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

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Summary

- Selective covalent inverse-agonists were identified by high-throughput screening against the human hormone receptor PPARG (peroxisome-proliferator activated receptor gamma)
- PPARG 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

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

Douglas L. Orsi, Elisabeth Pook, Nico Bräuer, Anders Friberg, Philip Lienau, Christopher T. Lemke, Timo Stellfeld, Ulf Brüggemeier, 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*

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Discovery and characterization of orally bioavailable 4-chloro-6-fluoroi-sophthalamides as covalent PPARG inverse-agonists

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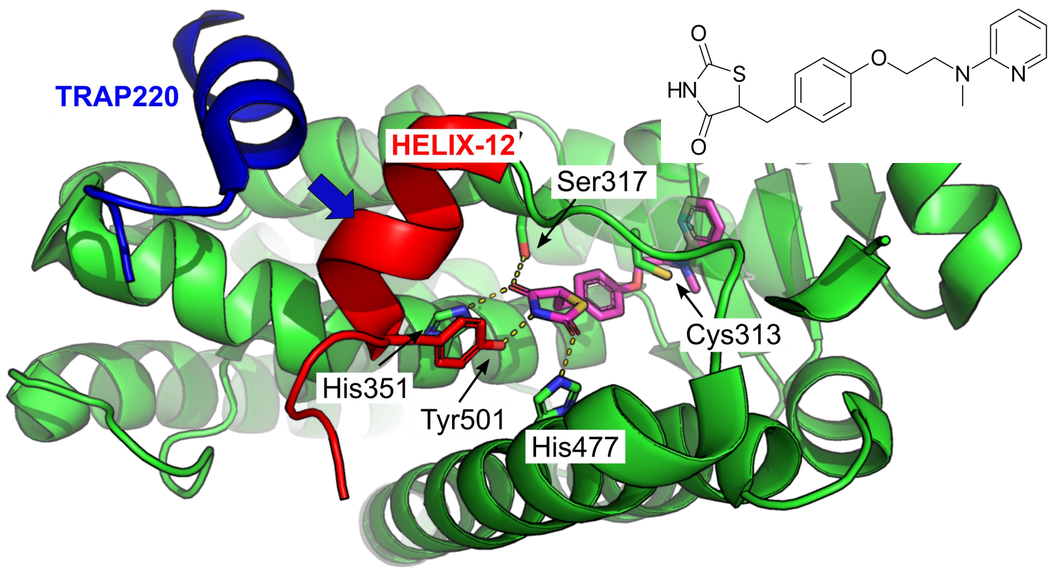
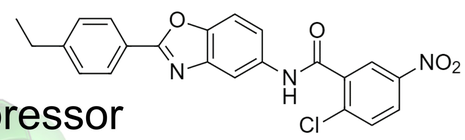
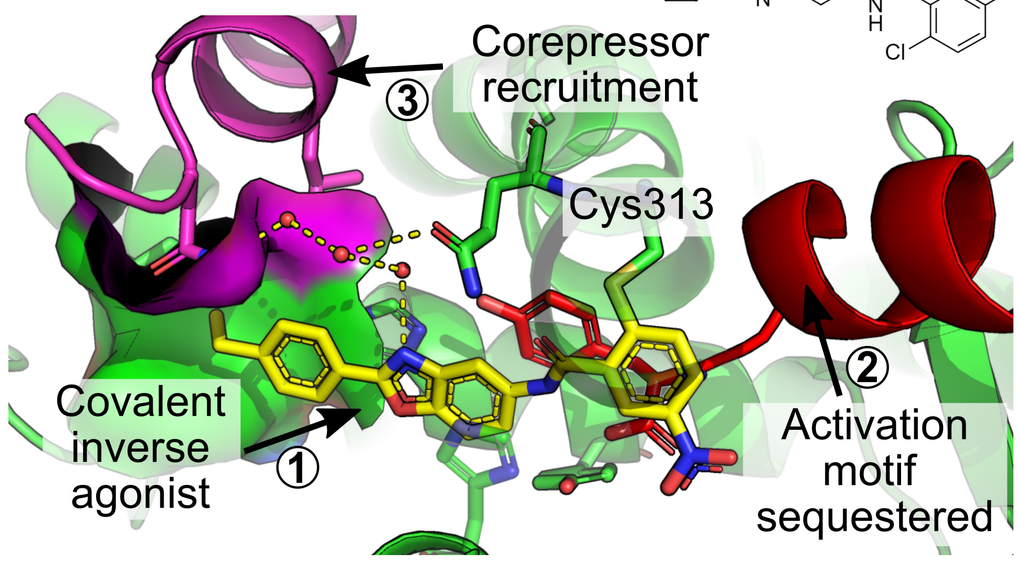
Rosiglitazone – a classic agonist



