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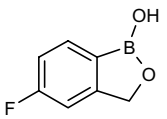
AN-2690

Topical Antifungal Agent
Treatment of Onychomycosis

5-Fluoro-1,3-dihydro-2,1-benzoxaborol-1-ol



$C_7H_6BFO_2$
Mol wt: 151.9307

CAS: 174671-46-6

EN: 415641

Abstract

Onychomycosis is a fungal infection of the nails that remains difficult to eradicate. AN-2690 is a small boron-containing antifungal compound in phase II trials as a topical therapy for onychomycosis. The compound has shown *in vitro* efficacy against a broad range of fungi, including the dermatophytes that cause onychomycosis, and it penetrates nails to reach sufficient concentrations in the nail bed to prevent fungal growth. Preclinical studies have indicated a good safety profile, and preliminary clinical data indicate its promise for the treatment of onychomycosis.

Synthesis

The oxaborole derivative AN-2690 can be synthesized as follows:

3-Fluorobenzaldehyde (I) is condensed with *p*-toluenesulfonylhydrazide to give the corresponding *N*-tosyl hydrazide (II). Subsequent reaction of (II) with boron tribromide in the presence of anhydrous ferric chloride, followed by refluxing with 2N NaOH, leads to the title oxaborole derivative (1). In an alternative method, 2-bromo-5-fluorobenzyl alcohol (III) is protected as the mixed acetal (V) by treatment with ethyl vinyl ether (IV) and pyridinium tosylate. Lithiation of (V), followed by reaction with trimethyl borate and quenching with 1N HCl, provides AN-2690 (2). Scheme 1.

Background

Onychomycosis, also known as tinea unguium, is a fungal infection of the fingernails and toenails, toenail infections being particularly common. It is a relatively common infection, with a prevelance of from 2% to 27% of the population, and the prevalence increases in individuals with diabetes, psoriasis and older subjects. Dermatophytes, especially *Trichophyton rubrum* and *Trichophyton mentagrophytes*, are responsible for 90% of onychomycosis cases, with yeasts and nondermatophyte molds responsible for the remainder. Systemic antifungal medications such as terbinafine (Lamisil®) are costly and require lengthy therapy and many oral antifungal agents are also associated with serious adverse effects, such as hematotoxicity and hepatotoxicity, as well as drug interactions. Topical preparations are usually not very effective for onychomycosis, although nail paints such as ciclopirox (Penlac®) are associated with a more favorable benefit/risk ratio and reduced cost, but require lengthy treatment, giving cure rates in U.S. studies of only 29-36% after 48 weeks of daily application. More recently, studies have shown improved efficacy for treatment with a combination of topical and oral medicines (3-8).

AN-2690 is a small boron-containing antifungal agent from Anacor Pharmaceuticals, specifically designed to effectively penetrate nails. It is currently in phase II clinical trials for the topical treatment of onychomycosis (9, 10).

Preclinical Pharmacology

The *in vitro* antifungal activities of AN-2690 were compared with those of ciclopirox, the only topical onychomycosis treatment approved by the FDA. AN-2690 showed activity against a broad spectrum of yeasts, molds and dermatophytes, with MICs ranging from 0.125 to 8 μg/ml; MICs for ciclopirox were similar and in the range < 0.5-4 μg/ml. When tested against a panel of 100 clinical isolates each of *T. rubrum* and *T. mentagrophytes*, the MIC_{50}/MIC_{90} of AN-2690 was 4/8 μg/ml and the MFC_{50}/MFC_{90} was 64/> 128 μg/ml; the corresponding values for ciclopirox were 0.25/0.5 μg/ml and > 16 μg/ml (9, 11, 12).

To determine the mechanism of action, AN-2690-resistant mutants of *Saccharomyces cerevisiae* were iso-

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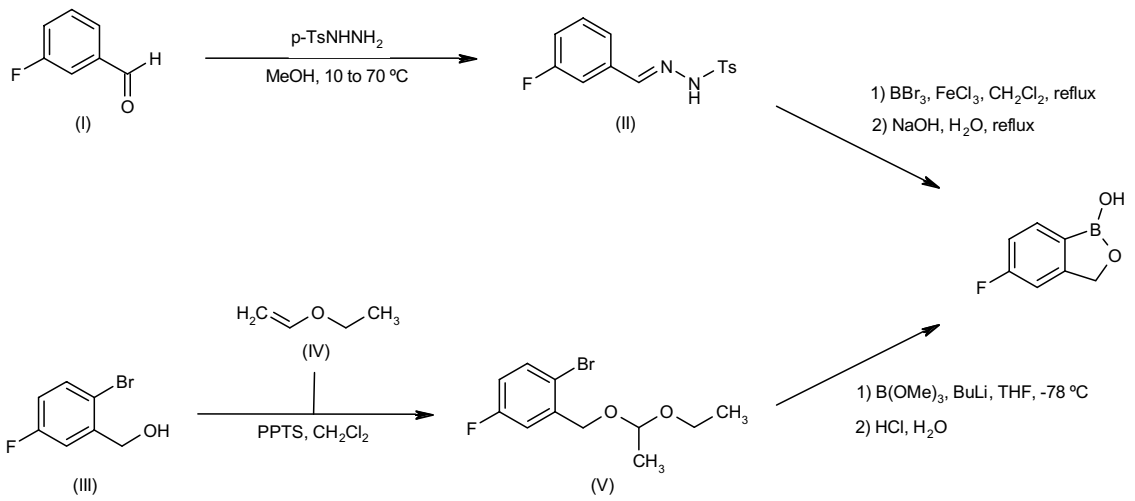
Scheme 1: Synthesis of AN-2690



