

Letters

Discovery of a New Boron-Containing Antifungal Agent, 5-Fluoro-1,3-dihydro-1-hydroxy-2,1-benzoxaborole (AN2690), for the Potential Treatment of Onychomycosis

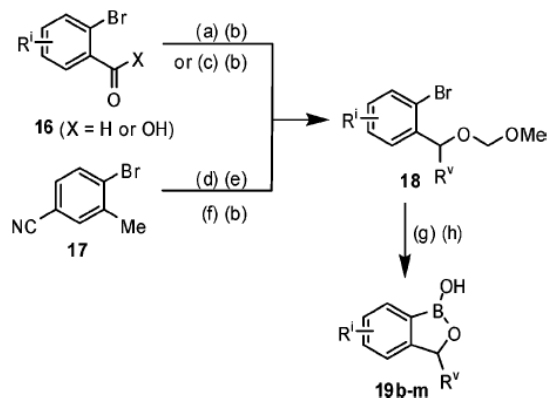
Stephen J. Baker,* Yong-Kang Zhang, Tsutomu Akama, Agnes Lau, Huchen Zhou, Vincent Hernandez, Weimin Mao, M. R. K. Alley, Virginia Sanders, and Jacob J. Plattner

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

Received March 29, 2006

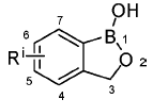
Abstract: A structure–activity relationship investigation for a more efficacious therapy to treat onychomycosis, a fungal infection of the toe and fingernails, led to the discovery of a boron-containing small molecule, 5-fluoro-1,3-dihydro-1-hydroxy-2,1-benzoxaborole (AN2690), which is currently in clinical trials for onychomycosis topical treatment.

Scheme 2^a



^a Conditions: (a) NaBH₄, MeOH, room temp (when X = H), or BH₃–THF, THF, room temp (when X = OH); (b) MeOCH₂Cl, *i*-Pr₂NEt, CH₂Cl₂, room temp; (c) MeMgBr, THF, –78 °C to room temp; (d) NBS, AIBN, CCl₄, reflux; (e) NaOAc, DMF, 70 °C; (f) NaOH, MeOH, reflux; (g) *n*-BuLi, (*i*-PrO)₃B, THF, –78 °C to room temp; (h) 6 N HCl, THF, room temp.

Table 3. Minimum Inhibitory Concentration (μg/mL) of 1,3-Dihydro-1-hydroxy-2,1-benzoxaborole Compounds (19)



compd	R ⁱ	<i>T. rubrum</i>	<i>T. mentagrophytes</i>	<i>C. albicans</i>	<i>C. neoformans</i>	<i>A. fumigatus</i>
19b	5-F	1	1	0.5	0.25	0.25
19d	5-Cl	1	2	1	2	1
19e	5-Me	8	4	2	8	2
19f	5-CF ₃	8	8	16	16	8
19g	5-NC	16	16	8	8	16
19h	5-MeO	64	32	>64	>64	>64
19i	5-HOCH ₂	64	64	>64	>64	>64
19j	6,7-benzo	4	2	32	32	32
19k	5-F-6-F	4	4	4	2	2
19l	4-F	16	16	64	32	32
19m	6-F	16	32	16	32	8
19n	7-F	16	16	32	32	4

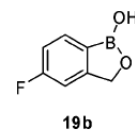


Figure 2. Structure of AN2690, currently in clinical trials for onychomycosis.