Poster

3D ED and Synchrotron Radiation SCXRD Combine to Solve a Drug Identification Puzzle.

M. R. J. Elsegood,[1] G. W. Weaver,[1] Y. Li,[1] H. Tawell,[1] and S. J. Teat.[2]

[1]Chemistry Department, Loughborough University, Loughborough, LE11 3TU, UK. [2]Advanced Light Source, Lawrence Berkeley Laboratory, Cyclotron Road, Berkeley, CA, 94720, USA.

m.r.j.elsegood@lboro.ac.uk

The Weaver research group are engaged in the synthesis of potential new drugs for the treatment of tropical diseases. As part of this programme, PhD student Yuqi Li first synthesised and characterised the compound shown in Fig. 1 [1]. Initial characterisation was via the usual 'sporting methods' including ^{1}H NMR spectroscopy. Yuqi was also able to grow some small single crystals with a thin plate/lath morphology which were sent to the ALS for single crystal X-ray structure determination, which was successful. Simon Teat obtained a good quality LT data set, and the refined structure had an *R* factor of 3.3%. So far, so relatively routine.

A subsequent PhD student, Hugh Tawell, then attempted to make more of this promising anti-trypanosomal (African sleeping sickness [2]) drug in a second, repeat, synthesis. A low yield was obtained. Despite many attempts, no crystals worthy of even sending to the synchrotron could be grown. The ^{1}H NMR spectrum of this material was also a little different from that of Yuqi's first batch. In particular, the morpholine ring signals were not a match.

We were conscious of the latest developments in electron diffraction instrumentation and followed up discussions with Rigaku at previous conferences to explore the possibility of determining the structure of this second batch of the drug via this technique. The sample was sent to Rigaku's lab in Germany. Dr. Truong used a XtalLAB Synergy ED instrument to analyse *ca*. 50 particles from our second batch. He also investigated the benefits of cryo-transfer and analysis of the samples. The experiments were successful, and the composition of the material obtained from the second synthesis was determined, which began to explain the ^{1}H NMR spectrum differences.

The poster will describe the NMR differences and give details of the ED processes and outcomes which solved the puzzle. There will also be an appraisal of the quality of the ED data set obtained, and the value of the technique when 'routine' SCXRD is not possible.

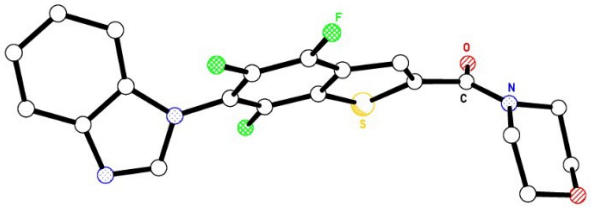

Figure 1. Crystal structure of drug from first synthesis.

Figure 2. What was the material formed in the second synthesis?

[1] Bhambra, A.S., Edgar, M., Elsegood, M.R.J., Li, Y., Weaver, G.W., Arroo, R.R.J., Yardley, V., Burrell-Saward, H. & Krystof, V. (2016). *Euro. J. Med Chem*.**108**, 347.

[2] Büscher, P., Cecchi, G., Jamonneau, V., & Priotto, G. (2017). *Lancet* **390**, 2397.

We would like to thank Dr. K-N. Truong at Rigaku for the ED data collection.

This research used resources of the Advanced Light Source, which is a DOE Office of Science User Facility under contract no. DE-AC02-05CH11231.