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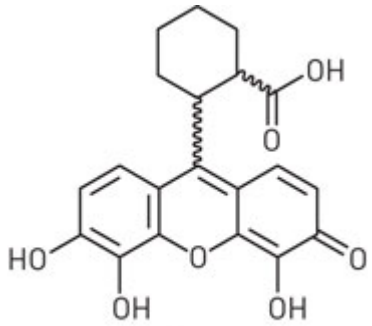
Pharmacology

Molecules Target Protein Hot Spots

Small molecules differentially modulate G protein interactions

Celia Arnaud

Many drugs target gprotein-coupled receptors. Small-molecule modulators that home in on the interface between G-proteins and their targets could enhance the efficacy, potency, and selectivity of existing drugs, says Alan V. Smrcka, a pharmacologist at the University of Rochester Medical Center. In some cases, those small molecules could even become drugs themselves.



M119

Now, Smrcka and coworkers describe a computer-based screening method that finds small molecules that selectively modulate interaction between G-protein subunits and their protein targets

(*Science* **2006,** *312*, 443).

Smrcka and coworkers first used peptides to map a "hot spot"—amino acids that are primarily responsible for binding target proteins—on the surface of the βγ subunit of heterotrimeric G-proteins. "We thought that if we could inspect smaller subsurfaces of the bigger surface, we would be able to selectively modify target interactions downstream," Smrcka says. Using computer modeling, the team screened a 1,990-compound library for small molecules that bind that hot spot and identified several high-affinity binders.

When they tested those molecules in cell cultures, they found that the molecules selectively affect different downstream proteins. The researchers suspect that the molecules bind to different regions of the hot spot.

In a mouse model, one of the compounds, identified as M119, increases the potency of morphine 11-fold. Smrcka plans to test the approach for finding G-protein modulators in animal models of several diseases, including heart failure, prostate cancer, and breast cancer.

The strategy makes it "possible not only to identify small molecules that directly modulate the function of heterotrimeric G-proteins, but also to find, with great efficiency, compounds that can turn off one signaling pathway while preserving or even augmenting others," John J. G. Tesmer of the Life Sciences Institute at the University of Michigan writes in a commentary in *Science*.

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