

Research Article

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Improving the Aqueous Solubility of Taxol Through Altering XLogP3

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ABSTRACT

Taxol (generic name paclitaxel) is an antineoplastic drug used to treat breast, lung, and ovarian cancer. It performs exceptionally well against a wide variety of tumors, including B16 melanoma, L1210 and P388 leukemias, MX-1 mammary tumor, and CX-1 colon tumor xenografts. However, despite Taxol's efficacy in antitumor activity, its aqueous solubility is extremely poor, decreasing its bioavailability and making it difficult for the body to absorb. The objective of this study is to improve the solubility of taxol, thus increasing the bioavailability of the drug in preventing cancer. By modifying the structure of taxol, four novel taxol derivatives were created with improved solubilities. Two of the derivatives were given an additional hydrogen donor and acceptor, and thus showed a pronounced positive change in solubility. The results of this work solve the issue of Taxol's inadequate solubility and show potential in increasing absorption of the drug.

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Cancer is a disease that arises from the uncontrolled division of the body's cells and can occur in any region of the body. In 2021, there were approximately 18.1 million cancer cases globally, and an estimated 608,570 patients died of cancer in the United States [1,2]. Due to the pervasiveness of the disease, it is critical to develop effective anticancer drugs. Antineoplastic drugs are medications designed to treat malignant (cancerous) diseases and are commonly administered through oral ingestion, intramuscular injection, subcutaneous injection, or intravenous injection [3]. The administration method is contingent on the type of drug and the type of cancer.

Taxol (generic name paclitaxel) is an antineoplastic drug used to treat breast, lung, and ovarian cancer [4]. It performs exceptionally well against a wide variety of tumors, including B16 melanoma, L1210 and P388 leukemias, MX-1 mammary tumor, and CX-1 colon tumor xenografts [5]. It is customarily delivered intravenously, but an oral form of taxol also exists [6]. A part of the taxane family of chemotherapy drugs, taxol works by attaching to microtubules and hindering depolymerization. Its antimetabolic properties allow it to interrupt normal spindle formation and cell growth during the cell cycle's M phase [7]. Taxol is often given with other chemotherapy drugs to treat cancers.

However, despite Taxol's efficacy in anti-tumor activity, the drug has many faults. Common side effects of intravenous taxol include, but are not limited to, fever, painful urination, skin rash, ulcers in the mouth, unusual bleeding or bruising, and dizziness. Severe, but rare, side effects include myocardial infarction, sepsis,

inflammation in the blood vessels, and high blood pressure [8].

In addition, the aqueous solubility of taxol is less than 0.01 mg/mL and has a logP of about four, meaning that its water solubility is extremely poor [9]. For reference, the ideal logP for drugs to achieve good oral and intestinal absorption is between 1.35 to 1.8. LogP is a factor in Lipinski's rule of 5, which is used to indicate the solubility of a drug and determine its effectiveness. XLogP3, a method used in this research, finds logP through adding the contributions of atoms in a molecule [10]. The XLogP3 value of taxol is estimated to be 3.66, which does not meet ideal logP standards for drugs.

Currently, to combat Taxol's poor solubility, the drug is given with polyoxymethylene castor oil and dehydrated ethanol, but this mixture can be irritating to the recipient and cause ancillary side effects [11]. Because of how crucial this drug is for cancer patients, developing taxol derivatives with improved solubility is imperative.

Related Works

Due to the pervasiveness of taxol in cancer treatment, many studies have been conducted in an effort to refine its solubility. Two studies with similar goals and processes are described below. In a study led by Mathew et al, 2'- and 7-amino acid taxol derivatives were created with the aim of improving aqueous solubility. The study included two different approaches to developing the taxol derivatives. The first approach used the polyoxymethylene (troly) protecting group for the 2'-hydroxyl group and esterified the 7-hydroxyl, deprotecting the amino and troy groups. The second approach involved a reaction between taxol and over two molar equivalents of the N-protected, or

N-dialkylated amino acids, resulting in 2',7-diamino acid esters of taxol. The culmination of the study can be found in the derivative with the best results in terms of chemical stability, solubility, and antitumor activity: $\text{COCH}_2\text{CH}_2\text{N}(\text{C}_2\text{H}_5)_2\cdot\text{CH}_3\text{SO}_3\text{H}$.

