Article

ADMET Investigations on a Synthetic Derivative of Genistein, and Molecular Docking Experiments Targeting Estrogen Receptor-α (ER-α) in the Pancreas

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Abstract

The main goal of the current research was to perform ADMET and molecular docking studies for a synthetic genistein derivative that can imitate Estrogen and function as an endocrine disruptor, activating the ER receptor on beta-cells in the pancreas to release insulin. The created molecule was molecularly docked using the online molecular docking research tool Dockthor. NGL viewer, an online program for viewing Dockthor data, displayed the docking experiment results. The 2D legend-protein interactions were estimated with BIOVIA Discovery Studio Visualizer. Estrogen-Receptor Alpha was the targeted target, while Compound-A was employed as the legend. In this study, we created a synthetic derivative of genistein, an analogue of Estrogen in terms of ER-α receptor binding. We used molecular docking to evaluate the affinity of compound-A binding to the ER-α and its 2D interactions and Ramachandran plots. We then ran ADMET experiments on the molecule, which revealed a substantial relationship with the molecule's Estrogen Receptor binding capabilities, as well as scores for absorption, distribution, metabolism, excretion, and toxicity.

Keywords

Genistein, ADMET, Ramachandran Plots, Molecular Docking, Protein-Legend Interactions, ER-α

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Introduction

There has been a substantial increase in the number of persons suffering from metabolic illnesses such as obesity and diabetes since the 1960s [1]. A rise from the present estimate of 415 million people who have the illness is anticipated by the International Diabetes Federation, which predicts that the number of people living with diabetes would climb to 642 million by the year 2040 [2] According to the World Health Organization, there are approximately 2 billion people across the globe who are overweight, and the number of obese people is expected to reach 650 million in the year 2016. This is a significant increase from the 350 million obese people who were estimated to exist in 1980 [3] These numbers are quite disheartening because of the mental anguish they cause in addition to the social and economic harm they cause [4-6]. If we want to stop the spread of this pandemic, we need to find out what factors contribute to the pathogenesis of metabolic disease in the first place, and then we need to mitigate the potentially disastrous effects that these pathogenetic factors have.

The scientific community has largely focused on endocrine disrupting chemicals, also known as Endocrine disrupting chemicals (EDCs), as a possible contribution to the general deterioration in metabolic health, and there is good grounds for this emphasis [7]. The fact that widespread use of EDC occurred at the same time as the incidence of metabolic disorders and obesity increased provides evidence that there is a causal connection between the two patterns of rising prevalence [8, 9]. Studies conducted on animals as well as those conducted on people have shown a diverse array of mechanisms through which EDCs may cause disruptions to the endocrine system and ultimately result in metabolic diseases. The significance of these results demonstrates the urgent need for quick regulation and action.

According to the findings of recent medical studies, the pathogenetic factors that are most closely associated with metabolic disorders are, in order of importance, advancing age, increasing calorie intake, insufficient physical activity, insufficient sleep, and inherited susceptibility. These factors have been found to be most closely associated with metabolic disorders [10]. Notwithstanding this, the data suggest that the risk factors that have been mentioned in previous discussions cannot entirely explain the rise in metabolic disease that has been recorded. In spite of the fact that individuals have not made significant changes in either their levels of physical activity or the foods that they consume over the last twenty to thirty years, the average weight of the population has been continuously increasing [11].

In this research we have synthesised a synthetic derivative of genistein, which in itself is an analogue of Estrogen in ER-α receptor binding. We performed molecular docking studies to determine the affinity of binding of compound-A to the ER-α and also determined its 2D interactions along with Ramachandran plots. We further performed ADMET studies on the molecule which also suggested significant interaction with the Estrogen Receptor binding capability of the molecule along with the absorption, distribution, metabolism, excretion, and toxicity scores.

Materials and Methods

Chemicals and Reagents

All the chemicals and reagents are of laboratory grade standard and were obtained from Sigma Aldrich.

Synthesis of Compound-A

After a 30-minute freezing of the solution in an ice bath, 13.5 millilitres (100 millimoles) of dimethyl sulphate was added drop by drop throughout the course of the subsequent six hours while the solution was stirred at a temperature of 25 degrees Celsius. Once all was said and done, the solution was filtered. To begin, genistein was dissolved in 100 millilitres in a solution containing 15% sodium hydroxide (8.1 g, 30 mmol). In the reaction mixture, 50 ml of a 10% NaOH solution was added, and after being agitated for 17-19 hours at 80 degrees Celsius, it was filtered on sand. Further purification was not performed on the combination at this point. Before undergoing extraction with AcOEt, the pH of the filtrate is lowered to 7 using 30% hydrochloric acid (330 ml). With the process of drying the combined organic extracts over anhydrous sodium sulphate, compound-A was produced in the form of a colourless crystal. [12]

