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Identification of chalcone derivatives as putative non-steroidal aromatase inhibitors potentially useful against breast cancer by molecular docking and ADME prediction

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Aromatase is an influential target to overcome estrogen receptor positive breast cancer, as the enzyme is responsible for conversion of androstenedione to estrone, a promising drug target for therapeutic management of breast cancer. Chalcones are prominent biosynthetic compounds and parent candidate for the synthesis of heterocycles with diversified biological activities. The prime objective of the present study is to evaluate the binding interaction of 2-hydroxyphenyl- prop-2-en-1-one (1A-1X), 2-hydroxy-4-methoxyphenyl- prop-2-en-1-one (3A-3X), 2,4-dihydroxyphenyl- prop-2-en-1-one (9A-9X) and 1-hydroxynaphthalen-2-yl-prop-2-en-1-one (5A-5X) derivatives with aromatase enzyme by molecular docking study and also check their ADME properties by maestro suit. The designed chalcones derivatives have been docked against our target protein with PDB id 3S7S retrieved from the protein data bank, whereas exemestane has been taken as the positive control. As docking data revealed that docking score of 1K, 1U, 1B 3K 3N, 5K, 5U, 9S, 9K, 9N and 9F compounds found less than exemestane and all of these compounds with appropriate ADME properties have proven their excellent absorption as well as solubility characteristics. The present findings provided valuable information about binding interactions of chalcones derivatives to the active site of aromatase. These compounds may serve as potential lead compound for developing new aromatase inhibitors in breast cancer treatment.

Keywords: Aromatase, molecular docking, chalcones, breast cancer, ADME

As per WHO database of developing and developed countries, breast cancer is the second leading cause of cancer death in women. About two-thirds of breast cancers are termed hormone-dependent breast cancer, which contains estrogen receptors (ER) and requires estrogen for tumour growth[1]. Aromatase is cytochrome P450 enzyme, responsible for the *in situ* biosynthesis of estrogen by converting the androgens including androstenedione and testosterone to the estrogen products, estrone and estradiol, respectively[2]. This enzyme is involved in the last step of the biosynthesis of estrogen from androgen and it is a potential target for reducing the level of estrogen in women and hence, prevent the estrogen dependent breast cancer[3] (Figure 1). Currently, there are two types of aromatase inhibitors which are available in market, namely type I (steroidal) and type II (non-steroidal). The type I agents are either competitive inhibitors which are structurally related to the substrate or suicide inhibitors derived from androstenedione like 4-OHA or Exemestane. The type II agents behave as competitive inhibitors, coordinating one of their heteroatoms (N, S, and O) to the iron in the heme of the cytochrome[4,5]. The list of marketed aromatase inhibitors as per their generation based on clinical development is listed in Table I[6].

Chemically, chalcones or (E)-1,3-diphenyl-2-propene-1-one are α, β- unsaturated carbonyl compounds[7]. Being a precursor of all of the other flavonoid groups, chalcones are very important biosynthetic compounds. Chalcones are also key precursors in the synthesis of many biologically important heterocycles such as benzothiazepine, pyrazolines, 1,4-diketones, and flavones[8]. Chalcone scaffold remained an obsession among researchers

List of Abbreviations: ADME/T: Absorption, Distribution, Metabolism, Excretion and Toxicity; PDB: Protein Data Bank; HEM(FE): Heme coordinating group; OPLS: Optimized Potentials for Liquid Simulations; RMSD: Root Mean Square Deviation; LRoF: Lipinski' rule of five

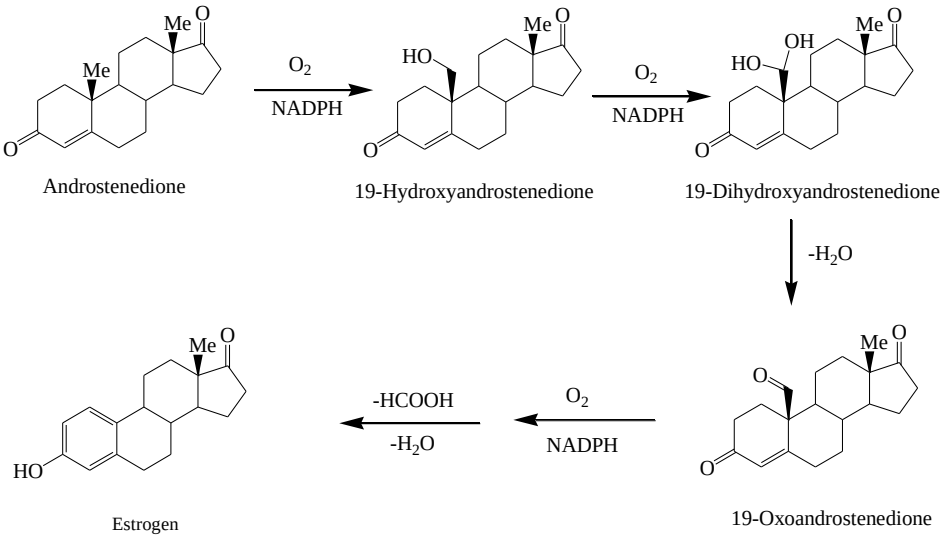


Figure 1 — Reaction mechanism for estrogen biosynthesis by aromatase enzyme

Table I — List of marketed aromatase precursors

Generation	Type-I Inhibitors (Steroidal)	Type-II Inhibitors (Non-steroidal)
First	Testolactone	Aminoglutethimide
Second	Formestane	Fadrozole
		Rogletimide
Third	Exemestane	Vorozole
		Anastrozole
		Letrozole

