Identification of a Potent Non-Peptidic Small Molecule Antagonist with Catalyst

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In this study, Singh *et al.* aimed to identify alternative nonpeptidic structures to replace a known peptidic molecule antagonist that is rapidly cleared from the body.

Experiments have indicated that the integrin binding motif of (Leu-Asp-Val) can be used as a starting point for the design of small molecule antagonists of α4β1. However, the potent molecule of 4-[N'-(2-methylphenyl) ureido]phenylacetyl-Leu-Asp-Val results in rapid clearance due to its peptidic nature.

Singh *et al.* developed a Catalyst model based on known structure activity relationship (SAR) data. A virtual compound library, which was based on commercially available reagents containing a free amine or a nitro group and a carboxyl group, was generated (~8500 compounds). The Catalyst pharmacophore model was then used to virtually screen the database. A total of 416 hits were retrieved, and removal of peptide-like compounds reduced this to 170 hits. Of these, 12 compounds were selected based on synthetic feasibility and reagents availability. The most potent hit yielded 1.3 nM activity.

In this project, Catalyst aided in the successful transformation of a peptide lead compound into discovery of a small molecule inhibitor. *In silico* screening with Catalyst identified novel and potent non-peptic, small molecule nM replacements for the peptidic portions of an existing α4β1 antagonist.

Reference

1. Singh, J., van Vlijmen, H., Liao, Y., *et al.*, "Identification of Potent and Novel a4b1 Antagonists Using in Silico Screening ," *J. Med. Chem.*, **2002**, *45*, 2988-2993.

Industry Sector

Pharmaceutical

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Key Products

Catalyst®

Workflow

1. Known SAR data of peptide-like molecules
2. Build Catalyst pharmacophore model
3. Generate virtual library of ~8500 compounds
4. 416 hits identified
5. 170 hits after removal of peptide-like hits
6. 12 compounds selected for synthesis and assay
7. 1.3nM non-petidic hits identified
8. Non-peptidic small molecule inhibitors identified

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