



Molecular Docking Investigation of Natural Compounds from *Inula viscosa* and Synthetic Derivatives against Breast Cancer Targets

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Abstract:

Novel compounds with significant medicinal properties have attracted considerable interest in therapeutic approaches to treating breast cancer. Different synthetic and natural inhibitors were collected from the literature and docked against (Aromatase, mTOR) receptors. The compounds' binding affinities were calculated after minimising interactions within the binding pockets of the macromolecular receptors (Aromatase, mTOR). In this work, we use molecular docking methods to identify the ligand that has the best interaction energy with the fourth macromolecule among synthetic and natural products extracted from *Inula Viscosa*, and also describe binding affinity in order to design new inhibitor ligands. The result shows that ligands (Nepetin, OSI-027) and (3-O-Methylquercetin, Formestane) best inhibited Aromatase and mTOR, respectively. The latter reaches the same conclusion as the study on experimental inhibition.

1. Introduction

The Asteraceae family comprises a large number of flowering and usually aromatic plants, mostly growing in the tropics and in cold arctic or alpine regions. It includes about 620 genera and 23,600 species, of which *Inula* is one of the most famous. The *Inula* genus comprises more than one hundred

species [1], mainly distributed in Europe, Africa, and Asia. *Inula viscosa*, commonly known as "Trehla or Magramane," is a widespread plant in the Mediterranean region. *Inula Viscosa* has traditionally been used as a remedy for wounds, skin diseases, rheumatic pain, lung disorders, diabetes, gastroduodenal problems, hypertension, cancer, bronchitis, tuberculosis, and infertility [1-

9]. It has been widely used in folk medicine for therapeutic purposes as an anthelmintic, antipyretic, antiseptic, anti-inflammatory, antiphlogistic, balsamic, expectorant, anti-scabies, diuretic, anti-anemic, and muscle-relaxant [2-10]. Many biologically active compounds have been identified from *I. viscosa*, such as guaianolides, sesquiterpenic acids, triterpenoids, azulenes, lactones, flavonoids, costic acid, and essential oils [1, 10-16]. Cytotoxic [8, 14, 16-21], antimicrobial [9, 18, 21-25], antioxidant [7, 24-27], antihypertensive [29], hypoglycemic [5], hypolipidemic [5], abortifacient, and anti-implantation [4] activities of *Inula Viscosa* have been investigated with experimental studies in the literature.

Breast cancer represents the second most prevalent cancer in females and is considered the second leading cause of death among women. Aromatase is an enzyme that plays a critical role in the development of estrogen receptor-positive breast cancer. As aromatase catalyzes the aromatization of androstenedione to estrone, a naturally occurring estrogen, it is a promising drug target for therapeutic management. Previous theoretical studies have compared steroidal and natural aromatase inhibitors via molecular docking and DFT [30]. The mTOR pathway is a key intracellular signaling pathway in the cell cycle that regulates multiple nutritional and environmental factors, including growth factors, energy levels, cell stress, and amino acids. However, dysregulation has been implicated in major diseases such as cancer, metabolic disorders, neurological diseases, and inflammation. Among the thousands of targets available for the treatment of breast cancer, mTOR (Mammalian Target of Rapamycin) is one of the most promising targets as the PI3K/ AKT/mTOR signaling pathway is deregulated predominantly in breast cancer [31].

Considering the enormity of research reports on the inflammatory and breast cancer effects of inhibitors naturals (molecules of *Inula viscosa*) and the importance of Aromatase and mTOR as a therapeutic target in breast cancer, we aimed to carry out an in-silico evaluation of compounds derived from *inula viscosa* against (Aromatase, mTOR) and synthetics (sulfasalazine, zileuton, amino benzoic acid, silibinin, varsapladib, Glycyrrhetic acid, anastrozole, estrone, formestane). By molecular docking, we can study the complex (enzyme/inhibitor) formation and consequently delay its progression, in order to determine the interaction of the complex (Natural and Synthetic) with the enzyme. The selected natural and synthetic inhibitors and synthetic [32-37] are given in Table 1. Our results will contribute

to the design of new active molecules as Aromatase and mTOR inhibitors, that can be synthesized basing on the molecular structures of bioactive compounds of *Inula viscosa* which are shown in Table 1

2. Materials and methods

2.1 Target receptor protein

The enzyme structures were downloaded from the Protein Data Bank archive-information database (www.rcsb.org/pdb): Aromatase (PDS ID: 5JKW), mTOR (PDS ID: 4JT6) [38]. Table 2 presents the target macromolecules and each of the native ligands. The protein structures were prepared using MOE (Molecular Operating Environment) software [39] to remove all non-receptor atoms, including water, ions, and miscellaneous compounds. The obtained structures were then saved as a PDB file.