In a study led by taxol Greenwald et al (1995) was conjugated with Polyethylene glycol (PEG) to improve solubility while also maintaining the parent molecule's ability to impede cancer cell division [12]. PEG can enhance water solubility while also reducing immunogenicity of protein adducts with high molecular weight, making it a reasonable candidate to conjugate with taxol. The study created at least 3 suitable PEG Taxol's with drastic improvement in solubility.

The work presented in this paper builds on previous research to develop alternative taxol derivatives with improved solubility. While earlier work focused on lab-based experimentation with building derivatives, the focus in this research is on creating novel derivatives using various utter software's. Furthermore, there is a strong emphasis on the experimental/clinical examination of the solubility of our derivatives.

Objective

The primary objective of this study is to improve the solubility of taxol to increase the effectiveness of the drug in preventing cancer cell division.

The structure of taxol was redesigned to create four distinct taxol derivatives with improved XLogP3 values. The parent taxol molecule and its four derivatives are modeled in scheme 1 below.

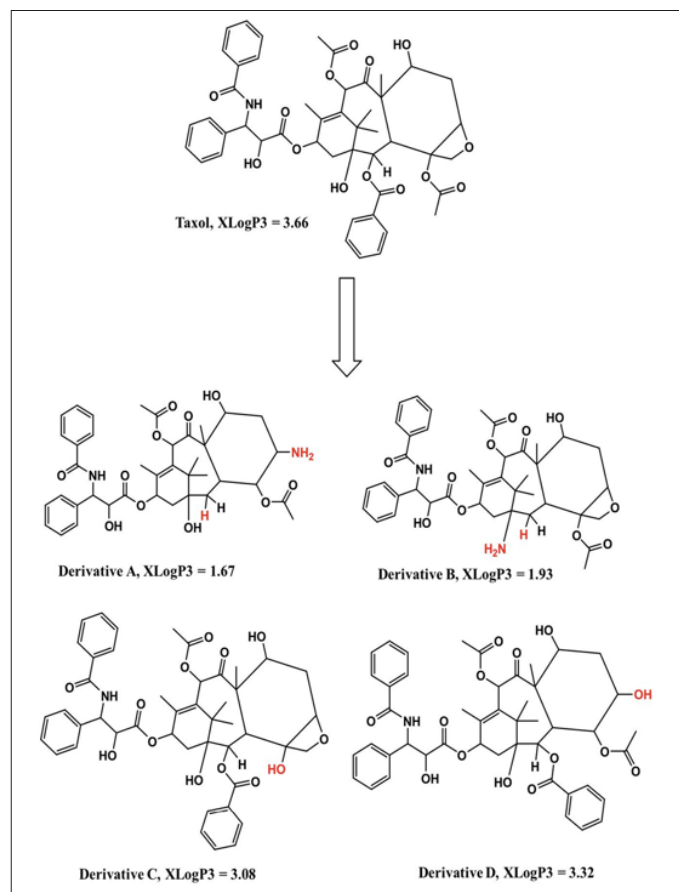


Figure 1: Parent Taxol vs Four Novel Derivatives

Methodology

The software Chera was used to create derivatives of taxol. Then, the software Sc finder Scholar was used to verify the originality of the created derivatives. After finding four novel derivatives of taxol, XLogP3 Online was used to calculate the XLogP3 value of each derivative, thus determining how well the altered molecule fit within the ideal logP range.

Results and Discussion

The four new derivatives of taxol demonstrated a lower XLogP3 when compared to the original. Among the four, two of the derivatives fit or neared the desired logP range for a drug (1.35-1.8). The other two did not fit within the target range, but were still lower than the original taxol molecule. The four derivatives can be sorted into two groups based on their specific alterations: one group received an additional H and NH_2 while the other received an additional OH. The results of this study will be discussed based on these two groups.

