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Research Article

Synthesis of isotopically labelled (3-^{14}C)- and (3,3-$^{2}H_2$)-5-fluoro-1,3-dihydro-1-hydroxy-2,1-benzoxaborole (AN2690), a new antifungal agent for the potential treatment of onychomycosis

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Abstract: 5-Fluoro-1,3-dihydro-1-hydroxy-2,1-benzoxaborole (AN2690) is a new antifungal agent for the potential treatment of onychomycosis. During the preclinical development phase, it was necessary to synthesize the radioisotope [3-^{14}C]-5-fluoro-1,3-dihydro-1-hydroxy-2,1-benzoxaborole and the deuterium isotope [3,3-$^{2}H_2$]-5-fluoro-1,3-dihydro-1-hydroxy-2,1-benzoxaborole for *in vitro* studies. We report the synthesis of these two isotopically labelled derivatives. Copyright © 2007 John Wiley & Sons, Ltd.

Keywords: oxaborole; antifungal; onychomycosis; AN2690

Introduction

Onychomycosis is a common fungal infection of the toe and fingernails and is mainly caused by the dermatophytes *Trichophyton rubrum and Trichophyton mentagrophytes*.[1] Onychomycosis usually involves the nail plate and the nail bed, hence, an effective treatment must disseminate throughout this area and achieve sufficient concentrations to kill the causative fungi. Onychomycosis is treated using systemic and/or topical therapies, however, treatment failures are high and recurrence of the disease is common.[2–4] Although topical therapy would seem the more obvious method of treatment, it is widely believed that clinical failure by this route is due to poor penetration of the topically applied drug throughout nail plate, nail bed and surrounding tissue.[5] In order to understand and overcome the poor penetration, comparison of the composition of the human nail in relation to the physicochemical properties and permeability of drugs through nails have been reported and reviewed.[5–9] Using this information, we have developed a boron-containing antifungal agent, AN2690, (Figure 1) designed to penetrate nails and treat onychomycosis topically.[10] First, in order to study its ability to penetrate human cadaver finger nail plates *in vitro*,[11] we required a radiolabelled version so we could accurately measure amounts within the nail plate and amounts that had penetrated through and into a collector using previously published methods.[12,13] For this purpose, we designed [3-^{14}C]-5-fluoro-1,3-dihydro-1-hydroxy-2,1-benzoxaborole, which incorporates the radioisotope into the 3-position of the oxaborole ring. Second, we required a bis-deuterium isotope to use as a reference sample for the mass spectrometry analysis of biological samples during pre-clinical development. For this purpose we designed [3,3-$^{2}H_2$]-5-fluoro-1,3-dihydro-1-hydroxy-2,1-benzoxaborole, which incorporates the two deuterium isotopes on the methylene carbon in the oxaborole ring. We wish to report the synthesis of these two isotopically labelled compounds.

Results and discussion

Synthesis of (3-^{14}C)-5-fluoro-1,3-dihydro-1-hydroxy-2,1-benzoxaborole (7)

5-Fluoro-1,3-dihydro-1-hydroxy-2,1-benzoxaborole is typically synthesized from 2-bromo-5-fluorobenzylal-

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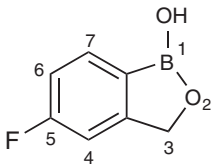


