Virtual Screening with 11βHSD-1 Resulting in Diverse New Leads

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The enzyme 11βHSD-1 is highly expressed in key metabolic tissues and has been linked with the control of visceral fat deposition. Our client asked Cresset's consulting team to generate new ideas for lead structures in this area, using the natural ligand as a starting point. Cresset's scientists used Blaze[1] (formerly FieldScreen) to find new active structures with diverse chemotypes.

Method

The enzyme 11β-hydroxysteroid dehydrogenase type 1(11βHSD-1) was originally thought to predominate as an oxidase, converting cortisol to cortisone. However, 11βHSD-1 has been shown to also act in vivo as a reductase for cortisone. This strongly suggests that the inhibition of 11βHSD-1 and the associated decrease of active cortisol could be important in the control of obesity, insulin resistant diabetes and cognition.

The 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, the Cresset consulting team modeled the binding action of the steroids cortisol and cortisone. Using a homology model of 11βHSD-1 to guide their understanding of the key parts of the binding, they deduced the important parts of the molecular field of the ligand (figure 1) and expressed this as a binding fragment.

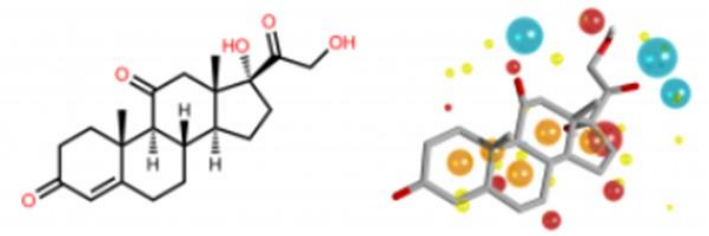

Figure 1. Cortisone, the natural ligand for 11-beta-HSD-1 in 2D and 3D with fields added.

This binding fragment was used as input to Blaze. Cresset's Blaze uses the shape and electrostatic character of ligands to rapidly search large chemical collections for molecules with similar properties. Using the molecular field pattern of the binding fragment, Blaze searched a database of 2 million commercially available structures to find compounds with a similar field pattern.

The results were ranked by field similarity to the seed structure and a list of the best 500 hits was submitted to the client biological evaluation. Of these 483 were acquired and tested in a single point percent inhibition determination at 10uM. Active compounds were further analyzed with full IC50 and where appropriate Ki determinations. 10 of these were active at <10μM, 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.

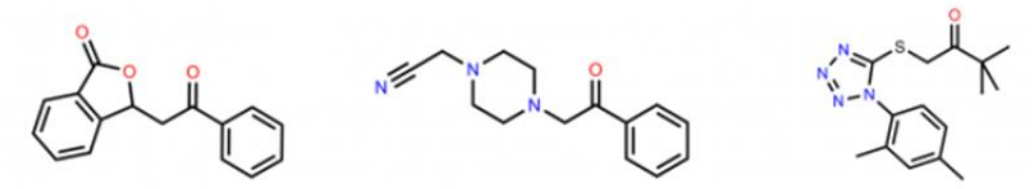

Figure 2. Right – IC50 570nM. Similar patents filed by Incyte; Middle – IC50 1100nM. Similar patents filed by AZ; Right – IC50 170nM. Client filed patent.

Conclusion

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 11βHSD-1 Xray crystal structures confirmed the validity of the original field binding pattern.

References

1. Blaze™, version 10.3.2, Cresset®, Litlington, Cambridgeshire, UK; Cheeseright, T.J.; Mackey, M.D., Melville, J.L.; Vinter, J.G. FieldScreen: Virtual Screening Using Molecular Fields. Application to the DUD Data Set. J. Chem. Inf. Model. 2008, 48 (11), 2108-2117; Cheeseright T., Mackey M., Rose S., Vinter, A.; Molecular Field Extrema as Descriptors of Biological Activity: Definition and Validation. J. Chem. Inf. Model. 2006, 46 (2), 665-676