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Dibenzocyclooctadiene lignans — A class of novel inhibitors of multidrug resistance-associated protein 1

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Abstract

We recently reported that dibenzocyclooctadiene lignans were a novel class of P-glycoprotein (P-gp) inhibitors. In this study, we demonstrated that the lignans of this class were also effective inhibitors of multidrug resistance-associated protein 1 (MRP1). The activities of 5 dibenzocyclooctadiene lignans (schisandrin A, schisandrin B, schisantherin A, schisandrol A, and schisandrol B) to reverse MRP1-mediated drug resistance were tested using HL60/Adriamycin (ADR) and HL60/Multidrug resistance-associated protein (MRP), two human promyelocytic leukemia cell lines with overexpression of MRP1 but not P-gp. The five lignans could effectively reverse drug resistance of the two cell lines to vincristine, daunorubicin, and VP-16. This study, together with our previous reports, proves that dibenzocyclooctadiene lignans have multiple activities against cancer multidrug resistance, including inhibition of P-gp and MRP1, and enhancement of apoptosis. Considering that cancer multidrug resistance (MDR) is multifactorial, agents with broad activities are preferable to the use of combination of several specific modulators to prevent drug–drug interaction and cumulative toxicity.

Keywords: Dibenzocyclooctadiene; Cancer multidrug resistance; Multidrug resistant associated protein 1

Introduction

Cancer multidrug resistance (MDR) is one of the major obstacles for the success of chemotherapy. Although there are many mechanisms of cancer MDR, overexpression of P-glycoprotein (P-gp, ABCB1) and multidrug resistance-associated protein 1 (MRP1, ABCC1), defective signaling in the apoptotic pathways and overexpression of anti-apoptotic proteins, account for most of the clinical cancer MDR (Gottesman et al., 2002; Loe et al., 1996; Pommier et al., 2004; Varadi et al., 2002).

P-gp is a transmembrane protein and functions as an ATP-dependent drug transporter which unilaterally transports the intracellular drugs out of the cells (Schinkel and Jonker, 2003; Gottesman and Pastan, 1993; Cole et al., 1992). Thus, the intracellular drugs in the MDR cancer cells are kept at sub-lethal level, and cancer cells evade the effective attack by the anticancer drugs. P-gp demonstrates a broad spectrum of substrate specificities toward vinca alkaloids, anthracyclines, taxanes, and epipodophylotoxins, among others, and is responsible for the intrinsic and acquired drug resistance in numerous human cancers (Endicott and Ling, 1989; Herzog et al., 1993; Ling, 1997). Like P-gp, MRP1 is also an ATP-dependent drug transporter. Unlike P-gp, which transports relatively hydrophobic substrates, MRP1 targets relatively hydrophilic molecules, organic anions, glutathione conjugates, glucuronides, and sulfates (Schinkel and Jonker, 2003; Campling et al., 1997; Hipfner et al., 1999). In addition, numerous reports have revealed that drug resistance of cancer cells could be acquired from other mechanisms, such as the defective signaling of apoptotic pathways or overexpression of anti-apoptotic proteins such as Bcl-2 (Palissot et al., 2005).

Pharmacological approaches to overcome cancer MDR are to use specific agents targeting P-gp or/and MRP1. To date,

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while several P-gp inhibitors have entered clinical trials, MRP1 inhibitors with high efficacy and safety remain an issue to solve. Recently, several P-gp inhibitors were found to cross-react with MRP1; among these, VX-710 (a pipecolinate derivative) and MS-209 (a quinoline derivative) are of particular interest (Minderman et al., 2004a,b; Narasaki et al., 1997; Robert and Jarry, 2003). Considering the multifactorial nature of cancer MDR, the MDR inhibitors with broad specificity are apparently preferable to the use of combination of several specific modulators as this will reduce the risk of drug–drug interaction and cumulative toxicity (Minderman et al., 2004a,b).

