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Original Scientific Paper

THE INHIBITION OF ACNE PROTEASE BY SOME FLAVONES: DFT, SWISSADMET AND MOLECULAR DOCKING

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ABSTRACT

This research sought to find a potent drug for the treatment of acne from six (6) flavones. DFT-B3LYP method was used to determine the molecular descriptors like HOMO, LUMO, Dipole moment, and volume of the ligands and standard drugs. SWISSADMET was employed to ascertain the pharmacokinetic properties of the ligands, and molecular docking was achieved by using PyRx and discovery studiosoft wares. It was observed that the six flavones showed better inhibition against acne main protease than the standard drugs, and from the binding affinity results, 5-hydroxy-2-phenylchromen-4-one best inhibited acne protease. The choice of flavones was based on the fact that they have good antibacterial properties because acne thrives in the presence of bacteria.

Keywords: Acne, Flavones, Molecular Docking, Spartan, DFT.

INTRODUCTION

Flavones are a subclass of flavonoids with biological activities. They are stable to hydrolysis and metabolically stable and can be found in flowers, leaves, and fruits of plants (Schmitz-Hoerner & Weissenbock, 2016). The anti-inflammatory, antimicrobial, and anticancer properties of flavones have received great attention over the years (Duarte et al., 2013; Akura et al., 2001). The anti-inflammatory properties are due to their ability to inhibit both cyclooxygenase and lipoxygenase, and their anticarcinogenic activity promotes apoptosis of cancer cells (Robak & Gryglweski, 1996).

Acne is a very common skin condition mostly found on the face, forehead, chest, shoulders, and upper back. The cause has been attributed to hormonal imbalance leading to fluctuation in hormonal levels, stress, high humidity, and the use of oily or greasy personal care products. Acne commonly affects teenagers and can affect other age groups (Mohuiddin, 2019).

It is a common skin condition involving the blockage of skin pores by hair, sebum (an oily substance), bacteria, and dead skin cells. Which consequently leads to blackheads, whiteheads, nodules, and other types of pimples. Statistics show that about 80% of human beings between the ages of 11 and 30 suffer from at least a mild form of acne, and most people are affected by it at some point in their lives (Bhate & Williams, 2013).

Treatment of acne depends upon its severity, and presently, various medications are being used for its treatment. This includes: Benzoyl peroxide, which targets surface bacteria, Salicylic acid is used as a cleanser or lotion which helps to remove the top layer of damaged skin. Azelaic acid, which is a natural acid found in grains, helps to kill microorganisms on the skin. Retinoids help break up blackheads and whiteheads and prevent clogged pores. While Antibiotics like Clindamycin, tetracycline, and Erythromycin help to control surface bacteria that facilitate the swelling of acne.Dapzone is a topical gel that contains some antibacterial properties, and Isotretinin has been reported to be the most effective drug for the treatment of acne as it shrinks the size of oil glands. However, one major common effect of Isotretinoin is that it causes dryness of the skin and can also lead to birth defects. Other therapies include: Steroids and Lasers (Zaenglein et al., 2016).

However, this research sought to investigate the efficacy of flavones as good inhibitors for acne.

EXPERIMENTAL

Materials and methods

The following softwares were used in this study: Spartan 14, Pubchem, Protein data bank, SWISSADMET, Discovery studio, and PyRx.

A Dell computer system with 8.00 GB installed RAM and 7.77 GB of usable memory was utilized for the computational study. Docking of the ligands with the protease was investigated by using discovery studio and PyRx software. The molecular descriptors of the compounds were optimized and calculated using density functional theory with B3LYP/6-31+G* via Spartan 14.

The acne inhibitory activities of the six ligands against the crystal structure of acne (PDB: 7LBU) were obtained. Dapsone, Isotretinoin, Benzyl Peroxide, and Doxycycline were

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used as the standard drugs. The 3D SDF conformer of the ligands and standard drugs were downloaded from the PubChem Database (https://pubchem.ncbi.nlm.nih.gov).

The protein crystal structure of acne (PDB: 7LBU) was downloaded in PDB format from the protein data bank (RCSB)

Frontier molecular features, HOMO and LUMO, were employed to calculate the band gap (BG). Hardness (η), softness (s), chemical potential (μ), electronegativity (χ), and electrophilicity index (ω) and values were obtained from the below equations:

$$BG = E_{LUMO} - E_{HOMO}. \quad (1)$$

$$EA = -E_{LUMO} - (eV). \quad (2)$$

$$IP = -E_{HOMO} - (eV). \quad (3)$$

$$\eta = \frac{(IP - EA)}{2} = \frac{E_{LUMO} - E_{HOMO}}{2}(eV). \quad (4)$$

$$s = \frac{1}{\eta}(eV). \quad (5)$$

$$\eta = \frac{(IP - EA)}{2} = -\chi(eV). \quad (6)$$

$$\omega = \frac{\mu^2}{2\eta} = \frac{(IP - EA)^2}{4(IP - EA)} = \frac{E_{LUMO} + E_{HOMO}}{4(E_{LUMO} - E_{HOMO})}(eV). \quad (7)$$

