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A. D. Folayan

folayanadeniyi@gmail.com

Federal University of Agriculture

J. K. Akintunde

Federal University of Agriculture

A. J. Akamo

Federal University of Agriculture

A. S Oyelakin

Federal University of Agriculture

Research Article

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Posted Date: September 24th, 2025

DOI: <https://doi.org/10.21203/rs.3.rs-6177103/v1>

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Additional Declarations: No competing interests reported.

Therapeutic impact of *Garcinia kola*-derived compounds against progesterone receptor in breast cancer using molecular docking.

A.D. Folayan^{a*}, J.K. Akintunde^a, A.J. Akamo^a, A.S Oyelakin^b

^a Drug Discovery and Molecular Toxicology Research Group, Department of Biochemistry, College of Biosciences, Federal University of Agriculture, Abeokuta, Nigeria.

^b Department of Pure and Applied Botany, College of Biosciences, Federal University of Agriculture, Abeokuta, Nigeria.

* Corresponding author: folayanadeniyi@gmail.com

Fax number: +234-8069002829

Abstract

Background

This study used molecular docking to examine the therapeutic impact of *Garcinia kola*-derived compounds against progesterone receptors in breast cancer.

Objective

The progesterone receptor (PR) is a well-established therapeutic target in managing hormone receptor-positive (HR+) breast tumours. Therefore, molecules that can inhibit PR act as novel breast cancer therapies. Thus, using molecular docking analyses, this study aims to assess the inhibitory impact of *Garcinia kola* oil components on progesterone receptors in breast cancer.

Methods

Garcinia kola oil was separated into constituents with the High-Performance Liquid Chromatography (HPLC) protocol via the Agilent Technologies 1200 HPLC series. The Maestro module version 11.8 was used to obtain the structure of the human PR. AutoDock Vina was used to dock the *Garcinia kola*-derived compounds against PR, and QikProp was used to assess the physicochemical and pharmacokinetic characteristics.

Results

The numerous results obtained in this study demonstrate the effectiveness of the oil constituents of Bitter kola (GKO). The HPLC findings for the *Garcinia kola* seeds reveal that Quercetin and Gallic acid exhibited the highest concentration, measuring 18.10 and 16.71 ppm respectively. The outcome of the docking of PR against the *Garcinia kola* oil compounds revealed a good interaction as Methyl 9-cis, 11-trans-octadecadienoate, Squalene, 8,11-Octadecadienoic acid, methyl ester had the most notable docking values of -14.699 kcal/mol, followed by squalene and 8,11-

Octadecadienoic acid, methyl, which had docking values of -10.398 kcal/mol and -8.351 kcal/mol respectively.

Conclusions

Compounds derived from *Garcinia kola* oil significantly mitigated breast cancer as revealed by the data from *in-silico* analyses, especially molecular docking, binding free energy, and predicted pIC₅₀ results. Taken together, *Garcinia kola* oil could be an innovative therapeutic lead against progesterone receptor-implicated breast cancer.

Keywords: Breast cancer, Progesterone receptor, *Garcinia kola* oil, Docking, squalene, Methyl 9-cis,11-trans-octadecadienoate, HPLC

1. Introduction

Breast cancer, which is characterised by an uncontrolled cell division often unresponsive to cellular growth check mechanisms in the mammary gland has been nicknamed ‘a global health concern’ [1, 2]. Undoubtedly, breast cancer-related mortality is the most common among women living with cancer [3]. To put this in perspective, almost 700, 000 deaths were recorded out of less than 2.5 million women diagnosed with breast cancer in 2022 [4]. According to projections, the cases of mortality due to breast cancer across the globe have been estimated to rise to over 1.5 million in 2050 [5]. Therefore, to minimise cancer-associated death while optimising treatment and improving quality of life, early diagnosis and management of breast cancer is essential.

The human progesterone receptor (HPR) has been recognised as a regulator of estrogen receptor alpha activity, and it is a vital indicator in the diagnosis of hormone-receptor breast malignancy [6]. Breast cancer with a clear fundamental prognosis has been shown to correlate positively with highly expressed progesterone receptors compared to their counterparts with an unclear fundamental prognosis. In context, over 70 out of 100 breast cancer cases are categorised as hormone receptor-positive [7]. This confirms that these malignant cells either express progesterone receptor, estrogen receptor or both which further establishes the indispensability of HPR in breast cancer treatment [8].

Recently, the fight against breast cancer has focused on developing molecular targets for key receptors identified in the development and progression of breast cancer. This has proven to be a novel way to abrogate the impacts of breast cancer [9, 10]. Thus, through molecular biology and bioinformatics methods including molecular docking, binding free energy, quantitative structure-activity relationship evaluation, pharmacodynamics and pharmacokinetics assessment, among others, the process of recognising therapeutic compounds from natural products has meaningfully

accelerated [11, 12]. Accordingly, Shahab *et al.* [13], engaged in molecular simulations to identify unique HPR inhibitors, affirming that HPR is a crucial therapeutic target in developing medicinal candidates against breast cancer.

Garcinia kola is widely known to possess novel therapeutic compounds essential in treating various illnesses including cancer and hypertension [14, 15]. Folayan *et al.* [16] established the inhibitory prowess of *Garcinia kola*-derived compounds against epidermal growth factor receptors (EGFR). Similarly, Eugene-Osokhia *et al.* [17] established the inhibitory ability of a flavonoid obtained from *Garcinia kola* seed on estrogen receptor alpha via *in-silico* analyses. Nevertheless, limited data exists on the inhibitory mechanism of *Garcinia kola* oil on progesterone receptors. This study therefore assesses the therapeutic impact of *Garcinia kola*-derived compounds against progesterone receptors in breast cancer using molecular docking.

2. Materials and procedures

2.1 Seed procurement and oil extraction

We purchased newly harvested *Garcinia kola* (Heckel) Guttiferae seeds on a farm in Ibadan, Nigeria, these were sorted to ensure they were neat enough. The identification and verification of the seeds were conducted at the Herbarium Laboratory of the Department of Botany, Faculty of Science, at the University of Ibadan, Ibadan, Oyo State, Nigeria after which they were assigned UI-00138/01 as the approval voucher [18]. The outer coat was removed, and the seeds were rinsed with water. Afterwards, they were thin-sliced and air-dried for 30 days. The air-dried products were ground with an electric grinder with stainless steel to avoid metals leaching into the ground seed. *Garcinia kola* oil was extracted from about 3 kilogrammes of the powder using the Soxhlet apparatus and n-hexane was used as the solvent. To ensure that n-hexane is completely removed, the oil was subjected to rotary evaporation and attached to a water bath to allow it to evaporate nicely at 40⁰C generating a deep brown honey-like *Garcinia kola* oil. This was preserved shortly in an airtight container for *in-silico* analyses [18].



Figure 1: *Garcinia kola* seeds



Figure 2: *Garcinia kola* oil in a sealed bottle

2.2 Separation of *Garcinia kola* oil via High-Performance Liquid Chromatography (HPLC)

Approximately 100 mg of *Garcinia kola* oil was dissolved with 5 mL of HPLC-compliant methanol in a conical flask. The filtrate obtained from the resulting solution was separated using a high-performance liquid chromatograph under the following chromatographic conditions.

Table 1: Chromatographic conditions

Parameters			Settings
Agilent	Technologies	1200	Reversed-phase chromatography
HPLC			
Mobile phase			Acetonitrile + 0.1% methanoic acid
Stationary phase			Hypersil BDS C18 (Agilent)
Column dimension			250mm x 4.0 mm
Flow Rate			0.6 mL/min
Volume injected			10 µL
Detector's Wavelength			280 nm
Elution mode			Gradient elution

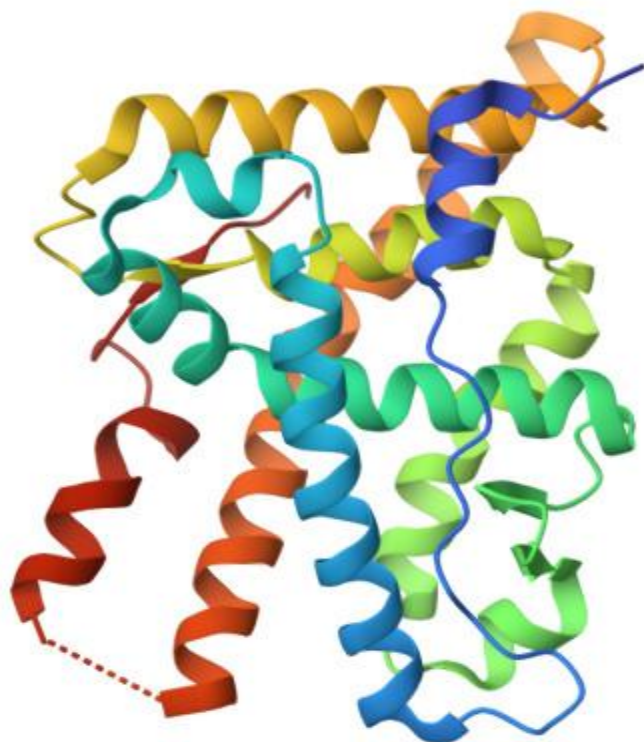


Figure 3: 3-D structure of human Progesterone receptor (HPR) [19].

2.3 Molecular Docking Analysis

Docking represents a computer-assisted procedure for forecasting the bound geometries of two or more molecules. Molecules can be docked either manually with computer graphics or via automated computer algorithms [20]. The molecular docking method is devised to assist in developing therapeutic drug candidates. It can be divided into rigid and flexible docking. Flexible docking requires a rigid and small molecular ligand while flexible docking requires a rigid receptor and a small flexible molecular ligand [21].

2.3.1 Protein Preparation

The 3D structure of the human progesterone receptor (PDB ID-4OAR) was obtained from the RCSB databank while the crystal structure was prepared via Maestro v11.8's protein preparation wizard engaging the technique expressed by [22, 23]. The protein preparation method addresses several defects inherent in a PDB structure, such as omitted hydrogen atoms, absent side chains, absent loops, and so on. Briefly, the 4OAR structure was included in the workspace on the Maestro interface, we launched protein preparation in the toolbar. Before protein preparation, the diagnosis was carried out via the diagnostic tab. The missing side chains were fixed. On the default settings optimising H-bond assignments, confirming pre-process and cleaning tasks were all toggled on [24, 25, 26]. The pre-processing stage was carried out where the missing side chains were fixed, water molecules beyond the specified distance (5.0 Å) were deleted, bond order was assigned, and hydrogen atoms were replaced [27]. pH was kept at 7.4 to reflect the experimental or physiological condition of the crystal structure to generate the protonation and tautomeric state for the het groups. The next phase was the hydrogen optimisation stage. Here, at pH 7.4, the hydrogen bond network was optimised using PROPKA [28, 29]. To relax our crystal structure a bit and ensure all atoms are in a reasonable location, a restrained minimisation was carried out during the clean-up phase.

It is restrained such that the heavy atom RMSD from the original is set at 0.3 Å. The geometry of the ligand-protein complex was refined using an OPLS3 force field [29]. After all the phases had been adequately checked, the protein preparation was run and the prepared protein was added to the entry list ready for docking after the different components of the crystal structure had been certified free of problems with side chains, water molecules and het groups among others. This process is in line with the Schrodinger Release [24].

2.3.2 Preparation of ligands using LigPrep

LigPrep is an instrument designed to reliably and quickly build high-quality tiny molecular ligand complexes for structure-based simulation and other computational procedures [26]. It uses Epik to create potential tautomeric, protonation and conformational states at a specific pH. The prepared protein was selected, followed by the ligand_3D builder and ligand_2D builder sketcher. Having set the pH range at 7.0 ± 2.0 , the maximum ligand size at 500 atoms and force field as OPLS 3.

This study employed LigPrep to construct the ligand structures required for the docking process and generate a specific low-energy 3D conformer with the proper bond dimensions for the 2D structures derived from *Garcinia kola* oil. Each ligand's ionisation states and every potential protomer were compiled at a pH of 7.4. For compounds devoid of stereogenic centres, stereoisomers were developed with at most 32 stereoisomers for each ligand. Having generated the tautomers, the study retained ligands with the least energy conformers and the output was set at maestro.

2.3.4 Phytocompounds preparation

Previously, Folayan *et al.* [16] employed GC-MS to identify the phytocompounds present in *Garcinia kola*-derived oil. Molview (<https://app.molview.com/>) was engaged in drawing the 2D and 3D structures as seen in Tables 3 and 8. Preparation of ligands was accomplished with LigPrep while subsequent processes such as the generation of stereoisomers were conducted accordingly. To accurately predict the protein-ligand binding measured over a wide range of targets and ligands, the force field (OPLS3) was employed in line with the technique detailed by Harder *et al.* [31].

2.3.5 Dimension of coordinates

A receptor grid generation panel created a receptor grid file which depicts the active region for the docking of ligands. To relax the non-polar regions of the receptor, the atomic parameters especially the scale factor are fixed at 1.0 having a partial cut-off of 0.25. The resolution of the grid box was determined at coordinates 9.8, 68.0, and 93.91, corresponding to the X, Y, and Z axes, using 3 as the coordinate system dimension [23].

2.3.6 Glide docking process

The docking of the *Garcinia kola*-derived compounds against the active pocket of crystals was conducted with improved accuracy via the glide docking process in line with the technique of Yang *et al.* [32].

2.3.7 Induced fit docking

The technique detailed by Sherman *et al.* [33] was followed while conducting the induced fit docking analysis.

2.3.8 Binding-free energy determined

The binding free energy of the complex formed between the ligand and receptor was determined via the Molecular Mechanics/Generalised Born Surface Area (MM-GBSA) panel and the MM-GBSA technology provided by Prime [27]. The MM/GBSA procedure is commonly employed to determine the binding-free energy between two molecules, such as a ligand and a receptor. After energy minimisation, MMGBSA calculated the energy difference between the bound and unbound states of the ligand and protein using the OPLS3 force field and VSGB as the continuum solvent model.

The MM/GBSA system used in this study was prepared by performing MD simulations on the bound complex (receptor-ligand), receptor-only, and ligand-only states. Snapshots were selected from the MD trajectory for analysis, which could represent the most populated or average structures. In MM/GBSA, the binding free energy (ΔG_{bind}) was arrived at by summing-up several energy components:

$$\Delta G_{\text{bind}} = \Delta E_{\text{MM}} + \Delta G_{\text{solvation}} - T\Delta S$$

where:

ΔE_{MM} : Molecular mechanics energy (includes van der Waals and electrostatic terms).

$\Delta G_{\text{solvation}}$: Solvation free energy (polar and nonpolar components).

$T\Delta S$: Entropic term (often approximated due to computational cost).

Each of these components is computed as follows:

a. Molecular Mechanics Energy (ΔE_{MM})

$$\Delta E_{\text{MM}} = E_{\text{vdW}} + E_{\text{electrostatic}}$$

Van der Waals Energy (EvdW): Calculated using the Lennard-Jones potential to represent attractive and repulsive forces between non-bonded atoms.

