discrimination of these channels by the use of ϖ-conotoxins is, therefore, important for understanding their contribution.

In an effort to elucidate structural differences in the pore-forming region between N-type and P/Q-type channels, a library of MVIIC analogues was synthesized[2]. A library of 47 individual compounds was synthesized on a solid support using a peptide synthesizer followed by chromatographic purification. Several analogues were obtained that retained a similar level of affinity to that of MVIIC for P/Q-type channels, while giving improved selectivity over the N-type channel. The binding activities of MVIIC and these analogues were estimated to be 10^{-8} M for competition with radiolabelled MVIIC. This work has given new insight into the specific groups required for selectivity over the N-type channel and might prove to be useful in the future for further defining the pharmacophore required for affinity at P/Q-type channels and reducing affinity for the N-type channel.

2 Sasaki, T. *et al.* (2000) Combinatorial synthesis of ϖ-conotoxin MVIIC analogues and their binding with N- and P/Q-type calcium channels. *FEBS Lett.* 466, 125–129

Polyketide natural products

The polyketides represent a rich reservoir of structurally complex, bioactive natural products, many having therapeutic importance as antibiotics, anticancer agents, antifungals, antiparasitics, immunosuppressants and cardiovascular agents. In the archetypal case of the erythromycin polyketide, the heptaketide precursor is assembled biosynthetically by the polyketide synthase from a starter unit and six extender units, with the growing chain bound to the acyl carrier protein. By mimicking this processive mechanism with a combinatorial library synthetic approach, which uses a greater variety of chain extending units, a larger amount of molecular diversity can be incorporated into final products belonging to this important bioactive natural product class[3].

A small library of five compounds was synthesized on a polystyrene-based solid support to demonstrate the potential of this method for generating diverse polyketide product libraries. Boron-mediated aldol reactions of five chiral ketones were used for the efficient generation of novel polyketide-type sequences. This approach mimics the processive mechanism of chain growth operating in the biosynthesis of polyketides and allows much greater structural and stereochemical diversification through variation of the chain-extension reagents, as well as in the stereochemistry of the aldol and reduction steps. Thus, this approach complements the combinatorial generation of new polyketide structures based on the genetically engineered reconstruction of biosynthetic pathways, and might help to produce novel polyketides with therapeutic importance.

3 Paterson, I. *et. al.* (2000) A combinatorial approach to polyketide-type libraries by iterative asymmetric aldol reactions performed on solid support. *Angew. Chem., Int. Ed. Engl.* 39, 3315–3319

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Drug delivery

Macromolecule absorption improved by nitric oxide donor

Intestinal absorption of highly polar drugs and macromolecules is often limited by their poor permeability through the intestinal walls. To enhance the absorption of these agents, they are often coadministered with absorption enhancers. However, there are drawbacks to most of the absorption enhancers currently available, including irritation to the mucosal lining of the intestine. Furthermore, most increase absorption of highly polar drugs and macromolecules in the rectum or large intestine.

There have been relatively few reports of absorption enhancers that improve absorption from the small intestine. Nitric oxide (NO), a free-radical gas derived from the guanidine nitrogen of L-arginine, is one of the most versatile mediators in mammalian biology. It has been reported that NO can increase the permeability of Caco-2 monolayers[1]. It was suggested that NO donors induce an increase in the permeability of Caco-2 monolayers and that the permeability enhancement effect is reversible. Since this initial report, the absorption-enhancing effect of an NO donor on the small intestine has not been investigated *in vivo*.

