

Discovery and Characterization of Covalent PPAR γ Inverse-agonists, or, The Impressive Skills of a Nuclear Hormone Receptor

Anders Friberg, PhD

Senior Scientist @ Innovation Campus Berlin / Structural Biology
NUVISAN ICB GmbH | Muellerstr. 178 | 13353 Berlin | Germany

Additional Nuvisan contributors:

Hanna Meyer & Vera Pütter (mass spectrometry & protein production)
Timo Stellfeld & Nico Bräuer (medicinal chemistry)
Simon Holton (structural biology)

Summary

- Selective covalent inverse-agonists were identified by high-throughput screening against the human hormone receptor PPAR γ (peroxisome-proliferator activated receptor gamma)
- PPAR γ represents a potential target for a new generation of anti-cancer therapeutics, especially in bladder and pancreatic cancers
- Two different series of inverse agonists were structurally characterized in detail by high-resolution protein crystallography
- The structural data displays the amazing repertoire of movements and conformations this hormone receptor can adopt
- Furthermore, the crystal structures facilitated the design of additional compounds by better understanding of their mode-of-action as well as by giving a molecular view of their interactions to the receptor

Journal of
**Medicinal
Chemistry**

Discovery and Structure-Based Design of Potent Covalent PPAR γ Inverse-Agonists BAY-4931 and BAY-0069

Douglas L. Orsi, Elisabeth Pook, Nico Bräuer, Anders Friberg, Philip Lienau, Christopher T. Lemke, Timo Stellfeld, Ulf Brüggemann, Vera Pütter, Hanna Meyer, Maria Baco, Stephanie Tang, Andrew D. Cherniack, Lindsay Westlake, Samantha A. Bender, Mustafa Kocak, Craig A. Strathdee, Matthew Meyerson, Knut Eis, and Jonathan T. Goldstein*

ELSEVIER

Biorganic & Medicinal Chemistry

journal homepage: www.elsevier.com/locate/bmc

Discovery and characterization of orally bioavailable 4-chloro-6-fluoroisophthalamides as covalent PPAR γ inverse-agonists

Douglas L. Orsi^{1,2}, Steven J. Ferrara³, Stephan Siegel⁴, Anders Friberg⁵, Léa Bouché⁶, Elisabeth Pook⁷, Philip Lienau⁸, Joseph P. Bluck⁹, Christopher T. Lemke¹⁰, Gizem Akcay¹¹, Timo Stellfeld¹², Hanna Meyer¹³, Vera Pütter¹⁴, Simon J. Holton¹⁵, Daniel Korr¹⁶, Isabel Jerchel-Furau¹⁷, Constantina Pantelidou¹⁸, Craig A. Strathdee¹⁹, Matthew Meyerson^{20,21,22}, Knut Eis²³, Jonathan T. Goldstein²⁴

¹ Center for the Development of Therapeutics, Broad Institute of MIT and Harvard, Cambridge, MA 02142, USA

² Research and Development, Pharmaceuticals, Bayer AG, 13353 Berlin, Germany

³ Nuvisan ICB GmbH, 13353 Berlin, Germany

⁴ Research and Development, Pharmaceuticals, Bayer AG, 42113 Wuppertal, Germany

⁵ Bayer US LLC, Research and Development Precision Molecular Oncology, Cambridge, MA 02142, USA