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

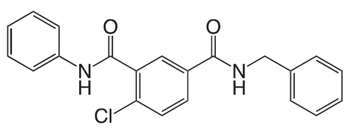
Inverse-agonist #1

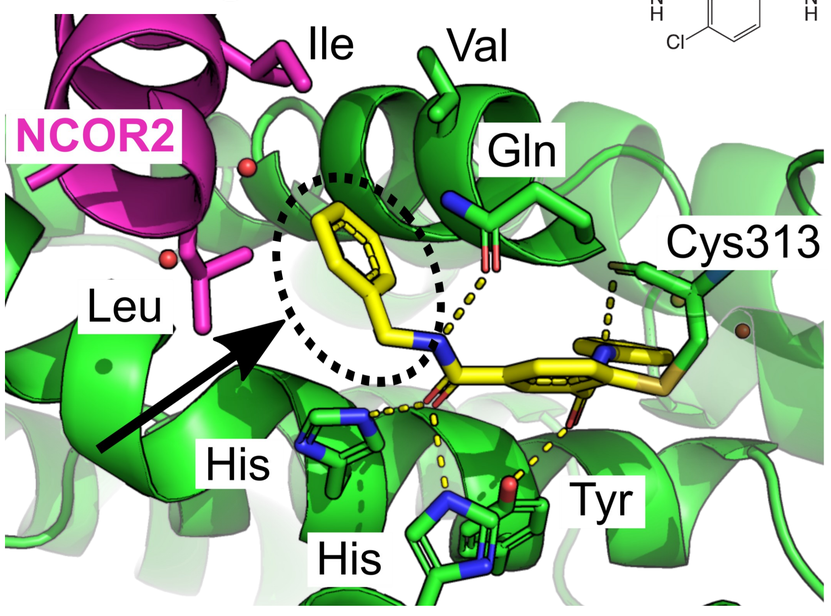




Surprisingly, the 1st series of inverse agonists (yellow) motivates PPARG to sequester Helix-12 (**red**) into the ligand binding pocket. This exotic conformation allows strong binding of co-repressor proteins, such as NCOR2 (**magenta**), which in turn induce repression of target genes.

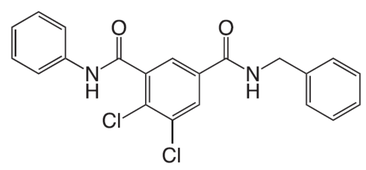
Inverse-agonist #2

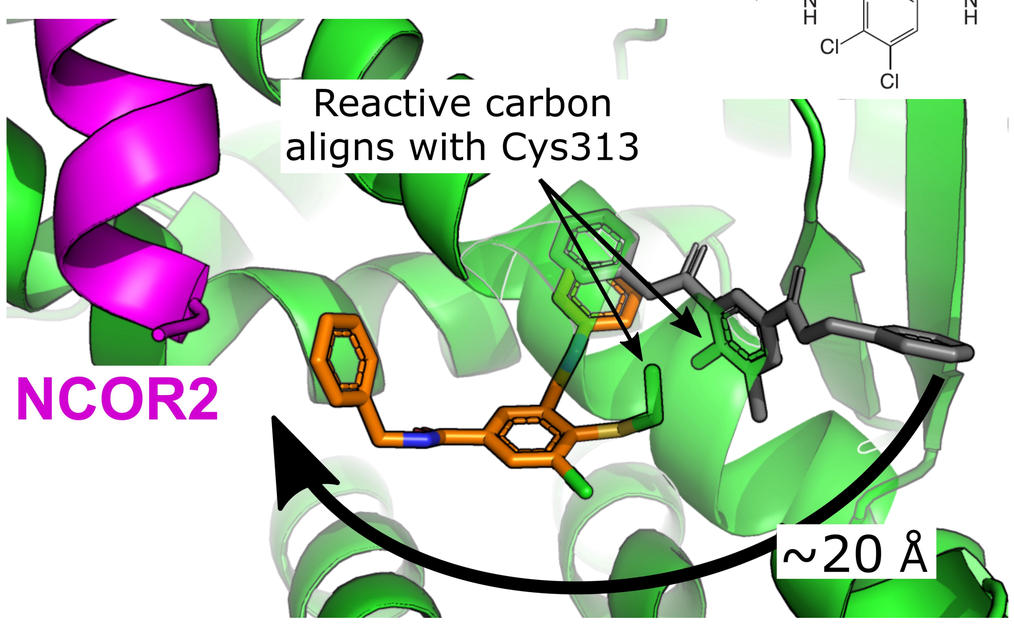




The 2nd series of covalent inverse agonists (yellow), exhibiting higher oral bioavailability, relies on spatial blocking of Helix-12 (displaced into solution) and recruitment of the co-repressor (**magenta**) by additional primarily hydrophobic interactions (circled).

Pre-covalent state of #2





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

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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 PPARG inverse agonists. **Please reach out to discuss your project!**

Drop us a line at hello@nuvisan.com