Numata and colleagues have recently reported the potential of an NO donor, 3-(2-hydroxy-1-methylethyl-2-nitrosohydrazino)-*N*-methyl-1-propanamine (NOC7), as an absorption enhancer for macromolecules[2]. NOC7 was shown to significantly increase the absorption of some model macromolecules, fluorescein isothiocyanate dextrans (FDs). NOC7 and FDs of various MW between 4000 Da (FD-4) and 20,000 Da were coadministered *in vivo* (male Wistar rats) by a closed loop method. When administered into a jejunal loop, FD-4 alone was poorly absorbed. FD-4 coadministered with NOC7 was rapidly absorbed, and the increase in absorption was NOC7-dose-dependent. The AUC value of FD-4 when coadministered with 6 mg NOC7 was approximately ten times that of control. To determine whether NOC7 itself or the NO derived from the NOC7 caused the absorption enhancement, another NO donor, *S*-nitroso-*N*-acetyl-DL-penicillamine (SNAP), was also investigated. The absorption of FD-4 was also enhanced in the jejunum by coadministration with SNAP. The AUC value of FD-4 when coadministered with 6 mg of SNAP was approximately five times that of control. Regional differences in the absorption enhancement effect of NOC7 when coadministered with FD-4 were also investigated by dosing closed loops

1359-6446/01/$ – see front matter PII: S1359-6446(01)01686-5

in the jejunum, rectum and colon. The result was that the enhancement effect was approximately the same regardless of the point of administration.

To further investigate whether the absorption enhancement effect is caused by NOC7 itself or the NO derived from the NOC7, the effect of coadministration of an NO scavenger was investigated. 2-(4-carboxyphenyl)-4,4,5,5-tetramethylimidazole-1-oxyl-3-oxide (carboxy-PTIO) is a stable free radical that reacts stoichiometrically with NO. When carboxy-PTIO was coadministered with FD-4 and NOC7, the absorption enhancement effect of NOC7 was reduced dramatically. The AUC values of FD-4 for control and FD-4 coadministered with NOC7 and carboxy-PTIO were 0.76 and 0.75 ($h \times \mu g\ ml^{-1}$), respectively. Finally, the effect of NOC7 on plasma concentrations of FDs of various MW was investigated. Using three different FDs, FD-4, FD-10 and FD-20, it was found that the enhancement effect of NOC7 decreased with the increase of FD MW.

In some cases, absorption enhancers exhibit mucosal toxicity and irreversible membrane damage. The reversibility of the absorption enhancement effect of NOC7 was investigated by measuring the plasma concentration of FD-4 in the jejunum and colon after pretreatment with NOC7. No significant differences were observed between the values of AUC in the control and those in an experiment in which the jejunum was pretreated with NOC7 30 min before administration of FD-4. As further evidence that NOC7 does not cause mucosal toxicity, the amounts of lactose dehydrogenase and protein released in the presence of NOC7 were not significantly different from those in the control. If the absorption enhancement effect of NOC7 proves to be applicable to other macromolecules, this reversibility and lack of cytotoxicity will be beneficial.

References

1 Salzman, A.L. *et al.* (1995) Nitric oxide dilates tight junctions and depletes ATP in cultured Caco-2Bbe intestinal epithelial monolayers. *Am. J. Physiol.* 268, G361–G373

2 Numata, N. *et al.* (2000) Improvement of intestinal absorption of macromolecules by nitric oxide donor. *J. Pharm. Sci.* 89, 1296–1304

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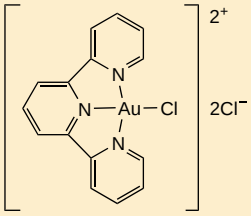
Erratum

Please note a correction to molecule **(i)** in the Novel antitumour molecules section of Monitor by Andrew Westwell, published in *Drug Discovery Today,* 15th February 2001, Volume 6, No. 4, 215. The structure should have been as follows:



(i)

We would like to apologize for this inaccuracy and any confusion that this might have caused.

Contributions to *Monitor*

We welcome recommendations of papers for review within *Monitor*, in the fields of combinatorial chemistry, pharmacogenomics, pharmacoproteomics, bioinformatics, new therapeutic targets, high-throughput screening, new drug delivery technologies and other promising lines of research. Details of recent papers or those *in press* should be directed to:

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