[P24] Investigating the Conformational Diversity of Endogenous Ligands

Joshua Meyers[1], Nathan Brown[1], Julian Blagg[1]

[1]*Cancer Research UK Cancer Therapeutics Unit, Division of Cancer Therapeutics, The Institute of Cancer Research, London, SM2 5NG, United Kingdom*

Many drug discovery projects target predefined sites of biological action, aiming to compete for binding with endogenous ligands such as ATP, NAD and SAM. Information about the properties of these native ligands can be used to guide medicinal chemistry[1].

A high quality set of protein-bound ligand structures was retrieved from the Protein Data Bank (PDB) for a range of pharmacologically relevant endogenous molecules, including examples relevant to the recently growing field of epigenetic therapies[2].

Endogenous ligands often contain many rotatable bonds and frequently their bound conformations do not correspond to conformational energy minima[3]; therefore, these compounds take on a wide range of conformations in a biological context (Figure 1). Conversely synthetic ligands are often characterised by restricted conformational freedom. Comparison of the spatial coverage of native ligands with those exemplified in synthetic ligand space can highlight how well screening libraries are directed towards biologically relevant chemical space. Further investigation of three-dimensional descriptors such as Plane of Best Fit (PBF)[4], dihedral angles and the spatial distribution of functional groups can help us identify trends in the shapes adopted by molecules in biological systems. Spatial clustering of endogenous ligands highlights a strong correlation between molecular shape and the protein family to which the ligand is bound[5]. Directing compound library design and synthetic chemistry efforts towards underrepresented regions in 3D chemical space could help improve the diversity of screening libraries. Additionally, learning from these 3D shapes has the potential to impact upon prediction of off-target effects and acquired drug resistance.

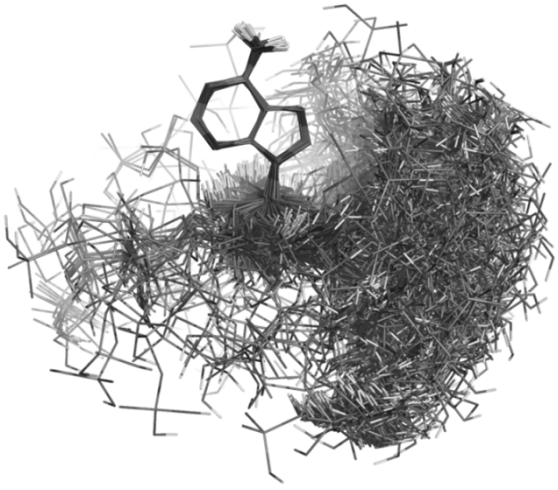

Figure 1. 741 conformations of the endogenous ligand, ATP taken from the Protein Data Bank overlaid on the adenine subunit.

[1] E. Fauman; B. Rai; E. Huang. Curr. Opin. Chem. Biol. 15 (2011) 463-468.
[2] C. Arrowsmith; C. Bountra; P. Fish; K. Lee; M. Schapira. Nat. Rev. Drug Discov. 11 (2012) 384-400.
[3] J. Bostrom; P. Norrby; T. Liljefors. J. Comput.-Aided Mol. Des. 12 (1998) 383-396.
[4] N. Firth; N. Brown; J. Blagg. J. Chem. Inf. Model. 52 (2012) 2516-2525.
[5] G. Stockwell; J. Thornton. J. Mol. Biol. 356 (2006) 928-944.