Sweet signal transduction

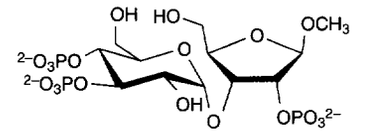
A quick and simple way to make a mimic of a second messenger molecule thought to be involved in manic depression has been devised by UK chemists. They say the compound is almost as potent as the natural compound and may help in the search for new drugs that intervene in brain-cell signalling.

D-*myo*-Inositol (1,4,5)-trisphosphate [Ins(1,4,5)P_3] relays information from chemical transmitters from other cells by triggering calcium release in a target cell. This second signal then affects other cellular events, such as the histamine triple response. Once the task is complete, the enzyme inositol monophosphatase (IMPase) recycles the inositol core. When the recycling process gets out of control, however, too much or too little Ins(1,4,5)P_3 is available, and researchers believe that this can lead to the wild mood swings associated with manic depression, and other disorders.

Lithium salts used to control manic depression have potentially severe side effects, such as kidney damage and thyroid abnormalities. According to Professor Barry Potter (School of Pharmacy & Pharmacology, University of Bath, UK) recent indications that the activity of lithium lies with IMPase open up the possibility of designing lithium surrogates. "The action of lithium is, unusually, uncompetitive," he explains, "design of inhibitory molecules is therefore a very difficult task".

Potter and his coworkers hope to find new ways of controlling the inositol polyphosphate 'cascade' through the design of novel synthetic agents. "An ever-increasing number of disorders are now being linked to malfunctions of cellular signalling pathways," explains Potter "our team has already synthesized a number of potent antagonists and enzyme inhibitors".

With support from the Wellcome Trust, Potter and his team have used the simple sugars glucose and ribose to build an Ins(1,4,5)P_3 mimic based on two microbial compounds known as adenophostins. The adenophostins, according to Potter, are 10–100 times more potent in triggering the inositol trisphosphate receptor than Ins(1,4,5)P_3, and are under study as potential leads. In their design, Potter and his team stripped away various chemical motifs from the adenophostins to come up with a range of potential mimics. One of their compounds, ribophostin, was a basic structure that retained inositol trisphosphate-like activity, [*J. Chem. Soc., Chem. Commun.* (1997) 449]. With an understanding of the chemical features needed to trigger the receptor Potter and his team can now begin looking for new molecules that block the receptor and inhibit the enzymes that work on inositol trisphosphate.



3-*O*-(α-D-glucopyranosyl)-β-D-ribofuranoside-2,3′,4′-trisphosphate

A D-myo-*inositol (1,4,5)-triphosphate mimic.*

Potter says that signal transduction therapy holds much promise, but cautions that not enough is understood about the major pathways of cellular signalling, so predicting *in vivo* responses is not yet possible. He sees increased understanding as an important goal of current research: "Progress in the design of phosphate-based prodrugs is very encouraging for the future, and the ability to start with cheap and readily available chiral sugars, such as here, is providing a new impetus for what is still a relatively young field," he says.

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New combinatorial chemistry

In February, the Society of Chemical Industry (SCI) brought experts from industry and academia together in London for a one-day symposium entitled *New Combinatorial Chemistry*. Novel solid-phase organic chemistry, new linker molecules and strategies for library design were some of the key topics.

The symposium was opened by Dr D. Hollinshead (Zeneca, Alderley Edge, UK), who outlined some general strategies used in combinatorial chemistry before introducing the first speaker of the day, Dr R. Shute (Zeneca), who spoke on compound libraries based on a homocysteine template. Zeneca's solid-phase synthesis group wanted a template that has a low molecular weight (total molecule < 800 Da), can accommodate three different substituents and is non-oligomeric, flexible and highly functionalized (for easy attachment of substituents) for library generation. Homocysteine was found to fit all these criteria and in addition is easily accessible through the cheap, readily available H-Cys-thiolactone (**1**). A method was developed to link this thiolactone to a solid support via the α-carbon, so that the template could be fully derivatized while remaining attached to the solid-support (Figure 1, Scheme 1). Immobilized thiolactone **2** was converted to the desired homocysteines **3** by acylation of the lactone's amine with excess anhydride, followed by ring opening with a primary amine, catalysed by $Hg(CF_3CO_2)_2$, and subsequent alkylation of the sulphur. This sequence of reactions was found to work well in a multi-parallel synthesis set-up, and is suitable for synthesizing pools of compounds.

'Privileged structure' libraries

The 'privileged structure' library concept was discussed by Dr Tony Baxter of Oxford Diversity (Abingdon, UK), the combinatorial chemistry division of Oxford Asymmetry. Privileged structures

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