NTU Singapore scientists develop new method for creating promising new sulphur-based medicines

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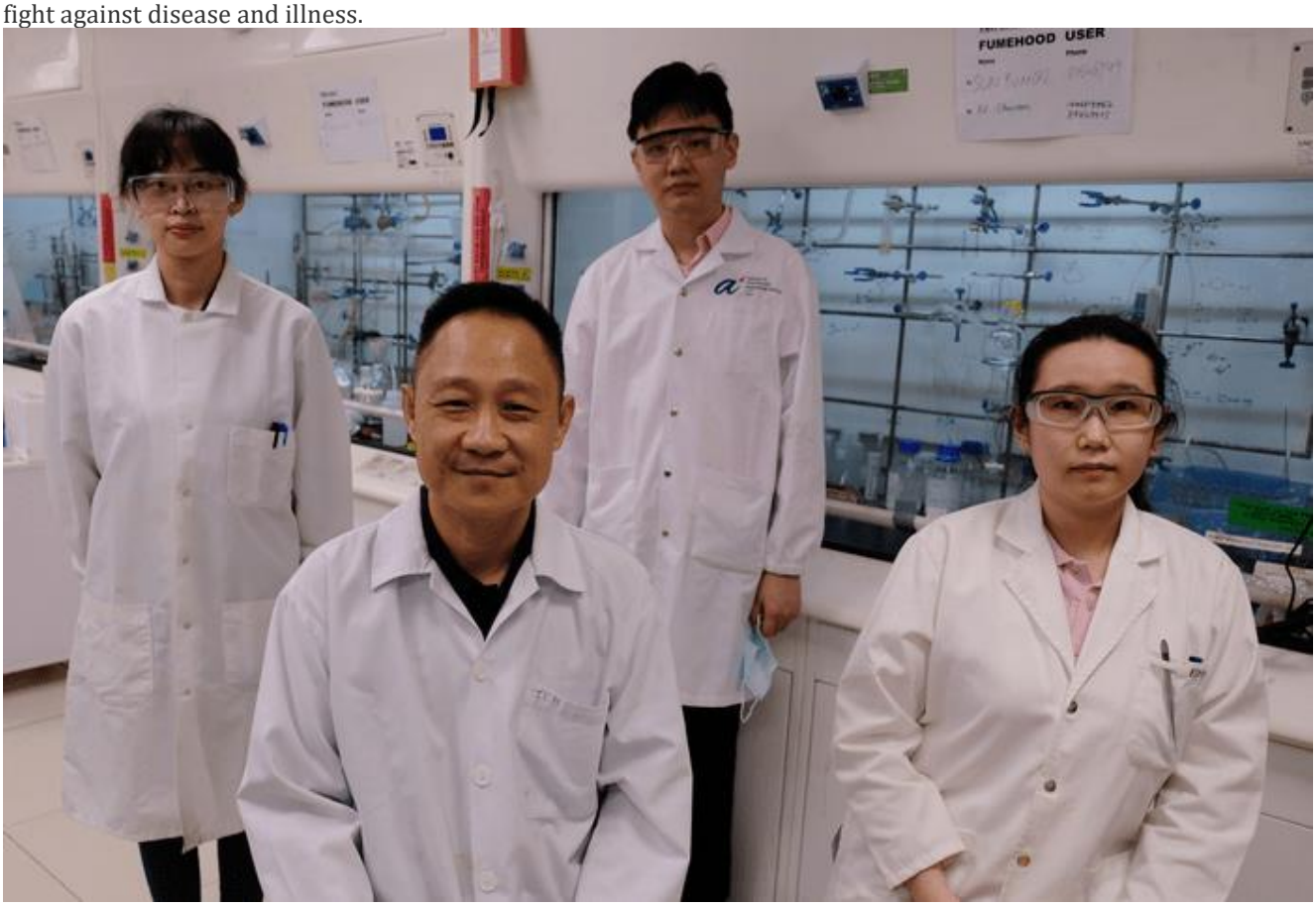

Credit: NTU Singapore

A key technical challenge in creating new sulphur-based medicines has been overcome by scientists at **Nanyang Technological University, Singapore (NTU Singapore)**, leading to the prospect of many new therapeutic 'weapons' in the fight against disease and illness.