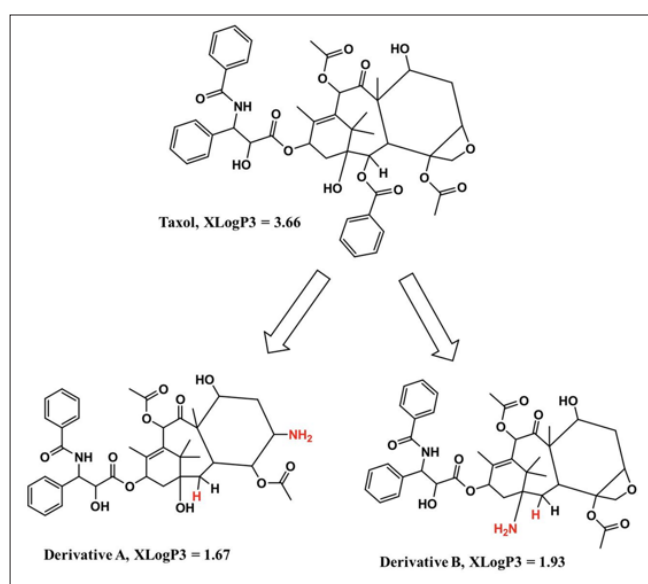


Figure 2: Parent Taxol vs Derivatives A and B (Group 1)

Group 1, composed of Derivatives A and B, received an additional H and NH_2 . In Derivative A, the benzoate group was replaced with a hydrogen. Additionally, an NH_2 was inserted where the cyclic ether (epoxide) was initially located. In Derivative B, a hydroxyl group was replaced with an NH_2 and a benzoate was replaced with a hydrogen.

Both derivatives A and B have better solubility than the parent taxol, as indicated by the XLogP3 values in Scheme 2 above. This is because the NH_2 acts as both a hydrogen bond donor and acceptor, thus enhancing the aqueous solubility of Derivatives A and B. The addition of NH_2 compensates for the loss of the benzoate, which is only a hydrogen bond acceptor.

XLogP3 is a factor in Lipinski's rule of 5, which is used to indicate the solubility of a drug and determine its effectiveness. The ideal logP for drugs to achieve good oral and intestinal absorption is between 1.35 to 1.8. The lower the XLogP3, the better the solubility and bioavailability.

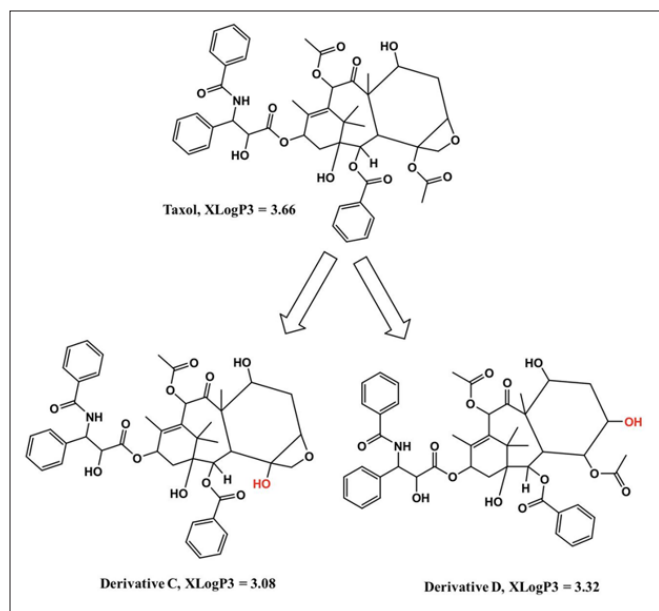


Figure 3: Parent Taxol vs Derivatives C and D (Group 2)

Group 2 is composed of Derivatives C and D, both of which were given an additional OH. An acetate group was replaced with an OH in Derivative C. In Derivative D, an epoxide group was replaced by the OH.