^{1}H NMR: δ 3.66-3.79 (5H, 3.71 (s), 3.74 (s)), 3.84-3.95 (6H, 3.89 (s), 3.90 (s)), 6.16-6.27 (2H, 6.21 (d, J = 1.6 Hz), 6.22 (d, J = 1.6 Hz)), 6.86 (2H, ddd, J = 8.8, 1.3, 0.5 Hz), 7.24 (2H, ddd, J = 8.8, 1.2, 0.5 Hz). ^{13}C NMR: δ 43.4 (1C, s), 56.0-56.0 (3C, 56.0 (s), 56.0 (s), 56.0 (s)), 98.7 (1C, s), 99.6 (1C, s), 107.0 (1C, s), 114.3 (2C, s), 130.0 (2C, s), 131.4 (1C, s), 159.8 (1C, s), 163.0-163.2 (2C, 163.1 (s), 163.1 (s)), 166.3 (1C, s), 198.5 (1C, s). ESI-MS: $C_{17}H_{18}O_{5,}$ $[M^{+}$ H$]^{+}$, 302.12. Yield; 72% and M.P: 150 1

3D Structure

The structure drawing and 3D structure of the molecule was obtained by using ChemBioDraw 3D Ultra version 8. (Figure 1 and 2)

ADMET Studies

Absorption, Distribution, Metabolism, Excretion and Toxicity (ADMET) properties of drug candidates or environmental chemicals play a key role in drug discovery and environmental hazard assessment. The ADMET structure-activity relationship server, entitled admetSAR, is a comprehensive knowledge and tool for predicting ADMET properties of drug candidates and environmental chemicals. In our server, over 200,000 ADMET annotated data points for about 96 thousand of unique compounds have been

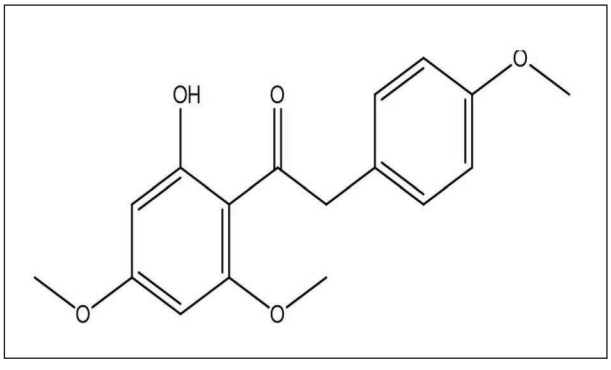

Figure 1. 1-(2-Hydroxy-4,6-dimethoxyphenyl)-2-(4-methoxyphenyl) ethanone (Compound A)

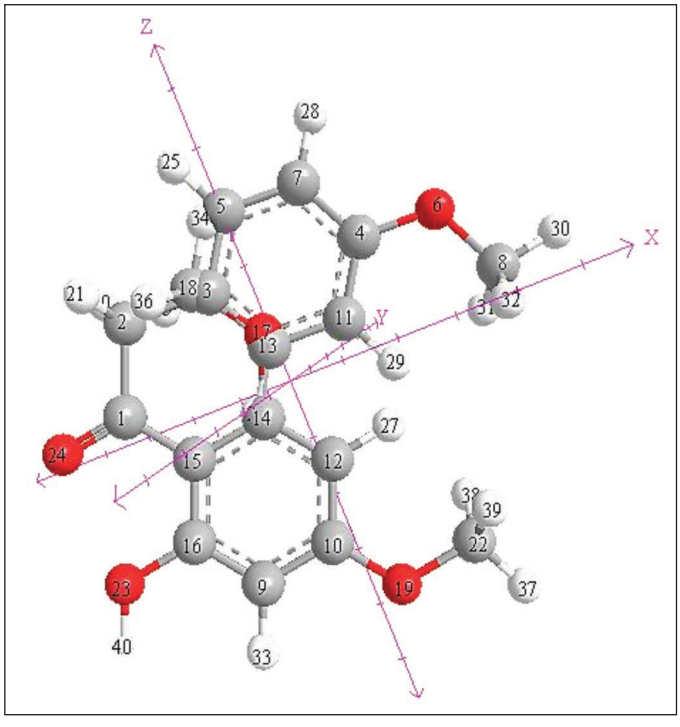

Figure 2. 3D structure of compound-A

manually curated from large literatures. The admetSAR server provides a user-friendly interface to easily search for chemical profiles, by CASRN, common name and similarity search. [13, 14]

Dockthor

The Dockthor is a web-based molecular docking service that greatly decreases the amount of time necessary to dock molecules as well as the number of resources that are needed. By using the web service provided by receptor-legend, comparing the docking scores of a legend protein to those of a target protein is a fairly simple process that takes very little time. The findings of the docking experiment are presented in the form of a table, and particular attention is paid to the top three affinity holders as well as the top 10 scores for single legend-receptor interactions. Use this URL to access the docking results page:

https://dockthor.lncc.br/v2/index.php?tab=DOCKING&page=RESULTS&jobId=researchX2_63917a905cdba [15-17]