2.2. Preparation of ligands

The 16 natural compounds from *Inula Viscosa* were used collectively as ligands in this study. The three-dimensional structures of ligands were downloaded from the PubChem database and were later optimized using density functional theory (DFT) level using Beck's three-parameter Lee–Yang–parr hybrid functional (B3LYP) at 6-31G basis set [40] to simulate chemical structures of the molecules at their minimum potential energy or most stable state in a real chemical system before subjecting them to the molecular docking process. The structure was then executed using an MMFF94X energy minimization force field implanted in the MOE program and AM1 [41] Hamiltonian. The conformations obtained were used as starting conformations for docking analysis. The physicochemical properties of the ligands are reported in Table 3. Lipinski's rule [42], which is a valuable tool for selecting good candidates by predicting drug-like properties, was also verified for all our ligands. In Figure 1, the enzyme active site with the co-crystallisation molecule is presented,

The table 3 reflects the fact that our ligands are non-toxic and can present biological activities

3. Results and discussion

3.1. Molecular docking

The molecular docking analysis was performed using the MOE program with 16 compounds, including flavonoids and sesquiterpenes. First, the validation method was employed to assess the

docking machine's capability. Figure 2 represents the validation result of the docking protocol. All of the redocking ligands showed similar conformation to the native redocking ligands, and the RMSD values were ≤ 2.0 Å

Each natural compound was then docked into each of four different targets. The lowest energy docked conformation of the best cluster was selected and analyzed. Table 4 summarizes the docking study results, presented as binding energy

The molecular docking results and the interactions of the 2 best natural and synthetic inhibitor ligands for each docked to target macromolecules are shown in Tables 5 and 6, and Figures 3 and 4. Residues are marked with their amino acid code of 3 letters, and job classification [43-44]. If there are multiple channels in the system, the positions are prefixed by the letters of the alphabet. Interactions between 2.5 Å and 3.1 Å are considered high, and those between 3.1 Å and 3.55 Å are average. Interactions greater than 3.55 Å are weak [45].

3.3. Interaction with Aromatase

The interaction of the co-crystallized natural substrate testosterone (Fig. 3) displayed hydrogen bonding of the CO group at position 17 with the amino group of the key amino acid Met374, which is well known to initiate the enzymatic oxidation cascade.

The MOE docking score of compounds ranged from -1.73 to -7.3203 kcal/mol (Table 4). The compounds 3-O-Methylquercetin and 3-O-Acetylpadmatin had high negative MOE docking scores of -7.3203 and -7.1806 kcal/mol, respectively. Based on the binding affinity, we selected the top two ligands, i.e., for intermolecular contact analysis as illustrated in Fig 3 and Table 5. As shown in Table 5, NE1 TRP 141(A) of Aromatase formed one strong hydrogen bonds H-acceptor

With the atom of 3-O-Methylquercetin. Similarly, N ALA 438 (A) formed a pi-H interaction with the ligand. 3-O-Acetylpadmatin at distance 4.53 Å and an energy of -1.0 kcal/mol

The complex formed with Formestane has the lowest energy (-7.42983532 Kcal/mol) and is more active than the complex formed with Anastrozole (-6.8813014 Kcal/mol), which is more active than the complex formed with Estrone (-5.8988533 Kcal/mole).

For complex (Figure 5): Formestane interacts with the amino acid [N MET 374 (A) H-acceptor] at a distance of 3.06 Å and an energy of -2.0 kcal/mol (strong interaction)

For complex (Figure 3): Anastrozole interacts with the amino acid [SG CYS 437 (A) H-acceptor] at a

distance of 3.04 Å and an energy of -2.0 kcal/mol (strong interaction)

The inhibitor of the co-crystallisation testosterone C₁₉ H₂₈ O₂ (5JKW)

Energy (Formestane (-7.42983532 Kcal/mol<Anastrozole -6.8813014 Kcal/mol)

Energy (3-O-Methylquercetin -7.3203 Kcal/mol<3-O-Acetylpadmatin -7.1806 Kcal/mol)

3-O-Methylquercetin and Formestane would be the best to slow down the evolution of studied pathology (breast cancer).

3.4. Interaction with mTOR

The native ligand showed the occurrence of three hydrogen bonds with OD2 ASP 2195 (A)

(H-donor), N VAL 2240 (A) (H-acceptor) and 6-ring TRP 2239 (A) (H-pi) at distances of 2.46, 2.74, and 4.03 Å and energies of -2.0, -3.5, and -0.7 kcal/mol, respectively

The model interaction of Nepetin and Hispidulin to the binding site of mTOR was similar to the model interaction of the native ligand.

