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Antifungal Sordarins. Part 4: Synthesis and Structure–Activity Relationships of 3′,4′-Fused Alkyl-Tetrahydrofuran Derivatives

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Abstract—A series of Sordarin derivatives bearing alkyl substituted tetrahydrofuran rings fused to C3′–C4′ bond of the sugar moiety have been prepared and their antifungal properties evaluated. Most of them show remarkable antifungal activity against *Candida* spp and *Cryptococcus neoformans*.

GR135402[1] is a naturally occurring compound isolated from a fermentation broth of *Graphium putredinis* which shows antifungal properties comprising moderate potency and spectrum of action. **GR135402** is a novel antibiotic structurally related to the known Sordarin[2] and Zofimarin.[3] We have demonstrated that Sordarin derivatives are selective inhibitors of fungal protein synthesis, which bind to elongation factor 2.[4]

In a previous paper,[5] we have reported the synthesis of a new family of 3′,4′-fused dioxolane and dioxane Sordarin derivatives of general formula **I** (Fig. 1). We found that certain 2′-deoxy-Sordarin derivatives, such as **GM193663**,[5,6] dramatically improved both potency and spectrum of action of parent compound **GR135402**.

Herein, we describe the synthesis and antifungal activity of a new generation of compounds structurally based on the lead **GM193663**. The structural novelty of this new family of compounds, with general formulas **II** and **III**, arises out from the replacement of an oxygen atom adjacent to position C3′ or C4′ by a carbon atom. Thus, two different bicyclic structures (**II** and **III**) that contain a tetrahydrofuran ring fused to C3′–C4′ bond are obtained.

Chemistry

The first synthesis of 2′-deoxy-derivatives of general formula **II** (Y = H) was carried out in nine steps starting from triol **GR163598**, a natural product obtained by fermentation.[7] The complete sequence (Scheme 1, R = H) comprised the initial preparation of 2′-deoxy-derivative **2**, which has been already reported by us[5] (route A).

Tin mediated selective alkylation[8] at the 4′-position led to 4′-*O*-allyl derivatives **4(a–d)**, which were transformed into their corresponding Xanthates **5(a–d)**. Radical cyclisation by treatment of **5(a–d)** with tributyl tin hydride in the presence of a catalytic amount of AIBN, led to couples of stereoisomers[9] which were separated

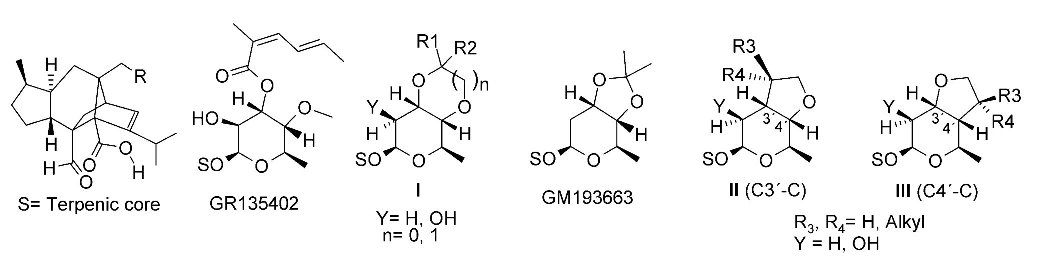

Figure 1.

