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Computational Model of Doxorubicin Conjugate with Docosahexaenoic Acid and Integrin $\alpha_v\beta_3$ Ligand for Anticancer

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ABSTRACT

Doxorubicin (DOX) is one of the most effective drugs for cancer treatment. However, the undesired side effects of DOX towards cardiotoxicity and drug resistance have raised concern about developing the safer medication. Therefore, the potency of DOX can be optimized by conjugating it with the other molecules. Integrin $\alpha_v\beta_3$ receptor which overexpressed in cancer cells can be used as a target for specific therapeutics. Fatty acids such as docosahexaenoic acid (DHA) is also known to improve the absorption of DOX in the cancer cell. Therefore, for the first time, the possibility of a conjugated drug composed of three components, i.e. DOX, integrin ligand, and DHA, is explored using the computational methods. This study aimed to propose a computational model of DOX conjugate with $\alpha_v\beta_3$ integrin ligand and DHA using structure-based design approach and to predict the pharmacokinetic properties of each component using *in silico* method. A peptidomimetic ligand was used as a template to develop new integrin ligand. Molecular docking was used to predict the best binding mode and energy of the ligand to enhance the selectivity of DOX conjugate. Molecular dynamics showed the stable binding of integrin ligand. *In silico* pharmacokinetics prediction showed that DHA might improve the overall permeability of DOX in the cancer cell.

INTRODUCTION

Cancer is a leading cause of mortality worldwide. A previous study revealed the mammography result from the 1000 examined female patients of which 20 of them were recommended for a needle biopsy while 5 of them were positively diagnosed with breast cancer (Mainiero *et al*., 2016). Doxorubicin (DOX) is an anticancer drug, which can prevent cancer cell replication by inhibiting the Topoisomerase-II enzyme through intercalation with DNA. DOX is considered to be one of the most effective anticancer medications and has been used for more than four decades. However, the major concerns of the DOX application as an anticancer agent are the drug's resistance and the toxic effect to the host. The clinical report estimated that DOX could induce cardiotoxicity that could lead to heart failure. The molecular mechanism of DOX cardiotoxicity was suggested as a result of the inhibition of Topoisomerase-IIb enzyme activity in cardiomyocytes (Zhang *et al*., 2012). Topoisomerase-IIb is one of the isozymes from the Topoisomerase with identical structure and catalytic action. Therefore, it is hypothesized that DOX has dual specificity: DOX is not only inhibited the replication of cancer cells, but it also affected the heart cells that could induce the heart failure. The health experts have limited the use of DOX in patients with high heart risk and emphasized the importance of the strategy of DOX given to patients with breast cancer (Barrett-Lee *et al*., 2009).

Although cases of drug resistance and cardiotoxicity of DOX have long been reported, the development of an alternative drug is not without challenge. Nowadays, the estimated cost required to develop a new drug until it is marketable is approximately USD 2.6 billion. The drug development from the beginning requires a minimum of 10 years (Peters, 2014).

The improvement in the effectiveness of anticancer properties of DOX through conjugation or derivatization could be an alternative option to suppress time and cost required to develop a new anti-cancer agent. There are two crucial factors

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in improving the DOX anti-cancer properties, i.e. the specificity against the cancer cells, and the permeability to the resistant cells.

Stafford and Thorpe reported that excessive molecular activation in cancer cells affects the localization of Phosphatidylamine (PE) on the surface of the cell. Thus, PE can be used as an advantageous molecular marker in the development of imaging or targeted therapeutic agents (Stafford and Thorpe, 2011). Moreover, a study revealed that the PE is specifically exposed on the surface of breast cancer cells (Zhu and Bakovic, 2012). Li *et al.* demonstrated that an anticancer agent, gemcitabine, conjugated with DHA fatty acid increased its specificity due to the DHA-PE interaction, which acts as the mediator in the uptake of gemcitabine into the cancer cells (Li *et al*., 2014). It is also observed that the conjugated DOX with linoleic acid had a better internalization cell compared to a single DOX compound (Huan *et al*., 2012).

