

Stony Brook University The Graduate School

Doctoral Defense Announcement

Abstract

Design, Synthesis, Biological Evaluation and Molecular Modeling of Novel Taxane-Based Anticancer Agents and Paclitaxel mimics

By

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Paclitaxel (Taxol[®]) is one of the most important anticancer drugs currently used in cancer chemotherapy. Paclitaxel binds to the β -tubulin portion of the α,β -tubulin dimer, promotes the polymerization of tubulins, stabilizes microtubules, and blocks microtubular dynamics, which eventually leads to apoptosis. However, paclitaxel has a number of undesirable side effects as well as multidrug resistance (MDR). The development of new-generation taxoids with higher potency, and better pharmacological properties could overcome the problems.

Second-generation taxoids were designed and synthesized with modifications at the C-10, C-3' and C-2 positions. These taxoids exhibit one to three orders of magnitude higher potency than paclitaxel against various cancer cell lines, including multidrug resistant cell lines. A series of C-seco taxoids with different functional groups at the C2 and C3' positions were synthesized, which exhibited much higher activity than paclitaxel against various drug-resistant cell-lines, overexpressing specific tubulin isotypes.

Based on the REDOR-NMR experiment as well as molecular modeling and molecular dynamics studies, we proposed a new biologically active conformation of paclitaxel — “REDOR-Taxol”. Based on the “REDOR-Taxol” structure, conformationally restricted macrocyclic taxoids bearing various linkers connecting different positions of the taxoid framework were synthesized and their biological activities evaluated. One of the macrocyclic taxoids, SB-T-2054, showed similar or slightly better activity in cytotoxicity and tubulin polymerization assay to that of paclitaxel, which strongly supports that the “REDOR-Taxol” structure is a valid binding structure, i.e., bioactive conformation, in tubulin/microtubule.

Novel baccatin-free anticancer agents, mimicking paclitaxel, with a tricyclic scaffold were designed and synthesized based on the “REDOR-Taxol” structure. The fused 5-6-6/5-7-6 tricyclic scaffolds were synthesized from a hydroxyproline derivative. These paclitaxel mimics exhibited moderate cytotoxicity

Docosahexanoic acid (DHA), linolenic acid (LNA) and linoleic acid (LA) were linked to the C2'-position of the second-generation taxoids. The new conjugates, assayed *in vivo*, exhibited highly promising antitumor activity against drug-resistant colon cancer xenograft (DLD-1) as well as drug-sensitive ovarian cancer xenograft (A121) in nude mice.

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Dissertation Advisor: Professor Iwao Ojima