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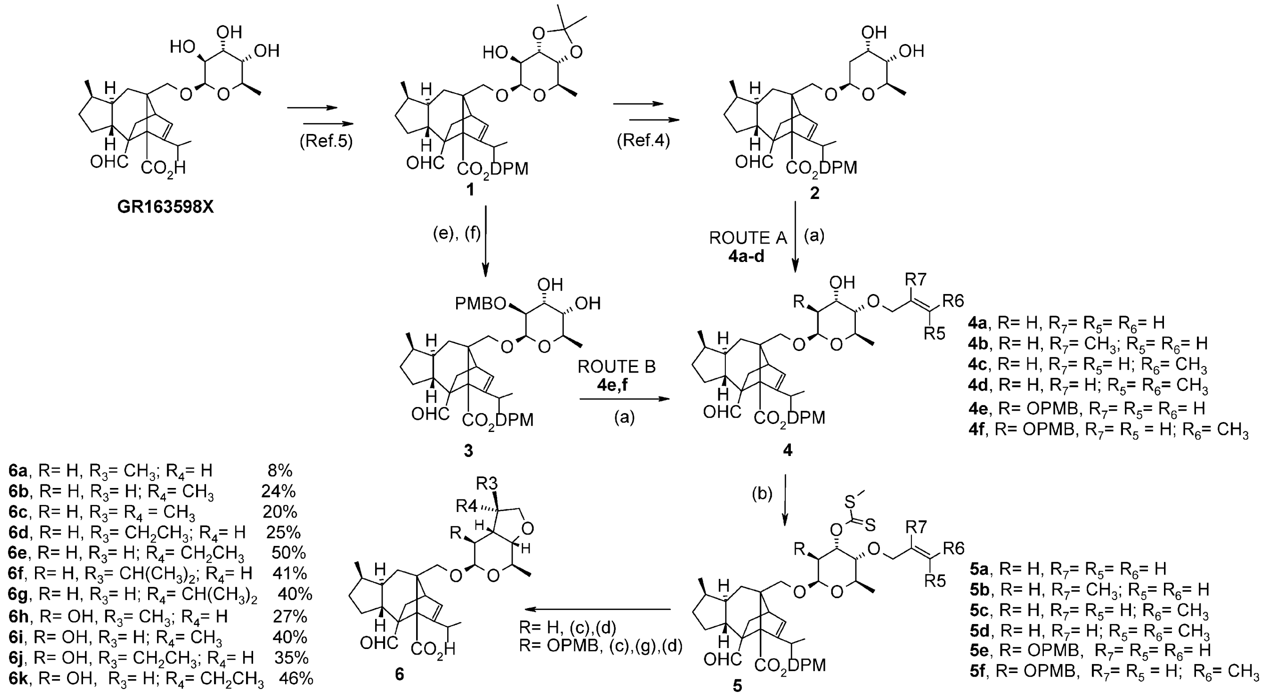


Scheme 1. (a) (i) Bu_2SnO, toluene, reflux; (ii) $R_5R_6C{=}C(R_7)CH_2$–Br, TBAF, rt, 60–70%; (b) (i) NaH, THF, 0 °C, (ii) CS_2, imidazole; (iii) MeI, 75–95%; (c) Bu_3SnH (1 equiv), AIBN, toluene, reflux; (d) H_2, Pd/C, EtOAc, quant; (e) Bu^tOK, THF, PMBBr, NaI; (f) 1 N HCl, MeOH/THF, 78% for steps e and f; (g) DDQ, DCM/H_2O, rt, 85%.

by using chromatographic techniques. Finally, removal of DPM protecting group by hydrogenation led to final compounds **6**(**a**–**g**).

As shown in Table 1, compounds **6a** and **6d**, both having *R* configuration at the carbon bearing the substituent,[10] appear as the most interesting members of this family of antifungals in terms of both potency and spectrum of action. However, these compounds are the minor components in the mixtures of stereoisomers obtained after free radical cyclisation, which is in accordance with the preferred formation of *endo* isomers ($R_3 = H$) in similar cyclisations leading to bicyclic systems.[11]

On the other hand, 2′-hydroxy-derivatives of general formula **II** (Y = OH), have been prepared following the synthetic route depicted in Scheme 1 (route B). As shown, the synthetic route leading to methyl and ethyl substituted tetrahydrofuran derivatives **6h**–**k** comprised protection of 2′-OH of compound **1** as PMB ether and further deprotection of isopropylidene group to furnish diol **3**. Selective introduction of the corresponding allylic chain at the 4′-position was accomplished by Tin mediated selective alkylation to afford the corresponding 4′-*O*-allyl derivatives[8] **4e** and **4f**, which were transformed into their corresponding Xanthates **5e** and **5f**. Finally, free radical cyclisation by treatment with tributyltin hydride/AIBN system gave the corresponding two couples of fully protected tetrahydrofuran derivatives, which were deprotected by concurrent hydrogenolysis of PMB and DPM groups to afford final 2′-hydroxy-methyl and ethyl substituted tetrahydrofuran derivatives **6h**–**i** and **6j**–**k**, respectively.

