Open Science – Improved Synthesis of an Important Drug via Undergraduate Collaboration

Dr Matthew Todd, School of Chemistry. matthew.todd@sydney.edu.au

Title: Preparation of an Important Drug as a Single Enantiomer

Summary: This experiment involves several areas of enquiry but students are free to choose individual components from: 1) hydrolysis of a widely-used drug, praziquantel (PZQ), to give an amine, praziquanamine (PZQamine); 2) resolution of PZQamine and 3) resynthesis of enantiomerically pure PZQ from the enantiomerically pure PZQamine.

Background: PZQ (**1**) is widely used on a huge scale worldwide for the treatment of the neglected tropical disease, schistosomiasis (Bilharzia). This "silent pandemic" is one of the most serious parasite infections affecting sub-Saharan Africa. PZQ is effective, but there is a danger of resistance developing because the drug is being so intensively used. Resistance would be catastrophic since there are no other drugs available for schistosomiasis. The World Health Organisation would like to increase the dose of the drug given, to kill partially resistant parasites and thus delay the emergence of resistance. PZQ is synthesised and administered as a racemate. The inactive (*S*)-enantiomer is associated with unpleasant side effects, and is responsible for the extremely bitter taste of the pill. The scientific challenge is to find a way to make the active (*R*)-enantiomer available while keeping the price low.

The Todd lab at The University of Sydney is leading an international project to solve this problem. Rather than working in isolation and in secret, they are adopting principles well known in the development of open source software. They are trying to solve the PZQ problem using "open science" where all data are available on the web, and anyone can participate in the project. All contributors can be named on resulting publications. By using this approach, working with collaborators worldwide, they have recently discovered a preliminary solution to the PZQ problem: a resolution of the enantiomers (Figure 1) *via* PZQamine (**2**). For this route to be economically viable on a ton scale, it must be optimized. The students' task is to help with this essential optimization. Several universities around the world will be taking part. All results are to be shared by using an online electronic laboratory notebook. Results will be written up for publication in a peer-reviewed academic journal.

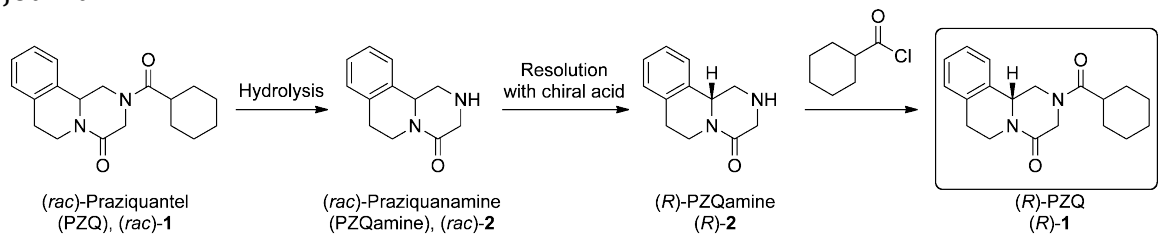

Figure 1. Current Resolution of Praziquantel through Resolution of PZQamine

Procedures:

PZQ will be provided to all participating labs. All other reagents are expected to be sourced locally, or synthesized, by those labs.

Option 1 – Hydrolysis optimization

Students will aim to find improved methods for the removal of the cyclohexanoyl group from PZQ to give PZQamine. The current procedure allows for the simple isolation of PZQamine by recrystallisation of a solid. Parameters for optimisation include concentration of acid/base, time and temperature of the hydrolysis, as well as solvent for the recrystallisation (currently the expensive solvent toluene).

Option 2 – Resolution optimization

a) Synthesis of the resolving agent. The resolving agent currently employed is dibenzoyl tartaric acid. The synthesis of this agent from tartaric acid benzoyl chloride needs to be optimised for yield, solvent and time. The method of its purification by crystallisation also needs to be optimised, again for yield, purity (through melting point analysis) and solvent.
b) Modification of the resolving agent. While benzoyl tartaric acid and anisoyl tartaric acid have both been successful at the resolution of PZQamine, these are the only two resolving agents for which we have plentiful data. Other acid chlorides need to be assessed in their reaction with tartaric acid to generate new resolving agents. These can be used in part c), but must first be synthesised and characterized fully.
c) Optimisation of the crystallization. For the formation of the salt between PZQamine and resolving agent there are many variables, most importantly solvent, concentration and time. These variables need to be explored, in conjunction with variation of the resolving agent. Salts obtained through these experiments would be subjected to base workup, the PZQamine isolated and yield and ee (by optical rotation) determined.

Option 3 – Optimization of the conversion of (R)-PZQamine to (R)-PZQ

The current reaction between PZQamine and cyclohexanoyl chloride (which may be bought or synthesised) requires improvement. For example the current solvent employed is dichloromethane, which should be substituted with a non-chlorinated solvent. Reaction time is also currently long (14 hours) and three recrystallisations are needed to bring the yield of PZQ up to 90%.

Write-up:

Rather than recording results in a traditional paper lab book, students will record what they do in an online electronic lab notebook (OELN). Samples of such OELNs can be seen at http://www.ourexperiment.org/racemic_pzq and

http://www.ourexperiment.org/racres_pzq. It is important that all data are freely available, to allow them to be shared and scrutinized by anyone. This also eliminates unnecessary duplication of effort between labs.

After several results have been acquired, and significant improvements in the resolution approach have been found, the work will be written up for publication in a peer-reviewed journal that accepts science that has previously appeared on the internet such as Nature Chemistry or PLoS One. Students will be involved in the writing of this paper, which will take place on a wiki-based website such as OpenWetWare (for a current example of this practice see http://openwetware.org/wiki/Todd:PZQ_Resolution).