Discovery of a Novel and Selective Cellular Inhibitor with Catalyst

Samuel Toba, Shikha Varma, Accelrys, Inc.

Catalyst technology was successfully used to screen an in-house library to identify a potent, yet selective, cellular inhibitor. No crystal structure of the target was available.

Proliferation of mesangial cells (MC) is a prominent feature of glomerular disease, including IgA nephropathy, membranoproliferative glomerulonephritis, lupus nephritis, and diabetic nephropathy. It is also known that MC proliferation is inhibited by many kinds of pharmacological drugs, such as ACE inhibitors, leukotrien D4 (LTD4) antagonists, PDGF inhibitors, matrix metalloproteinase (MMP) inhibitors, HMG-CoA inhibitors, cyclooxygenase inhibitors, cyclin-dependent kinase antagonists, *etc*. However, compounds that selectively inhibit the proliferation of MC versus normal cells at the pharmacological range have not been reported.

In an effort to find a potent and selective inhibitor of MC proliferation, Kurogi *et al.* performed a biological screening of an in-house benzylphosphonate library. The screening yielded four potent MC proliferation inhibitors. The best compound had 69% inhibitory activity against MC proliferation (at 100nM concentration), but also 30% inhibitory activity against normal cell proliferation (*i.e.* it was not selective). These four compounds were used as training set to generate a pharmacophore model using Catalyst. A seven-feature Catalyst model was picked to search the Maybridge commercial database of 47,000 compounds.

A total of 41 structurally novel compounds were identified from the virtual screening. Of these, four compounds were picked based on Catalyst hit score, compound availability for assay, *etc.* The best scoring Catalyst compound yielded 90% inhibition against MC proliferation and no inhibition of normal cell proliferation.

The use of Catalyst helped Kurogi *et al.* discover a compound that is a novel, potent, and more importantly, selective inhibitor of MC proliferation.

Industry Sector

Pharmaceutical

Organization

Accelrys

Key Products

Catalyst®

Workflow

1. Screened in-house benzylphosphonate library
2. Selected four best inhibitory compounds
3. Built Catalyst pharmacophore model
4. Virtually screened ~47,000 commercially available Maybridge compounds
5. 41 hits identified
6. Selected four compounds for assay
7. Mesangial cell and normal cell proliferation inhibitory assay performed
8. Potent + novel structure + selective inhibitor identified

Reference

1. Kurogi, Y., Miyata, K., Okamura, T., *et al.*, "Discovery of Novel Mesangial Cell Proliferation Inhibitors Using a Three-Dimensional Database Searching Method," *J. Med. Chem.*, **2001**, *44*, 2304-2307.

Accelrys Corporate Headquarters
10188 Telesis Court, Suite 100
San Diego, CA 92121, USA
Tel: +1 858 799 5000

Accelrys European Headquarters
334 Cambridge Science Park
Cambridge, CB4 0WN, UK
Tel: +44 1223 228500

Accelrys Asia Headquarters
Nishi-shimbashi TS Bldg 11F
Nishi-shimbashi 3-3-1, Minato-ku,
Tokyo, 105-0003, Japan
Tel: +81 3 3578 3860

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