In addition to PE, another specific molecule is excessively produced by the cancer cells, particularly the breast cancer cells, namely the integrin $\alpha_v\beta_3$. In general, epithelial cells express the integrin in small quantities or even almost undetectable. However, unlike in the normal cells, regulation of integrin on tumor cells increased significantly. Hence the integrin is expressed excessively specific to tumor or cancer cells. In addition, due to its locality on the cell surface, integrin could be applied as the molecular target of imaging agent or specific therapy (Desgrosellier and Cheresh, 2010). Therefore, a specific molecule with integrin $\alpha_v\beta_3$ interaction is required to carry DOX compound into the targeted breast cancer cells. A structure-based design approach can be used to design a particular molecule with a specific affinity to the integrin $\alpha_v\beta_3$ receptor One of the requirements of this method is the availability of a three-dimensional (3D) structure from the experimental study (X-ray diffraction and NMR). It is noted that the structure of the extracellular part of $\alpha_v\beta_3$ with a peptide-like ligand is available in the Protein Data Bank (Xiong *et al*., 2002). Therefore, the rational design of a conjugate compound composed of DOX, integrin ligand, and fatty acid, is interesting to be studied.

The aims of this study were to investigate the computational design of DOX conjugate with $\alpha_v\beta_3$ integrin ligand and fatty acid (DHA) using structure-based design approach and to predict the pharmacokinetic properties of each component using *in silico* method.

MATERIALS AND METHODS

Structural investigation of DOX and $\alpha_v\beta_3$ integrin ligand

The crystal structure of DOX in complex with DNA (PDB ID 1P20) was retrieved from Protein Data Bank (https://www.rcsb.org/pdb/home/home.do). The co-crystallized peptidomimetic ligand arginine-glycine-aspartate (RGD) in a crystal structure of $\alpha_v\beta_3$ integrin was also obtained with PDB ID 1L5G (Xiong *et al*., 2002). The 3D structure of DOX, RGD ligand, the ligand binding site integrin $\alpha_v\beta_3$ receptor, and all the ligand-receptor interactions were investigated using BIOVIA Discovery Studio Visualizer (BIOVIA, 2015).

Molecular docking of integrin ligand

The interaction between the integrin ligand and its receptor was studied using the molecular docking method by Autodock 4.2 program (Morris *et al*., 2009). The searching method used was the Lamarckian Genetic Algorithm (LGA) with following parameters: population size GA of 300; 25 millions of energy evaluation; GA generations of 27,000; mutation velocity of 0.02; crossover velocity of 0.8; maximum iteration of 300; local searching frequency of 0.06 and 100 docking runs. The integrin ligand docking was performed on the same binding site to the co-crystal ligand (RGD), which is at the Cartesian coordinates x = 18.854; y = 44.894; z = 43.944. The size of the binding site used as the searching area was 61 × 61 × 61 points with the distance between points was 0.375 Å. Thus the obtained box size was 22.875 $Å^3$. The results of docking simulation were then visualized using Discovery Studio Visualizer.

Molecular dynamics (MD) simulation

The tleap and antechamber programs from AmberTools 17 (Case *et al*., 2017) were used to prepare the complex model and to parameterize the integrin ligand, respectively. The system of the ligand-receptor complex was minimized by 500 steps of the conjugate gradient using minab module in Amberlite utilities. Molecular dynamics simulation was performed using mdnab module. The cutoff for non-bonded interactions was 12 Å. The time step used was 2 fs by rattle algorithm. The temperature was controlled by Langevin dynamics with a gamma_ln value of 2 during the production stage at a temperature of 300K. In the equilibrium phase, the system was gradually heated from 50K to 300K. Calculation of interaction energy was conducted using MMPBSA.py program.

In silico pharmacokinetics prediction

The octanol-water partition coefficient (LogP) was calculated using Atom-based method (Ghose and Crippen, 1986). The human intestinal absorption after oral administration was predicted using a model developed by Egan and colleagues, which involves 2D Polar Surface Area (PSA_2D) and LogP (Egan *et al*., 2000; Egan and Lauri, 2002). The inhibition of cytochrome P450 2D6 (CYP2D6) was predicted using a computational model developed from 151 of the various compound with a known CYP2D6 inhibition constant (Susnow and Dixon, 2003). The hepatoxicity was predicted using a model developed from 436 compounds which are toxic to the liver (Cheng and Dixon, 2003). All these methods were performed by ADMET descriptors module in BIOVIA Discovery Studio 4.5 (BIOVIA, 2015).

