MOLECULAR DOCKING STUDIES, ADMET PROPERTIES OF SOME ESTER DERIVATIVES OF BETULIN WITH AZT, D4T, AND 3TC

NGHIÊN CỨU DOCKING PHÂN TỬ, ĐẶC TÍNH ADMET CỦA CÁC HỢP CHẤT LAI BETULIN VỚI AZT, D4T VÀ 3TC

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ABSTRACT

Our previous study presented the synthesis and cytotoxicity of triterpenoid-AZT hybrids that inhibited KB and Hep-G2 cancer cell lines with IC_{50} values between 1 and 21μM. As part of our ongoing research, this study aims to explore the interaction of certain hit anticancer inhibitors of betulin derivatives with topoisomerase II through docking simulations. The obtained results indicated that the modification of the betulin compounds significantly improved their toxicity towards cancer cell lines, primarily due to the presence of attached AZT, d4T, and 3TC fragments. These moieties contribute to the crucial interactions with the receptor in the binding pocket. Furthermore, we predicted the physicochemical properties and ADMET profile of the most active compounds as a part of the drug development process.

***Keywords*:** *Topoisomerase II, betulin, AZT, d4T, 3TC, docking simulations.*

TÓM TẮT

Trong nghiên cứu trước đây, chúng tôi đã trình bày quá trình tổng hợp và đánh giá độc tính tế bào của các hợp chất lai triterpenoid-AZT, cho thấy khả năng ức chế các dòng tế bào ung thư KB và Hep-G2 với giá trị IC_{50} trong khoảng từ 1 đến 21μM. Tiếp nối hướng nghiên cứu này, công trình này nghiên cứu sự tương tác giữa một số dẫn xuất betulin có tiềm năng kháng ung thư với enzyme topoisomerase II thông qua mô phỏng docking phân tử. Kết quả cho thấy, việc biến đổi cấu trúc các hợp chất betulin đã góp phần nâng cao đáng kể độc tính đối với tế bào ung thư, chủ yếu nhờ sự hiện diện của các mảnh AZT, d4T và 3TC. Các nhóm chức này đóng vai trò quan trọng trong việc hình thành tương tác then chốt với thụ thể tại vị trí gắn kết. Bên cạnh đó, các đặc trưng tính chất hấp thu, phân bố, chuyển hóa, thải trừ và độc tính (ADMET) của những hợp chất thể hiện giá trị IC_{50} thấp nhất cũng được dự đoán nhằm phục vụ cho quá trình phát triển thuốc.

Từ khóa: *Topoisomerase II, betulin, AZT, d4T, 3TC, mô phỏng phân tử.*

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1. INTRODUCTION

In drug discovery, pharmacophore hybridization-the covalent linking of two bioactive moieties into a single hybrid entity-has emerged as a privileged strategy for the development of new molecules with pronounced biological activities. Triterpenoids are a group of terpenoids with a basic skeleton consisting of 30 carbon atoms. They exist naturally in plants and represent the

largest group of phytochemicals. Triterpenoids are used for a range of medicinal purposes, such as in the treatment of anticancer, anti-inflammatory, antibacterial, and antiviral [1-3]. First described in 1964, azidothymidine (AZT) served as an antiretroviral medication, preventing and treating HIV/AIDS [4]. Researchers suggested that combining triterpenoids [5-7] and azidothymidine (AZT) [8-12] in hybrid molecules would create some promising new cytotoxic agents. Our earlier study showed that the triterpenoid-AZT hybrid can kill KB and Hep-G2 cancer cells, with IC_{50} values between 1 and 21μM [13]. Important enzymes known as topoisomerases II control the higher-order structural state of DNA [13]. These include the top 2 alpha and top 2 beta isozymes. Drugs used to treat numerous cancer types always concern the inhibition of the topoisomerase II beta complex [14-16]. In recent years, molecular docking has become an essential tool for in-silico drug development. This tool enables researchers to study the behavior of small molecules with a target protein and contributes to explaining the biochemical process underlying this interaction [17-21]. Here, by molecular docking into the structure of topoisomerase IIβ, the interactions of some potential anticancer derivatives of betulin compounds were investigated.