NGL Viewer

Molecular visualisation may be accomplished via the use of a piece of software known as the NGL Viewer, which is a web-based application. It is possible to see a wide variety of molecules, including

RNA, DNA, and proteins, with the use of WebGL. Since the NGL Viewer consists of nothing more than a collection of static files, it is quite easy to alter it so that it is compatible with any web browser or computer operating system. In the event that you find it necessary to make improvements to this repository, it is recommended that you first create a copy of it on your own computer and save it before attempting any edits. The NGL Viewer may be imported as a library in the standalone build of the project, which can be located in the directory that is labelled dist/ngl.js. The examples directory has a graphical user interface (GUI) web application that may be used for testing purposes (GUI).

Biovia Discovery Studio Visualizer

The BIOVIA Discovery Studio is capable of combining the knowledge gained over the course of more than three decades of research with the most cutting-edge in silico research methods. This course goes through a tremendous amount of material, some of which includes molecular mechanics, computations of free energy, and biotherapeutics. Having said that, the items in this list are not all there is. Since scientists now have access to a wide spectrum of techniques for analysing protein chemistry, the process of designing small- and large-molecule therapeutics has been sped up significantly. The drug development pipeline refers to this process, which starts with the identification of a target and concludes with the optimization of a lead candidate. Using the tool, we conducted an investigation of 2D protein-ligand interactions in order to calculate probable binds and forces.

Results and Discussion

General Calculations

We used admetSAR for the prediction and simulations of the general properties of compound-A. The results revealed a molecular weight of 302.33 and octane/water partitioning of 2.84 meaning approximately 99.9 % of portioning in octane and 0.1% by water. Table 1 represents the general properties of compound-A.

Table 1. General Physiochemical properties of compound-A

Molecular Weight	302.33
AlogP	2.84
H-Bond Acceptor	5
H-Bond Donor	1
Rotatable Bonds	6
Applicability Domain	In domain

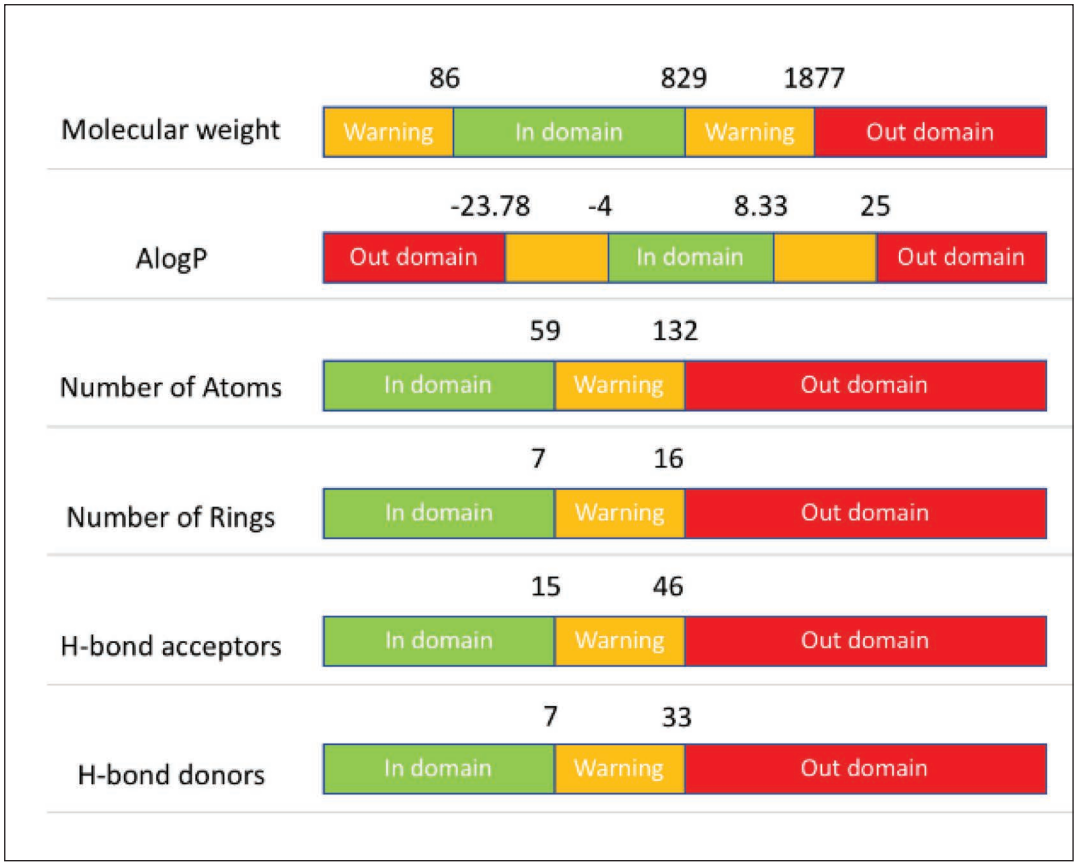

Figure 3. Colour indicator for ADMET analysis using admetSAR

Table 2. Results revealed by the ADME analysis using admetSAR.