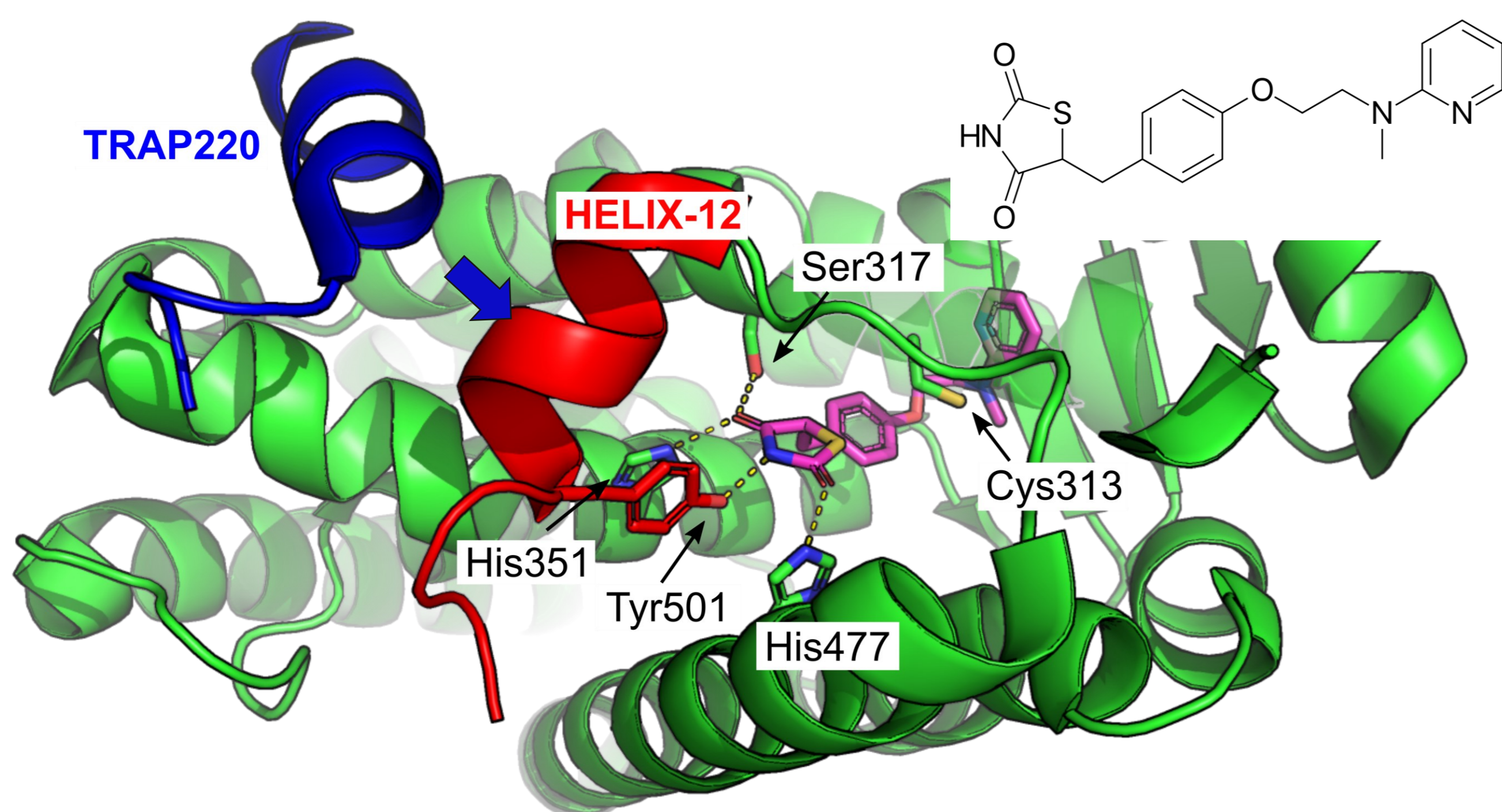
⁶ Cancer Program, Broad Institute of MIT and Harvard, Cambridge, MA 02142, USA

⁷ Department of Medical Oncology, Dana-Farber Cancer Institute, Boston, MA 02215, USA

⁸ Center for Cancer Genomics, Dana-Farber Cancer Institute, Boston, MA 02215, USA

