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Ligand conformational analysis enabling improved Nrf2 activators

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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, Nrf-2 activators have the potential to be efficacious on exacerbation rate with much a better tolerability profile. However, it has been difficult to create highly potent drug-like non-covalent inhibitors for the key Nrf2/Keap-1 protein-protein interaction (PPI). 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, which functions by blocking the interaction of Nrf2 with its repressor Keap-1. The variety of conformations that the free activator adopts in solution was precisely measured using the NMR methodology of Blundell *et al* and this data was combined with results from protein X-ray co-crystallography and *in-silico* docking. The synergistic combination of these techniques provides unique insights into the disruption of this protein-protein interface, and demonstrates the power of combining ligand-based and structure-based drug design approaches. These data provide clear, immediate and rational strategies for both conventional and conformational design of the ligand to achieve improved potency.

Biography

Thorsten Nowak completed his PhD from the University of Cambridge (UK) in the areas of aldol methodology and natural product synthesis. In 1996, he joined AstraZeneca where he worked on all stages of drug discovery from target to candidate selection in medicinal chemistry as team leader and project manager. His keen interest in new technologies motivated a career move from big pharma to platform technology business in 2012 when he joined C4X Discovery. In his current role, he is responsible for all internal drug discovery projects at C4X Discovery as well as continued development of the technology in the context of application to drug discovery.

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