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In Silico ADME Prediction and Molecular Docking of 1,2,3-Triazole-based Compounds Against Human Aromatase Cytochrome P450

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ABSTRACT

Objective: Inhibition of the human aromatase cytochrome P450 enzyme has been emphasized as being an efficient mechanism for reducing high estrogen levels in the treatment of breast cancer. **Methods:** Molecular docking and *in silico* ADME predictions were performed for a set of 1,2,3-triazole-based compounds aiming for the discovery of new therapeutics targeting the human aromatase cytochrome P450 enzyme. **Results:** The results showed that compounds **1-3** are capable of binding to the enzyme active site, while compounds **4-8** and **9-11** are capable of binding to the potential allosteric sites 1 and 2 of the enzyme, respectively. Furthermore, all compounds **1-7** and **9-11** were predicted to be orally bioavailable, and compounds **1-3**, **9**, and **11** were anticipated to be blood-brain barrier permeants. **Conclusion:** Most of the designed compounds possessed relatively good binding affinities to the human placental aromatase cytochrome P450 enzyme and promising *in silico* ADME-related properties for further optimization towards developing novel human aromatase inhibitors.

Keywords: *In Silico, ADME, Molecular Docking, Triazole, Aromatase Inhibitors*.

INTRODUCTION

The human aromatase enzyme belongs to the cytochrome P450 family and is a product of the CYP19A1 gene. To date, aromatase cytochrome P450 is the only known enzyme in vertebrates to catalyze the biosynthesis of estrogens from androgens. The enzyme mainly catalyzes the final and rate-limiting step of the biosynthetic pathway that involves the aromatization of androgens into estrogens. The catalysis proceeds through three successive steps, during each one molecule of oxygen and one molecule of NADPH are required. This results in the conversion of androstenedione, testosterone, and 16α-hydroxytestosterone into estrone, 17β-estradiol, and 17β,16α-estriol, respectively.[1-5]

The enzyme has become both a significant and an attractive target for the treatment of breast cancer as it has been shown that breast cancer tissues express more

aromatase enzymes and produce higher levels of estrogens than normal ones. The currently available aromatase inhibitors (AIs) are classified into steroidal and non-steroidal AIs. On one hand, steroidal AIs are similar in structure to the natural substrate of the aromatase enzyme, androstenedione (**ASD**), such as exemestane. Thus, these AIs bind to the active site of the enzyme after which they get converted into reactive intermediates that covalently bind to the enzyme in an irreversible manner. On the other hand, non-steroidal AIs perform reversible non-covalent interactions within the enzyme active site, especially with the heme moiety, such as **letrozole** and **anastrozole**.[5-8]

While AIs are now considered the standard treatment for postmenopausal women with hormone receptor-positive breast cancer, their efficacy may be limited by their adverse effects and the emergence of resistance.[5,6] Therefore, there is a crucial need to design and develop novel therapeutics to overcome such limitations. Among recent studies, the 1,2,3-triazole-containing compounds have been reported to exhibit aromatase inhibitory activity.[9-12] In this study, we report the *in silico* predicted ADME-related properties and the binding affinities of a group of our in-house 1,2,3-triazole-based compounds to the active site or the allosteric sites of the human placental aromatase cytochrome P450.

METHODS

ADME Prediction. The SwissADME website (http://www.swissadme.ch/)[13] was employed for the *in silico* calculation of the physicochemical and pharmacokinetic properties of all compounds **1-11** in addition to two triazole-containing FDA-approved aromatase inhibitors, **letrozole** and **anastrozole**, as reference drugs (**Figure 1**).

Molecular Docking. The co-crystallized ligand (**ASD**), the reference drugs (**letrozole** and **anastrozole**), and compounds **1-11** were built and minimized using Schrödinger Maestro 12.8[14] and then prepared for docking using AutoDock Tools 1.5.6[15]. For all ligands, Gasteiger charges were added, non-polar hydrogens were merged, aromatic carbons were located, rotatable bonds were detected, and torsions were set. The available human placental aromatase cytochrome P450 crystal structure (PDB ID: 3EQM)[16] was downloaded from the protein data bank and prepared for docking using AutoDock Tools 1.5.6 as well through the removal of water molecules, the addition of hydrogen atoms, merging non-polar hydrogens, and calculating Gasteiger charges. The grid box was adjusted to have the x, y, z size of 40*40*40 Å, the spacing of 1 Å, and the x, y, and z centers of 85.639, 54.467, and 45.921, respectively. The exhaustiveness was also adjusted to 20. Molecular docking of **ASD**, **letrozole** and **anastrozole**, and compounds **1-11** was then performed using AutoDock Vina[17]. First, docking validation was carried out by comparing the prepared and docked **ASD** to the co-crystallized one in the active site of the aromatase cytochrome P450 enzyme. The root mean square deviation (RMSD) was calculated using UCSF Chimera 1.15[18]. Second, each of the other ligands was docked using the same docking parameters. Third, the docking results were analyzed using both UCSF Chimera 1.15 and AutoDock Tools 1.5.6. Finally, all figures were prepared using UCSF Chimera 1.15.