2. EXPERIMENTAL

The crystal structures of topoisomerase IIβ (PDB ID: 3QX3) in complex with DNA and etoposide (PDB ID: EPV) were retrieved from the protein data bank. This structure was solved by X-ray crystallography at 2.16Å resolution. For the preparation of protein, water molecules, ligands, and heteroatoms were removed. Polar hydrogens and Kollman charges were then added. Structures of ligands were built by Chem3D and converted into *.pdbqt format after structural optimization. Finally, the selected compounds were docked into the same binding site of etoposide with the receptor. The grid box was set with grid spacing of 0.375Å and a grid volume of $40 \times 40 \times 40$Å. The conformation of the ligand with the highest binding energy (most negative) generated from the docking process with the lowest root-mean-square deviation (RMSD) of below 2Å was considered the best conformation to the receptor. The ligand-receptor interactions were visualized using Discovery Studio 2021. The molecular docking was performed using AutoDock 4.2.6 software. The calculation has been conducted using an Intel (R) Core (TM) i3-10400 CPU @ 2.90 GHz workstation.

3. RESULTS AND DISCUSSION

We successfully synthesized thirteen new ester conjugates of 28-O-acylbetulins with AZT, d4T, and 3TC (**2a-b**, **3a-f**, **4a-e**) from the starting 28-O-acylbetulins **1a-f**, as described in our previous study [22]. Figure 1 illustrates their structure.

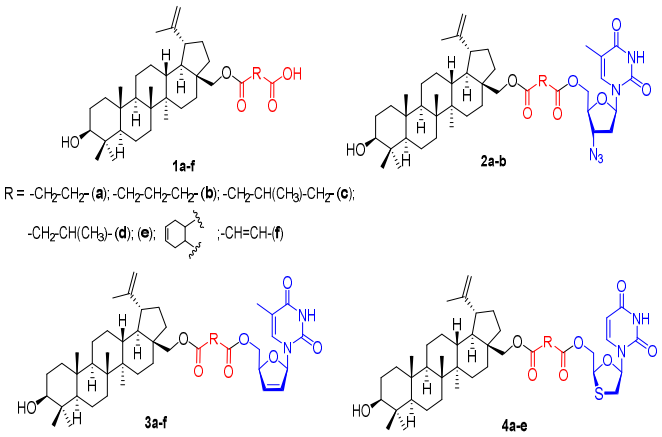


Figure 1. The structure of studied betulin derivatives with AZT, d4T, 3TC (**2a-b**, **3a-f**, **4a-e**, respectively)

The antitumor activities of all synthetic compounds against the KB and Hep-G2 human cancer cell lines were screened *in vitro* using the MTT assay. Some derivatives exhibited significant anticancer properties, with IC_{50} values between 1 and 21μM on the two cancer cell lines (Table 1). To investigate the binding pattern of target compounds within the topoisomerase IIβ binding site, docking of these compounds into topoisomerase IIβ was carried out using AutoDock Vina.

Etoposide (EPV) is a type II topoisomerase inhibitor that binds the enzyme in a covalent compound with DNA. Etoposide creates a ternary complex with the enzyme and DNA by attaching it to a pocket in topo IIβ's DNA-binding site, located near the cleavage site on the DNA molecule. This stabilizes the enzyme-DNA covalent complex, preventing the enzyme from releasing the DNA, which causes DNA damage and cell death. Firstly, we redocked the co-ligand EPV into the active site of topoisomerase II to validate the docking process. The results showed that the redocked conformers bound tightly to the EVP binding site of topoisomerase IIβ with a very high match with the co-crystallized structure (RMSD = 0.522Å) (Figure 2). The dock score for etoposide was found to be -13.6kcal/mol. Etoposide made important connections with the receptor in the pocket atoms by forming H-bonds with DNA nucleotides DC8, DG13, DG10, Asp479, and Gly478. Additionally, it exhibited hydrophobic interactions with the Arg503 residue and

with nucleotides DG13, Met72, and Pro819, contributing to the stabilization of the drug–enzyme complex (Figure 2). All interaction behaviors observed in the docking studies were found to be in accordance with the reported binding mode of the etoposide in the active site of TOP 2β [23].

