Antitumor Agents 291 Expanded B-Ring Modification Study of 6,8,8-Triethyl Desmosdumotin B Analogues as Multidrug-Resistance Selective Agents

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Abstract

Drug usefulessness frequently obstructed by the incidence of the multidrug resistance (MDR) phenotype and severe adverse effects. Exploiting collateral sensitive (CS) agents (in this case also called MDR-selective agents), which selectively target only MDR cells, is an emerging and novel approach to overcome MDR in cancer treatment. Prior to our studies, we found that 4'-methyl-6,8,8-triethyldesmosdumotin B (4'-Me-TEDB, 2) is an MDR-selective synthetic flavonoid with significant in vitro anticancer activity against a MDR cell line (KB-Vin) but without activity against the parent cells (KB) as well as other non-MDR tumor cells. Our recent results suggest the absolute MDR-selectivity varies depending on the cell-line system. In order to explore this further and to better understand the critical pharmacophores, we have synthesized nine novel analogues of 2, which contain heteroaromatic as well as acyclic alkyl B-rings. The new compounds were evaluated for cytotoxicity to explore the effect of B-ring modifications on MDR-selectivity. All analogues, except 7, 9 and 10, were identified as significant MDR-selective compounds. This observation solidifies the importance of the 5-hydroxy-6,8,8-triaryl-4H-chromene-4,7(8H)-dione skeleton (AC-ring system) for the pharmacological activity and establishes the B-ring as less critical for the broader spectrum MDR-selectivity. Notably, 5-furanyl (3) and 2-thiophenyl (6) analogues displayed substantial MDR–selectivity with KB/KB-Vin ratios of >12 and 16, respectively. Furthermore, 3 and 6 also exhibited MDR–selectivity in a second set of paired cell lines, the MDR/non-MDR hepatoma-cell system. Interestingly, a cyclohexyl analogue (11) showed moderate inhibition of A549, DU145, and PC-3 cell growth, while the other compounds were inactive. These new findings are discussed in terms of current understanding of mechanism and structure–activity relationship (SAR) of our novel MDR-selective flavonoids.

Keywords: Triethylidesmosdumotin B; Multi-drug resistance; MDR-selectivity (collateral sensitivity); Heteroaromatic ring; Cycloalkyl ring

Abbreviations: TEDB: 6,6,8-Triethyldesmosdumotin B; MDR: multi-drug resistance/resistant; CS: Collateral sensitivity; P-gp: P-glycoprotein; SAR: Structure–activity relationship

Introduction

While chemotherapy is a valuable cancer treatment, its usefulness is frequently obstructed by the incidence of the multidrug resistance (MDR) phenotype and severe adverse effects [1,2]. MDR in tumor cells is often correlated with the overexpression of P-glycoprotein (P-gp, MDR1) [3], which belongs to the superfamily of ATP-binding-cassette (ABC) transporters [4,5,6]. Resistance to one drug often implies simultaneous resistance to structurally and mechanistically diverse anticancer drugs. The emergence of MDR causes cancer drugs to be pumped out of the cell, thus reducing intracellular drug concentrations below cytotoxic levels. The current major pharmacological approaches to overcome MDR have focused on inhibition of the pump function, and/or down-regulation of pump over-expression or developing cancer drug candidates that are not pump substrates [7-10]. Many compounds have been identified as MDR (P-gp) inhibitors (or modulators), and are generally classified as first, second, or third generation chemosensitizers. Third-generation agents, such as tariquidar, zosuquidar, and triaryl imidazole ONT-093 have shown improved efficacy compared with early generation compounds, as well as higher potency and specificity for P-gp [11]. These compounds are currently in clinical trials; however, phase III trials with some of these agents have not been successful [12]. In addition, significant survival benefits using a P-gp inhibitor has yet to be demonstrated despite considerable efforts [13].