Electrostatic Energy ($E_{\text{electrostatic}}$): Calculated from Coulombic interactions between partial charges on atoms.

b. Solvation free energy ($\Delta G_{\text{solvation}}$)

Polar Solvation Energy: Computed using the Generalised Born (GB) model, which approximates the electrostatic solvation energy. This term accounts for the energy required to transfer a molecule to a polar solvent from a vacuum.

Nonpolar Solvation Energy: valued as a function of the solvent-accessible surface area (SASA). This term accounts for hydrophobic interactions.

$$\Delta G_{\text{solvation}} = \Delta G_{\text{polar}} + \Delta G_{\text{nonpolar}}$$

where:

ΔG_{polar} : Computed using GB calculations.

$\Delta G_{\text{nonpolar}} \approx \text{SASA} \times \gamma + b$ where γ is a coefficient (usually around 0.0072 kcal/mol/Å²) and b is a constant.

c. Entropy Contribution (TΔS)

Entropy changes TΔS are typically calculated through normal mode analysis, but this step is often skipped or approximated in MM/GBSA calculations due to its high computational demand. If entropy is included, it accounts for the changes in flexibility and order of the ligand and receptor upon/ binding.

Finally, MM/GBSA binding free energy was calculated as the variation in energy observed between the bound complex and the unbound states (ligand and receptor individually):

$$\Delta G_{\text{bind}} = (\text{EMM, complex} + \text{Gsolvation, complex}) - (\text{EMM, receptor} + \text{Gsolvation, receptor} + \text{EMM, ligand} + \text{Gsolvation, ligand}) \text{ [27].}$$

2.3.9 QSAR modelling

2.3.9.1 Dataset initiation and preparation

The experimental dataset containing the relevant inhibitor proteins was located via the ChEMBL repository. Furthermore, the internet server was used to BLAST the receptor's sequence. The data-warrior software (v.2) was used to adapt the Microsoft Excel document to structural data file (SDF) format, terminating the components without pIC₅₀, thereby enabling the determination of the proteins' inhibitors' bioactivities and pIC₅₀ [34].

A correct ligand preparation was made possible by transferring the SDF file to the maestro workstation. After the preparation, the chemicals were uploaded to Canvas cheminformatics. Samples were selected from each succeeding cluster after the inhibitors were canvassed for potential treatment possibilities. Clusters were discovered through this inquiry, and a representative was chosen from each cluster to create a QSAR model [35].

2.3.9.2 Model Descriptors Generation

The QSAR model was created using automation [36]. The descriptors were created via machine-learning analytical approaches to develop a QSAR model. The statistical indices, including the ranking values, Root Mean Square Error (RMSE), Standard Deviation (SD), Cross-validated coefficient (Q²) and Coefficient of Determination (R²) values, were determined computationally to assess the accuracy of the predictive model in line with established methods [37].

3. Results and Discussion

Numerous outcomes were obtained in this study, and all of these verify the therapeutic impact of the oil constituents of Bitter kola (GKO) in breast cancer management. First, the High-Performance Liquid Chromatography (HPLC) findings for the *Garcinia kola* seeds reveal that Quercetin and Gallic acid exhibited the highest concentration, measuring 18.10 and 16.71 ppm respectively, whilst Apigenin and P-Coumaric acid demonstrated the lowest quantity. Collectively, the significant concentration of these chemicals may suggest the presence of certain pharmacological actions (Table 2). Figure 4 displays the chromatogram acquired from HPLC. The examination was conducted for approximately 40 minutes using a wavelength of 280 nm, detecting nine (9) chemicals after the analysis. The graph displayed the retention times of different compounds on the horizontal axis. Gallic acid was the first component to be eluted, with a retention time of 4.688 minutes, while Naringenin had the longest retention time of 39.069 minutes.

Research has shown that the antioxidant activities of medicinal plants are mostly due to their phenolic and flavonoid content [38, 39]. This study's findings, via HPLC, showed that *Garcinia kola* oil expressed antioxidative prowess, possessed essential phytoconstituents, and thus may be a potential therapeutic agent in cancer management. The phenolic and flavonoid compounds in *Garcinia kola* oil detected using HPLC are presented in Table 2. All these substances have been known to have positive health effects. Quercetin had the highest concentration of all the substances found in the oil, followed by gallic acid with concentrations of 18.1 and 16.7 ppm, respectively. Quercetin is a potent flavonoid with various health benefits [40]. Accordingly, Asgharian *et al.* [41] investigated its potential mechanisms in cancer prevention. Gallic acid also demonstrated anti-cancer and antibacterial effects [42]. Correspondingly, its anti-hypercholesterolemic, and anti-atherosclerotic activities were reported by [43, 44].

Additionally, ferulic acid and its spin-offs have been shown to possess anticancer effects in several forms of cancer including breast cancer [45] while P-coumaric acid demonstrated chemoprotection against the low prognosis triple-negative human breast adenocarcinoma [46]. Rutin has been employed as a remedy for DMBA-induced breast cancer [47]. In addition, it can also function as a potent sensitiser for anticancer therapy [48].

Similarly, Apigenin is an antioxidative and chemo-preventive agent, particularly in the breast tissue [49]; it inhibits the expression of inflammatory mediators and can be used as a potent agent in numerous cancer treatments [50, 51, 52]. Kaempferol has antioxidant, and anti-cancer effects, while catechin has anti-inflammatory and anticarcinogenic properties [53, 54, 55]. Naringenin is a flavonoid that inhibits human cancer cells and induces programmed cell death [56]. As detailed in Table 3, *Garcinia kola* oil contains 20 constituents with their 2D structures. Previously, Folayan *et al.* [16] demonstrated that twenty phytochemicals are contained in *Garcinia kola* oil and these constituents have demonstrated anticancer activity against EGFR. Given the highly medicinal chemicals found in *Garcinia kola* oil, it may be reasonable to note that the oil may be a therapeutic candidate in the management of progesterone-receptor-implicated breast cancer.

Table 2: HPLC-identified compounds in *Garcinia kola* oil

<i>Garcinia kola</i> oil compounds	Concentration (ppm)
Gallic Acid	16.71
Catechin	4.37
P-coumaric acid	1.92
Ferulic acid	6.93
Rutin	5.55
Apigenin	1.92
Quercetin	18.10
Kaempferol	2.98
Naringenin	2.73

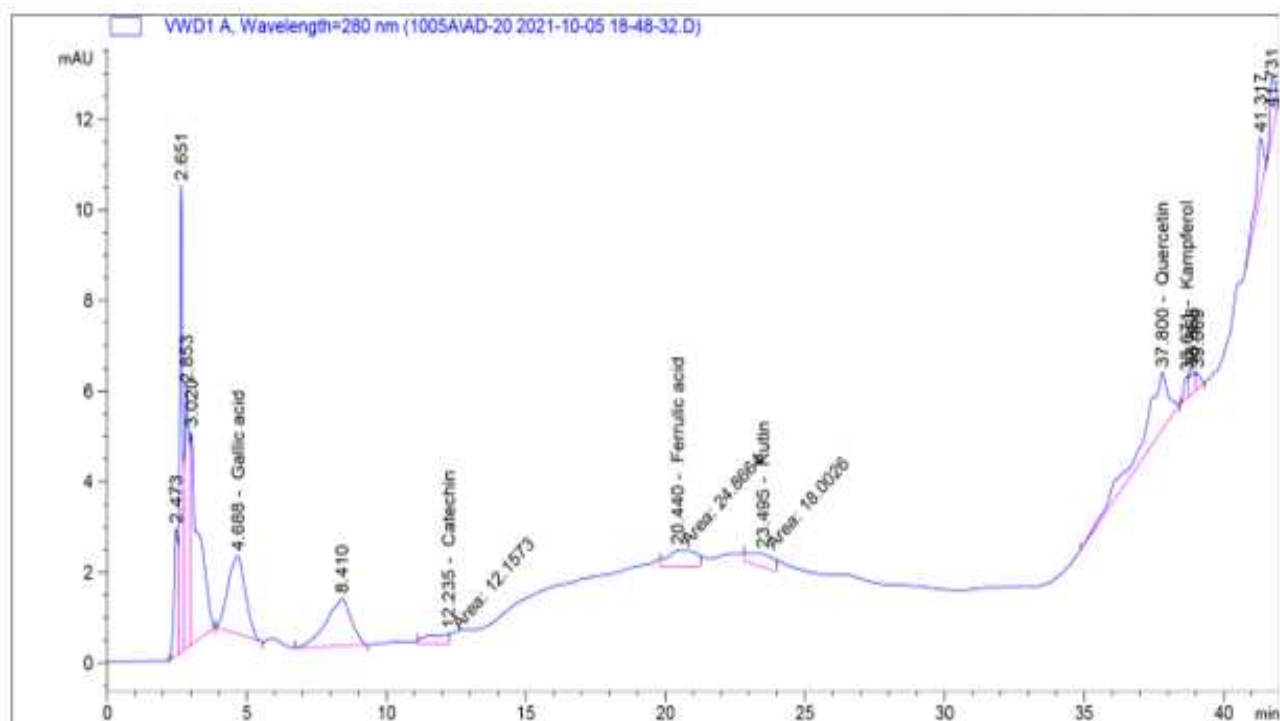
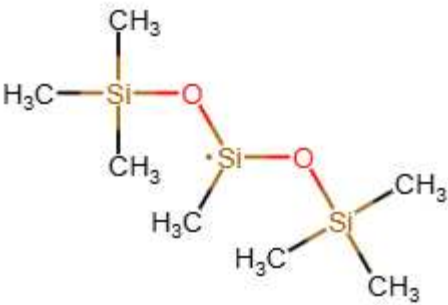
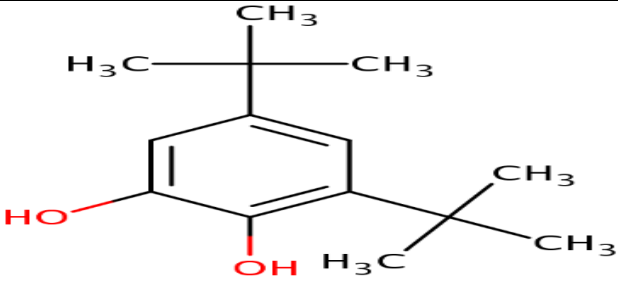
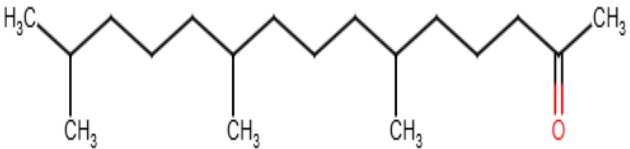
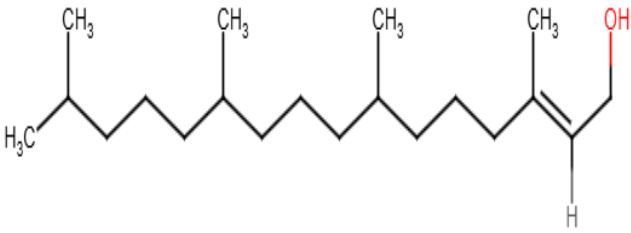


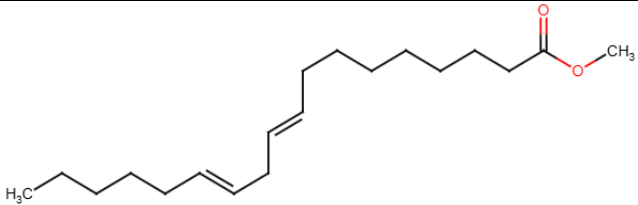
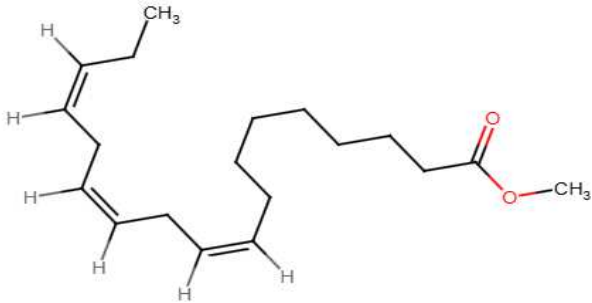
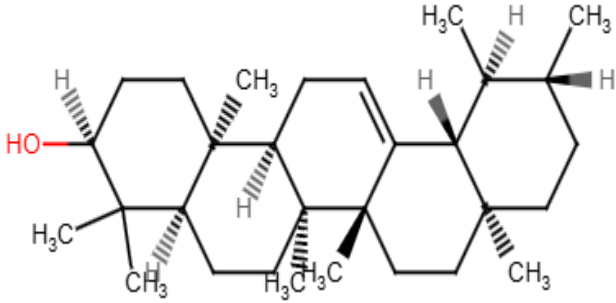
Figure 4: Chromatogram obtained from HPLC.

