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Ligand conformational analysis enabling improved Nrf2 activators

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Chronic Obstructive Pulmonary Disease (COPD) is an area of substantial unmet medical need. In particular, effective anti-inflammatory therapy is required in addition to bronchodilator therapy as disease severity progresses. While oral PDE4 inhibitors are currently used for this purpose and have been shown to be effective on exacerbation rates, their degree of efficacy is disappointing. In this regard, Nrf2 activators have the potential to be efficacious on exacerbation rate with a much better tolerability profile. However, it has been difficult to create potent non-covalent inhibitors of the key Keap1/Nrf2 protein-protein interaction.

Nrf2 is a master regulator of the cell's antioxidant response and its activation leads to a coordinated antioxidant and anti-inflammatory response. Here we present a detailed 3D-structural analysis of a publicly available Nrf2 activator [1], which functions by blocking the interaction of Nrf2 with its repressor Keap1.

In this study the variety of conformations that the free ligand adopts in solution is precisely measured using the methodology of Blundell *et al* [2]. Synergistic combination of the free ligand's conformational preferences with computational modelling and X-ray crystallography provides unprecedented insights into the disruption of this protein-protein interface. These data provide clear, immediate and rational strategies for conformational redesign of the ligand to achieve improved potency with novel chemical scaffolds.

References:

1. Hu, L., Magesh, S., Chen L., *et al.* Discovery of a small-molecule inhibitor and cellular probe of Keap1–Nrf2 protein–protein interaction. *Bioorg. Med. Chem. Lett.* **23**, 3039-3043 (2013).
2. Blundell, C.D., Packer, M. J. & Almond, A. Quantification of free ligand conformational preferences by NMR and their relationship to the bioactive conformation. *Bioorg. Med. Chem.* **21**, 4976–4987 (2013).