TO DREAM, PERCHANCE OF SLEEP

ACS MEETING NEWS: Chemists eye new way to fight insomnia as first-class molecule awaited approval

CARMEN DRAHL, C&EN WASHINGTON

FOR PAUL J. COLEMAN, presenting in the Moscone Center last month was like coming home again. The last time he fired up PowerPoint at a San Francisco American Chemical Society national meeting, in 2010, he unveiled the structure of a drug candidate known then as MK-4305. The molecule, a would-be sleep drug from Merck & Co., had a mechanism of action unlike anything on the market.

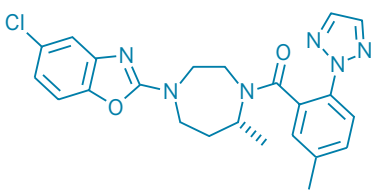
Coleman, an executive director of discovery chemistry at Merck, returned to the City by the Bay three weeks ago to lead a symposium about that very mechanism. His session in the Division of Medicinal Chemistry had dramatic timing. The fate of MK-4305, now dubbed suvorexant, was due to be decided by the Food & Drug Administration the very next day.

"I'd love to say that Scott and I planned it this way," Coleman joked before the meeting. His cochair, Scott D. Kuduk, a former Merck colleague, now directs chemistry at biotechnology firm Novira Therapeutics. Both saw the session's timing as a happy accident. "If suvorexant gets approved, it will be more than just a new sleep drug," Kuduk said. "It will be a success for neuroscience drug discovery. And those are rare."

Most sleeping pills, including poster child Ambien, act on γ-aminobutyric acid (GABA) receptors in the brain. Although effective, the mechanism isn't subtle. The GABA receptor is the main inhibitory switch in the nervous system. And the drugs have side effects including next-day sedation, which prompted FDA to cut recommended dosages in Ambien's case.

Suvorexant works differently. Merck's chemists designed it to act on two related proteins in the brain, orexin receptors 1 and 2 (*J. Med. Chem.* 2010, DOI: 10.1021/jm100541c). This biochemical circuitry promotes wakefulness when activated, so shutting it down with small molecules—orexin receptor antagonists—was a logical sleep-aid design strategy.

MERCK & CO.



MK-4305: 2006–11
Suvorexant: 2011–

Company: **Merck & Co.**
Indication: **Insomnia**
Target: **Orexin receptors 1 & 2**

THAT WAS THEN When MK-4305's structure was made public in 2010, Coleman (fourth from left) posed for C&EN with chemistry colleagues (from left) Michael J. Breslin, Swati P. Mercer, John D. Schreier, Christopher D. Cox, and Anthony J. Roecker.

Merck submitted suvorexant for FDA approval in 2012. In 2013, however, the agency's review panel concluded that the safety data didn't support approval of the 30- and 40-mg doses Merck recommended. The panel recommended approving a 10-mg dose but held off granting a formal green light until Merck showed that it could manufacture the 10-mg version consistently.

The agency's decision was a setback. Physiological effects of 10-mg doses were measurable in sleep labs. But patients were asked to keep diaries, and their entries suggested that the low doses didn't make them feel any better than placebos.

In February, Merck submitted the manufacturing data FDA requested. Then began the wait for a decision.

APPROVAL FOR suvorexant won't settle every question in the orexin field. It was these open questions—about dosing, selectivity, and more—that became themes in San Francisco.

Humans have two orexin receptors, so one big question is: Is it better for an insomnia drug to block one or both of them? Orexin-2 is more closely linked to the sleep-wake cycle. But it's not clear whether excluding orexin-1 might mean missing out on certain sleep benefits.

Several firms have developed selective orexin-2 antagonists. For example, Johnson & Johnson's Janssen Pharmaceuticals is working with Minerva Neurosciences, a Cambridge, Mass., biotechnology firm, to conduct dosing studies in healthy people with the antagonist MIN-202.

Merck has developed its own selective orexin-2 antagonists. The most advanced of those compounds is MK-1064, which Coleman reported has similar effects to antagonists of both orexin receptors at improving key parameters of sleep.

"There's been a lot of back-and-forth about what's better, dual or selective," Kuduk told C&EN. "Ultimately, the clinical evidence will decide."

"If suvorexant gets approved, it will be more than just a new sleep drug. It will be a success for neuroscience drug discovery."

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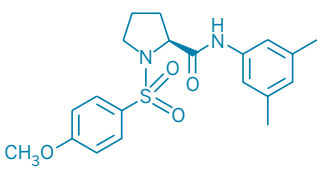
Suvorexant's story prompts the question of dosing. How can researchers determine the lowest possible dose that is effective for patients? Norihito Oi and colleagues at Japanese drug company Eisai are attempting to tackle the question with positron emission tomography (PET), a brain-imaging method. They're designing PET radiotracers that could one day associate orexin antagonist binding with efficacy and adverse effects.