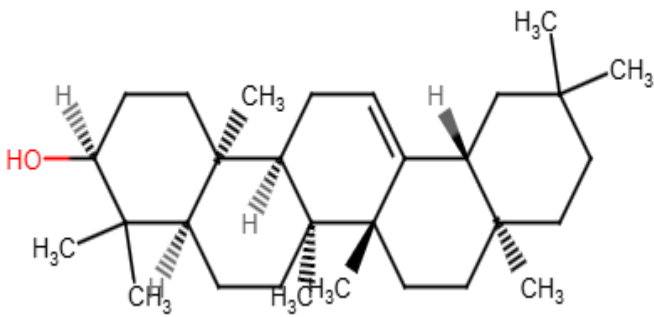
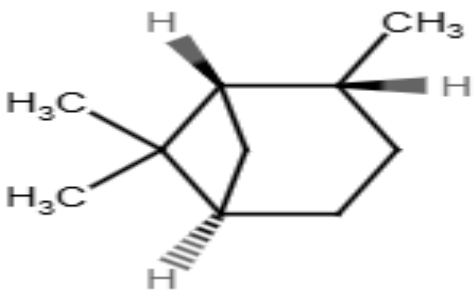
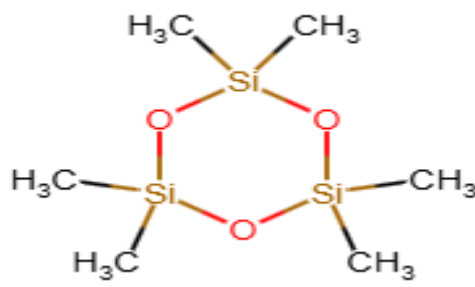
Table 3: The names and two-dimensional structure of constituents isolated from *Garcinia kola* oil

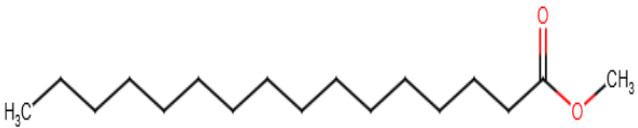
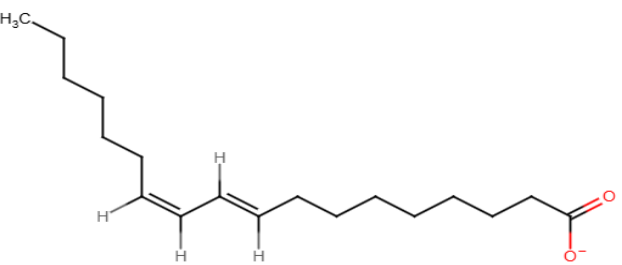
S/N	Quantity (%)	Name of compound	Two-dimensional structure

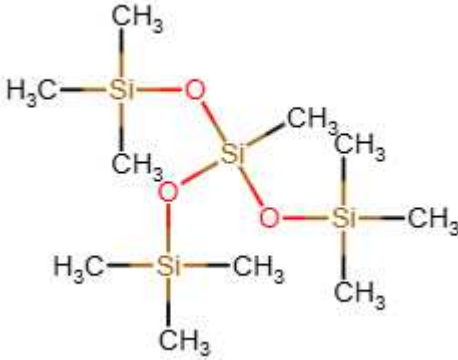
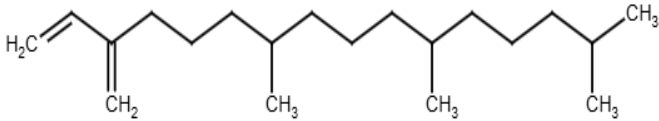
1	8.16	1,1,1,3,5,5,5-Heptamethyltrisiloxane	
2	0.48	1,2-Benzenediol, 3,5-bis(1,1-dimethylethyl)-	
3	1.70	2-Pentadecanone, 6,10,14-trimethyl-	
4	16.55	3,7,11,15-Tetramethyl-2-hexadecen-1-ol	

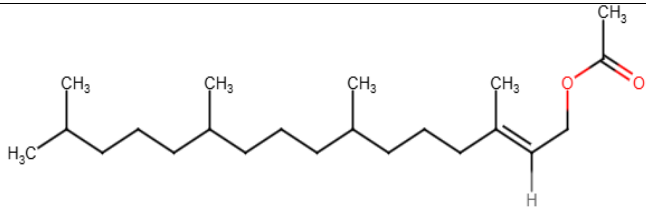
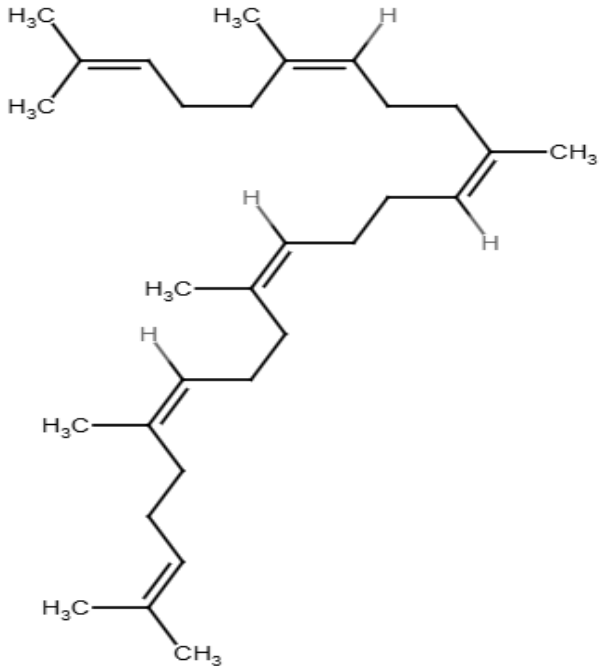
S/N	Quantity (%)	Name of compound	Two-dimensional structure
5	7.05	7,10,13-Hexadecatrienoic acid methyl ester	
6	0.75	8,11-Octadecadienoic acid methyl ester	

7	0.75	9,12-Octadecadienoic acid (Z, Z)-, methyl ester	
8	7.05	9,12,15-Octadecatrienoic acid, methyl ester, (9Z,12Z,15Z)-	
S/N	Quantity (%)	Name of compound	Two-dimensional structure
9	12.07	Alpha-Amyrin	

10	12.07	Beta-Amyrin	
11	1.04	Bicyclo [3.1.1] heptane, 2,6,6-trimethyl-, (1alpha,2beta,5alpha)-	
12	3.5	Cyclotrisiloxane, hexamethyl-	

S/N	Quantity (%)	Name of compound	Two-dimensional structure
13	18.54	Methyl hexadecanoic acid	
14	0.75	Methyl 9-cis,11-trans-octadecadienoate	
15	3.75	Methyl stearate	

16	0.48	Methyl tris (trimethyl siloxy) silane	
S/N	Quantity (%)	Name of compound	Two-dimensional structure
17	1.04	Neophytadiene	

18	1.04	Phyto acetate	 The chemical structure of phytyl acetate is shown. It consists of a long hydrocarbon chain with four methyl branches at the 3, 7, 11, and 15 positions. The chain ends with an acetate group (-O-C(=O)-CH₃), where the oxygen atom is highlighted in red.
19	2.83	Squalene	 The chemical structure of squalene is shown. It is a triterpene hydrocarbon with six methyl branches and three conjugated double bonds. The structure is drawn in a zig-zag conformation, showing the spatial arrangement of the carbon chain and its substituents.

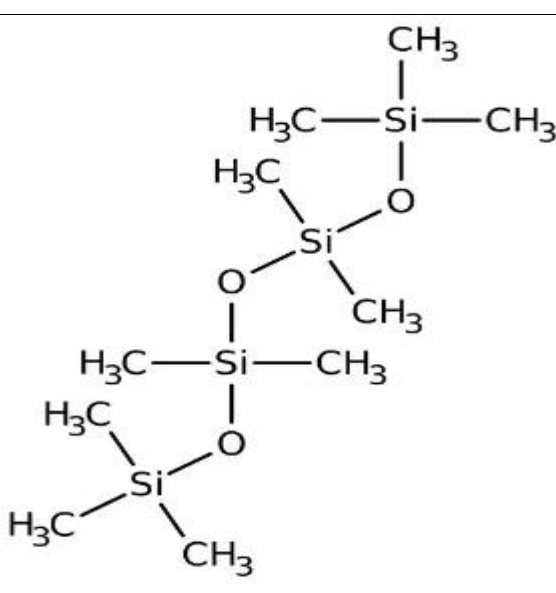
S/N	Quantity (%)	Name of compound	Two-dimensional structure
20	0.48	Decamethyltetrasiloxane	 The chemical structure of Decamethyltetrasiloxane is a linear chain of four silicon atoms connected by oxygen atoms. Each silicon atom is bonded to two methyl groups (CH₃). The structure is shown in a zig-zag conformation: the top silicon is bonded to a methyl group above and to the left, and another to the right; the second silicon is bonded to a methyl group to the left and another below and to the right; the third silicon is bonded to a methyl group below and to the left, and another to the right; the bottom silicon is bonded to a methyl group to the left and another below and to the right. The chain is represented as CH₃-Si(CH₃)₂-O-Si(CH₃)₂-O-Si(CH₃)₂-O-Si(CH₃)₂-CH₃.

Table 4: Docking outcomes and weight of derived compounds

Constituents	Docking outcome (kcal/mol)	Induced fit docking (kcal/mol)	Molecular weight	Predicted pIC50
1,2-Benzenediol, 3,5-bis(1,1-dimethylethyl)-	-8.131	-500.45	222.3	6.688
Phyto acetate	-8.201	-504.32	338.6	6.982
Squalene	-10.398	-506.98	410.7	6.672
Methyltris (trimethyl siloxy) silane	-5.15	-514.75	310.7	6.672
Tetrasiloxane, decamethyl-	-5.201	-515.10	310.7	6.672
9,12,15-Octadecatrienoic acid, methyl ester, (Z, Z, Z)-	-6.543	-501.39	292.5	6.965
2-Pentadecanone, 6,10,14-trimethyl-	-7.843	-501.59	268.5	6.981
9,12-Octadecadienoic acid (Z, Z)-, methyl ester	-7.087	-501.39	294.5	6.965
Bicyclo[3.1.1]	-5.614	-495.34	138.3	7.066

heptane, 2,6,6-trimethyl-				
Methyl stearate	-6.703	-498.51	298.5	6.942
3,7,11,15-Tetramethyl-2-	-3.746	-502.31	296.5	6.903
hexadecen-1-ol				
1,1,1,3,5,5,5-Hepta	-3.979	-503.93	221.5	6.672
methyltrisiloxa				
8,11-Octadecadienoic acid,	-8.351	-502.07	294.5	6.965
methyl				
Cyclotrisiloxane,	-3.944	-509.39	222.5	6.672
hexamethyl-				
Hexadecanoic acid,	-4.898	-499.07	270.5	6.942
methyl ester				
Methyl 9-cis,11-trans-	-14.699	-509.03	279.4	6.785
octadecadienoate				
7,10,13-Hexadecatrienoic	-7.755	-501.35	264.4	6.695
Acid, methyl ester				
Neophytadiene	-6.658	-500.54	278.5	6.769

In-silico studies have become increasingly popular in drug discovery because they are a powerful tool for predicting the curative properties of chemical compounds, resulting in reduced time and resources required for discovering effective drugs [57]. Based on this premise, *in-silico* analyses were carried out on the bioactive components of *Garcinia kola* oil to set the stage for a robust drug discovery process. Hormone-receptor-positive breast cancer cells express primarily estrogen or progesterone receptors, or both, and hence can be managed by hormone therapy medications that diminish estrogen levels or inhibit estrogen receptors. Therefore, inhibiting the hormones estrogen and progesterone from attaching to their receptors can prevent the development and progression of Hormone-receptor-positive breast cancer. The human progesterone receptor (HPR) is thus a key therapeutic focus for breast cancer care, necessitating the immediate recognition of small-molecule therapies that may efficiently block HPR. [8, 13]. Therefore, the aim of this study supports the premise that inhibiting the human progesterone receptor (PR) offers a crucial therapeutic target for breast cancer treatment.

Compared to existing approaches to docking ligands to the rigid 3D structure of a known protein receptor, Glide mimics an extensive thorough search of the docked ligand's conformational, orientational, and positional space [58]. Glide is the premier industrial option for dependable ligand-receptor docking. It streamlines and speeds up drug development based on structures for several applications, including virtual screening, binding mode prediction, and interactive 3D molecular design. Glide docking therefore represents a valuable approach to determining or establishing the therapeutic strength of compounds in the process of drug discovery [59].

Given the reliability of Glide docking, the report of these findings suggests that GKO might be a pool containing novel anticancer compounds based on the scores obtained. In perspective, within the purview of the current study, oil constituents of GKO were docked against PR, and the outcome

showed a promising PR-inhibitory and anticancer potency of GKO. The result of docking the constituents of GKO against PR presented the best interactions among all the proteins examined. The outcomes obtained via docking, binding energy, and the constituents' binding affinity to the PR binding site indicated that PR possesses promising anticancer effects in breast tissue. The docking scores for the isolated oil constituents with PR vary from -3.746 to -14.699 kcal/mol. Methyl 9-cis, 11-trans-octadecadienoate showed the maximum affinity having a docking value of -14.699 kcal/mol while squalene and 8,11-Octadecadienoic acid, methyl ester followed it with docking values of -10.398 kcal/mol and -8.351 kcal/mol in that order.

In comparison with the preceding findings, Shabah *et al.* [13] obtained important insights into the interactions among the chosen lead chemicals using molecular docking and simulations (TCM38057, TCM30460, ZINC32957366 and ZINC57487561) and the active site of the human progesterone receptor (HPR). The docking outcome showed that TCM38057/HPR demonstrated the most proficient docking value of - 9.76 kcal/mol closely trailed by TCM30460/HPR with a docking value of - 9.65 kcal/mol. Likewise, the docking value for ZINC32957366/HPR was - 9.54 kcal/mol and ZINC57487561/HPR complexes had a value of - 9.37 kcal/mol respectively. However, the docking outcomes of some GKO components; Methyl 9-cis, 11-trans-octadecadienoate had a better affinity with a docking value of - 14.699 kcal/mol and squalene - 10.398 kcal/mol thus suggesting that GKO could be a more potent anticancer therapy. Given the foregoing, *Garcinia kola-derived* oil may be capable of protecting against progesterone receptor-implicated breast cancer.

Methyl 9-cis, 11-trans- octadecadienoate which is one of the hit compounds in this study has been reported to possess *in-vivo* anticancer effects [60]. In the same vein, squalene has chemopreventive effects on its own. Due to its potentiation effect, it helps treat cancer directly or

indirectly. Furthermore, squalene has been reported to possess protective prowess by lessening the adverse effects induced by chemotherapy in cancer treatment [61]. Micera *et al.* [62] also reported that squalene effectively manages cardiovascular diseases. These findings also corroborate the outcome of Mazumder *et al.* [63]. However, it is pertinent to state that the accumulation of squalene may also be deleterious within the system, therefore, a safe limit of squalene must be maintained [64].

The induced Fit Docking (IFD) procedure is a computational tool that perfectly forecasts ligand binding modes and the resultant structural changes in the receptor molecule [65]. In this study, IFD depicted that the components of GKO had a sturdy interaction with PR. The interaction with Tetrasiloxane, and decamethyl- produced the highest docking scores for PR, with an IFD score of -515.10 kcal/mol. This was closely followed by Methyltris (trimethyl siloxy) silane and hexamethyl-cyclotrisiloxane, with IFD results of -514.75 kcal/mol and -509.39 kcal/mol, respectively. *The data generated from the IFD procedure also supports that the Garcinia kola-derived oil could positively impact progesterone-implicated breast cancer. Also, the results obtained from this study fared better than the investigation of Zhong et al. [66] who employed IFD analysis against EGFR but less robust than the outcome of Halder et al. [67] in their investigation while exploring and identifying PI3K α inhibitors for triple-negative breast cancer using in-silico studies. Considering these findings and the optimal ranges available for induced fit docking results in the literature, we can conclude that Garcinia kola-derived oil has good interaction with progesterone receptors and might therefore be fit to be named among potential PR inhibitors thus expressing their prowess as both therapeutic and anticancer agents.*

The molecular weight as seen in Table 3, attributes for drug prediction and all other parameters within the rule of thumb seem to fall within the safe range and have been established in our

laboratory. Thus, in line with Folayan *et al.* [16], the drug-likeness test, and the data obtained revealed that *Garcinia kola* oil components fulfilled, satisfied prerequisites for drug candidacy and showed anticancer potential via *in-silico* studies having complied with 75% of Lipinski's rule of thumb [68] while satisfying the permissible limits for rotatable bonds, topological polar surface area (TPSA), and other predictors. By implication, this indicates that most GKO constituents can be considered safe therapeutic options for managing cancer and other related conditions.

