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VIRTUAL SCREENING AND DOCKING STUDIES OF SYNTHESIZED CHALCONES: A POTENT ANTI- CANCER DRUGS

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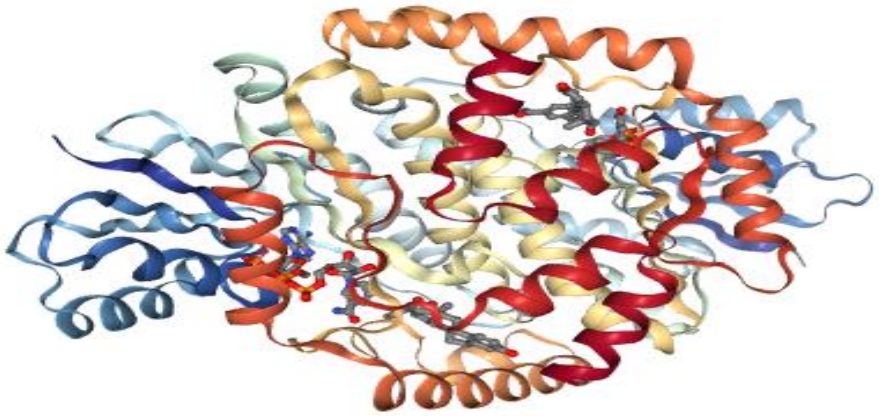
ABSTRACT

A novel series of chalcones are characterized by processing an enone moiety between two aromatic rings. The chalcone- like agents, during which the covalent bond of the enone system is embedded with in indole ring. Statistically significant structure –based qualitative structure activity relationship models were generated and validated through acceptable predictive ability to support internal and external set of compounds. Screening of most valuble drug among of pre-synthesized drug on the idea of binding efficiency to focus on receptor was administered by docking view. Molecular docking programme Glide iGEMDock was wont to determine binding feasibility of seven analogues of chalcones. The comparison of docking parameters showed, quite 5 analogues are better ligand of 3HB5. The binding of chalcones to 3HB5 is mediated by both hydrogen bonding, hydrophobic and polar interactions. Our result suggest that chalcones analogues are promising lead compounds for the event of anti-cancer drugs (mainly the brest cancer).

KEYWORDS: Chalcones, Docking, Binary And Ternary Of Novel Inhibitor Of 17 Beta-HSD, Structure Activity Relationship, Ligand, Indole, Igem Docking.



3D View of binary and ternary crystal structures of of novel inhibitor of 17 beta-HSD type 1 : lead compound for brest cancer.