For complex (Figure 4): Nepetin interacts with the amino acid [N VAL 2240 (A) H-acceptor 5-ring TRP 2239 (A) H-pi] at a distance of 3.31; 4.07 Å and an energy of -0.7; -0.9 kcal/mol respectively (for the 1st average interaction, 2nd weak interaction)

For complex (Figure 4): Hispidulin interacts with the amino acid [N VAL 2240 (A) H-acceptor 5-ring TRP 2239 (A) H-pi] at distances of 3.31; 4.07 Å and energies of -0.7; -0.9 kcal/mol respectively (for the 1st average interaction, 2nd weak interaction)

The complex formed with OSI-027 has the lowest energy (-7.94096422 Kcal/mol) and is more active than the complex formed with Palomid 529 (-7.92637825 Kcal/mol), which is more active than the complex formed with GSK1059615 (-7.53462267 Kcal/mol).

For complex (Figure 4): OSI-027 interacts with the amino acid [N VAL 2240 (A) H-acceptor; CE MET 2345 (A) pi-H; 6-ring TRP 2239 (A) pi-pi; 6-ring TRP 2239 (A) pi-pi] at distances of 3.51, 3.95, 3.96, 3.76 Å and an energies of -1.1, -0.6, -0.0, -0.0 kcal/mol (1st average interaction, 2nd,3rd,4th weak interaction)




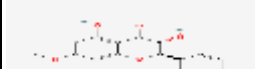

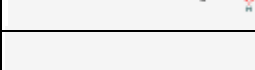

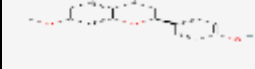


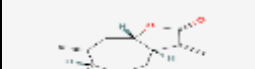
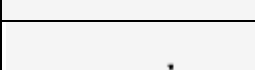

For complex (Figure 4): Palomid 529 interacts with the amino acid [OD2 ASP 2357 (A) H-donor; CE MET 2345 (A) pi-H; 6-ring TRP 2239 (A) pi-pi ;)] at distances of 3.08, 3.65, 3.91 Å and an energy of -1.7, -0.7, -0.0, kcal/mol (1st strong interaction, 2nd, 3rd weak interaction)

The inhibitor of the co-crystalisation 3-(4-morpholin-4-yl)pyrido[3',2':4,5]furo[3,2-d]pyrimidin-2-yl)phenol C₁₉ H₁₆ N₄ O₃ (4JT6)).

Energy (OSI-027 (-7.94096422Kcal/mol< Palomid 529 -7.92637825 Kcal/mol)
 Energy (Nepetin -7.53395605Kcal/mol< Hispidulin -7.34554195Kcal/mol)

Nepetin and OSI-027 would be the best to slow down the evolution of the studied pathology (breast cancer).

Table1. Synthetic and Natural for Aromatase, mTOR

ligand	IUPAC name	Structure	Cid
Genkwanin	5-hydroxy-2-(4-hydroxyphenyl)-7-methoxychromen-4-one		5281617
Isokaemperide	5,7-dihydroxy-2-(4-hydroxyphenyl)-3-methoxychromen-4-one		5280862
3-O-Methylquercetin	2-(3,4-dihydroxyphenyl)-5,7-dihydroxy-3-methoxychromen-4-one		5280681
Padmatin	(2R,3R)-2-(3,4-dihydroxyphenyl)-3,5-dihydroxy-7-methoxy-2,3-dihydrochromen-4-one		12313901
Dihydrokaempferol	3,5,7-trihydroxy-2-(4-hydroxyphenyl)-2,3-dihydrochromen-4-one		662
Isocostic acid	2-[(2R,4aR)-4a,8-dimethyl-2,3,4,5,6,7-hexahydro-1H-naphthalen-2-yl]prop-2-enoic acid		10922464
Sakuranetin	(2S)-5-hydroxy-2-(4-hydroxyphenyl)-7-methoxy-2,3-dihydrochromen-4-one		73571
Tomentosine	(3aR,7S,8aR)-7-methyl-3-methylidene-6-(3-oxobutyl)-4,7,8,8a-tetrahydro-3aH-cyclohepta[b]furan-2-one		155173
<u>3-Acetyl-7-O-methylaromadendrin</u>	(2R,3R)-5-hydroxy-2-(4-hydroxyphenyl)-7-methoxy-4-oxo-2,3-dihydrochromen-3-yl] acetate		15139424
Inuviscolide	(3aS,5aS,8R,8aR,9aR)-8-hydroxy-8-methyl-1,5-dimethylidene-3a,4,5a,6,7,8a,9,9a-octahydroazulenof[6,5-b]furan-2-one		176489
Ilicic Acid	2-[(2R,4aR,8R,8aR)-8-hydroxy-4a,8-dimethyl-1,2,3,4,5,6,7,8a-octahydronaphthalen-2-yl]prop-2-enoic acid		11876195
3-O-Acetylpadmatin	[(2R,3R)-2-(3,4-dihydroxyphenyl)-5-hydroxy-7-methoxy-4-oxo-2,3-dihydrochromen-3-yl] acetate		10406203
Taxifolin	(2R,3R)-2-(3,4-dihydroxyphenyl)-3,5,7-trihydroxy-2,3-dihydrochromen-4-one		439533