Because no chemotherapy is yet available to sufficiently overcome MDR phenotype, new agents possessing antitumor activity and unaffected by the MDR phenotype, which exploit the drug efflux phenomenon, are in high demand and would be valuable additions to the arsenal of new antitumor drugs. We are interested in both approaches and this report focuses on the latter-type, the hypersensitivity of drug-resistant cancer cells to certain drugs, which selectively kill MDR cells relative to the non-MDR parental cells, is a specific type of “collateral sensitivity” (CS) [14]. Exploiting CS agents is an exciting emerging approach to overcome MDR in cancer. For example, a thiosemicarbazone derivative (NSC73306) was discovered as a CS agent through the US National Cancer Institute (NCI) anticancer drug screen as a drug lead for targeting MDR tumor cell populations [15]. Although this compound was toxic toward a diverse panel of P-gp-expressing tumor cell lines, its highest selectivity ratio [IC50 (non-MDR)/IC50 (MDR)] was 7.3 (KB-3-1/KB-V1) [16].

We previously reported the structurally unusual flavonoid,
desmosdumotin B (1), as a MDR CS agent with selectivity ratio of >20 (KB/KB-Vin) [17]. Further modification of I revealed that active compounds containing both a trialkylated non-aromatic A-ring and a 6-nitro electronic B-ring inhibited only MDR-tumor cell growth. Compounds combining the same B-ring and a 10π electronic B-ring exhibited potent cytotoxicity against multiple tumor cells, acting at least in part by inhibition of tubulin [18]. 4′-Methyl-6,6,8-triyldesmosdumotin B (4′-Me-TEDB) was chromatographed on silica gel sheets (Kieselgel 60 F-254). Isco Companion layer chromatography (TLC) was carried out on Merck precoated reference to the residual solvent peak, chemical shifts δ in ppm, ice-cold 1 NHCl, and then extracted with CH2Cl2. The extract was washed with brine, dried over Na2SO4 and concentrated in vacuo. The residue was chromatographed on silica gel eluting with EtOAc–hexane (1:4) to obtain the target compound (3–9).

2-(Furan-3′-y1)-TEDB (3): Pale yellow prisms, mp 195–196 °C (EtOAc-hexane). 1H NMR (400 MHz, CDCl3) δ 13.05 (s, 1H, 5-OH), 7.95 (dd, 1H, δ = 1.3 and 3.0 Hz, 2′-H), 7.54 (dd, 1H, δ = 3.0 and 5.1 Hz, 5″-H), 7.54 (dd, 1H, δ = 1.3 and 5.1 Hz, 4″-H), δ 6.73 (s, 1H, 3-H), 2.45 (q, 2H, δ = 7.4 Hz, 6-CH2CH2), 2.31-2.19 (m, 2H, 8-CH2CH2), 1.04 (t, 3H, δ = 7.4 Hz, 6-CH2CH3), 0.67 (t, 6H, δ = 7.4 Hz, 8-CH2CH3) MS (ESI+ m/z): 328 (M+). Anal. Calc. for C27H22O6S: C, 57.86; H, 4.31. Found: C, 57.85; H, 4.30.

2-(Pyridin-3′-yl)-TEDB (9): Pale yellow prisms, mp 196–197 °C (EtOAc-hexane). 1H NMR (400 MHz, CDCl3) δ 13.03 (s, 1H, 5-OH), 7.70-7.63 (m, 2H, 3′- and 4′-H), 7.07 (dd, 1H, δ = 3.4 Hz, 3″-H), 6.78 (s, 1H, 3-H), 6.65 (dd, 1H, δ = 1.7 and 3.4 Hz, 4″-H), 2.44 (q, 2H, δ = 7.4 Hz, 6-CH2CH2), 2.27-2.21 (m, 2H, 8-CH2CH2), 1.98-1.86 (m, 2H, 8-CH2CH3), 1.03 (t, 3H, δ = 7.4 Hz, 6-CH2CH3), 0.66 (t, 6H, δ = 7.4 Hz, 8-CH2CH3) MS (ESI+ m/z): 344 (M+). Anal. Calc. for C29H24O6S: C, 65.69; H, 4.14; Found: C, 65.41; H, 5.56.

