# Structure-Based Anti-Inflammatory Drug Discovery: Design, Synthesis and Biological Evaluation of VSP-22 as a New, Safe and Highly Potent GR Agonist

The glucocorticoid receptor (GR), also known as NR3C1 (nuclear receptor subfamily 3, group C, member 1) is the receptor to which cortisol and other glucocorticoids bind. Many studies have also showed that it is the target protein for the well-known glucocorticoid class of anti-inflammatory drugs such as prednisone, dexamethasone (DEX) and budesonide, which have proven successful for the efficient treatment of inflammation and autoimmune diseases such as asthma, arthritis, lupus, and Crohn's disease.

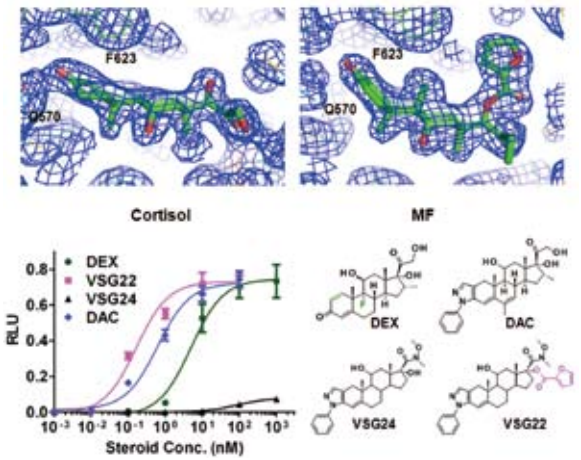
However, despite their excellent potencies in treating the above-mentioned diseases, these glucocorticoid drugs as GR agonists possess many severe side effects including diabetes, hypertension, obesity, and osteoporosis. Undoubtedly, there is an urgent need to discover new, safe and highly efficient glucocorticoids with improved therapeutic profiles.

It is generally observed that many of the side effects of glucocorticoids are associated with use of high-dose glucocorticoids. This differential response provides an opportunity for developing highly potent glucocorticoids that can be used at low doses to achieve full repression of inflammation signals, while minimizing the unwanted side effects.

Inspired by these, in this study researchers solved the X-ray structures of the glucocorticoid receptor (GR) ligand-binding domain (LBD) bound to its endogenous ligand, cortisol, which has relatively low potency, and a highly potent synthetic glucocorticoid, mometasone furoate (MF). The cortisol-bound GR LBD revealed that the flexibility of the C1-C2 single bond in the steroid A ring is primarily responsible for the low affinity of cortisol to GR.

In contrast, researchers demonstrated that the very high potency of MF is achieved by its C-17α furoate group completely filling the ligand-binding pocket, thus providing additional anchor contacts for high-affinity binding. A single amino acid in the ligand-binding pocket, Q642, plays a discriminating role in ligand potency between MF and cortisol.

On the basis of these, the researchers designed and synthesized several novel glucocorticoids with much improved potency and efficacy. Especially, VSG-22 was found to be the most potent GR agonist, which is better than the marketed anti-inflammatory drug DEX. More importantly, its main metabolite VSG-24 showed no agonistic activity on GR. The results suggested that VSG-22 can serve as a promising candidate for the treatment of increasingly popular asthma and as the lead for designing better and safer GR-based anti-inflammatory drugs.




Structure-based anti-inflammatory drug-VSG-22.(Image By SIMM)

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To view the study, please visit: http://www.nature.com/cr/journal/vaop/ncurrent/full/cr201452a.html