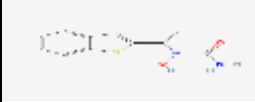

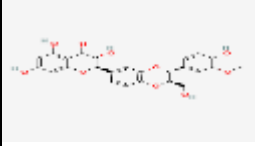
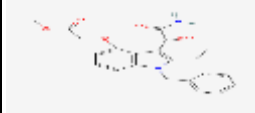
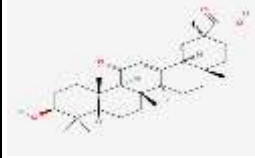
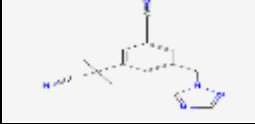

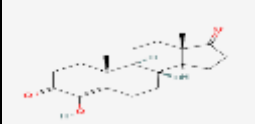


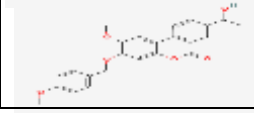
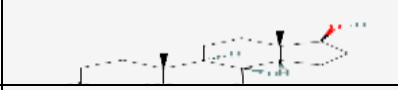
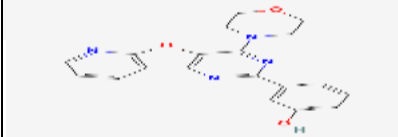
Nepetin	2-(3,4-dihydroxyphenyl)-5,7-dihydroxy-6-methoxychromen-4-one		5317284
Aromadendrin	(2R,3R)-3,5,7-trihydroxy-2-(4-hydroxyphenyl)-2,3-dihydrochromen-4-one		122850
Hispidulin	5,7-dihydroxy-2-(4-hydroxyphenyl)-6-methoxychromen-4-one		5281628
Sulfasalazine	2-hydroxy-5-[[4-(pyridin-2-ylsulfamoyl)phenyl]diazenyl]benzoic acid		5339
Zileuton	1-[1-(1-benzothiophen-2-yl)ethyl]-1-hydroxyurea		60490
Aminobenzoic acid	5-acetamido-2-hydroxybenzoic acid		65512
Silibinin	2R,3R)-3,5,7-trihydroxy-2-[(2R,3R)-3-(4-hydroxy-3-methoxyphenyl)-2-(hydroxymethyl)-2,3-dihydro-1,4-benzodioxin-6-yl]-2,3-dihydrochromen-4-one		31553
Varspladib	Methyl2-(1-benzyl-2-ethyl-3-oxamoylindol-4-yl) oxyacetate		9886917
Glycyrrhetic acid	(2S,4aS,6aR,6aS,6bR,10S,12aS,14bR)-10-hydroxy-2,4a,6a,6b,9,9,12a-heptamethyl-13-oxo-3,4,5,6,6a,7,8,8a,10,11,12,14b-dodecahydro-1H-picene-2-carboxylic acid		9897771
Anastrozole	2-[3-(2-cyanopropan-2-yl)-5-(1,2,4-triazol-1-ylmethyl)phenyl]-2 methylpropanenitrile		2187
Estrone	(8R,9S,13S,14S)-3-hydroxy-13-methyl-7,8,9,11,12,14,15,16-octahydro-6H-cyclopenta[a]phenanthren-17-one		5870
Formestane	8R,9S,10R,13S,14S)-4-hydroxy-10,13-dimethyl-2,6,7,8,9,11,12,14,15,16-decahydro-1Hcyclopenta[a]phenanthrene-3,17-dione		11273
GSK1059615	(5Z)-5-[(4-pyridin-4-ylquinolin-6-yl)methylidene]-1,3-thiazolidine-2,4-dione		23582824
OSI-027	4-[4-amino-5-(7-methoxy-1H-indol-2-yl)imidazo[5,1-f][1,2,4]triazin-7-yl]cyclohexane-1-carboxylic acid		135398516
Palomid 529	8-(1-hydroxyethyl)-2-methoxy-3-[(4-methoxyphenyl)methoxy]benzo[c]chromen-6-one		11998575

Table 2. Target macromolecules, pdb codes, native ligands, and ligand structures used in the docking study

Target macromolecule (pdb code)	Ligand	Structure
Aromatase (PDS ID: 5JKW)	Testosterone	
mTOR (PDS ID: 4JT6)	3-(4-morpholin-4-ylpyrido[3',2':4,5]furo[3,2-d]pyrimidin-2-yl)phenol	

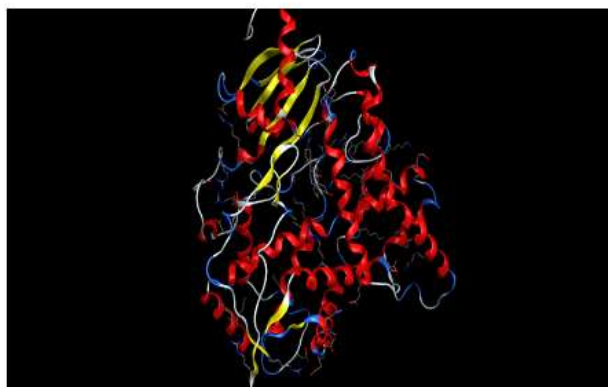


Figure 1.e. Simplified model of enzyme 5JKW.

