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Simultaneous Targeting of MYD88 and Nur77 as an Effective Approach for the Treatment of Inflammatory Diseases

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Abstract : Myeloid differentiation primary response protein 88 (MYD88) has long been considered a central player in the inflammatory pathway. Recent studies clearly suggest that it is an important therapeutic target in inflammation. On the other hand, a recent study on the interaction between the orphan nuclear receptor (Nur77) and p38α, leading to increased lipopolysaccharide-induced hyperinflammatory response, suggests this binary complex as a therapeutic target. In this study, we have designed inhibitors that can inhibit both MYD88 and Nur77 at the same time. Since both MYD88 and Nur77 are an integral part of the pathways involving lipopolysaccharide-induced activation of NF-κB-mediated inflammation, we tried to target both proteins with the same library in order to retrieve compounds having dual inhibitory properties. To perform this, we developed a homodimeric model of MYD88 and, along with the crystal structure of Nur77, screened a virtual library of compounds from the traditional Chinese medicine database containing ~61,000 compounds. We analyzed the resulting hits for their efficacy for dual binding and probed them for developing a common pharmacophore model that could be used as a prototype to screen compound libraries as well as to guide combinatorial library design to search for ideal dual-target inhibitors. Thus, our study explores the identification of novel leads having dual inhibiting effects due to binding to both MYD88 and Nur77 targets.

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