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# Molecular docking on a synthetic derivative of genistein targeting Estrogen Receptor-α

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***Abstract - The objective of this study is to conduct molecular docking analyses on a synthetic genistein derivative. The compound is hypothesised to mimic oestrogen and function as an endocrine disruptor by activating the ER-receptor on beta-cells in the pancreas, leading to insulin release. The synthesised molecule was subjected to molecular docking using Dockthor, an online research tool for molecular docking. The Dockthor data was analysed and visualised using the NGL viewer, a web-based software designed for docking experiments. The results of the analysis were presented through this programme. The analysis of 2D protein-legend interactions was conducted using the BIOVIA Discovery Studio Visualizer. Compound-2 was utilised as the legend, while the oestrogen receptor alpha was identified as the target receptor for oestrogen. Genistein was synthesised in the present study. This compound is known to mimic the action of oestrogen by binding to ER-receptors. The effectiveness of drug A's binding to the receptor was determined through the analysis of its 2D interactions with the ER- and Ramachandran plots using molecular docking.***

***Keywords - genistein, ADMET, Ramachandran plots, molecular docking, Protein-legend interactions, ER-α***

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## INTRODUCTION

Metabolic disorders, including diabetes and obesity, have witnessed a substantial increase since the 1960s [1]. As per the latest estimates, the current worldwide population of individuals diagnosed with diabetes is 415 million. According to the International Diabetes Federation's projections, the number of individuals with diabetes is anticipated to increase substantially to 642 million by the year 2040. The World Health Organisation has projected that the global population of 2 billion will have 650 million individuals who are morbidly obese by the year 2016. According to a report [3], the current number of overweight individuals has exceeded the estimated count of 350 million people in 1980. The statistical data falling within the range of 4-6 is a cause for concern due to its negative impact on socio-economic and financial factors, as well as human welfare. In order to hinder the advancement of metabolic disease, it is crucial to identify the elements that contribute to its development. After finishing the task, it is recommended to take measures to reduce the severe outcomes that could result from these factors.

Endocrine disrupting chemicals (EDCs) have been identified by the scientific community as a potential factor in the decline of metabolic health. This is a noteworthy undertaking. [7] The hypothesis that there is a causal link between the increased prevalence of endocrine disrupting chemicals (EDCs) and the concurrent rise in rates of obesity and metabolic disease [8,9] is supported by their correlation. This suggests a potential association between the two trends. Empirical evidence from research conducted on both human and animal subjects suggests that environmental hormone disruptors (EDCs) can cause disruptions in the endocrine system and metabolic function through various mechanisms. The results mentioned above are of significant importance and require prompt regulatory action and intervention.

Recent medical investigations have revealed that the most strongly correlated pathogenetic factors with metabolic disorders include advancing age, caloric surplus, inadequate physical activity or rest, and genetic susceptibility. According to the research results, the variables being studied exhibit significant correlations with metabolic disorders [10]. However, the findings suggest that the risk factors discussed in the previous lectures may not fully explain the observed increase in metabolic disorders. Over the past two to three decades, despite the consistent

levels of physical activity and dietary habits among individuals, there has been a gradual and steady rise in the average weight of the population [11]. Despite the consistency of individuals' dietary habits, this remains irrelevant.

A synthetic compound that mimics genistein was produced and has demonstrated the ability to bind to the oestrogen receptor (ER) in a manner similar to oestrogen. The binding affinity of Drug 2 with the ER was determined through Ramachandran plot analysis and molecular docking.

## MATERIALS AND METHODS

### The reagents and chemicals involved.

Sigma Aldrich is a reputable supplier of laboratory supplies and was the primary source of procurement for all reagents and chemicals.

