UCSD Chemists Bring Use Of Designer Molecules To Treat Common Diseases Closer To Reality

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By making use of model compounds in drug design, chemists at the University of California, San Diego identified a class of molecules that could lead to treatments for a wide range of diseases, including cancer, arthritis, and heart disease.

Enzymes-protein catalysts-in the body that help break down connective tissue like collagen are important in growth and wound healing, but also play a role in many diseases. For example, these enzymes are overactive in arthritis and are used by cancer cells to migrate through connective tissue and spread. While a number of drugs have been designed to inhibit these enzymes, only one has made it through clinical trials because of a variety of drawbacks.

In a study to be published in the July 14 issue of the *Journal of the American Chemical Society*, a group of chemists led by Seth Cohen in UCSD's Division of Physical Sciences has identified a promising set of inhibitors that may lack the drawbacks plaguing the previous generation of such compounds.

"Nearly all the compounds known to inhibit these enzymes are chemically similar," says Cohen, an assistant professor of chemistry and biochemistry. "But they tend to be toxic, cannot be taken orally, and are rapidly metabolized. We tested 11 new compounds selected for their chemical similarities and some differences to the known inhibitors. Many of the new compounds not only turned out to be excellent inhibitors, they are also less likely to have undesirable side effects. For example, one of the inhibitors we discovered is actually the food additive Maltol, which is used as a flavor enhancer."

All enzymes have an active site-a pocket with a particular shape and chemical composition, where molecules bind and react. Enzymes that break down connective tissue-matrix metalloproteases or MMPs-have a zinc ion at the active site, which is essential for providing the right chemical environment for a reaction to occur. Compounds that surround and bind to the zinc ion can inhibit the enzyme.

In the classical approach to drug design, chemists use computer programs to predict what compounds are potential inhibitors of an enzyme. This "computational" approach requires knowledge of the chemical groups at the active site of the enzyme and the three-dimensional shape of the active site. But it can be difficult to obtain and crystallize sufficient quantities of the enzyme to use X-ray crystallography-the method chemists employ to take detailed pictures of molecules using X-rays.

"The drug design process is much more challenging for proteins containing metal ions because computational chemistry is not as advanced for this," says Cohen. "It's a frontier area of research. But you can overcome the limitations of computational chemistry by using the model compounds to understand how the drug binds to just the metal part. Basically you take out the difficult part by using models."

Cohen and his colleagues tested the ability of the 11 compounds to inhibit an MMP enzyme in a test tube. They also studied the strength of binding of each of the 11 compounds to a chemical model that they had

designed to mimic the way the zinc is bound in the active site of the enzyme. The researchers found that the ability of the compounds to inhibit the enzyme increased as the strength of their binding to the model increased. This is what is expected if the inhibitor is working by binding to the active site of the enzyme, rather than some unknown mechanism.

There are actually 26 MMPs in the human body, so to avoid unwanted side effects, drugs need to be designed that target specific MMPs. Since the active site for each of these MMPs contains a zinc ion, the 11 inhibitors would not target just one MMP. Designing inhibitors that target a single type of MMP requires modifying the way the inhibitor binds to chemical groups of the enzyme unique to that enzyme. Modifying the inhibitors to make them target specific enzymes will be the researchers' next steps, but according to Cohen, there is a great deal of published work that will help them with this task. Computational chemistry can also help them now that they have figured out the tricky metal-binding part.

"Although the use of models in chemistry is very well established, we are among the first groups to aggressively use model chemistry as a part of drug design," says Cohen. "So far, our work has been particularly well received in the community of MMP research."

The other researchers that contributed to this work are David Puerta and Jana Lewis, graduate students in the Cohen lab. The study was supported by UCSD, a Chris and Warren Hellman Faculty Scholar award, and the American Heart Association.

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