

Medicinal Chemistry Of AN2690, A Novel Broad-Spectrum Antifungal Agent In Development For The Topical Treatment Of Onychomycosis

J.J. Plattner, S.J. Baker, Y-K. Zhang, T. Akama, A. Lau, H. Zhou, V. Hernandez, W. Mao, M.R.K. Alley, S.J. Benkovic, V. Sanders

Anacor Pharmaceuticals, Inc., 1060 East Meadow Circle, Palo Alto, CA 94303, USA.

ABSTRACT

AN2690 is a member of a new class of antifungal agent in clinical trials to treat onychomycosis topically. We report discovery of this broad-spectrum class of antifungal agent and the structure-activity-relationship (SAR) that led to the identification of AN2690.

1. INTRODUCTION

Onychomycosis, a common fungal infection of toe and fingernails, remains difficult to treat,¹ probably because current therapies have poor penetration throughout the nail unit.² AN2690, a novel boron-containing small molecule designed to penetrate nails, has broad spectrum antifungal activity and is in clinical trials to treat onychomycosis topically.

In this poster, we report the microbiological SAR that led to the identification of AN2690.

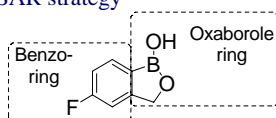
2. SYNTHESIS

A typical synthesis of 1,3-dihydro-2,1-benzoxaboroles (**4a-n**) is shown in Scheme 1. The protected *o*-bromobenzyl alcohol derivative (**3**), prepared from **1** or **2**, was converted into the corresponding phenyl boronic acid. Deprotection of the methoxymethyl ether using hydrochloric acid followed by spontaneous cyclization gave the target compounds **4a-n**. When compounds have functional groups sensitive to butyllithium, such as a nitrile group, an *in-situ* trap method was applied.³

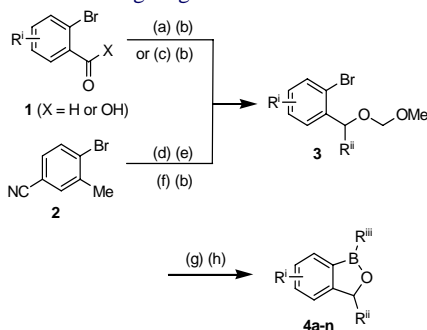
The six-membered benzoxaborin (**8**) was synthesized as shown in Scheme 2. The 6-fluoro benzaldehyde (**5**) was subjected to a Wittig reaction and the resulting enol ether was hydrolyzed to give the phenylacetaldehyde (**6**). Reduction of the carbonyl group, followed by protection of the resulting alcohol gave the methoxymethyl ether (**7**), which was converted to the final product **8** using the same chemistry described previously.

The carbon analog **10** was prepared from the corresponding indanone (**9**).

FIGURE 1. Structure of AN2690 (5-fluoro-1,3-dihydro-1-hydroxy-2,1-benzoxaborole) showing SAR strategy



SCHEME 1.^a Synthesis of benzoxaborole class of antifungal agents



^aConditions: (a) NaBH₄, MeOH, rt, or MeMgBr, THF, -78 °C to rt (when X = H), or BH₃-THF, THF, rt (when X = OH); (b) MeOCH₂Cl, *i*-Pr₂NEt, CH₂Cl₂, rt; (c) MeMgBr, THF, -78 °C to rt; (d) NBS, AIBN, CCl₄, reflux; (e) NaOAc, DMF, 70 °C; (f) NaOH, MeOH, reflux; (g) *n*-BuLi, RⁱⁱB(ORⁱⁱⁱ)₂, THF, -78 °C to rt; (h) 6N HCl, THF, rt.