lated. Mutations arose spontaneously at a frequency of 4 x 10^{-7}, similar to amphotericin B, and showed MIC values 16-128-fold higher than the parental *S. cerevisiae* ATCC201388 (MIC = 0.125 μg/ml). All mutations mapped to the *CDC60* gene, which codes for leucyl-tRNA synthetase (leucine—tRNA ligase), and more specifically, to the editing domain of *CDC60*. AN-2690 inhibited protein synthesis in *S. cerevisiae* in a concentration-dependent manner, and was noncompetitive with respect to leucine and ATP for inhibition of purified yeast leucyl-tRNA synthetase. These data suggest a unique mechanism of action for AN-2690, which appears to target the editing domain of the fungal leucyl-tRNA synthetase (12, 13).

The penetration of human nail plates by AN-2690 was compared to other antifungals in several studies. One study compared the penetration of AN-2690 (10%), ciclopirox (8%) and amorolfine (5%) in their commercial vehicles. The results demonstrated significantly better penetration for AN-2690; unlike the other agents, it reached concentrations exceeding the MIC for inhibition of dermatophyte growth (11). Similar experiments comparing the nail penetration of AN-2690 and ciclopirox gave comparable findings to the above study. AN-2690 achieved levels > 200 times those of ciclopirox under the nail plate. AN-2690 was then formulated in a nail lacquer at different concentrations (1-15% w/v) and applied to human cadaver fingernails. The optimal concentration appeared to be 7.5% w/v (14). Another study revealed that the nail penetration of AN-2690 is vehicle-independent. Again, very high levels of drug were detected, greatly exceeding the MIC against *T. rubrum* (15).

Pharmacokinetics and Metabolism

Results from an open-label study in 15 subjects with moderate to severe onychomycosis demonstrated minimal systemic absorption of AN-2690 following daily application of a 7.5% solution to the toenails for 28 days (16).

Safety

In preclinical toxicology studies, no inhibition was observed against a panel of receptors, cytochrome P-450 isozymes and the HERG channel at concentrations of AN-2690 up to 10 mM. No adverse effects on clinical pathology parameters were observed in rats administered once-daily oral doses of AN-2690 up to 200 mg/kg/day for 28 days. However, at 0.5 g/kg/day, 40% of the rats died and all of the rats died at 1 g/kg/day. Single oral doses up to 200 mg/kg had no effect on behavioral or neurological parameters in rats. In beagle dogs, no cardiovascular events were observed at 30 mg/kg p.o., although dose-dependent, reversible hypotension and increases in heart rate were seen at higher doses. AN-2690 showed no genotoxic effects in several assays. In tests of dermal toxicity, no systemic toxicity was observed when it was applied daily for 28 days to 5% of the body surface area of minipigs (doses up to 15% w/v in ethanol/propylene glycol 4:1). Local irritation was observed, however, at concentrations of 7% and above in minipigs, but no local irritation was seen in New Zealand white rabbits following a single application of a 10% solution to abraded skin. The 10% solution did not cause contact sensitization in guinea pigs. In tests of eye irritation in rabbits, both the vehicle and a 10% solution of AN-2690 caused irritation (17).

Clinical Studies

AN-2690 is being evaluated in two phase II clinical studies. The first is an open-label study in 60 patients with 20-60% of nail area affected. These patients receive either 5% or 7.5% AN-2690 once daily for 180 days. The

second is a double-blind placebo-controlled, 6-month trial in 180 onychomycosis patients receiving 2.5, 5 or 7.5% solutions of AN-2690 or placebo applied daily. Primary endpoints for both studies are a negative fungal culture of nail scrapings and > 5 mm clear nail growth at 6 months, or nails judged by investigators to be clear or almost clear (14, 18).