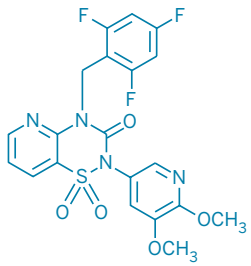
With Makoto Higuchi at Japan's National Institute of Radiological Sciences, Eisai's team developed a radioactive carbon-11 tracer that penetrates the blood-brain barrier in rats and rhesus monkeys and distributes primarily to regions of the brain where orexin-2 receptors are known to reside. However, the team had to block tracer-ejecting pump proteins to get a useful PET signal (*J. Med. Chem.* 2013, DOI: 10.1021/jm400772t). The tracer will become a lead for next-generation efforts, Oi said at the session.

Dosing also depends on a molecule's fate in the body. The ideal sleep drug would start working as soon as a person's head hits the pillow, last all night, and then immediately disappear in the morning. That's hard to achieve with a pill. Suvorexant's half-life in a person is approximately 12 hours, which means the drug is not completely gone the next day.



ACT-462206

Company: **Actelion Pharmaceuticals**
Target: **Orexin receptors 1 & 2**
Status: **Phase I clinical trials**



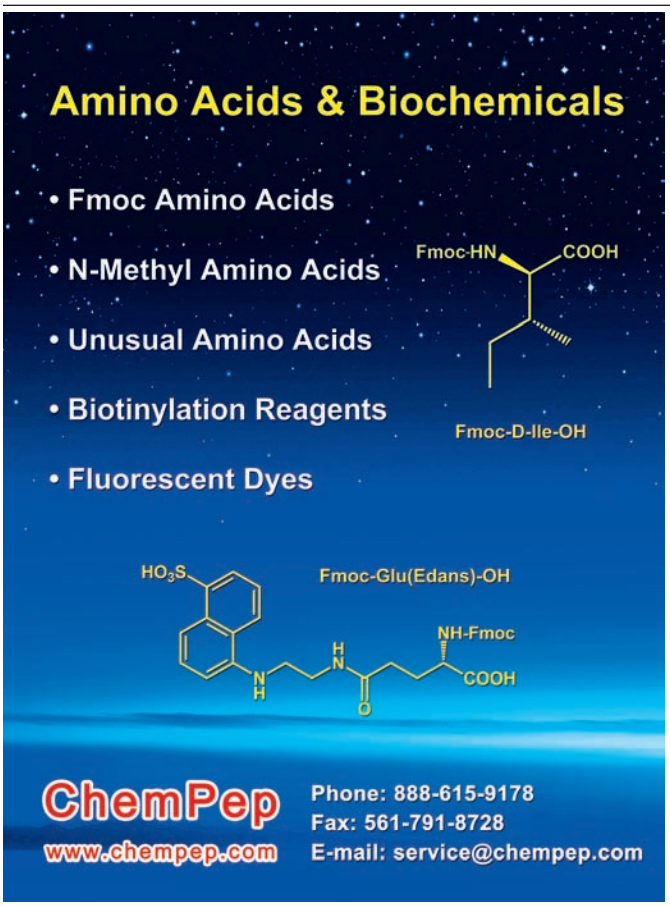
HTL6641

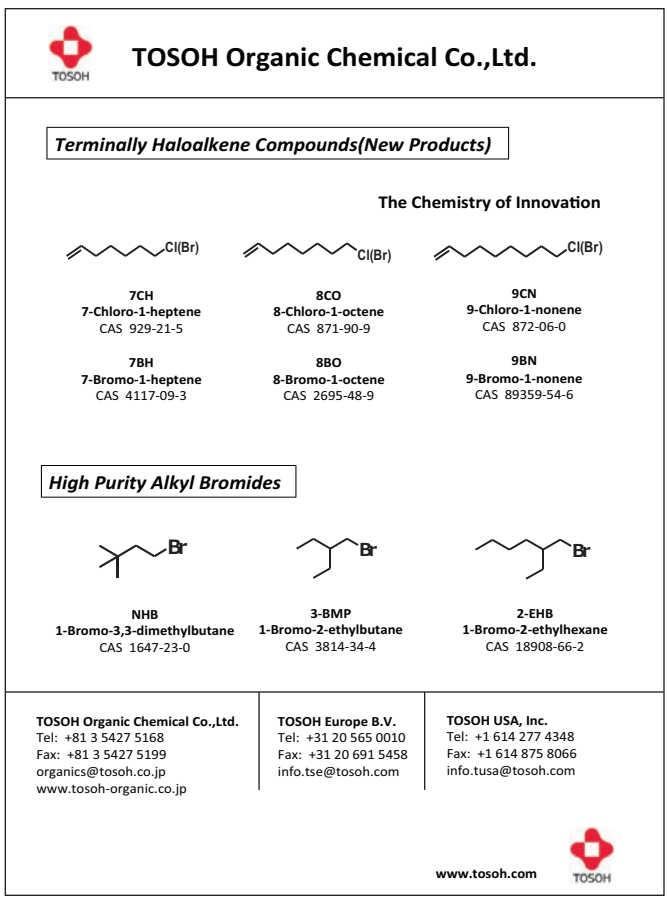
Company: **Heptares Therapeutics**
Target: **Orexin receptors 1 & 2**
Status: **Preclinical**

