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Review

Taccalonolide microtubule stabilizers

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ABSTRACT

This review focuses on a relatively new class of microtubule stabilizers, the taccalonolides. The taccalonolides are highly oxygenated pentacyclic steroids isolated from plants of the genus *Tacca*. Originally identified in a cell-based phenotypic screen, the taccalonolides have many properties similar to other microtubule stabilizers. They increase the density of interphase microtubules, causing microtubule bundling, and form abnormal multi-polar mitotic spindles leading to mitotic arrest and, ultimately, apoptosis. However, the taccalonolides differ from other microtubule stabilizers in that they retain efficacy in taxane resistant cell lines and in vivo models. Binding studies with the newly identified, potent taccalonolide AJ demonstrated covalent binding to β-tubulin at or near the luminal and/or pore taxane binding site(s) which stabilizes microtubule protofilaments in a unique manner as compared to other microtubule stabilizers. The isolation and semi-synthesis of 21 taccalonolides helped to identify key structure activity relationships and the importance of multiple regions across the taccalonolide skeleton for optimal biological potency.

Contents

1. Introduction

Nature has provided a wide range of compounds that affect the mammalian cytoskeleton, including compounds that bind to tubulin and disrupt the structure and function of cellular microtubules. Microtubule disrupting agents have been isolated from a wide variety of sources, including marine sponges, mycobacteria, cyanobacteria, and plants. Moreover, new microtubule active compounds with significant biological activities continue to be discovered from nature. Plant-derived compounds that destabilize microtubules include the vinca alkaloids, colchicine and the com-

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bretastatins. The first microtubule stabilizer identified, taxol, was isolated from the bark of the Pacific Yew. Plants of the genus *Tacca* have a history of use in traditional medicines for a wide variety of ailments, and while the chemical structures of the taccalonolides were elucidated in the 1980's, their microtubule stabilizing and antitumor activities were only discovered in the last 10 years.

2. Chemical isolation and structure elucidation of natural taccalonolides A–Y

A compound named taccalin was initially isolated from the tubers of *Tacca leontopetaloides* by the Scheuer laboratory in 1963, but the structure was not solved.[1] Twenty-five years later, Chen's group isolated and elucidated the structures of the taccalonolides A and B from the rhizomes of *Tacca plantaginea*.[2] The taccalonolide backbone consists of a highly oxygenated pentacyclic steroidal skeleton which contains a C2–C3 epoxide group and an enol-γ-lactone. Other natural taccalonolides were isolated by various laboratories from 1987 to 2008, including the taccalonolides A–M[2–6] and W–Y[7] from *Tacca plantaginea*, taccalonolides N[8] and R–V[9] from *Tacca paxiana*, and taccalonolides O–Q from *Tacca subflabellata*.[10,11] Only the taccalonolides A and G–K were reported to exhibit weak cytotoxic activity against P-388 leukemia cells in vitro.

3. Identification of the taccalonolides A and E as microtubule stabilizers

The ability of *Tacca chantrieri* extracts to cause bundling of interphase microtubules was discovered in a cell-based screen of crude extracts. Bioassay-guided fractionation led to the isolation of taccalonolides A and E, the most abundantly occurring secondary metabolites, as new microtubule stabilizers.[12] The highly acetylated pentacyclic skeleton of the taccalonolides makes them structurally distinct from all other microtubule stabilizers. The only structural difference between the taccalonolides A and E is the lack of an acetoxy group at C11 in taccalonolide E (Fig. 1).[12] Taccalonolides A and E cause bundling of interphase microtubules and mitotic arrest of cancer cells with multiple aberrant spindles that initiate apoptosis in a manner similar to paclitaxel.[12] However, the taccalonolides retain efficacy in cells containing mutations in the paclitaxel binding site as well as those expressing P-glycoprotein (Pgp),[12] a drug efflux pump which contributes to the clinical resistance of paclitaxel and docetaxel.[13,14] Additional studies with the taccalonolides A and E, as well as the semi-synthetic derivatives B and N, demonstrated their ability to overcome resistance due to expression of Pgp, the βIII-isotype of tubulin or the MRP7 drug efflux transporter.[15] Most importantly, the taccalonolides A and E were found to have excellent in vivo antitumor activity in a Pgp-expressing, paclitaxel and doxorubicin resistant syngeneic mammary tumor model.[15] Although the in vitro antiproliferative potencies of the taccalonolides A, E and N were at least 100-fold lower than paclitaxel, antitumor trials demonstrated that they had unexpectedly high in vivo potency comparable to or better than paclitaxel.[15,16] Thus, in spite of the low in vitro potencies of taccalonolides A and E, their excellent in vivo potency and efficacy coupled with their ability to overcome taxane resistance prompted further interest in this class of stabilizers.

