Docket #: S23-339

Novel small molecule negative allosteric modulators of the mu-opioid receptor

Researchers at Stanford University and Washington University in St. Louis have discovered a novel molecular pathway for the treatment of opioid overdose.

Opioids are a powerful tool for pain management when used in clinical care settings. However, in recent years these drugs have been misappropriated for recreational use, spurring a public health crisis. In the US alone there were over 80,000 deaths due to opioid overdose in 2022. Naloxone has proven to be a key tool in the fight against opioid overdose by acting as an agonist of the mu-opioid receptor (MOR). However, use of naloxone for opioid overdose has drawbacks, including that naloxone requires larger, repeated doses in response to more potent fentanyl. To this end, a need exists for novel negative allosteric modulators of the mu-opioid receptor (MOR) that are selective with limited off target effects.

Stage of Development
Research - in vitro

Stage of Research
Researchers sought to improve upon their previous finding (compound 368) via structure-based optimization in order to find compounds with enhanced medicinal chemistry properties. Specifically, researchers modified a potentially labile sulfide to an ether to improve its pharmacokinetic properties. Researchers found that this compound is an allosteric modulator of the MOR in vitro. While this molecule is still a full inhibitor of the MOR, it has a dampened ability to enhance naloxone affinity for the receptor, which in turn makes the molecule less dependent on co-administration with naloxone for activity.

Applications

- Novel treatment of opioid overdose

Advantages

- Potentially less dependent on co-administration with naloxone for therapeutic effects

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