**Compound-2 (**Figure 1)

The mixture was strained through sand after being stirred at 60 degrees Celsius for 17–19 hours with genistein, which had been mixed with 40 millilitres of a 10% sodium hydroxide solution. The process took place at 60 degrees Celsius. After the process of bringing the pH of the filter down to 7 with the use of a solution that included 30% HCl, the filtrate is then extracted using 3.3 millilitres of AcOEt. After being mixed with one another and then dried over anhydrous sodium sulphate, the organic extracts generated a powder that had a hue that was somewhere between yellow and orange.

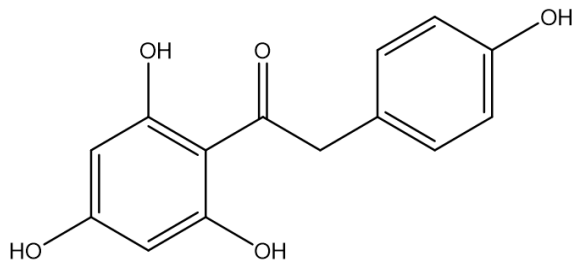


**Figure 1: Compound 2: 2-(4-Hydroxyphenyl)-1-(2,4,6-trihydroxyphenyl)**

**ethanone**

$^{1}$H NMR: δ 3.71 (2H, s), 6.20 (2H, d, *J* = 1.6 Hz), 6.72 (2H, ddd, *J* = 8.3, 2.3, 0.5 Hz), 7.24 (2H, ddd, *J* = 8.3, 1.4, 0.5 Hz). $^{13}$C NMR: δ 43.4 (1C, s), 101.1 (2C, s), 105.2 (1C, s), 115.7 (2C, s), 130.0 (2C, s), 131.4 (1C, s), 157.4 (1C, s), 163.1 (2C, s), 164.5 (1C, s), 198.5 (1C, s). ESI-MS $C_{14}H_{12}O_5$ $[M^+ H]^+$ 260.7.Melting point 160 ±2 $^{o}$C; Yield 52%

## RESULTS AND DISCUSSION

### Molecular Docking Results

- **ER-α**

The PDB file for the compound-2 was generated using ChemBioDraw3D Ultra version 11.0, and the PDB citation for the ER-α protein was deposited by Tananbaum et al., 1998. Before beginning the blind docking experiment, the proteins and their labels were both concealed. They consisted of the traditional approach, a million assessments, 750 individuals in the population, an initial velocity of -1985, 24 iterations, and a preference for moderate docking. The ER-α which was being targeted exhibited a strong affinity for chemical-2 when it was subjected to docking assays. The results showed highest docking score for poses 7, 22 and 1 bearing an affinity scores of-7.481, -7.294 and -7.368, respectively. Additionally, we found that the target compound 2 exhibited significant values for the total energy calculations, vandervaals energy and electrical energy including 34.914, 35.027 and 35.389; -9.465, -6.405 and -10.638 and -31.304, -33.553 and -29.773, respectively for the poses of 7, 22 and 1 against the target protein that is endocrine receptor-alpha (Table 1).

**Table 1: Molecular docking results as revealed interims of best docking poses by Dockthor of compound-2 with selected target ER-α.**

| Rank | File ID | Compound | Affinity | Total Energy | vdW Energy | Elec. Energy |
|---|---|---|---|---|---|---|
| 1 | c80a88c2a8 | ligand 1 | -7.481 | 34.914 | -9.465 | -31.304 |
| | | run 7 | -7.481 | 34.914 | -9.465 | -31.304 |
| | | run 22 | -7.294 | 35.027 | -6.405 | -33.553 |
| | | run 1 | -7.368 | 35.389 | -10.638 | -29.773 |
| | | run 22 | -7.311 | 35.671 | -8.461 | -31.518 |
| | | run 16 | -7.142 | 36.436 | -9.189 | -29.115 |
| | | run 5 | -7.005 | 38.594 | -0.642 | -36.923 |
| | | run 16 | -7.431 | 39.787 | -15.276 | -20.594 |
| | | run 7 | -7.517 | 40.521 | -13.234 | -22.720 |
| | | run 14 | -7.173 | 40.585 | -3.323 | -30.885 |
| | | run 10 | -7.282 | 40.800 | -1.530 | -33.323 |

### a) 3D visualization

Different interactions and visualizations from the NGL viewer were recorded as screenshots, zoomed pictures were also saved. The best docking poses for protein-legend binding of compound-2 and ER-α are shown in figures 2-4.

