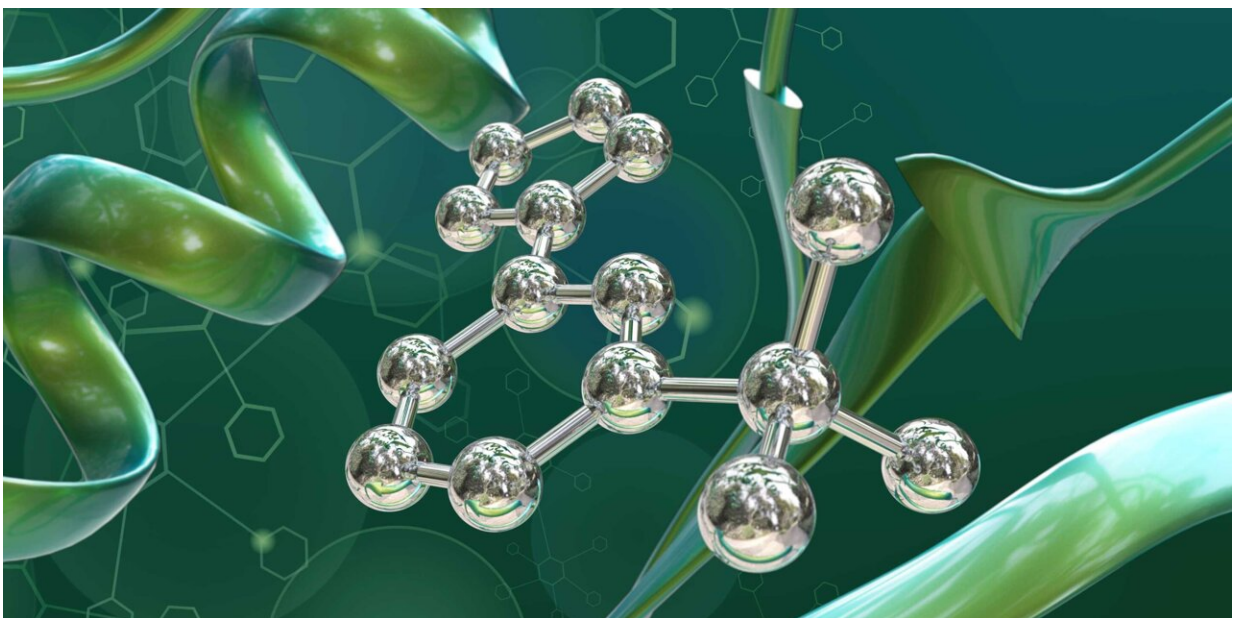# AI designs active pharmaceutical ingredients quickly and easily based on protein structures

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A new generative AI develops molecules from scratch in such a way that they precisely match the protein they are to interact with. Credit: ETH Zurich / Gisbert Schneider

A new computer process developed by chemists at ETH Zurich makes it

possible to [generate active pharmaceutical ingredients](#) quickly and easily based on a protein's three-dimensional surface. The new process, detailed in *Nature Communications*, could revolutionize drug research.

"It's a real breakthrough for [drug discovery](#)," says Gisbert Schneider, Professor at ETH Zurich's Department of Chemistry and Applied Biosciences. Together with his former doctoral student Kenneth Atz, he has developed an algorithm that uses [artificial intelligence](#) (AI) to design new [active pharmaceutical ingredients](#).

For any protein with a known three-dimensional shape, the algorithm generates the blueprints for potential drug [molecules](#) that increase or inhibit the activity of the protein. Chemists can then synthesize and test these molecules in the laboratory.

All the algorithm needs is a protein's three-dimensional surface structure. Based on that, it designs molecules that bind specifically to the protein according to the lock-and-key principle so they can interact with it.

Excluding side effects from the outset

The new method builds on the decades-long efforts of chemists to elucidate the three-dimensional structure of proteins and to use computers to search for suitable potential drug molecules. Until now, this has often involved laborious manual work, and in many cases the search yielded molecules that were very difficult or impossible to synthesize. If researchers used AI in this process at all in recent years, it was primarily to improve existing molecules.

Now, without human intervention, a generative AI is able to develop

drug molecules from scratch that match a [protein structure](). This groundbreaking new process ensures right from the start that the molecules can be chemically synthesized. In addition, the algorithm suggests only molecules that interact with the specified protein at the desired location and hardly at all with any other proteins.

"This means that when designing a drug molecule, we can be sure that it has as few side effects as possible," Atz says.

To create the algorithm, the scientists trained an AI model with information from hundreds of thousands of known interactions between chemical molecules and the corresponding three-dimensional protein structures.

Successful tests with industry

Together with researchers from the pharmaceutical company Roche and other cooperation partners, the ETH team tested the new process and demonstrated what it is capable of.

The scientists searched for molecules that interact with proteins in the PPAR class—proteins that regulate sugar and fatty acid metabolism in the body. Several diabetes drugs used today increase the activity of PPARs, which causes the cells to absorb more sugar from the blood and the blood sugar level to fall.

Straightaway the AI designed new molecules that also increase the activity of PPARs, like the drugs currently available, but without a lengthy discovery process. After the ETH researchers had produced these molecules in the lab, colleagues at Roche subjected them to a variety of tests. These showed that the new substances are indeed stable and non-toxic right from the start.

The researchers aren't now pursuing these molecules any further with a view to bringing drugs based on them to the market. Instead, the purpose of the molecules was to subject the new AI process to an initial rigorous test.

Schneider says, however, that the algorithm is already being used for similar studies at ETH Zurich and in industry. One of these is a project with the Children's Hospital Zurich for the treatment of medulloblastomas, the most common malignant brain tumors in children. Moreover, the researchers have published the algorithm and its software so that researchers worldwide can now use them for their own projects.

"Our work has made the world of proteins accessible for generative AI in drug research," Schneider says. "The new algorithm has enormous potential." This is especially true for all medically relevant proteins in the human body that don't interact with any known chemical compounds.

More information: Kenneth Atz et al, Prospective de novo drug design with deep interactome learning, *Nature Communications* (2024). DOI: 10.1038/s41467-024-47613-w

Provided by ETH Zurich