

Virtual library docking for cannabinoid-1 receptor agonists with reduced side effects

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ABSTRACT Virtual library docking can reveal unexpected chemotypes that complement the structures of biological targets. Seeking agonists for the cannabinoid-1 receptor (CB1R), we dock 74 million tangible molecules and prioritize 46 high ranking ones for de novo synthesis and testing. Nine are active by radioligand competition, a 20% hit-rate. Structure-based optimization of one of the most potent of these ($K_i = 0.7 \mu\text{M}$) leads to '1350, a 0.95 nM ligand and a full CB1R agonist of $G_{i/o}$ signaling. A cryo-EM structure of '1350 in complex with CB1R- G_{i1} confirms its predicted docked pose. The lead agonist is strongly analgesic in male mice, with a 2-20-fold therapeutic window over hypolocomotion, sedation, and catalepsy and no observable conditioned place preference. These findings suggest that unique cannabinoid chemotypes may disentangle characteristic cannabinoid side-effects from analgesia, supporting the further development of cannabinoids as pain therapeutics.