RESULTS AND DISCUSSION

ADME Prediction. The ADME-related properties of all the eleven compounds under computational study were calculated using the SwissADME web tool in comparison to the two reference compounds, **letrozole** and **anastrozole**. **ASD** was excluded in this part of the study as it is the endogenous substrate. Among the predicted properties, select physicochemical properties are shown in **Table 1** including the molecular weight (MW), number of rotatable bonds (RB), number of hydrogen bond acceptors (HBA), number of hydrogen bond donors (HBD), molar refractivity (MR), topological polar surface area (TPSA), and lipophilicity (Log P). The number of violations to the five medicinal chemistry and drug discovery rules that are implemented in SwissADME; the Lipinski (Pfizer), Ghose (Amgen), Veber (GSK), Egan (Pharmacia), and Muegge (Bayer) rules,[19-23], as well as the predicted bioavailability score for each compound, are depicted in **Table S1**. The applied filters according to the different rules are as follows: (a) Lipinski filter (MW ≤ 500, CLOGP ≤ 5 (or MLOGP ≤ 4.15), HBA ≤ 10, and HBD ≤ 5)[19], (b) Ghose filter (160 ≤ MW ≤ 480, -0.4 ≤ WLOGP ≤ 5.6, 40 ≤ MR ≤ 130, and 20 ≤ Atoms ≤ 70)[20], (c) Veber filter (RB ≤ 10 and TPSA ≤ 140)[21], (d) Egan filter (WLOGP ≤ 5.88 and TPSA ≤ 131.6)[22], and (e) Muegge filter (200 ≤ MW ≤ 600, -2 ≤ XLOGP ≤ 5, TPSA ≤ 150, Rings ≤ 7, Carbons > 4, Heteroatoms > 1, RB ≤ 15, HBA ≤ 10, and HBD ≤ 5)[23]. The values for all compounds **1-11**, **letrozole**, and **anastrozole** were predicted to comply with all the rules except for compound **8** which violated one or two parameters of each of the different rules. The bioavailability score of compounds **1-7** and **9-11** was predicted to be the same as that of **letrozole** and **anastrozole**, 0.55, however, compound **8** got a lower score of 0.17 (**Table S1**). In addition to the abovementioned properties, the bioavailability radars for all the individual compounds are demonstrated in **Figure 2**. The role of the radar is to predict the drug-like similarity of each compound and it contains a pink area that represents the optimal ranges of six different