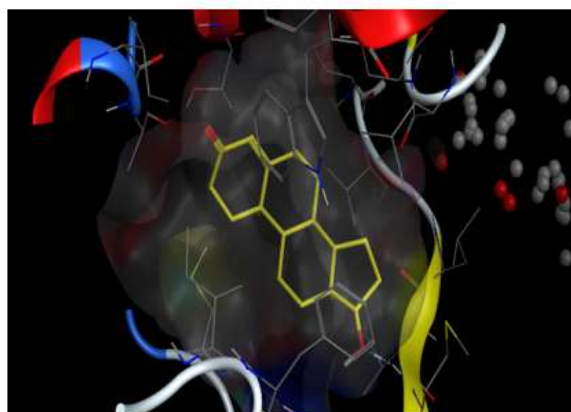


Figure 1.f. Active site enzyme isolated 5JKW

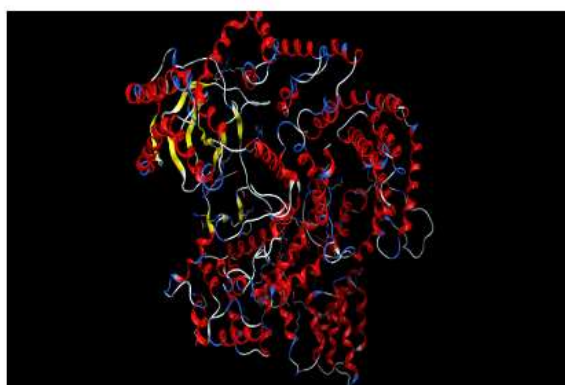


Figure 1.g. Simplified model of enzyme 4JT6.

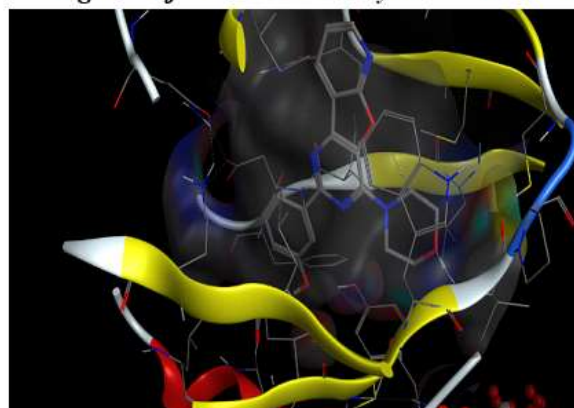


Figure 1.h. Active site enzyme isolated 4JT6

Table 3. Ligand properties (Weight: Molecular weight, TPSA (Å^2): Polar surface area, logP: Octanol-water partition coefficient, logS: aqueous solubility, H-donor: Number of H-bond donors, H-acceptor: Number of H-bond acceptors)

Ligand	Weight	H donor	H acceptor	Toxicity	TPSA	Log P	Log S
Genkwanin	284.26	2	5	NO	76	1.88	-4.02
Isokaempferide	300.26	3	6	NO	96.2	1.77	-3.70
3-O-Methylquercetin	316.26	4	7	NO	116	1.47	-3.33
Padmatin	318.28	4	7	NO	116	0.78	-2.26
Dihydrokaempferol	288.25	4	6	NO	107	1,58	-2,37
Isocostic acid	234.33	1	2	NO	37.3	3,93	-4,03
Sakuranetin	286.28	2	5	NO	76	2,91	-2,78
Tomentosin	248.32	0	3	NO	43.4	2,81	-1,66
3-Acetyl-7-O-methylaromadendrin	344.3	2	7	NO	102	2,45	-3,4
Inuviscolide	248.2	1	3	NO	46.5	2,21	-1,97
Illicic acid	252.35	2	3	NO	57.53	2,98	-3,09