2-(Thiophen-3′-yl)-TEDB (4): Pale yellow prisms, mp 183–184 °C (EtOAc-hexane). 1H NMR (400 MHz, CDCl3) δ 13.06 (s, 1H, 5-OH), 7.69 (dd, 1H, δ = 0.5 and 1.7 Hz, 5″-H), 7.07 (dd, 1H, δ = 3.4 Hz, 3″-H), 6.78 (s, 1H, 3-H), 6.65 (dd, 1H, δ = 1.7 and 3.4 Hz, 4″-H), 2.44 (q, 2H, δ = 7.4 Hz, 6-CH2CH2), 2.27-2.21 (m, 2H, 8-CH2CH2), 1.98-1.86 (m, 2H, 8-CH2CH3), 1.04 (t, 3H, δ = 7.4 Hz, 6-CH2CH3), 0.68 (t, 6H, δ = 7.4 Hz, 8-CH2CH3) MS (ESI+ m/z): 328 (M+). Anal. Calc. for C29H22O6S·1/2H2O: C, 64.57; H, 5.99. Found: C, 64.75; H, 5.69.

3-Pyridinecarbaldehyde was used as the aromatic aldehyde, Ba(OH)2 (2 eq. mole) or Cs2CO3 (4 eq. mole) was used as the base rather than NaOMe. The mixture was heated at 90 °C for 1.5–4 h. The mixture was quenched with ice-cold 1NHCl and then extracted with CH2Cl2. The extracts were combined, and the extract was washed with brine, dried over Na2SO4 and concentrated in vacuo. 4′-Methyl-6,6,8-triyldesmosdumotin B (4′-Me-TEDB), 2) displayed the most significant and unprecedented selectivity with a KB/KB-Vin ratio of 460 [19]. Results from our study indicated that the activity of 2 against KB-Vin was correlated with P-gp overexpression; however, 2 was not a P-gp-ginhibitor yet it interacted with the P-gp in a novel fashion [20,21].

To further investigate B-ring effects, we synthesized several TEDB analogues with heteroaromatic as well as cycloalkyl B-rings and evaluated their cytotoxicity against KB and KB-Vin to determine their MDR selectivity profiles. The active compounds were also evaluated using a second set of paired cell lines, in order to assess whether MDR selectivity to them was restricted or more generalized. Herein, we report the syntheses of the new analogues and their MDR-selective activity as well as a structure-activity relationship (SAR) study.

Material and Methods

Chemistry

All chemicals and solvents were used as purchased. All melting points were measured on a Fisher-Johns melting point apparatus without correction. 1H NMR spectra were recorded on a Varian instrument. Analytical thin-layer chromatography (TLC) was carried out on Merck precoated aluminium silica gel sheets (Kieselgel 60 F-254). Isco Companion systems were used for flash chromatography. All target compounds were characterized and determined by 1H-NMR, MS, and elemental analyses or high resolution MS.

General synthetic procedures for 3-9

A solution of 12 in EtOH–50%aq. KOH (1:1, v/v) and an excess of appropriate aromatic aldehyde (except 3-furaldehyde, 2- and 3-pyridinecarbaldehyde) was stirred at room temperature. After the reaction was complete, the mixture was poured into ice-cold 1 N HCl, and then extracted with CH2Cl2. The extract was washed with brine, dried over Na2SO4 and concentrated in vacuo. The residue was chromatographed on silica gel eluting with EtOAc–hexane as eluent to afford the chalcone 13. When 3-furaldehyde or 2- and 3-pyridinecarbaldehyde was used as the aromatic aldehyde, Ba(OH)2, (2 eq. mole) or Cs2CO3 (4 eq. mole) was used as the base rather than KOH. The resulting compound 13 was dissolved in 1% H2SO4 in DMSO, then I (0.1 eq. mole) was added and the reaction mixture heated at 90 °C for 1.5–4 h. The mixture was quenched with ice-cold 90%aq 10% Na2SO4 and extracted with EtOAc. The extract was washed with brine, dried over Na2SO4 and concentrated in vacuo. The residue was chromatographed on silica gel eluting with EtOAc–hexane (1:4 to 1:0, v/v) to afford the related 7-methoxy analogue 14, which was dissolved in anhydrous CH2Cl2. The mixture was cooled to -78 °C. BBr3 (3 eq. mole, 1.0 M solution in CH2Cl2) was added to the solution, which was warmed to 0 °C spontaneously and stirred until the starting material was consumed. After addition of water, the reaction mixture was extracted three times with CH2Cl2. The extracts were combined,
General synthetic procedures for 10 and 11