$$\chi = -\mu = -\frac{(IP - EA)}{2} = \frac{(E_{LUMO} + E_{HOMO})}{2}(eV). \quad (8)$$

$$\omega^{+} = \frac{(IP - 3EA)^2}{16(IP - EA)} = \frac{(E_{LUMO} + E_{HOMO})^2}{16\eta}(eV). \quad (9)$$

$$\omega^{-} = \frac{(3IP - EA)^2}{16(IP - EA)} = \frac{(3E_{LUMO} + E_{HOMO})^2}{16\eta}(eV). \quad (10)$$

$$\Delta\omega^{\pm} = \omega^{+} - (-\omega^{-}) = \omega^{+} + \omega^{-}. \quad (11)$$

Molecular docking and binding affinity scores of the ligands and the standard drugs against the Crystal structure of acne (PDB: 7LBU) were obtained using PyRx and Discovery studio software. The inhibition constants (Ki) μM were calculated from Equations (12), (13) and (14).

$$\Delta G = -nRT \ln K_{eq}. \quad (12)$$

$$K_{eq} = e^{-\frac{\Delta G}{nRT}}. \quad (13)$$

$$K_i = \frac{1}{K_{eq}}. \quad (14)$$

DISCUSSION

The six ligands and the standard drugs employed are listed in Table 1.

Table 1. Flavones and Standard Drugs.

S/N	Ligand Code	Ligand
1.	A1	2-phenylchromen-4-one
2.	A2	7,8-dihydroxy-2-phenylchromen-4-one
3.	A3	3-hydroxy-2-phenylchromen-4-one
4.	A4	5-hydroxy-2-phenylchromen-4-one
5.	A5	7-hydroxy-2-phenylchromen-4-one
6.	A6	2-phenylbenzo(h)chromen-4-one
7.	S1	Dapsone
8.	S2	Isotretinoin
9.	S3	Benzoyl peroxide
10.	S4	Doxycycline

Molecular Descriptors

The calculated molecular descriptors such as hydrophobicity (Log P), volume (V), Polar surface area (PSA), dipole moment (DM), HOMO, and LUMO energies obtained for the six flavones and the standard drugs are shown in Table 2. The HOMO and LUMO are vital descriptors that offer realistic qualitative facts about the excitation properties of molecules (Semire et al., 2012). The calculated electronic descriptors band gaps are 4.56eV for A1, 4.24eV for A2, 4.14eV for A3, 4.02eV for A4,4.59eV for A5, 4.29eV forA6.The band gap is in the order S3>S1>A5>A1>A2>A3>A4>S4>S2. The lower the band gap, the easier the excitation of electrons within the molecule and the better the ability of the molecule to donate electrons to its surroundings. The band gap plays an important role in protein-ligand interaction. S3, with the highest band gap, shows the greatest stability, and S2, with the least band gap is the least stable among the ligands and the standard drugs, implying S2 is the most chemically active standard drug while S3 is the least chemically active standard drug. The calculated Log p tells about the compound's ability to dissolve into non-aqueous solutions. The need for the compounds to permeate through the various biological membranes is very crucial. Lipophilicity is a measure of the distribution of the compound between non-aqueous and aqueous phases, and it reveals the biological activity of ligands (Abass et al., 2001). Furthermore, Log P estimates a compound's overall lipophilicity properties, it influences the behavior of compounds in biological membranes such ashepatetic clearance, lack of selectivity, and non-specific toxicity (Hughes et al., 2008). The acceptable log P value should not be higher than 5 (Meanwell, 2011). The calculated Log P values for the compounds are 3.18 for A1,

2.84 for A2, 2.93 for A3, 2.50 for A4, 4.09 for A5, 4.01 for A6, therefore the compounds have good lipophilicity properties. Furthermore, dipole moment, which is the product of the magnitude of the charge and the distance of separation between the charges, were 4.19 debye for A1, 5.63debye for A2, 5.08debye for A3, 5.00debye for A4,3.25debye for A5, 4.60debye for A6. Moreover, large values of dipole moment have been attributed to the anomalous property of individual molecules (Debendetti, 2003), therefore, the compounds are desirable in terms of dipole moment values because they have moderate values of dipole moment.

The electrophilicity index is in the order: S4>S2>A4>S3>A1>A2>A5>A6>S1as shown in Table 3. Ligand S4 with the highest electrophilicity index shows excellent character of an electrophile. While S1, with the least electrophilicity value possesses nucleophilicity character. S4 also gave the highest EA, which suggests readiness to accept electrons to form bonds. Furthermore, S2 and S4 showed good chemical softness properties, showing their good reactivity and drug stability properties (Asogwa et al., 2022).

Table 2. Geometries of a calculated molecular description of the ligands.