in the 21st century due to its simple chemistry, flexible structure, ease of synthesis and exhibiting broad spectrum biological activities like antimicrobial[9-15], antimalarial[16,17], anti-HIV[18-20], antileishmanial[21,22], antitubercular[23,24], antioxidant[25,26], Antihyperglycemic[27], immunosuppressive property[28], anti-inflammatory[29], estrogenic and anti-proliferative[30], antihelmintic[31], analgesic[32], antiulcer[33] including anticancer activity through multiple mechanisms thus comprise a class with important therapeutic potential. Several natural and (semi) synthetic chalcones have shown anti-cancer activity due to their inhibitory potential against various targets namely mTOR[34], aromatase and 17-β-hydroxysteroid dehydrogenase[35], 5α-reductase[36-38], ABCG2/P-gp/BCRP[39], topoisomerase-II[40], HDAC/Situin-1[41], cathepsin-K[42], proteasome[43], VEGF, VEGFR-2 kinase[44], B-Raf[45], NF-κB[46], JAK/STAT signaling pathways[47], CDC25B[48], and tubulin[49], *etc*. Chalcones have poor interaction with DNA and low risk of mutagenicity, while other anticancer drugs reported genotoxicity due to their interaction with amino groups in nucleic acids. In this regard, chalcones may be devoid of these side effects due to their structural flexibility[50].

Literature review on anticancer potency of chalcone highlights structural manipulation of both aryl rings and replacement of aryl rings with heteroaryl scaffolds. Methoxy (-OCH_3) and hydroxy (-OH) substitutions on both the aryl rings (A and B) of the chalcones, depending upon their positions in the aryl rings appear to influence anticancer and other activities. Similarly, heterocyclic rings replaced with ring B in chalcones, also influence the anticancer activity shown by this class of compounds. Moreover, chalcones have structural similarities with estrogen and it is a precursor for the synthesis of flavonoids. As per shown in Figure 2, A and C rings of flavone and A ring of chalcone, its unsaturated keto (-C=O) group mimics the action of C and D rings of steroidal substrate of Type –II steroidal aromatase inhibitors[51-53].

Based on the above extensive literature review and various structural activity relationship of chalcone derivatives, various benzaldehyde and acetophenone derivatives are proposed for docking and *in silico* ADME study. The list of various acetophenone and benzaldehyde are summarized in Figure 3. So, the aim of the present study is to investigate the binding affinity of various chalcone derivatives on aromatase enzyme by molecular docking studies and compounds exhibiting good binding affinity are further checked for the ADME/T (drug likeness) properties by using Maestro 10.4, Schrodinger program. The successful application of docking and ADMET properties will result into discovering of novel and potential anticancer agents based on chalcone scaffold, which reduce the blood estrogen level by inhibiting aromatase enzyme in the treatment of breast cancer.

Materials and Methods

Retrieval of the 3-D structure of target proteins

The crystal structure of human placental aromatase enzyme with PDB id 3S7S was retrieved from the protein data bank. The X-ray structure of protein contains aromatase enzyme complexed with exemestane as a ligand, the 3rd generation steroidal aromatase inhibitor and Cytochrome P450 19A1 protein with Protoporphyrin IX containing HEM (FE) as a nonstandard residues[54].

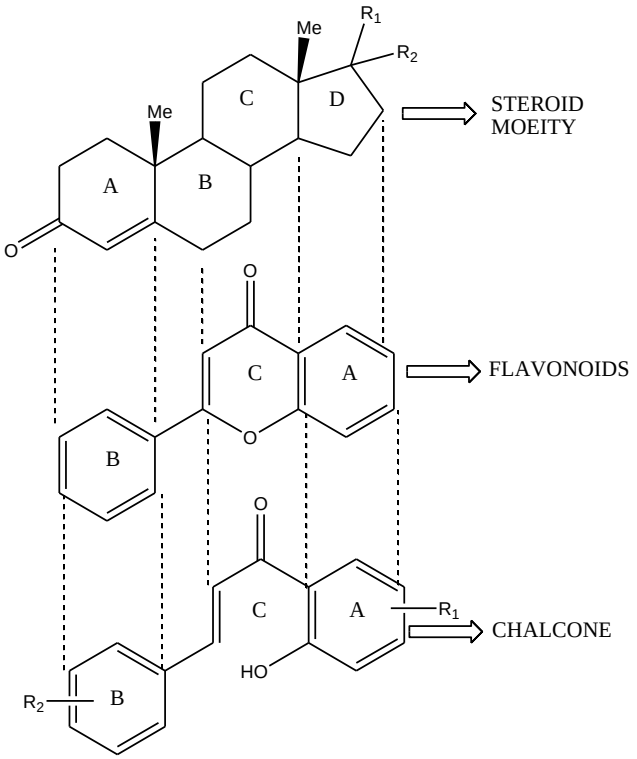


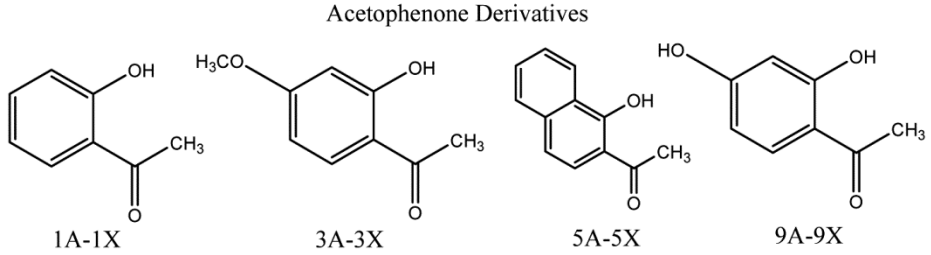
Figure 2 — Chalcone moiety mimics the action of steroidal substrate and flavones

Protein Preparation

The crystal structure of aromatase enzyme was imported and constructed by a multistep process through the protein preparation wizard of Maestro (version 10.4, Schrodinger, LLC, New York, NY). The integrity protein structure was checked and missing residues/loop segments near the binding site were added using the prime program of maestro. For obtaining optimized and minimized energy conformation of the protein, hydrogen atoms were added and water molecules within 5A° periphery of the co-crystallized ligand were removed. The protonation states of entire system was maintained to *p*H range of 7.0 ± 2.0 using Epik v3.4 and the geometry optimization was performed to a maximum RMSD of 0.3 A° with the OPLS 2005 force field[55-57].

