In Silico Analysis of Boron Derivate Compounds as Potential ER-α Inhibitor

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Abstract: Background :BornUSU I or Boronhafagama I (1,5-bis(4-hydroxyphenyl)-3-oxa-1,5-diaza-2,4-diboropentane-2,4-diol) and BornUSU II or Boronhafagama II (1-(4-hydroxynaphthalen-1-yl)-5-(4-hydroxyphenyl)-3-oxa-1,5-diaza-2,4diboropentane-2,4 diol) are boron derivate compounds which are boron neutron captured therapy (BNCT) candidates. Estrogen receptor alpha (ER-α) appear a crucial assignment in the growth and development of bone, breast and uterine pathology especially in human cancers, including breast cancer.Tamoxifen has been used as a cure for women who have been identified breast cancer for around four decades. Tamoxifen has high risks, such as the risk endometrial malignancy and hyperplasia varies from 1.5 to 6.9 fold after cumulative and long duration usage. Methods: In silico docking using PLANTS programme and visualized by Pymol programme. The model of three dimension enzyme structures used in this research was ER-α, binding pocket with the Protein Data Bank (PDB) code 3ERT. Results: Two and three dimension of compounds and 4-hydroxytamoxifen as the standard were generated using Marvin Sketch program. Both compoundsand standards inhibitedER-α with docking score -92.1697; -

1 INTRODUCTION

Breast cancer is the most incidence cancer and the second famous cause of cancer death in females (Jemal, et al., 2010). Then, breast cancer ranks as the fifth cause of death from cancer on the whole and the most frequent cause of cancer death in women in less developed countries, and the second cause of cancer death in developed countries after lung cancer. A recent study published which breast cancer is leading in the estimate new cancer cases, and the second most general death cause among women suffering from cancer in the America (Siegel, et al., 2010).

Estrogen plays a critical role in the growth and development of bone, breast and uterine pathology. There are two subtypes of estrogen receptor, ER-α (Estrogen Receptor alpha) and ER-β (Estrogen Receptor beta). ER-α plays a role in cell proliferation and has been found in the endometrial, breast cancer and ovarian stromalcell, as well as in the hypothalamus (Levin, 2005). Tamoxifen is also prescribe for breast cancer patients as hormonal inhibitor. The tamoxifen-bound ER complex inhibits the genes from being switched on by Estrogen, leading to the prevention of the Estrogenic leverage which accountable for cancer cell proliferation (Chang, 2012). Tamoxifen has high risks in women who have been it in their therapy (Subarnas, et al., 2015) after cumulative and long duration wear (Cohen, et al., 2003). With all of these risks many patients regardless this therapy. Thus, alternative treatments are needed.

Boron Neutron Capture Therapy (BNCT) is an progress form of radiotherapy technique which is potentially supreme to all conventional techniques for cancer treatment, as it is targeted at killing individual cancerous cells with minimal harm to surrounding healthy cells (Payudan. Et al., 2016). Boronic compounds has been before used in imaging and medicinal chemistry offering unique advantages associated with its low toxicity and stability (Trippier, and McGuigan, 2010). BornUSU 1 (1,5-bis(4-hydroxyphenyl)-3-oxa-1,5-diaza-2,4-diboropentane-2,4-diol) or Boronhafagama I and BornUSU 2 or Boronhafagama II (1-(4-hydroxynaphthalen-1-yl)-5-(4-hydroxyphenyl)-3-oxa-1,5-diaza-2,4diboropentane-2,4-diol). The chemical structures

