

Effect of Most Favored Regions of Estrogen Receptor β (ER β) Molecules on MolDock Score Using Tamoxifen Ligand

Novyananda Salmasfattah^{1*}, Agung Permata², Fendy Prasetyawan³

^{1*,3} Progam Studi Profesi Apoteker, Fakultas Ilmu Kesehatan, Universitas Kadiri

² Progam Studi Sarjana Farmasi, Fakultas Ilmu Kesehatan, ITS dr. Soepraoen

Email : salmasfattah@gmail.com

Abstrak : Molekul *estrogen receptor β* (ER β) merupakan salah satu protein target pada pengobatan kanker. Jenis molekul ER β pada *protein data bank* (PDB) menentukan nilai dari *most favoured regions* dan *MolDock score*. Tujuan penelitian ini untuk mengetahui pengaruh dari *most favoured regions* dari molekul ER β terhadap *MolDock score* menggunakan ligand Tamoxifen. Terdapat 37 molekul yang memiliki protein ER β , dipilih 7 molekul yang dianalisis nilai *most favoured regions* dan *MolDock score*, berdasarkan nilai *r* tabel, nilai *pearson correlation* $0.548 < 0.754$ (*r* tabel). Hal ini, juga sama jika dilihat dari nilai signifikansi $0.203 > 0.05$. Dapat disimpulkan tidak ada korelasi antara nilai *most favoured regions* dengan *MolDock score*.

Kata Kunci: Ramachandran; Estrogen receptor β ; Tamoxifen

Abstract : The estrogen receptor β (ER β) molecule is one of the target proteins in cancer treatment. The type of ER β molecule in the protein data bank (PDB) determines the value of most favored regions and MolDock score. The purpose of this study was to determine the effect of most favored regions of ER β molecules on MolDock score using Tamoxifen ligand. There are 37 molecules that have ER β protein, 7 molecules were selected to be analyzed for the value of most favored regions and MolDock score, based on the *r* table value, pearson correlation value $0.548 < 0.754$ (*r* table). This is also the same when viewed from the significance value of $0.203 > 0.05$. It can be concluded that there is no correlation between the value of most favored regions and MolDock score.

Keywords: Ramachandran; Estrogen receptor β ; Tamoxifen

INTRODUCTION

Estrogen receptor β (ER β) is a member of the nuclear receptor superfamily and shares common structural characteristics with the other members of this family including five distinguishable domains. They are named the A/B, C, D, E and F domains, respectively ¹. Estrogen is a key regulator of growth and differentiation in a broad range of target tissues, including the reproductive tract, mammary gland, and the central nervous and skeletal systems ^{2,3}. Estrogen is also known to be involved in many pathological processes such as breast and endometrial cancer ⁴ and osteoporosis ⁵.

Molecular Docking has become an essential aspect of in-silico drug development in recent years. This technique involves predicting the interaction between a small molecule and a protein at the atomic level ⁶. This enables researchers to study the behavior of small molecules, such as nutraceuticals, within the binding site of a target protein and understand the fundamental biochemical process underlying this interaction ⁷.

Ramachandran plot is a graphical representation of the allowed conformations of a peptide bond. The peptide bond is the chemical linkage between amino acids in a polypeptide chain. The presence of amino acid residues in the most favored regions indicates the quality and stability of a model ⁸. Meanwhile, MolDock score is a docking score that represents the energy of the interaction between a ligand and a receptor. It is calculated using a docking scoring function that is an extension of the piecewise linear potential (PLP) ⁹.

The large number of ER β molecules in PDB requires researchers to select these molecules based on the desired characteristics of ER β molecules. For example, selecting ER β molecules based on the most favored regions value. Determining the characteristics of ER β molecules like that, may affect the docking results or in this study is MolDock score. Therefore, this study aims to analyze the effect of the most favored regions value on the MolDock score especially on the target ERB molecule.

