Between Theory and Practice: Computational/Experimental Integrated Approaches to Understand the Solubility and Lipophilicity of PROTACs

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Abstract

Emerging drug candidates more often fall in the beyond-rule-of-five chemical space. Among them, proteolysis targeting chimeras (PROTACs) have gained great attention in the past decade. Although physicochemical properties of small molecules accomplishing Lipinski's rule-of-five can now be easily predicted through models generated by large data collections, for PROTACs the knowledge is still limited and heterogeneous, hampering their prediction. Here, the kinetic solubility and the coefficient of distribution at pH 7.4 (LogD7.4) of 44 PROTACs, designed and synthesized to cover a wide chemical space, were measured. Their generally low solubility and high lipophilicity required an optimization of the experimental methods. Concerning the LogD7.4, several in silico prediction tools were tested, which were quite accurate for classical small molecules but provided dissimilar outcomes for PROTACs. Finally, in silico models for the prediction of PROTACs' kinetic solubility and LogD7.4 were proposed by combining in-house generated experimental data with 3D description of PROTACs' structures.