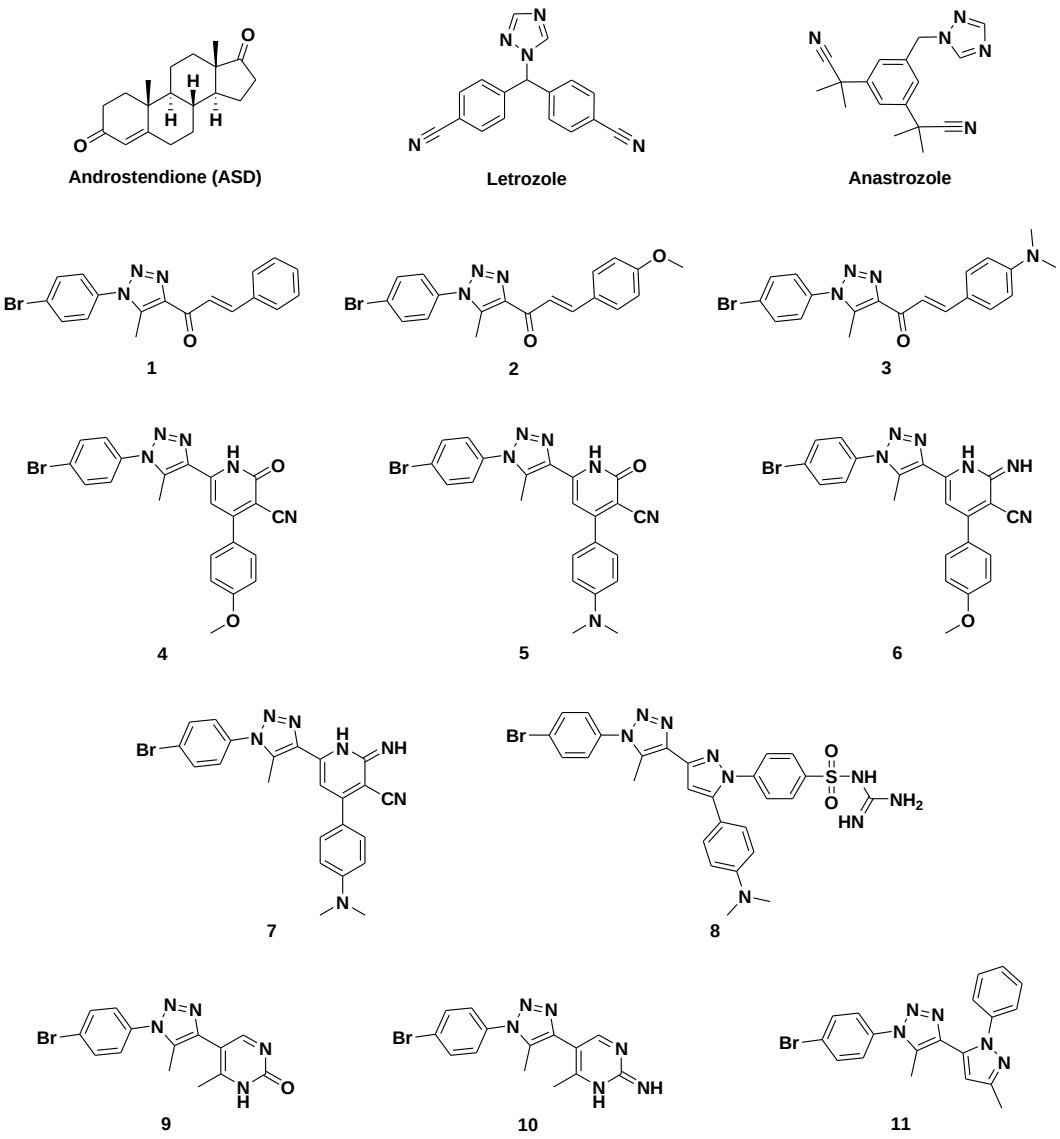

Figure 1. Androstenedione, letrozole, anastrozole, and compounds 1-11.

properties. The properties and their ranges include: (1) lipophilicity (with an XLOGP between -0.7 and 5.0), (2) size (MW between 150 and 500 g/mol), (3) polarity (TPSA between 20 and 130 Å²), (4) solubility (log S not higher than 6.0), (5) saturation (fraction of carbons with the sp^3 hybridization not less than 0.25), and (6) flexibility (no more than 9 rotatable bonds). Thus, molecules with all values in the pink area are expected to be orally bioavailable, while molecules with values outside the pink area are not expected to be orally bioavailable. **Anastrozole** was the only compound that had all the values within the specified ranges of the radar. **Letrozole** and compounds **1-7** and **9-11** had their values within the specified ranges as well except for the degree of unsaturation that fell outside its range. Compound **8** exhibited four values (size, polarity, solubility, and unsaturation) outside of their ranges, which together with its predicted bioavailability score, suggest that compound **8** would possess much less oral bioavailability than all the other compounds. Moreover, select pharmacokinetic properties are presented in **Table S2** involving the gastrointestinal (GI) absorption, blood-brain barrier (BBB) permeability, and the status of being a substrate of the multidrug-resistant P-glycoprotein (P-gp) and/or an inhibitor of five isozymes of the cytochrome P450 family (CYP1A2, CYP2C19, CYP2C9, CYP2D6, and CYP3A4).

Table 1. Select physicochemical properties.

Molecule	MW	RB	HBA	HBD	MR	TPSA	Log P[a]
Letrozole	285.3	3	4	0	79.69	78.29	2.32
Anastrozole	293.37	4	4	0	83.81	78.29	2.35
Compound 1	368.23	4	3	0	93.83	47.78	3.92
Compound 2	398.25	5	4	0	100.32	57.01	3.95
Compound 3	411.3	5	3	0	108.04	51.02	3.87
Compound 4	462.3	4	5	1	116.72	96.59	3.74
Compound 5	475.34	4	4	1	124.44	90.6	3.74
Compound 6	461.31	4	5	2	116.98	103.37	3.83
Compound 7	474.36	4	4	2	124.7	97.38	3.83
Compound 8	620.52	8	6	3	158.42	156.19	3.4
Compound 9	346.18	2	4	1	82.84	76.46	2.41
Compound 10	345.2	2	4	2	83.1	83.24	2.49
Compound 11	394.27	3	3	0	101.55	48.53	4.01