Studies were conducted to identify the mechanism of microtubule stabilization of the taccalonolides A and E. Surprisingly, in a comprehensive study of 19 structurally diverse agents that were reported to have microtubule stabilizing activity, Buey and colleagues found that the taccalonolides A and E were unable to interact directly with microtubules or to enhance the polymerization of purified tubulin.[17] Furthermore, taccalonolide A was unable to enhance the polymerization of tubulin even in cellular extracts that contained a full complement of cytosolic proteins.[18] These initial studies suggested that the taccalonolides A and E stabilize microtubules in cells independently of direct microtubule binding. However, later studies showed that the significantly more potent taccalonolides, AF and AJ, directly interacted with microtubules.[19] It is interesting to speculate that the taccalonolides A and E are

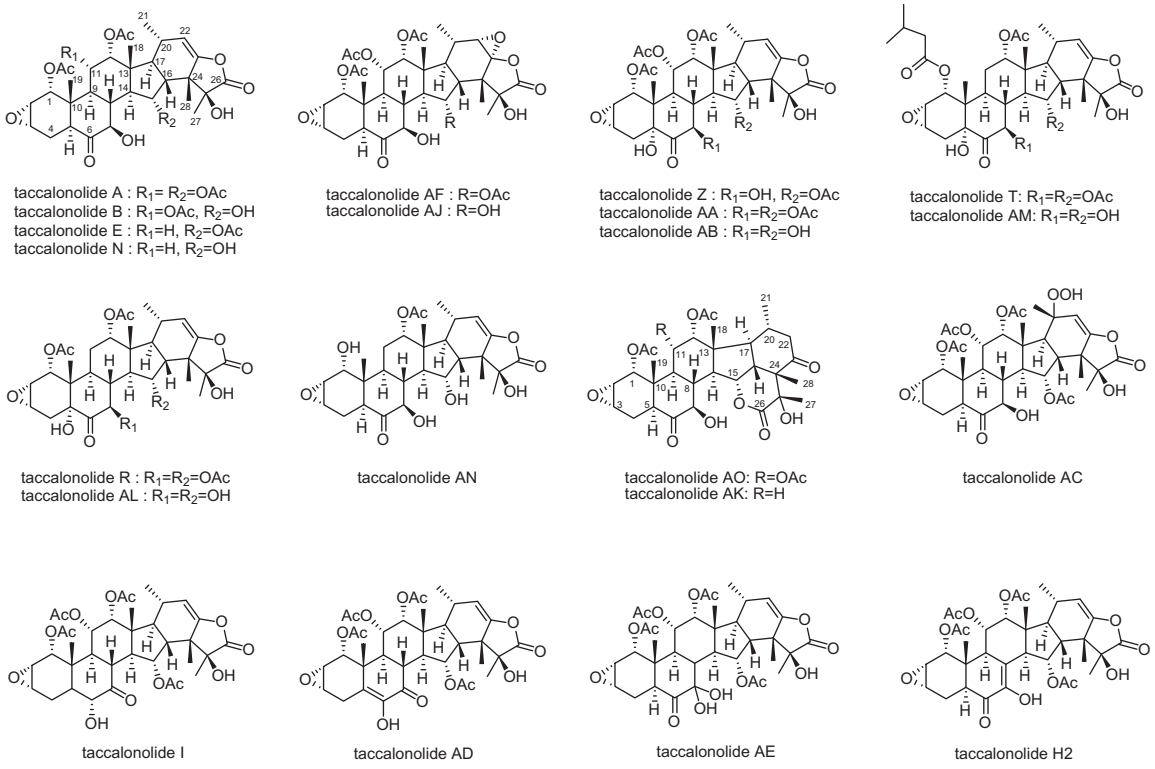

Figure 1. The Structures of taccalonolides described in this study.