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In This Issue

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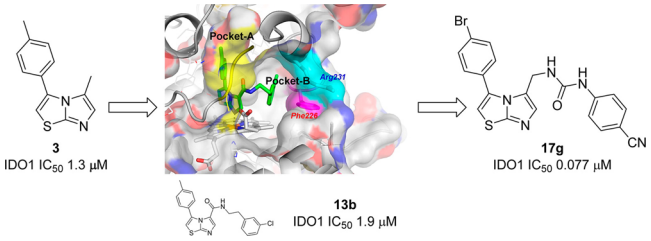
NOVEL INDOLEAMINE 2,3-DIOXYGENASE 1 INHIBITORS

X-ray crystallography plays a critical role in drug discovery. Analysis of the crystal structure of a target protein−ligand complex is important for structure-based drug discover (SBDD). The starting point of SBDD study is to obtain the suitable crystals of target protein/ligand complexes. Heme-containing proteins, including indoleamine 2,3-dioxygenase 1(IDO1), present a challenge due to difficulty in protein preparation.

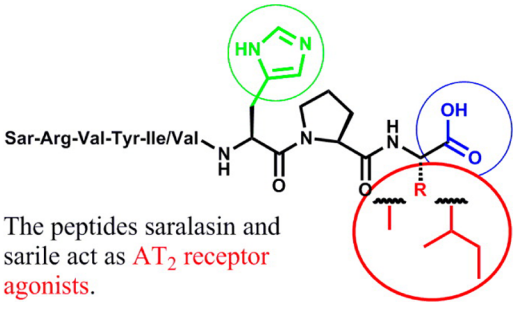
Here, Tojo et al. (DOI: 10.1021/ml500247w) report the crystal structures of two IDO1/IDO1 inhibitor complexes. The authors describe the identification and preliminary optimization of imidazothiazole derivatives as novel IDO1 inhibitors. This study can help in the understanding of the IDO1 activation mechanism and IDO1 drug discovery."



OLD TOOLS FOR A NEW RECEPTOR

Renin-angiotensin system (RAS) is an ideal target for new chemical entities with hypotensive actions, as supported by the clinical findings with angiotensin II (Ang II) receptor blockers, saralasin and sarile. Positive action of saralasin and sarile were attributed to the antagonistic effects elicited by octapeptides at the AT_1 receptor. Stimulation of a second receptor in RAS, the AT_2 receptor, which counteracts effects by AT_1, is currently being investigated as a new drug target.

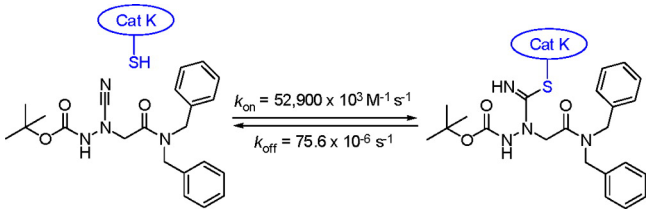
In this issue, Guimond et al. (DOI: 10.1021/ml500278g) demonstrate that the pharmacological tools, saralasin and sarile, not only bind to the AT_2 RAS receptor but also activate it. This can aid in the continuing investigation of the AT_2 receptor as a potential new drug target.



PEPTIDOMIMETIC INHIBITORS OF CYSTEINE CATHEPSINS

Cysteine cathepsins belong to the family of papain-like cysteine peptidases. When overexpressed, these enzymes have been known to cause a multitude of pathological conditions, including bone remodeling where the enzyme degrades bone matrix components.

Peptidomimetic nitrile-type inhibitors are known to interact with cysteine proteases in a covalent-reversible manner. In this issue's Featured Letter, Schmitz et al. (DOI: 10.1021/ml500238q) designed a chemotype of nitrile derivatives in which the cyano group is placed at a nitrogen atom and is centrally arranged in the inhibitor molecule. These inhibitors were found to be highly potent, in particular toward cathepsin K.



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