[a]*Consensus Log P*

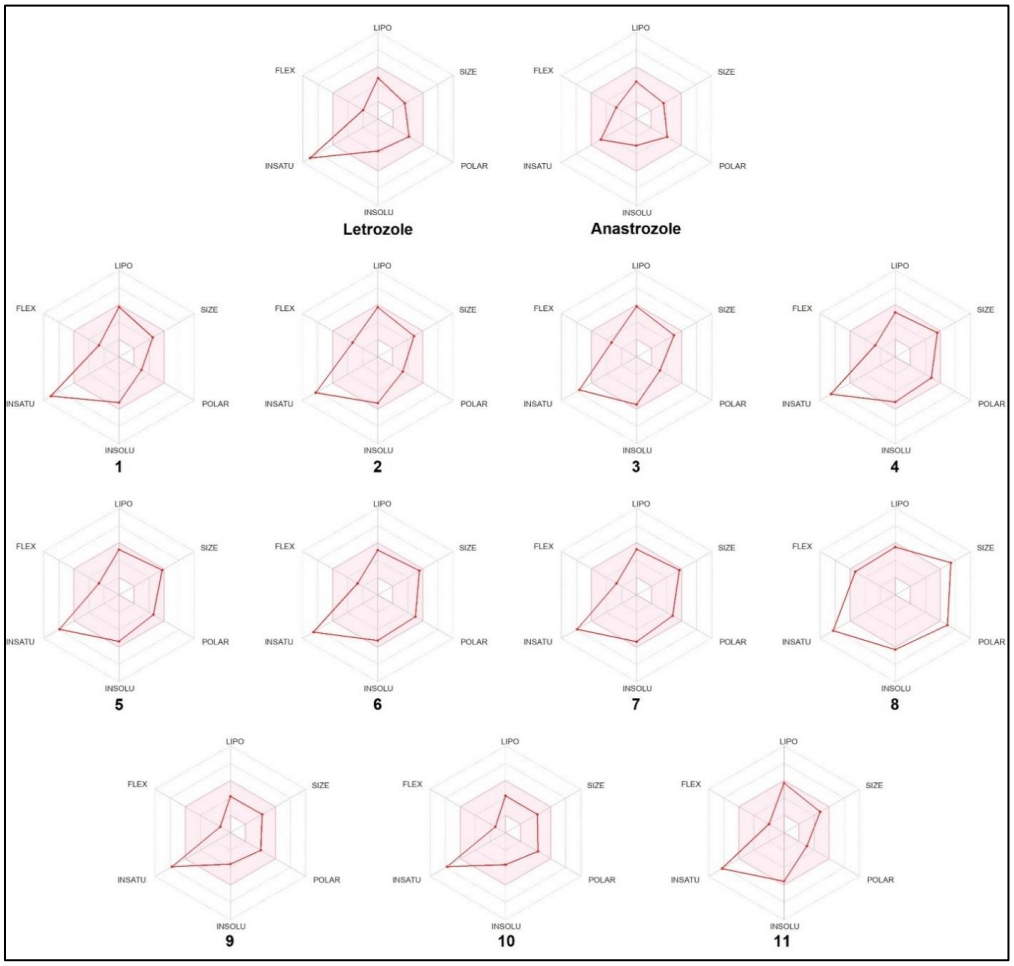

Figure 2. Bioavailability radars.

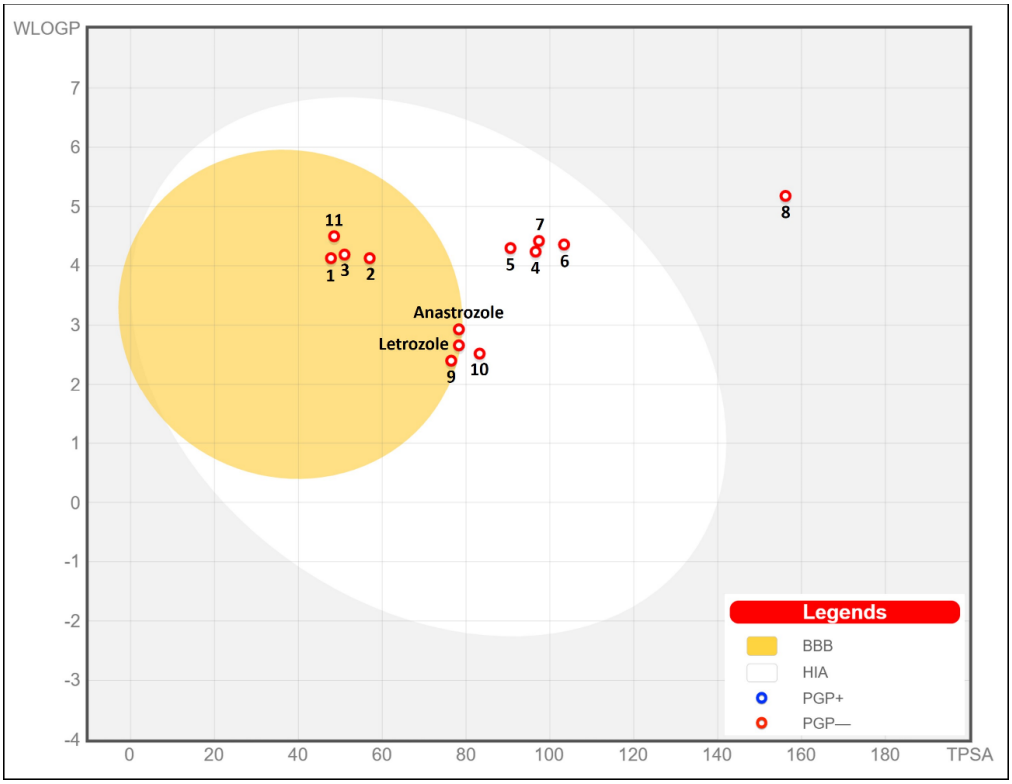

Figure 3. The boiled egg plot.

Letrozole, **anastrozole**, and compounds **1-7** and **9-11** were anticipated to have high GI absorption, while compound **8** was anticipated to have a low one. **Letrozole**, **anastrozole**, and compounds **1-3**, **9**, and **11** were predicted to be BBB permeants. All the compounds and reference drugs were found not to be substrates of P-gp. The results showed that **anastrozole** and compounds **8** and **10** may interact with only one of the CYP450 isozymes, while compounds **4-7** and **9** may interact with two isozymes. The results also suggested that compounds **1-3** and **11** can interact with three isozymes, while **letrozole** can interact with four isozymes.