3-O-Acetylpadmatin	360.3	3	8	NO	122.3	2.16	-3.04
Taxifolin	304.25	5	7	NO	107	1.28	-2.01
Nepetin	316.26	4	7	NO	116	2.13	-3.15
Aromadendrin	288.25	5	7	NO	107	1.58	-2.37
Hispidulin	300.26	3	6	NO	96.2	1.6	-3.7
Sulfasalazine	398.4	3	9	YES	150	3.70	-3.60
Zileuton	236.29	2	3	YES	94.8	2.83	-3.26
Aminobenzoic acid	195.17	3	4	NO	86.6	1.05	1.20
Silibinin	482.4	5	10	NO	155	2.55	-4.23
Varspladib	394.4	1	5	NO	101	2.74	-4.89
Glycyrrhetic acid	470.7	2	4	NO	74.6	6.41	-7.5
Anastrozole	293.4	0	4	NO	78.3	3.20	-3.28
Estrone	270.4	1	2	NO	37.3	3.82	-4.11
Formestane	302.4	1	3	NO	54.4	3.97	-3.49
GSK1059615	333.4	1	5	NO	97.2	3.62	-4.85
OSI-027	406.4	3	7	NO	131	1.96	-4.26
Palomid 529	406.4	1	6	NO	74.2	4.90	-6.71

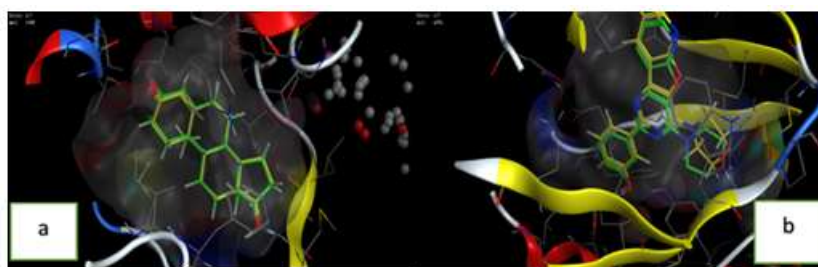


Figure 2. Overlay of the native ligands (green and redocking conformations (yellow)). a: Aromatase; b: mTOR

Table 4. Binding energy values of natural compounds docked to target macromolecules

Compound	Target macromolecules; binding energy (kcal/mole)	
	Aromatase	mTOR
Native ligand	-7.93799925	-7.68270063
Genkwanin	-6.66764975	-7.29410458
Isokaempferide	-6.64026356	-7.20955992
-O-Methylquercetin	-7.32033253	-7.13036156
Padmatin	-6.77696371	-6.95807457
Dihydrokaempferol	-6.5309844	-7.09474707
Isocostic acid	-5.72296953	-5.88483858
Sakuranetin	-6.50466204	-7.09026051
Tomentosin	-6.08291531	-6.23123217
3-Acetyl-7-O-methylaromadendrin	-6.77639961	-6.65298319
Inuviscolide	-5.78432655	-4.10180426
Illicic acid	-6.1924181	-4.67336988
3-O-Acetylpadmatin	-7.18064833	-7.13507795
Taxifolin	-6.23695421	-7.18906593
Nepetin	-6.51157475	-7.53395605
Aromadendrin	-6.31232071	-6.99058771
Hispidulin	-6.54323149	-7.34554195

Sulfasalazine	-	-
Zileuton	-	-
Aminobenzoic acid	-	-
Silibinin	-	-
Varspladib	-	-
18B Glycyrrhetic acid	-	-
Anastrozole	-6.8813014	-
Estrone	-5.8988533	-
Formestane	-7.42983532	-
GSK1059615	-	-7.53462267
OSI-027	-	-7.94096422
Palomid 529	-	-7.92637825