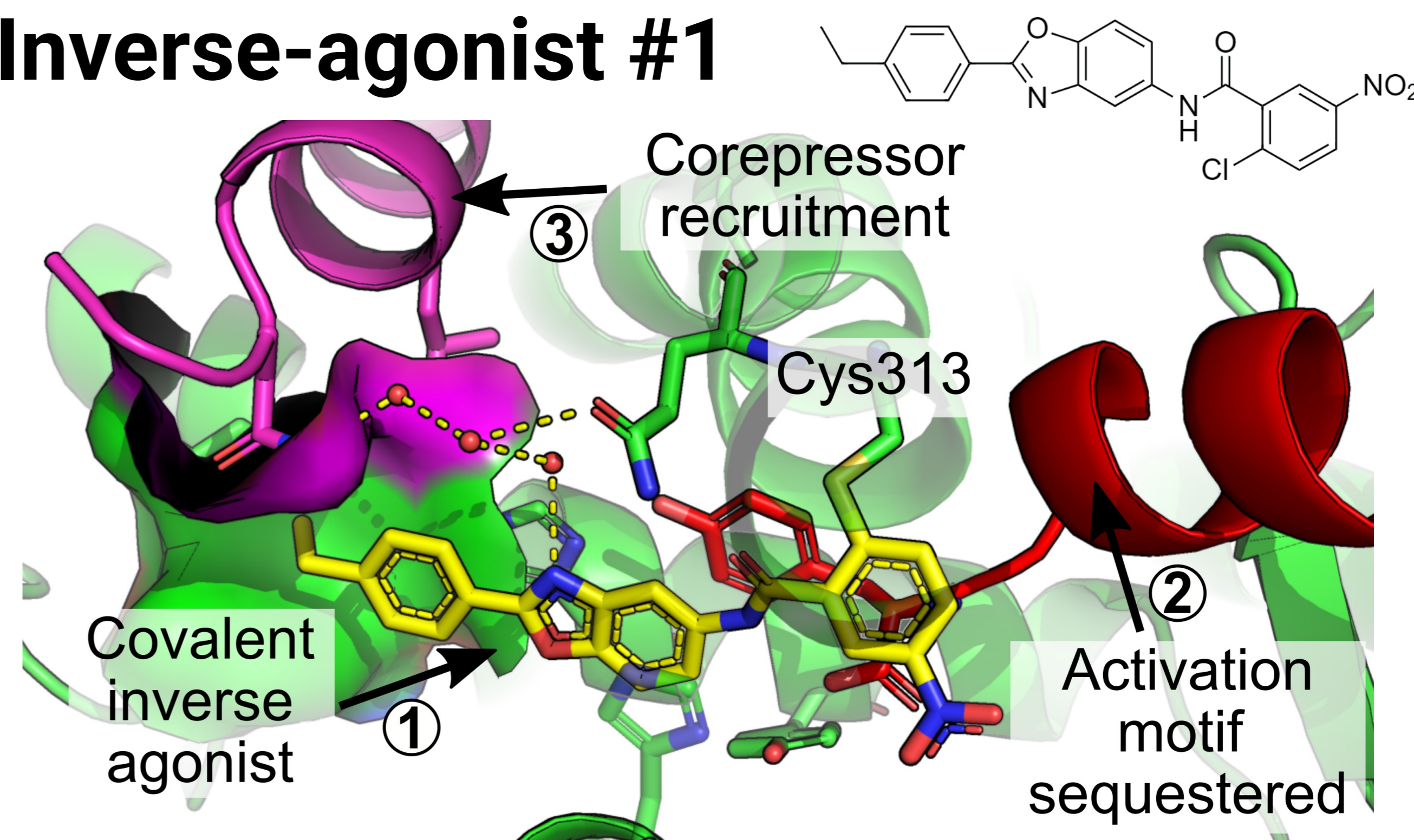
⁹ Department of Genetics and Medicine, Harvard Medical School, Boston, MA 02115, USA