RESULTS AND DISCUSSION

Determining the conjugation point of DOX

The known mechanism of therapeutic effect of DOX is the intercalation with DNA. The structural analysis of the co-crystal DOX with DNA (PDB ID 1P20) shows that the amine group at 3' position formed hydrogen bonds with DNA (Figure 1). Therefore, the chemical modification at the 3' position is expected to reduce the DOX affinity to DNA. Hence, the 3'-end is not preferred to be used as a conjugation point. On the other hand, the 14-C does not form a noncovalent bond with the DNA. Thus modification to this end is theoretically will not affect the DOX affinity to the DNA. For this reason, the conjugation of DOX in this study is proposed to be joined at the 14-C atom instead of 3' amine.

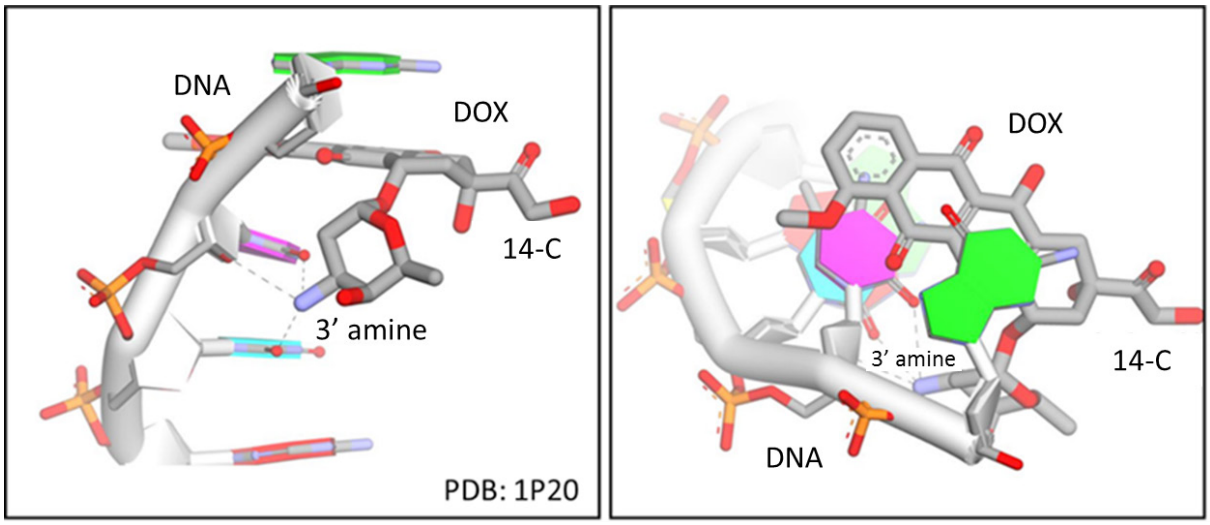

Fig. 1: Structural analysis of DOX in DNA (PDB ID 1P20) from the lateral (left) and top (right) views. The 3' amine group has a major role as the hydrogen bond donor with the furan oxygen and two-carbonyl oxygen in the DNA receptor.

The design of $\alpha_v\beta_3$ integrin ligand

In this study, the crystal structure of $\alpha_v\beta_3$ integrin receptor in complex with peptidomimetic RGD ligand was used as the template to understand the overall ligand-receptor interactions of $\alpha_v\beta_3$ integrin. A new ligand is required since a peptidomimetic (peptide-based ligand) generally has low pharmacokinetics, which is easily recognized by the peptide cleaving enzyme in vivo (Smith *et al*., 2011). Nevertheless, RGD is a good starting point for designing a new ligand due to its similarity with the substrate, thus having high compatibility with the integrin receptor (Xiong *et al*., 2002). Based on the structure of RGD ligand, three pharmacophore features were identified, i.e. the positively charged group (such as guanidine of arginine residue), hydrophobic (such as alkyl and phenyl groups) and negatively charged group (such as aspartic acid residue) (Figure 2).

