

P2422

AN2718 has Broad Spectrum Antifungal Activity
Necessary for the Topical Treatment of Skin
and Nail Fungal Infections

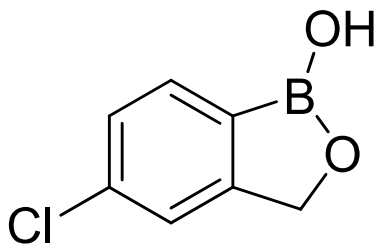
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Introduction

AN2718 (Baker *et al.*) is a member of a new class of antifungals, benzoxaboroles, which inhibit fungal growth by blocking protein synthesis (Rock *et al.*). AN2718 is being developed for the topical treatment of Tinea Pedis including the hard-to-treat moccasin-type, which at present is only treatable with oral antifungals.



AN2718 (5-chloro-1,3-dihydro-1-hydroxy-2,1-benzoxaborole)

Baker *et al.* (2006) *J Med Chem.* **49**:4447-50. Discovery of a new boron-containing antifungal agent, 5-fluoro-1,3-dihydro-1-hydroxy-2,1-benzoxaborole, for the potential treatment of onychomycosis.

Rock *et al.* (2007) *Science.* **316**:1759-61. An antifungal agent inhibits an aminoacyl-tRNA synthetase by trapping tRNA in the editing site.

AN2718 Has Broad-spectrum Antifungal Activity

Compound	Yeast MIC (µg/mL)				Molds MIC (µg/mL)		Dermatophytes MIC (µg/mL)			
	<i>Candida albicans</i>	<i>Candida glabrata</i>	<i>Candida parapsilosis</i>	<i>Cryptococcus neoformans</i>	<i>Fusarium solani</i>	<i>Aspergillus fumigatus</i>	<i>Epidermophyton floccosum</i>	<i>Microsporum canis</i>	<i>Trichophyton mentagrophytes</i>	<i>Trichophyton rubrum</i>
AN2718	1	0.25	4	2	4	1	2	4	1	0.5
Fluconazole	0.25	8	2	2	>128	>128	4	2	16	2
Terbinafine	1	64	0.5	0.125	64	4	0.015	0.03	0.015	0.008

AN2718 Has Good MIC₉₀ and MFC₉₀ Activity Against *Trichophyton* spp.

	AN2718 (µg/mL)			Terbinafine (µg/mL)		
	Range	MIC ₅₀	MIC ₉₀	Range	MIC ₅₀	MIC ₉₀
<i>T. rubrum</i> (n=100)	0.25 - 1	0.5	0.5	≤0.001 - 16	0.008	0.008
<i>T. mentagrophytes</i> (n=100)	0.25 - 1	0.5	1	0.002 - 0.06	0.008	0.015


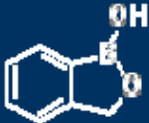
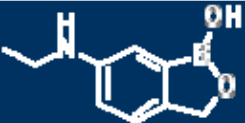
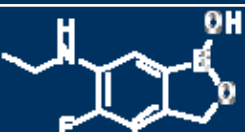
Data supplied by Center for Medical Mycology, OH

	AN2718 (µg/mL)			Terbinafine (µg/mL)		
	Range	MFC ₅₀	MFC ₉₀	Range	MFC ₅₀	MFC ₉₀
<i>T. rubrum</i> (n=100)	0.5 - 64	8	32	0.004 - >64	0.015	0.03
<i>T. mentagrophytes</i> (n=100)	0.5 - >32	8	16	0.002 - >0.5	0.03	0.12