ADMET predicted profile — Classifications	**Value**	**Probability**
Human Intestinal Absorption	+	0.9853
Caco-2	+	0.9695
Blood Brain Barrier	-	0.5750
Human oral bioavailability	+	0.5143
Subcellular localization	Mitochondria	0.9300
OATP2B1 inhibitior	-	1.0000
OATP1B1 inhibitior	+	0.9435
OATP1B3 inhibitior	+	0.9534
MATE1 inhibitior	-	0.9000
OCT2 inhibitior	-	0.9750
BSEP inhibitior	-	0.5149
P-glycoprotein inhibitior	-	0.5424

(Table 2 continued)

(Table 2 continued)

P-glycoprotein substrate	-	0.9027
CYP3A4 substrate	-	0.5598
CYP2C9 substrate	-	1.0000
CYP2D6 substrate	-	0.7565
CYP3A4 inhibition	-	0.5598
CYP2C9 inhibition	-	0.9109
CYP2C19 inhibition	+	0.9552
CYP2D6 inhibition	-	0.5062
CYP1A2 inhibition	+	0.8308
CYP inhibitory promiscuity	+	0.7180
UGT catelyzed	+	0.6000
Carcinogenicity (binary)	-	0.6978
Carcinogenicity (trinary)	Non-required	0.6872
Eye corrosion	-	0.9760
Eye irritation	-	0.6162
Ames mutagenesis	-	0.7000
Human Ether-a-go-go-Related Gene inhibition	+	0.6952
Micronuclear	-	0.5067
Hepatotoxicity	-	0.6301
skin sensitisation	-	0.9500
Respiratory toxicity	-	0.7111
Reproductive toxicity	+	0.5333
Mitochondrial toxicity	-	0.7000
Nephrotoxicity	-	0.5991
Acute Oral Toxicity (c)	III	0.5158
Estrogen receptor binding	+	0.8682
Androgen receptor binding	+	0.7147
Thyroid receptor binding	+	0.7278
Glucocorticoid receptor binding	+	0.7526
Aromatase binding	+	0.7056
PPAR gamma	-	0.5212
Honey bee toxicity	-	0.9565
Biodegradation	-	0.8250
Crustacea aquatic toxicity	-	0.5349
Fish aquatic toxicity	+	0.9472

Table 3. Toxicity studies using admetSAR

ADMET predicted profile — Regression	Value	Unit
Water solubility	-3.74	logS
Plasma protein binding	0.934	100%
Acute Oral Toxicity	2.466	log(1/(mol/kg))
Tetrahymena pyriformis	0.598	pIGC50 (ug/L)

Table 4. Molecular docking results of compound-A against ER-α

Rank	File ID	Compound	Affinity	Total Energy	vdW Energy	Elec. Energy
1	f8c63a8455	ligand 1	-7.090	69.151	-3.348	-30.230
		run 9	-7.090	69.151	-3.348	-30.230
		run 3	-7.096	69.156	-4.441	-28.957
		run 21	-7.509	72.278	-13.240	-17.312
		run 9	-7.043	72.370	-9.142	-21.068
		run 22	-8.263	72.574	-19.233	-10.498
		run 17	-7.198	72.694	-9.749	-21.284
		run 18	-7.124	72.718	-4.744	-25.157
		run 16	-6.828	72.754	-4.584	-25.124
		run 6	-7.910	72.789	-19.673	-11.928
		run 8	-7.536	72.888	-14.574	-16.144

ADMET Analysis

The results of the admetSAR showed positive and in domain results for the compound-A. The results of admetSAR are revealed in table 2 and the presence of different colour indicators are revealed in figure 3. Despite the fact that the admetSAR results showed out domain results for the estrogen receptors activity of the compound-A suggesting its higher susceptibility to get attached to the receptors throughout the body and in pancreas too to help releasing insulin. Besides higher effectives of our target drug shown by admetSAR study, our compound showed higher biodegradability and negative results for the carcinogenicity. The toxicity study results from admetSAR showed lower toxicity for the synthesized molecule (Table 3). Therefore, we recommend that the synthesized compound is worth further studies.