ID	HOMO (eV)	LUMO (eV)	BG	DM (Debye)	HBA	HBD	MW (amu)	Log P	V (A^3)	PSA (A^2)
A1	-6.36	-1.80	4.56	4.19	2	0	222.24	3.18	434	30.21
A2	-6.03	-1.79	4.24	5.63	3	1	238.24	2.84	434	50.44
A3	-5.87	-1.73	4.24	5.08	2	0	224.25	2.93	434	26.30
A4	-5.99	-1.97	4.02	5.00	5	2	284.26	2.50	434	79.90
A5	-6.31	-1.72	4.59	3.25	2	0	272.30	4.09	434	30.21
A6	-6.01	-1.72	4.29	4.60	2	0	272.30	4.01	434	30.21
S1	-5.67	-0.67	5.00	5.95	2	2	248.30	1.55	434	94.56
S2	-5.19	-2.07	3.12	2.60	2	1	300.44	1.55	302	37.30
S3	-7.42	-1.73	5.69	3.61	4	0	242.23	2.91	434	52.60
S4	-5.64	-2.43	3.21	3.89	9	6	444.43	-0.24	302	181.62

*BG: band gap($E_L - E_H$), DM: Dipole Moment, MW: Molecular Weight, HBA: Hydrogen bond acceptor, HBD: Hydrogen bond donor, PSA: Polar Surface Area, V: Volume.

Table 3. Global reactivity descriptor values.

Ligand	Hardness (η)	Softness (s)	Chemical Potential (μ)	Electrophilicity index (ω)	ω^+	ω^-	$-\Delta\omega^{\pm}$
A1	2.28	0.44	4.08	3.65	1.90	3.34	1.44
A2	2.12	0.47	3.91	3.61	1.92	5.83	3.91
A3	2.29	0.44	3.80	3.49	1.85	5.65	3.80
A4	2.01	0.50	3.98	3.94	2.20	6.18	3.98
A5	2.30	0.44	4.02	3.51	1.79	5.81	4.02
A6	2.15	0.47	3.87	3.48	1.82	5.68	3.86
S1	2.50	0.40	3.17	2.01	0.74	3.91	3.17
S2	1.56	0.64	3.63	4.22	2.60	6.23	3.63
S3	2.85	0.35	4.58	3.68	1.75	6.32	4.58
S4	1.61	0.62	4.04	5.07	3.26	7.29	4.04

ADMET studies of the flavones

The ligands were subjected to an ADMET study using SWISSADMET server to predict their pharmacokinetic properties shown in Table 4. It was revealed that all six flavones have high GI Absorption (Gastrointestinal absorption) properties; this shows that the flavones will be able to be absorbed through the biological membranes. The Blood-brain barrier is the specialized system of the brain microvascular endothelial cells that shields the brain from toxic substances in the blood and filter harmful substances from the brain back to the bloodstream; with the exception of A4 others have good BBB permeant properties. All the ligands have no P-gp substrate property and are good inhibitors of CYP1A2, suggesting good drug candidates with good absorption and oral bioavailability. The basic enzymes for drug biotransformation are the cytochrome P450 (CYP) enzymes which include: CYP1A2, inhibitor, CYP2C19 inhibitor, CYP2C9 inhibitor, CYP2D6 inhibitor, and CYP3A4 inhibitor. Consequently, those ligands having an inhibitory effect on CYP3A4 enzymes may cause an increase in concentration and overdose of drugs. While, those ligands with no inhibitory effect on CYP3A4 enzyme will be easily converted after oral treatment. The more negative the log Kp, the less skin permeant property of the ligand, and the recommended value of log Kp being -9.63 cm/s suggests that all the flavones under investigation have good skin permeant properties.

Molecular docking analysis

The molecular docking method was validated by docking the six ligands into the active sites of the protein crystal structure of Acne protease (PDB: 7LBU). This was done in order to obtain binding affinities and the inhibition constants of the ligands and the standard drug. The docking results are shown in Table 5.

The 2D-structures of the interactions of ligands/standard drugs with aminoacids residues are shown in Figure 1.

Table 4. Pharmacokinetic properties.

Ligand	GI Absorption	BBB Permeant	P-gp Substrate	CYP1A2 Inhibitor	CYP2C19 Inhibitor	CYP2C9 Inhibitor	CYP2D6 Inhibitor	CYP3A4 Inhibitor	LogKp (cm/s)
A1	High	Yes	No	Yes	Yes	No	No	No	-5.13
A2	High	Yes	No	Yes	Yes	No	Yes	Yes	-5.34
A3	High	Yes	No	Yes	No	No	No	No	-5.44
A4	High	No	No	Yes	No	Yes	Yes	Yes	-5.66
A5	High	Yes	No	Yes	Yes	No	No	No	-4.55
A6	High	Yes	No	Yes	Yes	No	No	No	-4.82

Table 5. Amino acid residues of the ligands.

