Reducing Side Effects
Professor Alex Makriyannis seeks ways to rid the body of drugs once their job is done.

When medications linger in the human body, they sometimes produce toxic side effects.

Professor Alexandros Makriyannis, the George D. Behrakis Trustee Chair in Pharmaceutical Biotechnology and director of the Center for Drug Discovery at Northeastern, explained that many things can happen to a drug inside our bodies once it is ingested. For instance, the drug can be modified into by-products with their own undesirable effects. Or, the drug can concentrate in the body’s fatty tissues and then be slowly released into the circulatory system.

“If you had a way of controlling how long this drug sits in the body,” Makriyannis said, “that would be a beneficial effect. It would be a safer drug.”

In research recently published in the Journal of Medicinal Chemistry and Medicinal Chemistry Letters,

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PROFESSOR ALEX MAKRIYANNIS

Makriyannis and his team present not just one such drug, but a whole series of them. “We call this concept controlled deactivation,” he explained.

In this research, Makriyannis’ team presents more than 100 compounds that are variants of drugs the researchers previously patented. These new drugs target the endocannabinoid system, which includes receptors on the surface of cells throughout our bodies that are responsible for functions like pain, mood, memory, and appetite modulation.

The original versions of the new drugs bind to the cannabinoid receptors—which were initially named for their recognition of the tetrahydrocannabinol molecule found in marijuana—and produce some effects such as increased appetite or euphoria. However, development of these drugs has been limited by the negative side effects they elicit. In one high-profile case, a cannabinoid-receptor blocker called Acomplia was designed to produce an effect opposite to the “munchies” associated with cannabis. The drug was intended to treat obesity, but was pulled from the market when it was linked to increased rates of suicidal ideation.

“Our lab works to design and make safer drugs with more controllable action,” Makriyannis said. So with funding from the National Institute on Drug Abuse, he and his team set out to develop drugs that feature a timing mechanism that would allow a drug to be deactivated as soon as it has performed its function and to be transformed into inactive products. This timing mechanism, Makriyannis said, is relatively simple—it just takes some very smart and specific chemistry.

The new drugs are chemically modified to be biodegradable by particular enzymes in the blood. The enzymes would recognize these drug’s new chemical features and “chew them up” right at that spot. The time it takes for the enzymes to finish their action can be controlled, and the resulting by-products from this enzymatic activity are completely safe, according to Makriyannis.

Additionally, the drugs’ chemical modifications ensure they don’t stick around in the body's fatty tissues as long and are thus expelled much more quickly.

“When we started making these new compounds, we weren’t sure if they would be successful, but actually, they worked even better than we’d hoped.” Not only do the compounds have fewer side effects than the original versions of the drugs, they are also more potent and effective.

While the drugs in the present research all target receptors in the endocannabinoid system, the approach can be applied to virtually any small-molecule drug, Makriyannis said.

“We are controlling the fate of a drug by just designing these molecules in a manner that allows them to act predictably,” he said. “It’s a general concept that we’ve used to make analgesic compounds that are safer and very potent, but the same concept could be used to make neuroprotective drugs or other therapeutic agents.”