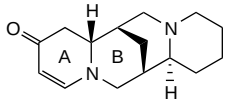
Quinolizin-2-one derivatives as novel hypoglycaemic agents

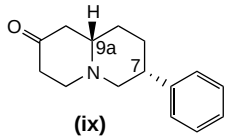
Diabetes, a disease that causes high levels of mortality worldwide, appears as two forms, namely: insulin dependent diabetes mellitus (IDDM) and non-insulin dependent diabetes mellitus (NIDDM). Although insulin is the most effective drug for both types, it has drawbacks, mostly associated with its way of administration. Therefore, new effective drugs are highly desirable.

The alkaloid (–)-multifluorine **(viii)**, is known to have hypoglycaemic activity[7]. In addition, the plants from which it is isolated, namely *Lupinus hirsutus* and *Lupinus termis* (leguminosae), are present in the traditional medicine for the treatment of diabetes.



(viii)

Recently, (–)-multifluorine has been chosen as a lead compound by researchers[8] in a project that aims to determine the essential structural requirements of non-insulin dependent hypoglycaemic agents. In particular, the researchers assumed that rings A and B of **(viii)** would be responsible for its activity. On these bases they synthesized a series of quinolizin-2-one derivatives, which were preliminary screened on STZ-induced diabetic mice. The most interesting compound was (7R*,9aS*)-7-phenyl-octahydroquinolizin-2-one **(ix)**.



(ix)

When further investigated in a glucose tolerance test in normal mice, **(ix)** demonstrated a hypoglycaemic effect ~fourfold higher than the model **(viii)**. It should be noted that the stereochemistry at the C-7 of **(ix)**, similar to that of (–)-multifluorine, plays an important role. Indeed, its inversion led to a completely inactive compound. The quinolizidin-2-one ring system is different from conventional drugs used in the treatment of diabetes. Therefore, it could potentially be considered in the development of novel agents for the treatment of both NIDDM and IDDM.

7 Murakoshi, I. *et al.* (1992) Japanese Patent N° 4295480

8 Kubo, H. *et al.* (2000) The hypoglycaemic effect of (7R*,9aS*)-7-phenyl-octahydroquinolizin-2-one in mice. *Biol. Pharm. Bull.* 23, 1114–1117

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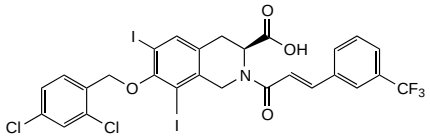
Combinatorial chemistry

Inhibition of protein phosphatase cdc25B

Protein phosphatase cdc25B is a member of a specific family of protein phosphatases that catalyze the dephosphorylation and activation of cyclin-dependent kinases. This step is necessary for cells to undergo mitosis. Inhibition of cdc25B could prove to be therapeutically useful as a treatment for cancer. A solid-phase parallel synthesis approach was used for lead optimization of a template discovered from HTS of the Pharmacia & Upjohn (Peapack, NJ, USA) research compound collection, which possessed inhibitory activity against protein phosphatase cdc25B (Ref. 1). Two libraries containing a total of 75 individual compounds were synthesized on Wang solid-phase resin. The compounds were tested for inhibition against protein phosphatase cdc25B. Several compounds were identified with equivalent or better activity compared with the initial lead compound identified from HTS.

One of the most potent compounds isolated, which was resynthesized and purified before being rescreened, was **(i)**, which possessed an IC_{50} of 23 μM against cdc25B. This work might, therefore, prove to be useful in the further optimization of the lead compounds identified in this library for the production of even more potent and novel inhibitors of protein phosphatase cdc25B.

1 Fritzen, E.L. *et al.* (2000) The solid phase synthesis of tetrahydroisoquinolines having cdc25B inhibitory activity. *Bioorg. Med. Chem. Lett.* 10, 649–652



(i)

N- and P/Q-type calcium channels

Voltage-sensitive calcium channels control various biological processes, such as neurotransmitter release and muscle contraction, and are classified on the basis of electrophysiological properties as L-, N-, P/Q-, R-, or T-type calcium channels. Although their molecular basis has been established in terms of diversity of the α_1 subunit, the contribution of each channel to a total calcium current is often dissected pharmacologically by using specific blockers. ω-Conotoxins, derived from the venom of marine *Conus* snails, are one of the most prominent among various classes of blockers, particularly for blocking N- and P/Q-type calcium channels. ω-Conotoxin GVIA and ω-conotoxin MVIIA bind to N-type channels and ω-conotoxin MVIIC binds to P/Q-type channels with high affinity, and to N-type channels with low affinity. The N- and P/Q-type calcium channels regulate neurotransmitter release in presynaptic nerve terminals and play distinct roles in the nervous system;

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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

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