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Antitumor Agents. 280. Multidrug Resistance-Selective Desmosdumotin B Analogues

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6,6,8-Triethyldesmosdumotin B (**2**) was discovered as a MDR-selective flavonoid with significant in vitro anticancer activity against a multidrug resistant (MDR) cell line (KB-VIN) but without activity against the parent cells (KB). Additional **2** analogues were synthesized and evaluated to determine the effect of B-ring modifications on MDR-selectivity. Analogues with a B-ring Me (**3**) or Et (**4**) group had substantially increased MDR selectivity. Three new disubstituted analogues, **35**, **37**, and **49**, also had high collateral sensitivity (CS) indices of 273, 250, and 100, respectively. Furthermore, **2**–**4** also displayed MDR selectivity in an MDR hepatoma-cell system. While **2**–**4** showed either no or very weak inhibition of cellular P-glycoprotein (P-gp) activity, they either activated or inhibited the actions of the first generation P-gp inhibitors verapamil or cyclosporin, respectively.

Introduction

Incidences of drug resistance still present major and serious obstacles to the effective chemotherapeutic treatment of cancer, despite many efforts to overcome it.[1,2] Resistance to one drug often implies simultaneous resistance to structurally and mechanistically diverse anticancer drugs. This efflux phenotype, called multidrug resistance (MDR[a]),[3,4] is in part mediated by the overexpression of plasma membrane transporters, such as P-glycoprotein (P-gp, MDR1, or ABCB1, localized at 7q21.1, a 170 kDa protein),[5] MDR-associated proteins (MRP1 or ABCC1, localized at 16p13.1, a 190 kDa protein, and MRP2),[6] or breast cancer resistant protein (BCRP or ABCG2, localized at 4q22, a 72 kDa protein).[7−9] These three kinds of proteins belong to the superfamily of ATP-binding-cassette (ABC) transporters.[10] The emergence of MDR pumps causes cancer drugs to be pumped out of the cell, thus reducing intracellular drug concentrations below cytotoxic levels. Because P-gp has broad substrate specificity, tumor cells that overexpress P-gp show resistance to many classical and newer molecular-targeted antitumor drugs. The development of agents targeted toward MDR1 or MRP1 is greatly needed in order to improve anticancer chemotherapeutic strategies. MDR1/P-gp is a well-characterized efflux system and a major mediator of MDR.[11−14] Intrinsic or acquired overexpression of P-gp dramatically reduces drug response, at times to less than one-quarter, causing poor clinical outcomes following chemotherapy.[15]

To date, the major pharmacological approaches to overcome MDR have focused on inhibition of the pump function and/or down-regulation of pump overexpression.[16−19] Numerous pump inhibitors (or modulators) have been found and are generally classified as first, second, or third generation chemosensitizers. Many second and third generation inhibitors, such as valspodar, zosuquidar, and tariquidar, are more potent and less toxic than first generation compounds like verapamil (VERAP) or cyclosporine A (CSA). Although some of these new generation compounds are still in clinical trials, the benefits of chemosensitization remain disappointing in part because the modulator causes undesirable changes in drug pharmacokinetics.[20]

Flavonoids are the most widespread natural compounds produced in plants, and they exhibit diverse, important biological activities, including antioxidant, anticarcinogenic, anti-inflammatory, antiproliferative, antiangiogenic, and antiestrogenic effects.[21] Many reports have demonstrated that flavonoids can also interact with ABC transporters, and some act as P-gp modulators.[22−25] We found that the flavonoid desmosdumotin B (**1**, Figure 1) exerted unique in vitro anticancer activity against a P-gp expressing MDR tumor cell line (KB-VIN, ED_{50} = 2.0 μg/mL), resulting in a >20 fold index of selectivity over the drug sensitive KB parent cell line.[26] We also discovered that 6,8,8-triethyldesmosdumotin B (TEDB, **2**) and its 4′-methyl (**3**) and 4′-ethyl (**4**) analogues were significantly more potent and showed MDR-selectivity of >250.[27] In contrast, the related 6,8,8-tripropyl and 6,8-diethyl compounds were less optimized for MDR selectivity.

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[a]Abbreviations: ABC, ATP-binding-cassette; ArCHO, substituted benzaldehyde; BCRP, breast cancer resistant protein; CS, collateral sensitivity; CSA, cyclosporine A; MDR, multidrug resistance/resistant; NCI, National Cancer Institute; P-gp, P-glycoprotein; SAR, structure–activity relationship; TEDB, 6,8,8-triethyldesmosdumotin B; VERAP, verapamil

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