The boiled egg plot for all compounds is also presented in **Figure 3**. The plot represents a relationship between lipophilicity (WLOGP) and topological polar surface area (TPSA). It displays compounds **1-3**, **9**, and **11** to possess both GI absorption and BBB permeability similar to **letrozole** and **anastrozole** as they all fell in the overlapped egg yolk and white area. The plot also shows compounds **4-7** and **10** to exhibit only GI absorption but not BBB permeability as they fell in the egg white area, while compound **8** to exhibit neither one. In addition, it confirms that all the compounds are not P-gp substrates as they all appear in red.

Molecular Docking. The molecular docking part of the study was performed to evaluate the binding affinities of compounds **1-11** to the crystal structure of the human placental aromatase cytochrome P450 enzyme (PDB ID: 3EQM)[16] in comparison to **letrozole** and **anastrozole** as reference drugs. Not only the binding affinity to the enzyme active site was assessed but also to two other binding sites that have been previously identified and illustrated by Magistrato and co-researchers.[24-26] The two binding sites were introduced as potential allosteric site 1 and site 2 for which novel allosteric modulators of the aromatase enzyme can be designed leading to fewer adverse effects than those caused by the inhibitors that bind to the active site.[24-26] Therefore, the docking grid box was adjusted to surround the active site in addition to these two potential allosteric sites. To validate the molecular docking protocol, **ASD** was first docked against the enzyme. The RMSD value of the docked **ASD** in comparison to the co-crystallized one in the enzyme active site was calculated to be 0.4 Å. The binding energy of the lowest energy pose of the docked **ASD** was found to be -13.7 kcal/mol. Both the docked and co-crystallized **ASD** molecules exhibited a hydrogen bond between the C=O group and the backbone NH of MET374 (**Figure 4A**). Thus, the same protocol was employed for docking the different compounds and reference drugs against the enzyme. The molecular docking results of the lowest binding energy pose of each ligand are available in **Table 2**.

Table 2. Molecular docking results against human placental aromatase cytochrome P450.

Binding Site	Ligand	Binding Energy (kcal/mol)	Number of Hydrogen Bonds	Groups forming Hydrogen Bonds	
				Ligand	Residue
Active Site	ASD	-13.7	1	C=O	MET374 NH
	Letrozole	-8.4	1	C≡N	MET374 NH
	Anastrozole	-9.1	1	Triazole N	MET374 NH
	Compound 1	-8.7	0	-----	-----
	Compound 2	-8.4	1	CH_3O	GLN218 NH_2
	Compound 3	-8.1	1	$(CH_3)_2N$	GLN218 NH_2
Allosteric Site 1	Compound 4	-8.1	2	C≡N Triazole N	GLN218 NH_2 GLN225 NH_2
	Compound 5	-8.1	2	C≡N Triazole N	GLN218 NH_2 GLN225 NH_2
	Compound 6	-8.1	3	CH_3O C≡N Triazole N	ARG192 NH_2 GLN218 NH_2 GLN225 NH_2
	Compound 7	-8.1	2	C≡N Triazole N	GLN218 NH_2 GLN225 NH_2
	Compound 8	-8.6	3	$S(=O)_2$ C=NH C=NH	ARG192 NH_2 ARG192 NH_2 PRO308 C=O
Allosteric Site 2	Compound 9	-7.4	3	Pyrimidine N C=O C=O	GLN428 NH_2 PHE430 NH LYS440 NH_3^+
	Compound 10	-8.0	4	Pyrimidine N C=NH C=NH C=NH	GLN428 NH_2 GLN428 C=O PHE430 NH LYS440 NH_3^+
	Compound 11	-8.3	3	Triazole N Triazole N Triazole N	GLN428 NH_2 GLN428 NH_2 LYS440 NH_3^+

The binding energies of the reference drugs, **letrozole** (**Figure 4B**) and **anastrozole** (**Figure 4C**), were calculated to be -8.4 and -9.1 kcal/mol, respectively. Both drugs were capable of interacting with the active site residues of the enzyme forming one hydrogen bond between their C≡N or triazole N, respectively, and the backbone NH of MET374, in a similar manner to that of **ASD**. Moreover, the triazole N of **letrozole** coordinated with the iron of the heme moiety. Among all the docked ligands, only compounds **1-3** possessed good binding affinity to the active site of the human placental aromatase cytochrome P450 which has been comprehensively illustrated by Ghosh *et al*[16]. The three compounds also exhibited comparable binding energy values to that of **letrozole** within the enzyme active site. Compound **1** possessed a binding energy of -8.7 kcal/mol and a significant π-π interaction between its phenyl ring and the phenyl ring of PHE221 (**Figure 4D**). Compound **2** exhibited a binding energy of -8.4 kcal/mol, a π-π interaction between its phenyl ring and the phenyl ring of PHE221, and a hydrogen bond between its methoxy O and the NH_2 of GLN218 (**Figure 4E**). Similarly, compound **3** had a binding energy of -8.1 kcal/mol, a π-π interaction between its phenyl ring and the phenyl ring of PHE221, and a hydrogen bond between its dimethylamine N and the NH_2 of GLN218 (**Figure 4F**).