Ligand/Standard Drug	Amino Acid Residue	Binding Affinty(Kcal/mol)	Inhibition Constant/10^{-6}
A1	H- bonding: VAL A: 348. Pi-Alky Bonding: ARG A:289, PRO A:292, ILE A:184, ILE A:288, ALA A:347, VAL A:110, ALA A:46, LEU A:10	-9.5	0.108
A2	H - bonding: VAL A:348, THR A:47. Pi-Alkyl bonding: PRO A:292, ILE A:288, ALA A:347, ALA A:46, LEU A:10, ILE A:184, ARG A:289	-9.7	0.077
A3	H-bonding: ARG A:289, VAL A:348. Pi-Alkyl bonding: ILE A:184, PRO A:292, ALA A:347, ALA A:46, LEU A:10, VAL A:110, ILE A:288	-9.7	0.077
A4	H-bonding: VAL A:348. Pi-Alkyl bonding: ALA A:46, VAL A:110, ALA A:347, LEU A:10, PRO A:292, ILE A:184, ARG A:289	-9.8	0.065
A5	H-bonding: VAL A:348 Pi-Alkyl bonding: ARG A:289, ILE A:184,ILE A:288, PRO A:292, ALA A:347, LEU A:10. Unfavorable donor-donor: THR A:47	-9.7	0.770
A6	Pi-Alkyl bonding: ILE A:184, ARG A:289, PRO A:292, LEU A:10, ILE A:288, ALA A:347, VAL A:110, ALA A:46	-9.6	0.091
S1	H-bonding: THR A: 47, ARG A: 289 GLU A:238. Pi-Alkyl bonding: LEU A:10, ILE A: 184, PRO A:292	-8.2	0.970

S2	H-bonding: ARG A: 249, ARG A:41, Unfavorable donor-donor: ARG A:315	-.6.4	0.201
S3	H-bonding: THR A: 47. Pi-Donor hydrogen bond: VAL A: 348. Carbon Hydrogen Bonding: ALA A:46. Pi-Alkyl bond: ALA A:347, PRO A:292, LEU A:10, ILE A:288	-8.0	1.358
S4	H-bonding: ARG A:315, ARG A:41, ASP A:66. Unfavorable Donor-donor bonding: ARG A:249	-8.8	0.352

Docking with A1

The compound interacted with hydrogen bonds with VAL A:348 and Pi-Alky Bonding with ARG A:289, PRO A:292, ILE A:184, ILE A:288, ALA A:347, VAL A:110, ALA A:46, and LEU A:10. The binding affinity and the inhibition constant (Ki) were -9.5 Kcal/mol and 0.108 x 10^{-6} respectively. The binding affinity result of A1 is better than each of the standard drugs under investigation.

Docking with A 2

The ligand interacted with H – bonding with VAL A:348, THR A:47, Pi-Alkyl bonding with PRO A:292, ILE A:288, ALA A:347, ALA A:46, LEU A:10, ILE A:184, and ARG A:289. The interaction gave a better binding affinity of -9.7Kcal/mol and a lower inhibition constant (Ki) of 0.077x 10^{-6}as compared to A1.

Docking with A3

A3 interacted with H-bonding with ARG A:289, VAL A:348 and Pi-Alkyl bonding with ILE A:184, PRO A:292, ALA A:347, ALA A:46, LEU A:10, VAL A:110, ILE A:288. The values of the binding affinity and the inhibition constant were the same as that of A2.

Docking with A4

Ligand A4 interacted with H-bonding with VAL A: 348, Pi-Alkyl bonding with ALA A:46, VAL A:110, ALA A:347, LEU A:10, PRO A:292, ILE A:184 and ARG A:289. The binding affinity of -9.8 Kcal/mol for ligand A4 is the best among the ligands and the standard drugs. Furthermore, the calculated inhibition constants of 0.065x 10^{-6} were the least compared to the other ligands and the standard drugs.

Docking with A5

Ligand A5 showed interaction with H-bonding with VAL A:348, Pi-Alkyl bonding with ARG A:289, ILE A:184, ILE A:288, PRO A:292, ALA A:347, LEU A:10 and Unfavorable donor-donor with THR A:47. The binding affinity and inhibition constant results were the same for A2 and A3.

Docking with

*A6*A6 interacted with Pi-Alkyl bonding with ILE A:184, ARG A:289, PRO A:292, LEU A:10, ILE A:288, ALA A:347, VAL A:110, ALA A:46. The values of the binding affinity and calculated inhibition constants for the interaction were -9.6 Kcal/ mol and 0.091 x 10^{-6} respectively.

Docking with standard drug S1

The standard drug, S1 interacted with H-bonding with THR A: 47, ARG A: 289 GLU A:238, and Pi-Alkyl bonding with LEU A:10, ILE A: 184, PRO A:292. The binding affinity of -8.2 Kcal/mol is poor with high inhibition constant compared to those of A1, A2, A3, A4, A5, and A6.

