ANACOR PHARMACEUTICALS — Developing Small Molecule therapeutics derived from our boron chemistry platform

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Pre-clinical Chemistry of GSK2251052: A First in Class Boron-Containing Antibacterial Agent

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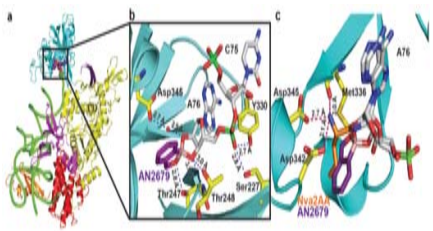
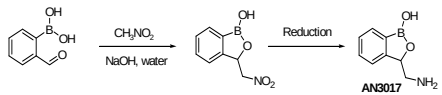
Introduction

GSK2251052 (formerly AN3365), a novel boron-containing heterocycle with *in vitro* activity against Pseudomonas aeruginosa and multidrug-resistant Enterobacteriaceae, is being developed for the treatment of serious Gram-negative bacterial infections. GSK2251052 and related benzoxaborole compounds inhibit leucyl tRNA synthetase by trapping tRNA in the editing domain.[1] Structure-based analysis of the AN2679 *E. coli* $tRNA^{leu}$ complex revealed a key binding site which was not being utilized. The lead compound, AN3017, incorporated an aminomethyl at the 3-position to gain these critical interactions. Further utilization of SBDD created AN3213 designed to further stabilize the adduct, based on the postulation that a C-7 hydroxypropoxy substitution on AN3017 would be able to acquire additional interactions with the tRNA.[2] The synthesis of these designed molecules and the resolution of their enantiomers to provide AN3334 and GSK2251052 are described in this poster.

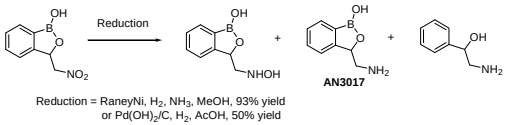


AN3017

We envisioned a Henry reaction with 2-formylphenylboronic acid and nitromethane followed by nitro reduction to produce AN3017.[3] We were surprised by the lack of literature precedent for the reduction of an aliphatic nitro to an amino in the presence of an arylboronic acid or ester.

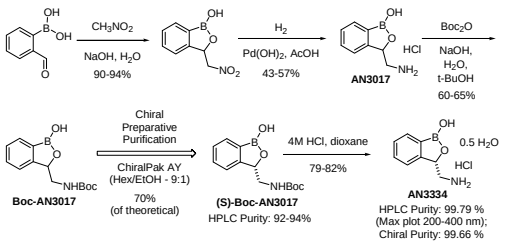


After extensive investigation, the best conditions to generate AN3017 balanced under reduction (hydroxylamine formation) and over reaction (proto-deboronation). Although Raney Nickel appeared superior yield wise, the variability and its pyrophoric nature prompted us to utilize Pearlman's catalyst for scale-up.



The S-enantiomer of AN3017 (AN3334) proved to be the more active.

AN3334 Synthesis



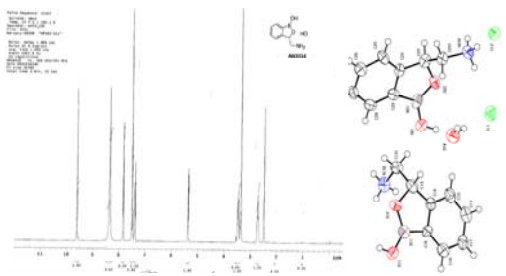
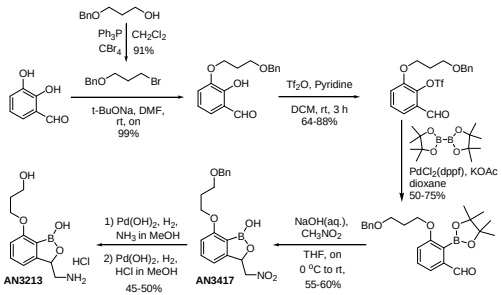
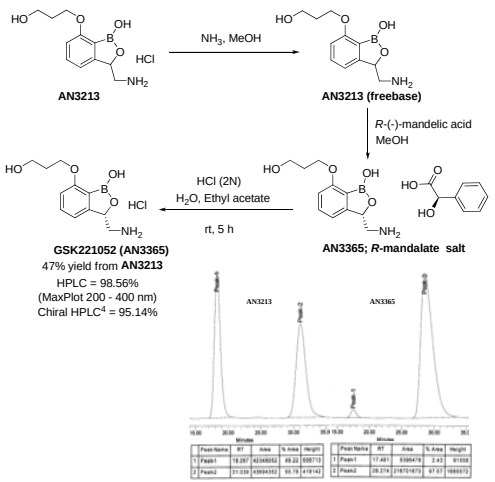


Figure 1. ^{1}HNMR (d_6-DMSO) and Single Crystal X-ray of AN3334

AN3213 Synthesis



GSK2251052 *via* Resolution



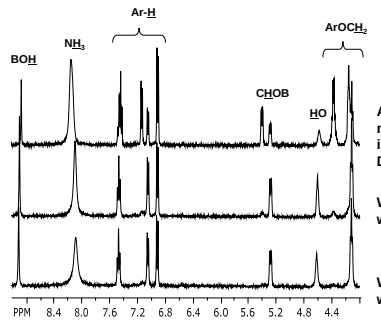


Figure 2. ^{1}HNMR (d_6-DMSO) of AN3213 with added H_2O

The ^{1}HNMR of many benzoxaboroles can show significant complexation in non-polar solvents, such as $CDCl_3$. The ^{1}HNMR of AN3213 shows equilibrium even in non-anhydrous d_6-DMSO.

Conclusions

- Conditions to successfully reduce an aliphatic nitro in the presence of an arylboron enabled the facile syntheses of two novel benzoxaboroles.
- Although unique equilibria and chemistries can be observed when employing benzoxaboroles, their excellent stability tolerates numerous synthetic, resolution and purification protocols.
- Based on the chemistries shown, the production of kilogram quantities of AN3334 and GSK2251052 have been accomplished for further therapeutic evaluation.

References

1) Rock FL, *et al. Science*, **2007**, *316*, 1759-61.
2) Hernandez V, talk in this conference Wednesday, May 23 at 11:05 am.
3) This Henry reaction was previously reported in Tschampel, P.; Snyder, H.R.; *J. Org. Chem.* **1964**, *29*, 2168 -2172.
4) Enantiomeric purity was determined using Crownpak CR(+) column, eluting with 85:15 pH 1 perchloric acid in H_2O/MeOH mobile phase.