Furthermore, the predicted pIC_{50} ranged from 7.066 to 6.672. Thakur *et al.* [69] established that pIC_{50} is essential for comparing drug efficacy and potency. The pIC_{50} value is significant in determining drug potency. It is calculated as the negative logarithm of the IC_{50} value, which indicates the half-maximal inhibitory concentration. It denotes the efficacy of a drug to block a particular biological or metabolic function [70]. The outcome of this study showed that the pIC_{50} obtained for the isolated compounds of GKO compared favourably with the reported pIC_{50} in the previous survey used to predict the anti-cancer activity of some protein P38 MAP kinase inhibitors and human (MCF-7) breast cancer cell line [71, 72]. This outcome also aligns with the findings of Moussaoui *et al.* [73]. These pieces of evidence suggest that the oil of *Garcinia kola* has a more therapeutic impact on progesterone-implicated breast cancer compared to several natural compounds.

Table 5: Information on molecular interactions between ligand and protein-formed complex

Protein/Compounds	No of H-	Metal		Salt	
	bond	H-Bond	Interaction	bridge	Pi cation
PR					
Methyl 9-cis,11-trans-octadecadienoate	1	LYS 919		LYS 919	
		TRP 755			
1,2-Benzenediol, 3,5-bis(1,1-dimethylethyl)-	1	LEU 718			

Key: LEU- Leucine, LYS-Lysine, TRP-Tryptophan

Proteins' main structure consists of hundreds of amino acid residues, although only a small portion appears to be involved in most of their actions. This region is frequently referred to as a "binding site," "active site," or "catalytic site" depending on the context and the function connected with it [74]. Table 5 summarises the interactions between the residues in the complex produced by the protein and ligand, as seen by the 2D and 3D poses displayed in Figures 5 to 18. The binding poses of PR demonstrated that 1,2-Benzenediol, 3,5-bis(1,1-dimethylethyl)-formed hydrogen interaction with LEU 718. Also, Methyl 9-cis,11-trans-octadecadienoate formed a hydrogen bond with LYS 919 and TRP 755 and a salt bridge with LYS 919. It is well-recognised that important residues from a protein's active pocket make up its binding site. Analysis of these residues yields additional

insights into the molecular interactions between ligands and proteins [75]. Similarly, TRP 755 is essential within the binding region of the progesterone receptor and Leu 718 is very crucial within the hydrophobic pocket of the progesterone receptor [76, 77]. The Structural binding characterization of Bisphenol A (BPA), 4-Methyl-2,4-bis-(P-Hydroxyphenyl) Pent-1-Ene—A Potent Metabolite of BPA, and 4-Tert-Octylphenol with PR using *in silico* methods demonstrated unique interactions with the residue LEU 718. This further supports the claim that LEU 718 is an essential residue in progesterone receptors [78]. Previous findings have demonstrated how TRP 755 has been crucial in the binding of asoprisnil to PR in the treatment of uterine fibroid and endometriosis [77]. This outcome matches the conclusion of [79, 80] and further validates the claim of this research that GKO components possess sturdy anti-endometrial and anti-cancer abilities.

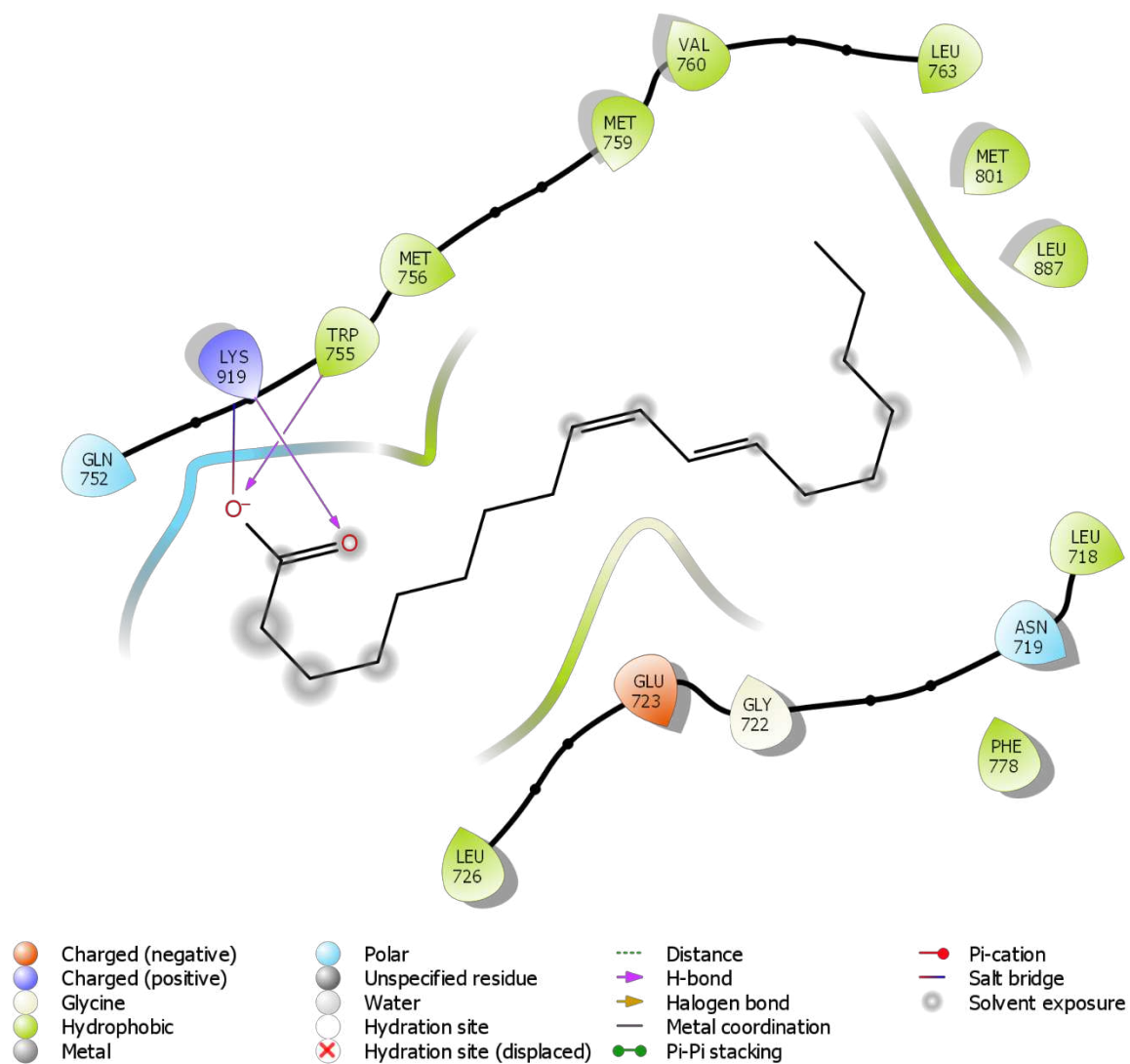


Figure 5: Binding pose of Methyl 9-cis,11-trans-octadecadienoate with progesterone receptor revealing interacting amino acid residues within the active site in 2D.

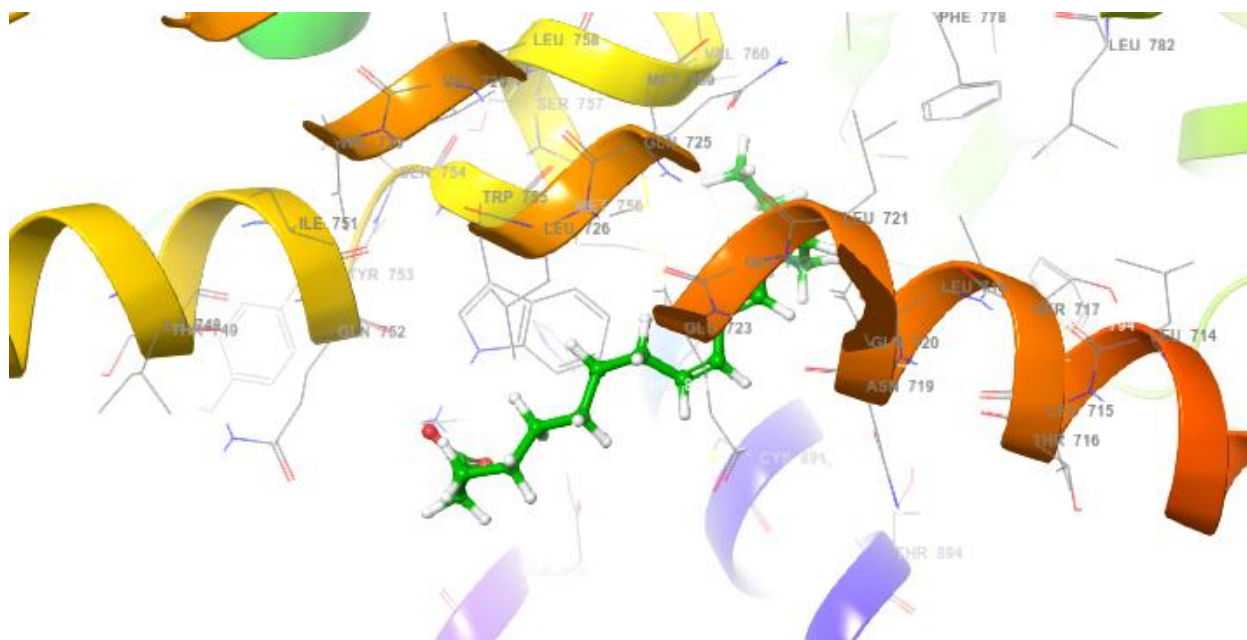


Figure 6: Binding pose of Methyl 9-cis,11-trans-octadecadienoate with progesterone receptor revealing interacting amino acid residues within the active site in 3D.

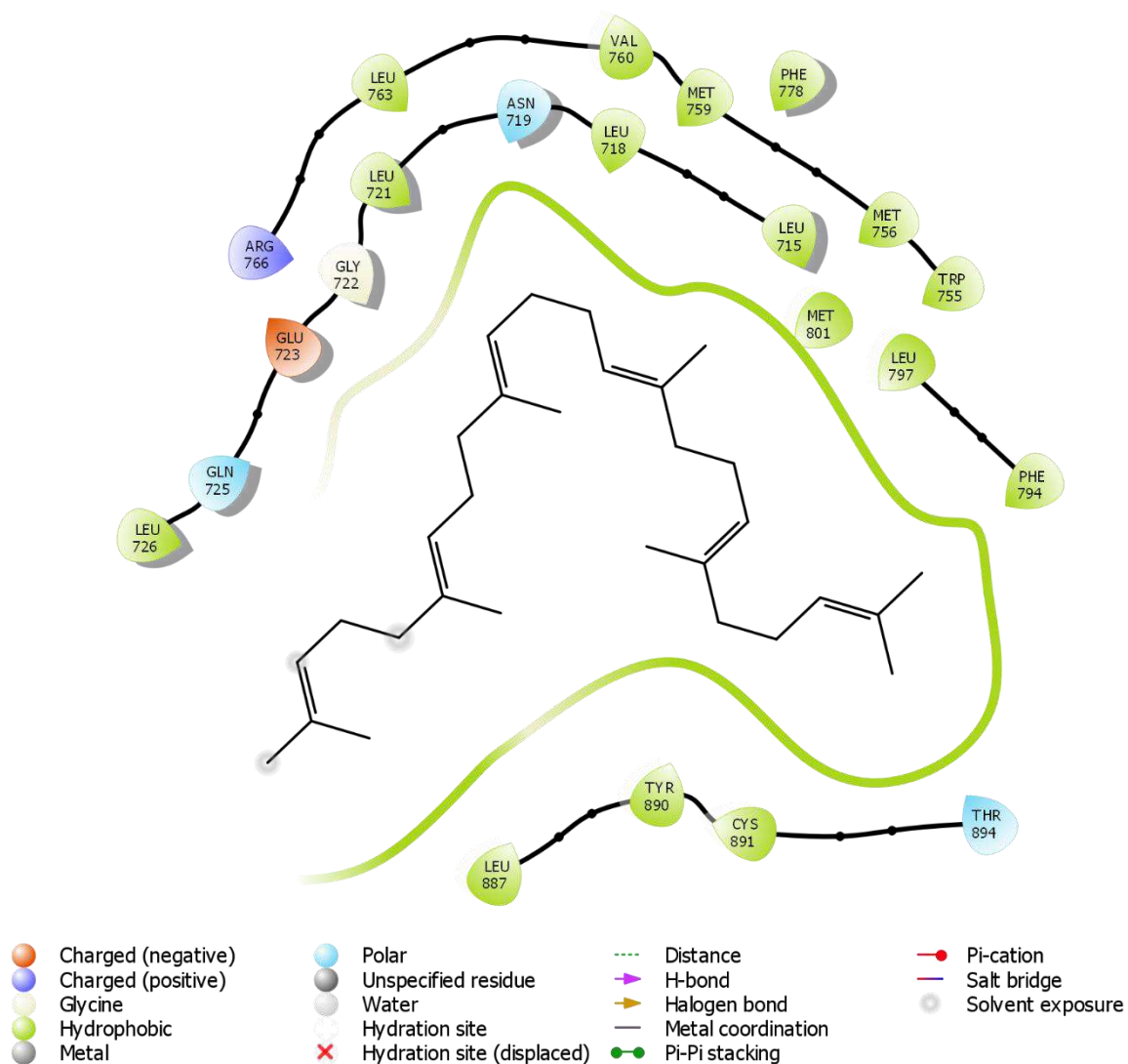


Figure 7: Binding pose of squalene with progesterone receptor revealing interacting amino acid residues within the active site in 2D.

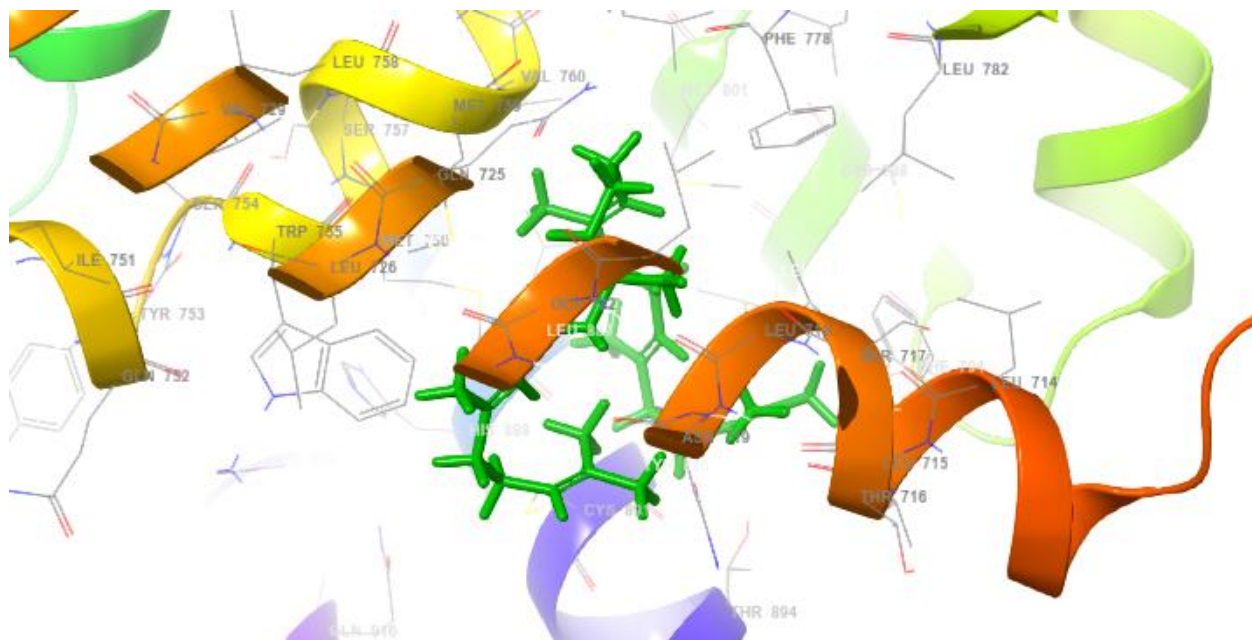


Figure 8: Binding pose of squalene with progesterone receptor revealing interacting amino acid residues within the active site in 3D.

