A better-fitting molecular 'belt' for making new drugs

November 16 2021, by Laura Arenschield

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The most common pharmaceuticals on the market are made by chaining together rings of molecules to create the drugs that treat conditions including pain, depression and leukemia.

But creating those rings and forming them in a way that is tailored to each individual disease has always been a cumbersome and expensive process in medicinal chemistry.

New research, published today in the journal *Chem*, proposes a way to simplify that transformation. The discovery will likely make it easier to produce new drug candidates, the researchers say.

David Nagib, senior author of the study and associate professor of chemistry at The Ohio State University, likened the chain of molecules to a belt with no holes: With no way to fasten the circle and no measurements for where holes might go, the belt can't be assembled in a way that keeps it closed.

"The problem we were trying to solve is how do you punch the hole so that it fits you perfectly, and get it right on the first try without measuring," Nagib said. "The trick here was we had to put the holes in just the right place, but we had to figure out precisely where the holes should go, without any markings to tell us where that might be."

The "belt" in this case is a string of carbon-hydrogen bonds, the most ubiquitous bonds in all of nature and medicines. Most drugs contain rings of carbon-hydrogen bonds, linked together by a "bridging" nitrogen atom, within complex structures that interact precisely with cellular components in the body—like a key fitting into a lock. The most common ring found in all medications are six-sided ones, called a piperidine.

But piperidines have long been difficult and expensive to produce, primarily because chemists could not quickly or cheaply replace a carbon-hydrogen bond with other chemical bonds.

Researchers in Nagib's lab at Ohio State found a way to replace that

bond—establishing the "hole" that allowed them to close the belt—by oxidizing two carbon-hydrogen bonds. Doing that allowed them to select hydrogen molecules and remove them from the molecule chain. Then, they used light and a copper catalyst to turn one of those bonds into the needed nitrogen ring. The light worked to excite catalysts in a chain process similar to photosynthesis, the way plants use light to create food for themselves.

The process solves a problem for making early-stage drug candidates still in development—it is still too expensive to be used to mass-produce medication. Nagib said future work will focus on using a cheaper starting material to scale up production.

"This discovery is something that can make it possible to more rapidly create a library of drug candidates for testing, so you can identify the right, most potent, most effective one more quickly," Nagib said.

More information: Leah M. Stateman et al, Aza-heterocycles via copper-catalyzed, remote C–H desaturation of amines, *Chem* (2021). DOI: 10.1016/j.chempr.2021.10.022

Provided by The Ohio State University