RESEARCH METHODS

Estrogen receptor β (ER β) and Tamoxifen

Estrogen receptor β (ER β) molecules were obtained from <https://www.rcsb.org/> and selected molecules that have ER β structures. The PDB ID of ER β used is 3OLS, then enter the Go to UniProtKB page to see molecules that have similarities with ER β and the value of most favored regions. Meanwhile, Tamoxifen was obtained from <https://pubchem.ncbi.nlm.nih.gov/> with PubChem CID code 2733526 and in the form of a 3D structure.

Docking of Estrogen receptor β (ER β) Molecule with Tamoxifen

Estrogen receptor β (ER β) molecules were grouped and the top two, middle three, and bottom two were selected based on the MolDock Score value, then docked with tamoxifen ligand and viewed the MolDock Score. The docking stage used Molegro Virtual Docker 5.5 software.

RESULT AND DISCUSSION

Most favorable region values of estrogen receptor β (ER β) molecules

The review in 2012 showed that most but not all of the studies indicated an association between higher levels of ER β -like protein and better clinical outcome, often in patients who were treated with tamoxifen (TAM) ¹⁰. Notably, more than one study found that the expression of ER β protein had no significant correlation with clinical variables, including tumor size, age, or axillary nodal status ^{11–13}. In addition, playing a role in anticancer, ERB plays a role in Activation of these nuclear receptors provides sexual differentiation, reproductive function, bone growth, and memory storage, among others ¹⁴.

The role of ERB in the human body requires that research on molecular docking involving ERB must be more expert. In this study, 37 types of ERB molecules were obtained which have different most favored regions values (see table 1). The most favored regions in a Ramachandran plot are usually shown in red. A Ramachandran plot is a two-dimensional graph that shows the distribution of torsion angles in a protein's backbone. The plot is considered one of the best ways to evaluate the quality of an experimental structure model

¹⁵. A Ramachandran plot analysis with at least 90% of residues in the most favored regions (A, B, and L) is considered to be a well-structured protein (see figure 1). A structure with this level of accuracy is comparable to a 2Å-resolution crystal structure ¹⁶. Table 1 shows that high resolution values do not align with most favored regions values, so it is possible that the two variables are not related.

Table 1. Resolution and most favored regions values of ER β molecules

NO	PDB ID	Resolution (Å)	Most favoured regions	NO	PDB ID	Resolution (Å)	Most favoured regions
1*	1NDE	3.00 Å	82.8	20*	7XWR	2.16 Å	94.5
2*	2YLY	3.20 Å	91.5	21	1U9E	2.40 Å	94.6
3	2FSZ	2.20 Å	91.9	22	1X76	2.20 Å	94.6
4	1ZAF	2.20 Å	92.0	23	2JJ3	2.28 Å	94.6
5	1U3Q	2.40 Å	92.2	24	2QTU	2.53 Å	94.7
6	1L2J	2.95 Å	92.5	25	2I0G	2.50 Å	95.0
7	1YY4	2.70 Å	92.9	26	2GIU	2.20 Å	95.0
8	1X78	2.30 Å	93.0	27	3OLL	1.50 Å	95.0
9	1YYE	2.03 Å	93.2	28	7XWP	1.92 Å	95.2
10	1X7B	2.30 Å	93.5	29	7XWQ	1.89 Å	95.2
11	1U3S	2.50 Å	93.6	30	3OMQ	1.97 Å	95.3
12	2YJD	1.93 Å	93.6	31	2Z4B	2.34 Å	95.5
13	1X7J	2.30 Å	93.7	32	5TOA	2.50 Å	95.7
14	3OMP	2.05 Å	93.7	33	4J24	2.10 Å	95.9
15	2NV7	2.10 Å	93.9	34	4ZI1	2.10 Å	96.3
16	3OMO	2.21 Å	94.1	35	4J26	2.30 Å	96.5
17	3OLS	2.20 Å	94.1	36*	1QKM	1.80 Å	96.6
18*	7XVZ	2.08 Å	94.3	37*	7XVY	1.54 Å	96.9
19*	1U3R	2.21 Å	94.4				

Analysis of most favored regions and MolDock scores of estrogen receptor β

In the analysis of most favored regions and MolDock score of estrogen receptor β , the top two, middle three, and bottom 2 were selected based on the most favored regions score. The selected estrogen receptor β molecules are 1NDE, 2YLY, 7XVZ, 1U3R, 7XWR, 1QKM, AND 7XVY. In Table 2, there is no direct relationship between most favored regions and MolDock score, so a low MolDock score does not guarantee high most favored regions.