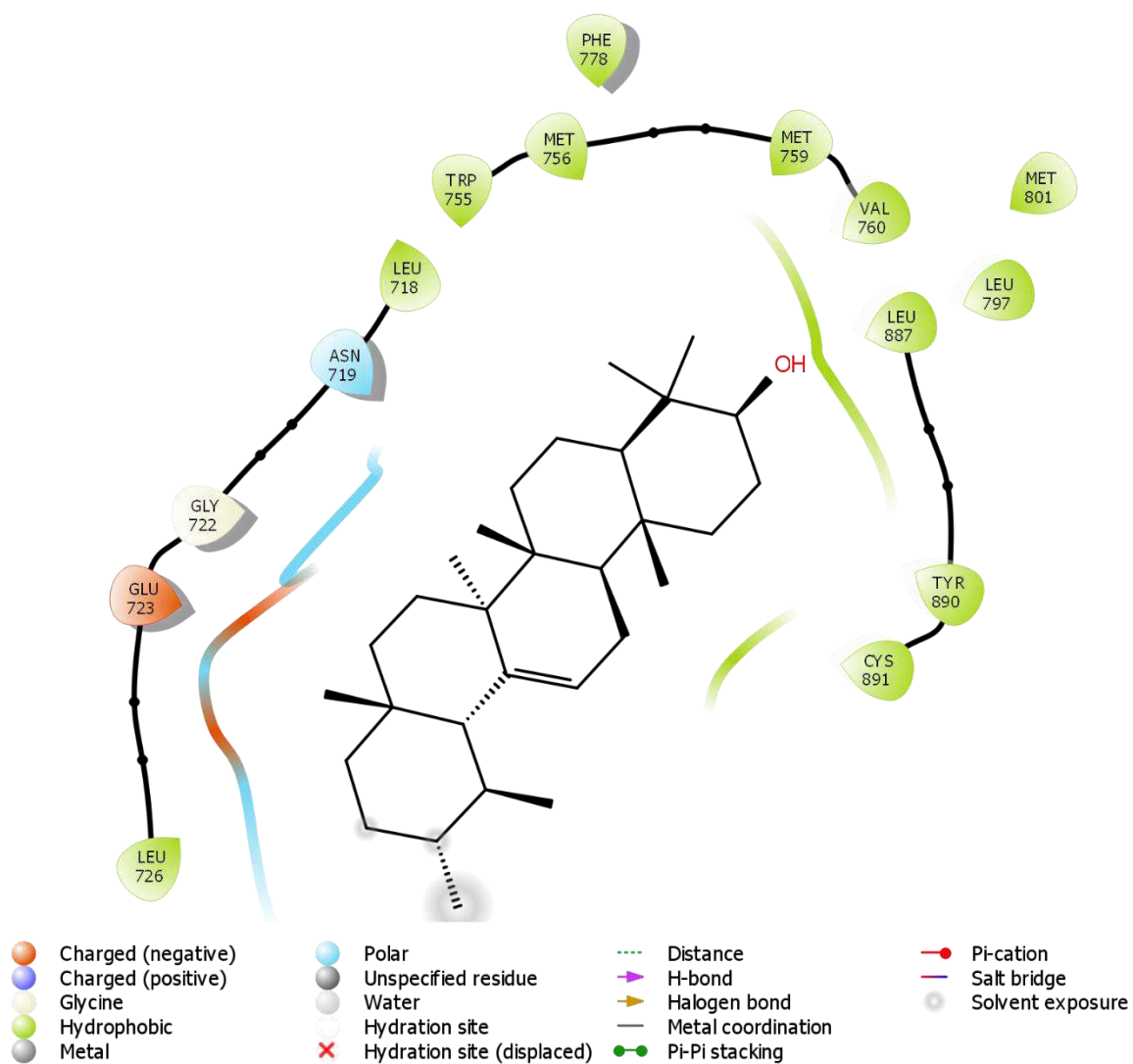


Figure 9: Binding pose of alpha amyryn with progesterone receptor revealing interacting amino acid residues within the active site in 2D.

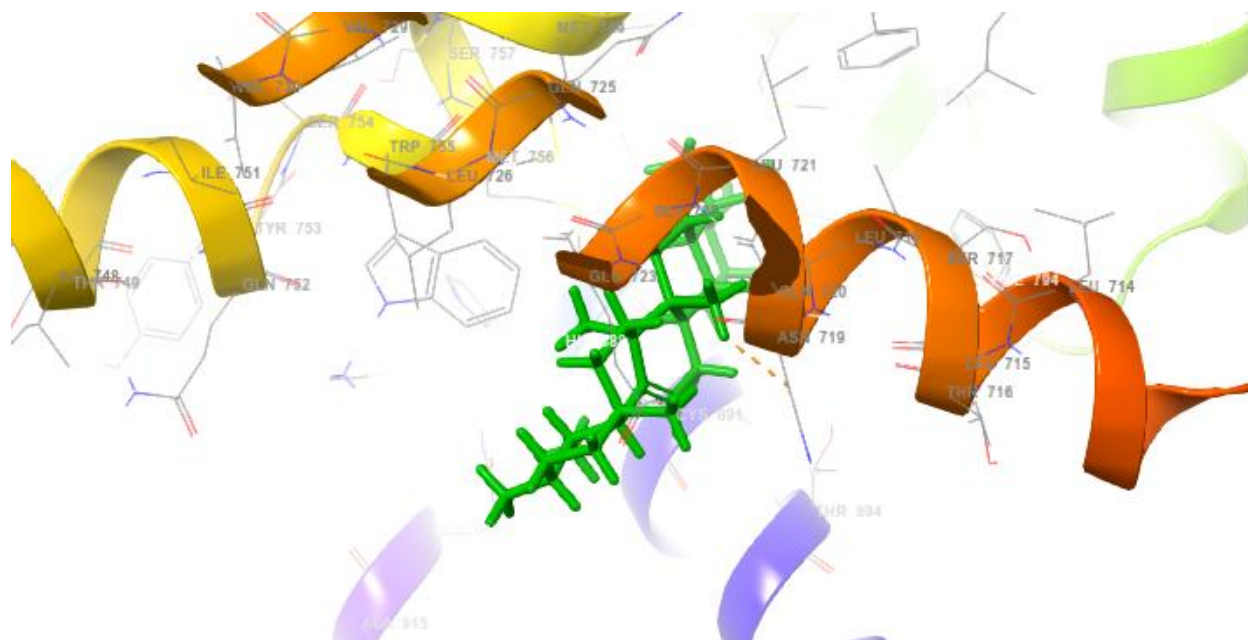


Figure 10: Binding pose of alpha myrin with progesterone receptor revealing interacting amino acid residues within the active site in 3D.

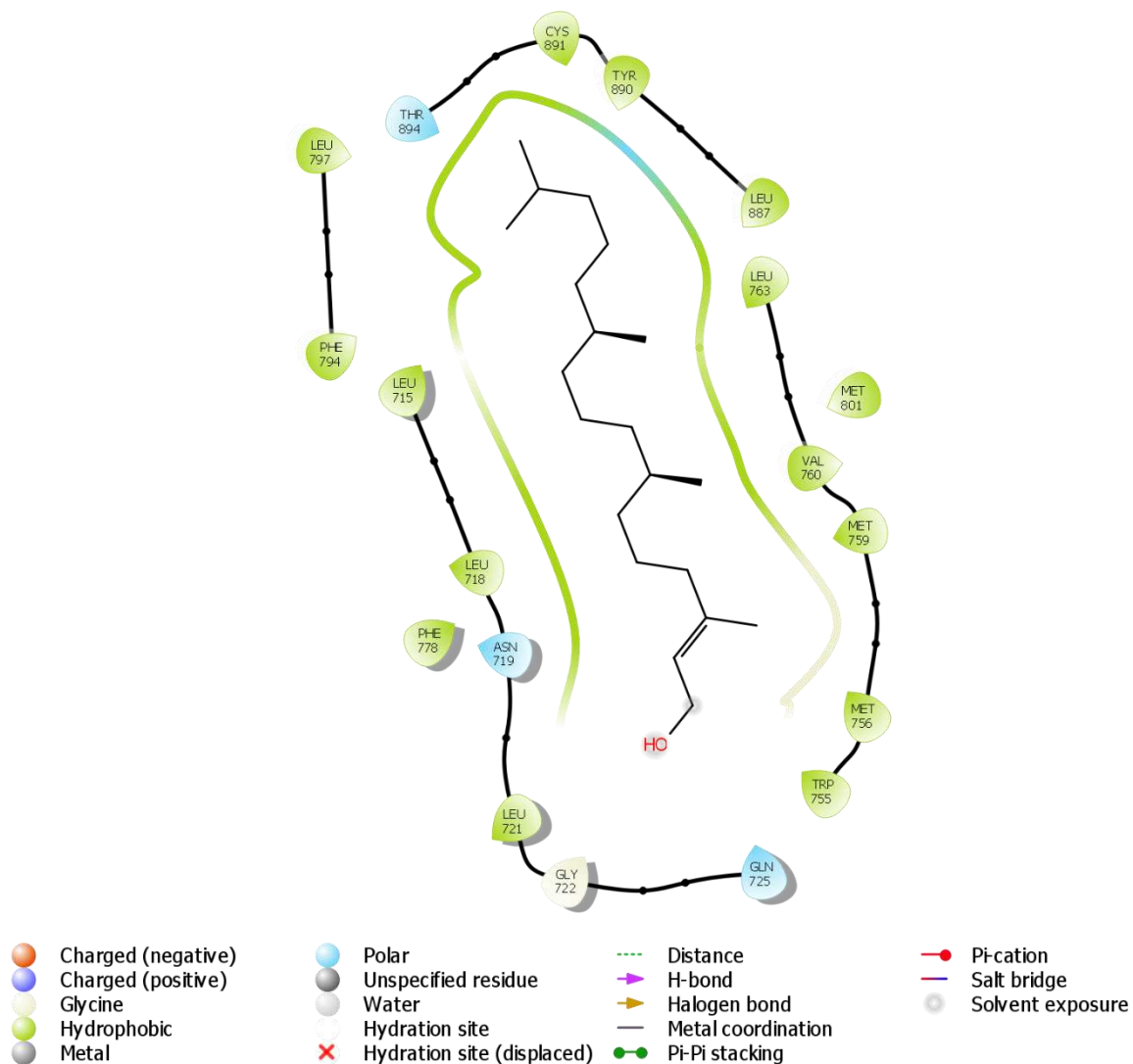
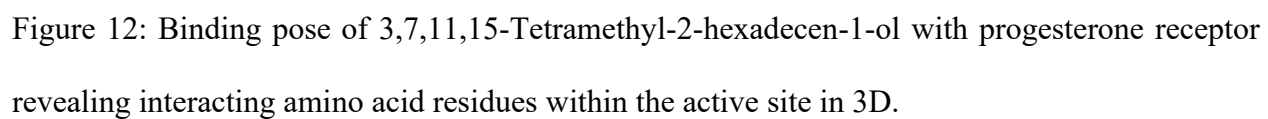


Figure 11: Binding pose of 3,7,11,15-Tetramethyl-2-hexadecen-1-ol with progesterone receptor revealing interacting amino acid residues within the active site in 2D.



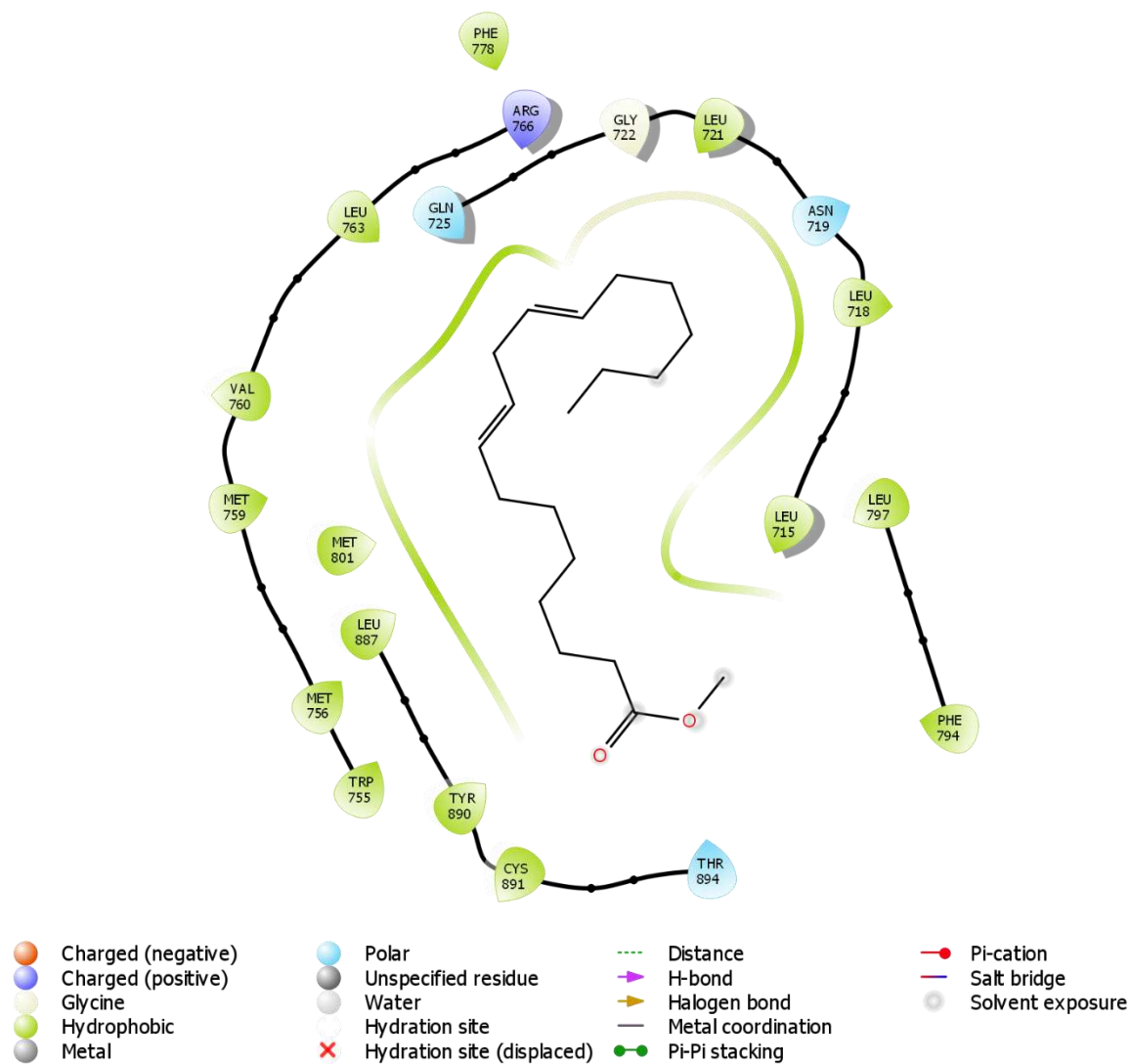


Figure 13: Binding pose of 8,11-Octadecadienoic acid methyl ester with progesterone receptor revealing interacting amino acid residues within the active site in 2D.

