Putting the brakes on drug-resistant HIV

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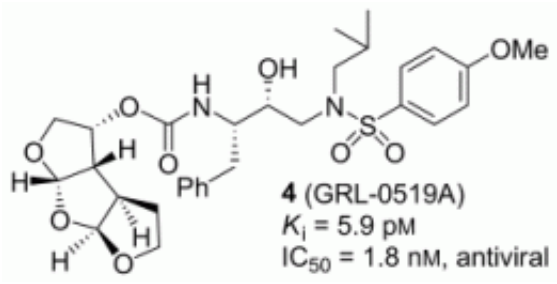

(PhysOrg.com) -- HIV-1 protease inhibitors were added as a component of highly active antiretroviral therapy (HAART) in the mid-1990s, and have played a key role in that treatment regimen ever since. However, the emergence of multidrug-resistant HIV strains requires the discovery and design of conceptually new therapeutics for the treatment of patients infected with multidrug-resistant HIV strains.

In addressing this issue, the research group of Arun K. Ghosh at Purdue University developed stereochemically defined, fused tetrahydrofuran (THF) ligands based on the X-ray crystal structures of HIV--ligand complexes. The results of this project, carried out with collaborators at Georgia State University, Kumamoto University in Japan, and the National Cancer Institute, are reported in the journal *ChemMedChem*.

The fused THF ligands contain five contiguous chiral centers, and were synthesized in optically active form by enzymatic resolution, radical

cyclization, and stereoselective reduction as key steps. The resulting HIV-1 protease inhibitors are designed to interact specifically with protein backbone atoms by hydrogen bond formation and by filling the hydrophobic active site pocket. One compound in particular, GRL-0519A, shows remarkable protease inhibition and antiviral activity.

Moreover, this compound is extremely potent against various multidrug-resistant HIV-1 variants, with IC50 values ranging from 0.6 to 4.3 nanomolar. In fact, GRL-0519A is at least 10-fold better than darunavir, an FDA-approved HIV protease inhibitor that emerged from previous research by Ghosh's group.

More information: Arun K. Ghosh, Probing Multidrug-Resistance and Protein-Ligand Interactions with Oxatricyclic Designed Ligands in HIV-1 Protease Inhibitors, *ChemMedChem*, dx.doi.org/10.1002/cmdc.201000318

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