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Antitumor Agents 286. Design, Synthesis, and Structure–Activity Relationships of 3′*R*,4′*R*-Disubstituted-2′,2′-dimethyldihydropyrano[2,3-*f*]chromone (DSP) Analogues as Potent Chemosensitizers to Overcome Multidrug Resistance

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In this study, various 3′*R*,4′*R*-disubstituted-2′,2′-dimethydihydropyrano[2,3-*f*]chromone (DSP) derivatives were discovered as potent chemosensitizers in the treatment of multidrug resistant cancer cells. Twenty-four DSP analogues (**5**–**28**) were synthesized and evaluated against a multidrug resistant (MDR) cell line (KB-Vin) with and without vincristine (VCR). All DSP analogues exhibited low intrinsic cytotoxicity. However, in combination treatment, most DSPs reversed resistance to VCR and lowered the GI_{50} value of VCR by 12–349-fold. At a concentration of 1 μg/mL, three compounds, **11**, **14**, and **21**, fully reversed resistance to VCR in KB-Vin cancer cells, a 2-fold increase compared to verapamil, a first-generation chemosensitizer. Detailed structure–activity relationship (SAR) conclusions were established based on 3′ and 4′ substitutions. Moreover, a preliminary mechanism study indicated that the chemosensitizing activity of DSP analogues results from inhibition of P-glycoprotein (P-gp) overexpressed in MDR cancer cells.

Introduction

Resistance of cancer cells to anticancer drugs remains one of the major obstacles in achieving an effective treatment for cancer. Three primary mechanisms of anticancer drug resistance have been identified: decreased uptake of water-soluble drugs, various changes in cells that affect the capacity of cytotoxic drugs to kill cells, and the most commonly encountered, increased energy-dependent efflux of hydrophobic cytotoxic drugs by one of a family of energy-dependent transporters, such as P-gp (also known as MDR1[a]).[1] One approach used in clinical research to reverse MDR is the development of chemosensitizers, especially drugs that target P-gp and inhibit its activity. Verapamil and cyclosporine A (Figure 1) are examples of first-generation chemosensitizers that inhibit the activity of P-gp and were evaluated clinically as adjuvants for chemotherapy. Both compounds are able to increase the intracellular concentration of cytotoxic agents, such as VCR, cyclophosphamide, dexamethasone, and doxorubicin, in MDR cells.[2,3] Moreover, both verapamil and cyclosporine A are widely used medications, verapamil as a calcium channel blocker to treat hypertension and cyclosporine A as an immunosuppressant to reduce the activity of the patient's immune system in postallogeneic organ transplant. However, clinical studies showed that both compounds were generally toxic at the doses required to attenuate P-gp function.[4] Since then, several potent and selective next-generation inhibitors have been developed and investigated, but none of them have yet shown significant clinical benefit. Inhibition of P-gp by chemosensitizers may also be problematic because drug distribution and elimination can be affected by these agents.[4,5] However, it is still possible that the ideal chemotype for a chemosensitizer has yet to be identified and developed.

It has been reported that the naturally existing pyranocoumarin (±)-praeruptorin A (PA) and its khellactone analogues with 3′,4′-modifications (Figure 2) can reverse P-gp-mediated MDR.[6,7] (±)-3′-*O*-4′-*O*-Bis(3,4-dimethoxycinnamoyl)-*cis*-khellactone (DMDCK, **3**) showed the highest potency among these analogues. At a concentration of 4 μM, **3** was able to increase the activity of the chemotherapy drug vinblastine over 110-fold.[7] However, even at such a high concentration, **3** was unable to completely reverse vinblastine resistance in the liver cancer cell system used.[7] In addition, it was also reported that the side chains at the 3′ and 4′ positions of the khellactone system play an important role in maintaining high activity. Unfortunately, only a few khellactone analogues with 3′,4′ modifications have been reported to show potent chemosensitizing activity, so detailed SAR information is unavailable. Therefore, continuing research to develop novel active analogues is merited and forms the basis for the work on the DSP series reported herein.

Design

Even before the structure of P-gp protein was resolved,[8] a general pharmacophore model for P-gp binding and inhibition

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[a]Abbreviations: DSP, 3′*R*,4′*R*-disubstituted-2′,2′-dimethyldihydropyrano[2,3-*f*]chrmone; MDR, multidrug resistance; VCR, vincristine; P-gp, P-glycoprotein; PA, (±)-Praeruptorin A; DMDCK, (±)-3′-*O*-4′-*O*-bis(3,4-dimethoxycinnamoyl)-*cis*-khellactone; HB, hydrogen bond.

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