The docking results of compounds **4-8** did not prove binding affinity to the active site of the enzyme. However, the five compounds showed good binding affinity to the potential allosteric site 1. Also, the docking results of compounds **9-11** illustrated that these compounds exhibit binding affinity to the potential allosteric site 2 and not the active site of the enzyme. The positions of the two allosteric sites with respect to the active site of the enzyme are illustrated with each group of bound ligands overlaid in **Figure 5**.

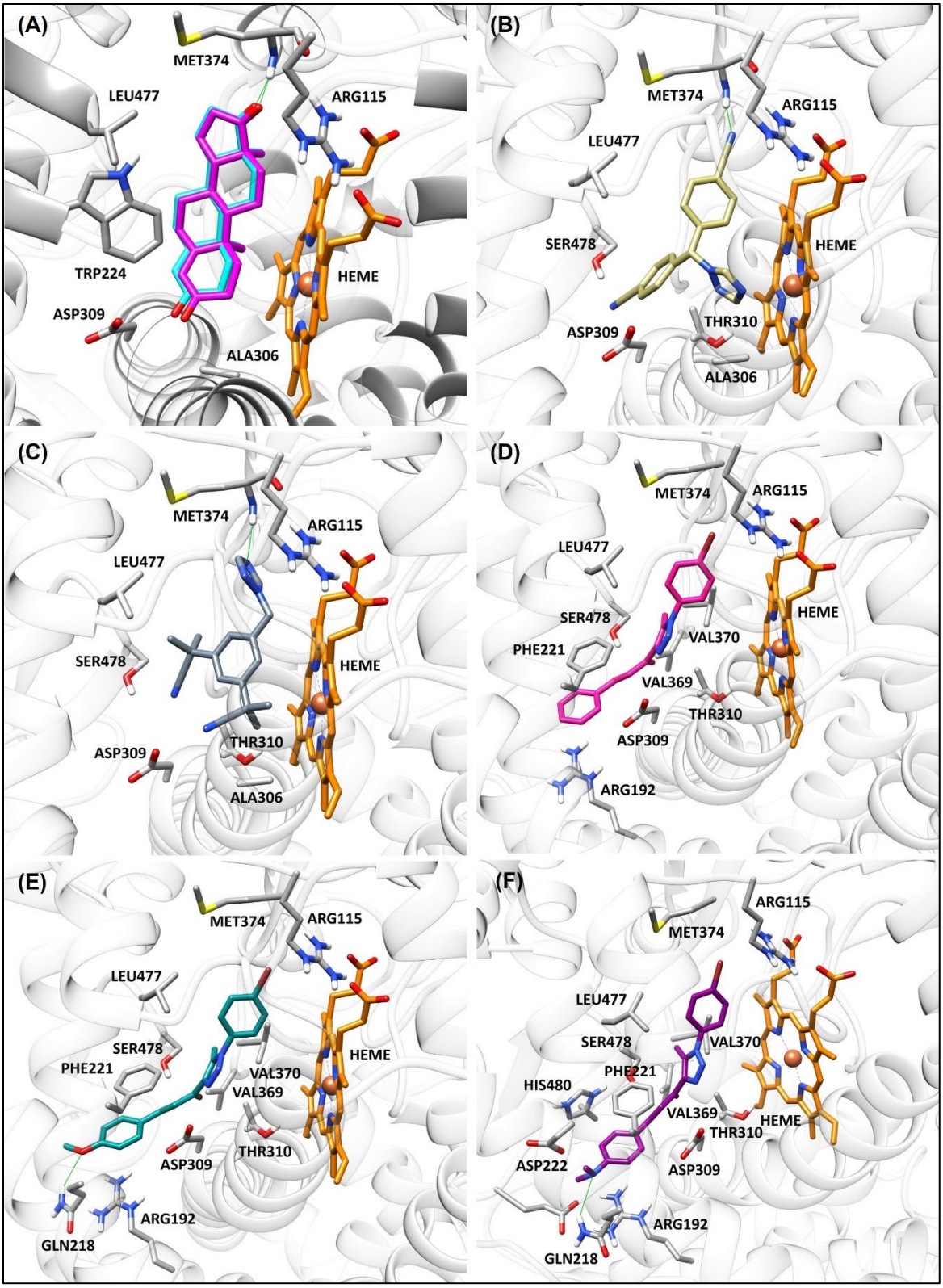

Figure 4. Ligands bound to the active site of the enzyme: (A) Docking validation results of the docked ASD (in magenta) and co-crystallized ASD (in cyan). Docked poses of (B) letrozole, (C) anastrozole, (D) compound 1, (E) compound 2, and (F) compound 3.

