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Interpreting computed crystal energy landscapes for pharmaceutical molecules

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Crystal Structure Prediction (CSP) algorithms aim to generate the thermodynamically feasible crystal structures of a molecule from the chemical diagram, ranking their relative stability by a necessarily approximate estimate of the crystal energy. Such calculations are becoming feasible for molecules of a size and flexibility of small molecule pharmaceuticals. Contrasting the crystal energy landscape, the computer generated structures that are thermodynamically plausible as polymorphs, with the results of experimental polymorph screening, shows that CSP studies are not limited to being a search for the most thermodynamically stable crystal structure but can play a valuable role in understanding polymorphism and the potential complexity of crystallisation behaviour.[1] This presentation will illustrate the use of CSP as a complement to industrial-type solid form screening activities. Examples will include olanzapine, [2] tazofelone, two closely related 5-HT2a agonists and 6-[(5-chloro-2-([(4-chloro-2-fluorophenyl)methyl]oxy)phenyl)methyl]-2-pyridinecarboxylic acid (GSK269984B).[3] This illustrates the use of the crystal energy landscape to understand disorder, help structurally characterise metastable polymorphs and suggest whether there are additional polymorphs to be targeted. Since crystal energy landscapes usually include a wider range of crystal structures than known polymorphs, it raises the scientific question as to what determines which structures can be observed as metastable polymorphs. Thus both scientific as well as technological challenges need to be overcome before we can predict polymorphs.

[1] *S.L. Price, Acta Crystallogr., Sect. B. 2013, 69, 313-328.,* ***[2]*** *R.M. Bhardwaj, S.L. Price, S. M. Reutzel-Edens, et al. Cryst. Growth Des. 2013, 13, 1602-1617.,* ***[3]*** *S.Z. Ismail, C.L. Anderton, S.L. Price, et al. Cryst. Growth Des. 2013, 13, 2396-2406.*

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