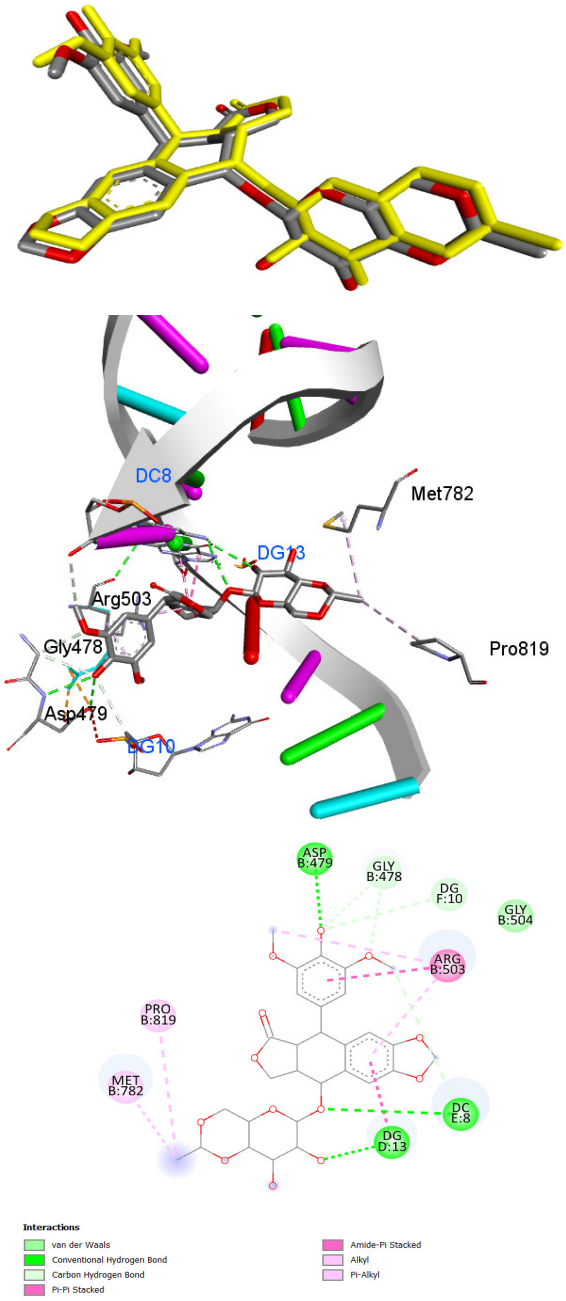


Figure 2. The redocked result of EPV into the binding sites of protein

Subsequently, we docked the synthesized compounds into the protein's active site. The results (Table 1) demonstrated a reasonably good correlation between the binding free energy from docking simulations (ΔGdock) and the experimental free energies (ΔGexp) with correlation coefficients between ΔGdock and ΔGexp of KB and Hep-G2 cancers being R = 0.75 and 0.8, respectively. The calculation of ΔGexp was based on the IC_{50} value, using the following equation [24-26]:

$$\Delta G_{exp} = RT(\ln IC50.10^{-6})/1000$$

Where:

- R is the gas constant of 1.987cal/mol.K;

- T is the temperature T is set at 298.15K;

- IC_{50} values obtained from our previous report and expressed as μM.

Table 1. Binding free energy values (kcal mol1) of studied compounds with two cancer cell lines

Entry	Compounds	IC_{50} (μM)		ΔG_{exp}		ΔG_{dock}
		KB	Hep-G2	Hep-G2	KB	
1	**1a**	>150	>150	-5.2	-5.2	-5.0
2	**1b**	>150	>150	-5.2	-5.2	-4.2
3	**1c**	>150	>150	-5.2	-5.2	-5.1
4	**1d**	64.6	>150	-5.2	-5.7	-5
5	**1e**	61	99	-5.5	-5.7	-6.6
6	**1f**	135	138	-5.3	-5.3	-5.9
7	**2a**	4.3	9.4	-6.9	-7.3	-7.2
8	**2b**	>158	116	-5.4	-5.2	-5.6
9	**3a**	8.9	88.3	-5.5	-6.9	-5.5
10	**3b**	18	49.1	-5.9	-6.5	-5.3
11	**3c**	12	59.5	-5.8	-6.7	-6.7
12	**3d**	105	122	-5.3	-5.4	-6.7
13	**3e**	11	84.5	-5.6	-6.8	-6.6
14	**3f**	0.8	2.8	-7.6	-8.3	-7.7
15	**4a**	12.4	23.2	-6.3	-6.7	-7.1
16	**4b**	10.4	21	-6.4	-6.8	-6.2
17	**4c**	14.6	21.1	-6.4	-6.6	-6.9
18	**4d**	5.5	5.6	-7.2	-7.2	-7.2
19	**4e**	9.8	90	-5.5	-6.8	-7.1
20	Ellipticine	1.3	1.5	-7.9	-8.0	-9.5