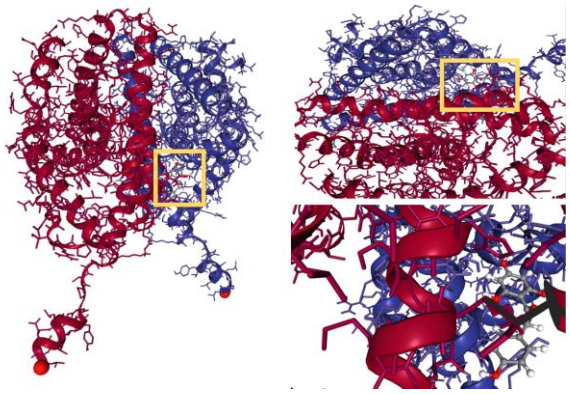

**Figure 2: NGL viewer image for pose 7.**

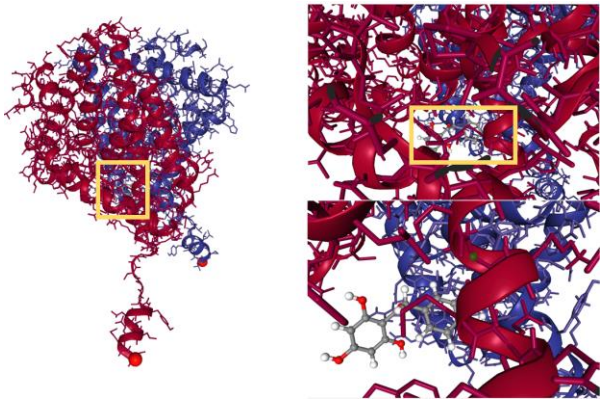

**Figure 3: NGL viewer image for pose 22.**

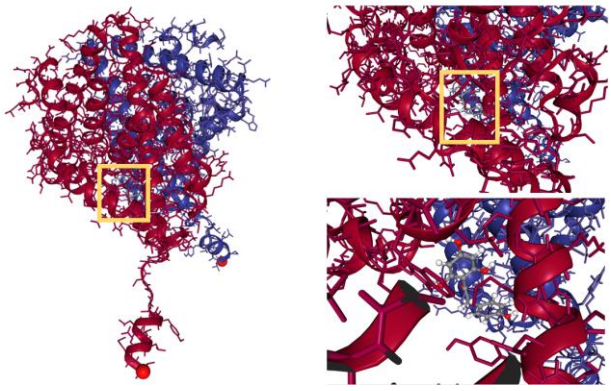

**Figure 4: NGL viewer image for pose 1.**

**b) 2D visualization**

The interactions that were determined in pose 7 of the legend and protein interaction that is compound-2 and ER-α are given bellow. The van der waals interactions existed between the legend and the TRP B 79, ALA B 78, LEU B 80, GLU B 81, HIS A 21, GLU B 219, and TYR B 222. The conventional hydrogen bonding existed with the GLU B 76 (3.95), SER B 214 (4.46), CYS B 77 (4.24), ASN B 215 (3.44), GLU A 218 (4.53) and LYS A 215 (5.79). The pi-cation and pi-sulfur interactions existed between LYS A 215 (5.78) and MET B 218 (4.73) protein subunit and legend, respectively (Figure 5). In poses 22 (Figure 7), the van derwaals interactions were found between legend and CYS A 76, ASN A 214, GLU A 218, TYR A 221 and HIS B 212. The conventional hydrogen bonding exhibited with LYS B 216 (6.33), GLU B 219 (4.81), and GLU A 75 (4.29 and 4.00). pi-cation bonding existed with LYS B 216 (6.33), and amide-pi stacking existed between MET A 217 (3.87). The similar interactions were found between the protein and the legend in pose 1 (Figure 9), the only differences determined were in the interaction distances.

