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Elucidation of drug metabolite structural isomers using molecular modeling coupled with ion mobility mass spectrometry

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Ion mobility-mass spectrometry (IM-MS) in combination with molecular modeling offers the potential for small molecule structural isomer identification by measurement of their gas phase collision cross sections (CCSs). Successful application of this approach to drug metabolite identification would facilitate resource reduction, including animal usage, and may benefit other areas of pharmaceutical structural characterization including impurity profiling and degradation chemistry. However, the conformational behavior of drug molecules and their metabolites in the gas phase is poorly understood. We investigated the gas phase conformational space of drug and drug-like molecules as well as the influence of protonation and adduct formation on the conformations of drug metabolite structural isomers. The use of CCSs, measured from IM-MS and molecular modeling information, for the structural identification of drug metabolites has also been critically assessed. Detection of structural isomers of drug metabolites using IM-MS is demonstrated and, in addition, a molecular modeling approach has been developed offering rapid conformational searching and energy assessment of candidate structures which agree with experimental CCSs. Here, it is illustrated that isomers must possess markedly dissimilar CCS values for structural differentiation, the existence and extent of CCS differences being ionization state and molecule dependent. The results present that IM-MS and molecular modeling can inform on the identity of drug metabolites and highlight the limitations of this approach in differentiating structural isomers.

Biography

Eamonn Reading has completed his PhD from the University of Oxford and completed a year's Post-doctoral study at King's College London with Prof. Paula Booth before being awarded a BBSRC Future Leader Fellowship in 2016. His main research focus is on "Developing new analytical techniques and protocols for structural biology, particularly in the areas of membrane protein folding, function and drug and lipid interactions".

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