Data supplied by Center for Medical Mycology, OH

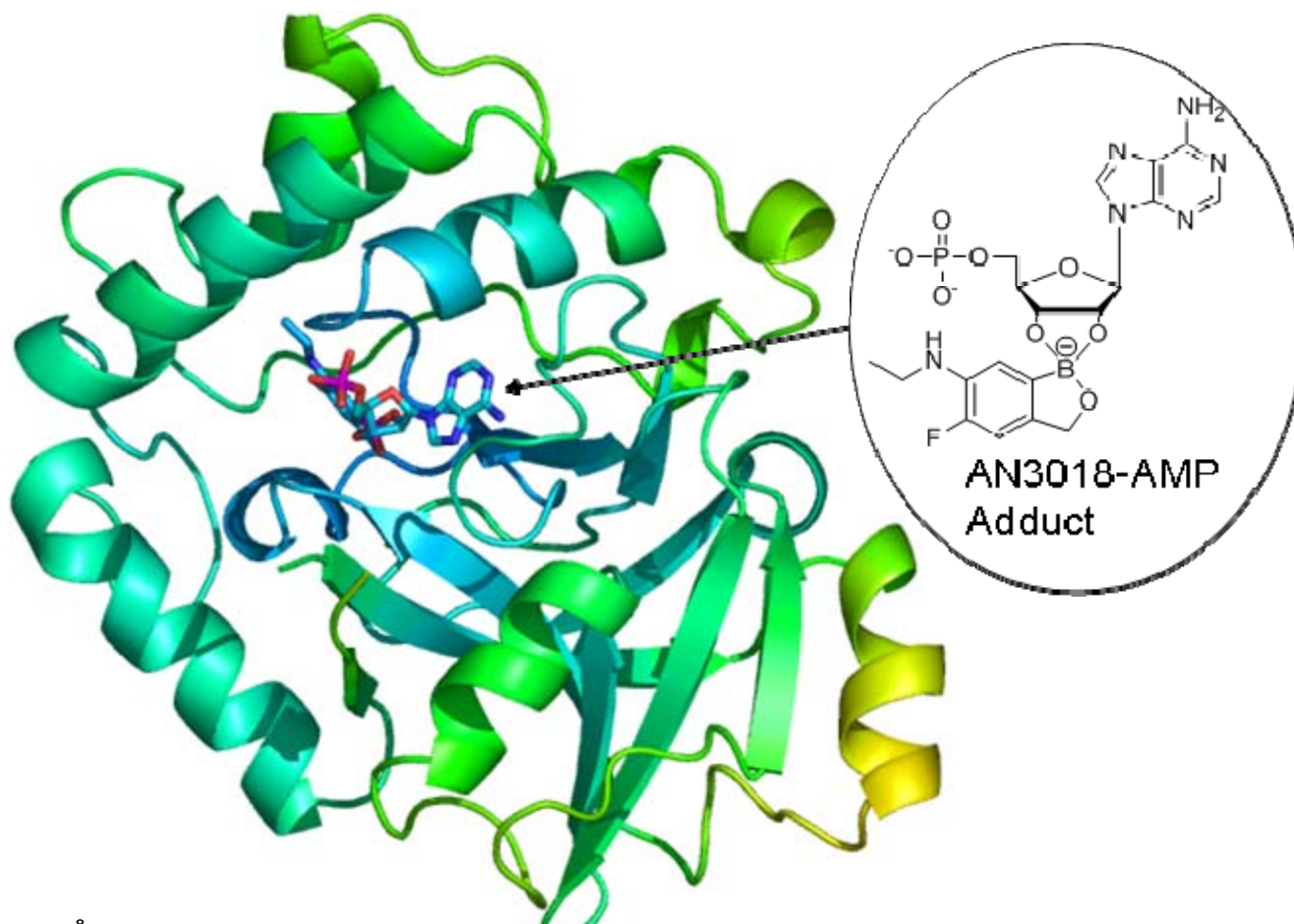
AN2718 Inhibits Fungal Leucyl-tRNA Synthetase

- Inhibition of leucyl-tRNA Synthetase (LeuRS) blocks protein synthesis
- Close analogues of AN2718 are also LeuRS inhibitors

Compound	Structure	<i>C. albicans</i>		<i>A. fumigatus</i>	
		LeuRS IC ₅₀ (μM)	MIC (μg/mL)	LeuRS IC ₅₀ (μM)	MIC (μg/mL)
AN2718		4.2	1	2	1
AN2679		5.7	1	2.6	2
AN3009		4.3	8	4.1	>64
AN3018		38	2	19.4	64

AN2718 Analogues Inhibit LeuRS by Trapping tRNA on The Fungal Enzyme

- AMP mimics the terminal nucleotide of tRNA^{Leu}
- AN3018, an analogue of AN2718, covalently binds to the free *cis*-diols of the terminal nucleotide of tRNA^{Leu}



Conclusions

- AN2718 inhibits LeuRS by a novel mechanism of action
 - the OBORT (*Rock et al.*) mechanism of trapping tRNA^{Leu} in the editing active site of LeuRS
- AN2718 has good MIC₉₀ activity against the dermatophytes, *T. rubrum* and *T. mentagrophytes*
- These data support the further evaluation of AN2718 as a topical agent to treat Tinea Pedis

Rock FL, *et al.* Science. 2007 316:1759-61. An antifungal agent inhibits an aminoacyl-tRNA synthetase by trapping tRNA in the editing site.