Sleep solutions [1]

Discovery [2]

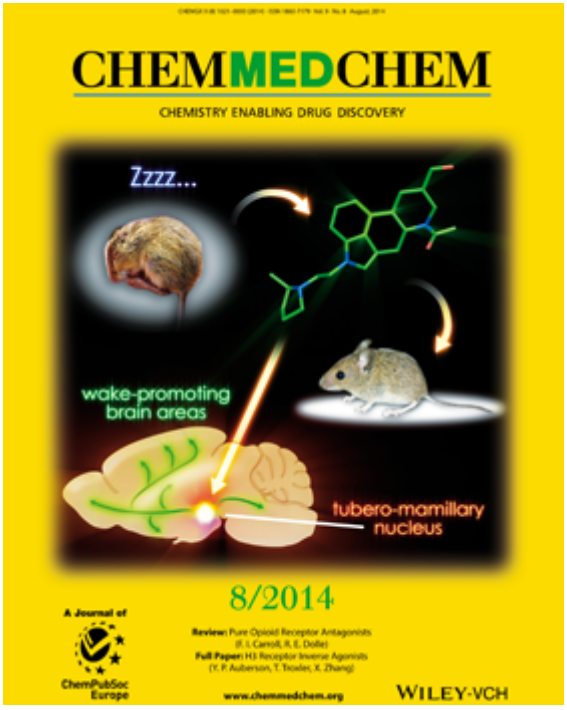
For patients with narcolepsy, falling asleep can be just as hard as staying awake. To function during the day, they often take medications—including stimulants—that remain active through the evening, causing insomnia. With each new treatment introduced, hopes rise and then fall as the same side effect emerges.

Narcolepsy with cataplexy—a sudden loss of voluntary muscle tone that makes a person go limp—affects between 25 and 50 individuals per 100,000. A team of chemists at the Novartis Institutes for BioMedical Research and ChemPartner, a company in Shanghai, are working on a potential solution for some of these patients. They've identified a class of compounds that temporarily blocks a receptor involved with regulating wakefulness. The compounds were optimized so that their activity was limited to a short duration in animal models, a finding published in the August issue of *ChemMedChem* [3]. This research supports the use of such compounds as templates for potential future drugs. Many steps remain to prove safety and efficacy in humans.

Novartis and ChemPartner scientists targeted a receptor involved with narcolepsy, work featured on the cover of the August issue of ChemMedChem.

"The goal is to provide narcolepsy patients with a pill that they could take during the day to stay alert without affecting their sleep at night," says Yves Auberson, a co-first author on the paper who is an executive director in Global Discovery Chemistry at the Novartis Institutes for BioMedical Research.

The project was inspired by work outside Novartis on the human histamine receptor (H3R), which is known to play a role in sleep disorders. Histamine is a neurotransmitter that helps keep us alert. When bound to the H3R receptor, histamine inhibits its own release, creating a negative feedback loop that's essential for the sleep-wake cycle. H3R is constitutively active, which means that it's "on" all the time to some extent, pushing us toward sleep, even when histamine is not bound to it.



After H3R was cloned in 1999, companies set out to develop “cruise control” for the receptor, hunting for molecules that would normalize its activity. Specifically, they searched for “inverse agonists,” compounds that would dampen its baseline signaling and keep histamine from binding it. The goal was to block the negative feedback loop and thereby boost histamine levels in the brain.

The first compound to reach the clinic as a result of these efforts helped keep patients with narcolepsy awake during the day. It had a half-life of 11 hours, however, leading to insomnia.

When it became clear that insomnia was a problem, Novartis decided to search for a solution. In 2009, a team identified a starting point for a new H3R program—a derivative of the ergoline alkaloids, a class of natural products synthesized by fungi. Novartis has a long history of working with natural products, especially ergoline alkaloids. When the team discovered that this particular derivative binds H3R, they figured that Novartis chemists had a shot at turning it into something useful for patients, based on experience. They were also encouraged by the novel structure of the starting point.

“From a structural perspective, the ergoline derivative was different from all the compounds in the clinic for H3R,” says Thomas Troxler, another co-first author on the paper and a senior investigator in Global Discovery Chemistry at the Novartis Institutes for BioMedical Research. “Having a different structure gave us the opportunity to go for a different profile.”

The team resolved to modify the ergoline derivative, which was already highly potent. They wanted to achieve two things—high initial occupancy of the H3R receptor and rapid clearance. The ideal compound would stick to the receptor when first administered and then fall off after just a few hours.

Instead of modifying and testing compounds in-house, the team turned to ChemPartner for assistance, with Mark Bock of Novartis (who recently retired) guiding the collaboration. Over several years, chemists and biologists from both companies met regularly to discuss the project and advance the best ideas. They eventually succeeded in generating molecules with

the desired properties, including the one featured in the *ChemMedChem* paper. ChemPartner conducted all of the lab work with input from Novartis.

“This successful collaboration shows how we can work with external chemistry and biology partners to augment our in-house expertise and resources,” says Karin Briner, global head of chemistry at the Novartis Institutes for BioMedical Research.

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Tags:
Novartis Institutes for BioMedical Research [4]

Links
[1] https://www.novartis.com/stories/discovery/sleep-solutions
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[3] http://onlinelibrary.wiley.com/doi/10.1002/cmdc.201402055/abstract
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