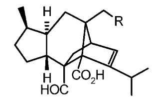
Regarding tetrahydrofuran derivatives of general formula **III** (Y = H), we have tackled only the preparation of the corresponding methyl substituted derivative (Scheme 2). As shown, we have taken advantage of the high selectivity shown by the tin mediated alkylation at the 4′-position[8] for the protection (as PMB ether) of the 4′-hydroxyl group in 2′-deoxy-diol **2** to afford compound **7**. From this point, the sequence involved successively introduction of the allylic chain at 3′-position, oxidative cleavage of PMB group and activation of the 4′-position by formation of Xanthate to afford intermediate **8**. Likewise to that observed in the case of (C3′-C) derivatives, AIBN mediated radical cyclisation with tributyl–tin hydride gave a mixture of the two possible stereoisomers, which were separated by chromatography. Finally, hydrogenolysis of DPM ester yielded desired compounds **9a** and **9b**.

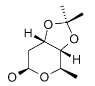
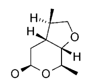
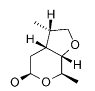
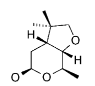
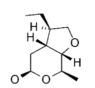
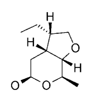
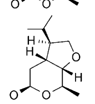
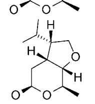
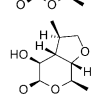
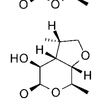
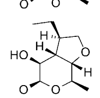
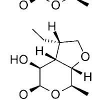
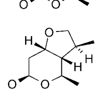
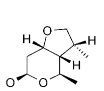
Results and Discussion

Table 1 shows the in vitro antifungal activity (refered to MIC, the minimum concentration inhibiting fungal cell growth)[6,12] of compounds synthesised. This assay was carried out in broth microdilution using RPMI + glucose as culture medium.

In general terms, 2′-deoxy-alkyl substituted derivatives **6a**–**g** and **9a**,**b** have shown very high potencies against strains of *Candida albicans*, *Candida pseudotropicalis* and *Candida tropicalis*, along with moderate activities in strains of *Candida glabrata* and *Cryptococcus neoformans*. On the other hand, the presence of an hydroxyl group at the 2′-position in compounds **6h**–**k** has always led

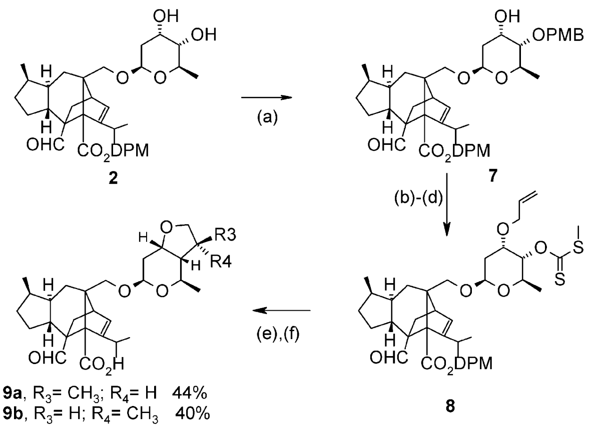
Table 1. Antifungal activity of Sordarin derivatives bearing alkyl substituted tetrahydrofuran rings