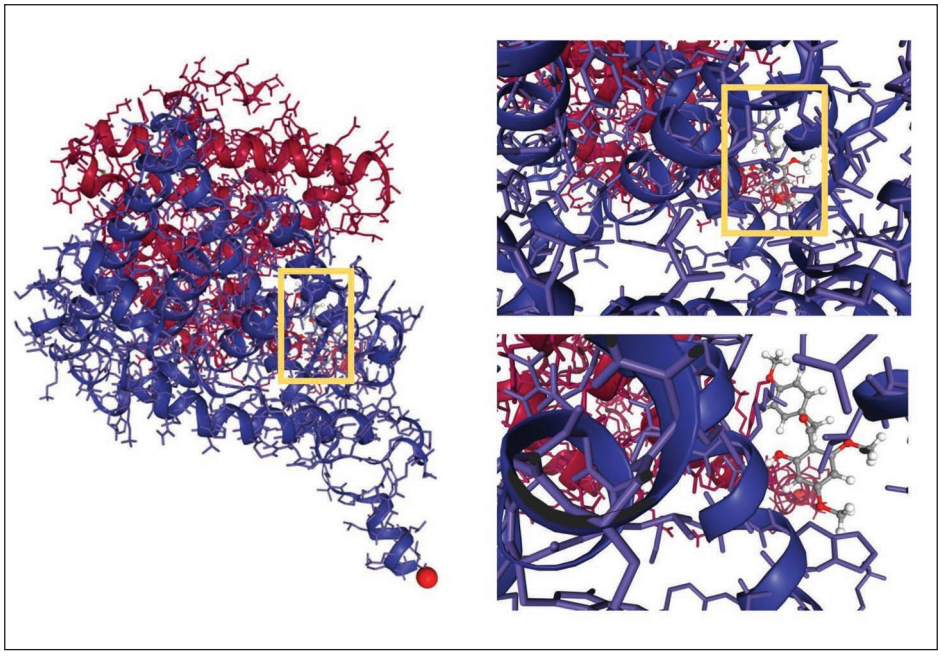

Figure 4. : Pose 9

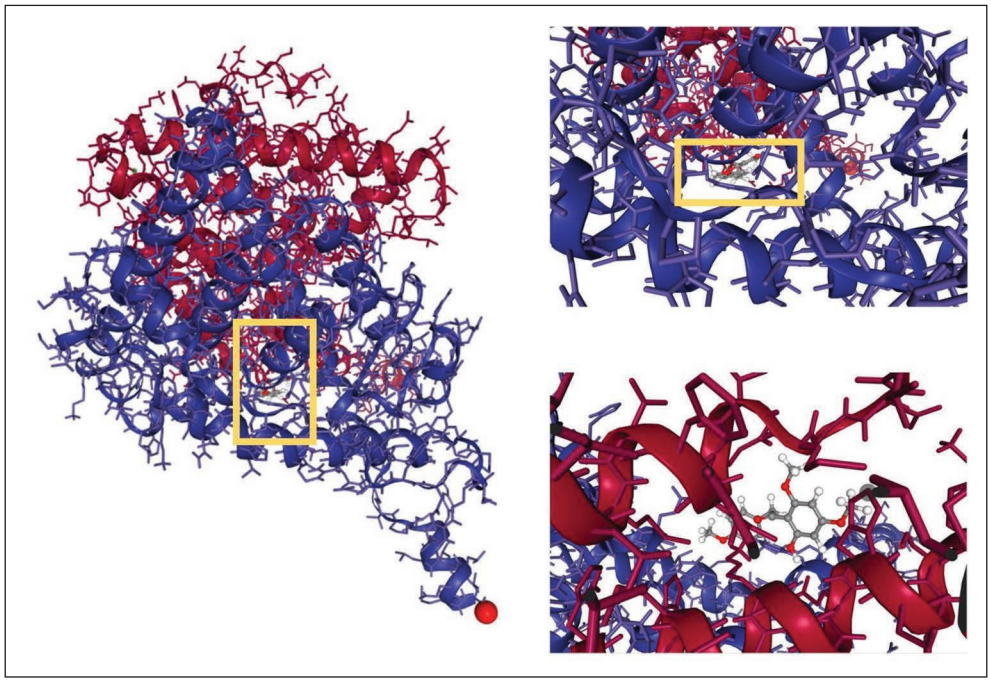

Figure 5. : Pose 3

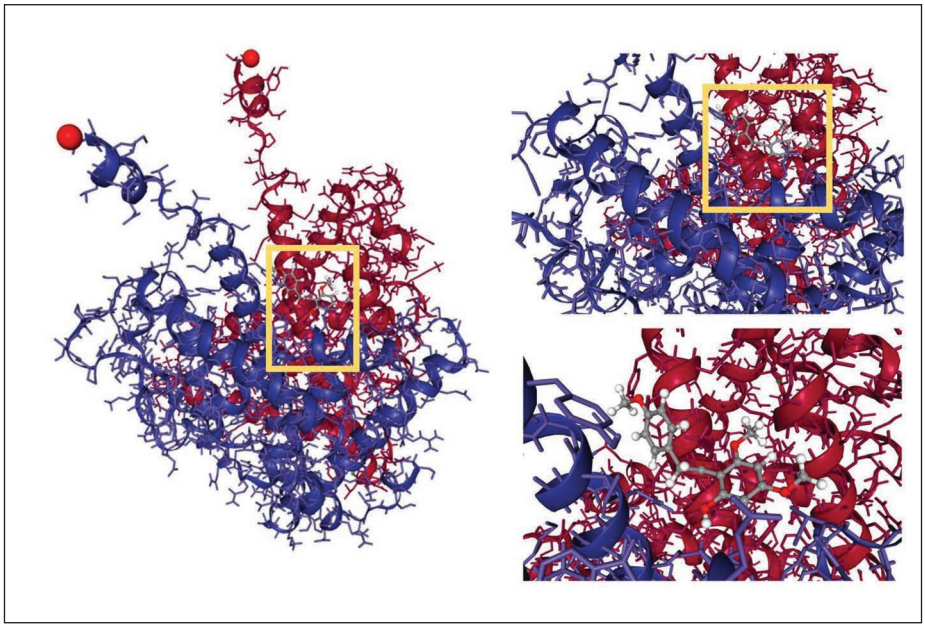

Figure 6. Pose 21

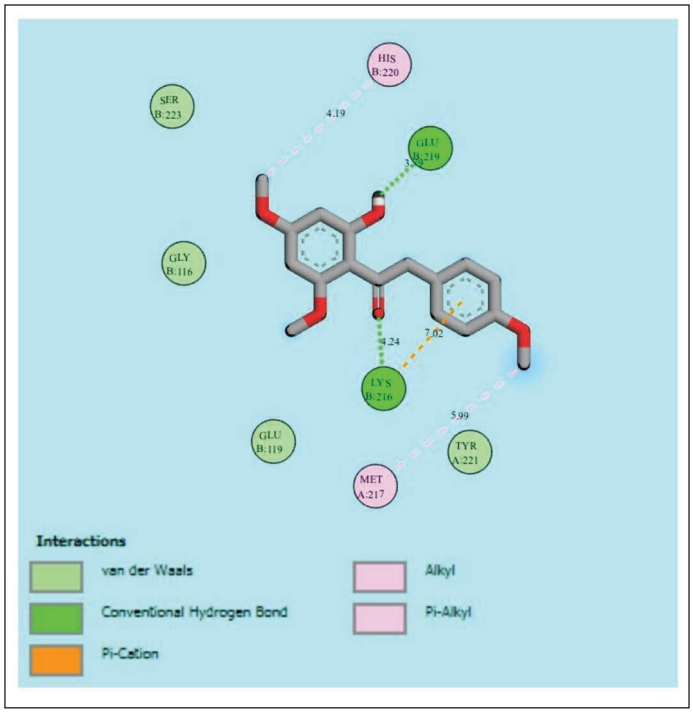

Figure 7. Interactions with protein residues in pose 9.

Molecular Docking Results

The molecule was saved as protein data bank (pdb) format and the protein structure was obtained from the pdb cite with an pdb id of 1A52. The structure of estrogen-receptor alpha was deposited by Tanenbaum et al. in 1998 [18]. Both the pdb structures legend and protein were loaded to the Dockthor without implementing a cofactor and with blind docking rather than selecting a manual grid. We got good docking scores for our molecule binding to ER-α ranging from -6.828 to -8.263 (Table 4), with highest docking scores of -7.090, -7.096 and -7.509 for different docking poses of 9 (figure 4), 3 (Figure 5) and 21 (Figure 6).

