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. Although Raney Nickel appeared superior yield wise, the variability and its pyrophoric nature prompted us to utilize Pearlman’s catalyst for scale-up.

We envisioned a Henry reaction with 2-formylphenylboronic acid and nitromethane followed by nitro reduction to produce AN3017. 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.

AN3213 Synthesis

AN3334 Synthesis

GSK2251052 via Resolution

Figure 1. 1H NMR (d_6-DMSO) and Single Crystal X-ray of AN3334

Figure 2. 1H NMR (d_6-DMSO) of AN3213 with added H_2O

We envisioned a Henry reaction with 2-formylphenylboronic acid and nitromethane followed by nitro reduction to produce AN3017. 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.

Conclusions

• Conditions to successfully reduce an aliphatic nitro in the presence of an arylboron enable 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

2) Hernandez V, talk in this conference Wednesday, May 23 at 11:05 am.
3) This Henry reaction was previously reported in Tischampel, 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 paratrichlor in H_2O/DMSO mobile phase.