Rosiglitazone – a classic agonist



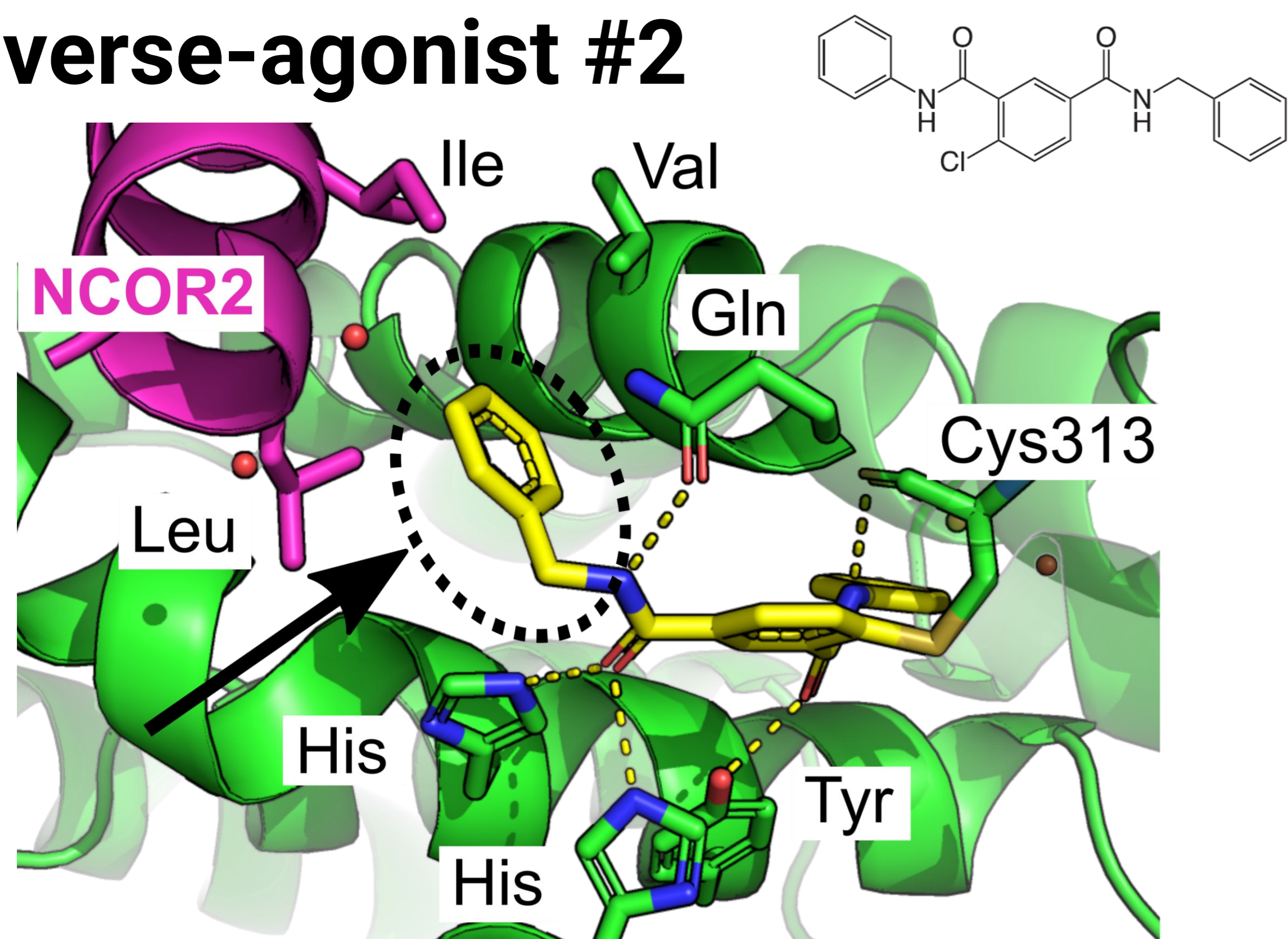
Agonist binding (magenta) drives transcriptional activation by recruitment of the co-activator TRAP220/ MED1 (blue), via stabilization of Helix-12 (red).