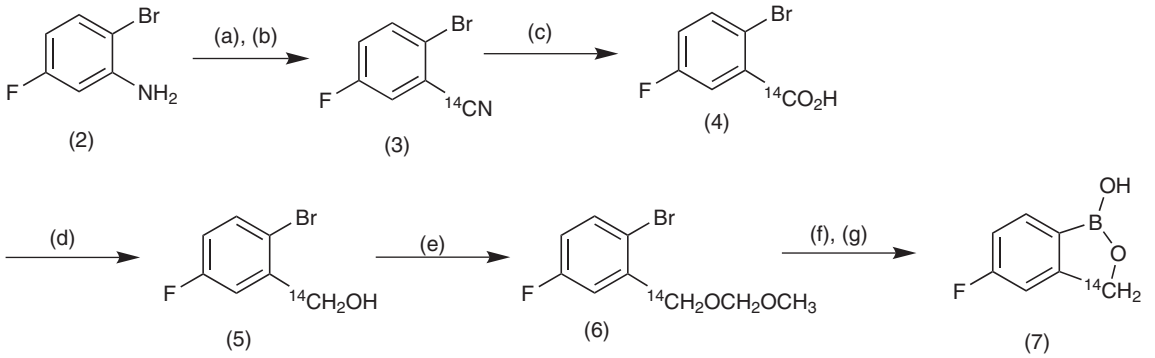
(1)

Figure 1 Structure of 5-fluoro-1,3-dihydro-1-hydroxy-2,1-benzoxaborole (AN2690).

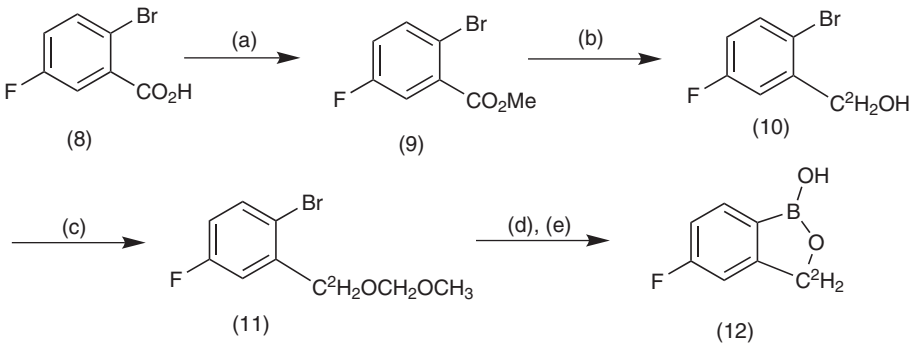
cohol,[10] therefore, we designed a synthesis that would be compatible with both our previous experience and ability to introduce a radiolabel (Scheme 1). Radioactivity was incorporated into the molecule using the Sandmeyer reaction. 2-Bromo-5-fluoroaniline (**2**) was diazotized using sulfuric acid, hydrochloric acid and sodium nitrite. The reaction was neutralized using aqueous sodium carbonate then added to a mixture of potassium and copper(I) [^{14}C]cyanides in water at 0°C to give the 2-bromo-5-fluorobenzo[^{14}C]nitrile (**3**) as a dark orange solid in 61% yield. Hydrolysis of the nitrile group using 50% sulfuric acid at 140°C gave the desired benzoic acid (**4**) as a white solid in 76% yield, which was reduced with borane–tetrahydrofuran complex to give the benzyl alcohol (**5**) as a white solid in quantitative yield. Protection of the alcohol using chloromethyl methyl ether gave the MOM protected ether (**6**) in 82% yield. In the final step, the MOM protected ether (**6**) was treated with *n*-butyl lithium at −78°C followed by triisopropyl borate. Hydrolysis of the reaction mixture with hydrochloric acid gave the crude product, which was purified by HPLC and recrystallization to furnish (**7**) as a white solid in 22% yield with a specific activity of 55 mCi/mmol.

Synthesis of (3,3-$^2H_2$)-5-fluoro-1,3-dihydro-1-hydroxy-2,1-benzoxaborole (12)

In order to synthesize the bis-deuteriated derivative, we designed the synthesis shown in Scheme 2, which introduces the isotopes via reduction of a methyl ester using a deuteriated reducing agent. 2-Bromo-5-fluorobenzoic acid (**8**) was converted to its methyl ester (**9**) in



Scheme 1 Conditions: (a) 1 M H_2SO_4, 4 M HCl, $NaNO_2$, water, 4°C; (b) $Cu^{14}CN$, $K^{14}CN$, water 0°C; (c) H_2SO_4, 140°C; (d) BH_3–THF, THF; (e) $ClCH_2OCH_3$, $(i\text{-Pr})_2NEt$, CH_2Cl_2; (f) *n*-BuLi, THF, $B(O\text{-}i\text{-Pr})_3$, −78°C to room temperature; and (g) 6 N HCl.