The in vitro test results demonstrated that compounds **2a**, **3f** and **4d** are the most promising inhibitors against KB and Hep-G2 cells, exhibiting relatively low IC_{50} values. These results are in good agreement with the expected theoretical values for the binding energies calculated from docking simulations, which are -7.7, -7.2, and -7.2 (kcal/mol), respectively. Figure 3 present the plot of ΔGexp against ΔGdock. Some outliers, such as compounds **1b**, **1e**, and **3d**, may araise from the fact that ΔGexp values are influenced by

experimental conditions such as pH, ionic strength, and temperature. Meanwhile, docking simulations strongly depend on docking algorithms, conformational changes, entropic contributions, and so on, leading to deviations between the predicted and actual binding affinities.

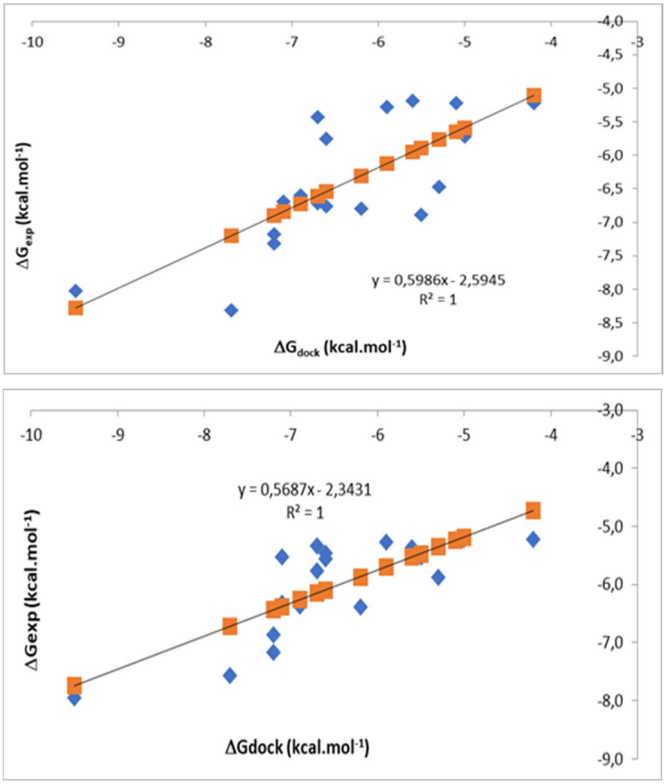
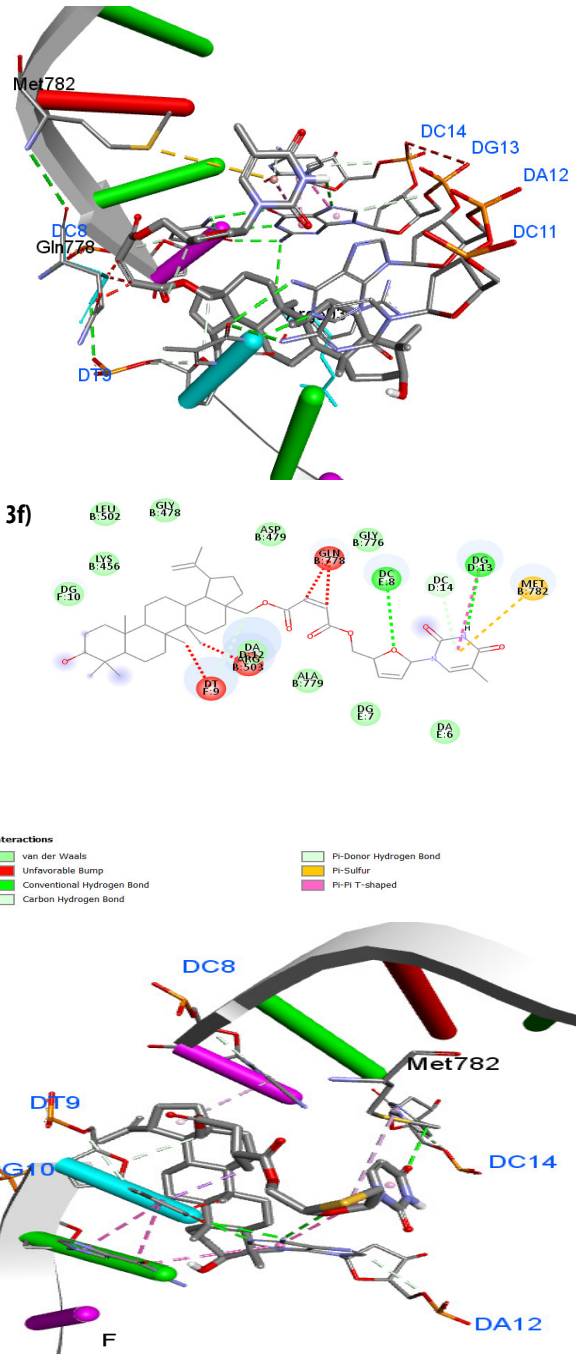