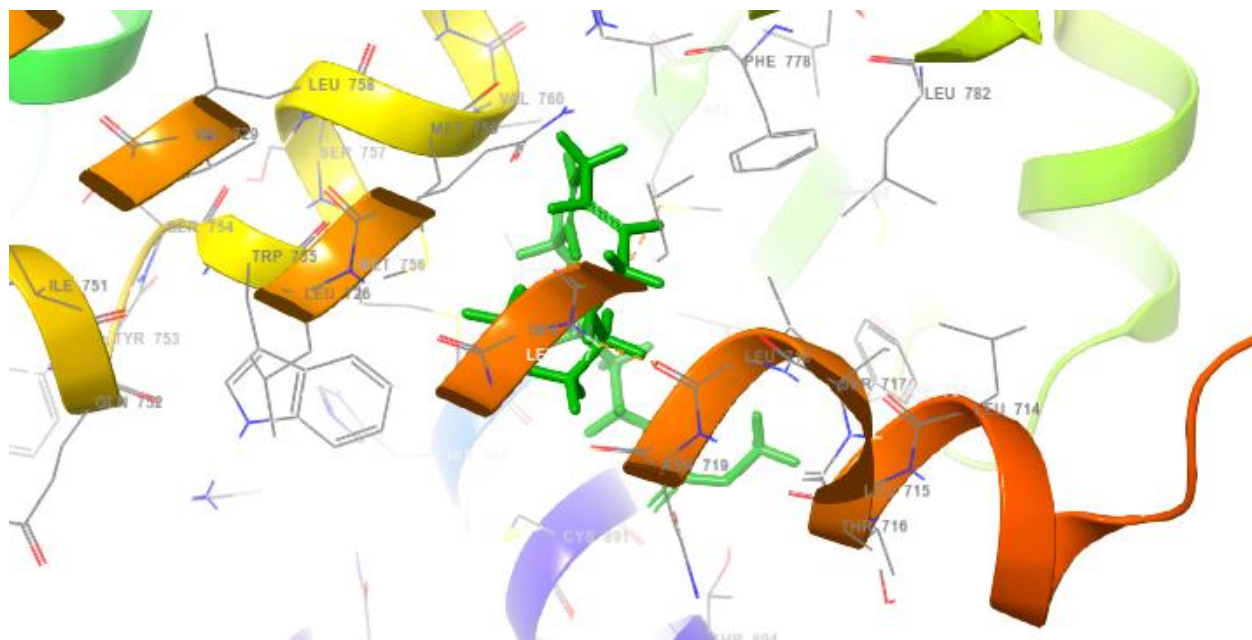


Figure 14: Binding pose of 8,11-Octadecadienoic acid methyl ester with progesterone receptor revealing interacting amino acid residues within the active site in 3D.

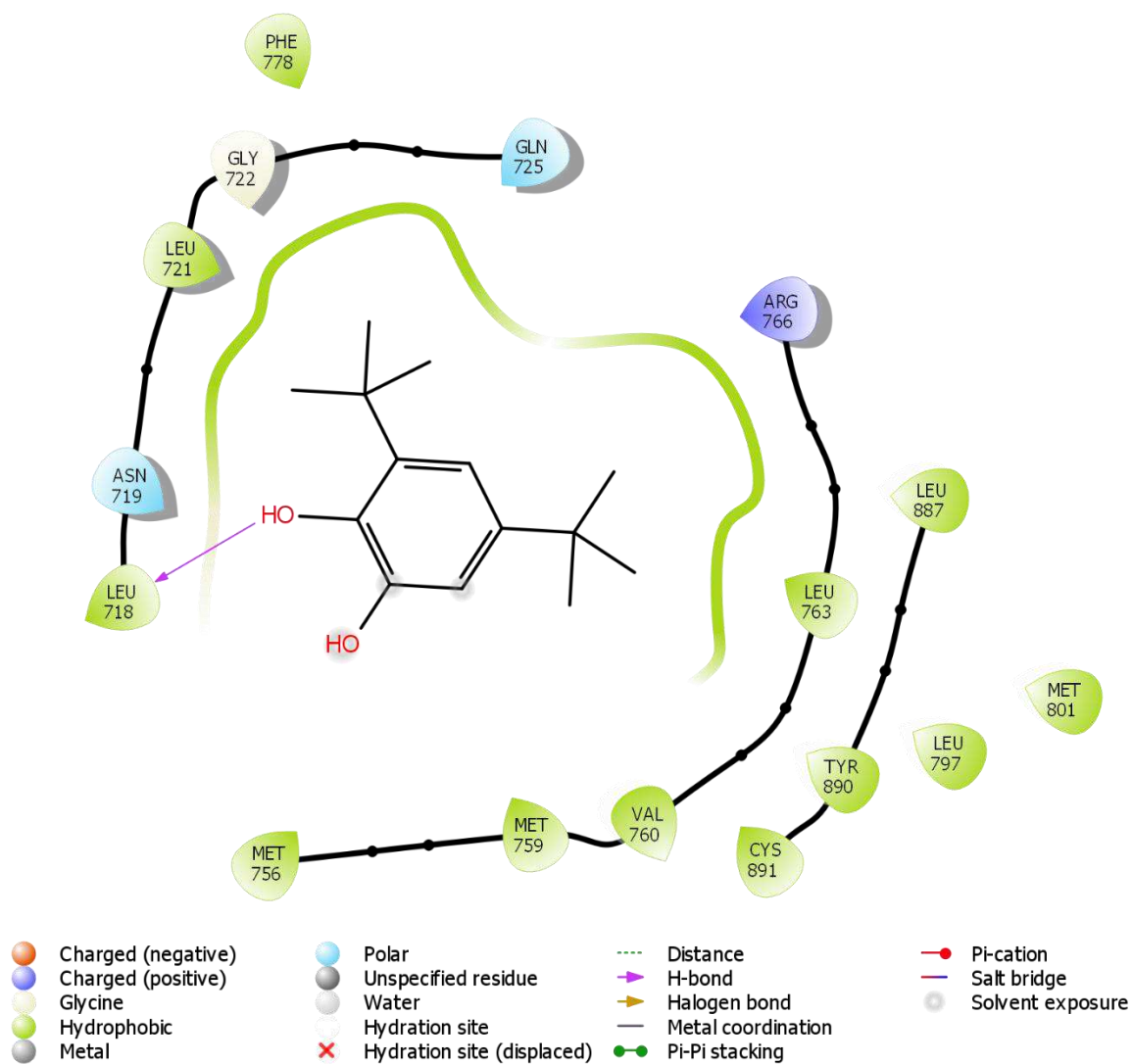


Figure 15: Binding pose of 1,2-Benzenediol, 3,5-bis(1,1-dimethylethyl)- with progesterone receptor revealing interacting amino acid residues within the active site in 2D.

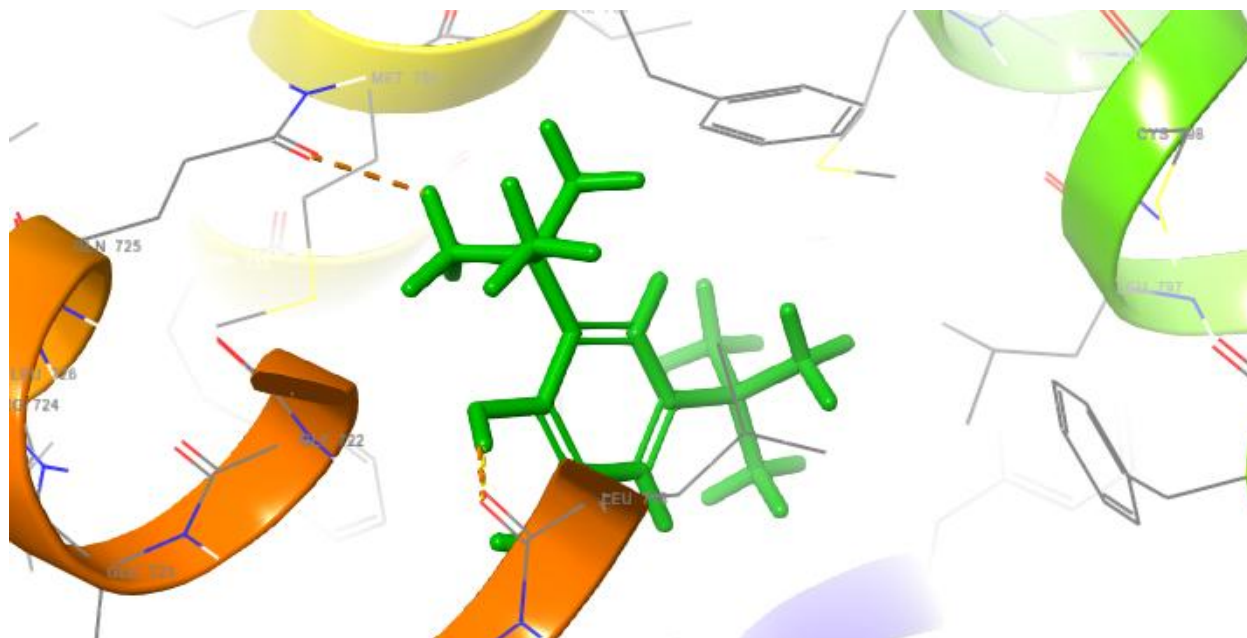


Figure 16: Binding pose of 1,2-Benzenediol, 3,5-bis(1,1-dimethylethyl)- with progesterone receptor revealing interacting amino acid residues within the active site in 3D.

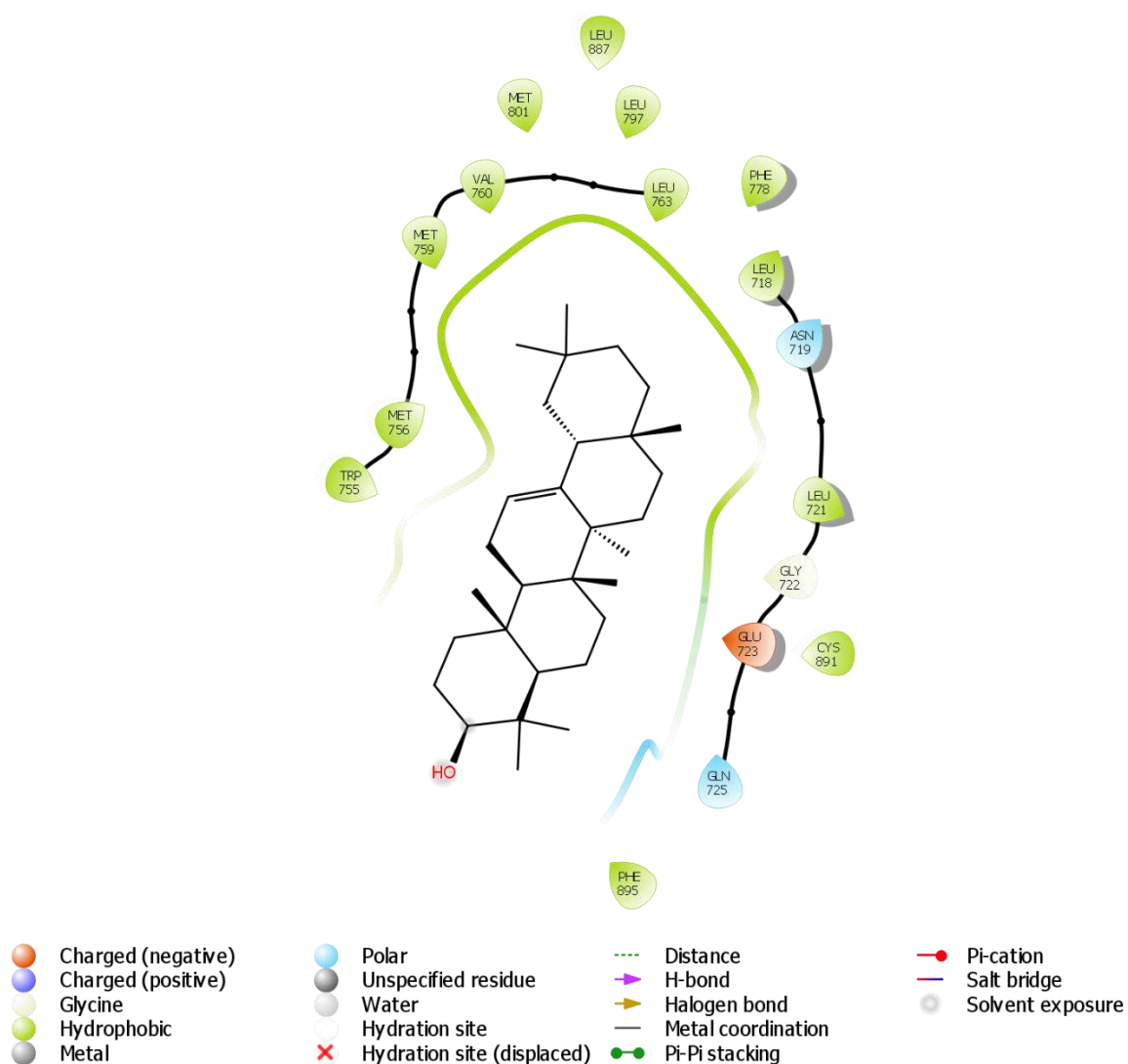


Figure 17: Binding pose of beta amyrin with progesterone receptor revealing interacting amino acid residues within the active site in 2D.

