Mimicking natural evolution with 'promiscuous reactions' to improve the diversity of drugs

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George Karageorgis prepares reaction arrays: 96 different reactions can be quickly tested in a plate the size of a DVD. Credit: Steven Kane / University of Leeds

A revolutionary new scientific method developed at the University of Leeds will improve the diversity of 'biologically active molecules', such as antibiotics and anti-cancer agents.

The researchers, who report their findings online today in the journal *Nature Chemistry*, took their inspiration from evolution in nature. The research may uncover new pharmaceutical drugs that traditional methods would never have found.

"Nature produces some amazing structures with really interesting biological activity, but the plant or animal did not design them. Instead the organisms gradually evolved both the chemical structures and the methods to produce them over millennia because they were of benefit. We wanted to capture the essence of this in our approach to discovering new drugs," said George Karageorgis, a PhD student from the School of Chemistry and the Astbury Centre for Structural Molecular Biology at the University of Leeds, and first author of the study.

The traditional method for discovering new drugs involves preparing new biologically active molecules by adjusting the chemical structure of an existing one slightly and analysing the results. This trial and error method is both time consuming and limits the variety of new types of drugs that are developed.

"There is a known problem with limited diversity in drug discovery. It's like a baker always going to the same storage cupboard and using the same ingredients, yet hoping to create something that tastes different," said Dr Stuart Warriner from the School of Chemistry and the Astbury Centre for Structural Molecular Biology at the University of Leeds, a co-author of the research paper.

"Our novel approach is like taking lots of different ingredients – including things you may never think will work together – and trying different combinations of these in each cup of a cupcake tray. If the result 'tastes' promising then we use this as the starting point for another set of experiments. Only at the end, when we have something really good, do we work out exactly what we have made."

In the study, the researchers investigated the reactions of 12 types of an organic molecule called a 'diazo' compound. The researchers chose to study reactions of diazo compounds as they have many possible outcomes, depending on the specific reaction conditions (such as the temperature and concentrations used) and the choice of the reaction catalyst.

Different types and quantities of the reaction 'ingredients' were added to each of the 96 wells of an experiment tray and the products of the reaction were then tested to see if they had the required biological effect.

"The key to our method is using very promiscuous reactions which can lead to many different interesting products. Normally, these are the sort of reactions that chemists would steer well clear of, but in this case it's actually an advantage and gives us the chance of finding some diverse and active structures," said Dr Warriner.

To assess the effectiveness of the reaction products as drugs, the researchers studied how well they could activate a particular biologically relevant protein called the 'androgen receptor', which is important in the progression of certain cancers.

The results informed two further rounds of experiments on the most promising candidates, from which the researchers eventually identified three biologically active molecules.

"It's very unlikely that anyone would have ever designed these molecules or thought to use these compound classes against this target, but we have reached that result very efficiently and rapidly using our methodology," said Karageorgis.

Professor Adam Nelson from the School of Chemistry and the Astbury

Centre for Structural Molecular Biology at the University of Leeds, a co-author on the paper, concludes: "The beauty of our approach is that pharmaceutical companies could start using it tomorrow, as you don't need any specialist equipment. What we need to do now is to run further studies and add even more diversity to the potential products of our reactions to convince other scientists to adopt this new technique."

More information: Efficient Discovery of Bioactive Scaffolds by Activity-Directed Synthesis, *Nature Chemistry*, dx.doi.org/10.1038/nchem.2034

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