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Chemistry and biological activity of antitumour taxoids

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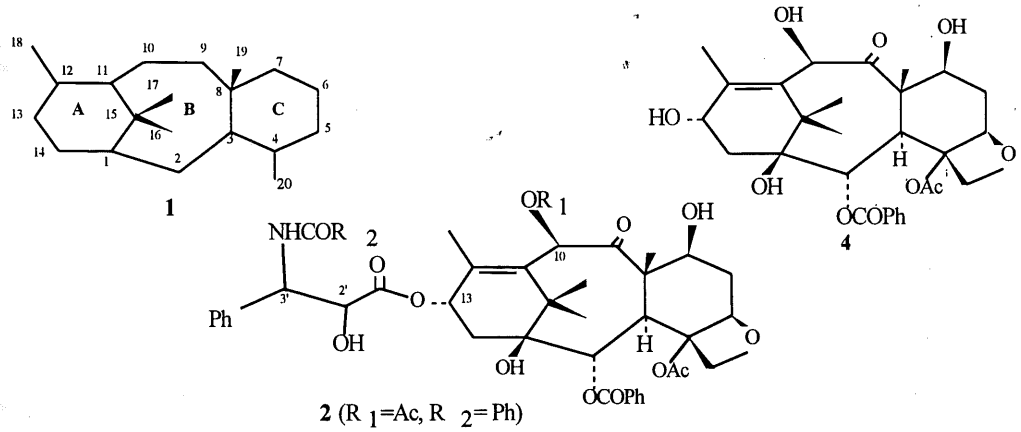
ABSTRACT Semi-synthetic approaches to paclitaxel, docetaxel and their derivatives were discussed. Their structure-activity relationship was also explained.

ABSTRAK Pendekatan semi-sintetik paklitaksel, dositaksel dan terbitannya dibincangkan. Kaitan struktur dengan aktiviti juga diterangkan.

(Taxoid, antitumor, semi-synthesis, paclitaxel, docetaxel)

INTRODUCTION

Taxoids are a group of diterpenes having in common a tricyclo [9.3.1.0] pentadecane skeleton **1**, also named taxane skeleton. In addition to their complex structure, some taxoids possess strong antitumor properties and a unique mechanism of action on microtubules. Taxol® (generic name: paclitaxel) **2**, initially isolated from the stem bark of the Pacific yew, *Taxus brevifolia* [1], was the first taxoid to enter clinical trials. Its mechanism of action on microtubules was described in 1979. The use of paclitaxel in the treatment of resistant ovarian cancer was finally approved by the Food and Drug Administration in 1992. Taxotere® (generic name: docetaxel) **3** is a synthetic taxoid which was obtained from 10-deacetylbaccatin III **4**, a natural taxoid first isolated from the leaves of the European yew tree, *Taxus baccata*. Docetaxel was shown to possess strong antitumor properties on various tumors and is used for the treatment of breast cancer.

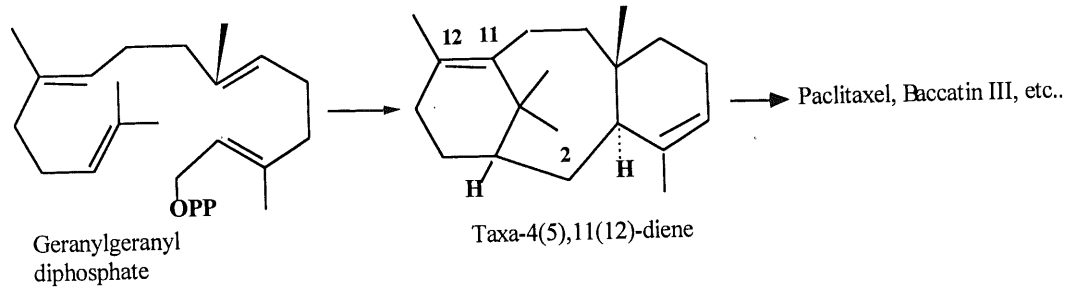


Because of the strong antitumor properties of these diterpenes, a number of studies have been engaged, all over the world, in the chemical, biological and clinical fields. This paper will summarize the biosynthesis, chemistry and structure-activity relationships of some taxoids.

