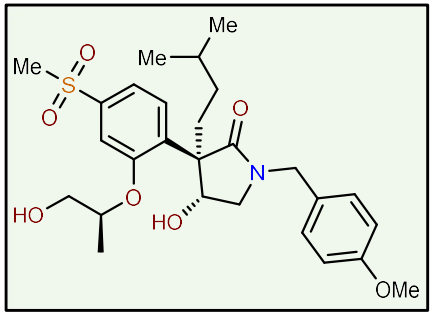
# Nonpeptidic HIV-1 Protease Inhibitors



## Background info:

- Novel drug discovery strategy: “Pocket-to-Lead”.
- HIV-1 protease used as a model target.
- Starting from the pharmacophore analysis of the binding pocket of the HIV-1 protease, virtual screening was conducted, leading to a virtual fragment hit that had the essential interactions.
- An extensive *de novo* design cycle was carried out, to give a tailor-made molecule that had pharmacophore features matching with the binding pocket of the HIV protease.

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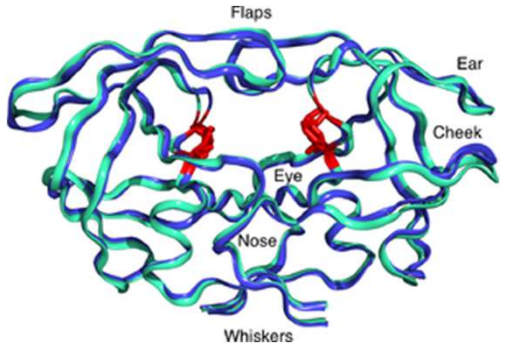
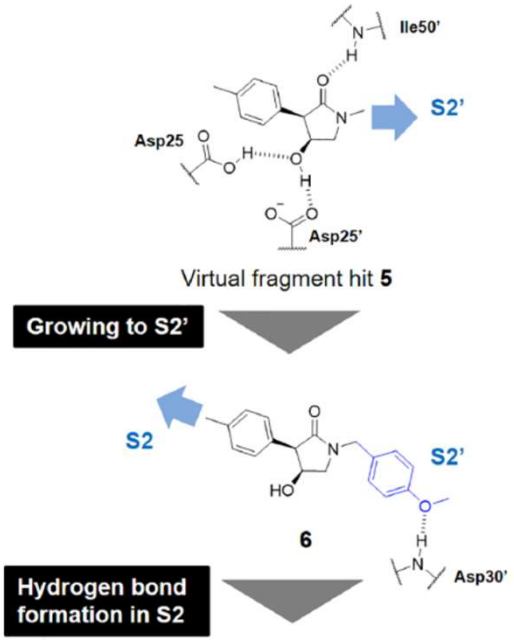
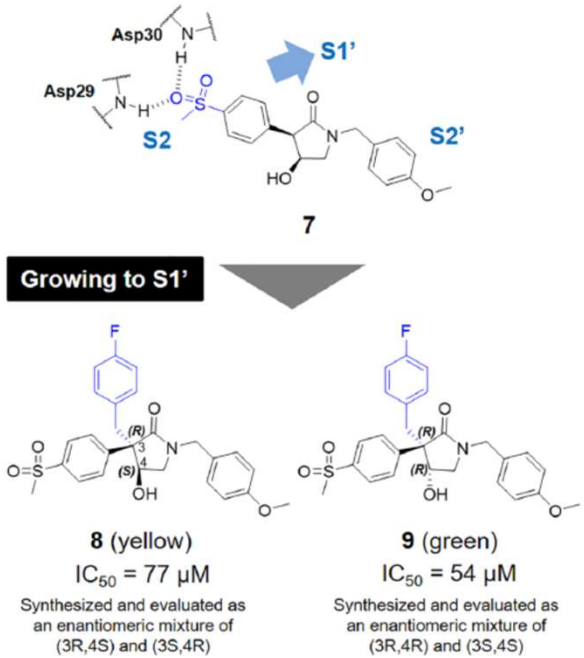



## Approach:




“Pocket-to-Lead” advantages:

- No large-scale “real” screening is needed. Only the structure of the target protein is required.
- The ligands are designed via combination of analogs (by medicinal chemists) and digital (*in silico*) approaches by using the structure of the binding pocket as a template.
- Since the compounds are build through relatively simple functionalities, they are synthetically feasible even if the molecules are novel and highly functionalized.
- Once the compounds with the desired activity are found, the activity can be improved by slight modification of the structures.

Tachibana, Y. *J. Med. Chem. ASAP.* https://doi.org/10.1021/acs.jmedchem.1c02217

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## Synthesis: