Understanding and predicting cell permeability in the beyond Rule of 5 space

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We have studied the conformations of orally absorbed drugs and PROTACs in the bRo5 space using NMR spectroscopy and by analysis of crystal structures, which revealed that such compounds often behave as molecular chameleons. In a nonpolar, membrane-like environment they populate less polar and more compact conformational ensembles than in a polar environment such as water. As a result of the balance between rigidity and flexibility molecular chameleons combine aqueous solubility, cell permeability and target binding; properties that otherwise would have been mutually exclusive for compounds in the bRo5 space.

Predicting the conformations and properties of molecular chameleons is difficult, but classification models developed by machine learning show promise for differentiation between compounds that have high or low cell permeability. Molecular dynamics using an explicit solvent model, followed by QM refinement of the conformations provided accurate results for moderately flexible macrocycles. Results for a small set of PROTACs indicate that molecular dynamics provides insight into their conformational preferences and could be useful to assess their cell permeability.