Based on the r table value, the pearson correlation value is $0.548 < 0.754$ (r table). So, it can be concluded that there is no relationship between the value of most favored regions and MolDock score. This is also the same when viewed from the significance value of $0.203 > 0.05$, it can be concluded that there is no correlation between the value of most favored regions and MolDock score.

Tabel 2. Most favoured regions dan MolDock score dari molekul ER β

No	PDB ID	Most favoured regions	MolDock score
1	1NDE	82.8	-138.808
2	2YLY	91.5	-132.771
18	7XVZ	94.3	-106.245
19	1U3R	94.4	-138.143
20	7XWR	94.5	-110.462
36	1QKM	96.6	-98.947
37	7XVY	96.9	-128.395

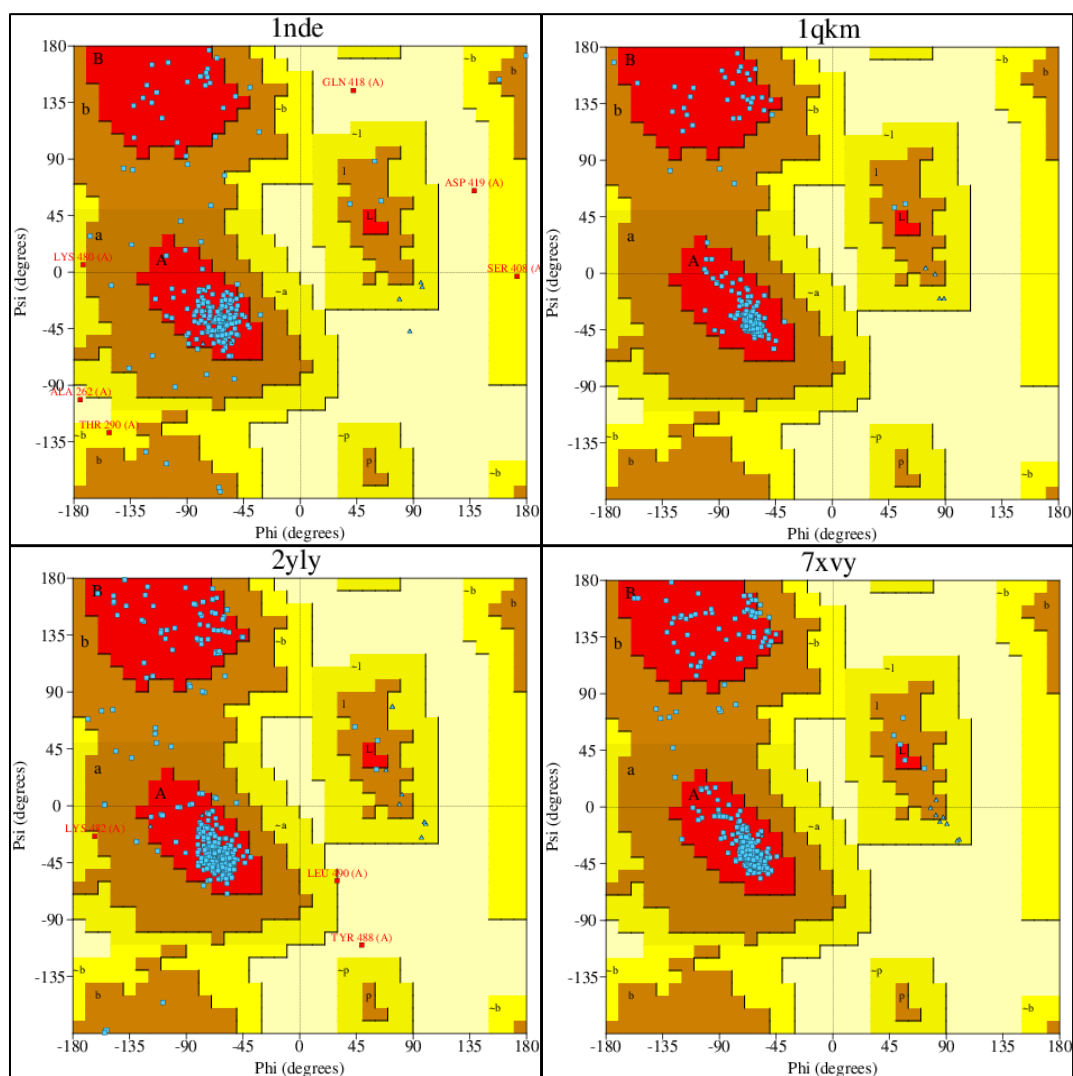


Figure 1. Ramachandran 2D plot of ER β molecules 1DNE, 2YLY, 1QKM, and 7XVY

CONCLUSION

Based on the r table value, pearson correlation value $0.548 < 0.754$ (r table). This is also the same when viewed from the significance value of $0.203 > 0.05$. It can be concluded that there is no correlation between the value of most favored regions and MolDock score.

REFERENCE

1. Gronemeyer, H. & Laudet, V. Transcription factors 3: nuclear receptors. *Protein Profile* **2**, 1173–1308 (1995).
2. Couse, J. F. & Korach, K. S. Estrogen receptor null mice: what have we learned and where will they lead us? *Endocr Rev* **20**, 358–417 (1999).

3. Pettersson, K. & Gustafsson, J. A. Role of estrogen receptor beta in estrogen action. *Annu Rev Physiol* **63**, 165–192 (2001).
4. Henderson, B. E., Ross, R. & Bernstein, L. Estrogens as a cause of human cancer: the Richard and Hinda Rosenthal Foundation award lecture. *Cancer Res* **48**, 246–253 (1988).
5. Horowitz, M. C. Cytokines and estrogen in bone: anti-osteoporotic effects. *Science* **260**, 626–627 (1993).