Ligand Preparation

Chemdraw was used to draw the structure of chalcones derivatives. Further their energy was minimized by MOPAC program of Chem3D ultra-software of Chemoffice, and single low energy 3D conformer with acceptable bond lengths and angles for each 2D structure was generated. Ligand structures were submitted to the energy minimization using the OPLS force field until the energy difference between subsequent structures was 0.001 kJ/molA.



Aldehyde Derivatives

A. Verataldehyde
B. 3 Hydroxy Benzaldehyde
C. 4 Methoxy Benzaldehyde
D. 4 Chloro Benzaldehyde
E. 4 Fluoro Benzaldehyde
F. 3 Chloro Benzaldehyde
G. 3 Methoxy Benzaldehyde
H. Pyrolle 2 - Carboxyldehyde
I. Pyridine 2 Carboxyldehyde
J. Pyridine 3 Carboxyldehyde
K. Pyridine 4 Carboxyldehyde
L. Cinnamaldehyde
M. 2,4,6 tri methoxy Benzaldehyde
N. 2,3 Dimethoxy Benzaldehyde
O. 4- Ethoxy 3 Methoxy Benzaldehyde
P. 2,4 Dimethoxy Benzaldehyde
Q. 4 Bromo Benzaldehyde
R. Benzaldehyde
S. 3 Bromo Benzaldehyde
T. 2,4 Dihydroxy Benzaldehyde
U. 3,4 Dihydroxy Benzaldehyde
V. 2-Imidazolecarboxaldehyde
W. 4-Imidazolecarboxaldehyde
X. 1-Methyl-2-imidazolecarboxaldehyde

Figure 3 — Selection of various chalcone derivatives for docking studies

The final ligand databases were in the mol2 format (3D structures). All possible tautomers of ligands by maintaining their stereochemistry were explored using LigPrep software, and it produced multiple conformations using confgen. Moreover, ligand ionization states were also generated by using Epik 3.4 software.

Molecular Docking Study

The Glide program was used to predict the binding affinity between the designed chalcones derivatives and the active site of aromatase enzyme. During docking study, the receptor grid generation file was used, and it was defined as an enclosing box at the centroid of the co-crystallized ligand (*i.e*., 3S7S) to include the cofactor and substrate binding sites. The protein structure having a grid box of 30×30×30 Å with a default inner box (10×10×10 Å) which was centred on the corresponding ligand. The LigPrep treated ligands were carried out to predict the binding pocket of protein 3S7S using the docking program. Initially, a soften potential docking with the van der waals radii scaling of 0.7 for the proteins was performed to retain the maximum number of 32 poses per ligand and residues within 5.0 Å of ligand poses were kept free to move in the Prime refinement step. Successively, single low energy 3D structure of ligands with correct chirality were docked with the binding site using the "extra precision (XP)" which uses MCSA (Monte Carlo Based Simulated Algorithm) based minimization. The best docked pose (with lowest G-score value) were obtained from Glide and analysed[55-58].

ADME Property Prediction and Analysis

The QikProp program was used to access the drug-like properties of all designed analogues. The software provided the ranges for comparing particular molecule properties with those of 95% of known drugs. The Lipinski's rule of five (LRoF) and Veber's rule were used to evaluate the acceptability of analogues and ensured the drug likeness properties, while performing rational drug design approach. Varied physicochemical descriptors as well as pharmaceutically important properties of chalcones derivatives were analysed. The prominent descriptors, which predict drug likeness properties of designed analogues, were reported. The H-bond Donor and acceptor, predicted water/gas partition and octanol/water coefficients, predicted aqueous solubility descriptors were considered to analyze the result[59,60].

Result and Discussions

The docking score with binding energy and their corresponding intermolecular energy, electrostatic energy, hydrogen bonding and hydrophobic interaction for each class of flavonoids with aromatase enzyme (PDB ID: 3S7S) are given in Table II-V. Figure 4 shows the interaction of Exemestane (steroidal aromatase inhibitor) with aromatase enzyme. The *in silico* predicted active sites for target protein (PDB ID: 3S7S) were MET374, ARG115, LEU372, LEU477, PHE134, VAL370,THR310, PHE221, VAL369, ASH309, SER478, ALA309, ALA306, TRP224, ILE305, HEM600, VAL373 The keto (-C=O) exemestane was interacted with MET 374 by H- bonding interaction.