Docking with standard drug S2

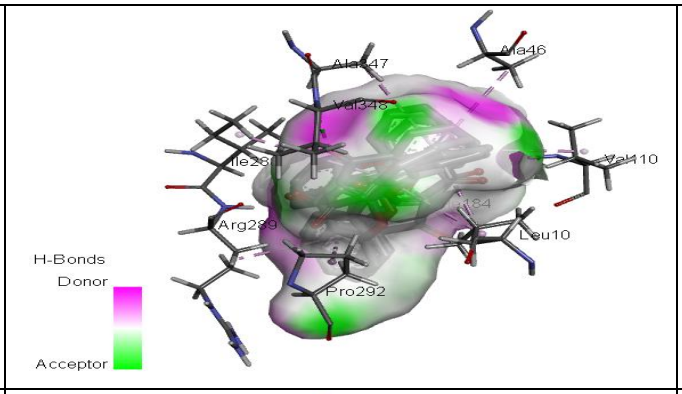
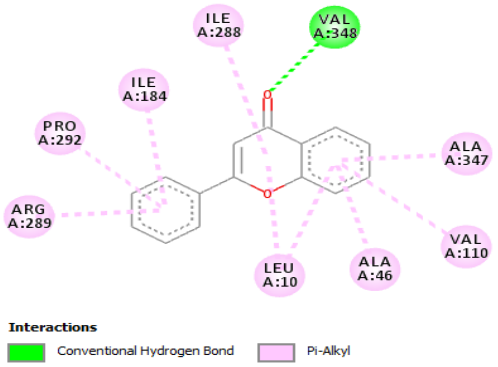
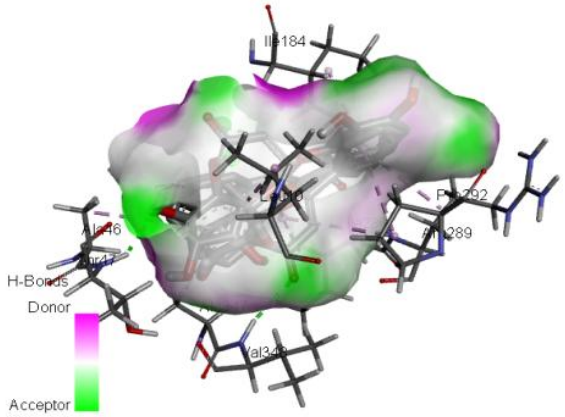
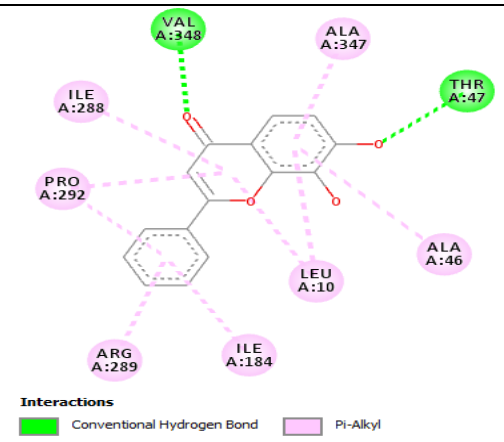
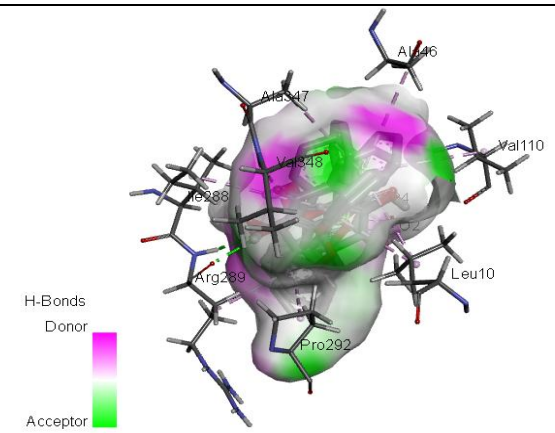
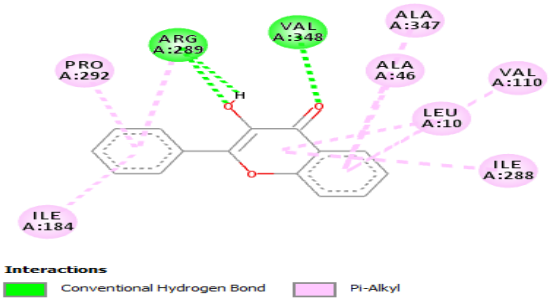
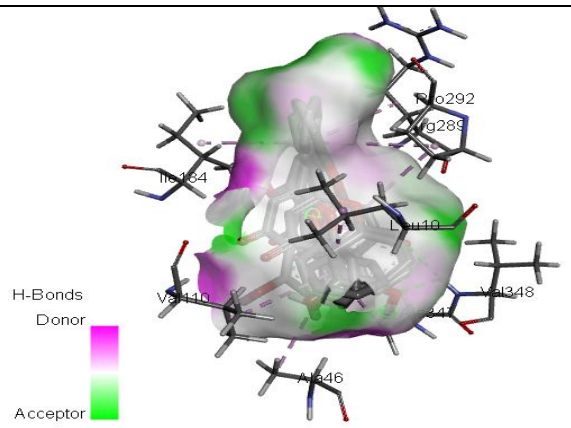
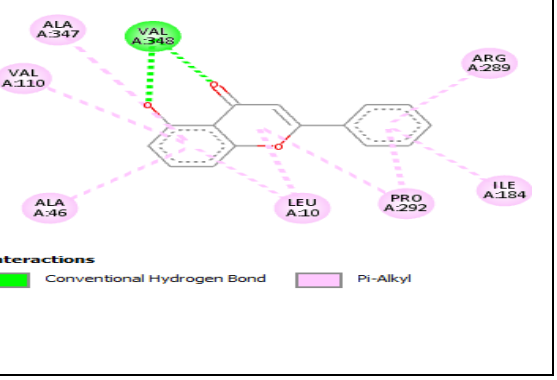
The second standard drug S2 interacted with H-bonding with ARG A:249, ARG A:41, Unfavorable donor-donor with ARG A:315. The binding affinity of -6.4 Kcal/mol is poor compared to A1, A2, A3, A4, A5, A6 and S1. The calculated inhibition constant 0f 0.201 x 10^{-6} is better than those of A4, A5, and S1.

