Poster

Crystallizing natural products via high-throughput nanodroplet crystallisation protocols.

Alexandra Longcake[1], Nicholas H. Oberlies[2], Michael J. Hall[1] and Michael R. Probert[1]

[1]Department of Chemistry, School of Natural and Environmental Sciences, Newcastle University, Newcastle upon Tyne, NE1 7RU, United Kingdom. [2]Department of Chemistry and Biochemistry, The University of North Carolina, Greensboro, North Carolina 27402, United States.
alexandra.longcake@newcastle.ac.uk

Natural products a rich source of inspiration for the development of new medicines. Natural products and their derivatives have been used to treat a host of diseases and conditions, such as pain management (aspirin and morphine), cancer (paclitaxel and doxorubicin), heart disease (captopril and enalapril) and infection (penicillin and tetracycline).[1, 2] In fact, more than 50 % of small molecule drugs developed in the United States between 1981-2014 were derived from natural products or semisynthetic derivatives.[2] However, absolute structure determination of new bioactive molecules – an essential step in the development of a clinical drug – remains a time-consuming practical impediment. Therefore, methods to increase the speed at which the 3D molecular structure of an unknown natural product can be solved must be developed in order to alleviate this "bottleneck" in the discovery process of clinical compounds.

Herein, we demonstrate the successful deployment of a highly parallelised crystallisation approach to rapidly access crystals of complex organic molecules that are otherwise challenging to crystallise using techniques now offered through the UK National Crystallography Service. Using encapsulated nanodroplet crystallisation (ENaCt) protocols, a significant number of natural products have been obtained as single crystals and structurally characterised by single crystal X-ray diffraction (Fig. 1).[3, 4] The 3D structures of these molecules have been unambiguously confirmed by single crystal X-ray diffraction analysis, both at Newcastle University and through collaboration with the UK National Crystallography Service and Diamond Light Source (the UK's national synchrotron science facility). The first results of this highly successful proof of concept project are soon to be published, thus allowing other groups to apply our approaches to related problems, particularly in cases were traditional solution phase characterisation techniques yield ambiguous results which require further verification.

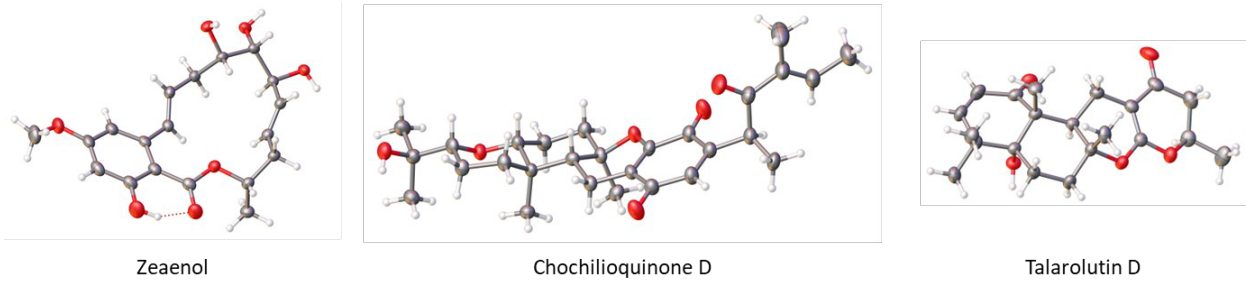

Figure 1. Examples of natural products crystallised using ENaCt protocols.

[1] A. G. Atanasov, S. B. Zotchev, V. M. Dirsch, the International Natural Product Sciences Taskforce and C. T. Supuran, *Nat. Rev. Drug Discov.,* 2021, **20**, 200-216.

[2] F. Li, Y. Wang, D. Li, Y. Chen and Q. P. Dou, *Expert Opin. Drug Discov.*, 2019, **14**, 417-420.

[3] A. R. Tyler, R. Ragbirsingh, C. J. McMonagle, P. G. Waddell, S. E. Heaps, J. W. Steed, P. Thaw, M. J. Hall and M. R. Probert, *Chem*, 2020, **6**, 1755-1765.

[4] Q. Zhu, L. Wei, C. Zhao, H. Qu, B. Liu, T. Fellowes, S. Yang, A. Longcake, M. J. Hall, M. R. Probert, Y. Zhao, A. I. Cooper, and M. A. Little, *J. Am. Chem. Soc*. 2023, **145**, 23352–23360.

We thank the EPSRC UK National Crystallography Service (EP/W021129/1) for access to ENaCt technology and the collection of associated crystallographic data.