Seven steps to 'billion dollar' drugs

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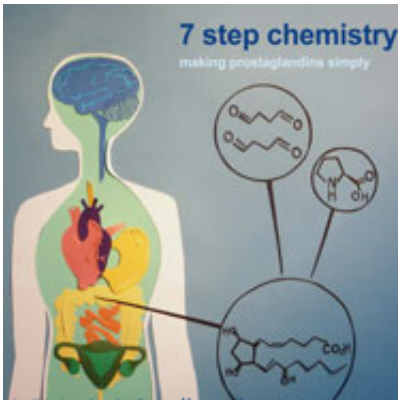

(Phys.org) -- A highly efficient method for making prostaglandins -- natural, hormone-like chemicals that have pharmaceutical applications -- is reported by University of Bristol scientists this week in *Nature*. Some synthetic analogues of prostaglandin are 'billion dollar' drugs; the prostaglandin analogue latanoprost, which is used to treat glaucoma and ocular hypertension, generates approximately $1.6 billion in sales each year.

Prostaglandins are some of the most important molecules in biology and medicine as they regulate a broad range of activities in the body, including blood circulation, digestion and reproduction.

The breadth of biological activity, coupled with their challenging molecular architecture has made prostaglandins popular targets in

synthesis for over 40 years. However, since these molecules cannot be isolated from natural sources in sufficient quantities, they have to be synthesised, but routes are lengthy. For example, the current synthesis of latanoprost requires 20 steps and uses the methodology and strategy developed by E. J. Corey, a giant in the area of synthesis (he was awarded the Nobel Prize in Chemistry, in 1990 "for his development of the theory and methodology of organic synthesis"). Until now, despite huge synthetic effort in industry and academia, advances in the synthesis of prostaglandins since Corey's contributions have been limited.

Professor Varinder Aggarwal, who led the research at the University's School of Chemistry, and colleagues now report a concise synthesis of prostaglandin PGF2a, which relies on the use of an organocatalyst, a small organic molecule, to catalyse a key step in the process. The key step not only produces a key intermediate, but it also does so with exquisite control over relative and absolute stereochemistry. The new process uses a new disconnection which has enabled them to complete the synthesis in just seven steps. It should be possible to modify the authors' synthetic route to obtain other known prostaglandin-based drugs, e.g. latanaprost in a more cost-effective manner and to make it easier to discover new biologically active prostaglandin analogues.

In a follow-up patent, the authors have described the application of this technology to a simple synthesis of prostaglandin-based drugs, e.g. latanoprost and bimataprost. The methodology should now make it easier to discover new biologically active prostaglandin analogues. It is a major advance and represents a step change in the synthesis of this important class of compounds.

Professor Aggarwal said: "Despite the long syntheses and the resulting huge effort that is required for the preparation of these molecules, they are still used in the clinic, because of their important biological activity.

"Being able to make complex pharmaceuticals in a shorter number of steps and therefore more effectively, would mean that many more people could be treated for the same cost."

More information: Stereocontrolled organocatalytic synthesis of prostaglandin PGF2a in seven steps published in Nature by Graeme Coulthard, William Erb & Varinder K. Aggarwal from the University of Bristol, DOI: 10.1038/nature11411

Provided by University of Bristol