Our interaction was found to be within the permissible parameters after doing the Ramachandran plot analysis for pose 7, which yielded these results. Simmilarly, the permissible results were yielded for pose 22 and 1, respectively. (Figure 6, 8 and 10)

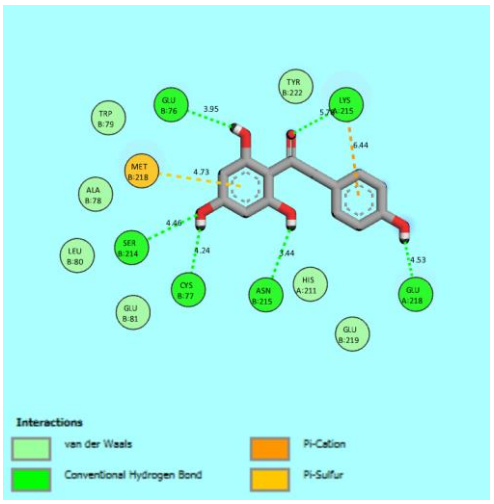


**Figure 5: 2D docking interactions between ER-α and compound-2 in pose 7.**

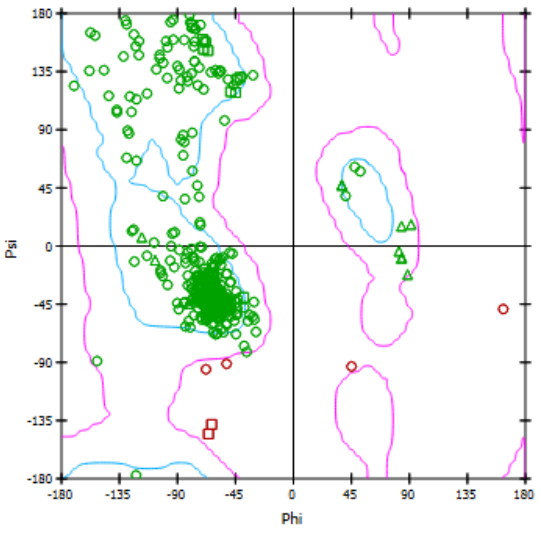


**Figure 6: Ramachandran plot for the interactions between ER-α and compound-2 in pose 7**

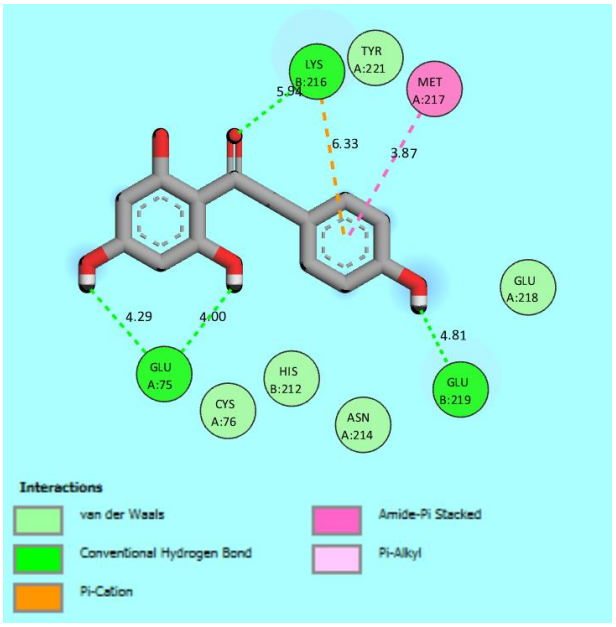


**Figure 7: 2D docking interactions between ER-α and compound-2 in pose 22.**

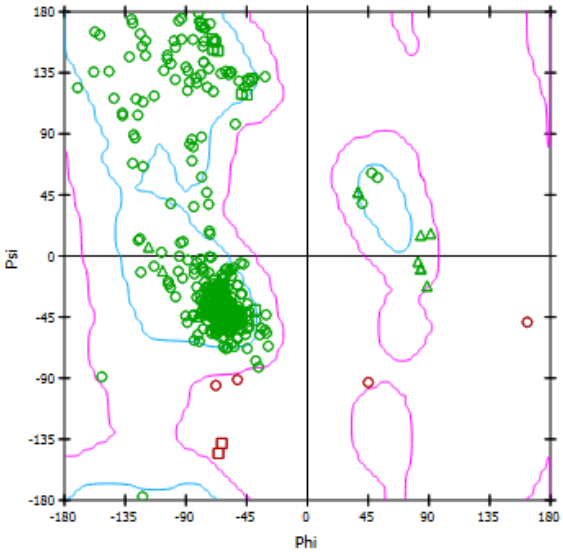


**Figure 8: Ramachandran plot for the interactions between ER-α and compound-2 in pose 22**

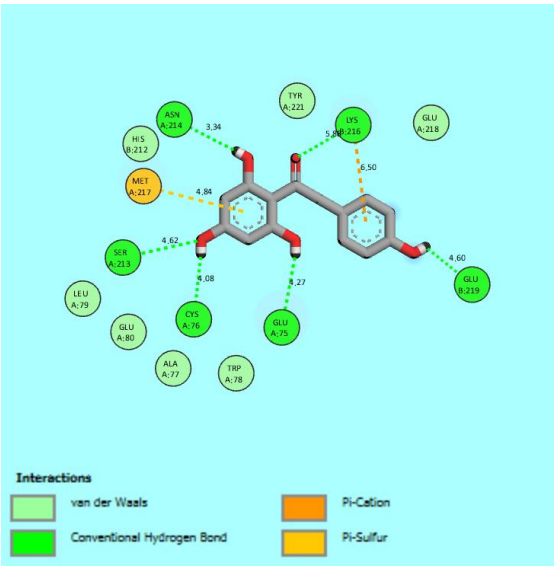


