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Core-Modified Sordaricin Derivatives: Synthesis and Antifungal Activity

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Abstract—Core-modified sordaricin derivatives were prepared via biotransformation followed by chemical modification and tested for antifungal activity. The antifungal activity proved to be very sensitive to modifications in the sterics and/or lipophilicity of the diterpene skeleton. Introduction of polar groups such as hydroxyl in the diterpene core results in loss of potency while small and lipophilic groups such as fluorine and the 7,8-olefin are well tolerated.

The rapid emergence of resistance to current antifungal therapies and the prevalence of opportunistic systemic fungal infections in HIV-AIDS patients has stimulated the search for new antifungals with novel mechanisms of action.[1] In this context the natural product Sordarin has received a great deal of attention in recent years.[2] Sordarin (**1**) selectively binds and stabilizes the EF-2/ribosome complex in fungi by impeding the RNA translocation step (Fig. 1).[3,4]

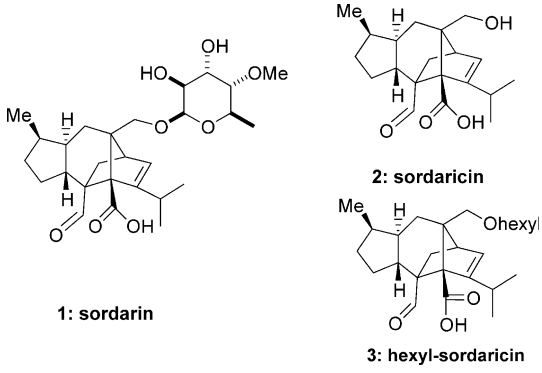

Figure 1. Sordarin, its aglycone and hexyl-sordaricin.

To date most of the synthetic efforts to discover analogues endowed with potent and broader spectrum of antifungal activity have been directed towards modification and replacement of the sugar moiety[2a–d,2f,g] or alteration of the diterpene core, especially the cyclopentane ring by biotransformation.[2e] Despite earlier attempts to simplify the tetracyclic aglycone[5] and replace the aldehyde functionality with a cyano group,[2c] little has been reported regarding core modified sordarin derivatives. In this communication, we report the results of our expanded SAR investigation directed at alteration of the diterpene skeleton by biotransformation followed by subsequent chemical manipulation.

Modifications to the diterpene skeleton have remained a difficult task mainly due to lack of functionalities in this part of the natural product. Fortunately, biotransformation provided an excellent method for installing a hydroxyl group in the cyclopentane ring of sordaricin (**2**) (Scheme 1). Prolonged exposure[6] of **2** to *Nocardia species* SC11274 and *Nocardia orientalis* SC4044 afforded respectively 7-hydroxy (**4**) and 6-hydroxysordaricin (**5**).[7] These two compounds were protected with benzyl-isopropyl isourea followed by alkylation with L-iodohexane to afford **6a** and **7a**.[8] The carboxylic acid was unmasked by hydrogenolysis to render **6b** and **7b** in 27 and 23% yield, respectively, for the three steps.

Both hydroxy groups in the cyclopentane core could be further elaborated to produce other core-modified sordaricin derivatives. Thus, acid promoted dehydration of **4**, using 6 N HCl in acetone at room temperature for 12 h, generated regioselectively 7,8-deshydrosordaricin (not

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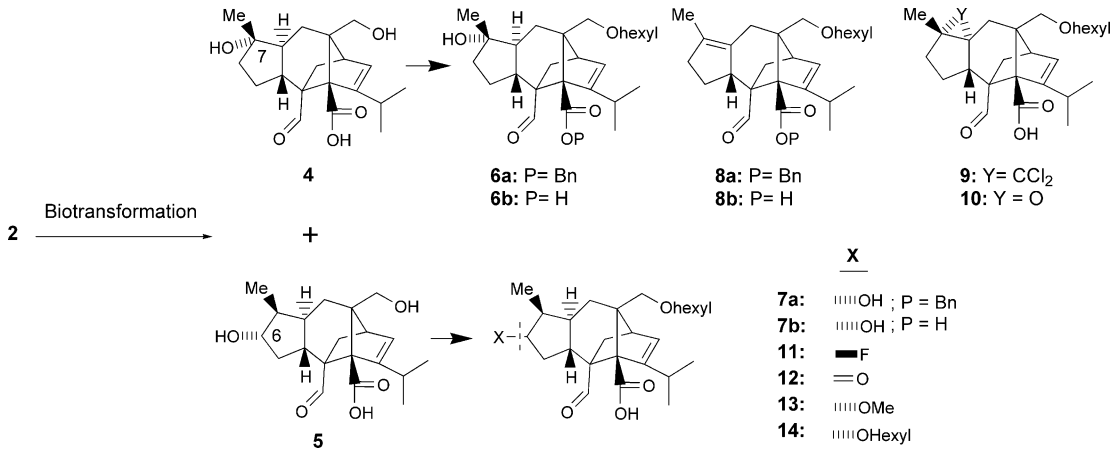

Scheme 1. Core-modified sordaricin analogues.

shown), which was subjected to the benzylation/alkylation/deprotection protocol described above to afford **8b** in 35% yield from **4**. Cyclopropanation of **8a** with chloroform, aqueous NaOH and a phase transfer catalyst at 50 °C occurred regio- and stereo-selectively[9] at the 7,8-olefin to give, after hydrogenolysis, dichlorocyclopropane **9** in 55% yield. Epoxidation with *m*CPBA occurred in the same facial-selective manner[9] to produce, after deprotection, epoxide **10**. The 6-(*R*)-fluoro analogue **11** was prepared in 32% yield by treatment of **7a** with DAST in the presence of pyridine[10] followed by hydrogenolysis. Ketone **12** was obtained in 56% yield from **7a** by TPAP oxidation followed by deprotection. Finally, the 6-hydroxyl group in **7a** was alkylated with methyl and hexyl-iodide followed by hydrogenolysis to afford 6-alkoxy-sordaricin analogues **13** and **14** in 44 and 40% yield, respectively.