While the solubilities of Derivatives C and D did improve when compared to the solubility of taxol, the change was not as drastic as Derivatives A and B. The solubilities of Derivatives C and D do not meet the ideal logP for drugs (between 1.35 to 1.8), as shown in Scheme 3 above.

The difference in solubility enhancement between Groups 1 and 2 can be attributed to the nature of the changes made. In Group 2, Derivatives C and D were changed by the newly introduced OH.

In Group 1, an NH_2 was introduced. OH, only has one hydrogen, while NH_2 possesses two. This means that NH_2 has two hydrogens that it is able to donate, while OH has one hydrogen that it can donate. Thus, the aqueous solubility of Group 1 is significantly better than that of Group 2.

Conclusion

The primary objective of this study is to improve the solubility of taxol to increase the bioavailability of the drug in preventing cancer. By modifying the structure of taxol, we created four novel taxol derivatives with improved solubilities. Derivative A (XLogP3: 1.67) and Derivative B (XLogP3: 1.93) showed improved solubility when compared to taxol (XLogP3: 3.66) as they either neared or fit within the ideal range for logP values (1.35 to 1.8). Derivatives A and B showed the most success in terms of solubility because of the added NH_2 , which gave both derivatives a hydrogen donor and acceptor. Derivative C (XLogP3: 3.08) and Derivative D (XLogP3: 3.32) showed improved solubilities as well, but are not close enough to the ideal logP range.

This is because the Group 2 derivatives were given an OH instead of an NH_2 , meaning they only have one hydrogen to donate. Thus, altering the chemical structure of taxol ultimately created two novel derivatives that show potential in terms of aqueous solubility.

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References

1. Worldwide cancer data World Cancer Research Fund International <https://www.wcrf.org/cancer-trends/worldwide-cancer-data/>.
2. Cancer Facts & Figures American Cancer Society <https://www.cancer.org/research/cancer-facts-statistics/all-cancer-facts-figures/cancer-facts-figures-2021.html>.
3. Types of Chemotherapy Drugs SEER Training <https://training.seer.cancer.gov/treatment/chemotherapy/types.html>.
4. Taxol Uses Side Effects Risks and Benefits <https://www.verywellhealth.com/taxol-paclitaxel-chemotherapy-430562>.
5. Mathew AE, Mejillano MR, Nath JP, Himes RH, Stella VJ (1992) Synthesis and evaluation of some water-soluble prodrugs and derivatives of taxol with antitumor activity. Journal of medicinal chemistry 35: 145-151.
6. Is Oral Paclitaxel Better Than IV Paclitaxel for Metastatic Breast Cancer? <https://www.breastcancer.org/research-news/oral-vs-iv-paclitaxel-for-abc>.
7. Wang X, Pan L, Mao N, Sun L, Qin X, et al. (2013) Cell-cycle synchronization reverses Taxol resistance of human ovarian cancer cell lines. Cancer cell international 13: 77.
8. Paclitaxel (Intravenous Route) Side Effects Mayo Clinic <https://www.mayoclinic.org/drugs-supplements/paclitaxel-intravenous-route/side-effects/drg-20065247>.
9. Sadeghi-Oroumiyeh A, Valizadeh H, Zakeri-Milani P (2021) Determination of Paclitaxel Solubility and Stability in the Presence of Injectable Excipients. Pharm Chem J 55: 983-987.
10. Cheng T, Zhao Y, Li X, Lin F, Xu Y, et al. (2007) Computation of octanol-water partition coefficients by guiding an additive model with knowledge. Journal of chemical information and modeling 47: 2140-2148.
11. Nakamura J, Nakajima N, Matsumura K, Hyon SH (2010) Water-soluble Taxol Conjugates with Dextran and Targets Tumor Cells by Folic Acid Immobilization. Anticancer Research 30: 903-909.
12. Greenwald RB, Pendri A, Bolikal D (1995) Highly Water-Soluble Taxol Derivatives: 7-Polyethylene Glycol Carbamates and Carbonates. The Journal of Organic Chemistry 60: 331-336.

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