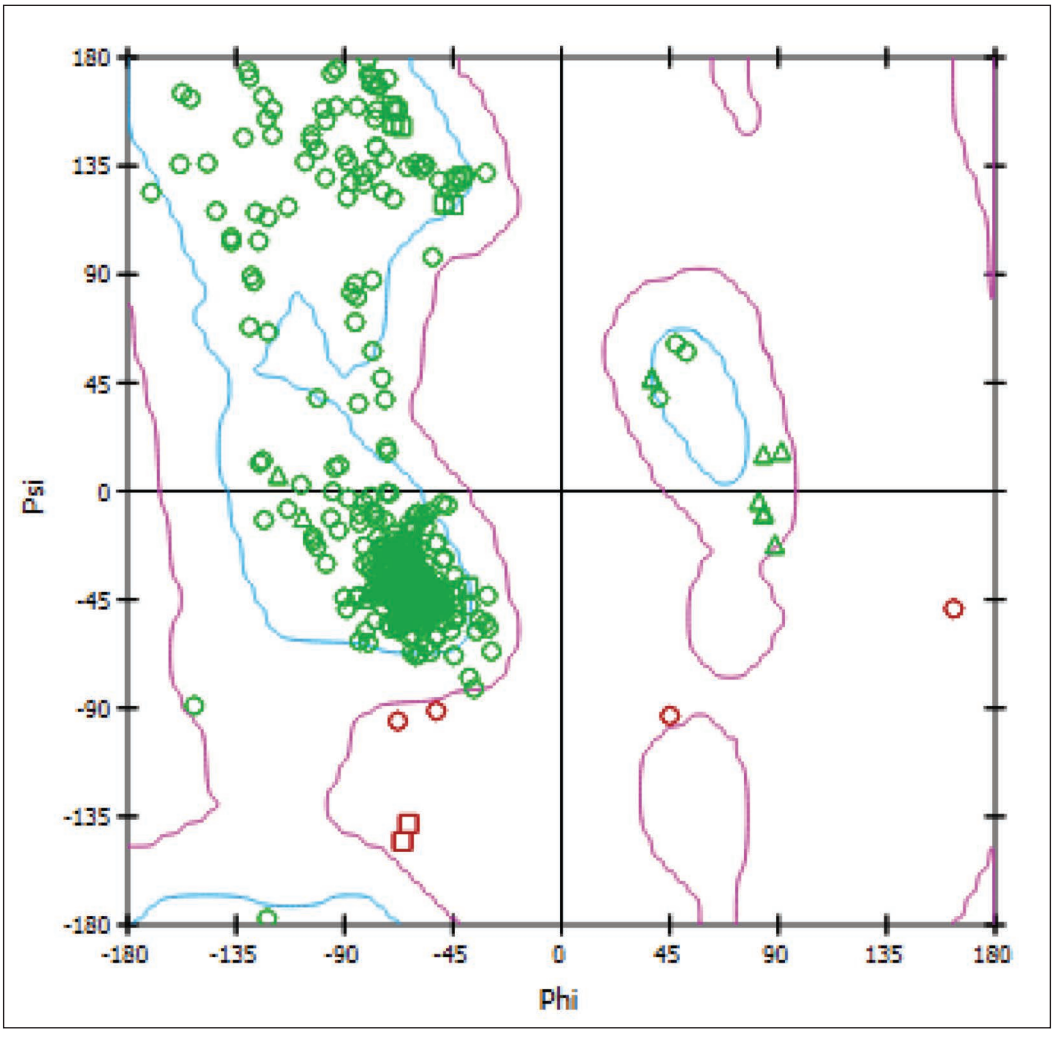

Figure 8. Ramachandran plot for Pose 9

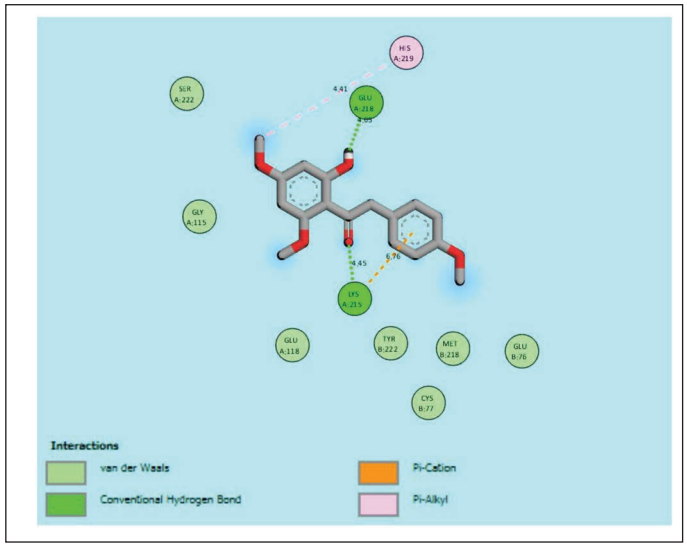

Figure 9. Protein legend interaction at binding site with protein residues in pose 3.