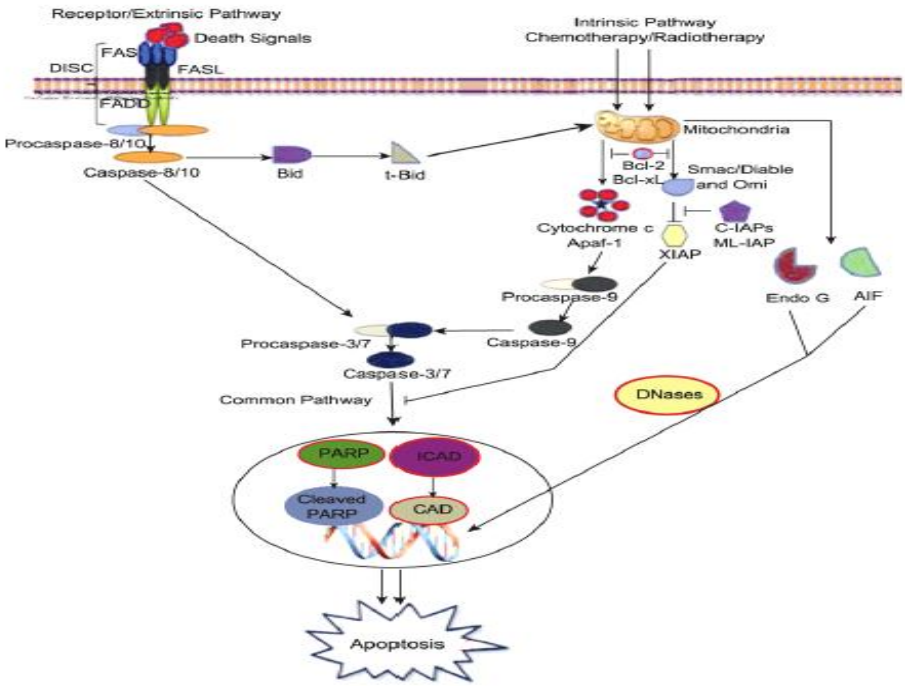
INTRODUCTION

Chalcones are an important class of natural compounds. Chalcones, or 1, 3-diaryl-2-proppen-1-ones, belong to the flavonoid family. they're precursors for flavanoid biosynthesis, which play ecological role in regard to plant color. Chemically they contains open-chain flavanoids during which the aromatic ring join by a three-carbon α, β unsaturated carbonyl system.[1,2]

Anti-cancer agents are usually evaluated for his or her ability to induce apoptosis. Indoles are verified to inhibit proliferation, expansion and invasion of human cancer cells.[3,4,5-7] Many mechanisms of apoptosis stimulation

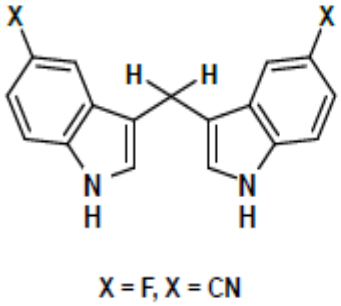
of indole derivatives, I3C and DIM, were reported for, (a): down-regulation of anti-apoptotic gene products like Bcl-2 (B-cell lymphoma 2) and Bcl-XL (B-cell leukemia-extra large), (b): down-regulation of the inhibitor of apoptosis proteins, e.g. CIAPs, X-chromoso-me linked inhibitor of apoptose protein (XIAP) and sur-vival, (c): up-regulation of pro-apoptotic factors like Bax gene, (d): liberation of mitochondrial cytochrome additionally to stimulating of caspase-9 and caspase-3[8], and (e): inhibition of the NF-kB signaling pathway.[9-14] an enormous number of diverse mechanisms of apoptosis in-duction by indoles have also been reported[15-19] Figure 1 demonstrates the extrinsic and thus the intrinsic pathways of apoptosis (programmed cell death). The Extrinsic Route: within the extrinsic pathway, signal molecules identified as ligands, which are released by the immune system's nat-ural killer cells possess the Fas ligand (FasL) on their exterior to connect to transmembrane death receptors on the target cell. After the binding of the death ligand to the death receptor the target cell triggers multiple receptors to aggregate together on the surface of the target cell. The aggregation of these receptors recruits an adaptor protein mentioned as Fas-associated death domain protein (FADD) on the cytoplasmic side of the receptors. FADD, in turn, recruits Caspase-8. Caspase-8 will then be acti-vated and may be now able to directly activate caspase-3 and caspase-7. The activation of caspase-3 will initiate the degradation of the cells.[20] The Intrinsic Route: The intrinsic pathway is triggered by cellular strain, particu-larly mitochondrial stress caused by factors like DNA damage from chemotherapy or UV exposure. Upon de-livery of the strain signal, the pro-apoptotic proteins within the cytoplasm (Bcl-2-like protein 4 (BAX) and BAX-like Bcl-2 homology domain 3 protein (BID)) bind to the outer membrane of the mitochondria to signal the discharge of the inside content.

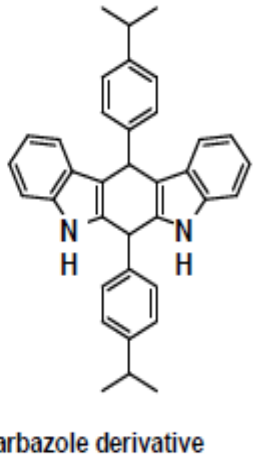
The interaction between the pro-apoptotic (BAX and BID) and the antiapoptotic proteins (Bcl-2) on the sur-face of the mitochondria is thought to be important in the formation of the PT pores in the mitochondria, and hence, the release of cytochrome c and the intramembrane con-tent from the mitochondria. Following the release, cyto-chrome c forms a multi protein complex known as apop-tosome which consists of cytochrome c, Apaf-1, procas-pase-9 and ATP. Following its formation, the complex will activate caspase-9. The activated caspase-9 will then turn the procaspase-3 and procaspase-7 into active caspase-3 and active caspase-7. These activated proteins initiate cell degradation or cell death. Besides the release of cytochrome c from the intramembrane space, the intramembrane also releases Smac/Diablo proteins to inhibit the inhibitor of apoptosis (IAP). IAP is a protein family which consists of 8-human derivatives. Their function is to stop apoptotic cell death by binding to caspase-3, caspase-7 and caspase-9 and inhibit them, the schematic representation of these pathways are shown in *Figure 1*.[21]



