



SMART Teams 2013-2014

Research and Design Phase

Divine Savior Holy Angels High School SMART Team

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"I Wanna New Drug"

Manipulating Kappa Opioid Receptor Ligands to Induce a Pain Relieving Response

PDB: 4DJH

Primary Citation: Huixian Wu, Daniel Wacker, Mauro Mileni, Vsevolod Katrich, Gye Won Han, Eyal Vardy, Wie Liu, Aaron A. Thompson, Xi-Ping Huang, F. Ivy Carroll, S. Wayne Marcarella, Richard B. Westkaemper, Philip D. Mosier, Bryan L. Roth, Vadim Cherezov, Raymond C. Stevens (2012). Structure of the human K-opioid receptor in complex with JD(Tic). Nature (485): 327-332.

Format: Alpha carbon backbone

RP: Zcorp with plaster

Description:

Dangerous painkillers may cause serious problems for those who fall into drugs' addictive trap, such as former NFL quarterback Brett Favre. The addictiveness of painkillers such as OxyContin and Vicodin is largely attributed to the response they trigger in proteins such as mu opioid receptors (MOPs). This receptor activates cellular signaling pathways responsible for dulling pain; however, the protein also has the ability to stimulate cellular signaling pathways that makes MOP-based painkillers rewarding. An alternate target that alleviates pain but does not produce reward is the kappa opioid receptor (KOP). Unfortunately, many KOP agonists also activate intracellular signaling pathways that produce hallucinogenic effects. To investigate the changes that occur when KOP binds to different ligands, the Divine Savior Holy Angels SMART (Students Modeling A Research Topic) Team has used 3D printing technology to model the active site of the KOP with the neoclerodane diterpene, salvinorin A, to see how the induced fit changes the signal transduction pathways in a neuron of post-synaptic cells. KOP acts as a target for agonists, which are chemicals that bind to a receptor of a cell to trigger a response that activates chemical signaling pathways in cells. Manipulating receptor proteins such as the KOP to inhibit pain pathways without the addictive effect of MOP-targeting painkillers would represent a significant breakthrough in chronic pain management. Computer-aided drug design is being used to streamline the development of KOP ligands that activate this receptor in ways that result in less hallucinogenic effects.



Specific Model Information:

- Alpha helices in the kappa receptor are highlighted in red.
- The G-protein is highlighted in yellow.
- Salvinorin, displayed in ball and stick, can be magnet docked to the active site.
- Thr111, Tyr312, Tyr313, Cys315 and Tyr320, displayed in ball and stick and colored cpk, are amino acids located in the active site of the kappa opioid receptor.
- Hydrogen bonds are colored white.
- Structural supports are lemon chiffon.

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

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