Interim analysis of the former study was reported for all 60 subjects through day 60 and 49 subjects through day 90. Compared to a 100% KOH-positive rate at baseline, 63%, 81% and 41% were positive at days 14, 30 and 60, respectively. Dermatophyte culture-positive rate at days 14 and 60 was 3% *versus* 50% at baseline. At least 1 mm of clear nail growth was seen in 67% of subjects at day 90, with an average of 3.5 mm, and > 5 mm of clear nail growth was achieved in 16% of subjects. Good tolerance was reported by most subjects (18).

Source

Anacor Pharmaceuticals, Inc. (US).

References

1. Austin, P.W., Kneale, C.J., Crowley, P.J., Clough, J.M. (Zeneca Ltd.). *Oxaboroles and salts thereof, and their use as biocides*. WO 9533754.

2. Hinklin, R.J., Wallace, O.B. (Eli Lilly and Company). *Pentacyclic oxepines and derivaeastives thereof, compositions and methods*. WO 2004009578.

3. Hainer, B.L. *Dermatophyte infections*. Am Fam Physician 2003, 67(1): 101-8.

4. Prous Science Drug R&D Backgrounders: *Fungal infections: Dermatotomycoses – online publication*. Updated June 8, 2006.

5. Baran, R., Kaoukhov, A. *Topical antifungal drugs for the treatment of onychomycosis: An overview of current strategies for monotherapy and combination therapy*. J Eur Acad Dermatol Venereol 2005, 19(1): 21-9.

6. Noble, S.L., Forbes, R.C., Stamm, P.L. *Diagnosis and management of common tinea infections*. Am Fam Physician 1998, 58(1): 163-74, 177-8.

7. Harrell, T.K., Necomb, W.W., Replogle, W.H., King, D.S., Noble, S.L. *Onychomycosis: Improved cure rates with itraconazale and terbinafine*. J Am Board Fam Pract 2000, 13(4): 268-73.

8. Gupta, A.K., Fleckman, P., Baran, R. *Ciclopirox nail lacquer topical solution 8% in the treatment of toenail onychomycosis*. J Am Acad Dermatol 2000, 43(4, Suppl.): S70-80.

9. Plattner, J.J., Baker, S.J., Zhang, Y.-K. et al. *Medicinal chemistry of AN2690, a novel broad-spectrum antifungal agent in development for the topical treatment of onychomycosis*. 67th Annu Meet Soc Invest Dermatol (May 3-6, Philadelphia) 2006, Abst 775.

10. *AN-2690: Preclinical update of topical treatment of onychomycosis*. DailyDrugNews.com, March 7, 2006.

11. Sanders, V., Baker, S.J., Alley, M.R.K. et al. *Microbiological activity of AN2690, a new antifungal agent in development for the topical treatment of onychomycosis*. 64th Annu Meet Am Acad Dermatol (AAD) (March 3-7, San Francisco) 2006, Abst P1608.

12. Mao, W., Rock, F., Alley, M. *AN2690, a topical antifungal agent in development for the treatment of onychomycosis represents a new class of inhibitor and has a novel mechanism of action*. 67th Annu Meet Soc Invest Dermatol (May 3-6, Philadelphia) 2006, Abst 769.

13. Mao, W., Alley, M.R.K. *Initial characterization of resistant mutants to AN2690, a new antifungal agent in development for the topical treatment of onychomycosis, predicts a novel mechanism of action*. 64th Annu Meet Am Acad Dermatol (AAD) (March 3-7, San Francisco) 2006, Abst P1607.

14. Baker, S.J., Sanders, V., Hold, K.M. et al. *In vitro nail penetration profile of AN2690, a novel broad-spectrum antifungal agent in development for the topical treatment of onychomycosis*. 67th Annu Meet Soc Invest Dermatol (May 3-6, Philadelphia) 2006, Abst 750.

15. Baker, S., Hui, X., Sanders, V. et al. *Nail penetration of AN2690: Efficacy coefficient and effect of formulation*. J Invest Dermatol 2006, 126 (Suppl. 3): Abst 091.

16. Beutner, K., Jones, T., Sanders, V. *An open-label, multiple-dose study of the absorption and systemic pharmacokinetics of AN2690 applied as a 7.5% solution to all toenails of adult patients with moderate to severe onychomycosis*. J Invest Dermatol 2006, 126 (Suppl. 3): Abst 566.

17. Ip, E.Y., Sanders, V., Baker, S.J., Bellinger-Kawahara, C., Maples, K.R. *Preclinical toxicology of AN2690, a new antifungal agent in development for the topical treatment of onychomycosis*. 64th Annu Meet Am Acad Dermatol (AAD) (March 3-7, San Francisco) 2006, Abst P1611.

18. Beutner, K., Toledo-Bahena, M., Barbosa, A.H. et at. *Interim results of a multi-center study to evaluate the safety and efficacy of topically applied AN2690 5.0% and 7.5% solution for the treatment of onychomycosis of the great toenail*. J Invest Dermatol 2006, 126 (Suppl. 3): Abst 565.