Biologically Active Diterpenoids: Synthesis of Anlogues of Paclitaxel and Resiniferatoxin

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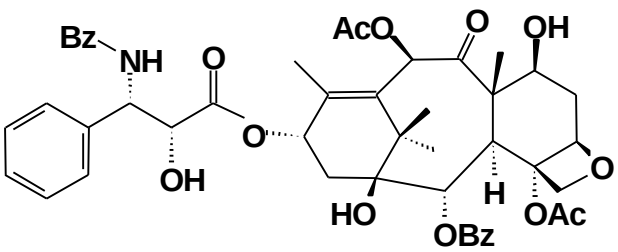
Natural products are an important source of probes to investigate biological processes at the molecular level. In this context, paclitaxel (Taxol®, **1**) and resiniferatoxin (RTX, **2**) are preeminent examples for their unique mechanism of activity and great pharmacological potential. Paclitaxel is an anticancer drug, approved by FDA for the treatment of ovarian, breast, and lung cancer. RTX is undergoing clinical trials to relieve pain associated with diabetic neuropathy, and to control the bladder hyperreflexia underlying urinary incontinence. In both cases, the pharmacophore is still ill-defined, and the modification of the natural products is important to further our knowledge of structure-activity relationships. This might eventually lead to the design of structurally simplified and totally synthetic analogues with a better pharmacological profile.

Two series of novel paclitaxel analogues (*C*-secotaxols and pyrazolinetaxols) were prepared exploiting the nucleophilic trapping of the *C*-seco aldehydic tautomer of taxanes of the 10-deacetyl-10-dehydrobaccatin III-type. As an example of utilization of alkaloidal left-overs from yew biomass, the synthesis of taxoids with potential dual target specificity (β-tubulin and P-gp) is presented. Finally, the design and synthesis of compounds where structural elements of the pharmacophore of capsaicin- and RTX are implanted on phorbol is discussed. These pharmacological hybrids displayed a unique pattern of biological activity, and proved useful to dissect receptor subclasses of the vanilloid receptor.



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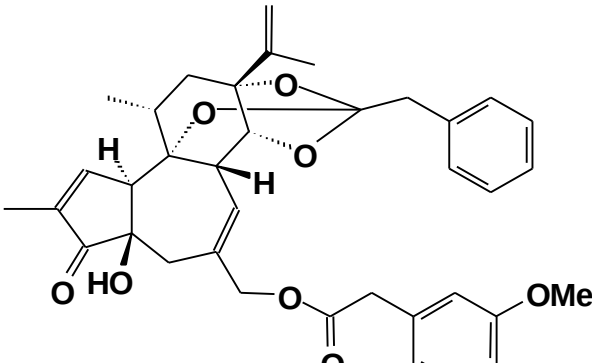

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