Inverse-agonist #1



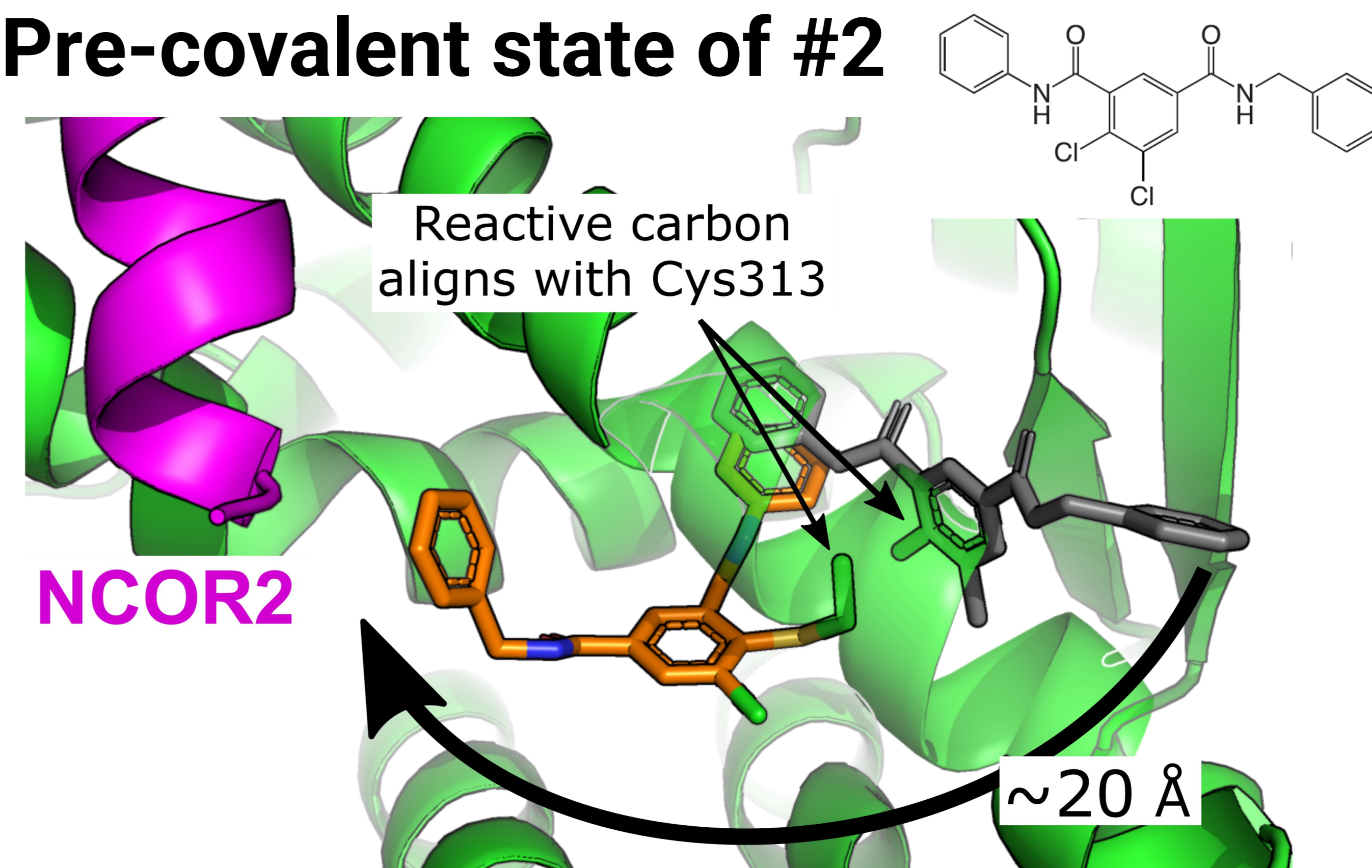
Surprisingly, the 1st series of inverse agonists (yellow) motivates PPAR γ to sequester Helix-12 (red) into the ligand binding pocket. This exotic conformation allows strong binding of co-repressor proteins, such as NCOR2 (magenta), which in turn induce repression of target genes.

Inverse-agonist #2



The 2nd series of covalent inverse agonists (yellow), exhibiting higher oral bioavailability, relies on spatial blocking of Helix-12 (displaced into solution) and recruitment of the co-repressor (magenta) by additional primarily hydrophobic interactions (circled).

Pre-covalent state of #2



The structural studies also allowed for the comparison of the covalent state of the inverse agonist (orange – WT PPAR γ) and its proposed pre-covalent pose (gray - C313A PPAR γ). A fascinating 20 Å movement of the terminal benzyl group became evident.

Interested in structural biology support tailored to your project needs?

Have a look at our established and ready-to-go crystallization systems



In conclusion, in a fully integrated setup Nuvisan ICB supported the project with medicinal chemistry, protein science and structural biology in the successful discovery and optimization of two series of covalent PPAR γ inverse agonists. Please reach out to discuss your project!

Drop us a line at hello@nuvisan.com

