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Expanding the scope of fragment screening libraries: Thinking in 3D

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Fragment-based drug discovery (FBDD) methods are a proven strategy for hit identification, providing diverse, high quality start points for numerous drug discovery programmes. Many fragment hits have been optimised and transitioned to the clinical setting with one, namely Vemurafenib gaining FDA approval to treat late stage V600E mutant B-Raf driven malignant melanoma. Critical for successful fragment screening is a high quality compound library. Whilst fragment screening techniques have evolved over the years, increasing in sensitivity and throughput, fragment library molecules have received less attention. Many fragment libraries are chemically diverse and have been selected based on a good balance of properties, however, they all tend to have limited 3-dimensional diversity, typically being composed of flat sp²-rich aromatic and heteroaromatic compounds. This move towards “flatter” molecules not only reduces the sampling of chemical space available for fragments but also fails to capitalise on the additional attributes of sp³ character. Recently, two groups have independently published data showing the improvements in profile and project progression by, for example, increasing the proportion of sp³ centres contained in molecules or reducing lipophilicity. In addition, there are multiple examples in the literature reporting the positive impact of increasing sp³ness or 3-dimensionality through inducing conformational twist. This talk will discuss fragment library composition along with suggestions and practical examples of how future, more structurally diverse fragments which occupy different regions of chemical space to the vast majority of current fragment libraries can be designed and selected.

Biography

Angelo Pugliese is a Senior Scientist (computer-aided drug design) at the CRUK Beatson Institute in Glasgow (UK) since 2011. He received his PhD in Molecular Modelling from the University of Nottingham in UK. He moved to Minnesota in 2007 for his Post-doctoral training at the Hormel Institute (Mayo Clinic-University of Minnesota) and then to Maryland at the National Cancer Institute having been awarded an ORISE Fellowship. He is a coauthor on more than 20 publications; reviewer for several highly regarded journals and has been serving as an advisory board member for the 3rd International Conference Drug Design 2014 (Oxford, UK).

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