Every successful drug has a part of it that physically fits into the exact biochemical pathway it is trying to disrupt. This part of the drug is known as a 'pharmacophore' and generating new ones is a key goal in drug discovery.

Sulphur-based pharmacophores are highly versatile and seen as very promising to drug developers but are rare due to the challenges of synthesising them.

Now, scientists at NTU Singapore have designed a method to generate sulphur pharmacophores using a catalyst specially developed by the scientists themselves, known as pentanidium.

Their method could be used to synthesise a broad range of new pharmacophores that could be paired with different types of molecules to form new drugs.

They also showed that the new sulphur pharmacophores could be used to modify and repurpose existing drugs, potentially leading to new therapies. Their work is published in the top peer-reviewed scientific journal *Nature* today.

Professor Tan Choon Hong, **Chair of School of Physical and Mathematical Sciences and lead author of the study**, said: "The process of drug discovery is akin to finding the right key to a lock – it involves testing drug candidates with different pharmacophores until a certain combination proves to be effective in modulating a biological pathway. We essentially developed a method that could allow us to make many different types of sulphur-based pharmacophores that are compatible with different drug compounds. This is a valuable addition to the toolkit of drug discovery programmes."

This research is in line with the NTU2025 five-year strategic plan, which aims to focus on health and society as one of the six clusters with the potential for significant intellectual and societal impact.

Synthesis of pharmacophores

Pharmacophores are the key part of a drug that gives the drug its function. More than half the drugs used today are chiral, meaning that they can exist in either a left- or right-handed form that are mirror images of each other.

While identical in chemical makeup, the different arrangement of its atoms means one form can behave very differently from the other: one may help to alter the course of a disease, while the other could be inactive, or even toxic.

Being able to synthesise a pharmacophore in the desired single form is a crucial goal in the design and development of drugs to eliminate possible side effects.

Medicinal chemists are interested in the use of sulphur-based compounds as pharmacophores, but synthesising them into the single left- or right-handed form is challenging and current methods typically focus on making only one type of pharmacophore.

By contrast, the NTU scientists say that their method gives rise to a series of sulphur-based pharmacophores with enough variation to make the drug discovery process more efficient and fruitful.

Their sulphur pharmacophores are developed through a process called asymmetric synthesis, a chemical reaction that results in just a single form, rather than a mixture of both forms being produced.

The process starts with adding a sulphur compound to an acyl chloride (a derivative of carboxylic acid) and a thiolate (a class of organic chemical compounds similar to the alcohols but containing a sulphur atom in place of the oxygen atom). This reaction is catalysed by pentanidium, a catalyst developed by the NTU scientists which was shown in an earlier study[1] to induce asymmetric synthesis.

To demonstrate that their approach is a valuable addition to the drug discovery toolkit, the NTU scientists tested their synthesis method on Celecoxib, a drug approved for arthritis. This resulted in a few different pharmacophores that could be used to develop similar drugs.

Prof Tan said: “Our approach not only allows us to make variations of pharmacophores to speed up drug discovery but also allows us to pair a pharmacophore with an existing drug and see how it alters the drug’s function. This is exciting to the medicinal chemist because you can now improve on existing drugs or develop new therapies without having to start from scratch.”

The NTU research team is led by Prof Tan and former research fellow Zhang Xin. Other members of the team are NTU graduate students Yang Ziqi and Esther Ang, and NTU research scientist Kee Choon Wee, who is also from the Institute of Chemical and Engineering Sciences at the Agency for Science, Technology and Research (A*STAR).

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