Docking analysis of 2-hydroxyphenyl- prop-2-en-1-one (1A-1X)

The 2-hydroxyphenyl- prop-2-en-1-one (1A-1X) derivative's binding energy were in the range ~ -9.166 to -5.069 kcal/mol (Table II). Amongst them, chalcone (1K, 1U, 1B) derivatives possessed lowest binding energy than selected ligand (Exemestane). Figure 5(A) has shown the binding interactions of 1B with aromatase enzyme like H- bonding with LEU 372 and π- π stacking with ARG 115 and HEM 600. In 1K derivative, where ring's **"N"** atom exhibits the H-bonding interaction with MET 374 and -OH (hydroxyl group) with ASH 309, where π- π stacking with ARG 115 [Figure 5(B)]. While 1U

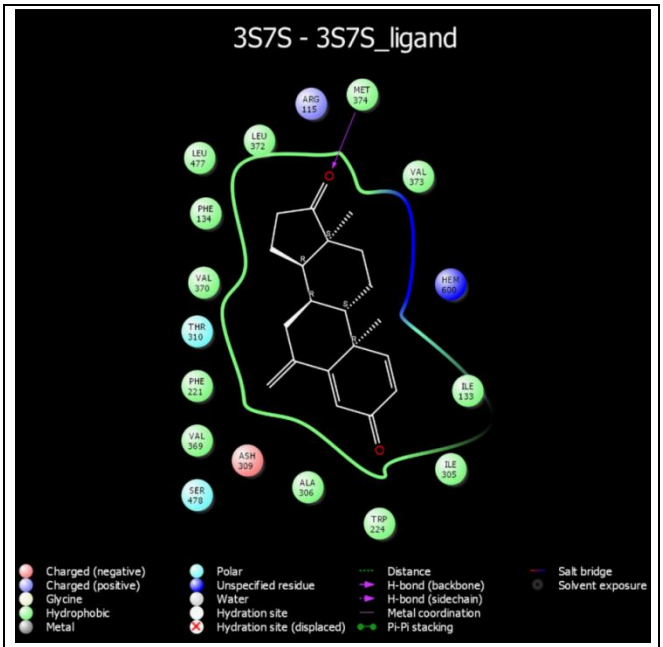
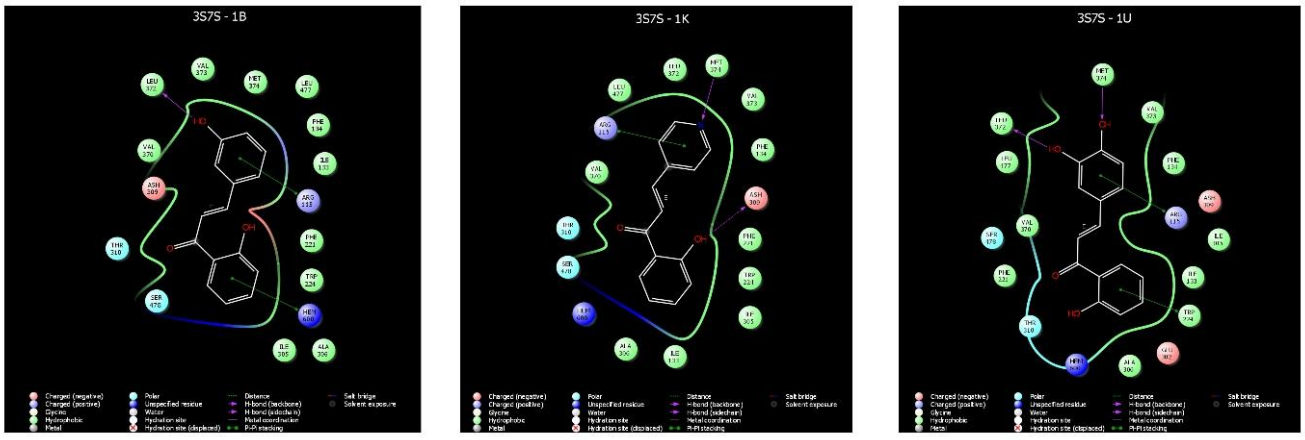


Figure 4 — Interaction of Exemestane with aromatase enzyme

Table II — Docking result of 2-hydroxyphenyl- prop-2-en-1-one (1A-1X) derivatives

Sr. No	Compd	Docking score	Glide energy	Glide emodel	XP HBond	XP PhobEn	XP Electro
1	1K	−9.166	−39.084	−57.379	−0.869	−0.918	−0.375
2	1U	−8.944	−39.422	−56.312	−1.564	−0.875	−0.561
3	1B	−8.285	−39.549	−54.571	−1.158	−0.826	−0.317
4	1S	−7.799	−38.848	−48.897	−0.96	−0.71	−0.375
5	1T	−7.664	−40.169	−53.543	−0.673	−0.671	−0.4
6	1M	−7.501	−34.006	2.971	−0.447	−0.35	−0.259
7	1Q	−7.428	−11.434	−23.659	−0.748	−1.574	−0.27
8	1F	−7.374	−32.866	−49.068	−0.96	−0.631	−0.356
9	1N	−7.37	−39.891	−50.234	0	−0.575	−0.184
10	1J	−7.297	−37.949	−54.489	−0.96	−0.705	−0.404
11	1R	−7.29	−37.781	−52.63	−0.96	−0.413	−0.359
12	1G	−7.207	−37.506	−49.288	−0.96	−0.698	−0.319
13	1I	−7.027	−37.336	−52.955	−0.96	−0.8	−0.377
14	1H	−6.921	−33.236	−49.682	−0.96	−0.8	−0.301
15	1O	−6.846	−25.365	9.938	−1.18	−0.125	−0.243
16	1W	−6.837	−37.047	−53.207	−1.553	−0.574	−0.26
17	1P	−6.803	−35.777	−44.156	−0.48	−0.553	−0.031
18	1V	−6.733	−38.003	−56.548	−0.96	−0.641	−0.427
19	1X	−6.489	−35.413	−54.344	−0.96	−0.927	−0.394
20	1E	−6.464	−30.791	−49.365	−0.96	0	−0.21
21	1A	−6.452	−26.032	−31.471	−0.48	−0.427	−0.026
22	1C	−6.35	−36.842	−29.267	−1.045	0	−0.294
23	1D	−6.275	−29.079	−40.706	−0.48	−1.072	−0.181
24	1L	−5.069	−26.98	−28.646	0	0	0.063
25	EXE	−8.354	−45.954	−41.842	−0.7	−0.657	−0.204



(A) (B) (C)

Figure 5 — (A) Interaction of 2-hydroxyphenyl- prop-2-en-1-one derivative (1B) with aromatase enzyme; (B) Interaction of 2-hydroxyphenyl- prop-2-en-1-one derivative (1K) with aromatase enzyme; (C) Interaction of 2-hydroxyphenyl- prop-2-en-1-one derivative 1U) with aromatase enzyme

derivatives -OH (hydroxyl group) interact with MET 374/ LEU 372 and π- π stacking with ARG 115 and TRP 224 [Figure 5(C)]. Other derivatives like 1S, 1T, 1M, 1Q, 1F, 1N, 1J, 1R, 1G, 1I and 1H also possessed significantly good binding energy compared to ligand.

