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Taxane Anticancer Agents

Basic Science and Current Status

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Chapter 17

Practical Semisynthesis and Antimitotic Activity of Docetaxel and Side-Chain Analogues

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Docetaxel (Taxotere®) and a variety of semisynthetic side-chain analogs have been prepared and evaluated for their potency in inhibiting microtubules disassembly and for their antitumor activity in *in vitro* and *in vivo* experimental models. Their partial syntheses were achieved using stereoselective approaches. Different protection/deprotection strategies have been investigated. Structure-activity relationship studies demonstrate that biological activity is very dependent on the position and nature of substituents on the aromatic ring of 3'-modified-phenyl analogs. New carbamates have also been synthesized. Yet *tert*-butoxycarbonyl remains the substituent of choice for the 3'-nitrogen atom. Among all the new taxoids reported here, 3'-*para*-fluoro-docetaxel was identified as one of the most powerful analogs of docetaxel.

The structure of the natural antitumor agent paclitaxel (Taxol®, **1**) was first established by Wani, Wall *et al.* in 1971 (*1*). This diterpene, extracted from the bark of the Western Yew, *Taxus Brevifolia* Nutt (Taxaceae) (*2*), has proved highly cytotoxic against a wide number of cancer cell lines in *in vitro* and *in vivo* experimental models (*3*).

In the early 1980's, as the supply of paclitaxel for clinical evaluation was becoming scarce, Potier's group, i.e. Guéritte-Voegelein, Guénard *et al.*, at Gif-sur-Yvette started the partial synthesis of new taxane diterpenoids (taxoids) from 10-deacetyl-baccatin III **2**, an abundant constituent of the needles of the European yew species *Taxus baccata* L. (*4*). Using conveniently O-protected derivatives of baccatin III and 10-deacetyl-baccatin III (such as **3**) as key precursors (*5*), their semisynthetic work led to the

compounds act by promoting tubulin assembly into stable microtubules. Clinical trials of both taxoids are currently underway utilizing Cremophor EL-ethanol for paclitaxel and polysorbate for docetaxel as formulation solvents. Paclitaxel and docetaxel clinical activities have been reported against many types of tumors such as advanced breast, ovarian and non-small cell lung cancers (*3,9*). Paclitaxel has received FDA registration approval for the treatment of metastatic ovarian cancer and breast cancer after failure of first line therapy.

A wide number of analogs of docetaxel and paclitaxel have already been prepared by different pharmaceutical and academic groups (*10*). Furthermore, two total syntheses of paclitaxel by Nicolaou *et al.* (*11*) and by Holton *et al.* (*12*) have been very recently reported. These major achievements from these two groups not only illustrate the present know-how of organic chemists in synthesizing complex structures but also may open the way to new and thus far inaccessible analogs.

Structure-activity relationships

The structural differences between paclitaxel and docetaxel are a *tert*-butoxycarbonyl (Boc) group instead of a benzoyl group on the nitrogen atom at C-3' on the side chain and an hydroxyl function instead of an acetate at the 10-position of the diterpene moiety (figure 1). These structural modifications lead to an increase of cytotoxicity in certain experimental models (*13*). These results suggested the possibility of further improvement by introducing, for instance, new side-chain modifications.

Structure-activity relationships of taxoids have already been reviewed (*10*) and our present knowledge in this area can be outlined as depicted in figure 2. The C-13 phenylisoserine side-chain and the diterpene moiety of paclitaxel are both crucial for biological activity. Thus baccatin III and its derivatives without the phenylisoserine side-chain at C-13 are neither active in the tubulin assay nor cytotoxic (*14*).

Studies on the diterpene moiety showed that the oxetane ring is essential for biological activity (*15*). Structural and molecular modelling studies show that this 4-membered ring is involved in a conformational lock of the diterpene skeleton and the C-13 side-chain through a pseudo chair conformation of ring C (*6, 16*). Paclitaxel and docetaxel rearrangement products possessing contracted (*17*) or cleaved (*18*) A-rings are significantly less bioactive products. B-ring contracted analogs have been reported as maintaining antitumor activity (*19*). A wide number of modifications can be introduced at the 7-position without significant loss of activity as noted with epimerization and acylation (acetyl, glutaryl, phenylalanyl, alanyl, N,N-dimethyl-glycyl, etc.) products

Figure 1. Structures of docetaxel, paclitaxel and baccatin III derivatives.