1- Biosynthesis of taxoids

Taking into account the main skeletal groups of natural taxoids, many authors have speculated upon the origin of the taxane skeleton. The current view was that taxoid originates from the common

isoprenoid intermediate geranylgeranyl diphosphate by different cyclization steps followed by a number of oxidative steps. The formation of the N-benzoylphenylisoserine side chain of paclitaxel was shown to originate from phenylalanine by Floss *et* al [2]. Recently, Croteau et al [3] isolated a 'taxadiene cyclase' from a cell free extract of yew saplings of *T. brevifolia*. This enzyme was shown to catalyze the conversion of radioactive geranylgeranyl diphosphate into a tricyclic taxadiene. It was then demonstrated that this cyclic diterpene led to paclitaxel and other taxoids *in vivo* (Scheme **1**).



Scheme 1. Biosynthesis of taxoids

2-Chemistry of 10-deacetylbaccatin III, precursor of antitumor taxoids.

Natural 10-deacetylbaccatin III **4** was first isolated from the leaves of the European yew tree, *Taxus baccata*, following an antitubulin activity-guided fractionation. The concentration of 10-deacteylbaccatin III in the leaves depends on the type of yew species as well as the times of collection. Up to date the largest amount of 10-deacteylbaccatin III (about 1g/Kg) was found in the leaves of *T. baccata*. 10-deacetylbaccatin III **3a** which is not cytotoxic, is a suitable precursor for the synthesis of paclitaxel, docetaxel and various taxoids modified on the skeleton and/or the side chain at C-13. The first semi-synthesis of paclitaxel and docetaxel came from the application of an oxyamination reaction on the C-13 cinnamoyl derivative of 10-deacetylbaccatin III protected at C-7 and C-10. This led to the 2'R,3'S and 2'S, 3'R diastereoisomers. Then, efficient semi-synthetic approaches to paclitaxel and docetaxel have been studied by different teams. It relies on the asymmetric synthesis of the acid side chain followed by its coupling with 7-protected or 7-, 10-diprotected derivatives of 10-deacteylbaccatin III. This semi-synthetic approach allowed the synthesis of a variety of side chain analogs as well as a number of paclitaxel and docetaxel derivatives modified on the skeleton.

Figure 1 shows the main structural modifications which have been performed on 10-deacetylbaccatin III, [3,4,5,6,7].

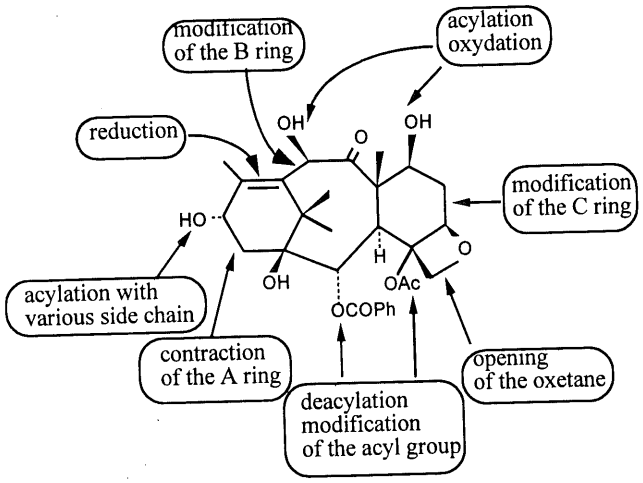


Figure 1: Modifications on 10-deacetylbaccatin III

When treated with basic reagents, 10-deacetylbaccatin III epimerizes easily at carbon 7. In fact, all taxoids bearing a β-hydroxyl group at carbon 7 and a keto group at carbon 9 converted to the 7α isomer after a retro-aldolisation process under mild basic conditions. Selective deacylation was studied on 10-deacetylbaccatin III. Under basic or reductive conditions, 7-protected 10-deacetylbaccatin III led mainly to 4-deacetyl-10-deacetylbaccatin III derivative. On the contrary, 13, 7-diprotected 10-deacetylbaccatin III baccatin III derivatives afforded 2-debenzoyl analogs. The selective deacylation reactions are due to the particular conformation of 10-deacetylbaccatin III in which the hydroxyl group at C-13 is close to the C-4 acetyl. For example, under basic conditions, a C-4, C-13 transacetylation occurs in 7-protected derivatives. On the other hand, if the free hydroxyl group at C-13 is protected, the hydrolysis or reduction of the benzoyl group first occurs. Under acidic conditions, chemoselective rearrangement occured on the oxetane or on the A ring of taxoids, depending of the nature of the reagent, leading respectively to opened oxetane derivatives or A-ring contracted products.