In San Francisco, chemist Stephen P. Andrews explained how researchers at British biopharmaceutical firm Heptares Therapeutics used structural biology to find an antagonist that could dissociate more quickly from orexin receptors and result in a lower risk of next-day sleepiness.

Heptares applied its proprietary technology to stabilize the orexin receptors and obtain their X-ray crystal structures for the first time. The structures helped Heptares chemists associate certain hydrogen bonds between drug candidate and receptor with slow or fast off rates. Andrews revealed the structure of HTL6641, which has a predicted human half-life of seven hours. The molecule has not yet been tested in humans.

For the public, the big question about orexin antagonists will be how they stack up against drugs already on the $1.5 billion U.S. insomnia market. Suvorexant has not been compared with Ambien





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SNOOZEFEST The drugs that dominate the $1.5 billion U.S. prescription sleep-aid market all act on GABA signaling.

Zolpidem
Generic Ambien makes up the lion's share of prescriptions
37 million Rxs

Temazepam
This generic was originally marketed as Restoril
8.2 million

Zolpidem ER
Extended-release version of generic Ambien
3.6 million

Lunesta
The only branded drug in the top five
3.3 million

Triazolam
This onetime blockbuster (brand name Halcion) fell out of favor
1.2 million

SOURCES: IMS Health, Truven Health Analytics, National Academies Press, Merck Index

in a head-to-head clinical trial, the gold standard for drug comparisons. But some of the speakers in San Francisco attempted to address the question with animal study data.

At doses that gave a rat or a rhesus monkey a comparable amount of sleep, Coleman and his colleagues have shown that the dual orexin receptor antagonist DORA-22 had fewer effects on memory and attention than established drugs (*Sci. Transl. Med.* 2013, DOI: 10.1126/scitranslmed.3005213). DORA-22 is an analog of filorexant (MK-6096), a Merck sleep drug candidate in Phase II clinical trials.

Christoph Boss explained that a dual orexin antagonist induces more natural sleep patterns in rats and dogs compared with Ambien. Boss was at the meeting representing Swiss firm Actelion Pharmaceuticals, which was first to prove that orexin antagonists could help insomniacs sleep (*Nat. Med.* 2007, DOI: 10.1038/nm1544). Actelion halted development of the molecule that reached that milestone, almorexant, for safety reasons. But the company applied lessons from almorexant to its new leading insomnia drug candidate, ACT-462206, which was found to be safe in a study of 56 healthy men (*J. Clin. Pharmacol.* 2014, DOI: 10.1002/jcph.297).

THE MOST TANTALIZING question at the session was about other potential uses for orexin-targeted drugs. The orexin-1 receptor is thought to be important in craving, "so it could have a potential role in substance addiction," Miles Congreve, Heptares's vice president of chemistry, told C&EN. Heptares is working on its own orexin-1 selective receptor antagonists using its X-ray structures as guides.

Stanford University's Luis de Lecea has long wondered whether an orexin agonist, an activator of the receptors, might treat narcolepsy, a condition in which people spontaneously fall asleep. A neuroscientist, de Lecea led one of the teams who discovered orexin nerve circuitry in 1998. "The more orexin compounds there are, the better for the public and for science," he said.

The session in San Francisco wrapped up at lunchtime. As is ACS meeting tradition, Coleman and Kuduk had reservations for lunch with the other speakers. The group sat down at Italian eatery La Briciola. "And then a couple of phones started vibrating," Coleman said. It was big news: FDA had approved suvorexant at doses of 5, 10, 15, and 20 mg. The agency advised people taking the 20-mg dose against driving the next day.