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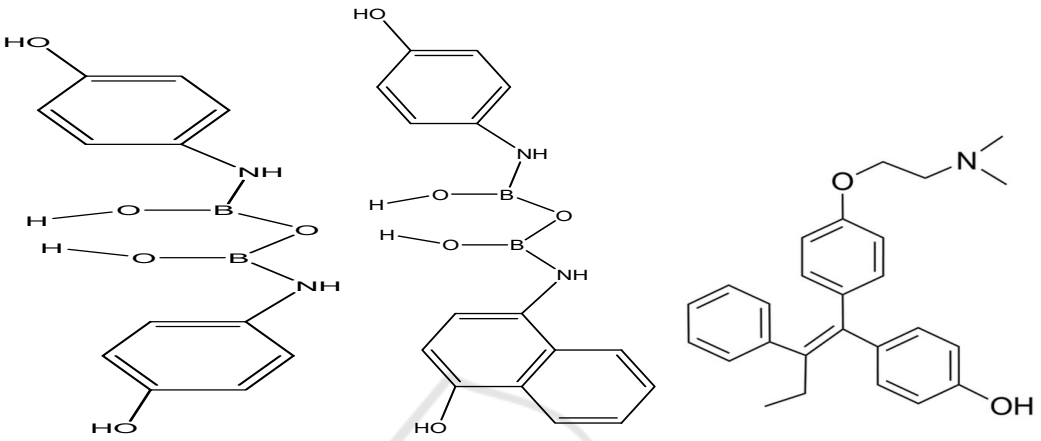
of BornUSU I, BornUSU II, tamoxifen and 4-hydroxy tamoxifen are showed in Figure 1.

Computational analysis are being expanded to evaluation in predict the compounds activity. In silico approaches contribute significantly to beginning pharmaceutical research and notable in object discovery. (Bharath, et al., 2011). The purpose of our study was to identify how ER-α inhibitors are working for cancer using in silico molecular docking method. The purposes of this research was to assess the activity of BornUSU I, BornUSU II, tamoxifen and 4-hydroxy tamoxifen in inhibiton ER-α with in silico method.



a b c

Figure 1. Structure of (a) BornUSU I, (b) BornUSU II, and (c) 4-hydroxy tamoxifen.

2 METHODS

Aspire E1-470 series operated by Windows 7 Home Premium, Intel® Core™ i3 -3217U (1,8 GHz, 3MB L3 cache), 32-bit, hard disc drive 500 GB and RAM memory 2 GB DDR3 L were used to run the molecular docking process.

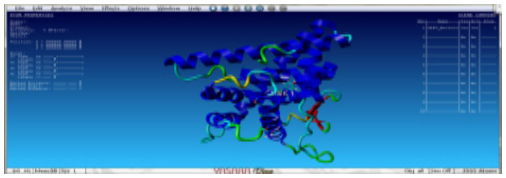
In silico docking using PLANTS program and visualized by pymol programmee. Co Pen Drive Linux KDE program was used to connecting Windows operation system to Linux operation system. The model of three dimension of enzyme structure used in this research was ER-α binding pocket with the Protein Data Bank (PDB) code 3ERT. It was obtained through from http://www.rscb.org/pdb. Two and three dimension conformation models of BornUSU 1, BornUSU 2 and 4-hydroxy tamoxifen as the standard inhibitor were generated by Marvin Sketch program.

3 RESULT

The Root Mean Square Deviation (RMSD) values resulted from these ligand docking was 1.6276Å for 3ERT. The RMSD was obtained less than 2.0000 Å indicating that the docking methods were valid (Terstappen., and Reggiani, 2001). In silico docking between BornUSU 1, BornUSU 2, tamoxifen and 4-hydroxy tamoxifen into 3ERT binding pocket result inthe docking scorein Table 1 isshowed the results of docking score into 3ERTbinding pocket. Figure 2 and 3 are showed the results of visualization of BornUSU 1, BornUSU 2 and 4-hydroxy tamoxifen to ER-α using pymol.

Table 1. Docking score between ligand and protein target

No	Ligand Name	Docking Score
		ER-α
1	4-hydroxy tamoxifen	-99.0879
2	BornUSU I	-92.1697
3	BornUSU II	-100.1940



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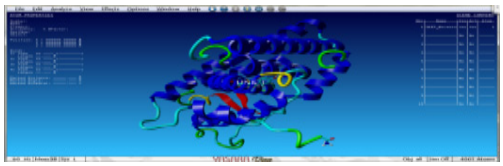

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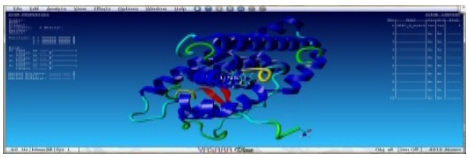


c

Figure 2. Visualization of interaction between.