A cooperative program between our laboratory and Rhône-Poulenc Rorer resulted in the synthesis of a number of taxoids modified on the skeleton or/and on the side chain. From these studies and those of other laboratories, a structure-activity relationships profile has been proposed (see Figure 2).

3-Structure-activity relationships in the taxoid series (Figure 2)

With the exception of *in vivo* assays, measurement of the cytotoxicity on tumor cells lines and monitoring of temperature induced tubulin-microtubules assembly or disassembly are the most utilised tools for evaluating the antimitotic activity of the compounds. Different *in vitro* assays have been used to determine the activity of paclitaxel and docetaxel congeners on tubulin. For example, the evaluation of taxoids on the promotion of microtubule assembly or on the inhibition of microtubule disassembly at 4°C can be used to evaluate the activity of taxoids [8,9]. Figure 2 summarizes the influence of the different functional groups on the antitubulin activity.

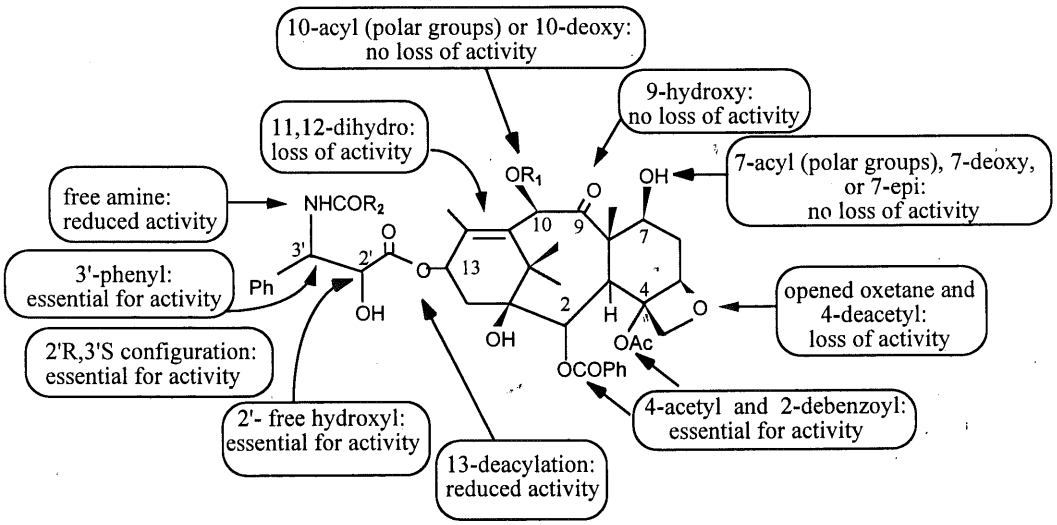


Figure 2. Structure-Activity Relationships of Taxoids

From these SAR studies [6] it was found that the substituents on the bottom part of the molecule at C-2 and C-4, and the substituents of the side chain play an important role in the interaction with tubulin. Moreover, conformational studies show that these substituents are in close proximity. Two structural types have been proposed from these studies to correspond to active taxoids. One conformation possesses the 3'-amido group close to the 2-benzoyl group. This conformation was obtained from X-ray analysis as well as NMR experiments in apolar solvents and molecular modeling. The other conformation was found when paclitaxel or docetaxel are in a polar environment. In that case, the 3'-phenyl is close to the 2'-benzoyl groups. Moreover, depending on the environment, different intermolecular interactions in docetaxel and paclitaxel were found to occur between the oxygenated functions of the upper part of the molecule and the side chain or the ester group at C-2.

In conclusion, the promising therapeutic activities of antitumor taxoids led to a number of chemical, biological and clinical studies all over the world.

In the chemistry field, these programs allowed a better knowledge of the chemical reactivity and of the conformation of active taxoids interacting with microtubules. It led also to three total synthesis of baccatin III and an improved semi-synthesis of paclitaxel and docetaxel. From all these results, one can hope that a second-generation antitumor taxoids will be soon discovered for their improved biological activity.

NOTES

Taxol® is a registred trademark of Bristol-Myers Squibb. Paclitaxel is the generic name of Taxol®. Taxotere® (generic name: docetaxel) is a registered trademark of Rhône-Poulenc Rorer.

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