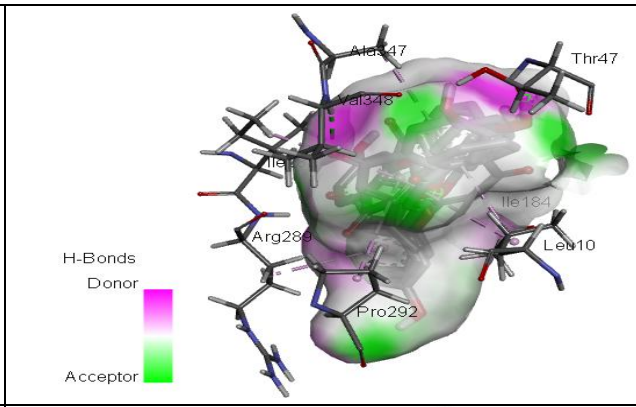
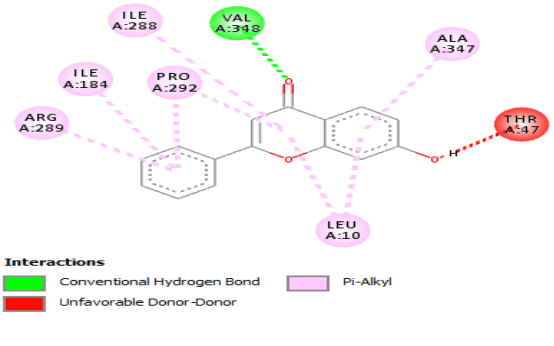
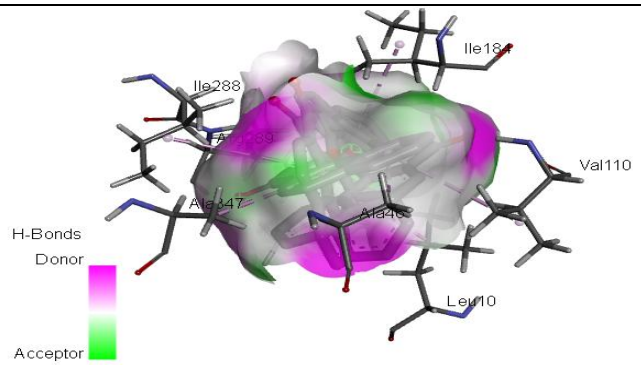
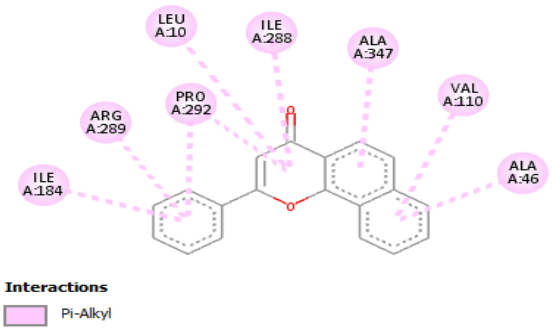
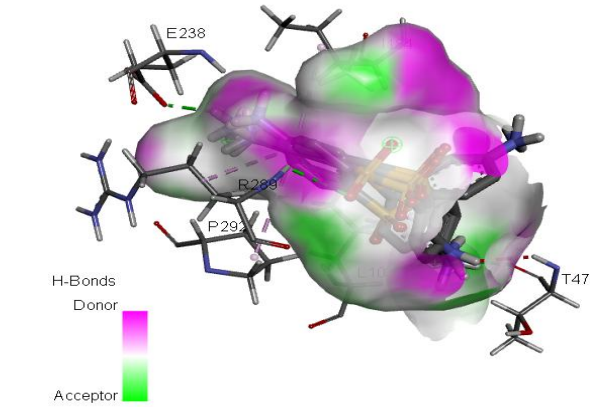
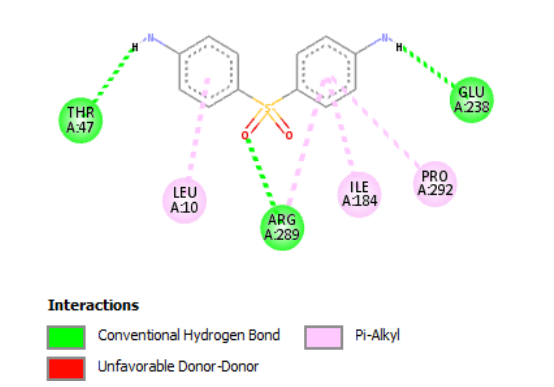
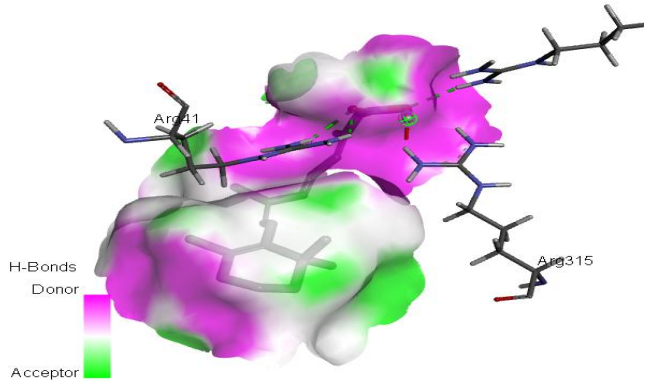
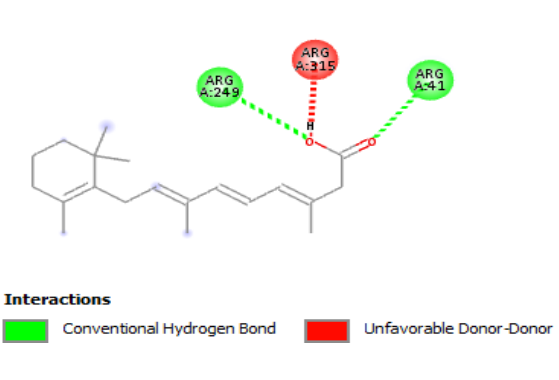
Docking with standard drug S3