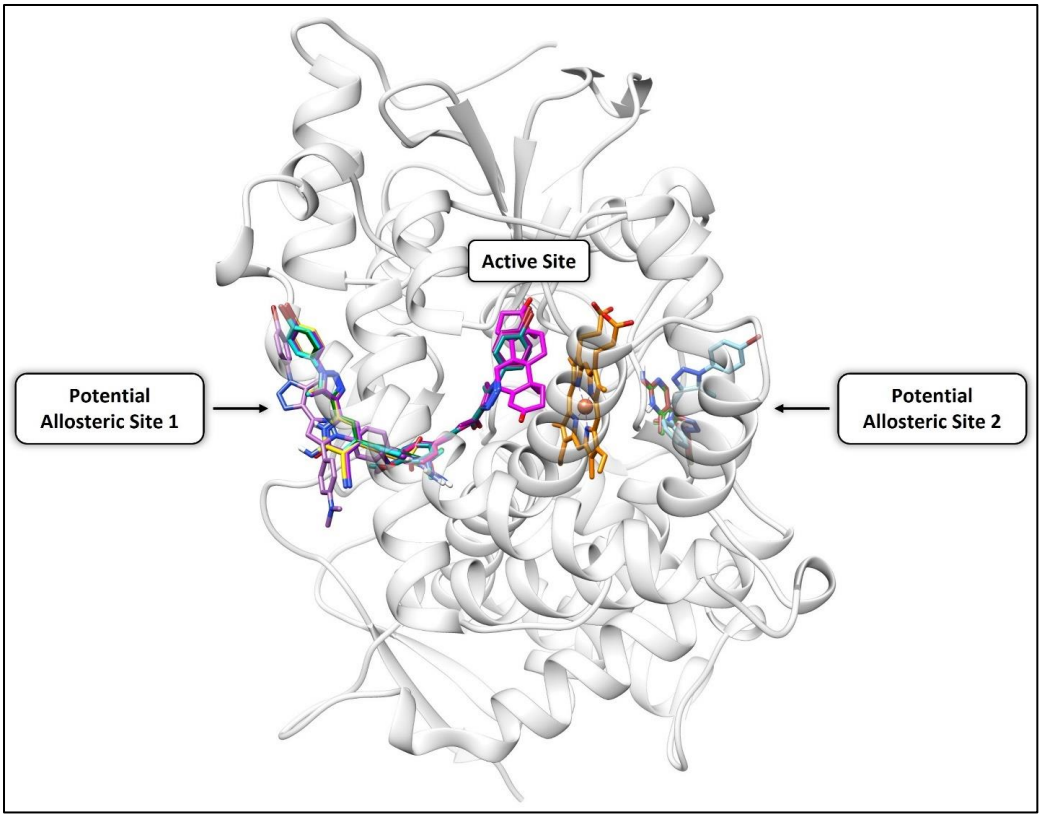

Figure 5. Human placental aromatase cytochrome P450 (PDB ID: 3EQM)[16]with ASD and compounds 1-3 in the active site of the enzyme, compounds 4-8 in the potential allosteric site 1, and compounds 9-11 in the potential allosteric site 2. All ligands are displayed as sticks and colored by heteroatoms and custom colors. The protein is shown as a light gray ribbon, while the heme moiety is shown as orange sticks and colored by heteroatoms.

The figure also shows the overlap between the terminal parts of compounds **1-3** in the active site and compounds **4-8** in the allosteric site 1 through a connecting channel between both sites. In the potential allosteric site 1, compounds **4-7** possessed the same binding energy of -8.1 kcal/mol in addition to similar binding modes (**Figures 6A, 6B, and S1**). The four ligands exhibited two hydrogen bonds, one hydrogen bond between their nitrile N and the NH_2 of GLN218, while the other hydrogen bond between their triazole N and the NH_2 of GLN225. Compound **6** displayed an additional hydrogen bond between its methoxy O and the NH_2 of ARG192. The binding mode of compound **8** involved a binding energy of -8.6 kcal/mol and three hydrogen bonds. The first hydrogen bond is shown between the sulfonyl O of compound **8** and the NH_2 of ARG192. The second and third hydrogen bonds are shown between the imine (C=NH) of the compound and both the NH_2 of ARG192 and the backbone C=O of PRO308, respectively (**Figure S2**).

The surface view of the enzyme reveals a similarity between the orientation of compounds **4-8** in the allosteric site 1. It also demonstrates that both the active site and the allosteric site 1 are connected through a channel that may act as an access channel to the active site of the enzyme as has been hypothesized before[24-26] (**Figure S3**).

In the potential allosteric site 2, compound **9** had a binding energy of -7.4 kcal/mol, a π-π interaction between its triazole ring and the phenyl ring of TYR361. Compound **9** also exhibited three hydrogen bonds between its pyrimidine N and the NH_2 of GLN428, and between its C=O group and both the backbone NH of PHE430 and the NH_3^+ of LYS440 (**Figure 7A**). Compound **10** possessed a binding energy of -8.0 kcal/mol in the same binding site and a π-π interaction between its triazole ring and the phenyl ring of TYR361. The compound also possessed four hydrogen bonds between its pyrimidine N and the NH_2 of GLN428, and between its imine (C=NH) group and functional groups of three residues; the C=O of GLN428, the backbone NH of PHE430, and the NH_3^+ of LYS440 (**Figure 7B**).