Figure 3. Correlation between the calculated binding free energy (ΔG_{exp}) and the theoretical binding free energy (ΔG_{dock}) of KB and Hep-G2 cancer cell line

Docking simulation revealed that AZT, d4T, and 3TC fragments primarily contributed to the potent inhibitors' high cytotoxicity against cancer cell lines (Figure 4). All compounds inhibited topoisomerase IIβ by intercalating into DNA and forming crucial interactions within the binding pocket. The results demonstrated a correlation between the binding score of the compounds and the values of hydrogen bonds, hydrophobic interactions, and the number of flexible torsions present in the synthesized compounds. Among the tested compounds, **3f**, **a** derivative of betulin-d4T, exhibited the highest binding affinity with a binding score of -7.7 kcal/mol (Table 1). It formed four H-bond interactions with active site residues: DC8, DC13, DC14, and DT9. Additionally, DG13 and Met782 interacted with the pyrimidinedione ring using pi–pi T-shaped and pi-sulfur interactions, respectively. Compound **4d**, a derivative of betulin-3TC, showed H-bond interactions between DC14 and the C=O group of the pyrimidinedione ring, as well as between DA12 and the 1,3-oxathiolane ring via an oxygen atom. The 1,3-oxathiolane ring also exhibited an alkyl interaction with Met782. The betulin moiety contributes three interactions: to DT9 through the H-bond and pi-sigma bond, and to DC8 through the alkyl bond. Compound **2a**, a derivative of betulin-AZT, displayed three H bond interactions with active site residues: DG7, DT9, and Met782; two pi-sigma bonds with DT9 and DA12; one pi-pi stacked bond with DA12; and one pi-alkyl bond with DC8. Based on the molecular docking results, these active compounds may stop the growth of cancer cell lines by stopping topoisomerase IIβ.