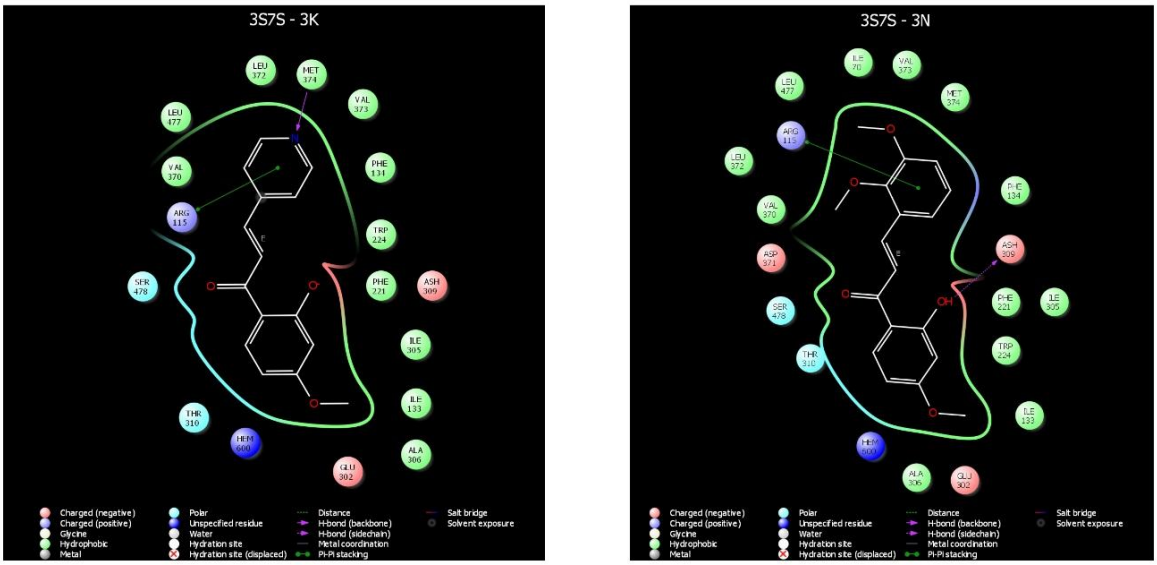
Docking analysis of 2-hydroxy-4-Methoxyphenyl-prop-2-en-1-one (3A-3X) derivatives

The 2-hydroxy-4-Methoxyphenyl- prop-2-en-1-one (3A-3X) derivative's binding energy were in the range ~ –8.893 to -4.463 kcal/mol (Table III). Amongst them chalcone 3K and 3N derivatives

possessed lowest binding energy than selected ligand (Exemestane). Figure 6(A,B) shows the binding interaction of 3K/3N with various amino acids of aromatase enzyme. In 3K derivative, where ring's **"N"** atom exhibits the H-bonding interaction with MET 374 where π- π stacking was observed with ARG 115. While in 3N derivatives, -OH (hydroxyl group) interacted with ASH 309 and π- π stacking was

Table III — Docking result of 2-hydroxy-4-Methoxyphenyl- prop-2-en-1-one (3A-3X) derivatives

Sr. No	Compd	Docking score	Glide energy	Glide emodel	XP HBond	XP PhobEn	XP Electro
1	3K	−8.893	−43.473	−63.109	−1.061	0	−0.279
2	3N	−8.535	−41.57	−24.641	−0.48	−0.798	−0.093
3	3W	−8.066	−40.558	−60.153	−1.163	0	−0.24
4	3P	−8.057	−26.293	67.948	−1.435	−0.751	−0.491
5	3G	−7.995	−36.659	−38.81	−1.484	−0.713	−0.378
6	3M	−7.885	−39.255	−48.938	−1.18	−0.125	−0.456
7	3J	−7.867	−38.228	−42.992	−1.459	−0.718	−0.414
8	3T	−7.802	−38.58	−38.385	−0.858	−0.791	−0.418
9	3U	−7.795	−38.083	−47.586	−0.696	−0.95	−0.251
10	3I	−7.291	−34.667	−43.591	−1.159	−0.663	−0.316
11	3H	−7.204	−37.457	−50.856	−0.887	−0.657	−0.395
12	3X	−7.203	−36.701	−49.346	−1.362	−0.777	−0.37
13	3V	−7.061	−37.447	−54.622	−0.975	−0.775	−0.436
14	3A	−6.855	−25.407	6.665	−0.96	−0.125	−0.278
15	3S	−6.751	−32.533	−33.415	−0.96	0	−0.032
16	3F	−6.264	−25.899	−34.494	−0.96	−0.05	0.008
17	3C	−6.201	−17.81	26.203	−0.96	−0.251	−0.113
18	3L	−6.023	−30.021	−25.431	−0.48	0	0.11
19	3E	−5.99	−32.326	−36.87	−0.48	−0.05	0.096
20	3R	−5.932	−31.133	−51.06	−0.645	−0.025	−0.006
21	3O	−5.805	−25.289	−13.223	−0.99	0	−0.133
22	3B	−5.364	−41.451	−58.927	−0.7	0	−0.351
23	3Q	−4.652	−13.003	11.789	−0.48	0	0.045
24	3D	−4.463	−18.129	−6.353	−0.943	0	−0.157
25	EXE	−8.354	−45.954	−41.842	−0.7	−0.657	−0.204