All new analogues[11] were evaluated for antifungal activity against *Candida albicans* and *Candida glabrata*. Compounds showing MICs <128 μg/mL[12] are summarized in Table 1.[13]

Structure–activity relationships of the terpenoid core illustrated that introduction of small and non-polar substituents in the diterpene skeleton afforded very potent compounds such as olefin **8b** (MIC = 0.125 μg/mL) and 6-(*R*)-fluoro derivative **11** (MIC = 0.25 μg/mL). These transformations are of particular interest since they may help to prevent the in vivo metabolism of sordarin derivatives by impeding the hydroxylation at positions C6 and C7.[14] The dichlorocyclopropane **9** also maintained moderate anti-*Candida* activity, although the more polar epoxide was not tolerated (**10**). The more lipophilic tertiary alcohol **6b** showed modest MIC = 4 μg/mL while the secondary alcohol **7b** was inactive. Activity could be regained by increasing the lipophilicity via conversion to ketone **12** or methylether **13**. However, the bulkier hexylether **14** lacked activity, which seems to indicate that steric factors in this part of the molecule play an important role in biological activity. In conclusion, several core-modified sordaricin derivatives were synthesized and screened against a panel of fungi. The antifungal activity proved to be very sensitive to modifications on the steric environment and/or lipophilicity of the diterpene skeleton. Introduction of polar groups, such as hydroxyl results in a loss of potency while smaller and more lipophilic groups, such as fluorine and the 7,8-olefin, are well tolerated.

Table 1. In vitro antifungal activity for selected compounds[13]

	MIC[a] (μg/mL)		
	C. albicans		*C. glabrata*
	A28235 (WT)	A28660 (WT)	A28790 (WT)
1	16	—	>128
3	0.06	0.06	0.125
6b	4	8	32
8b	0.125	0.5	8
9	32	32	64
11	0.25	0.5	1
12	4	8	32
13	32	64	>128

[a]MIC value defined as the lowest drug concentration required to inhibit 90–100% visible growth relative to controls.

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References and Notes

1. Akiran, S.; Rex, J. H. *Emerg. Drugs* **2000**, *5*, 135.
2. (a) Domínguez, J. M.; Kelly, V. A.; Kinsman, O. S.; Marriot, M. S.; Gómez de las Heras, F.; Martín, J. J. *Antimicrob. Agents Chemother.* **1998**, *42*, 2274. (b) Cuenca-Estrella, M.; Mellado, E.; Díaz-Guerra, J. M.; Monzón, A.; Rodríguez-Tudela, J. L. *Antimicrob. Agents Chemother.* **2001**, *45*, 1905. (c) Tse, B.; Balkovec, J. M.; Blazey, C. M.; Hsu, M. J.; Nielsen, J.; Schmatz, D. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 2269. (d) Balkovec, J. M.; Tse, B. PCT Int. Appl. WO9815178, 1998. (e) Hall, R. M.; Dawson, M. J.; Stead, P.; Taylor, N. L. *J. Antibiot.* **2001**, *54*, 948. (f) Kaneko, S.; Uchida, T.; Shibuya, S.; Honda, T.; Kawamoto, I.; Harasaki, T.; Fukuoka, T.; Konosu, T. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 803. (g) Ser-

rano-Wu, M. H.; St. Laurent, D. R.; Mazzucco, C. E.; Stickle, T. M.; Barrett, J. F.; Vyas, D. M.; Balasubramanian, B. N. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 943.
3. Domínguez, J. M.; Gómez-Lorenzo, M. G.; Martín, J. J. *J. Biol. Chem.* **1999**, *274*, 22423.
4. Capa, L.; Mendoza, A.; Lavandera, J. L.; Gómez de las Heras, F.; García-Bustos, J. *Antimicrob. Agents Chemother.* **1998**, *42*, 2694.
5. Cuevas, J. C.; Lavandera, J. L.; Martos, J. L. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 103.
6. Biotransformation was performed accordingly to experimetal conditions described in ref 2e.
7. Regiochemistry was assigned using ^{1}H NMR and the stereochemistry was confirmed by NOE studies in the case of **4** and X-ray crystallography for **5**.
8. We decided to employ the known hexyl-sordaricin[2c,d] (**3**) as a reference when evaluating the biological activity (MIC values) of our newer analogues.
9. Compounds **8** and **9** showed both NOE couplings between the methyl group in the cyclopentane ring and the H4 proton in the bridgehead.
10. We anticipated the synthesis of the diastereomeric 6(*S*)-fluoro analogue under similar conditions from the 6(*R*)-hydroxy derivative. However, efforts to invert the stereochemistry of the C-6 hydroxyl in **7a** or reduction of ketone **12** failed to provide the desired product.
11. All new compounds were characterized by analytical methods (^{1}H NMR and LRMS).
12. Compounds **7b**, **10**, and **14** showed MIC >128 μg/mL.
13. MICs were detemined accordingly to NCCLS standards: Reference Method for Broth Dilution Antifungal Susceptibility Testing of Yeasts. Approved Standard. NCCLS document M27-A. NCCLS, 1997.
14. Inactive 6-hydroxy and 7-hydroxy sordarins are the major metabolites found in rats and may contribute to the reduced in vivo antifungal activity of sordarin. See ref 5.