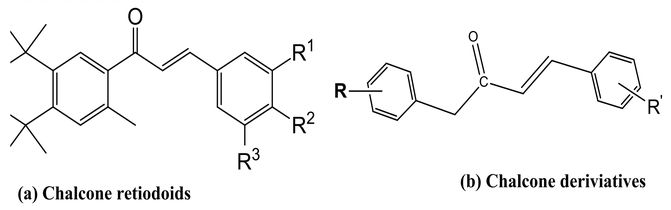


Fig.1. Structures of chalcones derivatives having anticancer activity

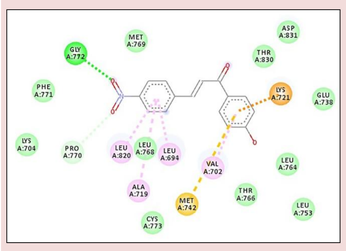


Fig 2: CHL2 - interaction with EGFR

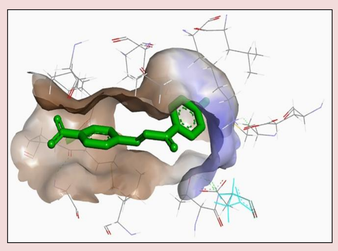


Fig 3: CHL2 – interaction with EGFR in hydrophobic cavity

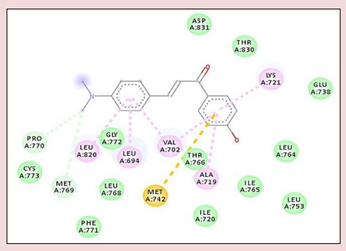


Fig 4: CHL3 - interaction with EGFR

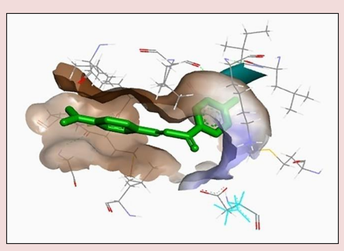


Fig 5: CHL3 – interaction with EGFR in hydrophobic cavity

Introduction

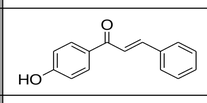
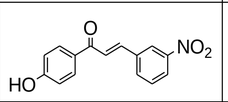
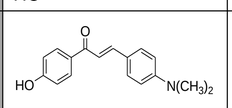
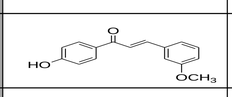
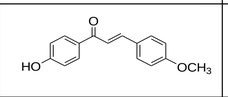
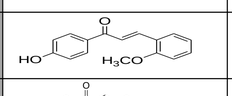
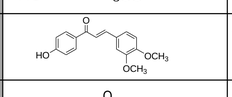
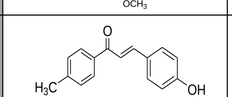
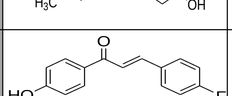
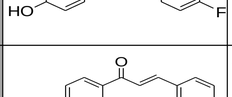
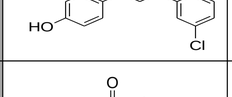
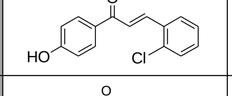
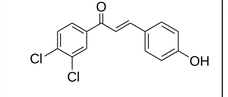
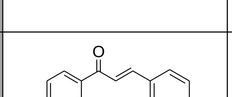
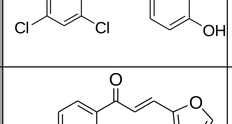
Chalcones are secondary metabolite precursors of flavonoids and isoflavonoids, which are commonly found in edible plants. These comprise one of the main classes of naturally occuring small molecules with very promising anticancer activity. There are a number of reports on the activity of chalcones against several cell lines including prostate 1 and breast cancer 2 in low nanomolar concentrations [1]. Novel compounds of chalcone- retinoids Fig. 1. (a), have been synthesized and evaluated for their cytotoxic activity against HT-29, a colon cancer cell-lines[2]. Chalcone analogues consisting of substituted benzene with groups such as methoxy, halogens, and hydroxyl, result in molecules with potent anticancer activity against colon cancer cell lines exhibiting IC_{50} value below 1µM [3]. Chalconesis a useful structural motif for displaying potent antitumor activity. Epidermal growth factor receptor is kind of protein kinases, were proved to be a viable target for anticancer drug development [4]. In addition, EGFR-TK is one of the most important kinases that plays a fundamental role in signal transduction pathways [5Peng-Cheng et al., 2010). EGFR and its ligands, epidermal growth factor (EGF) and transforming growth factor-α (TGF-α) have been implicated in numerous tumors of epithelial origin [6 Ullrich and Schlessinger, 1990).

