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Synthesis and activities towards resistant cancer cells of sulfone and sulfoxide griseofulvin derivatives

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ABSTRACT

Griseofulvin, an antifungal drug, has been shown in recent years to have anti-proliferative activities. We report here the synthesis of new analogs of griseofulvin, substituted in 2′ by a sulfonyl group or in 3′ by a sulfinyl or sulfonyl group. These compounds exhibit good anti-proliferative activities against SCC114 cells, an oral squamous carcinoma cell line showing pronounced centrosome amplification, and unexpected cytotoxic activities on HCC1937 cells, a triple negative breast cancer cell line resistant to microtubule inhibitors.

Griseofulvin **1** (Fig. 1) is a natural product initially isolated from *Penicillium griseofulvum*,[1] and used to treat fungal infections in humans and animals. Griseofulvin is also of interest as anti-cancer agent, due to its low toxicity and efficacy in inhibiting proliferation of cancer cells.[2] Although several studies have suggested that tubulin is the main target of griseofulvin, the exact mechanism of action remains still unclear.[3] In order to increase the anti-tumor properties of griseofulvin, several 2′-oxygen and 2′-sulfur analogs of griseofulvin were synthesized by Clausen and co-workers.[4] Among these compounds, GF-15 **2** (Fig. 1) has been reported to have tumor growth inhibition through centrosomal clustering inhibition.[5] Based on these observations, and since a part of our research programs is dedicated to the quest for anti-cancer natural products, we considered that griseofulvin could provide a good molecular basis to initiate a medicinal chemistry program. However, the research field of anti-mitotic microtubule-interfering agents is a mature area that counts several marketed drugs but is still dynamic owing to recent approvals in the last decade.[6] One of the major clinical issues faced by these chemotherapeutic agents is intrinsic or acquired-drug resistance of tumor cells which has different origins, such as efflux protein expression or tubulin mutations, among others. Having these considerations in mind, we

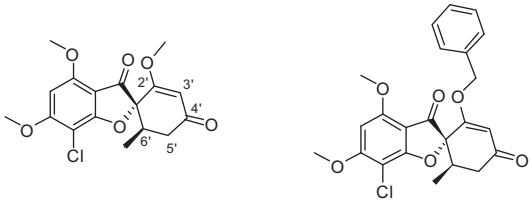

Figure 1. Structures of griseofulvin **1** and GF-15 **2**.

conducted a program to identify potent anti-cancer griseofulvin derivatives that could overcome resistance. We report here our efforts in the synthesis of 2′-sulfone, 3′-sulfoxide and 3′-sulfone griseofulvin analogs, as well as their antiproliferative activities, notably against a resistant cancer cell line.

2′-Demethoxy-2′-sulfonylgriseofulvin analogs **5a–c** were obtained in a three steps synthetic process, starting from commercial griseofulvin (Scheme 1).

Griseofulvin **1** was reacted with lithium chloride and phosphoryl chloride in refluxing dioxane,[4] affording the 2′-vinyl chloride **3** in 40% yield, after separation of its 4′-vinyl chloride isomer. The addition of thiols on **3** was performed using an excess of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in refluxing dioxane.[4] 2′-Sulfur compounds **4a–c** were obtained with an average yield of 80% for the three compounds, then oxidized to 2′-sulfone by addition of

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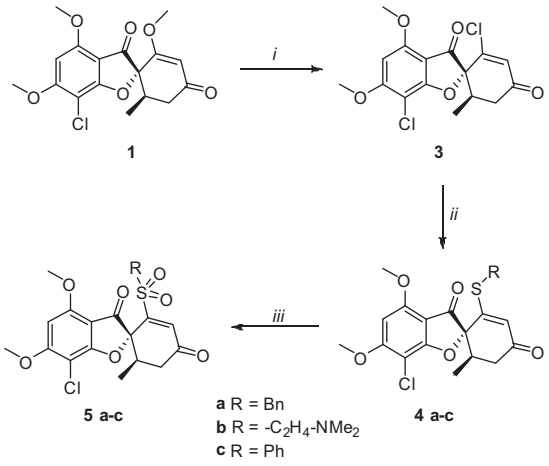
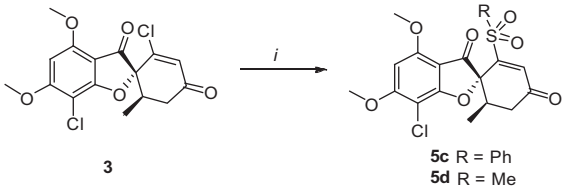


Scheme 1. Reagents and conditions: (i) LiCl (3 equiv), $POCl_3$ (5 equiv), 1,4-dioxane, 100 °C, 1 h, 40%; (ii) R-SH (1–2 equiv), DBU (2.5 equiv), 1,4-dioxane, 100 °C, 18 h; (iii) oxone (6 equiv), H_2O/MeOH/THF 5:1:1, rt, 16 h, 8–26% over 2 steps.