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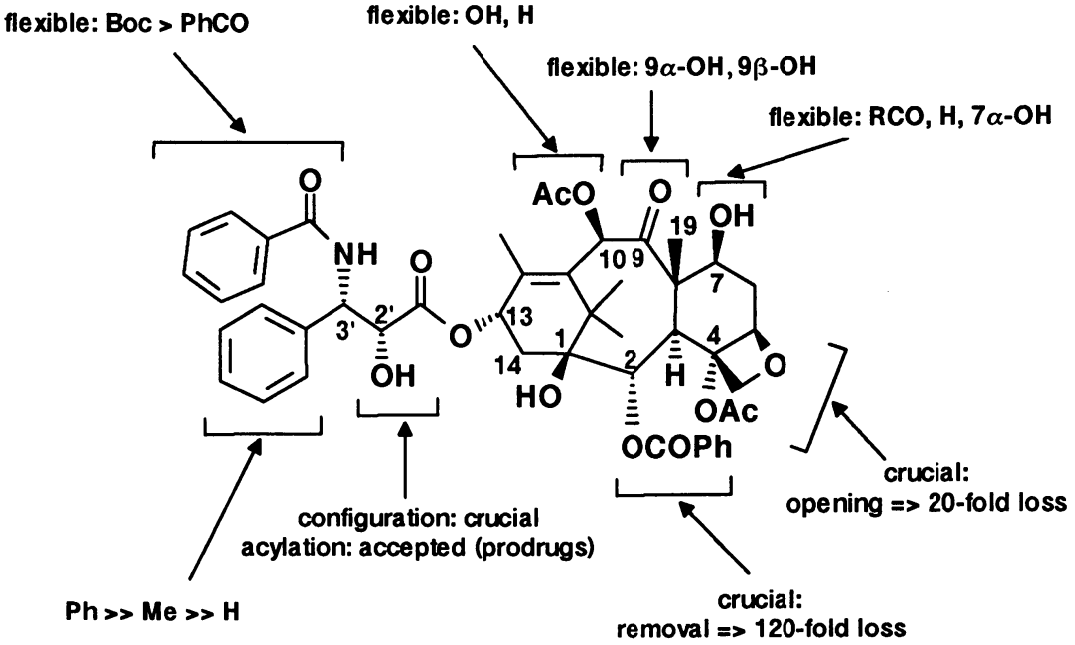
(*20*). All of these C-7-modified derivatives showed activity comparable to paclitaxel in the microtubule disassembly assay but have generally slightly reduced cytotoxicity. Oxidation at C-7 is known to reduce bioactivity (*21*). Interestingly enough, 7-deoxy-paclitaxel exhibited *in vitro* activity similar to paclitaxel while 7,10-dideoxy-paclitaxel proved to be slightly less cytotoxic (*22, 23*).

Figure 2. Modifications influencing the cytotoxicity of paclitaxel.



As reported by Klein with 9α-hydroxy-paclitaxel (*24*) and researchers at Rhône-Poulenc Rorer with 9α-and 9β-hydroxy-docetaxel (*25*), cytotoxicity of these reduced compounds is similar to paclitaxel and docetaxel respectively. Kingston *et al.* (*26*), Chen *et al.* (*27*), Holton *et al.* (*28*) as well as our own group (*25*) have all reported different approaches for preparing 10-deoxy-paclitaxel and 10-deoxy-docetaxel which were found to have comparable antitumor activity with respect to paclitaxel and docetaxel. Recently our group noted that 19-hydroxy-docetaxel, obtained from natural 10-deacetyl-19-hydroxy-baccatin III, has activity similar to docetaxel (*29*). Furthermore Chen *et al.* observed in the paclitaxel series an unprecedented rearrangement product possessing a cyclopropane moiety involving carbons C-7, C-8 and C-19 (*30*). This constrained analog of paclitaxel exhibits cytotoxicity equivalent to paclitaxel. Thus the top part of the diterpene moiety, that is positions 7, 9, 10 and 19, tolerate a wide variety of substituents. This allows us to assume that this region of taxoids may not play a

Perhaps more than anyone else, Potier, Guéritte-Voegelin, Guénard *et al.* have focused on the study of structure-activity relationships of side-chain modified taxoids (*34*).
They observed that the regio- and stereochemistry of each hetero atom at the 2'- and 3'-positions are crucial for retaining biological activity (*34*). The hydroxyl group at C-2' is critical since 2'-deoxy-paclitaxel is nearly 70-fold less cytotoxic than paclitaxel while isosteric 2'-deoxy-2'-fluoro-paclitaxel and 2'-O-methyl-paclitaxel proved to be nearly 100-fold and 200-fold less active respectively than the natural product (*35*). Introduction of an acyl group at 2' such as acetyl or hydrophilic acyl groups reduced activity in the tubulin assay but many of these derivatives retain activity *in vivo* or in cell-based assays since they are very likely to act as prodrugs (*36*). Replacement of the 3'-phenyl group of paclitaxel with methyl or hydrogen drastically lowers cytotoxicity (*34, 37*). The importance of an aryl group at C-3' was emphasized in Rhône-Poulenc Rorer (*38*) and Florida State University (*39*) patents as well as by the work of other groups (*40*) with the preparation of a wide number of very active analogs. Klein *et al.* (*19a*) observed that 3'-dephenyl-3'-isobutyl-9-dihydro-paclitaxel is highly cytotoxic, while Holton *et al.* patented 3'-dephenyl-3'-isobutenyl-paclitaxel (*41*) and 3'-dephenyl-3'-cyclohexyl-paclitaxel (*42*) as highly cytotoxic new taxoids. Our group (*43*) as well as Holton *et al.* (*39*) and more recently Georg *et al.* (*44*) reported that heteroaromatic groups at C-3' such as thienyl, furyl or pyridyl retain cytotoxicity.
Regarding modifications of the nitrogen atom at C-3', a free amino group as well as deletion of the amine function lead to less active analogs (*34*). Replacement of the 3'-benzoyl group of paclitaxel with other acyl groups such as tigloyl (cephalomanine), tosyl, butyryl and substituted benzoyl gives access to equally or less active compounds (*34, 45*) whereas introduction of a 3'-*tert*-butyloxycarbonyl substituent (docetaxel) leads to a more active compound in experimental models (*13*).
These preliminary results suggested that other modifications at C-3' might further improve the antitumor efficacy. We report herein some of our results regarding the stereoselective semisynthesis of docetaxel and new taxoids with either a 3'-modified-phenyl ring or a 3'-N-modified-carbamate moiety, along with their biological activity.

Chemistry.

Semisynthetic taxoid work has generated a demand for new stereoselective preparations of isoserine-type structures. This demand has been met during the last three years by a wide number of papers describing new approaches to phenylisoserinates or structurally related β-lactams (*46*). Our own efforts in this area have provided different stereoselective approaches.

Stereoselective approaches to 3'-modified-phenyl taxoids. Our first method used an

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