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Antitumor Agents. 284. New Desmosdumotin B Analogues with Bicyclic B-Ring as Cytotoxic and Antitubulin Agents

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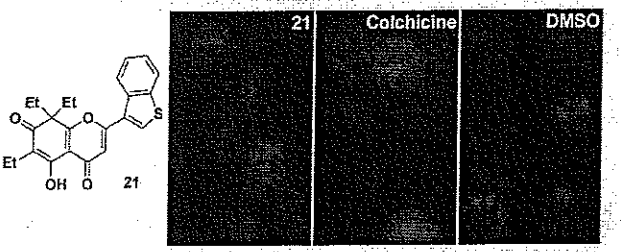
Supporting Information

ABSTRACT: We previously reported that the biological activity of analogues of desmosdumotin B (1) was dramatically changed depending on the B-ring system. A naphthalene B-ring analogue 3 exerted potent in vitro activity against a diverse panel of human tumor cell lines with GI_{50} values of 0.8−2.1 μM. In contrast, 1 analogues with a phenyl B-ring showed unique selective activity against P-glycoprotein (P-gp) overexpressing multidrug resistant cell line. We have now prepared and evaluated 1 analogues with bicyclic or tricyclic aromatic B-ring systems as in vitro inhibitors of human cancer cell line proliferation. Among all synthesized derivatives, **21** with a benzo[*b*]thiophenyl B-ring was highly active, with GI_{50} values of 0.06−0.16 μM, and this activity was not influenced by overexpression of P-gp. Furthermore, **21** inhibited tubulin assembly in vitro with an IC_{50} value of 2.0 μM and colchicine binding by 78% as well as cellular microtubule polymerization and spindle formation.



INTRODUCTION

We previously reported that desmosdumotin B (**1**, Figure 1) exerted selective inhibition of a P-glycoprotein (P-gp) overexpressing multidrug resistant (MDR) tumor cell line with significantly lower activity against non-MDR tumor cells.[1] The observed selectivity index [collateral sensitivity (CS),[2] activity ratio of MDR line versus non-MDR line] was greater than 20. This selective in vitro antitumor activity was further enhanced by replacing the three methyl groups at C-6 and C-8 with ethyl groups (**2**, Figure 1) and also by adding an alkyl group at the C-4′ position. During this study, we also found that analogues in which the phenyl B-ring was replaced with a naphthyl moiety (**3**, Figure 1) had dramatically different activity profiles, displaying strong cytotoxicity against multiple cancer cells, regardless of MDR expression, with GI_{50} values of 0.8−2.1 μM. Thus, placing a larger, more electron-rich aromatic B-ring at C-2 resulted in broader antiproliferative activity and loss of specific activity against the MDR cell line. These compounds also induced rapid cell rounding without immediate detachment, leading us to hypothesize antitubulin activity as a mechanism of action, which was tested and confirmed using biochemical assays. Compound **3**, therefore, represents a new scaffold for targeting tubulin assembly.

Design and synthesis of compounds targeting the microtubule constitute an attractive strategy for the discovery of new antitumor agents.[3] The microtubule network is an essential component of the cytoskeleton, and its timely depolymerization and repolymerization are critical for the cell to construct a functional mitotic spindle. Typically, cells arrested in apparent mitosis eventually undergo apoptosis. Antimitotic agents targeting tubulin are generally classified into two groups, compounds that either stimulate or inhibit microtubule assembly, depending on their effects on the tubulin-microtubule equilibrium. Taxoids and epothilones are well-known enhancers of microtubule polymerization.

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