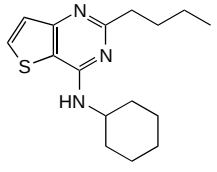
Although thalidomide was not shown to inhibit PDE4, it is possible that the TNF-α activity is a consequence of the inhibition of PDE4 by a thalidomide metabolite.

A fourth series of PDE4 inhibitors, reported by Crespo, M.I. and coworkers, is based on a nitraquazone pharmacophore [*J. Med. Chem.* (1998) 41, 4021–4035]. Of the compounds investigated, compound **11** has been shown



11

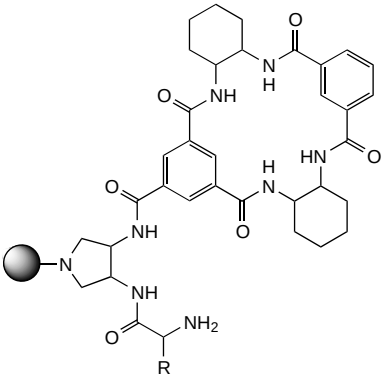
to have an interesting pharmaceutical profile and is presently being evaluated *in vivo* as a potential anti-asthmatic agent.

Combinatorial chemistry

Kinetic resolution by libraries

Ensuring that all chiral molecules are synthesized and tested as single enantiomers in biological systems is an essential requirement of modern drug discovery. Consequently, resolution of racemic materials, possibly using chiral HPLC, is often necessary to separate enantiomers. Combinatorial chemistry has recently been applied in the search for novel chiral selectors that will react enantiospecifically with racemic chemical compounds, specifically in this case, cyclic amino acid derivatives [Weingarten, M.D. *et al. J. Am. Chem. Soc.* (1998) 120, 9112–9113].

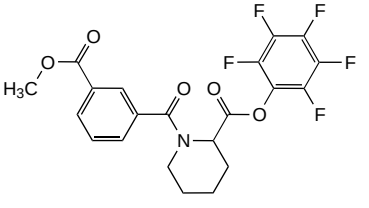
Using Still's encoded split synthesis method on resin beads, a small library of 60 selector molecules (**1**) containing a chiral amine were prepared. The beads containing these molecules were incubated with a mixture of L- and D-proline pentafluorophenyl esters to investigate whether the library compounds would selectively react with one of the two enantiomers by the formation of a new amide bond. To permit the recognition of beads that demonstrated such chiral discrimination, the two enantiomeric probe molecules were labelled with either a red or blue dye. Thus, if a bead contained a selector molecule that reacted enantiospecifically, it could be visually identified by a change of colour to red



1

or blue. Beads that exhibited no chiral discrimination would be stained brown as they will have reacted equally with both enantiomers.

Running the reaction and by selecting the reddest and bluest beads, it was determined that resolution with enantiomeric excesses measured at 45–75% had been obtained. Subsequently, the preferred selector molecules were used in a kinetic resolution and filtration process to separate the enantiomers of related cyclic amino acid derivatives. Particular success with the homoproline (**2**) was reported in the paper, and there is every possibility of extending this methodology for the resolution of many other types of chiral molecule.



2

High loading single resin beads

The mix-and-split combinatorial method is a highly effective way of generating combinatorial libraries of huge size suitable for the discovery of novel pharmacologically active compounds. As the quantity of material available on each bead is often a limiting factor, considerable effort has been invested into finding novel polymer beads with high loading. One solution to this problem has been Bradley's method by which TentaGel beads can be derivatized with a dendrimer linker that allows significant increases in loading levels.

A recent publication from Bradley's group describes the ability of these high-loading beads to generate sufficient material for full structural analysis [Wells, N.J. *et al. J. Org. Chem.* (1998) 63, 6430–6431]. The peptide Fmoc-Val-Phe-Ala-OH was prepared using standard peptide-coupling conditions on the HMP linker. Sufficient material was available from one resin bead to permit 500 MHz NMR by *in situ* cleavage of the peptide in the NMR tube using 1% F_3CCOOD in deuterochloroform. HPLC analysis revealed that ~32 nmol of essentially pure material had been prepared.

In a separate experiment a small library of 20 Leu-enkephalin analogues were prepared and analysed by HPLC and ESMS, demonstrating the robustness and versatility of these high-loading beads. One additional comment made in the paper was that chemical derivatization of the dendrimer-derivatized material generally proceeded rapidly and under non-forcing conditions.

Nick Terrett
Discovery Chemistry
Pfizer Central Research
Sandwich, Kent, UK
fax: +44 1304 655419
e-mail: nick_terrett@sandwich.pfizer.com

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