The third standard drug, S3 interacted with H-bonding with THR A:47, Pi-Donor hydrogen bond with VAL A:348, Carbon -Hydrogen Bonding with ALA A:46 and Pi-Alkyl bond with ALA A:347, PRO A:292, LEU A:10, ILE A:288. The binding affinity of -8.0 Kcal/mol is far better than that of S2 and it gave the poorest (highest) inhibition constant of 1.358 10^{-6} compared to all the ligands and the standard drugs under investigation.

Docking with standard drug S4

The standard drug, S4 interacted with H-bonding with ARG A: 315, ARG A:41, ASP A:66 and Unfavorable Donor-donor bonding with ARG A:249. It gave the best binding affinity of -8.8 Kcal/mol compared to all the standard drugs under study. It has an inhibition constant 0f 0.352 x 10^{-6}, which is second best after S2 in comparison to the standard drugs.

A1	 Ala46 Ala347 Val348 Ile288 Val110 Arg289 Leu10 Pro292 H-Bonds Donor Acceptor	 ILE A:288 VAL A:348 ILE A:184 PRO A:292 ALA A:347 ARG A:289 VAL A:110 LEU A:10 ALA A:46 Interactions Conventional Hydrogen Bond Pi-Alkyl
A2	 Ile184 Pro292 Arg289 Ala46 Ala347 Val348 H-Bonds Donor Acceptor	 VAL A:348 ALA A:347 THR A:47 ILE A:288 PRO A:292 ALA A:46 LEU A:10 ARG A:289 ILE A:184 Interactions Conventional Hydrogen Bond Pi-Alkyl
A3	 Ala46 Ala347 Val110 Val348 Ile288 Arg289 Leu10 Pro292 H-Bonds Donor Acceptor	 ARG A:289 VAL A:348 ALA A:347 PRO A:292 ALA A:46 VAL A:110 LEU A:10 ILE A:288 ILE A:184 Interactions Conventional Hydrogen Bond Pi-Alkyl
A4	 Pro292 Arg289 Ile184 Leu10 Val110 Val348 Ala46 H-Bonds Donor Acceptor	 ALA A:347 VAL A:348 VAL A:110 ARG A:289 ALA A:46 LEU A:10 PRO A:292 ILE A:184 Interactions Conventional Hydrogen Bond Pi-Alkyl