(A) **(B)**

Figure 6 — (A) Interaction of 2-hydroxy-4-Methoxyphenyl- prop-2-en-1-one derivative (3K) with aromatase enzyme; (B) Interaction of 2-hydroxy-4-Methoxyphenyl- prop-2-en-1-one derivative (3N) with aromatase enzyme

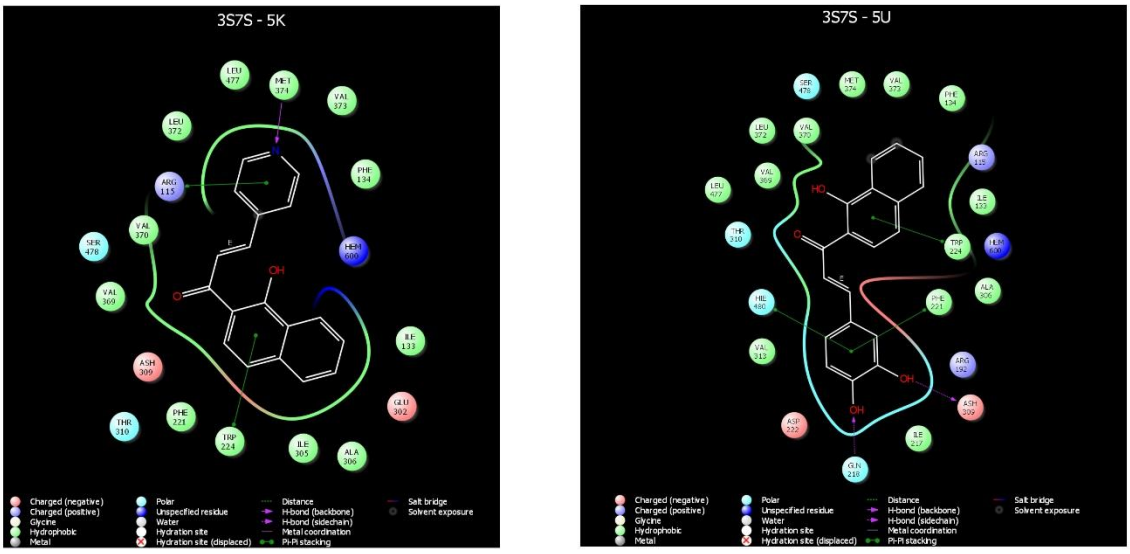
observed with ARG 115. Other derivatives like 3W, 3P, 3G, 3M, 3T, 3U, 3I, 3H, 3X also possessed significantly good binding energy compared to ligand.

Docking analysis of 1- hydroxynaphthalen-2-yl-prop-2-en-1-one (5A-5X) derivatives

The 1- hydroxynaphthalen-2-yl-prop-2-en-1-one (5A-5X) derivative's binding energy were in the range ~ -9.915 to -4.228 kcal/mol.(Table IV) Amongst them, chalcone 5K and 5U derivatives possessed lowest binding energy than selected ligand (Exemestane). Figure 7(A,B) was shown the binding interactions of 5K/5U with various amino acids of aromatase enzyme. In 5K derivative, where ring's **"N"** atom exhibits the H-bonding interaction with MET 374 where π- π stacking observed with ARG 115 and TRP224. While

Table IV — Docking result of 1- hydroxynaphthalen-2-yl-prop-2-en-1-one (5A-5X) derivatives

Sr. No	Compd	Docking score	Glide energy	Glide emodel	XP HBond	XP PhobEn	XP Electro
1	5K	−9.195	−34.986	−33.108	−0.7	0	−0.476
2	5U	−8.867	−31.148	−14.617	−1.855	−0.802	−0.408
3	5T	−8.224	−23.603	8.202	−0.7	−0.833	−0.456
4	5W	−7.915	−29.375	−47.162	−0.7	−0.135	−0.213
5	5S	−7.615	−31.033	−25.228	−0.48	−0.793	−0.136
6	5A	−7.421	−29.736	−6.404	−0.987	−0.61	−0.227
7	5E	−7.305	−24.971	−16.924	−0.48	−0.914	−0.189
8	5D	−7.07	−22.831	4.393	−0.48	−0.817	−0.223
9	5X	−6.985	−34.279	−41.778	−0.48	0	−0.055
10	5P	−6.911	−15.901	10.788	−0.48	0	−0.072
11	5J	−6.884	−27.727	−18.321	−0.48	−0.717	−0.143
12	5F	−6.783	−23.192	−9.686	−0.48	−0.913	−0.173
13	5V	−6.679	−31.907	−39.85	−0.48	0	−0.033
14	5I	−6.671	−27.071	−18.945	−0.48	−0.688	−0.05
15	5H	−6.669	−27.25	−24.207	−0.48	−0.774	−0.104
16	5Q	−6.361	−9.706	17.211	−0.48	−1.001	−0.153
17	5B	−6.359	−33.857	−27.482	−1.18	0	−0.45
18	5L	−6.168	−30.459	−27.682	−0.48	−0.556	−0.091
19	5M	−5.727	−13.027	16.102	−0.48	0	−0.121
20	5R	−5.656	−30.696	−15.427	−0.48	0	−0.101
21	5N	−5.591	−26.783	1.094	−0.72	0	−0.08
22	5G	−5.402	−26.038	5.544	−0.48	0	−0.183
23	5C	−4.228	−16.019	11.755	0	0	−0.046
24	5K	−9.195	−34.986	−33.108	−0.7	0	−0.476
25	EXE	−8.354	−45.954	−41.842	−0.7	−0.657	−0.204



(A) **(B)**

Figure 7 — (A) Interaction of 1- hydroxynaphthalen-2-yl-prop-2-en-1-one derivative (5K) with aromatase enzyme; (B) Interaction of 1-hydroxynaphthalen-2-yl-prop-2-en-1-one derivative (5U) with aromatase enzyme

in 5U derivatives -OH (hydroxyl group) interacted with GLN 218/ASH 309 and π- π stacking was observed with HIE 480, PHE 221 and TRP224. Other derivatives like 5T, 5W, 5S, 5A, 5E and 5D also possessed significantly good binding energy compared to ligand.