**Figure 9: 2D docking interactions between ER-α and compound-2 in pose 1.**

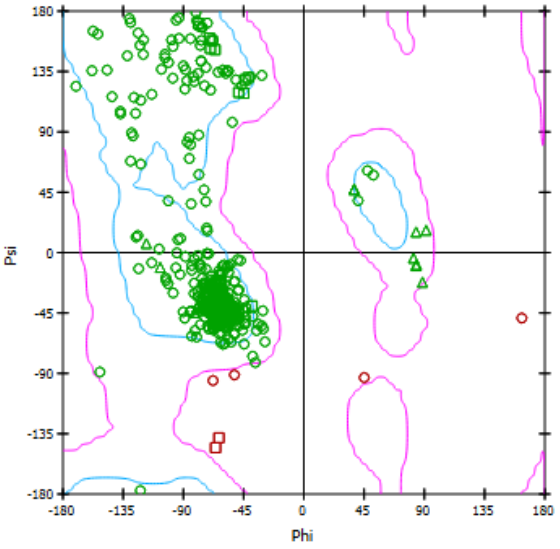


**Figure 10: Ramachandran plot for the interactions between ER-α and compound-2 in pose 1**

## CONCLUSION

In the course of the study, a synthetic derivative of genistein was synthesised that demonstrates a comparable binding selectivity to oestrogen at the ER receptor-Alpha. The investigation employed Ramachandran plots and molecular docking methodologies to examine the two-dimensional interactions of compound A and assess its binding affinity with the ER. The substance's ability to bind to oestrogen receptors was impacted by the significant interactions that were detected.

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