Scheme 2 Conditions: (a) MeOH, H_2SO_4, room temperature for 2 days then reflux for 1 day; (b) $LiEt_3B^2H$, THF 0°C, 16 h; (c) $ClCH_2OCH_3$, $(i\text{-Pr})_2NEt$, CH_2Cl_2; (d) *t*-BuLi, THF, $B(OMe)_3$, −78°C to room temperature; and (e) 6 N HCl.

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95% yield by heating to reflux with methanol in the presence of sulfuric acid. The isotopes were then introduced into the molecule by reducing the methyl ester (**9**) to the corresponding alcohol (**10**) with super deuteride ($LiEt_3B^2H$) in quantitative yield. The resulting alcohol (**10**) was treated with chloromethyl methyl ether to give the MOM-protected ether (**11**) in 79% yield. In the final step, the MOM protected ether (**11**) was treated with *t*-butyl lithium at −78°C followed by trimethyl borate. Hydrolysis of the reaction mixture with hydrochloric acid gave the desired product (**12**) as a white solid in 42% yield.

Use of isotopically labelled (3-^{14}C)-AN2690 (7) and (3,3-$^2H_2$)AN2690 (12) as internal standards

[3-^{14}C]-AN2690 (**7**) was used to quantify the penetration of AN2690 from a topical formulation consisting of 10% AN2690 w/v in ethanol/propylene glycol (4:1). The results of this study will be reported elsewhere.[11] [3,3-$^2H_2$]-AN2690 (**12**) was used as an internal standard for negative ion LC/MS/MS analysis to quantify AN2690 in plasma samples. The mass difference of 2 Da has proven to be satisfactory for our analytical requirements. The two isotopes of boron ^{10}B and ^{11}B have a natural abundance of 19.9 and 80.1%, respectively. The isotopic distribution of AN2690 in negative ion mass spectrometry is m/z 150 (18.25%), 151 (75.75%), 152 (5.60%) and 153 (0.38%) and for [3,3-$^2H_2$]-AN2690 (**12**), it is m/z 152 (18.25%), 153 (75.75%), 154 (5.60%) and 155 (0.38%). In quantitative analysis, the MS/MS transitions followed for AN2690 and [3,3-$^2H_2$]-AN2690 (**12**) are $151 \rightarrow 43$ and $153 \rightarrow 43$, respectively. Thus, there is overlap of the AN2690 M + 2 signal at $m/z = 153$ with that of [3,3-$^2H_2$]-AN2690 (**12**). In a 1:1 mixture of AN2690 and [3,3-$^2H_2$]-AN2690 (**12**) this overlap amounts to 0.5%. This is well below the 5% limit set in the standard operating procedure for the plasma assay. This limit allows a maximum ratio of AN2690:[3,3-$^2H_2$]-AN2690 (**12**) of 10:1. In our plasma assays we typically use [3,3-$^2H_2$]-AN2690 (**12**) at a concentration of 1250 ng/mL and remain within a ratio of 8:1 AN2690:[3,3-$^2H_2$]-AN2690 (**12**). Another point if note is that although there is a small amount of unlabelled material present in the [3,3-$^2H_2$]-AN2690 (**12**) sample, at the concentrations we use, the contribution of this impurity to the signals at 151 and 153 is negligible. If, in the event that an increase in ULOQ is required, an M + 3 internal standard could be synthesized by using a combination of the chemistry described in Schemes 1 and 2 and using ^{13}C in place of ^{14}C to yield the triple labelled [3-^{13}C]-[3,3-$^2H_2$]-5-fluoro-1,3-dihydro-1-hydroxy-2,1-benzoxaborole.