"Fig. 1": Intrinsic and extrinsic pathways leading to apopyosis [available from https://innspubnet.files.wordpress.com/2015/04/ mitochondrial-pathway.jpg].

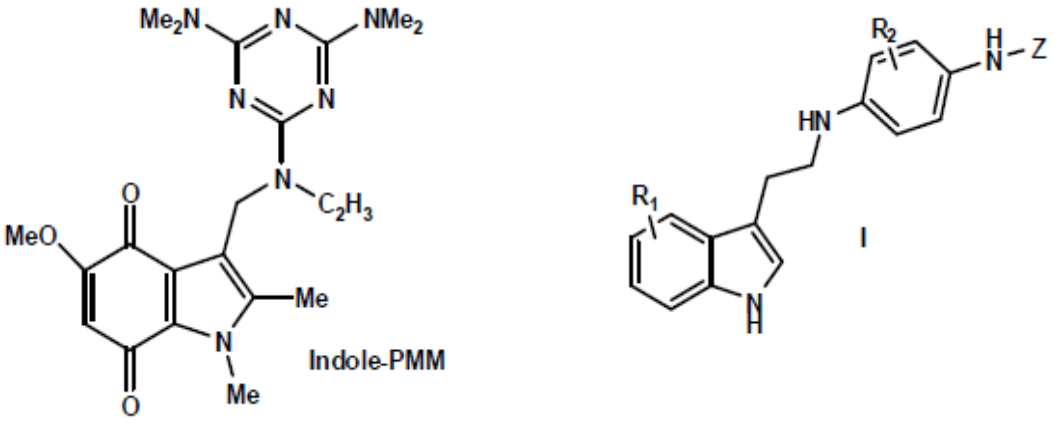
Nowadays, clinical association of human sex organ cancers requests new chemotherapeutics. In recent times, tons of hard works are done to arrange antiproliferative signaling pathway of indole-3-carbinol and its foremost indole metabolite 3, 3′-diindolylmethane (DIM).[22-28] While DIM significantly reduces the occur-rence of impulsive and carcinogen induced mammary tumor establishment (Figure 2).[29-31] It also exhibits unpleasant promoting action in convinced investigation procedure.[32,33] As a result, the choice was to seem for novel effective chemotherapeutics amongst 3, 3′-diin-dolylmethane derivatives. Moreover, the X-ray studies of 5, 5′-dimethoxy-3,3′-methanediyl-bis-indole[34] revea-led its 'butterfly' conformation, which is analogous to the one proposed earlier for inhibitors of HIV-1 polymerase, sharing the mode of action of nevirapine.[35] Other diindolylmethane derivatives and their corre-sponding tetrahydroindolocarbazoles are synthe-sized and screened for anti-cancer activity during which two compounds indicated were significantly more sensi-tive for several neoplastic cell lines like their GI50 values. the very best antipoliferative activity record-ed for the carbazole derivatives during a nanomolar scale towards the three certain cancers cell lines: non-small lung cell NCIeH460 with GI = 616 nmol/L, ovarian can-cer cell line OVCAR-4 with GI = 562 nmol/L and brea-st neoplastic cell line 50 nmol/L scale MCF7 with GI = 930 nmol/L (Figure 2).[36]





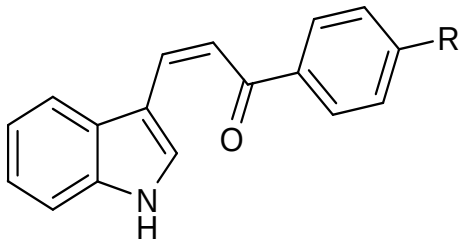
"Fig. 2": 3, 3′-diindolylmethane derivatives and tetra hydro- indolocarbazoles.

