A Combined Computational and Experimental Study to Understand Solid Form Landscape of beyond Rule of 5 Molecule

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There has been significant increased interest in the discovery and development of orally available beyond rule of 5 (bRo5) drugs in the pursuit of less druggable high value targets specially to meet unmet medical needs. bRo5 molecules are generally good fit for large, flexible, groove, flat, or featureless binding sites characteristics of "difficult to-drug" targets. An existence of significant number of orally bioavailable drugs and clinical candidates in this space points to the opportunities in bRo5 space. However, these opportunities come with challenges including poor invitro-in vivo correlation, higher synthetic complexity, purification complexities, prolific solvate formation, higher tendency to form non-stochiometric solid forms, requirement of enabling solid form/formulation due to poor solubility and permeability. In this presentation, we will be discussing challenges associated with solid form screening and selection of bRo5 molecules. Case study of a bRo5 molecule will be presented where experimental and computational approaches were used in conjunction to underpin the link between the structural features and derived properties. In addition, we will also be discussing the chameleonicity of bRo5 molecule, where it can hide/expose its polarity depending on the environment and its implications by detailing the conformational journey from gas phase-solid-state-formulation-receptor ligand complex explored by computational methods.