

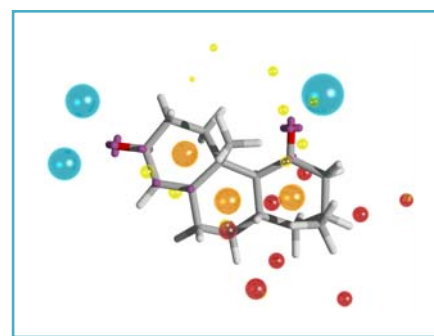
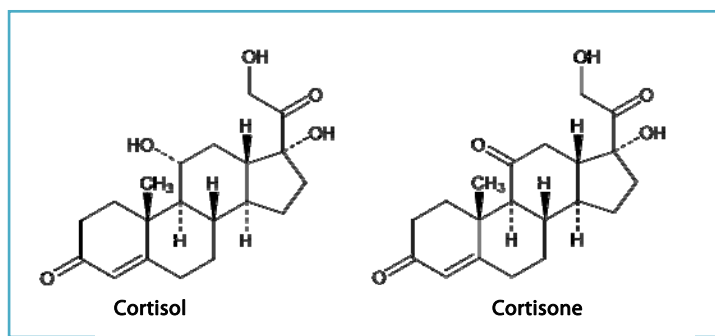


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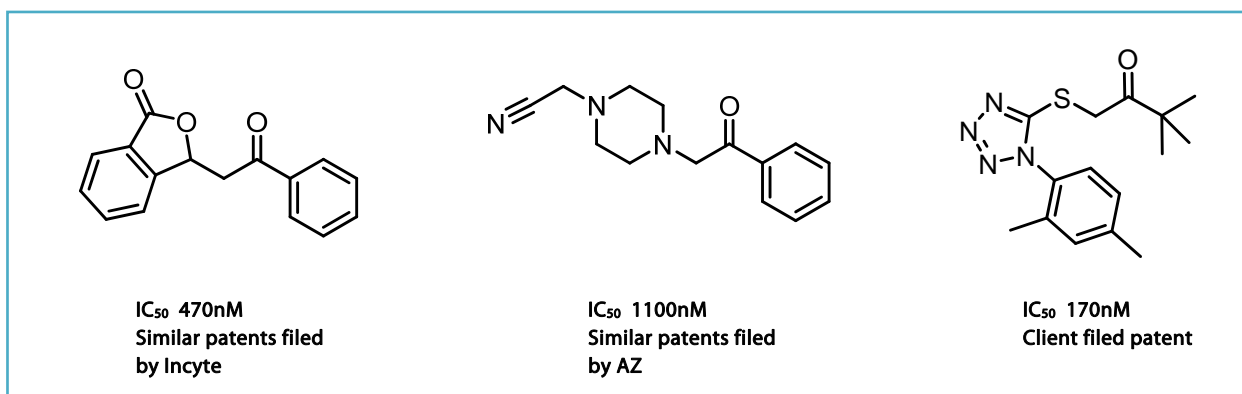
## Class Hopping / Lead Generation - Inhibition of 11 $\beta$ -Hydroxysteroid Dehydrogenase-1

A local role for 11 $\beta$ -hydroxysteroid dehydrogenase type 1 (11 $\beta$ HSD-1) in the control of visceral fat deposition has been established in the literature. Although originally thought to predominate as an oxidase, converting cortisol to cortisone, this enzyme has been shown to act as a reductase *in vivo* for cortisone. This strongly suggests that the inhibition of 11 $\beta$  HSD-1 and the concomitant decrease of active cortisol, could be important in the control of obesity, insulin resistant diabetes and cognition.



Our client wanted to generate new ideas for lead structures in this area, but had only the natural ligand as a starting point. In the absence of specific X-ray data at the time of the project, we modeled how the steroids bound and extracted the molecular Field of the binding fragment (shown above right). This binding fragment was used as a seed for FieldScreen to search the Field database which then contained 2M commercially available compounds. The search results were ranked by Field similarity to the seed structure.

A list of the best 500 hits was submitted to the client, from which they purchased 408 structures. When tested, 10 of these were active at < 10 $\mu$ M, 1 was active at 470nM and the best was active at 170nM. Three of the most active compounds are shown below, illustrating the diverse chemotypes that Field screening is designed to find.



On the basis of these results, further financing was granted to our client to develop the tetrazole chemotype. Independent patent filings were subsequently submitted for the benzofuranones and piperazines by other drug discovery companies. These patents and the subsequent appearance of many 11 $\beta$ HSD-1 X-ray crystal structures confirmed the validity of our original Field binding pattern.