Experimental

Materials and methods

Copper [^{14}C]cyanide and potassium [^{14}C]cyanide were obtained from GE Healthcare. All other starting materials, reagents and solvents were purchased from Sigma-Aldrich. For the synthesis of [3-^{14}C]-5-fluoro-1,3-dihydro-1-hydroxy-2,1-benzoxaborole (**7**) preparative chromatography was performed using Merck silica gel 60 (0.040–0.063 mm). The analytical HPLC systems were: System 1 – HP1100 series HPLC, column; Betabasic 3 μm C-18 (150 × 4.6 mm), solvent A; 0.1% phosphoric acid in water, solvent B; acetonitrile, gradient; 5–100% B over 10 min, held for 10 min, flow rate; 1 mL/min, detection; radiochemical and UV at 254 and 220 nm. System 2 – column; Genesis Aq 7 μm C18 (150 × 4.6 mm), solvent A; 0.05% trifluoroacetic acid in water, solvent B; 0.05% trifluoroactic acid in acetonitrile, gradient; 25% B (10 min), then 25–50% B over 10 min, held for 10 min, flow rate; 1 mL/min, detection; radiochemical and UV at 254 nm. Preparative HPLC was performed on a Gilson 305 series HPLC, reverse phase was performed at 20 mL/min on either a Genesis AQ 7 μm (250 × 22.5 mm) or a Phenomenex Prodigy 10 μm ODS-Prep (21.2 × 250 mm); normal phase was performed at 20 mL/min on a Dynamax Microsorb 60-8 Si (21.4 × 250 mm). ^{1}H-NMR spectra were measured on a Brucker Avance 400. Mass spectra (electron impact) were measured on a Jeol DX300.

For the synthesis of [3,3-$^2H_2$]-5-fluoro-1,3-dihydro-1-hydroxy-2,1-benzoxaborole (**12**) ^{1}H-NMR spectra were recorded on Oxford 300 (300 MHz) spectrometer (Varian). Melting points were obtained using a Mel-Temp-II melting point apparatus and are uncorrected. Mass spectra were determined on API 3000 (Applied Biosystems). HPLC purity was determined using ProStar Model 330 (Varian) coupled with a binary solvent delivery module, an autosampler and a photodiode array detector. Column: Thermo BetaBasic-18, 5 μm, (4.6 × 150 mm), solvent A; 0.1% phosphoric acid in water, solvent B; acetonitrile, gradient; 5–100% B over 10 min, held for 10 min, flow rate 1 mL/min.

2-Bromo-5-fluorobenzo(^{14}C)nitrile (3)

2-Bromo-5-fluoroaniline (**2**, 513 mg, 2.7 mmol) was dissolved in a mixture of 1 M sulfuric acid (5.4 mL), 4 M hydrochloric acid (0.7 mL) and water (24 mL) and stirred at 4°C throughout the dropwise addition of a solution of sodium nitrite (205 mg, 3 mmol in 2.5 mL water). A solution of sodium carbonate (572 mg, 5.4 mmol) in water (3 mL) was then immediately added

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to neutralize the mixture. This solution was then added by Pasteur pipette into a previously prepared solution of copper [^{14}C]cyanide (43 mCi, 56 mCi/mmol, 0.77 mmol) and potassium [^{14}C]cyanide (102 mCi, 56 mCi/mmol, 1.82 mmol) in water (8 mL) in an ice bath. When the addition was complete the mixture was swirled for 5 min at 0°C and then swirled whilst the mixture warmed to room temperature. The flask was then sealed and shaken at intervals over 15 min. The product was extracted into dichloromethane, dried over sodium sulfate, filtered and concentrated. The residue was purified over silica gel eluting with dichloromethane, hexane (1:5). Pure fractions (92 mCi) were combined and concentrated by rotary evaporation to an orange-brown solid (61%). The material co-chromatographed with an authentic marker by TLC on silica gel (diethyl ether, hexane 1:4; R_F 0.37).

