



## 2016-2017 Research and Design Model

### Whitefish Bay High School SMART Team

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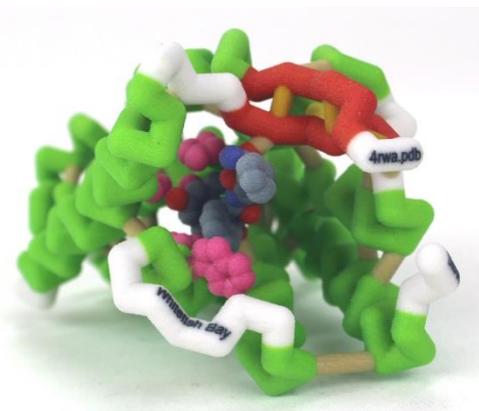
### Inhibition of $\delta$ -Opioid Receptors to Prevent Painkiller Addiction

**PDB:** 4RWA

**Primary Citation:** Fenalti, G., et. al. (2015). Structural basis for bifunctional peptide recognition at human  $\delta$ -opioid receptors. *Nature Structural & Molecular Biology* 22: 265-268.

**Format:** Alpha carbon backbone

**RP:** Zcorp with plaster



**Description:** Opioid addiction and abuse affects between 26 and 36 million people worldwide (Volkhow), prompting researchers to try to design a drug that both has painkilling effects but does not create a dependency. Most opioid analgesics work through activation of mu opioid receptors (MOR). They naturally bind to opioid peptides, such as endomorphins 1 and 2, in order to regulate pain. Another important target is the delta opioid receptor (DOR). Inhibition of DOR has been shown to slow the development of addiction to MOR agonists in animal models of pain. DOR are proteins that transpermeate the cell membrane with seven alpha helices. Schiller and colleagues first reported an endomorphin analogue, DIPP-NH<sub>2</sub>, that activates MOR and also inhibits DOR. DIPP-NH<sub>2</sub> is structurally similar to the natural endomorphins, so it can bind DOR through similar mechanisms. The DIPP-NH<sub>2</sub> interacts with the Met132, Tyr129, Val217, Ile277, and Trp284 on the DOR. Moreover, one of the two methyl groups on DIPP-NH<sub>2</sub> engages Val281 and Ile277. Finally, a salt bridge forms between the DIPP-NH<sub>2</sub> N-terminus and Asp128, and this salt bridge is crucial for opioid receptor ligand recognition. The Whitefish Bay High School SMART team (Students Modeling a Research Topic) is modeling DOR. DIPP-NH<sub>2</sub> may be the basis of a non-addictive painkiller, which would be a significant advancement toward alleviating the major societal problem of opioid addiction.

**Secondary Citation:** Volkhow, Nora D. "America's Addiction to Opioids: Heroin and Prescription Drug Abuse." *National Institute on Drug Abuse (NIDA)*, National Institute on Drug Abuse, 14 May 2014, [www.drugabuse.gov/about-nida/legislative-activities/testimony-to-congress/2016/americas-addiction-to-opioids-heroin-prescription-drug-abuse](http://www.drugabuse.gov/about-nida/legislative-activities/testimony-to-congress/2016/americas-addiction-to-opioids-heroin-prescription-drug-abuse).

**Specific Model Information:**

- Alpha Helices are colored chartreuse
- Beta sheet is colored red
- Hydrogen bonds are colored goldenrod
- Struts are colored tan
- Disulfide bond is colored yellow
- Asp128, which is crucial for opioid receptor ligand recognition, is colored orange
- Val217, Val281, Ile277, Trp284, Met 132, Tyr129, which are the binding sites on the receptor for DIPP-NH<sub>2</sub>, are colored hotpink
- DIPP-NH<sub>2</sub>, the delta opioid receptor antagonist that prevents opioid addictions from forming, is colored CPK

<http://cbm.msoe.edu/smartTeams/smartTeamsLocal.php>