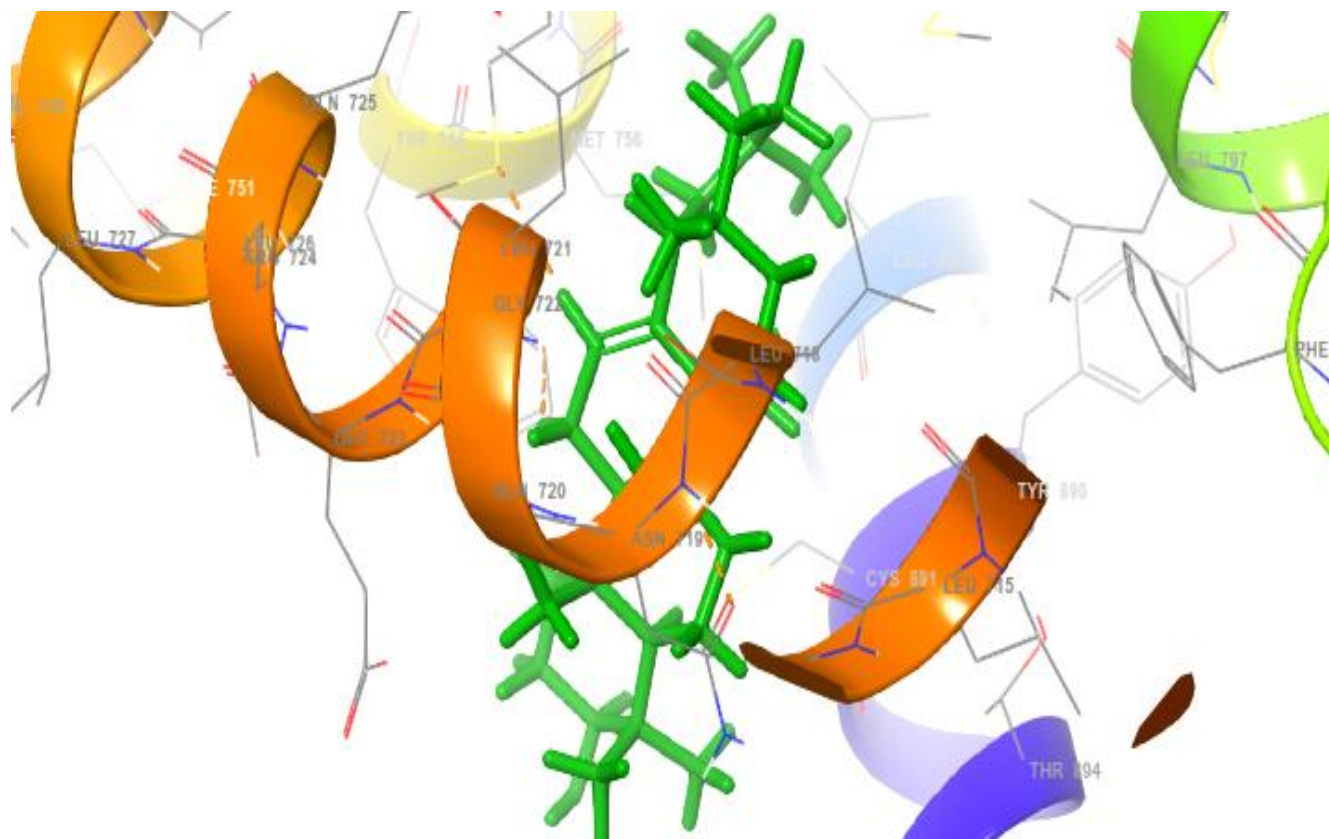


Figure 18: Binding pose of beta amyrin with progesterone receptor revealing interacting amino acid residues within the active site in 2D.

3.1. Binding energy Assessment

One of the ways to verify docking scores is free binding energy assessment. In line with the previous studies [81, 82]. MMGBSA presents the most efficient means of ranking the affinity of ligands with their receptor and it is reported in kcal/mol. Apart from its reproducibility, it is simple and accurate [83]. As seen in Table 6, the binding free energy estimation was presented and it reveals the scores generated from its various contributors such as hydrogen bond, solvation, Coulomb, and lipophilic energies which all advance the binding attraction of the *Garcinia kola*-derived compounds against its target.

In comparison to previous research, Zarezade *et al.* [84] conducted an *In silico* evaluation of new progesterone receptor blockers through molecular dynamics. Of the twenty compounds investigated comprising of 10 control PR inhibitors (Levonorgestrel, ORG-33628, Asoprisnil, Ulipristalacetate, Promegestone, Onapristone, Mifepristone, Telapristoneacetate, Lilopristone. Lonaprisan, Mometasonefuroate, ZK112993) and 10 natural compounds (ZINC00936598, ZINC01020370, ZINC00869973, ZINC00057872, ZINC00117321, ZINC00468904, ZINC00936596, ZINC00130087, ZINC00852626, ZINC00057677). The binding energy obtained during analysis ranged between -5.82 and -9.03 kcal mol⁻¹. Given that the results of the binding energy obtained in this study range from 19.61 to 59.06 kcal/mol, this indicates that the *Garcinia kola* oil-derived compounds might be a better inhibitor of the human progesterone receptor and consequently, a potent anticancer agent.

Table 6: Binding free energy values (PR)

Title	Name of isolated constituents	ΔG Bind^a	ΔG Bind Coulomb^b	ΔG Bind Solv GB^c	ΔG-Bind Lipo^d	ΔG Bind Hbond^e
1	Squalene.1	-59.06	-0.67	22.74	-36.1	0
2	1,2-Benzenediol, 3,5-bis(1,1-dimethylethyl)-.1	-28.53	-4.73	12.49	-15.53	-0.67
3	Methyl 9-cis,11-trans-octadecadienoate.1	-34.12	-20.26	30.37	-14.43	-2.12
4	9,12-Octadecadienoic acid (Z,Z)-,methylester.1	-46.27	-0.35	14.67	-23.05	-0.56
5	beta-Amyrin.1	-30.85	0.66	20.72	-22.6	0
6	2-Pentadecanone, 6,10,14-trimethyl.1	-48.35	-7.03	13.9	-21.9	-0.53
7	alpha-Amyrin.1	-37.05	-2.69	19.92	-17.93	0
8	3,7,11,15-Tetramethyl-2-hexadecen-1-ol.1	-33.36	-1.08	16.22	-28.36	0
9	Bicyclo[3.1.1]heptane, 2,6,6-trime.1	-24.12	-0.15	8.17	-12.53	0
10	9,12,15-Octadecatrienoic acid, methyl ester, (Z,Z,Z)-.1	-47.73	-3.62	15.39	-23.68	-0.07
11	Methyl stearate.1	-45.42	-4.82	15.67	-19.95	-0.51

12	7,10,13-Hexadecatrienoic acid, methyl ester.1	-41.62	-1.37	15.35	-17.98	0
13	Hexadecanoic acid, methyl ester.1	-49.78	-6.04	13.25	-23.2	-0.54
14	Methyltris(trimethylsiloxy)silane.1	-27.38	0.74	5	0	0
15	Neophytadiene.1	-44.9	0.83	13.73	-24.2	0
16	Tetrasiloxane, decamethyl-.1	-28.69	-0.76	4.97	0	0
17	Cyclotrisiloxane, hexamethyl-.1	-28.87	-0.89	1.79	0	0
18	1,1,1,3,5,5,5-Heptamethyltrisiloxa.1	-19.61	-0.41	5.47	0	0
19	8,11-Octadecadienoic acid, methyl.1	-35.78	-1.87	13.88	-25.5	-0.42
20	Phytolacetate	-44.62	-10.04	22.52	-17.03	-0.72

^aMM-GBSA binding free energy (kcal/mol)

^binput from Coulomb energy

^cinput from solvation energy

^dinput from lipophilic binding

^einput from hydrogen bonding

3.4. QSAR Analysis

For the QSAR analysis conducted in this study, the auto QSAR panel employed a machine-learning mode of prediction. Similarly, ChEMBL is a manually maintained database of bioactive compounds that exhibit drug-like characteristics. It integrates chemical, bioactivity, and genetic data to help translate genomic knowledge into successful novel medications and was engaged to obtain a good collection of chemical compounds totalling precisely 187 compounds to build the models [36]. We randomised the compounds into a ratio of ~ 3:1 (76% of train and 24% of test dataset as shown in Table 5). The model generated was KPLS_RADIAL_15. The variables for validating the model and their scores were also presented in Table 6 and the graphical plot detailing the predicted and experimental pIC_{50} . The imperativeness of recognising that docking precision varies directly with diminishing RMSD outcomes has been established therefore, RMSD outcomes below 2.0 Å are usually deemed optimal [85, 86]. Also, the scores obtained for the variables required for validation of the model fall within the permissible range. Given these findings, QSAR analysis is therefore encouraging, especially with the substantially optimum RMSD, R^2 and Q^2 values.

Table 6: Observed and predicted pIC₅₀ activities comparison

S/N	PubChem ID	Set	Observed pIC ₅₀	Predicted pIC ₅₀	Residue Error
1	Compound 1	Test	5.8600	6.6079	0.7479
2	Compound 2	Train	9.5200	8.1533	-1.3667
3	Compound 3	Train	7.4700	8.4582	0.9882
4	Compound 4	Train	5.3400	5.8682	0.5282
5	Compound 5	Train	6.5400	5.7928	-0.7472
6	Compound 6	Train	6.5500	6.1210	-0.4290
7	Compound 7	Test	9.8900	9.6921	-0.1979
8	Compound 8	Train	6.1100	7.0910	0.9810
9	Compound 9	Test	8.1000	8.0584	-0.0416
10	Compound 10	Test	7.0000	7.9013	0.9013
11	Compound 11	Test	6.5300	7.2804	0.7504
12	Compound 12	Train	8.0900	7.9246	-0.1654
13	Compound 13	Test	6.2800	6.5326	0.2526
14	Compound 14	Train	5.8500	5.9937	0.1437
15	Compound 15	Train	6.0200	5.9005	-0.1195
16	Compound 16	Train	5.4000	5.9013	0.5013
17	Compound 17	Train	9.2200	9.6921	0.4721
18	Compound 18	Test	8.4800	8.4826	0.0026
19	Compound 19	Train	6.3500	6.0179	-0.3321
20	Compound 20	Train	6.5800	6.5900	0.0100

21	Compound 21	Test	6.7900	6.7060	-0.0840
22	Compound 22	Train	6.3800	6.5103	0.1303
23	Compound 23	Train	6.3000	7.1401	0.8401
24	Compound 24	Test	7.8900	7.6324	-0.2576
25	Compound 25	Train	7.4600	7.6360	0.1760
26	Compound 26	Train	8.1500	7.6326	-0.5174
27	Compound 27	Test	6.3000	6.4765	0.1765
28	Compound 28	Train	5.5000	5.6213	0.1213
29	Compound 29	Test	5.1100	6.2673	1.1573
30	Compound 30	Train	6.5900	6.3856	-0.2044
31	Compound 31	Train	7.3800	7.0700	-0.3100
32	Compound 32	Train	7.8500	6.7149	-1.1351
33	Compound 33	Train	8.0000	9.0603	1.0603
34	Compound 34	Train	6.5100	7.1620	0.6520
35	Compound 35	Test	6.8700	6.7198	-0.1502
36	Compound 36	Train	7.0000	6.7647	-0.2353

S/N	PubChem ID	Set	Observed pIC ₅₀	Predicted pIC ₅₀	Residue Error
37	Compound 37	Test	7.2000	7.3230	0.1230
38	Compound 38	Train	7.3000	7.4696	0.1696
39	Compound 39	Train	7.6000	7.9450	0.3450
40	Compound 40	Test	7.5000	7.7101	0.2101

41	Compound 41	Test	6.8200	6.5108	-0.3092
42	Compound 42	Train	6.9500	6.5103	-0.4397
43	Compound 43	Train	8.4300	7.9991	-0.4309
44	Compound 44	Train	6.3800	6.6501	0.2701
45	Compound 45	Train	6.2800	5.9619	-0.3181
46	Compound 46	Train	6.7300	8.0141	1.2841
47	Compound 47	Train	8.0200	7.6412	-0.3788
48	Compound 48	Test	8.1200	8.0725	-0.0475
49	Compound 49	Test	9.2200	9.6921	0.4721
50	Compound 50	Train	8.0000	8.0275	0.0275
51	Compound 51	Train	6.8500	8.0536	1.2036
52	Compound 52	Train	8.6200	8.7571	0.1371
53	Compound 53	Train	8.4700	8.7729	0.3029
54	Compound 54	Train	7.8000	7.8156	0.0156
55	Compound 55	Train	5.8700	5.9573	0.0873
56	Compound 56	Train	6.4500	6.3955	-0.0545
57	Compound 57	Train	6.4000	5.9721	-0.4279
58	Compound 58	Train	6.3800	6.0927	-0.2873
59	Compound 59	Test	6.1300	6.3466	0.2166
60	Compound 60	Test	5.6100	6.5203	0.9103
61	Compound 61	Train	5.8200	6.5327	0.7127
62	Compound 62	Train	9.1000	9.2435	0.1435
63	Compound 63	Train	8.6000	8.4814	-0.1186

64	Compound 64	Train	8.0700	8.4436	0.3736
65	Compound 65	Test	9.1800	9.6439	0.4639
66	Compound 66	Train	9.3600	9.2120	-0.1480
67	Compound 67	Train	10.1400	9.2537	-0.8863
68	Compound 68	Train	5.2600	6.1436	0.8836
69	Compound 69	Test	7.5400	7.9013	0.3613
70	Compound 70	Train	7.5700	8.0056	0.4356
71	Compound 71	Train	6.8400	6.8300	-0.0100
72	Compound 72	Test	7.1200	6.1706	-0.9494

S/N	PubChem ID	Set	Observed pIC₅₀	Predicted pIC₅₀	Residue Error
73	Compound 73	Train	7.0500	6.7098	-0.3402
74	Compound 74	Train	6.6900	7.6482	0.9582
75	Compound 75	Train	7.3000	7.6506	0.3506
76	Compound 76	Train	7.9200	7.5321	-0.3879
77	Compound 77	Test	5.8900	7.2705	1.3805
78	Compound 78	Train	7.3900	8.1139	0.7239
79	Compound 79	Train	7.8000	7.7714	-0.0286
80	Compound 80	Train	6.3600	5.9129	-0.4471
81	Compound 81	Train	6.9800	6.6129	-0.3671
82	Compound 82	Train	7.5800	7.0575	-0.5225
83	Compound 83	Train	5.7500	5.9343	0.1843

84	Compound 84	Train	6.1800	6.5612	0.3812
85	Compound 85	Test	8.4200	7.9246	-0.4954
86	Compound 86	Train	7.6000	8.0085	0.4085
87	Compound 87	Train	6.8900	6.5560	-0.3340
88	Compound 88	Train	5.8000	6.1174	0.3174
89	Compound 89	Train	5.7600	5.7273	-0.0327
90	Compound 90	Train	6.6900	6.7861	0.0961
91	Compound 91	Train	7.1900	7.0824	-0.1076
92	Compound 92	Train	6.3800	6.5561	0.1761
93	Compound 93	Train	7.8000	7.6584	-0.1416
94	Compound 94	Test	6.5500	6.3098	-0.2402
95	Compound 95	Train	9.7000	9.6921	-0.0079
96	Compound 96	Train	6.3400	5.9989	-0.3411
97	Compound 97	Train	7.1000	7.3305	0.2305
98	Compound 98	Train	10.6000	9.4395	-1.1605
99	Compound 99	Train	7.4800	7.2045	-0.2755
100	Compound 100	Train	6.9900	7.2462	0.2562
101	Compound 101	Train	8.4800	8.6013	0.1213
102	Compound 102	Test	9.7000	9.6921	-0.0079
103	Compound 103	Test	8.0000	8.5021	0.5021
104	Compound 104	Train	5.9000	6.6807	0.7807
105	Compound 105	Train	7.1000	7.1489	0.0489
106	Compound 106	Train	7.5300	7.0098	-0.5202