2-Bromo-5-fluoro(α-^{14}C)benzoic acid (4)

The crude 2-bromo-5-fluorobenzo[^{14}C]nitrile (92 mCi, 1.64 mmol) was only partially hydrolyzed by 50% sulfuric acid (10 mL) in an open system over 5 h at 140°C due to the tendency of the nitrile to sublime. The mixture was cooled and extracted with ether to recover product and starting material and the reaction was continued by placing the material in 50% sulfuric acid (10 mL) in a sealed tube. The tube was placed in an oven at 140°C for 4 h and then cooled and opened. The mixture was diluted with water (50 mL) and extracted into ether (100 mL). The ether layer was washed with water (2 × 30 mL) then saturated sodium chloride solution and dried over sodium sulfate. Filtration and concentration gave the crude acid. This was purified by reverse phase HPLC (Genesis Aq) in four injections eluting with 0.1% aqueous trifluoroacetic acid, acetonitrile (3:7). Pure fractions were combined (76.6 mCi) and concentrated to afford an aqueous suspension. This was extracted with ether (100 mL, 25 mL) and then diluted with dichloromethane before drying over sodium sulfate. Filtration and concentration gave a white solid. (76%). The material co-chromatographed with an authentic marker by analytical HPLC (System 2): $t_R = 8.51$ min. MS (EI-): m/z 218/220/222 (M+); specific activity 56 mCi/mmol.

2-Bromo-5-fluoro(α,-^{14}C)benzyl alcohol (5)

2-Bromo-5-fluoro[α-^{14}C]benzoic acid (**4**, 70 mCi, 1.25 mmol) was dissolved in tetrahydrofuran and treated with 1 M borane–tetrahydrofuran complex (10 mL) and stirred at room temperature for 2.5 h. Excess methanol was added under ice cooling and the solvent rotary evaporated off. Water (30 mL) was added and the product was extracted into dichloromethane (2 × 30 mL) and dried over sodium sulfate. Filtration and concentration gave a residue which was purified by chromatography over silica gel eluting with a mixture of ether and hexane (1:4). Pure fractions (71 mCi) were combined and concentrated to a white solid product. The material co-chromatographed with an authentic marker by TLC on silica gel (diethyl ether, hexane 1:2; R_F 0.25).

(2-Bromo-5-fluoro(α,-^{14}C)benzyl)(methoxymethyl) ether (6)

Chloromethyl methyl ether (115 μl, 1.54 mmol) was added to a solution of 2-bromo-5-fluoro[α,-^{14}C]benzyl alcohol (**5**, 70 mCi, 1.25 mmol) and diisopropylethylamine (260 μl) in dichloromethane (4.7 mL) at 0°C. The mixture was stirred at room temperature for 50 h. Water (5 ml) was added and the organic layer was separated and washed with saturated sodium chloride solution (2 × 2 mL) and dried over sodium sulfate. Filtration and rotary evaporation gave a residue which was purified by chromatography over silica gel eluting with hexane, ether (95:5). Some un-reacted starting material was recovered and this was reworked as above. Material from both runs was further purified by HPLC on silica gel eluting with hexane, ether (199:1) to afford pure material (57.5 mCi) which was concentrated by rotary evaporation (82% yield). The material co-chromatographed with an authentic marker by TLC on silica gel (diethyl ether, hexane 1:2; R_F 0.41).

(3-^{14}C)-5-Fluoro-1,3-dihydro-1-hydroxy-2,1-benzoxaborole (7)