Docking analysis of 2, 4-dihydroxyphenyl- prop-2-en-1-one (9A-9X) derivatives

The 2, 4-dihydroxyphenyl- prop-2-en-1-one (9A-9X) derivative's binding energy were in the range ~ -8.649 to -4.485 kcal/mol.(Table V) Amongst them chalcone 9S, 9K, 9N and 9F derivatives possessed lowest binding energy than selected ligand (Exemestane). Figure 8 has shown the binding interactions of 9S, 9K, 9N and 9F with various amino acids of aromatase enzyme. The 9K derivative's hydroxyl (-OH) group exhibits the H-bonding interaction with ALA 306 and pyridine ring's "N" atom exhibit H- bonding interaction with MET374 where π- π stacking observed with PHE 134 and

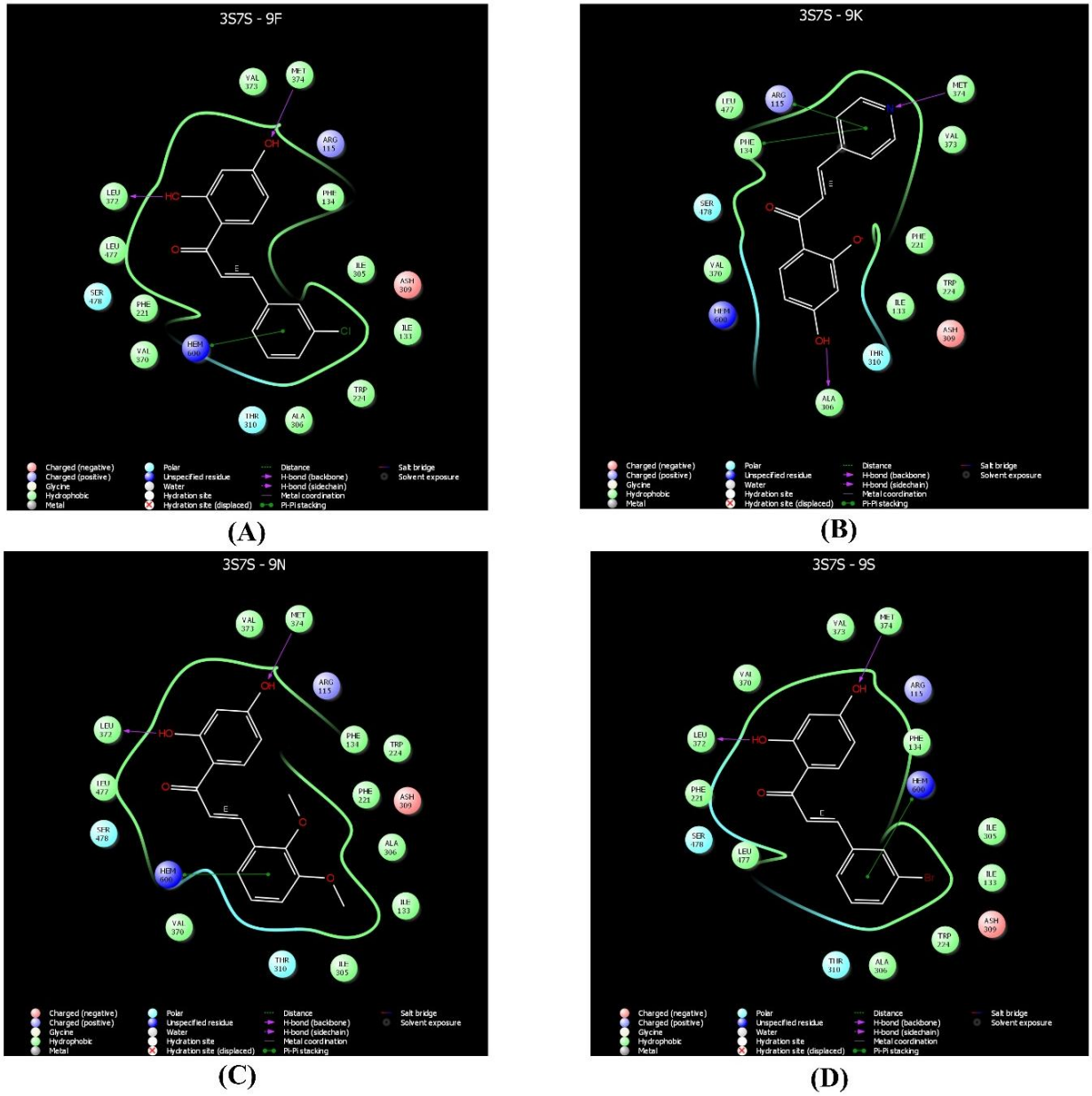


Figure 8 — (A) Interaction of 2, 4-dihydroxyphenyl- prop-2-en-1-one derivative (9F) with aromatase enzyme; (B) Interaction of 2, 4-dihydroxyphenyl- prop-2-en-1-one derivative (9K) with aromatase enzyme; (C) Interaction of 2, 4-dihydroxyphenyl- prop-2-en-1-one derivative (9N) with aromatase enzyme; (D) Interaction of 2, 4-dihydroxyphenyl- prop-2-en-1-one derivative (9S) with aromatase enzyme