107	Compound 107	Test	6.3800	6.7236	0.3436
108	Compound 108	Train	6.6000	6.0109	-0.5891

S/N	PubChem ID	Set	Observed pIC ₅₀	Predicted pIC ₅₀	Residue Error
109	Compound 109	Train	7.5200	7.5880	0.0680
110	Compound 110	Train	8.0500	7.3144	-0.7356
111	Compound 111	Train	5.7000	6.0109	0.3109
112	Compound 112	Train	5.5500	5.9962	0.4462
113	Compound 113	Train	5.4700	5.9737	0.5037
114	Compound 114	Train	6.0000	6.4585	0.4585
115	Compound 115	Test	6.0900	6.6952	0.6052
116	Compound 116	Train	6.6600	5.9968	-0.6632
117	Compound 117	Test	5.8000	6.0681	0.2681
118	Compound 118	Train	5.5800	5.9263	0.3463
119	Compound 119	Train	6.4800	6.5352	0.0552
120	Compound 120	Train	5.9600	5.9363	-0.0237
121	Compound 121	Test	7.6000	7.8516	0.2516
122	Compound 122	Test	7.1800	7.1685	-0.0115
123	Compound 123	Train	7.5400	7.9608	0.4208
124	Compound 124	Train	7.1900	7.8644	0.6744
125	Compound 125	Train	9.5700	9.5174	-0.0526
126	Compound 126	Test	6.9700	6.6101	-0.3599

127	Compound 127	Test	10.3000	9.6921	-0.6079
128	Compound 128	Train	10.2700	9.6921	-0.5779
129	Compound 129	Train	6.8400	6.7769	-0.0631
130	Compound 130	Train	5.8400	5.7520	-0.0880
131	Compound 131	Train	5.4600	6.2405	0.7805
132	Compound 132	Test	6.3500	6.6819	0.3319
133	Compound 133	Train	7.7000	7.9854	0.2854
134	Compound 134	Train	7.3600	6.8594	-0.5006
135	Compound 135	Train	7.4600	6.8289	-0.6311
136	Compound 136	Train	7.0000	6.6275	-0.3725
137	Compound 137	Train	9.7400	9.6921	-0.0479
138	Compound 138	Train	6.4800	6.4878	0.0078
139	Compound 139	Train	6.8900	6.5560	-0.3340
140	Compound 140	Train	6.5200	6.5751	0.0551
141	Compound 141	Train	6.1100	5.9183	-0.1917
142	Compound 142	Train	5.5900	6.0025	0.4125
143	Compound 143	Train	6.2700	6.4571	0.1871
144	Compound 144	Train	6.9200	6.3905	-0.5295

S/N	PubChem ID	Set	Observed pIC ₅₀	Predicted pIC ₅₀	Residue Error
145	Compound 145	Train	7.1900	6.6029	-0.5871
146	Compound 146	Train	5.7700	5.9826	0.2126

147	Compound 147	Test	6.4400	6.6497	0.2097
148	Compound 148	Train	7.0800	6.0109	-1.0691
149	Compound 149	Train	6.6200	6.2876	-0.3324
150	Compound 150	Train	6.0000	6.2478	0.2478
151	Compound 151	Train	4.8000	6.1208	1.3208
152	Compound 152	Train	7.0100	6.2517	-0.7583
153	Compound 153	Train	6.3000	5.9624	-0.3376
154	Compound 154	Train	4.8000	6.2808	1.4808
155	Compound 155	Train	7.6200	6.2478	-1.3722
156	Compound 156	Test	5.4600	5.9926	0.5326
157	Compound 157	Test	5.5200	5.9378	0.4178
158	Compound 158	Train	5.6600	6.1897	0.5297
159	Compound 159	Train	5.7200	5.8708	0.1508
160	Compound 160	Test	7.0200	7.6747	0.6547
161	Compound 161	Test	7.0900	8.3812	1.2912
162	Compound 162	Train	7.8900	8.1530	0.2630
163	Compound 163	Train	6.2600	6.2509	-0.0091
164	Compound 164	Test	6.6000	6.1507	-0.4493
165	Compound 165	Train	5.7000	6.0157	0.3157
166	Compound 166	Train	6.5000	6.1658	-0.3342
167	Compound 167	Train	8.3000	7.5841	-0.7159
168	Compound 168	Train	7.1400	6.6028	-0.5372
169	Compound 169	Train	9.3700	8.5857	-0.7843

170	Compound 170	Train	9.7000	8.7919	-0.9081
171	Compound 171	Test	7.7100	7.8673	0.1573
172	Compound 172	Train	8.1700	8.2172	0.0472
173	Compound 173	Train	8.3900	7.9516	-0.4384
174	Compound 174	Train	6.7100	7.7307	1.0207
175	Compound 175	Test	6.5000	6.4901	-0.0099
176	Compound 176	Train	10.5500	9.6921	-0.8579
177	Compound 177	Train	7.1000	8.0332	0.9332
178	Compound 178	Train	6.8000	6.9960	0.1960
179	Compound 179	Train	6.4000	6.9960	0.5960
180	Compound 180	Train	8.6000	7.1991	-1.4009

S/N	PubChem ID	Set	Observed pIC ₅₀	Predicted pIC ₅₀	Residue Error
181	Compound 181	Train	6.8900	6.3705	-0.5195
182	Compound 182	Train	5.8200	6.4585	0.6385
183	Compound 183	Test	7.4000	7.6301	0.2301
184	Compound 184	Train	7.8900	7.6324	-0.2576
185	Compound 185	Test	7.8900	7.4859	-0.4041
186	Compound 186	Train	7.0000	6.7016	-0.2984
187	Compound 187	Test	5.7000	6.6343	0.9343

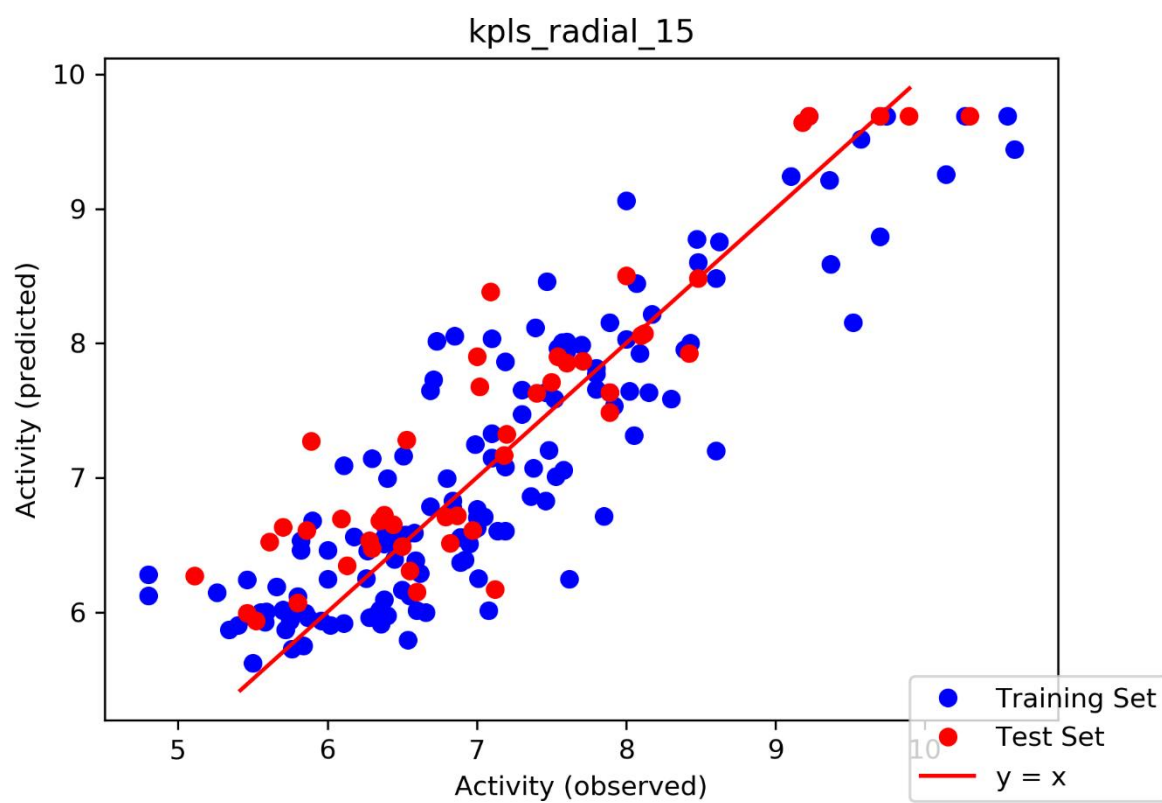


Figure 19: Scatter plots of the QSAR model

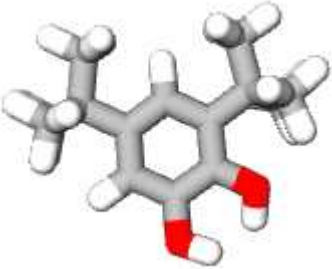
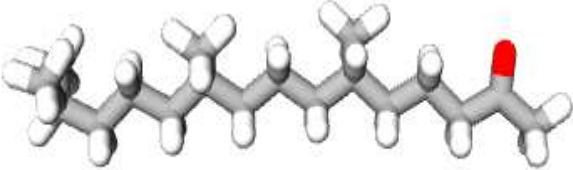
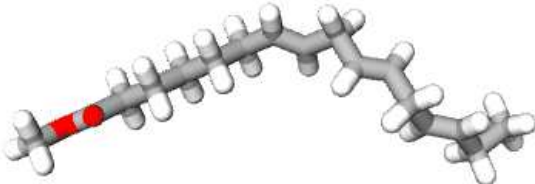
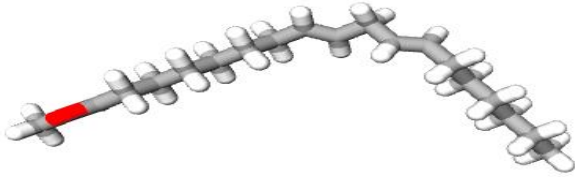
3.5. QSAR model validation

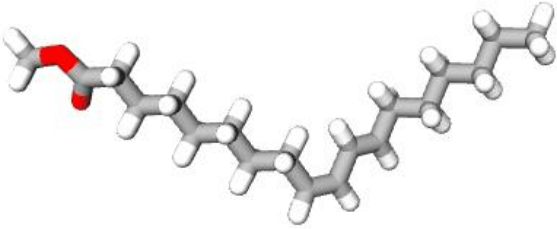
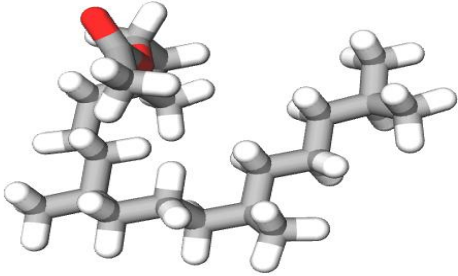
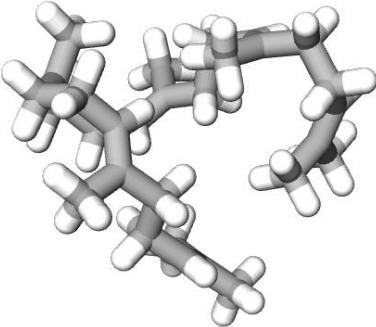
Validation is acknowledged as one of the crucial procedures for testing the reliability, predictability, and dependability of any quantitative structure-activity relationship (QSAR) model to establish its credibility [87]. The root-mean-squared error (RMSE) is one of the widely used metrics for evaluating the QSAR models [88]. Table 7 shows a couple of the prerequisites for external validation, including a cross-validated coefficient (Q^2) value of 0.7959 and a correlation coefficient (R^2) of 0.7835. The regression coefficient is often quoted as R^2 in which case values over 0.6 are considered a good fit [89]. Similarly, Tropsha *et al.* [90] outlined the prerequisites for QSAR models to be trustworthy and predictable. They stated that models ought to be (1) statistically substantial and strong, (2) validated by making correct predictions for external data sets that were not used in model creation, and (3) have clear application borders. They additionally clarified the statistical requirements for a QSAR model to be predictive, which are a coefficient of determination (R^2) > 0.6 and a cross-validated coefficient of determination (Q^2) > 0.5 . These data meet the specifications required to indicate the predictive capabilities of the model chosen. There have been several controversies on the values of RMSE. In line with the findings of Tarafdar [91], RMSE values should stay between 0.2 to 0.5 and it is generally accepted that the lower the RMSE values the better suit the dataset. Meanwhile, the RMSE value obtained in this investigation is 0.54. On the contrary, Etuk [92] argued that there's not likely to be any acceptable value for RMSE. He opined that it is better interpreted and applied comparatively than absolutely. In tune with this argument, Richard [86] concluded that the optimum RMSE value ranges between ≤ 0.75 and < 2.0 . Based on these findings, our model can be said to be accurate and reproducible, thus establishing that *Garcinia kola*-derived compounds are sturdy inhibitors of the human progesterone receptor and can offer a vital therapeutic intervention in breast cancer treatment.

Table 7: Parameters fitting the best appropriate model from Auto-QSAR (PR)

Model Code	S.D	R ²	RMSE	Q ²
KPLS_RADIAL_15	0.5669	0.7835	0.544	0.7959

Table 8: The 3-D structure of hit components from *Garcinia kola*-derived compounds

S/N	Name of compound	Three-dimensional structure
1	1,2-Benzenediol, 3,5-bis (1,1-dimethylethyl)-	
2	2-Pentadecanone, 6,10,14-trimethyl-	
3	7,10,13-Hexadecatrienoic acid methyl ester	
4	8,11-Octadecadienoic acid methyl ester	
S/N	Name of compound	Three-dimensional structure

5	Methyl 9-cis,11-trans-octadecadienoate	
6	Phytol, acetate	
7	Squalene	

4. Conclusion

In drug discovery the interaction between the ligand and receptor is crucial. Given the foregoing, the results obtained in this study showed a compelling chemotherapeutic prowess displayed by the *Garcinia kola*-derived compounds as they demonstrated an inhibitory action against human progesterone receptor-implicated breast cancer. Accurately, the bioactive components isolated from *Garcinia kola* oil demonstrated favourable docking scores, IFDs, free energy of binding, and predicted pIC₅₀ scores, all of which met the requirements for drug candidacy. Altogether, these imply that *Garcinia kola*-derived compounds may be classed as a lead anti-cancer therapeutic agent that inhibits the progesterone receptor, potentially delaying the growth of tumours. Therefore, further studies are recommended to validate this study's findings.

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