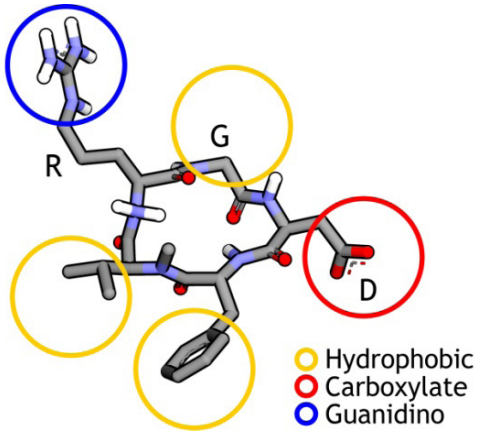

Fig. 2: Structure-based pharmacophore features of RGD ligand.

Therefore, a new integrin ligand should satisfy the three pharmacophore features of RGD ligand (Figure 3). The new ligand could have a pyrimidine ring, instead of the guanidine group, to increase the stability or rigidity of the positively charged group. For the hydrophobic feature, a phenyl group might be used to minimize the degree of freedom of the ligand, instead of the alkyl chain. Lastly, the carboxylate group should be retained to have the negatively charged feature. In physiological pH, the carboxylate group will be deprotonated to form a negative ion.

Since the integrin ligand will be used to carry DOX covalently, then a reactive conjugation point is required without disrupting the main pharmacophore features of integrin ligand. A reactive-primary amine was added to the end of the carboxylic group, which connected by the sulfonamide group to mimic a peptide bond between the carboxylic group and the conjugation point. This peptide bond is expected to be cleaved by a protease *in vivo*, hence facilitating the internalization of the DOX-conjugated molecule to reach the therapeutic target. Finally, the possible design of new integrin ligand which is ready to be conjugated with DOX is shown in Figure 4.

Based on the conformation of RGD ligand in the binding site of integrin receptor, the distance between the positively and negatively charged features was approximately 16 Å. Therefore, ideally, the new integrin ligand should have a similar length with RGD to obtain optimal binding and to avoid sterical hindrance. Interestingly, the length between the aforementioned features in the new integrin ligand was also 16 Å (Figure 5).

Molecular docking of the designed integrin ligand

The affinity of designed integrin ligand was predicted using molecular docking method. The conformation with the lowest binding energy was selected and visualized in Figure 6. Figure 6a shows that the designed integrin ligand has an identical mode of interaction with the co-crystal ligand of RGD peptide in the crystal structure 1L5G. The three cofactors, Mn^{2+} ions, on the β_3 subunit of integrin interacted with the negatively charged carboxyl group, which present in both RGD and designed integrin ligand. Similar residues interacted with the carboxyl group of two compounds to form hydrogen bond interactions. Three amino acids act as a hydrogen bond donor, namely: S121, S123, and N215. The carboxyl group on the co-crystal RGD peptide was stabilized by the hydrogen bonds with N215, while the S121 and

S123 stabilized the designed integrin ligand. A similar interaction was also observed in the positively charged groups (guanidine and pyrimidine in the RGD peptide and the designed integrin ligand, respectively). It is shown that the guanidine group (and its derivative) in both ligands formed hydrogen bonds and salt bridges with the D218 from the integrin subunit α_v. Figure 6b shows a detail interaction between the designed integrin ligand and $\alpha_v\beta_3$ receptor. The sulfonamide group acts as a hydrogen bond donor to the carbonyl oxygen of the main chain of Y122. The amino group formed electrostatic interactions with N215 and R216. The phenyl group in this ligand formed a hydrophobic interaction with Y178. In dynamics, this group also possibly forms the pi-pi stacking interactions with Y178.