Suvorexant will be marketed as Belsomra once the Drug Enforcement Administration has made its final decision on the drug's abuse potential. Coleman announced the news to the table. "And the rest of the day, I was walking on clouds," he said.

The newly minted medication will enter a competitive market dominated by cheap generic Ambien and its ilk. At the end of the day, real-world tests of suvorexant's effectiveness will determine whether it becomes a commercial success.

But for a chemist like Coleman, suvorexant's story is about how teams of scientists, working together, learned something new about how sleep works and developed a drug to precisely target that biology. "We've worked against really long odds," he said. "I think this is a real success for chemistry." ■

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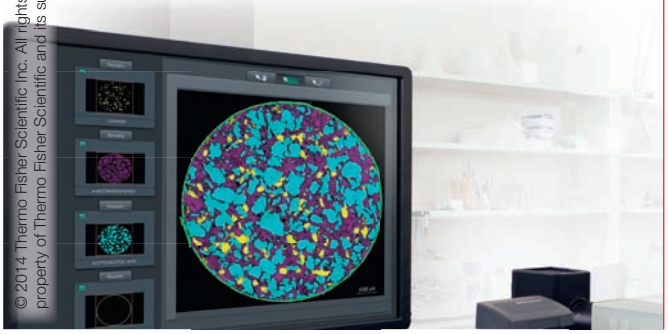

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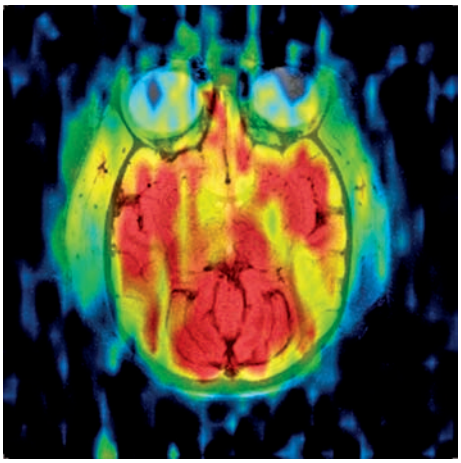

INSIDE JOB
Eisai's PET tracer candidate illuminates a rhesus monkey's brain.

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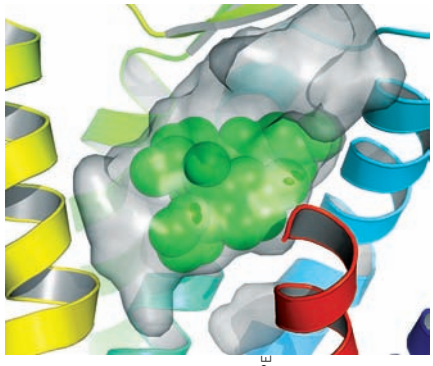
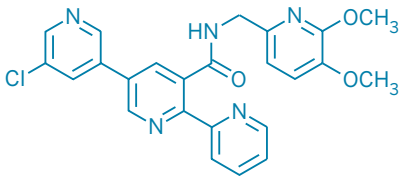
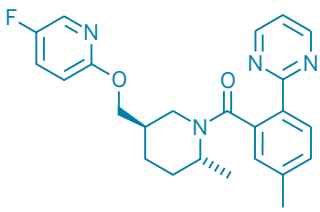


HEPTARES THERAPE

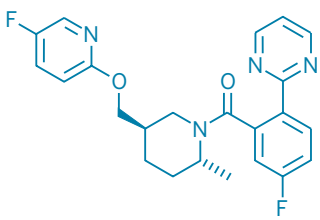
FLEXIBLE FIT
Having obtained the first-ever crystal structures of orexin receptors, Heptares is learning how drug candidates bind. Here, suvorexant (green spacefill) interacts with the orexin-1 receptor. "What we found is that different chemical series all bind in the same pocket of the orexin receptors, but the molecules don't necessarily form the same binding contacts," Miles Congreve, Heptares'



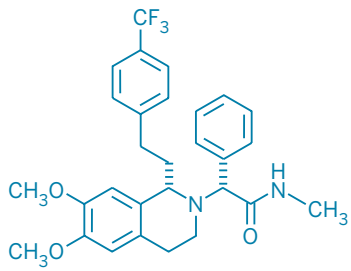
MK-1064



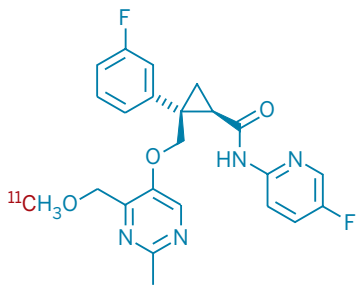
Filorexant (MK-6096)



DORA-22



Almorexant



PET tracer lead

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