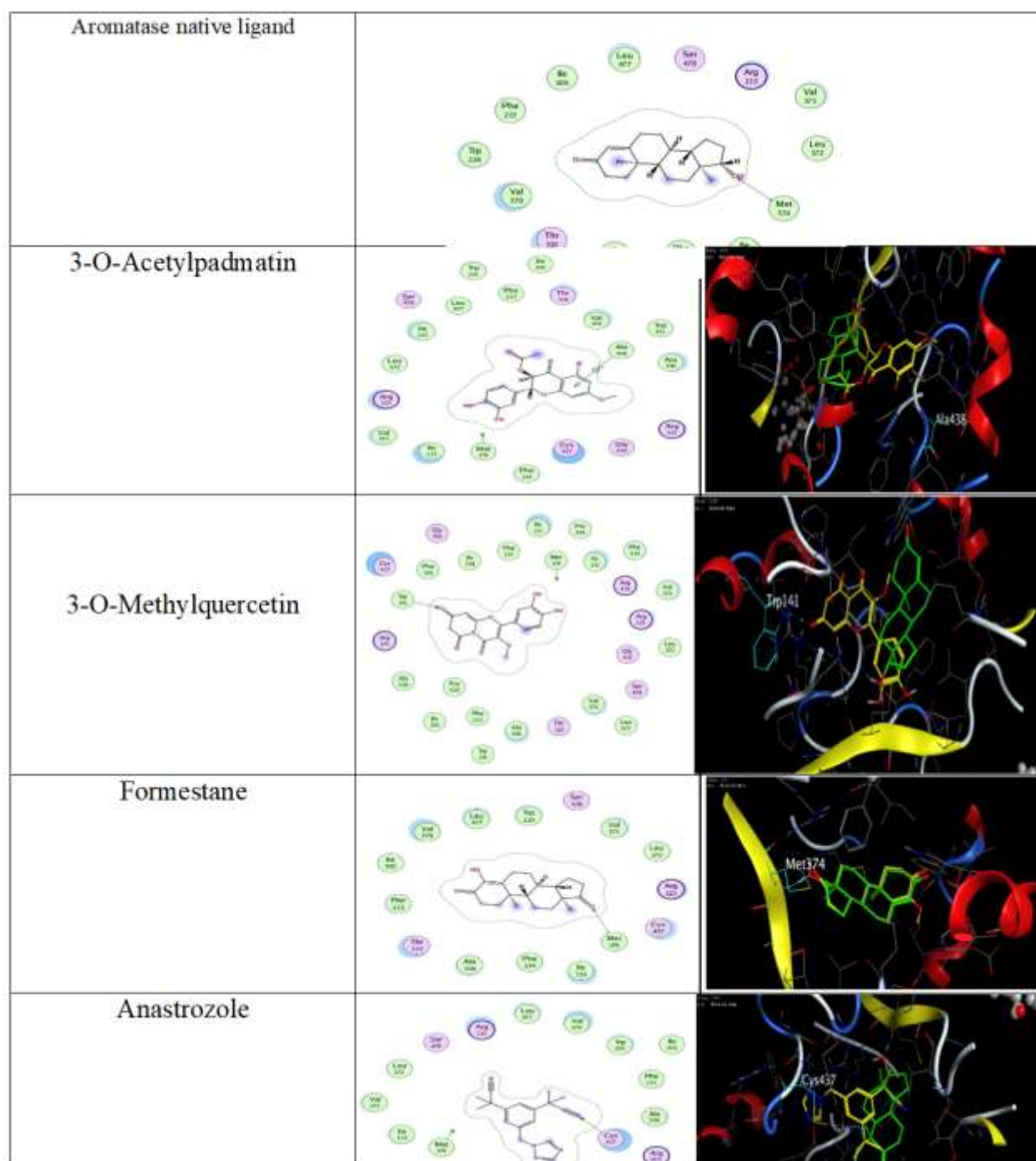


Figure 3. Model interaction of Aromatase native ligand, 3-O-Acetylpadmatin, and 3-O-Methylquercetin, Formestane, Anastrozole

Table 5. Interactions patterns observed in the determined complexes between the ligands and the corresponding amino acid in Aromatase

Ligands	Receptor	Interactions	Distances (Å)	Energies (Kcal/mol)
TES	N MET 374 (A)	H-acceptor	2.69	-3.1
3-O-Methylquercetin	NE1 TRP 141 (A)	H-acceptor	3.12	-2.0
3-O-Acetylpadmatin	N ALA 438 (A)	pi-H	4.53	-1.0
Formestane	N MET 374 (A)	H-acceptor	3.04	-2.0
Anastrozole	SG CYS 437(A)	H-acceptor	3.91	-0.7