Dorota et al.[37,38] in 2005 synthesized the disubstituted diindolylmethanes flouro and cyano derivatives which decrease the expansion of MCF7 (breast), NCI–H460 (lung) and SF-268(NCS) cells, considerably 5,5′-difluoro-3,3′-methanediyl-bis-indole and 5,5′-dicyano-3, 3′-methanediyl-bis-indole were tested against the MCF7 (breast), NCI-H460 (lung) and SF-268 (CNS) tumor cell lines. The results are reported because the proportion of growth of the tested cells to untested control cells (Figure 3). F-derivative at concentration 1.10–4.00 mol/L reduces the expansion of MCF7, NCI-H460, and SF-268 cell lines to 1 / 4, 0% and 2%, whereas the CN derivative at concen-tration 5.10–5.00 mol/L to 4%, 1% and 9%, respectively. Both compounds are extremely cytotoxic in vitro to-wards those tumor lines. Their cytotoxicity indicates that they could be motivating as prospective antitumoral chemotherapeutics.[37,38] Indoles (I3C and DIM or its derivatives) are revealed to induce apoptosis in breast[39-45], squa-mous cell carcinoma[46], cholangiocarcinoma[47], colon[48-51], cervical[52], ovarian[53], pancreatic[54,55] and prostate[56-59] cancer cells. Many other indole derivatives that were reported as active anti-cancer agents as follow: the po-tential prodrug (1,2-dimethyl-3-(*N*-(4,6-bis(dimethy-lamino)-1,3,5-triazin-2-yl)-*N*-trideuteronmethylaminomethyl)-5-methoxyindole-4,7-dione), pentamethylmelamine (PMM) in which the labeled pentamethylmelamine is attached to an indole-4,7-dione moiety has attracted much interest as an anti-tumor agent for over 35 years (*Figure 3*). It entered clinics in the 1970s for the treat-ment of ovarian carcinoma but difficulties were encountered, as it was insoluble in water and thus is difficult to formulate. However, it has recently been recognized as a second-line treatment for ovarian carcinoma.[60-67,68-70]



"Fig. 3": Structure of prodrug indole-PMM derivative and tryptamine derivatives.

MATERIALS AND METHODS



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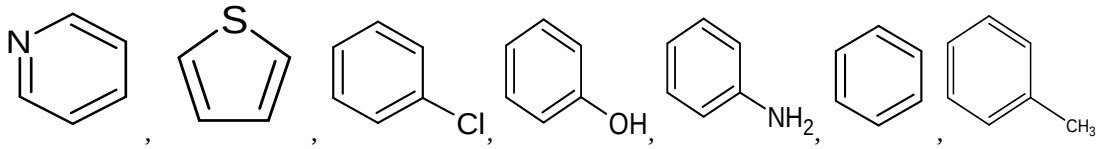

Table 1: Interaction of chalcone A1-A7 with 3HB5 (Total energy, logP, Vander Waals energy, H-bonding energy) and with different amino acids.

LIGAND	LOG P	TOTAL ENERGY	VDW	H-BOND	V-M-GLY-148	V-S-PRO-150	V-M-VAL-276	V-M-PHE-284	H-S-ASN-90	V-M-GLY-9	V-S-SER-11	V-S-ARG-37	H-S-ARG-132	V-S-ARG-76	V-M-VAL-79	H-M-THR-3	H-S-ARG-83	HS-ASP-85	H-M-SER-134	V-S-THR-3
A1	3.68	-77.37	-73.54	-3.83	-7.4	-9.6	-7.9	-4.5	0	0	0	0	0	0	0	0	0	0	0	0
A2	2.61	-79.05	-79.05	0	-4.2	-5.9	-5.4	0	0	0	0	0	0	0	0	0	0	0	0	0
A3	4.46	-79.55	-73.5	-6.05	0	0	0	0	-3.5	-8.1	-4.2	4.4	0	0	0	0	0	0	0	0
A4	3.30	-84.98	-70.69	-14.29	0	0	0	0	0	0	0	0	-3.5	-6.7	-4.6	0	0	0	0	0
A5	2.86	-83.62	-79.49	-4.12	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
A6	3.78	-76.53	-68.53	-8.01	0	0	0	0	0	0	0	0	0	0	0	0	0	-3.5	-3.2	-6.6
A7	4.23	-83.59	-79.26	-4.33	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