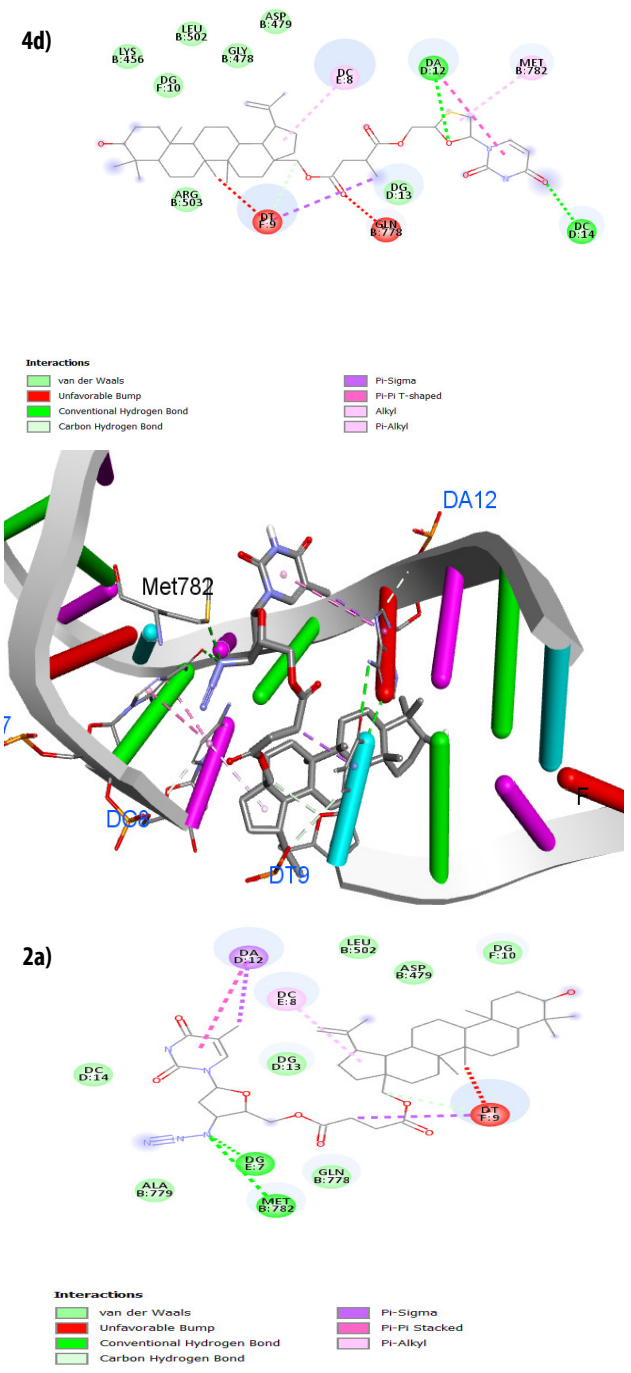


Figure 4. The 3D and 2D interactions of the potential inhibitors (**2a**, **3f** and **4d**) and EPV with the target receptor 3QX3

The highly active derivatives **2a**, **3f** and **4d** were evaluated for their physicochemical characteristics and the proposed ADMET profile. These compounds violated Lipinski's Rule of Five (except compound **3f**) and exhibited low GI absorption, indicating good absorption in the human intestine; none hold the BBB permeant (except compound **3f**). Because phase-1 metabolism (oxidation) includes the main liver enzyme system, Cytochrome P (CYP) plays a significant role in drug metabolism. To date, 17 CYP families have been identified in humans, though only CYP1, CYP2, CYP3, and CYP4 are associated with drug metabolism, with CYP (1A2, 2C9, 2C19, 2D6, and 3A4) being responsible for the biotransformation of more than about 90% of the drugs undergoing phase I metabolism. Inhibition of these isoenzymes may cause negative side effects by reducing medication solubility and accumulating metabolites. This model predicts that three compounds are CYP2C19 and CYP3A4 substrates. In addition, compound **4a** is the inhibitor of CYP2B6 and CYP2C8. Prediction of the toxicity of these compounds showed that they are not hERG blockers, suggesting a low cardiotoxicity effect. Moreover, the compounds did not exhibit any acute toxicity in rats' oral cavities, nor did they cause corrosion or irritation in their eyes. Moreover, compound **4d** demonstrated no interaction with the respiratory system.

Table 2. Physicochemical characters and the ADMET profile of three potential compounds **2a**, **3f** and **4d**

Predicted parameters	**2a**	**3f**	**4d**
Physicochemical property			
Molecular Weight	791.48	746.45	768.44
nA	13	10.0	10.0
nD	2	2	2
logP	5.635	4.956	5.718
TPSA	185.68	136.92	136.92
Absorption			
Gastrointestinal absorption	low	low	low
P-gp substrate	yes	yes	yes
Log Kp (skin permeation)	-4.66cm/s	- 4.78cm/s	-4.76cm/s
Human Intestinal Absorption	0	0	0
Distribution			
Plasma protein binding	97.1%	97.8 %	98.2 %
Volume distribution	1.203	0.681	1.044
Blood–brain barrier (BBB) penetration	No	yes	No
Metabolism			
CYP interaction	CYP1A2 substrate CYP2C19 substrate CYP3A4 substrate	CYP2C19 substrate CYP3A4 substrate	CYP2B6 Inhibitor CYP2C8 inhibitor CYP3A4 substrate CYP2C19 substrate

