

Metal-containing compounds show promise as HIV weapon

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A molecule consisting of two "cages" of metallic atoms bound to carbon has shown great promise in preliminary tests of becoming a new weapon in the anti-HIV arsenal, researchers at UT Southwestern Medical Center report. The molecule – called metallacarborane – and its variants appear to fight HIV protease, an enzyme critical in the virus' life cycle. Protease inhibitors are some of the key drugs used to fight HIV/AIDS, but they have side effects, and viruses can develop resistance to them.

"This molecule has all the characteristics of a good starting point for a new class of compounds," said Dr. Zbyszek Otwinowski, associate professor of biochemistry at UT Southwestern and an author on the study, which appears in the Proceedings of the National Academy of Sciences and is currently available online.

Researchers from UT Southwestern, the Czech Republic and Germany studied the structure and inhibition properties of the basic molecule as well as several variants with chains of other atoms hanging off them. The researchers found that at very low concentrations, the new molecules inhibit protease in infected cultured human cells with no obvious toxicity toward the cells.

The 12-pointed, cagelike molecule of boron bound to carbon, called carborane, has been known for more than 50 years but just recently came to the attention of researchers in the Czech Republic as a possible AIDS drug, Dr. Otwinowski said.

The Czech group bound the metallacarboranes they were studying to the proteases, then brought the diffraction data to UT Southwestern to have the structures interpreted. The structures were determined by a process called X-ray crystallography, in which the crystals are bombarded with X-rays, and then the patterns made when the component atoms deflect the rays are deciphered.

The metallacarboranes appeared to occupy the portion of the protease used to hold key proteins in place as part of the infective cycle of HIV, preventing the proteases from working.

Other advantages are that the compounds are stable and can be modified in many ways by attaching other strings of atoms to them. Further research may reveal that one modified version may be more stable or less toxic than another, for example. These compounds were also found to bind to the protease in a different location than the current class of protease inhibitors, so they may be effective against HIV strains that have become resistant to that class.

Dr. Pavlina Rezacova, postdoctoral researcher in biochemistry at UT Southwestern, also participated in the study, as did researchers from the Academy of Sciences of the Czech Republic; the Institute of Chemical Technology and Charles University in the Czech Republic; the University of Heidelberg in Germany.

Source: UT Southwestern

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