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Poster presentation

Rapid discovery of new leads for difficult targets: application to CCK2 and 11beta-HSD1

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We wanted to discover novel chemotypes for 2 targets which lacked x-ray data, CCK2 and 11beta-HSD1. Our approach was to undertake ligand-based virtual screening using the molecular fields of active compounds as our template to define activity. Our hypothesis was that the field pattern of an active molecule describes its key binding features and molecules with a similar field have a high probability of showing the same biological activity.

For CCK2, we took the 2D structures of 3 active ligands and used FieldTemplater to identify the bioactive conformations which were used as templates for virtual screening. Twenty-seven hits were found from 88 compounds tested.

There was no x-ray structure for 11beta-HSD1 at the time of this study, so using structural information from related enzymes, we generated a cut-down version of cortisone and used this as our virtual screening template. Subsequent testing of 410 compounds identified 23 hits in 4 chemical series. Two of these series were subsequently patented by pharmaceutical companies and one has now been patented by our co-workers.

References

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