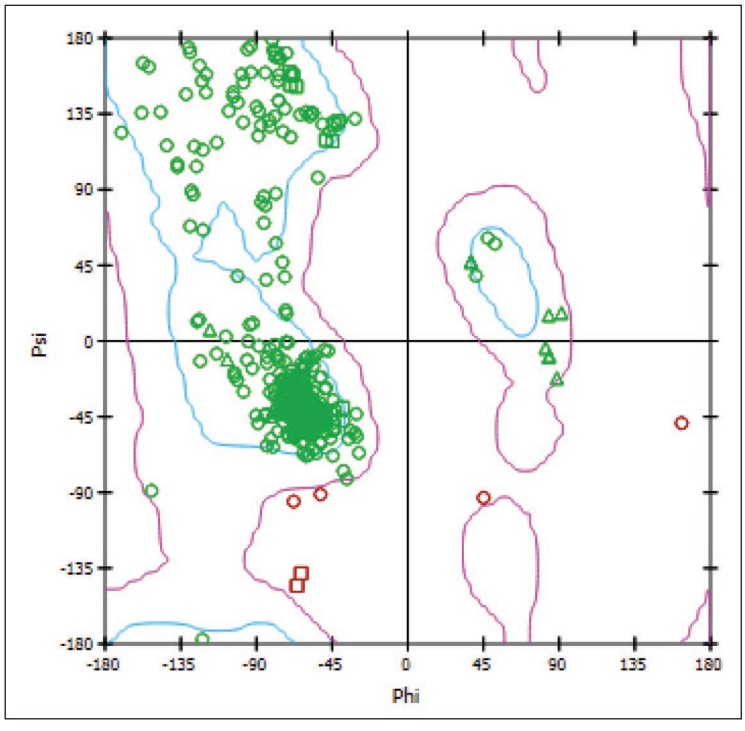

Figure 10. Ramachandran plot for Pose 3

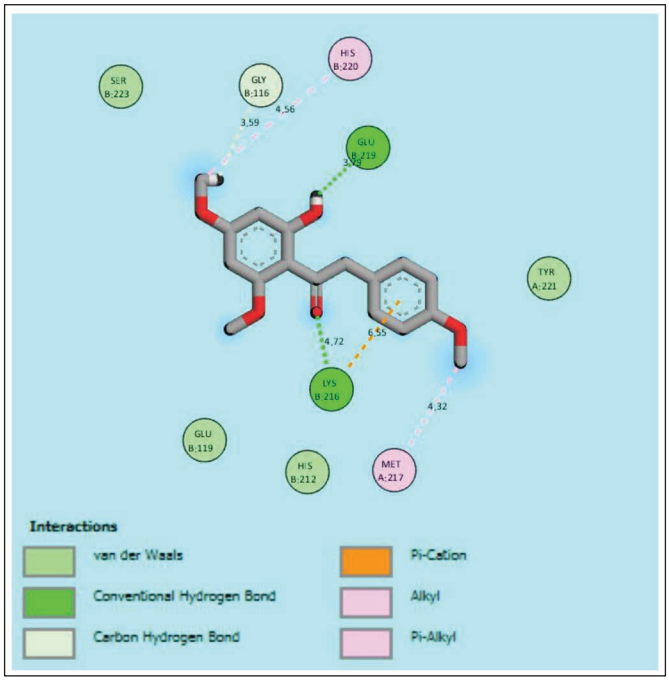

Figure 11. Protein legend interaction at binding site with protein residues in pose 21

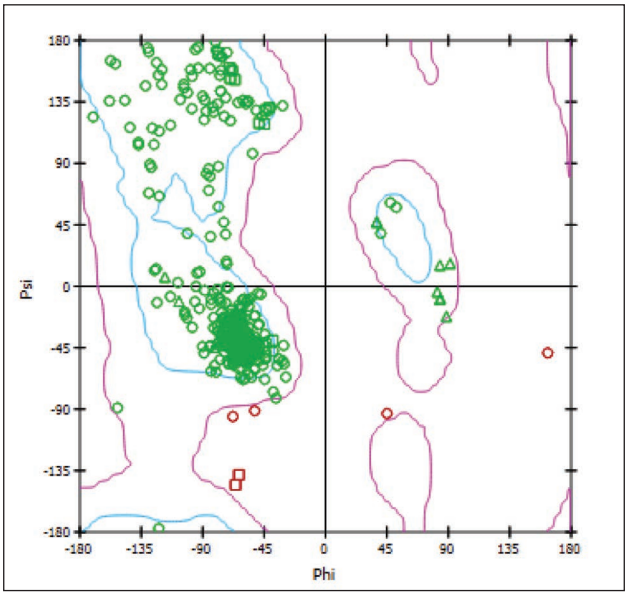

Figure 12. Ramachandran plots for Pose 21

2D Molecular Interactions

On studying the 2D interactions between the legend and the protein we found six types of interactions that existed between the legend and the protein including hydrogen bonding, carbon-carbon bond, Vander walls forces of attraction, pi-cation, pi-allyl and allyl interactions. for each interaction is shown in figures 7, 9 and 11 wile the Ramachandran plot for each separate pose is shown in Figures 8, 10 and 12. The Ramachandran plot using BIOVIA Discovery Studio visualizer, a Ramachandran plot was created to show which amino acid residues fall into the "accepted region" and which do not. More than 90% of the amino acid residues in a 3D protein model should be in the optimal region of the Ramachandran Plot.

Conclusion

In this study, we created a synthetic counterpart of genistein, which binds to the ER-receptor similarly to Estrogen. We used Ramachandran plots and molecular docking to analyse drug A's 2D interactions and assess its affinity for binding to the ER. We also conducted ADMET experiments on the compound, which indicated substantial interactions with the capacity of the compound to bind to oestrogen receptors as well as the scores for absorption, distribution, metabolism, excretion, and toxicity.

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Conflict of Interest

None.

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