Adapting Ritalin to tackle cocaine abuse

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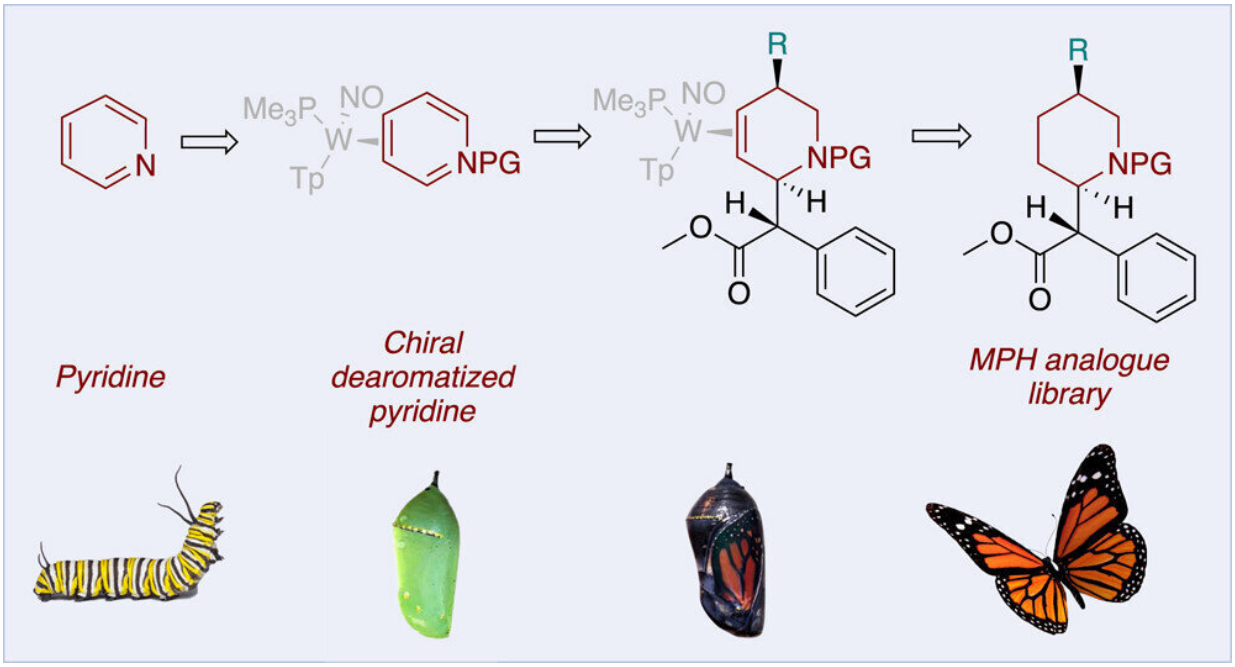

Graphical abstract. Credit: *ACS Central Science* (2023). DOI: 10.1021/acscentsci.3c00556

Cocaine use continues to be a public health problem, yet despite concerted efforts, no drugs have been approved to resolve cocaine addiction. Research suggests that the attention-deficit/hyperactivity disorder drug methylphenidate (MPH; Ritalin) could serve as a cocaine-replacement therapy, but clinical results have been mixed. Although several labs have produced MPH derivatives for testing, parts of the molecule remained chemically inaccessible. Now, researchers reporting

in *ACS Central Science* have cleared that hurdle.

According to the Centers for Disease Control and Prevention, more than 5 million Americans reported actively using cocaine in 2020, and almost 25,000 Americans died of a cocaine-related overdose in 2021. Although small-molecule drugs have proven effective in treating other drug addictions—for example, methadone as a therapy for heroin abuse—no such medication exists for cocaine abuse.

MPH has been considered a potential treatment because it behaves similarly to the illicit drug, increasing dopamine levels in the brain by blocking dopamine reuptake. Additionally, clinical studies have shown that MPH has a lower risk of abuse than cocaine.

Although studies in animals have shown that MPH can reduce cocaine dependence, studies in humans have offered more mixed results. Thus, researchers are developing libraries of MPH derivatives, searching for molecules with improved clinical efficacy. Until recently, however, it was difficult to create derivatives of one chemical component of MPH: its piperidine ring. W. Dean Harman and colleagues wanted to address this shortcoming by taking an organometallic approach.

Using a tungsten-based reagent, the researchers synthesized a library of MPH analogs specifically modified at the piperidine ring with a variety of chemical groups. And whereas MPH is a mixture of four isomers—otherwise identical molecules with small structural differences—the new method allowed the researchers to synthesize and purify compounds that were predominantly comprised of a single isomer.

This could be important in clinical studies, as different isomers of some drugs can have significant impacts on therapeutic efficacy or safety. Whether any of these MPH analogs prove effective against cocaine

addiction remains to be determined, but the researchers noted that the new protocol could be widely applicable to pharmaceutical development, given the ubiquity of the piperidine ring in small-molecule drugs.

More information: The Tungsten-Promoted Synthesis of Piperidyl-Modified erythro-Methylphenidate Derivatives, *ACS Central Science* (2023). DOI: 10.1021/acscentsci.3c00556

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