Excretion			
Clearance (CL)	4.71 (low)	5.244 (moderate)	1.687 (low)
Half-life (T1/2)	0.663 h (short)	0.698 h (short)	1.438h (short)
Toxicity			
hERG Blockers	Low (0.055)	Low 0.126	Low (0.063)
Rat oral acute toxicity	Moderate (0.468)	No (0.203)	No (0.244)
Eye Corrosion	No (0.0)	No (0.0)	No (0.0)
Eye Irritation	No (0.553)	No (0.007)	No (0.003)
Respiratory	yes (0.995)	yes (0.908)	No (0.076)

4. CONCLUSION

It was much more effective for the inhibition of HepG2 and KB cell lines when betulin, AZT, d4T, and 3TC were linked together using an ester linker. The docking studies of the interaction between potential inhibitors and topoisomerase IIβ revealed that the AZT, d4T, and 3TC parts in the hybrid compounds of 28-O-acylbetulins play a crucial role in their high cytotoxicity against cancer cell lines. The hit compounds exhibited low binding scores and key interactions with pi-pi stacking and hydrogen bonding, specifically 3f (-7.7kcal/mol), **4d**, and **2a** (-7.2kcal/mol). The ADMET prediction indicates that these high-performing compounds could potentially function as lead-like candidates. Taken together, the hybrid conjugate of certain active components could serve as a promising starting point for the development of new lead compounds in anticancer studies.

ACKNOWLEDGMENT

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[22]. - Preparation of 28-O-acylbetulins **1a–f**: A solution of betulin (2 g, 4.5 mmol) and Et_3N (546 mg, 5.4 mmol) in dichloromethane (20 ml) was stirred at room temperature for 15 min. Acid anhydrides (18 mmol) was then added and the resulting mixture was stirred at room temperature for 24 h. Afterwards, the solvent was removed in vacuo, and the residue was redissolved in EtOAC (20 mL) and washed with water (20 mL). The aqueous phase was extracted with EtOAc (20 ml x 3). Drying (Na_2SO_4), filtration of the drying agent, and removal of the solvent in vacuo afforded 28-O-acylbetulins **1a–f**, which were further purified by means of column chromatography on silica gel using n-hexane/ethyl acetate (8 : 2).

- Preparation of betulin-AZT conjugates **2a,b**: To a solution of 28-O-acylbetulin **1a,b** (0.8 mmol) in DMF (5 ml) was added DCC (248 mg, 1.2 mmol), HOBt (183.7 mg, 1.2 mmol), and DIPEA (155 mg, 1.2 mmol) and stirred for 5-10 min at room temperature. AZT (256.5 mg, 0.96 mmol) was then added and the resulting mixture was stirred at room temperature for 20 h. Afterwards, the solvent was removed in vacuo, and the residue was redissolved in EtOAC (20 mL) and washed with water (20 mL). The aqueous phase was extracted with EtOAc (20 ml x 3). Drying (Na_2SO_4), filtration of the drying agent, and removal of the solvent in vacuo afforded betulin-d4T conjugates **2a,b**, which were further purified by means of column chromatography on silica gel using n-hexane/ethyl acetate (3 : 7).

- Preparation of betulin-d4T conjugates **3a–f, 4a–e**: To a solution of 28-O-acylbetulin **1a–f** (0.6 mmol) in DMF (5 ml) was added DCC (186 mg, 0.9 mmol), HOBt (138 mg, 0.9 mmol), and DIPEA (116 mg, 0.9 mmol) and stirred for 5-10 min at room temperature. Stavudine (202 mg, 0.9 mmol) or lamivudine (206 mg, 0.9 mmol) was then added, and the resulting mixture was stirred at room temperature for 20 h. Afterwards, the solvent was removed in vacuo, and the residue was redissolved in EtOAC (20 mL) and washed with water (20 mL). The aqueous phase was extracted with EtOAc (20 ml x 3). Drying (Na_2SO_4), filtration of the drying agent, and removal of the solvent in vacuo afforded target conjugates **3a–f** and **4a–e**, which were further purified by means of column chromatography on silica gel using n-hexane/ethyl acetate (3 : 7).

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