# Target identification and structural optimization of the natural product celastrol

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Natural products remain a major source of drug discovery. We recently conducted several approaches to identify the biological targets and to enhance the drug developability of celastrol and diphyllin, two high-value natural products.[1-2] Celastrol is a highly active natural product extracted from the roots of Tripterygium wilfordii, but its clinical use is limited due to its severe side effects and unknown biomechanism. Here, we developed a web-server tool that identified peroxiredoxin 1 (PRDX1) was the ROS-manipulating target protein of celastrol in colorectal cancer. The surface plasmon resonance (SPR) assay, mass spectra analysis, and high-resolution crystal structure studies revealed that celastrol directly binds with PRDX1. However, celastrol also shows moderate inhibitory activity against other peroxiredoxins (eg. PRDX2, PRDX3, PRDX5). Therefore, we conducted a structure modification campaign based on the crystal structure. A new derivative named **19-048** showed improved potency and selectivity. Meanwhile, **19-048** reduced toxicity *in vivo* compared to celastrol. In colorectal cancer xenograft, **19-048** displayed significant anti-tumor efficacy. Meanwhile, the anti-tumor efficacy was dramatically diminished in xenograft nude mice bearing PRDX1 knock-down colorectal cancer cells. Furthermore, several downstream genes of the p53 signaling pathway were significantly up-regulated with **19-048** or celastrol treatment. Our findings reveal that PRDX1 is indeed the target of celastrol and its derivative in colorectal cancer, and the side effects of celastrol could be reduced via structural modification.
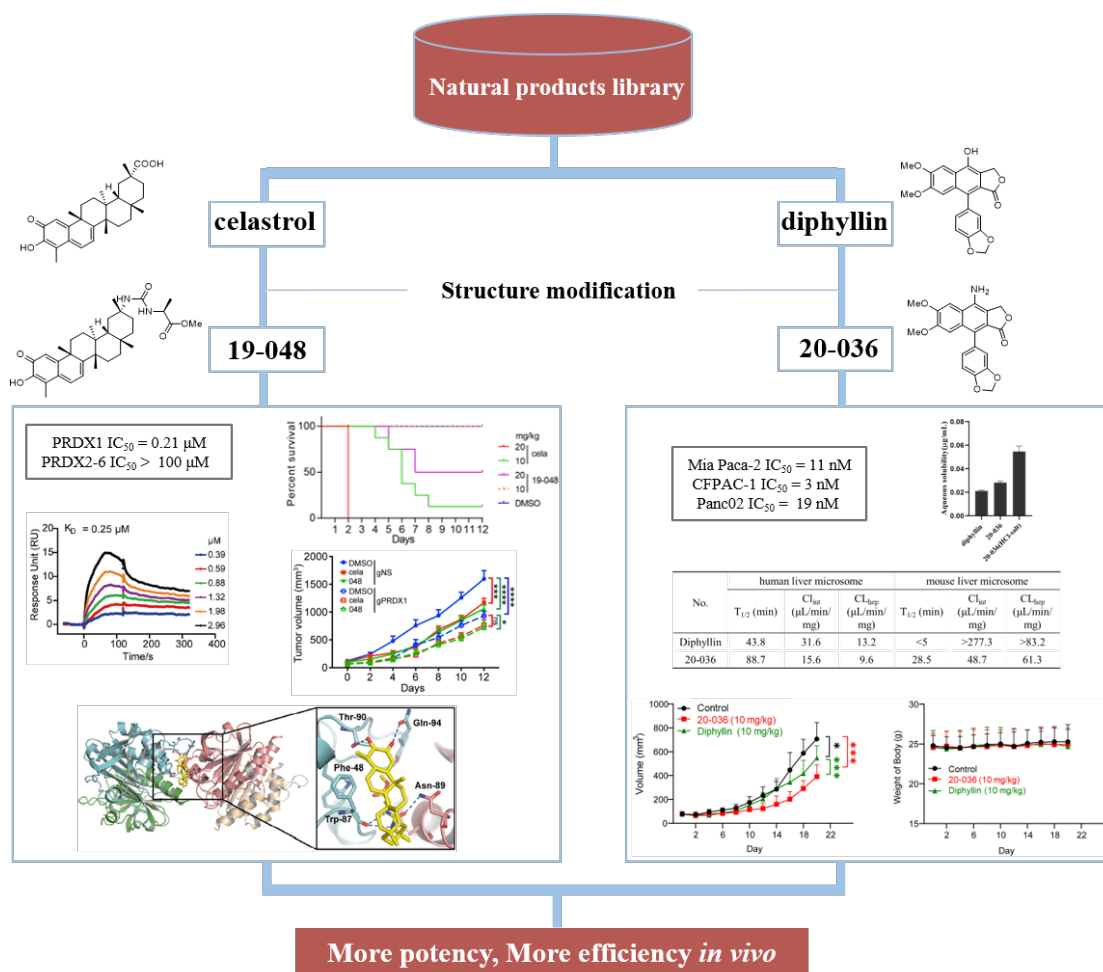
Figure 1. Natural products-based drug discovery.

Reference:

[1] Heng Xu[#], Hongfang Zhao[#], Chunyong Ding[#], Defang Jiang, Zijie Zhao, Yang Li, Xiaoyu Ding, Jing Gao, Hu Zhou, Cheng Luo, Guoqiang Chen, Ao Zhang[*], Ying Xu[*], Hao Zhang[*]. Celastrol suppresses colorectal cancer via covalent targeting peroxiredoxin 1. *Signal Transduction and Targeted Therapy*. 2023, 8, 51.

[2] Yang Li[#], Qing Lu[#], Ruoxuan Xiao[#], Jing Ma, Yuqi Tang, Wantao Chen, Ruihan Zhang, Lingxi Jiang, Hao Chen, Baiyong Shen, Ao Zhang[*], Chunyong Ding[*]. Synthesis and anti-tumor activity of nitrogen-containing derivatives of the natural product diphyllin. *European Journal of Medicinal Chemistry*. 2022, 243, 114708.