	R	MIC (μg/mL)							
		C. albicans 4711E	*C. albicans* 2005E	*C. glabrata* 2375E	*C. pseudo* 2371E	*C. tropical* 2808E	*C. parapsil* 2372E	*C. neoform* 2867E	*A. flavus* C1150
Fluconazole		0.12	—	4	—	2	0.5	—	—
GM193663		0.004	< 0.001	31	0.004	0.12	> 125	0.12	> 125
6a		< 0.001	< 0.001	0.50	0.004	0.008	2.00	0.25	62.00
6b		< 0.001	0.001	04.00	0.001	0.004	> 125	4.00	> 125
6c		< 0.001	< 0.001	8.00	< 0.001	0.06	> 125	4.00	> 125
6d		< 0.001	< 0.001	0.50	< 0.001	< 0.001	4.00	< 0.25	62.00
6e		< 0.001	< 0.001	4.00	< 0.001	< 0.001	> 125	1.00	> 125
6f		< 0.001	< 0.001	2.00	< 0.001	0.004	16.00	0.25	> 125
6g		< 0.001	< 0.001	62.00	< 0.001	2.00	> 125	4.00	> 125
6h		1.00	0.50	31.00	1.00	2.00	125.00	1.00	> 125
6i		0.25	0.008	62.00	0.25	0.50	125.00	31.00	> 125
6j		0.12	0.03	8.00	0.06	0.50	125.00	< 0.25	> 125
6k		0.12	0.015	16.00	0.06	0.25	125.00	< 0.25	> 125
9a		< 0.001	< 0.001	8.00	< 0.001	0.008	> 125	1.00	> 125
9b		0.004	0.001	16.00	< 0.001	0.03	> 125	0.50	> 125

to a significant loss of antifungal activity compared with their corresponding 2′-deoxy counterparts **6a**,**b** and **6d**,**e**.

It is noteworthy that several compounds have widened the spectrum of action, in comparison with other families of Sordarin derivatives containing fused rings at the sugar moiety previously synthesized by us.[5] Indeed, measurable MIC's values have been observed for the first time in *C. parapsilosis* (**6a**, **6d**, **6f**) and *A. flavus* (**6a** and **6d**). In this regard, it seems that the configuration at the carbon atom bearing the substituent at the tetrahydrofuran ring seems to play an important role in the antifungal activity, particularly against *C. glabrata*, *Candida parapsilosis, C. neoformans* and even *Aspergilus flavus*. In general, the isomers with R configuration (**6a**, **6d** and **6f**) are clearly more potent that their counterparts with *S* configuration (**6b**, **6e** and **6g**). Compound **6c**, which bears two methyl groups attached to the



Scheme 2. (a) (i) Bu_2SnO, toluene, reflux; (ii) PMBCl, TBAF, rt, 67%; (b) (i) NaH, THF, 0 °C; (ii) allyl bromide, THF, rt, 95%; (c) DDQ, DCM/H_2O, rt, quant; (d) (i) NaH, THF, 0 °C; (ii) CS_2, imidazole; (iii) MeI, 86%; (e) Bu_3SnH (1 equiv), AIBN, toluene, reflux; (f) H_2, Pd/C, EtOAc, rt, quant.

tetrahydrofuran ring is structurally similar to S isomer **6b**, as demonstrated its ^{1}H NMR spectrum and the high MIC's values observed in the above mentioned strains. A complete in vitro study of compound **6a** has been already reported.[6]

On the other hand, this effect seems to be no significant to the antifungal activity in (C4′-C)-tetrahydrofuran derivatives. Compounds **9a** and **9b**, having *S* and *R* configuration respectively, show very similar antifungal profile, being very potent against *C. albicans*, *C. pseudotropicalis* and *C. tropicalis,* whereas moderately potent against *C. glabrata* and *C. neoformans*. Both compounds were inactive against *C. parapsilosis* and *A. flavus*.

In conclusion, the attachment of tetrahydrofuran rings to the C3′-C4′ bond of the original sugar moiety, has led to a dramatic enhacement of the antifungal activity within the Sordarin family of compounds. The differences found between stereoisomers having *R* and *S* configuration at the carbon bearing the substituent attached to the tetrahydrofuran ring, suggest a highly stereospecific interaction of these Sordarin derivatives in their Ribosome–EF2 complex binding site, and warrant further exploration on the synthesis of these new class of antifungals.

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References and Notes

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