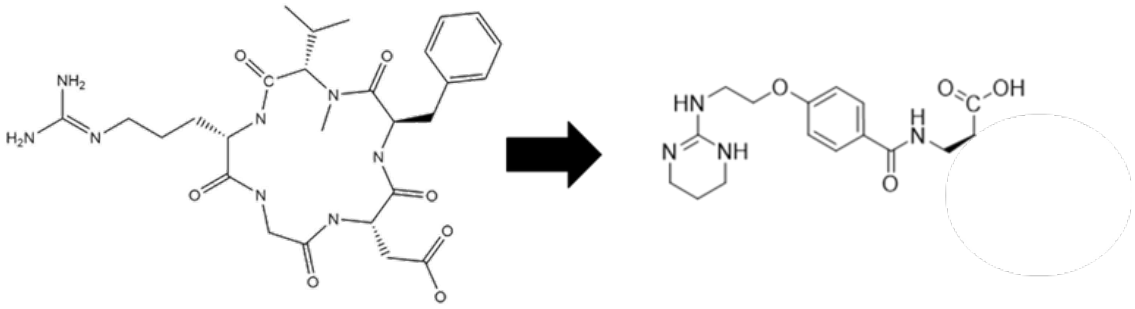

Fig. 3: One of the possible conversions from RGD to the new integrin ligand.

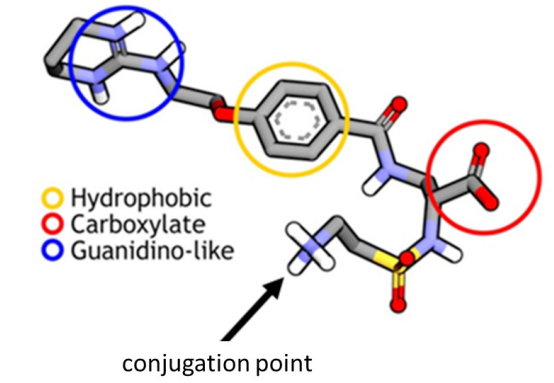

Fig. 4: One of the possible designs of new integrin ligand based on the RGD pharmacophore features. The amine group was added as the conjugation point.

The docking result indicates that the three pharmacophores in the designed integrin ligand formed a favorable interaction with the $\alpha_v\beta_3$ receptor. Whereas the reactive amino group, which was added purposely for the conjugation point with DOX, was exposed to the solvent. Hence, the conjugation with DOX is predicted will not disturb the key interactions with the receptor.

The calculated free energy binding and Ki of the designed ligand were −11.46 kcal mol^{-1} and 3.9 nM, respectively. This calculated Ki is comparable to the inhibition value of several integrin antagonists which are under the preclinical stage (Miller *et al*., 2002).

Molecular dynamics simulation of integrin ligand

A short 100 ps of MD simulation was conducted before interaction energy calculation using MM/GBSA method. The RMSD (root mean square deviation) profile of binding site residues (amino acid within 5 Å from the ligand) and integrin ligand showed that the system was stable after 60 ps (Figure 7). Therefore, the last 40 ps was selected for the calculation of binding energy. The predicted free energy of binding, i.e. −46.3 ± 3.5 kcal/mol, showed that the integrin ligand binding was stable during simulation, indicating a good inhibitory activity of integrin ligand.

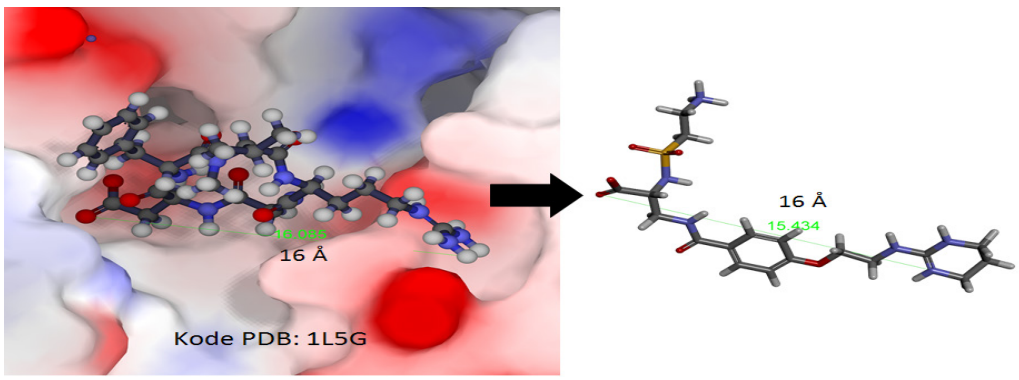

Fig. 5: The binding site of integrin $\alpha_v\beta_3$ receptor with RGD ligand (left). The surface of binding site was colored according to its electronic charge (positively charged = blue, negatively charged = red). The length between a positively charged group and a negatively charged group in RGD and new ligand (right) are similar.

