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Chemistry breakthroughs open new doors to drug developers and cancer researchers

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Two independent chemistry breakthroughs have opened a plethora of doors that were previously locked to drug developers and cancer researchers.

The discoveries, which involved adding new materials to a previously unstable chemical scaffold and building molecules onto the "pigments of life", will also offer new possibilities to molecular engineers, materials and computer scientists, and energy researchers.

Thinking inside the box

In the first case, scientists solved a decades-old challenge by developing new tools for a synthetic (man-made) molecule – cubane – that is widely used in the pharma industry. Cubane molecules consist of eight carbon atoms arranged at the corners of a perfect cube. Yet despite the simplicity of the shape, modern chemistry has, until now, had a very tough time handling its unique reactivity. By deciphering how to circumvent this inherent reactivity, the door is now open for drug developers to create new, more diverse therapeutics from cubane and its derivatives.

The scientists were led by a team from Trinity College Dublin's School of Chemistry. Their discovery was recently published in the international journal *Chemistry – A European Journal*, in which it features as a VIP paper and on the journal front cover.

A team of six researchers under the supervision of Professor of Organic Chemistry at Trinity, Mathias O. Senge, discovered how to circumvent the inherent reactivity of the cubane core, while Senior Research Fellow, Dr Bernhard, and the other team members essentially filled the empty cubane toolbox, which allowed them to establish new connections and craft important residues onto the cubane scaffold.

Professor Senge said: "I often challenge my students to think outside the box so I was really surprised when they pitched the idea of thinking inside the box. However, it is the apparent simplicity of the cubane core that really underlies the impact of the present accomplishment."

"We have a structurally unique building block which has been neglected by the majority of synthetic chemists up to now, precisely because this cube is so difficult to work with. However, with great risk comes great reward. I am delighted with our present success and intrigued about the avenues it will open in fields ranging from new drug discovery to 21st century computer chip generation!"

"The results from this long-term, fundamental research project will have significant benefits in the years to come as we can now prepare a greater variety of tailored compounds. We are very grateful to have received continuous long-term funding from Science Foundation Ireland to support this work, without which we would not have made this important discovery."

Reconfiguring the pigments of life

Another group of scientists, also led by Professor Senge, recently discovered how to reconfigure porphyrins, the "pigments of life", which have long held untapped potential as useful players in the fields of cancer therapy, solar energy, and materials science.

In nature, porphyrins are responsible for the green colour of leaves and the red colour of blood. All their functionality is based along the same core chemical structure: four smaller rings connected to one larger ring, with a little cavity in the centre. Most of their functions in nature (photosynthesis, oxygen transport) arise when they host different 'guest metals' (magnesium, iron, cobalt, nickel) in the centre of the molecule. Different metals spark different functions in these 'metalloporphyrins'.

The five-strong research team discovered that by overcrowding the large porphyrin ring, they could force it to turn inside out and change into a shape similar to a saddle. Importantly, this little trick enabled them to exploit the special properties of the formerly inaccessible core.

Professor Senge and his team worked closely with Professor Stephen Connon, an expert in the field of organocatalysis in the pursuit, and recently published their work in leading international journal *Chemical Communications*, which features the study on the front cover.

Professor Senge said: "By bending the porphyrin core we thought we would be able to make use of the formerly buried functionalities by using the porphyrin as a catalyst."

"A catalyst is a compound that attracts other molecules and converts them into new entities and catalytic processes are at the heart of chemistry and nature, so they are of significant industrial and commercial interest. The discovery that these metalloporphyrins act as efficient metal-free catalysts now opens new horizons for these natural pigments. Soon, we hope to tailor porphyrins according to specific requirements and use our rational design approach for various applications in chemistry, biochemistry, physics and beyond."

More information: Stefan S. R. Bernhard et al, Cubane Cross-Coupling and Cubane-Porphyrin Arrays, *Chemistry - A European Journal*

(2017). DOI: 10.1002/chem.201704344 M.

Roucan et al. Conformational control of nonplanar free base porphyrins: towards bifunctional catalysts of tunable basicity, *Chemical Communications* (2017). DOI: 10.1039/C7CC08099A

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