6. Sahoo, R. N., Pattanaik, S., Pattnaik, G., Mallick, S. & Mohapatra, R. Review on the use of Molecular Docking as the First Line Tool in Drug Discovery and Development. *Indian Journal of Pharmaceutical Sciences* **84**, 1334–1337 (2022).
7. Meng, X.-Y., Zhang, H.-X., Mezei, M. & Cui, M. Molecular docking: a powerful approach for structure-based drug discovery. *Curr Comput Aided Drug Des* **7**, 146–157 (2011).
8. Peptide Bonds And Ramachandran Plots. <https://www.pw.live/exams/csir-net/peptide-bonds-and-ramachandran-plots/>.
9. MolDock: a new technique for high-accuracy molecular docking - PubMed. <https://pubmed.ncbi.nlm.nih.gov/16722650/>.
10. Murphy, L. C. & Leygue, E. The role of estrogen receptor- β in breast cancer. *Semin Reprod Med* **30**, 5–13 (2012).
11. Hopp, T. A. *et al.* Low levels of estrogen receptor beta protein predict resistance to tamoxifen therapy in breast cancer. *Clin Cancer Res* **10**, 7490–7499 (2004).
12. de Cremoux, P. *et al.* Quantitation of estradiol receptors alpha and beta and progesterone receptors in human breast tumors by real-time reverse transcription-polymerase chain reaction. Correlation with protein assays. *Biochem Pharmacol* **64**, 507–515 (2002).
13. Chang, J. *et al.* Expression of ER β gene in breast carcinoma and the relevance in neoadjuvant therapy. *Oncology Letters* **13**, 1641–1646 (2017).
14. Libby, A. E., Jones, B., Lopez-Santiago, I., Rowland, E. & Levi, M. Nuclear receptors in the kidney during health and disease. *Molecular Aspects of Medicine* **78**, 100935 (2021).
15. Sobolev, O. V. *et al.* A global Ramachandran score identifies protein structures with unlikely stereochemistry. *Structure* **28**, 1249-1258.e2 (2020).
16. Protein structure prediction - ScienceDirect. <https://www.sciencedirect.com/science/article/abs/pii/B9780323897754000237>.