n-Butyllithium 1.6 M (708 μl, 1.133 mmol) was added dropwise to a solution of (2-bromo-5-fluoro[α,-^{14}C] benzyl)(methoxymethyl) ether (**6**, 57.5 mCi, 1.03 mmol) in tetrahydrofuran (1.4 mL) at −78°C. The mixture was stirred for 5 min and triisopropyl borate (269 μl, 1.164 mmol) was added dropwise. The reaction mixture was allowed to warm to room temperature over 1.5 h. Water (1 mL) was added at 0°C and the mixture was acidified to pH 1 with 6 M hydrochloric acid and heated at 60°C for 8 h. On cooling, the material was partitioned between water (10 mL) and ethyl acetate (10 mL) and the organic layer separated and washed with saturated sodium chloride solution (3 × 5 mL). The solvent was removed by rotary evaporation, re-dissolved in ethyl acetate (30 mL) and dried over sodium sulfate. The drying agent was filtered and the solvent removed by rotary evaporation. The crude product was purified by reverse-phase HPLC (Phenomenex Prodigy) eluting with water, acetonitrile, trifluoroacetic acid (70:30:1). Pure

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fractions were rotary evaporated to remove acetonitrile and the product was extracted with dichloromethane (2×30 mL). The combined extracts were washed with saturated sodium chloride solution (30 mL) and dried over sodium sulfate. Filtration gave a clear solution (24 mCi) which was concentrated to a solid. This was recrystallized from diisopropyl ether/pentane and dried under vacuum to give a white solid (35.7 mg, 0.248 mmol, 22%). The specific activity was determined as 367.4 μCi/mg, equivalent to 56 mCi/mmol, corresponding to 13.88 mCi, The material was consistent with an authentic sample provided by mass spectrometry, NMR spectroscopy and HPLC. HPLC (system 1): $t_R = 8.48$ min, radiochemical purity 99.3%. ^{1}H-NMR (DMSO-d^6, 400 MHz): $\delta = 9.22$ (s, 1H), 7.78 (dd, 1H), 7.25 (dd, 1H), 7.19 (m, 1H) 4.98 (s, 2H). MS (EI): m/z 151/153 (M−1); specific activity 55 mCi/mmol.

2-Bromo-5-fluorobenzoic acid methyl ester (9)

A solution of 2-bromo-5-fluorobenzoic acid (**8**, 10.29 g, 46.98 mmol) and 98% sulfuric acid (3 mL) in methanol (150 mL) was stirred at room temperature over a weekend and then refluxed for 24 h under nitrogen atmosphere. The solution was concentrated to about 50 mL and then slowly added to a cold saturated aqueous $NaHCO_3$ solution (300 mL). Sodium chloride-saturated water (200 mL) was added and the mixture was extracted with ethyl acetate (2×200 mL), dried over $MgSO_4$, filtered and evaporated. The residue was dissolved in hexane, dried again, filtered and evaporated to give the title methyl ester as a colorless liquid (10.42 g, yield 95%). ^{1}H NMR (DMSO-d$_6$, 300 MHz) δ 3.85 (s, 3H), 7.39 (td, $J_t = 8.1$ Hz, $J_d = 3.3$ Hz, 1H), 7.62 (dd, $J = 9.3$ and 3.3 Hz, 1H), 7.78 (dd, $J = 9.0$ and 5.1 Hz, 1H).

2-Bromo-5-fluoro(α,α-$^2H_2$)benzyl Alcohol (10)

To a solution of 2-bromo-5-fluorobenzoic acid methyl ester (**9**, 10.4 g, 44.63 mmol) in anhydrous THF (180 mL) was added dropwise lithium triethylborodeuteride (super deuteride, 1 M THF solution, 95 mL, 95 mmol) at 0°C. The mixture was stirred overnight at 0°C to room temperature, then recooled to 0°C and 6 N HCl (30 mL) was slowly added under nitrogen atmosphere. Rotary evaporation gave a residue that was mixed with brine and extracted with ethyl acetate. The solution was dried over $MgSO_4$, filtered and evaporated to provide the title alcohol as a white solid (9.4 g, yield 100%). The ^{1}H NMR data indicated the presence of 2.0 mol% non-deuteriated alcohol in the product. ^{1}H NMR (DMSO-d$_6$, 300 MHz) δ 5.54 (s, 1H), 7.07 (td, $J_t = 8.6$ Hz, $J_d = 3.3$ Hz, 1H), 7.29 (dd, $J = 9.9$ and 3.3 Hz, 1H), 7.59 (dd, $J = 9.0$ and 5.1 Hz, 1H).

