

New class of compounds offers great potential for research and drug development

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Scientists from The Scripps Research Institute have identified a class of compounds that could be a boon to basic research and drug discovery.

In a new study, published online in [Nature Chemical Biology](#) on May 15, 2011, the researchers show the new compounds powerfully and selectively block the activity of a large and diverse group of enzymes known as "serine hydrolases." Previously discovered serine hydrolase-blocking compounds have been turned into drugs to treat obesity, diabetes, and Alzheimer's disease, and are currently in testing as treatments for pain, anxiety, and depression.

"There are more than 200 serine hydrolases in [human cells](#), but for most we've lacked chemical inhibitors of their activity," said team leader Benjamin F. Cravatt III, professor and chair of the Department of Chemical Physiology at Scripps Research and a member of its Skaggs Institute for Chemical Biology, "so we've had only a limited ability to study them in the lab or to block them to treat medical conditions. This new research allows us to greatly expand our list of these inhibitors."

A Scaffold on Which to Build

Hints from previous work by the Cravatt lab and other groups led the team to investigate a group of molecules known as ureas for their ability to inhibit serine hydrolase activity. In initial tests using recently advanced techniques for measuring enzyme-inhibition strength and

specificity, the Scripps [Research scientists](#) found that molecules known as 1,2,3-triazole ureas could powerfully inhibit some serine hydrolases without affecting other enzymes.

In the next set of tests, the team synthesized a basic "scaffold" of 1,2,3-triazole urea, and found that it inhibited many more serine hydrolases – still without affecting other enzyme classes – than did an existing broad inhibitor known as a carbamate. The team then began modifying the scaffold compound to refine its inhibitory activity to specific serine hydrolase targets. This chemical tweaking would once have been a lengthy and burdensome task, but in this case it was done using simple "click chemistry" techniques developed at Scripps Research by Nobel laureate Professor K. Barry Sharpless and his colleague Associate Professor Valery Fokin.

"We can make these modifications in just two chemical steps, which is a great advantage," said Alexander Adibekian, a postdoctoral fellow in the Cravatt lab and first author of the new paper. "And despite this technical simplicity, we were able to generate compounds that were extremely potent and selective."

From the 20 compounds the scientists generated this way, they found three with powerful and highly specific inhibitory effects on individual serine hydrolases with many unknown characteristics.

Most of the study's enzyme-inhibition tests were conducted in mouse cell cultures, a more realistic biochemical environment than traditional "test-tube" biochemical preparations; but for one of the group's inhibitor compounds, AA74-1, the scientists extended their inhibition-measurement techniques to animal models, showing that the compound potently blocked the activity of its target serine hydrolase, acyl-peptide hydrolase, or APEH, without significantly affecting other enzymes.

Not much had been known about APEH, but with its inhibitor AA74-1, the team was able to illuminate the enzyme's normal role in the chemical modification of proteins, showing the levels of more than two dozen proteins dropped sharply when APEH was inhibited.

"This was unexpected and unusual," said Adibekian. "But it's what one wants to see with these compounds—strong enzyme-inhibiting activity in different tissues, at a low dose. And it's the first time this kind of evaluation has been done in both cultured cells and animal tissues."

The Cravatt lab is now using the expanding number of inhibitors that team members have generated so far to study serine hydrolases with previously unknown or uncertain biological functions.

"We're also using the techniques described in this paper to try to systematically generate more of these inhibitor compounds," said Cravatt. "We see these [compounds](#) as basic tools that enable us to determine the roles of serine hydrolases in health and disease. As we understand these [enzyme](#) roles better, we expect that some of their inhibitors could become the bases for medicines."

Provided by The Scripps Research Institute

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