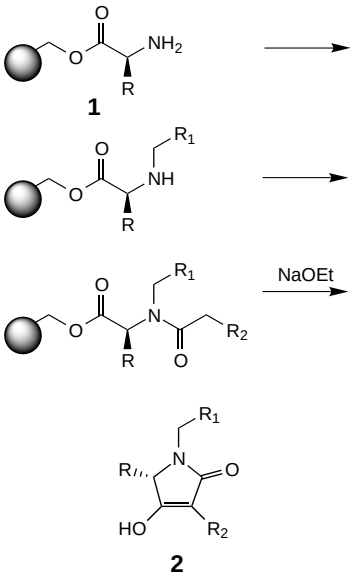
Combinatorial chemistry

Tetramic acid libraries

Some biologically-active molecules contain the tetramic acid nucleus; for example, antimicrobials such as streptolydigin and tirandamycin contain 3-acyltetramic acids, and 5-oxotetramic acids are known as active glycolic acid oxidase inhibitors. To investigate novel tetramic acid derivatives with pharmacological potential, a three-step solid-phase synthesis of these compounds has been derived [Matthews, J. and Rivero, R.A. *J. Org. Chem.* (1998) 63, 4808–4810].

Following reductive amination of a Wang resin-linked α-amino acid (**1**), coupling with a carboxylic acid was successfully carried out. Sodium ethoxide promoted cyclization, and cleavage generated the product tetramic acids (**2**), which were worked up by elution of the sodium salt through an ion-exchange column. The final compounds were isolated in >95% purity.



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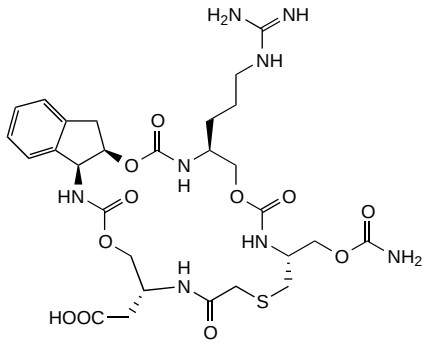
Oligocarbamate libraries

Several unnatural oligomers have been synthesized on solid phase as peptidomimetics with enhanced pharmacokinetics over the corresponding natural peptides. In each case it has been anticipated that the unnatural oligomers would not undergo the rapid metabolism and clearance experienced by peptides. In a recent disclosure, three libraries of oligocarbamates (one linear and two cyclic structures) have been prepared on solid phase using the 'one bead, one compound' combinatorial approach, and high affinity ligands for the GPIIb/IIIa receptor have been discovered [Cho, C.Y. *et al. J. Am. Chem. Soc.* (1998) 120, 7706–7718].

A set of 27 diverse monomers based on both natural and unnatural amino acids were employed, and the synthesis proceeded by the stepwise coupling of N-protected amino-*p*-nitrophenyl carbonate monomers in the presence of HOBt. Coupling steps were demonstrated to have proceeded in >95% yield by evidence of the Kaiser ninhydrin test, leading to a library of 20,000 cyclic trimers and two tetramer libraries of 530,000 compounds each.

The library compounds were assayed by ELISA against the GPIIb/IIIb receptor and active compounds were structurally analysed by MALDI mass spectrometry using the partial termination synthesis method that has previously been used for peptide sequencing. Many active sequences were determined including the cyclic trimer, cyclo (S) Gly-asp^c-ind^c-Arg^c-Cys^c-NH_2, (**3**) with an IC_{50} value of 3.9 nM that approaches the activity of peptide inhibitors.



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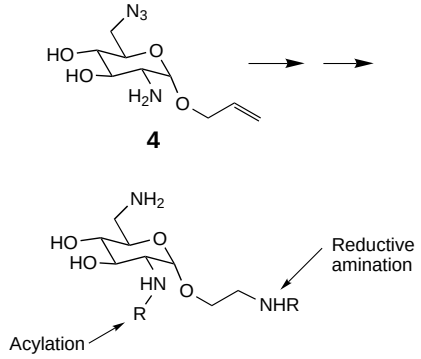
RNA binders

RNA is a key factor in many biological processes. In addition to the translation of genetic information, RNA has recently been shown to have catalytic activity, and as such presents itself as a possible target for pharmacological intervention. Indeed, several natural products including the aminoglycosides are known to recognize RNA. A recent paper from The Scripps Research Institute describes the use of combinatorial chemistry in the preparation of small molecules that bind to RNA [Wong, C-H. *et al. J. Am. Chem. Soc.* (1998) 120, 8319–8327].

The structure of aminoglycosides has inspired the design of compounds that contain a 1,3-hydroxyamine function, and in particular the glucosamine template **4** was chosen for the combinatorial library design, varying two positions through acylation and reductive alkylation. A range of four amino acids were independently attached to the amine and each product was further functionalized by reductive amination of a side-chain aldehyde revealed following ozonolysis.



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The 24 products were individually tested for binding at a range of concentrations to various RNA targets using a surface plasmon resonance (SPR) assay methodology. A range of binding affinities were obtained from the compounds demonstrating that the 1,3-hydroxyamine core structure was a useful RNA ligand.

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