3. MICROBIOLOGY

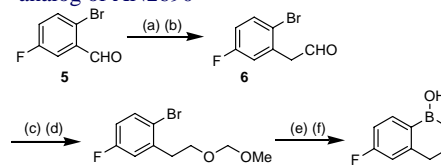
Minimum inhibitory concentrations (MIC) were determined against the dermatophytes, *T. rubrum* and *T. mentagrophytes*, and against the yeasts *C. albicans*, *C. neoformans* and mold *A. fumigatus*. Ciclopirox, the only commercial topical treatment available in the USA, was used as a reference.

From the results we found the following:

- The 5-F derivative (**4b**, AN2690), increased potency 4-8 fold over our lead **4a**
- The 5-F derivative (**4b**, AN2690) was a more active regioisomer than 4-, 6- or 7- derivatives, **4g-i**
- A methyl group on the 5-membered boron ring to give **4k** was not tolerated
- The six-membered ring analog, **8** was inactive
- Substitution of the hydroxy group of **4b** with a phenyl, vinyl or thiophenyl (**4l-m**) did not greatly affect activity.
- The carbon analog, **10**, was inactive.

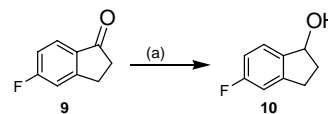
This led us to select the 5-fluorobenzoxaborole **4b** (AN2690) as our lead compound for onychomycosis.

SCHEME 2.^a Synthesis of benzoxaborin analog of AN2690



^aConditions: (a) Ph₃PCH₂OMe.Cl, *t*BuOK, DMF, 0 °C to rt; (b) 6N HCl, THF, reflux; (c) NaBH₄, MeOH, rt; (d) MeOCH₂Cl, *i*-Pr₂NEt, CH₂Cl₂, rt; (e) *n*-BuLi, (*i*-PrO)₃B, THF, -78 °C to rt; (f) 6N HCl, rt.

SCHEME 3.^a Synthesis of carbon analog of AN2690



^aConditions: (a) NaBH₄, MeOH, rt.

TABLE 1. MIC (μg/mL) values of AN2690 and analogs

	R ⁱ	R ⁱⁱ	R ⁱⁱⁱ	<i>T. rubrum</i>	<i>T. mentagrophytes</i>	<i>C. albicans</i>	<i>C. neoformans</i>	<i>A. fumigatus</i>
Ciclopirox				0.5	0.5	0.5	0.5	1
4a	H	H	OH	8	4	2	1	2
4b, AN2690	5-F	H	OH	1	1	0.5	0.25	0.25
4c	5-Cl	H	OH	1	2	1	2	1
4d	5-Me	H	OH	8	4	2	8	2
4e	5-NC	H	OH	16	16	8	8	16
4f	5-MeO	H	OH	64	32	>64	>64	>64
4g	4-F	H	OH	16	16	64	32	32
4h	6-F	H	OH	16	32	16	32	8
4i	7-F	H	OH	16	16	32	32	4
4k	5-F	Me	OH	32	16	16	32	16
4l	5-F	H	Ph	1	2	0.5	2	2
4m	5-F	H	vinyl	4	2	1	4	2
4n	5-F	H	thiophen-3-yl	1	4	1	1	1
8	6-F	n/a		32	32	64	>64	32
10	Carbon analog			>128	>128	>128	nt	nt

4. CONCLUSIONS

AN2690, a novel boron-containing compound in clinical trials to treat onychomycosis topically, exhibits broad spectrum antifungal activity against dermatophytes, yeasts and molds.

- Benzoxaboroles show MIC values in the low μg/mL range
- 5-membered ring containing boron is essential
- Halo-substituted benzo-rings increased activity
- The 5-position was optimal for activity
- The 5-fluoro-benzoxaborole (AN2690) gave best potency

References

1. J.E. Arrese and G.E. Piérard. *Dermatology*, 2003, 207, 255.
2. S. Murdan. *Int. J. Pharmaceutics*, 2002, 236, 1.
3. Li, W.; Nelson, D.P.; Jensen, M.S.; Hoerrner, R.S.; Cai, D.; Larsen, R.D.; Reider, P.J. *J. Org. Chem.* 2002, 67, 5394-5397.