A1: (*Z*)-3-(1*H*-indol-3-yl)-1-(thiophen-2-yl) prop-2-en-1-one.
A2: (*Z*)-3-(1*H*-indol-3-yl)-1-(pyridin-2-yl) prop-2-en-1-one.
A3: (*Z*)-1-(4-chlorophenyl)-3-(1*H*-indol-3-yl) prop-2-en-1-one.
A4: (*Z*)-1-(4-hydroxyphenyl)-3-(1*H*-indol-3-yl) prop-2-en-1-one.
A5: (*Z*)-1-(4-aminophenyl)-3-(1*H*-indol-3-yl) prop-2-en-1-one.
A6: (*Z*)-3-(1*H*-indol-3-yl)-1-phenylprop-2-en-1-one.
A7: (*Z*)-3-(1*H*-indol-3-yl)-1-*p*-tolylprop-2-en-1-one.

EXPERIMENTAL

Compound selection and ligand preparation

All the compounds (7 compounds) were drawn on Chem Draw as in Table 1 and were optimized using MOPAC (a computational tool) using AMI calculation and closed shell restricted with RMS gradient.

Protein preparation: Bioinformatics is seen as emerging field with the potentinal to significantly improve how drugs are found, brought to the clinical trials and eventually released to the marketplace. The cystal structure of 3HB5 having PDB ID: 1MVT was take (http://www.rcsb.org/). The protein was prepared using Molegro Molecular viewer 2.5 and the same was used for the virtual drug screening.

Docking studies: Herein, iGEMDock was used for the drug screening as in table1.iGEMDock is a molecular docking tool and generates diversity of chalcones conformations from different seed with high temperature molecular dynamics. Then, it orients the chalcones conformations within the defined protein active site by translating the center of the surfactant. Each orientation is subjected to simulated annealing molecular dynamics and sorted according to the interaction energy. IGEMDOCK energy function consists of electrostatic, steric, and hydrogen- bonding potentials. Steric and hydrogen bonding potentials use a linear model. There are four main steps which are used here. Parameters used for drug screening in iGEMDOCK were as followed: initial step sizes (σ= 0.8 and ψ=0.2), family competition length (L=2), population size (N=200), and recombination probability (pc=0.3). Optimization is set to generate 70 iterations for which it generated 1200 solutions in one generation process and if exceeded then it terminated after 84,000 solutions.

Docking studies not only provide an understanding of the binding mode of the ligands but are also employed to validate homology models. The molecular models for *3HB5* were generated by Molegro Molecular Viewer 2.5 docking module. Among the docked poses for each ligand, one with the highest dock score was chosen as the final conformations. Docking allows screening a database of compounds and calculating the strongest binders based on various scoring functions. It explores ways in which two molecules, such as drugs and an enzyme, fit together and docks to each other well. The molecule may bind to receptor and modify their function. The interaction of drug and receptor complex was identified via docking and their relative stabilities were evaluated using molecular dynamics and also evaluated their binding affinities using free energy simulations.

RESULTS AND DISCUSSION

Docking studies are used extensively in drug discovery such as in the prediction of ligand-receptor complex structures and also to rank the ligand molecules based upon the binding energies of the corresponding ligand-enzyme complex. The objective of our docking study is to elucidate the potential interaction mode of the chalcones with 3HB5. A general conclusion derived from these docking results is that the side chain of the VAL and TYR forms hydrogen bonding with the chalcone, The details mentioned in Table 1. Interestingly, this interaction is almost conserved with all studied inhibitors. The docking calculations provided us with a general static picture of the most energetically favourable binding orientation of inhibitors to the enzyme. To obtain further insight into the dynamic changes of the docked inhibitors within the enzyme active site pocket over time, the lowest energy docked complex of the most active inhibitor, 7, was subjected to unconstrained MD simulations. The standard drug Lichochalone A and the logP value of A3 and Lichochalone A are found similar.

CONCLUSION

The continued development of novel anti-cancer chemotherapies, particularly those aimed toward new pathways, is important for the successful treatment of cancer as resistance to presently utilized drugs becomes more widespread. Unlike its human host, the cancer parasite doesn't possess a salvage pathway for indole and must believe de novo biosynthesis for its metabolic needs.

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