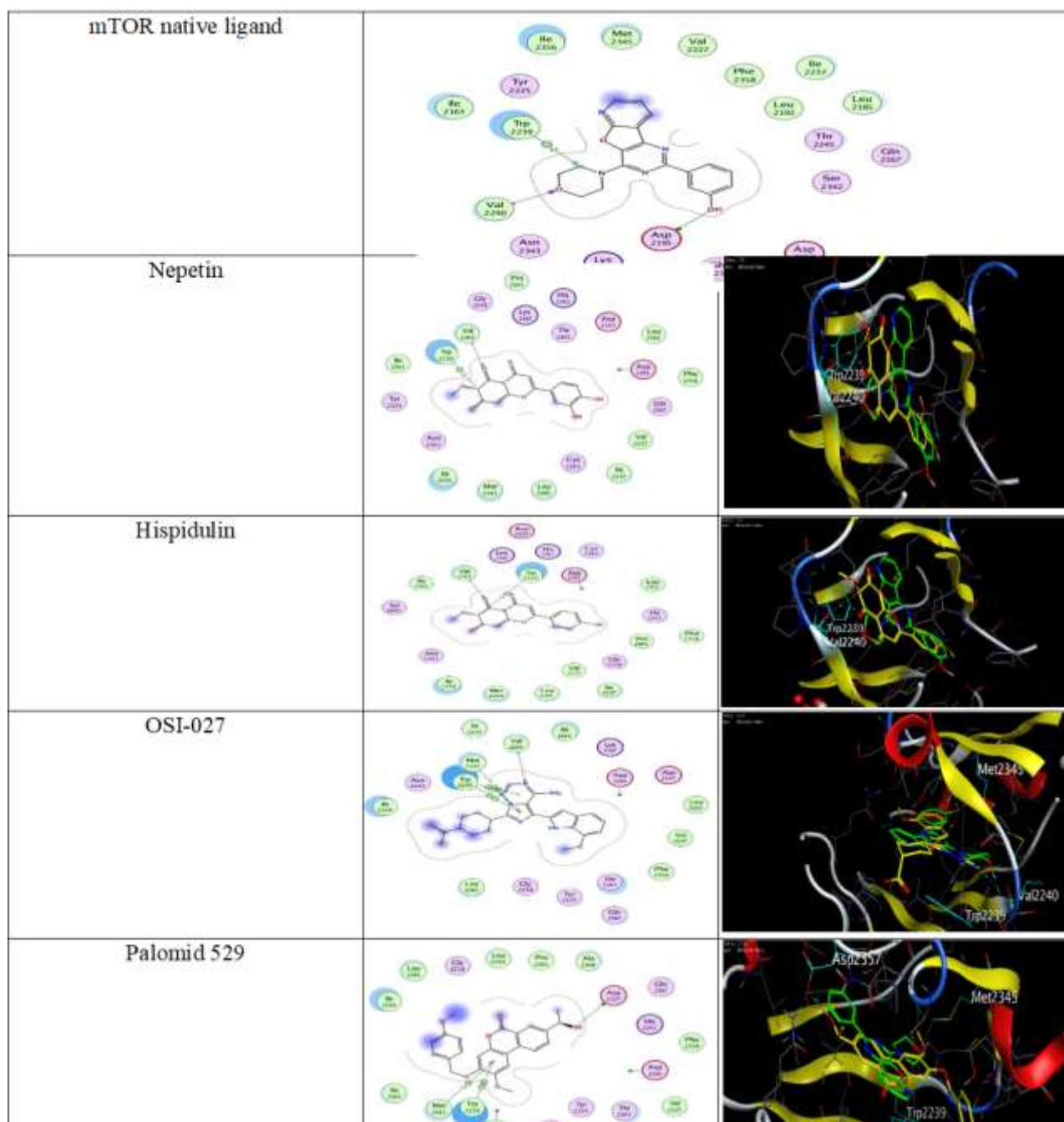


Figure 4. Model interaction of mTOR native ligand, Nepetin, and Hispidulin, OSI-027, Palomid 529

Table 6. Interaction patterns observed in the determined complexes between the ligands and the corresponding amino acid in mTOR

Ligands	Receptor	Interactions	Distances (Å)	Energies (Kcal/mol)
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X6K	OD2 ASP 2195 (A)	H-donor	2.46	2.0
	N VAL 2240 (A)	H-acceptor	2.74	-3.5
	6-ring TRP 2239 (A)	H-pi	4.03	-0.7
Nepetin	N VAL 2240 (A)	H-acceptor	3.31	-0.7
	5-ring TRP 2239 (A)	H-pi	4.07	-0.9
Hispidulin	N VAL 2240 (A)	H-acceptor	3.31	-0.8
	5-ring TRP 2239 (A)	H-pi	4.07	-0.7
OSI-027	N VAL 2240 (A)	H-acceptor	3.51	-1.1
	CE MET 2345 (A)	pi-H	3.95	-0.6
	6-ring TRP 2239 (A)	pi-pi	3.96	-0.0
	6-ring TRP 2239 (A)	pi-pi	3.76	-0.0
Palomid 529	OD2 ASP 2357 (A)	H-donor	3.08	-1.7
	CE MET 2345 (A)	pi-H	3.65	-0.7
	6-ring TRP 2239 (A)	pi-pi	3.91	-0.0

4. Conclusions

The present study demonstrated the inhibitory potential of natural ligands of *Inula viscosa* and synthetic compounds against Aromatase and mTOR through computational approaches. Those four macromolecule inhibitors have emerged as promising candidates for the treatment of breast cancer (aromatase, mTOR). Thus, searching for safer and potent inhibitors of the two enzymes from natural sources is desirable. Accordingly, in the present study (The interaction to aromatase: the natural compound such as Nepetin and synthetic such as OSI-027, and for the interaction to mTOR, 3-O-Methylquercetin and Formestane would be the best to slow down the evolution of studied pathology (breast cancer). Natural compounds are in accordance with Lipinski rules for oral drug administration [42]. On the other hand one comparing those two inhibitors, we conclude that the natural inhibitor presents better activity compared to the synthetic one, and it can contribute as an efficient treatment of the pathology (breast cancer)

Author Statements:

- **Ethical approval:** The conducted research is not related to either human or animal use.
- **Conflict of interest:** The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper
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- **Data availability statement:** The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.
- **Use of AI Tools:** The author(s) declare that no generative AI or AI-assisted technologies were used in the writing process of this manuscript.

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