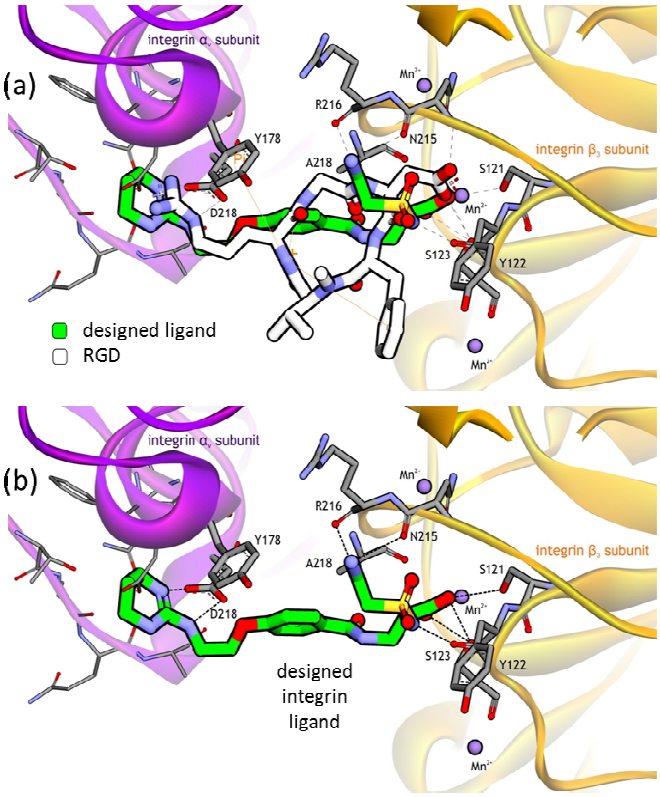

Fig. 6: (a) The molecular docking simulation showed that the designed integrin ligand has an identical mode of interaction with the co-crystal RGD peptide. (b) The designed integrin ligand was predicted to form hydrogen bonds with D128 from the integrin subunit α_v, and the residue S121, Y122, S123, N215, R216 and A218 of integrin subunit β_3.

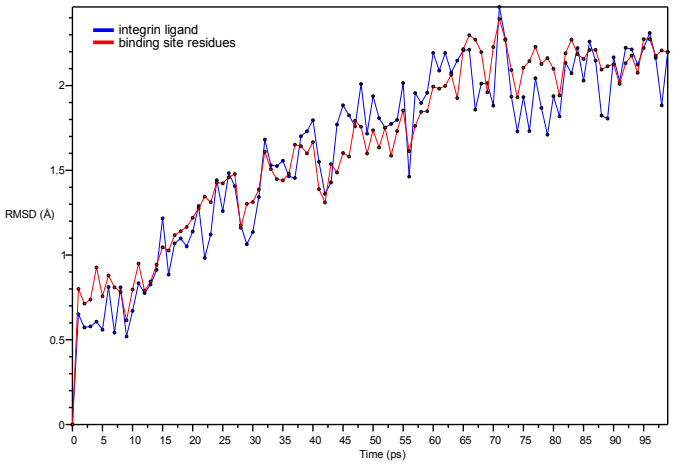

Fig. 7: The RMSD plot of integrin ligand and binding site residues throughout MD simulations.

In silico pharmacokinetics prediction of conjugate components

The pharmacokinetics parameters of DOX, a designed integrin ligand, and a selected fatty acid (DHA) were predicted using BIOVIA Discovery Studio program. The calculated parameters were the LogP value, intestinal absorption level, inhibition level of CYP2D6, and hepatotoxicity (Table 1).

The LogP value for the DOX and integrin ligand was −0.377 and −4.460, respectively, which indicates that both molecules were polar and hence poor membrane permeability. However, the LogP of DHA was higher than DOX and integrin ligand, i.e. 6.462. Therefore, the presence of DHA in the conjugated DOX compound would improve the overall permeability. Nevertheless, the absorption level of a compound is not only determined by the LogP, but also by the Polar Surface Area (PSA) which represents a surface consisting of polar atoms (Ertl *et al*., 2000). A PSA value higher than 150 is predicted to have a very low absorptivity. Although DHA has a good absorption level, altogether, the PSA value of conjugated compound would be high (~424). Despite the general use of DHA as a nutritional supplement (suitable for intra-oral delivery), the conjugated DOX compound should be delivered intravenously (through injection) to reach the cellular target.