A5	 Ala347 Thr47 Val348 Ile184 Arg289 Leu10 Pro292 H-Bonds Donor Acceptor	 ILE A:288 VAL A:348 ALA A:347 ILE A:184 PRO A:292 ARG A:289 THR A:47 LEU A:10 Interactions Conventional Hydrogen Bond Pi-Alkyl Unfavorable Donor-Donor
A6	 Ile184 Ile288 Val110 Ala347 Ala46 Leu10 H-Bonds Donor Acceptor	 LEU A:10 ILE A:288 ALA A:347 VAL A:110 PRO A:292 ARG A:289 ILE A:184 ALA A:46 Interactions Pi-Alkyl
S1	 E238 T47 H-Bonds Donor Acceptor	 THR A:47 GLU A:238 LEU A:10 ARG A:289 ILE A:184 PRO A:292 Interactions Conventional Hydrogen Bond Pi-Alkyl Unfavorable Donor-Donor
S2	 Arg41 Arg315 H-Bonds Donor Acceptor	 ARG A:315 ARG A:249 ARG A:41 Interactions Conventional Hydrogen Bond Unfavorable Donor-Donor

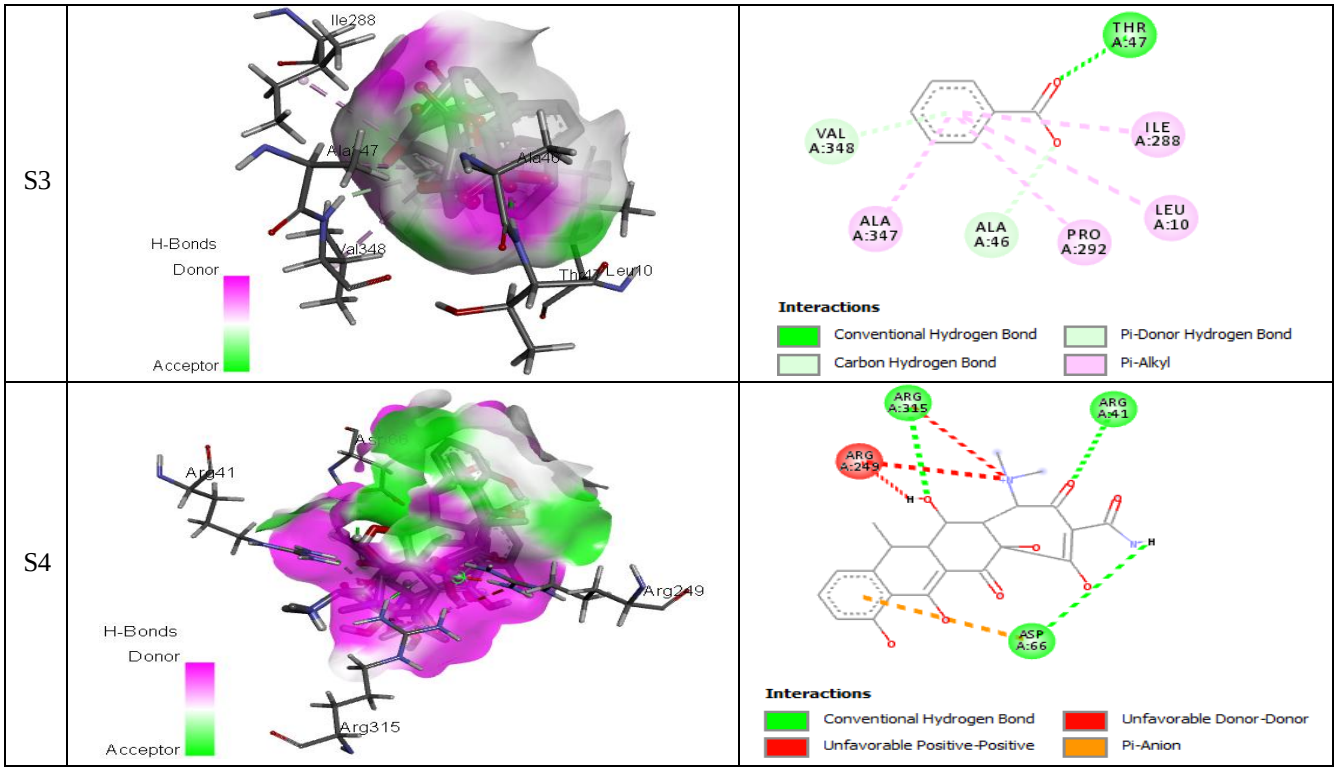


Figure 1. Interaction of ligands/standard drugs with respective amino-acid residues.

CONCLUSION

The molecular binding results revealed that all the flavones under investigation gave better binding affinities than the standard drugs, with A4 being the most preferred and having the least inhibition constant. However, S4 is the best among the standard drugs studied, with the highest electrophilicity index, ionization potential, and softness properties. The skin permeant properties of all the flavones are good and have minimal toxicity. All the flavones have good absorption and oral bioavailability properties. Ligands A1, A3, A5, and A6 are not CYP450 Inhibitors and therefore accessible after oral treatment. Flavones have antibacterial properties and can be employed to combat acne, which is a disease promoted by bacteria. The relatively good lipophilicity property of the flavones makes them good cosmetic products.

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