A solution of 12 in anhydrous THF was cooled to -78°C under Ar. LiHMDS (5 eq. mol, 1.0M solution in THF) was slowly added and the mixture was gradually warmed to 0°C over 1.5 h. After stirring additional 2 h at 0°C, the mixture was cooled to -78°C. The appropriate acyl chloride (2 eq. mole) was added and stirred at -78°C for 1 h. The whole was warmed to rt spontaneously, and keep stirring overnight. The mixture was poured onto ice-cold 2NHCl, stirred for 1 h and the mixture was gradually warmed to 0°C over 1.5 h. After stirring additional 2 h at 0°C, the mixture was cooled to -78°C. The appropriate cycloalkyl acid chloride in the presence of LiHMDS and EtOAc–hexane eluting with pyridinecarbaldehyde were carried out using Ba(OH)₂, and Cs₂CO₃, respectively, rather than KOH. For analogues 10 and 11, the intermediates (14) were obtained by the treatment of 12 with the appropriate cycloalkyl acid chloride in the presence of LiHMDS, followed by treatment with acid.

All synthesized analogues 3–11 were evaluated in vitro against two human tumor cell lines, the KB-VIN cell line, an MDR P-gp expressing cloned subline stepwise selected using vincristine, and its parental non-MDR KB cell line. The cytotoxic activity data including KB/KB-VIN selectivity are listed in Table 1. While none of the 2-analogues with a hetero aromatic B-ring (3–9) inhibited the non-MDR tumor cell (KB) growth, most of them did significantly (3–6) or moderately (8) inhibit the MDR tumor cell (KB-VIN) growth. The inhibitory effects of 7 and 9 against KB-Vin were moderate at best and likely insignificant. The detailed SAR shows 2-(furan-3'-yl)-TEDB (3) and 2-(thiophen-2'-yl)-TEDB (6) displayed KB/KB-VIN hypersensitivity of >12 and 16 with IC₅₀ values of 5.2 and 3.2 µM against KB-VIN, respectively, which is greater than the thiosemicarbazone prototype NSC73306. The non-substituted furanyl and thiophenyl B-ring (five-membered

![Scheme 1: Syntheses of TEDB Analogues.](image)

**Results**

Analogues 3–6 were prepared through a three-step sequence, Claisen-Schmidt condensation of 12 with the corresponding aromatic aldehyde (RCHO) and 50% aq. KOH, cyclization, and C-7 demethylation of 14 with BBr₃ according to the reported method [12,14] (Scheme 1). Claisen-Schmidt condensation with 3-furaldehyde and pyridinecarbaldehyde were carried out using Ba(OH)₂ and Cs₂CO₃, respectively, rather than KOH. For analogues 10 and 11, the intermediates (14) were obtained by the treatment of 12 with the appropriate cycloalkyl acid chloride in the presence of LiHMDS, followed by treatment with acid.

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![Figure 1:](image)

**Figure 1:**
The most active analogues 3 and 6 were also evaluated in vitro against a human hepatoma MDR cell system, and the data are shown in Table 2. HepG2-Vin cells are P-gp-expressing and selected from the parent non-MDR HepG2 cell line using vincristine. The MDR-selectivity ratios measured for 3 and 6 were 3.8 and 18.3, respectively. This finding shows that the MDR-selectivity displayed by 3 and 6 is not limited to a single MDR-cell line.

The results in this and our prior studies indicate that MDR-selectivity of 2-analogues is not critically dependent on the type of B-ring. Although the structural features of the pendant B-ring can affect the activity as well as selectivity, compounds with acyclic B-ring, including mono-phenyl, heteroaromatic, and cycloalkylrings, but not bicyclic ring systems, acted as MDR-selective agents. Thus, the 5-hydroxy-6,8,8-trialkyl-4H-chromene-4(7H)-dione skeleton (A/C-ring system in 1) appears to be the crucial factor for the MDR selectivity. It is intriguing that structural variation of the B-ring is well tolerated. This suggests that interaction with P-gp, the presumed target, is relaxed, just as it is for substrates of the enzyme, including flavonoids, where structural variation is well tolerated. A similar finding was recently reported for new thiosemicarbazone-derived MDR-selective agents [13], although these actives are not thought to be enzyme substrates or inhibitors.

