The in Silico Molecular Interaction of Organoboron Compounds as Curative Measure toward Cervical Cancer

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Abstract

The hazard of cervical cancer is a real threat in the developing countries. Rational drug design technology has successfully created useful drugs, such as SAHA, to combat the cervical cancer. However, it has certain side effects. In order to overcome the effects, novel organoboron based drug candidates have been developed. In this paper, the LigX tool in MOE 2008.10 has been successfully elucidated the molecular interactions between HDACs and its respective ligands.

Keywords: Cervical Cancer, HDAC, LigX, MOE, SAHA

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Introduction

As one of the most deadly disease for women in developing countries, cervical cancer is a serious problem for the public health. It is already proven that cervical cancer was caused by Human papilloma virus (HPV) infection (zur Hausen, 2009). Therefore, biomedical researcher has tried to develop drugs to inhibit the HPV (Park et al., 2000). One of the well-known drugs for cervical cancer is SAHA compound, which is useful for inhibiting the Histone Deacetylase (HDAC) class II Homo sapiens enzyme (Finnin et al., 1999). In addition, it is already known that organoboron compound is useful for combating the progression of cancer (Petasis, 2007). However, our group has successfully generated in silico modified SAHA compounds that could be useful as lead compounds (Tambunan, Bramantya, & Parikesit, 2011). SAHA modification is necessary to relieve its side effects, for instance on bone loss (McGee-Lawrence et al., 2011). SAHA-modified compounds have been successfully generated by core-hopping method that developed from fragment based method (Zang et al., 2014). Hence, that research has limited approach on its molecular interaction feasibility. In this end, the molecular interaction between lead compound and its respective receptor or enzyme should be observed to determine whether the compounds bind deeply to the receptor, and if there is any strong hydrophobic contact to the catalytic site (Qamar et al., 2014). Thus, the LigX tool of MOE could be utilized to observe molecular interaction with the minimization step to adapt both the ligand and the protein (Sarker et al., 2010).

The purpose of this computational research is to observe the molecular interactions of novel drugs for Cervical Cancer, by modifying the SAHA compound with organoboron-based chemical groups (Tambunan, Bakri, Prasetyia, Parikesit, & Kerami, 2013). The molecular interaction of the compounds will be elucidated by using LigX tool in MOE 2008.10 (Tambunan, Parikesit, Prasetyia, & Kerami, 2013).

Methodology

The multiple sequence alignment and homology modelling methods were utilized for constructing the HDAC proteins model (Aniba, Poch, & Thompson, 2010; Hillisch, Pineda, & Hilgenfeld, 2004; Thompson, Gibson, & Higgins, 2002). The 3D structure of the HDAC was downloaded from http://www.rcsb.org/pdb/home/home.do. Whereas, the organoboron ligands were drawn from http://www.organoborons.com/ website, and saved in mol (MDL information system) format (Weininger, 1988). The SAHA compound was modified with the organoboron based chemical groups by using ACDLabs ChemSketch 12 (Spessard, 1998). The interaction between the ligands and the chemical groups that bind to amino acid residues in the active site and cofactor of the enzyme can be elucidated with LigX tool in MOE 2008.10 (Vilar, Cozza, & Moro, 2008).

Results and Discussion

The results of our study showed that the interactions between HDAC5 and the closo-organoboron ligand were indeed the most feasible of all. It is already proven by our group that the pharmacological...
properties of closo-organoboron compounds are indeed feasible as lead compound (Bakri, Parikesit, Satriyanto, Kerami, & Tambunan, 2014). The Figure 1 exposes the designated interactions.

Figure 1: Illustrations of the interactions between HDAC 5 and a) Nova2(95752-88-8) b) Nova2(16876-27-0) c) Nova2(513246-99-6) d) Nova2(279262-23-6)

The role of Zinc ion as bridging agent in enzyme-inhibitor complex already confirmed in the laboratory experiment of BABIM and Serine protease (Thorp, 1998). This bridging phenomenon could be observed as well in our research. In one hand, figure 1 has shown that the interaction between Zn\(^{2+}\) and ligands were favouring the inhibition of HDACS. In the other hand, the amino acid residues in HDACS also showed favourable interactions toward the ligands. Zinc ion is important for supporting the catalytic sites due to its role in group transfer reaction, and its coordination number of up to 6 (Lipscomb & Sträter, 1996). The interaction of the ligand Nova2 (95752-88-8) with HDACS’s zinc binding part was mediated with covalent coordination bonding with Zn\(^{2+}\) as a cofactor of the enzyme. Within HDACS, the amino acid residues that interact with the Zn\(^{2+}\) are Histidine (His832). This phenomenon confirmed the efficacy of our ligands as the histidine residue is one of the important constituent of HDAC catalytic site (Dceluve, Khan, & Davie, 2012). Hence, the amine functional group at the HDACS’s hydrophobic cap has active role during the interactions. The LigX tool also showed that the closo-carborane group was favouring good interactions in the HDACS-ligand complex. This finding is confirming the existing trend that carboranes have useful versatile cores for drug development (Armstrong & Valliant, 2007). The strong molecular interactions between closo-carborane functional group and zinc co-factor were eventually favouring the solid inhibition of HDAC enzyme. The stabilization of lead compound by closo-carborane has already confirmed both in the in silico study and wet laboratory (Barry & Sadler, 2013; Calvaresi & Zerbetto, 2011). Thus, this structural-based approach of inhibition is indeed a feasible ground for drug candidate development (Anderson, 2003).
Closo-carborane based compounds have been proved to have good bioavailability both during in vitro and in vivo studies (Morrison et al., 2010; Valliant et al., 2002). Moreover, the HDAC bioassay kit has already provided for in-vitro testing of organo-metal(loid) based compounds (Rosse, 2013; Sirignano et al., 2013; Spencer et al., 2011). However, before undergoes in vitro and in vivo testing, synthesize the closo-carborane based modified SAHA will remain a cardinal issue that should be addressed (Bakri et al., 2014). Before a solid methodology for synthesizing our compounds were yet to be found, gathering information from bioinformatics studies will always be a feasible choice for giving contribution in this field (Davidov, Holland, Marple, & Naylor, 2003; Gershell & Atkins, 2003).

Conclusions

LigX tool has been indispensable for elucidating the interactions between HDACs and closo-carborane based ligands. It could be inferred that closo-carborane-based modification on SAHA could be a feasible option as drug candidate.

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