***In-silico* modeling and docking studies:**

The 3D structures of all the 15 designed chalcone derivatives were sketched using chemsketch and geometric optimization with 1000 iteration was carried out using universal force field in Argus Lab until each ligand converged to lowest energy state and saved in .pdb format for docking process. Receptor, (Epidermal Growth Factor Receptor tyrosine kinase domain with 4-anilinoquinazoline inhibitor Erlotinib), Pdb-id: 1M17 was undertaken for the analyses. Molecular modeling and docking approaches have been implemented to compare the binding efficiency between the indigenous inhibitor Erlotinib, designed 15 chalcone derivatives with EGFR kinase of Chalcone derivative to EGFR.

At binding site region, the search space were defined to include residues of the related active sites within the grid size of X 48A˚ x Y 32A ˚ x Z 28A ˚ and center value with X 22.104A˚ x Y -0.12A ˚ x Z 53.165A ˚, water molecules and cocrystallized ligands were removed.

flexibility: no more than 9 rotatable bonds), drug likeness is calculated using Lipinski rule of five.

Ligand	Chemical Structure	Docking energy kcal/mol	Interaction with amino acids in the Ligand binding domain	
			Hydrogen bond	Pi-interaction
Erlotinib		-7.6	Met 769, Gly 772	Leu 694, Val 702, Ala 719, Lys 721, Leu 820
CHL1		-7.5	Thr 766	Phe 699, Val 702, Lys 721, Asp 831
CHL2		-7.7	Pro 770, Gly 772	Leu 694, Ala 719, Val 702, Lys 721, Met 742, Leu 820
CHL3		-7.5	Met 769, Pro 770	Leu 694, Val 702, Ala 719, Lys 721, Met 742, Leu 820
CHL4		-7.3	Thr 766	Phe 699, Val 702, Lys 721, Asp 831
CHL5		-7.5	--	Leu 694, Ala 719, Lys 721, Met 742, Leu 820
CHL6		-7.8	Glu 738	Leu 694, Lys 721, Met 742, Leu 820
CHL7		-7.2	Thr 766	Phe 699, Val 702, Lys 721, Asp 831
CHL8		-7.7	--	Phe 699, Val 702, Lys 721, Met 742, Leu 764, Asp 831
CHL9		-7.6	Met 769	Leu 694, Ala 719, Lys 721, Met 742, Leu 820
CHL10		-7.6	--	Phe 699, Val 702, Lys 721, Met 742, Asp 831
CHL11		-7.9	Met 769	Leu 694, Ala 719, Lys 721, Leu 764, Leu 820
CHL12		-7.9	--	Leu 694, Phe 699, Val 702, Ala 719, Lys 721, Met 742, Asp 931
CHL13		-7.7	Ala 719, Leu 764, Thr 766	Phe 699, Val 702, Lys 721, Asp 831
CHL14		-6.9	Lys 721, Thr 766	Phe 699, Val 702, Lys 721, Met 742, Asp 831
CHL15		-8.1	Met 769	Leu 694, Val 702, Ala 719, Lys 721, Met 742

Conclusion:

As per the study we conclude, the advancement in the computational methodologies, in the present work attempt of in-silico molecular modeling studies, molecular docking analyses and assessment of toxicity by using computational tools is reported with the hope of reducing above mentioned threats.

Key References

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2. P. Shiby, S. Nanjoo, A.M. Rimando, Synthesis and biological evaluation of chalcones as inhibitors of cancer, Bioorg. Med. Chem. Lett., 20 (2010) 7387-7392
3. S. M. Cassia, P. Shiby, S. Nanjoo, A. M. Rimando, Synthesis and biological evaluation of retinoid-chalcones as inhibitors of colon cancer cell growth, Bioorg. Med. Chem. Lett., 20 (2010) 7385–7387
4. Wu et al., 2012; Levitzki, 2012; Cheng et al., 2011). Kinases are involved expression of cancers where their overexpression can lead to different types of malignancies (Roymans and Slegers, 2001; Malumbres and Barbacid, 2007