Detailed mechanism of action studies coupled with the development of new probe compounds designed to study target interaction will be key to further understand and develop 2-analogs as drug candidates in future studies. Such work is planned and will be worthwhile in order to fully exploit MDR and overcome the resistance barrier of cancer chemotherapy.

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Table 1: Activity of 1–11 against KB and KB-VIN.

| Compounds | IC50 (µM)a | Selectivity | ED50 (µM)b | Selectivity |
|-----------|------------|-------------|------------|-------------|
| KB        | KB-VIN     | KB/KB-VIN   | X          | R           | KB          | KB-VIN      | KB/KB-VIN   |
| 1 Desmosdumotin B | -         | >135        | 6.8        | >20         |             |             |             |
| 2          | -         | 39.2        | 0.08       | 460         |             |             |             |
| 3          | O         | >61         | 5.2        | >12         |             |             |             |
| 4          | S         | >58         | 8.7        | >6.7        |             |             |             |
| 5          | O H       | >61         | 7.9        | >7.7        |             |             |             |
| 6          | S H       | 50.9        | 3.2        | 16          |             |             |             |
| 7          | S Me      | 37.7        | 27.4       | 1.4         |             |             |             |
| 8          | -         | 51.6        | 15.6       | 3.3         |             |             |             |
| 9          | -         | >59.0       | 42.8       | >1.4        |             |             |             |
| 10         | -         | >33         | >33        | 1           |             |             |             |
| 11         | -         | 30.8        | 8.3        | 3.7         |             |             |             |
| NSC73308   | -         | 10.65 (KB-3-1) | 1.47       | 7.3         |             |             |             |
| Paclitaxel | 0.007     | 1.77        | 0.004      |             |             |             |             |

*Cytotoxicity as ED50 values for each cell line, the concentration of compound that caused 50% reduction in absorbance at 562 nm relative to untreated cells using the sulphorhodamine B assay. Epidermoid carcinoma of the nasopharynx (KB), and MDR line overexpressing P-glycoprotein (KB-VIN). The data were cited from ref [10].

Table 2: MDR-selectivity of 3 and 6 against hepatocellular carcinoma.

| Compounds | IC50 (µM)a | Selectivity |
|-----------|------------|-------------|
|            | HepG2    | HepG2-Vin   | HepG2/ HepG2-Vin |
| 3          | >61       | 16.0        | >3.8            |
| 6          | 43.8      | 2.4         | 18.3            |
| Paclitaxel | 0.63      | 0.26        | 0.28            |

*Cytotoxicity as ED50 values for each cell line, the concentration of compound that caused 50% reduction in absorbance at 562 nm relative to untreated cells using the sulphorhodamine B assay. Hepatocellular carcinoma (HepG2), and its MDR line (HepG2-Vin).

Compounds 10 and 11 contain cyclopropyl and cyclohexyl B-rings, respectively. Compound 11 exhibited moderate cytotoxicity against KB-Vin with a 3.7 ratio of MDR selectivity, while 10 did not show significant cytotoxicity or any selectivity. Interestingly, compound 11 exhibited moderate cytotoxicity against other non-MDR tumor cells, such as A549 (IC50 = 18.1 µM), DU145 (IC50 = 15.4 µM), and PC-3 (IC50 = 17.8 µM), despite the fact that other 2-analogues, including 1 and 2, did not show any cytotoxicity against these three cell lines.

The most active analogues 6 and 7 were also evaluated in vitro against a human hepatoma MDR cell system, and the data are shown in Table 2. HepG2-Vin cells are P-gp-expressing and selected from the parent non-MDR HepG2 cell line using vincristine. The MDR-selectivity ratios measured for 6 and 7 were 3.8 and 18.3, respectively. This finding shows that the MDR-selectivity displayed by 6 and 7 is not limited to a single MDR-cell line.

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