(2-Bromo-5-fluoro(α,α-$^2H_2$)benzyl)(methoxymethyl) ether (11)

To a mixture of 2-bromo-5-fluoro[α,α-$^2H_2$]benzyl alcohol (**10**, 9.4 g, 45 mmol) and diisopropylethylamine (12 mL, 67.5 mmol) in methylene chloride (150 mL) was added dropwise chloromethyl methyl ether (4.3 mL, 56.3 mmol) at 0°C under a nitrogen atmosphere. After being stirred overnight at room temperature, the mixture was washed with $NaHCO_3$ solution, dried, filtered and evaporated. The oil residue was purified by flash column chromatography over silica gel eluted with a mixed solvent of hexane and ethyl acetate (5:1, v/v) to afford the title ether compound as a colorless liquid (8.87 g, yield 78.5%). ^{1}H NMR (DMSO-d$_6$, 300 MHz) δ 3.30 (s, 3H), 4.71 (s, 2H), 7.13 (td, $J_t = 8.7$ Hz, $J_d = 3.3$ Hz, 1H), 7.31 (dd, $J = 9.9$ and 3.3 Hz, 1H), 7.64 (dd, $J = 9.0$ and 5.4 Hz, 1H).

(3,3-$^2H_2$)-5-Fluoro-1,3-dihydro-1-hydroxy-2,1-benzoxaborole (12)

To a solution of (2-bromo-5-fluoro[α,α-$^2H_2$]benzyl) (methoxymethyl) ether (**11**, 8.86 g, 35.3 mmol) in anhydrous THF (150 mL) was added dropwise *tert*-butyl lithium (1.7 M solution in hexane, 25 mL, 42.5 mmol) at −78°C under nitrogen atmosphere. After being stirred for 5–10 min at −78°C, B(OMe)$_3$ (3.93 mL, 35.3 mmol) was added in one portion, and then the cooling bath was removed. The reaction mixture was stirred for 30 min before the reaction flask was placed into a room temperature water bath with additional 1.5 h stirring. Hydrochloric acid (6 N, 16 mL) was added and THF was removed by rotary evaporation. Methanol (125 mL) was added to the acidic aqueous residue and the resulting solution was stirred overnight at room temperature to hydrolyze the methoxymethyl group. The solution was evaporated to give a residue that was mixed with brine and extracted with ethyl acetate. The residue after evaporation was purified by flash column chromatography over silica gel eluted with a mixed solvent of hexane and ethyl acetate (3:1, v/v) to produce a solid (3.0 g) that was stirred in *n*-pentane (25 mL). Sonication of the suspension and then filtration afforded the final compound 1,3-dihydro-5-fluoro-1-hydroxy-[3,3-$^2H_2$]-2,1-benzoxaborole as a white solid (2.29 g, yield 42%). The ^{1}H NMR data indicated the presence of 1.5 mol% undeuteriated compound 1,3-dihydro-5-fluoro-1-hydroxy-2,1-benzoxaborole in the product. M.p. 120–125°C; ^{1}H NMR (DMSO-d$_6$, 300 MHz) δ 7.15 (td, $J_t = 8.9$ Hz, $J_d = 2.4$ Hz, 1H), 7.23 (dd, $J = 9.6$ and

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2.0 Hz, 1H), 7.64 (dd, $J = 7.8$ and 5.7 Hz, 1H), 9.21 (s, 1H); MS (ESI-): m/z 153 (M − 1); HPLC: 95.7% at 220 nm.

Conclusion

In conclusion, we report the successful synthesis of two isotopically labelled derivatives of AN2690, a novel oxaborole antifungal for the potential treatment of onychomycosis. These isotopically labelled derivatives were used for *in vitro* pre-clinical studies. The result of one of these studies will be reported in due course.[11]

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