Table V — Docking result of 2, 4-dihydroxyphenyl- prop-2-en-1-one (9A-9X) derivatives

Sr. No	Compd	Docking score	Glide energy	Glide emodel	XP HBond	XP PhobEn	XP Electro
1	9S	−8.649	−41.966	−49.757	−1.625	−0.766	−0.542
2	9K	−8.601	−38.436	−58.602	−1.616	−0.579	−0.296
3	9N	−8.506	−39.916	−55.841	−1.625	−0.663	−0.582
4	9F	−8.444	−39.905	−49.629	−1.568	−0.694	−0.531
5	9R	−8.303	−41.397	−59.654	−1.625	−0.583	−0.557
6	9I	−7.905	−42.777	−56.426	−1.625	−0.479	−0.593
7	9U	−7.834	−43.362	−61.629	−1.74	−0.596	−0.599
8	9G	−7.728	−39.929	−50.354	−1.625	−0.3	−0.512
9	9E	−7.5	−29.25	−46.62	−1.357	−0.696	−0.252
10	9X	−7.436	−43.429	−66.143	−1.625	−0.371	−0.597
11	9B	−7.432	−38.844	−57.954	−1.625	−0.284	−0.491
12	9T	−7.424	−37.56	−51.439	−0.7	−0.784	−0.334
13	9V	−7.419	−42.882	−64.921	−1.625	−0.618	−0.59
14	9H	−7.372	−39.489	−58.58	−1.625	−0.428	−0.474
15	9M	−7.116	−39.255	−48.938	−1.18	−0.125	−0.456
16	9W	−7.009	−42.409	−64.099	−1.625	−0.569	−0.565
17	9P	−6.966	−33.299	−35.295	−1.18	−0.45	−0.232
18	9D	−6.288	−29.733	−28.403	−0.424	−1.165	−0.115
19	9C	−6.163	−32.747	−33.097	−1.18	0	−0.49
20	9L	−6.049	−25.321	−28.771	−1.18	−0.275	−0.264
21	9Q	−5.943	−23.781	−21.677	−0.192	−1.211	−0.089
22	9A	−5.486	−33.328	−33.739	−0.7	0	−0.225
23	9O	−4.594	−26.048	3.568	−0.028	−0.05	−0.058
24	9J	−4.485	−32.177	−47.226	−0.813	−0.025	0.086
25	EXE	−8.354	−45.954	−41.842	−0.7	−0.657	−0.204

Table VI — *In silico* predicted ADME/T properties of Chalcone Derivatives by using *QikProp*

Compd	H-Bond Donor	H-Bond Acceptor	QPlogPoct (8.0-43.0)*	QPlogPw (5.0-48.0)*	QPlogPo/w (−2.0-6.0)*	QPlogS (−6.0-0.5)*
1K	0	3.25	10.854	6.052	2.48	−2.671
1U	2	3.25	14.137	8.763	2.034	−2.919
1B	1	2.5	12.123	6.687	2.69	−3.314
3K	0	4	11.665	6.287	2.449	−2.789
3N	0	4	12.627	5.454	3.566	−3.896
5K	0	3.25	12.704	6.539	3.383	−3.654
5U	2	3.25	16.329	9.52	3.117	−4.343
9S	1	2.5	12.907	6.372	3.218	−4.072
9K	1	4	13.037	8.218	1.879	−2.89
9N	1	4	13.867	7.299	2.885	−3.515
9F	1	2.5	12.787	6.4	3.179	−4.067
Exemestane	0	4	13.942	6.081	3.036	−3.747

* Standard value of properties

ARG 115 [Figure 8(B)]. In 9S/9N/9F derivatives two -OH (hydroxyl group) interacted with MET374/LEU 372 and π- π stacking was observed with HEM 600 (heme coordinating moiety) [Figure 8(A,C,D)]. Other derivatives like 9R, 9I, 9U, 9G, 9E, 9X, 9B, 9T, 9V, 9H, 9M and 9W also possessed significantly good binding energy compared to ligand.

In silico ADMET Study

All designed compounds were checked for their ADME/T properties by QikProp (*V4.6*, 2015). Among them, ADMET properties of eleven (1K, 1U, 1B, 3K, 3N, 5K, 5U, 9S, 9K, 9N, and 9F) compounds which having good docking score and binding affinity compared with standard ligand (Exemestane) are

reported in Table VI, these analogues have also shown good drug likeness properties.

Conclusion

The amino acid of enzyme and ligand interaction is important while drug designing and discovery study. In the present work; binding, interactions and drug likeness properties of chalcone derivatives with aromatase enzyme have been studied using Schrodinger software. During the study, it was observed that majority of the compounds have shown significant binding interactions with enzyme. The hydrogen bond interactions and π- π stacking also contributed to the strong binding of these compounds to the binding site of aromatase. It was observed that 3rd and 4th position "B" ring of chalcone derivatives substituted with –OH (hydroxyl), -OMe (methoxy) and Cl/Br (halogens) are important to evoke aromatase inhibition. The "N" atom of 4-pyridine derivatives (1K, 3K, 5K and 9K) were found to be interacted with MET 374 by strong H- Bonding. So, H- bonding interactions were predominant in all the classes of compounds taken for study and were found to be important for inhibition. Based on Quik Pro analysis of the all the analogues, it was proved that, those compounds having better drug like properties and following the Lipinski rule of five (LRoF).

Conflict of Interest

Authors have no conflict of interest.

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