In screening of the naturally occurring compounds with potential activities against multiple targets related to cancer MDR, we found that schisandrin B, the most abundant dibenzocyclooctadiene lignan present in *Schisandra chinensis* (Turcz.) Baill, was a relatively potent inhibitor of P-gp (Qiangrong et al., 2005). We further proved that this compound could also reverse MRP1-mediated MDR (Sun et al., 2006). In addition, this compound could enhance anticancer drug-induced apoptosis in cancer cells but not normal cells, through a mechanism not associated with P-gp or MRP1, but related to an enhanced activation of mitochondrial apoptotic pathways

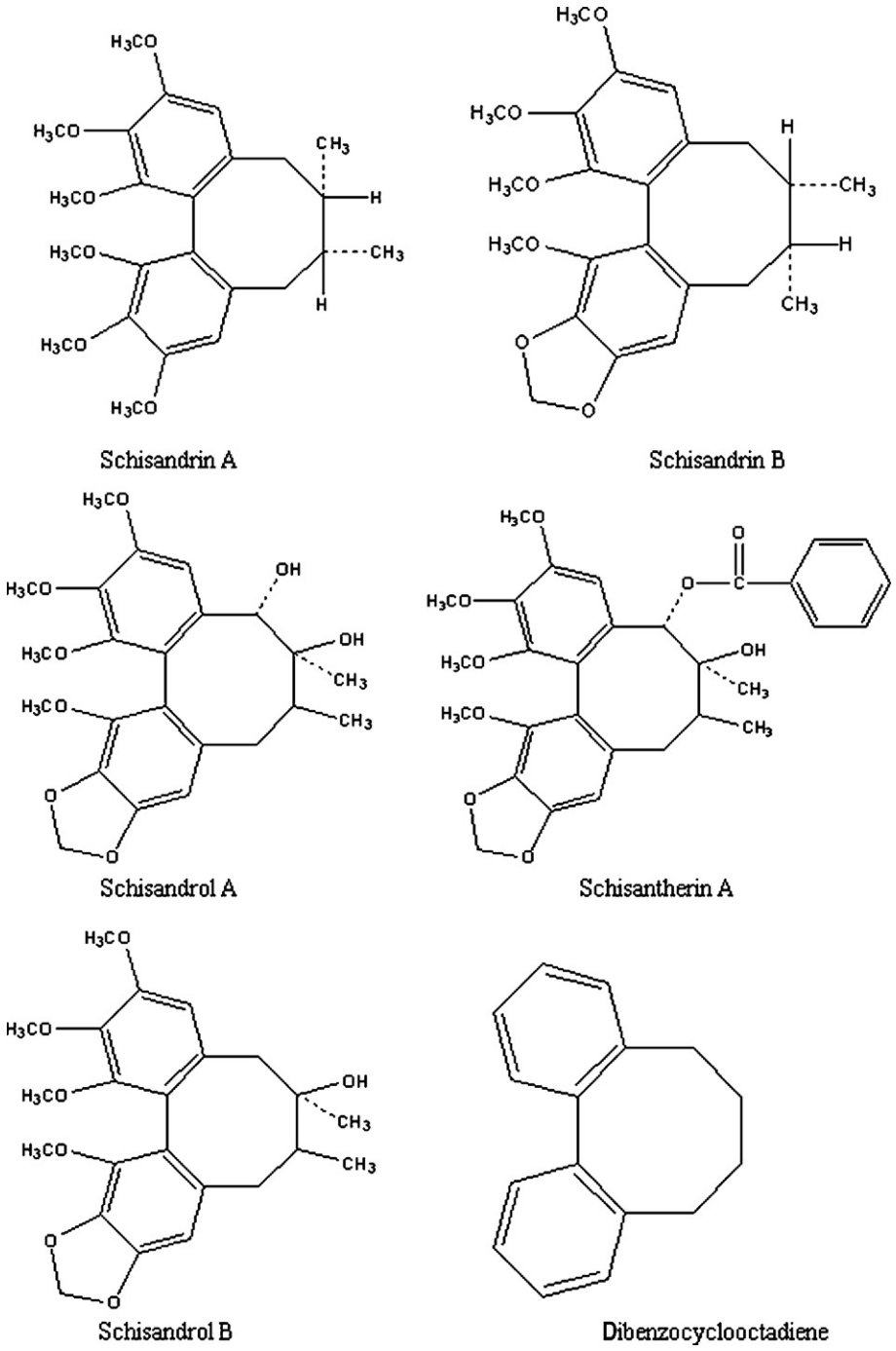

Fig. 1. The structures of five lignans and dibenzocyclooctadiene.