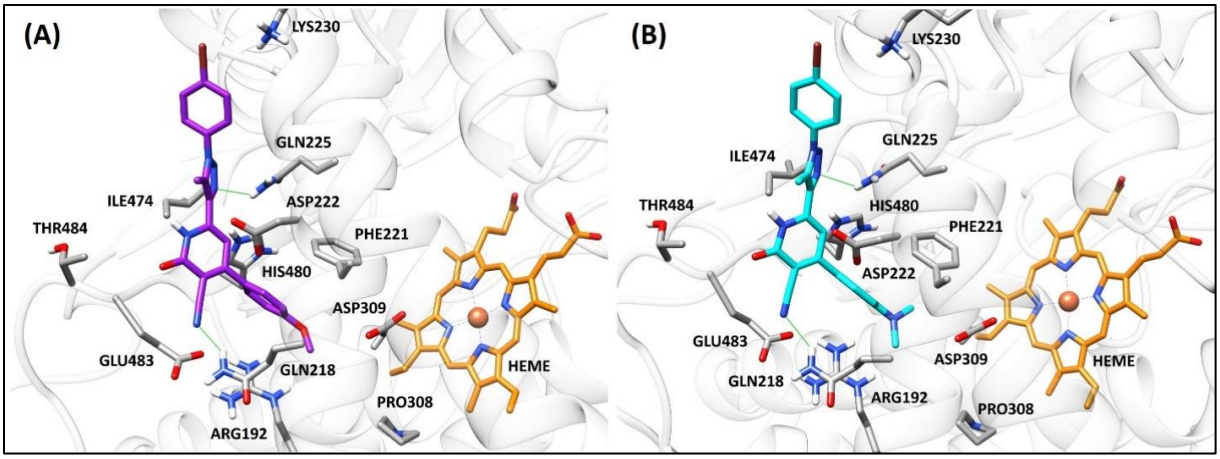

Figure 6. Docked poses of (A) compound 4 and (B) compound 5 in the potential allosteric site 1 of the enzyme.

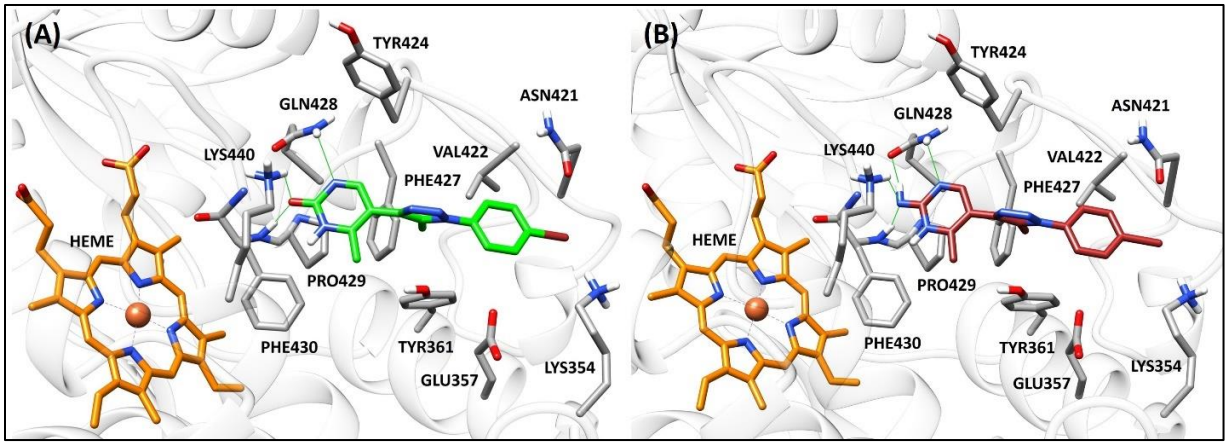

Figure 7. Docked poses of (A) compound 9 and (B) compound 10 in the potential allosteric site 2 of the enzyme.

The binding mode of compound **11** involved the binding energy of -8.3 kcal/mol and three hydrogen bonds between the triazole N of the compound and both the NH_2 of GLN428 and the NH_3^+ of LYS440. Moreover, π-π interactions were formed between the phenyl and triazole rings of compound **11** and the phenyl ring of TYR424, and between the pyrazole ring of the compound and the phenyl ring of TYR441 (**Figure S4**). Visualizing the surface of the enzyme demonstrated the different orientations of compounds **9** and **10** versus compound **11** in the potential allosteric site 2 (**Figure S5**).

CONCLUSION

The molecular docking of the compounds under study suggests that compounds **1-3** would bind to the active site of the human placental aromatase cytochrome P450 similar to **letrozole** and **anastrozole**, while compounds **4-8** and compounds **9-11** would rather bind to the potential allosteric site 1 and site 2, respectively. The *in silico* ADME calculations anticipate that compounds **1-7** and **9-11** possess comparable ADME properties to those of **letrozole** and **anastrozole** and that compounds **1-3**, **9**, and **11** would be BBB permeants similar to both reference drugs as well. Thus, further experimental studies against the human aromatase cytochrome P450 could be carried out to assess the activity of the compounds as potential inhibitors of the enzyme through binding to either its active site or allosteric sites 1 or 2.

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Conflict of interest

The authors declare that there is no conflict of interest regarding the publication of this paper.

Supplementary Information

Table S1 and S2, Figures S1-S5 can be found at: https://aprh.journals.ekb.eg/jufile?ar_sfile=1197872

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