(a) BornUSU 1 with ER-α
(b) BornUSU 2 with ER-α
(c) 4-hydroxy tamoxifen with ER-α

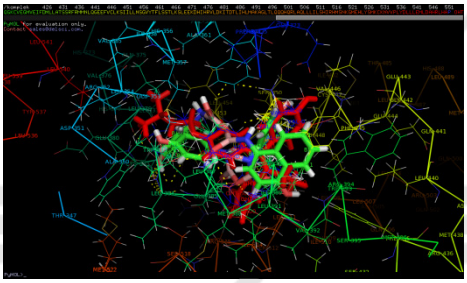
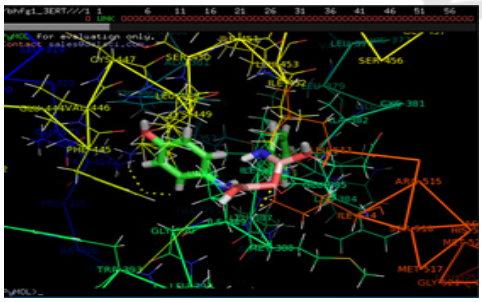


Figure 3. Overlay interaction of 4-hydroxy tamoxifen, BornUSU 1 and 2 with Receptor of Estrogen Alpha with pymol.



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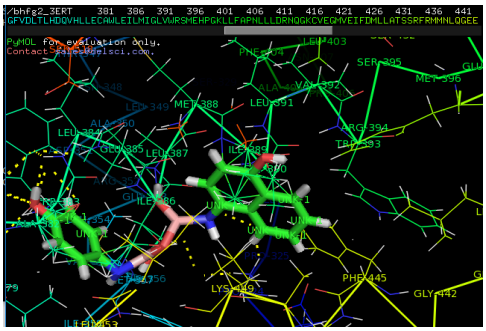

b

Figure 4. Interaction of BornUSU I and BornUSU 2with Receptor of Estrogen Alpha with pymol.

Visualization interaction of 4-hydroxy tamoxifen with Estrogen alpha receptor (ER-α) shown at Picture 4. Some of amino acids from ER-α which is role in the mechanism of action of 4-hydroxy tamoxifen are: Met-242, Leu-346,Thr-347, Leu-349, Ala-350, Asp-351, Glu-353, Trp-383, Leu-284, Leu-387, Met-388, Leu-391, Arg-394, Phe-404, Glu-420, Met-421, and Leu-428. Oxygen from hydroxyl group to form hydrogen bond with water, Arginin-394(Arg-394) and Glutamat-353(Glu-353), while Leusin- 387(Leu-387) participate in stabilize hydrogen bond between oxygen with both of amino acids which mentioned above.

Several amino acids from ER-α which is role in BornUSU I or in Boronhafagama I are Ile-386, Met-357, Ala-382, Trp-383, Leu-384, Glu-385, Leu-387, Met-388, Ile-389, Gly-390, Phe-445, Val-446, Lys-449, Ile-452 and Ile-514.Several amino acids from ER-α which is role in BornUSU II or Boronhafagama II are Met-357, Trp-360, Ala-361, Leu-378, Leu-379, Glu-380, Cys-381, Ala-382, Trp-383, Leu-384, Glu-385, Ile-386, Leu-387, Gly-390, Phe-435, Leu-440, Phe-445, Val-446, Leu-448, Lys-449, Ile-452, Leu-453, Ser-456 and Ile-514.Although docking score of BornUSU 2 is higher than 4-hydroxy tamoxifen but this score is not significance. BornUSU 2 interaction with 24 amino acids from ER-α while 4-hydroxy tamoxifen interaction with 17 amino acids from ER-α.

4 DISCUSSION

The docking score represents the binding affininty of the ligand to the target protein. The docking of ER-α target with compounds using docking procedure was mentioned that all the computationally predicted lowest energy complexes of ER-α is stabilized by

intermolecular hydrogen bonds and stacking interactions (Levin, 2005).

Docking score of BornUSU II were lower than tamoxifen and 4-hydroxy tamoxifen but BornUSU I is lower than 4-hydroxy tamoxifen and higher than tamoxifen. In silico drug design can play a significant role in all of stages of drug development from preclicial assesment to the end of clinical development (Levin, 2005). The results were obtained at in silico screening have shown that it represents the best step (way) to get an accurate result in a short time and saving manner (Terstappen and Reggiabi, 2001).

5 CONCLUSIONS

BornUSU I and II are boron derivate compounds. They were showed to have the activity in inhibition of cancer growth through ER-α pathways and they are potential to develop as anticancer.

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