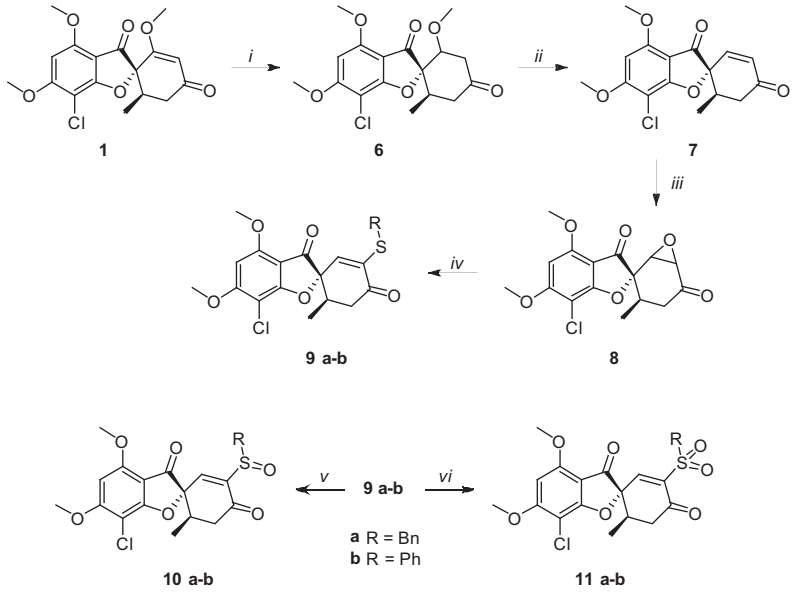


Scheme 2. Reagents and conditions: (i) R-SO_2Na (1 equiv), DMF, rt, 16 h, 86%.

an excess of aqueous oxone. Derivatives **5a–c** were obtained in yields of 11–32%. An alternative route using sulfinates as nucleophiles was found to improve the overall yield of the process. For example, starting from 2′-vinyl chloride **3**, addition of sodium phenylsulfinate or methylsulfinate in DMF directly led, respectively, to compounds **5c** or **5d** with 85% yield each (Scheme 2).

2′-Demethoxy-3′-sulfinyl griseofulvin analogs **10a–b** and 2′-demethoxy-3′-sulfonyl griseofulvin analogs **11a–b** were obtained through a five steps synthetic sequence (Scheme 3). Griseofulvin **1** was reduced in the presence of Pd/C 10% and hydrogen in ethyl acetate to afford intermediate **6**. Elimination of the methoxy group was performed with sulfuric acid 2 N, in refluxing ethanol to afford **7**.[7] Epoxidation of the resulting double bound with hydrogen peroxide led to compound **8** with an overall yield of 94% over three steps, starting from commercial griseofulvin. When **8** was treated with thiols in basic conditions, 3′-vinyl sulfur derivatives **9a–b** were obtained with 15–25% yields. Although the conversion seemed to be complete (monitoring of the reaction by LCMS), these disappointing yields were obtained after purification and were maybe due to a lack of solubility or instability of the compounds over silica gel. Moreover, in our hands, the reaction was found to be poorly reproducible and adaptable to a range of thiols, and sodium hydroxide at different concentrations (1 N for **9a** or 0.1 N for **9b)** was eventually found to give the best results. Thereby, the use of other bases, such as sodium hydride or sodium ethoxide, did not allow us to improve the reaction yields, leading to complex mixtures. Oxidation of 3′-vinyl sulfur **9a** with a stoichiometric amount of *meta*-chloroperbenzoic acid (*m*-CPBA) led to **10a** with a moderate yield of 30%. **9b** was oxidized with sodium periodate and led to sulfoxide **10b**, as a mixture of two diastereoisomers, with moderate yields of 35%. Oxidation of 3′-vinyl sulfur **9a** and **9b** with an excess of *m*-CPBA led to the formation of sulfones **11a** and **11b**, respectively, with 79% and 45% yield.

Compounds **5a–d**, **10a–b** and **11a–b**[8] were evaluated for their antiproliferative activities against HCC1937 cells,[9] a triple negative breast cancer cell line resistant to most microtubule inhibitors.[10] These derivatives were compared to reference compounds such as paclitaxel, epothilone B, vinorelbine, griseofulvin and GF-15 (Table 1). Compounds with IC_{50} values higher than 10 μM were regarded as inactive. 2′-Vinyl sulfones **5a–d** were found to be active on the HCC1937 cell line, having IC_{50} values in the micromolar range, whereas references were found to be inactive. The degree of oxidation of the 2′-sulfur has a real impact on the antiproliferative activities for this particular cell line as parent compounds **4a–b** were inactive. The size and aromaticity of the substituent borne



Scheme 3. Reagents and conditions: (i) Pd/C 10%, EtOAc, H_2, rt, 6 h, 100%; (ii) H_2SO_4 2 N (10 vol), EtOH, 80 °C, 16 h, 99%; (iii) NaOH 2 N (1.4 equiv), H_2O_2 (1 equiv), EtOH, 0 °C, 1 h, 95%; (iv) R = Ph: PhSH (1.2 equiv), NaOH 1 N (30 vol), THF, 70 °C, 15% or R = Bn: BnSH (1.2 equiv), NaOH 0.1 N (30 vol), THF, rt, 25%; (v) R = Bn: *m*CPBA (1 equiv), CH_2Cl_2, 0 °C, 1 h, 30%; R = Ph: $NaIO_4$ (1.5 equiv), MeOH/H_2O 2:1, 50 °C, 16 h, 35% (vi) *m*CPBA (2.7 equiv), CH_2Cl_2, rt, 0.5–1 h, 45–79%.