Furthermore, the ability of a compound to inhibit the cytochrome P450 2D6 (CYP2D6) should be considered carefully, since this enzyme plays a significant role in drug metabolism. Inhibition of CYP2D6 may cause drug interactions, which leads to an inefficient drug performance (Susnow and Dixon, 2003). Neither DOX, integrin ligand or DHA were predicted to inhibit the CYP2D6.

Among the three single compounds, only DOX that was predicted with hepatotoxic properties. This result is in agreement with the former studies (El-Sayyad *et al*., 2009; Damodar *et al*., 2015), who demonstrated the hepatotoxic effect of DOX as an unfavorable side effect of anticancer. Interestingly, DHA is not predicted to have hepatoxicity. Therefore, a conjugation of DHA with DOX might reduce the hepatoxicity effect, as also demonstrated earlier (Tulubas *et al*., 2013). Tulubas and colleagues showed that the formulation of DOX with omega-3 fatty acids, including DHA, resulted in protective activity against hepatotoxicity.

Based on the structure-based investigations and also *in silico* pharmacokinetics prediction, a conjugate of DOX with integrin ligand and DHA is interesting to be further studied. The scheme of this conjugate compound is illustrated in Figure 8. A linker is required to be the center of this complex molecule, which can be cleaved by certain enzymatic activity *in vivo*, or auto-cleaved by a certain pH condition in cancer cell environment.

Table 1: The calculated pharmacokinetic parameters of DOX and the designed integrin ligand.

Compound	LogP	Polar Surface Area (Å²)	Absorption level	CYP2D6 inhibition	Hepatotoxicity
DOX	−0.377	194	low	none	yes
Integrin ligand	−4.460	192	low	none	none
DHA	6.462	38	high	none	none

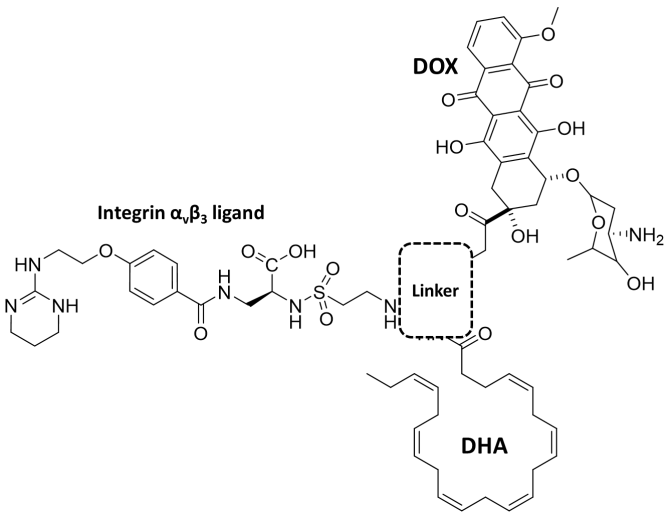

Fig. 8: The possible scheme of DOX conjugate with integrin ligand and DHA using a linker as a center of the molecule.

CONCLUSION

In this study, DOX is designed to be conjugated with integrin $\alpha_v\beta_3$ ligand and DHA to improve the specificity and permeability of a cancer cell, respectively. The structure-based approach suggests that DOX should be conjugated at the 14-C position, not the other sides, to prevent the binding disruption to DNA. Whereas for the integrin ligand, a reactive group (primary amine) is suggested to be added to the carboxyl-end to preserve the ligand interaction with integrin $\alpha_v\beta_3$ receptor. Based on the *in silico* pharmacokinetics prediction, DHA might increase the whole DOX conjugate's permeability while decreasing its hepatotoxicity effect. Therefore, it is suggested that the combination of DOX with integrin ligand and DHA should provide a better chemotherapeutic agent, especially regarding cancer cell specificity and permeability, to reduce the unfavorable side effect of the DOX therapy.

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