monitor

MOLECULES

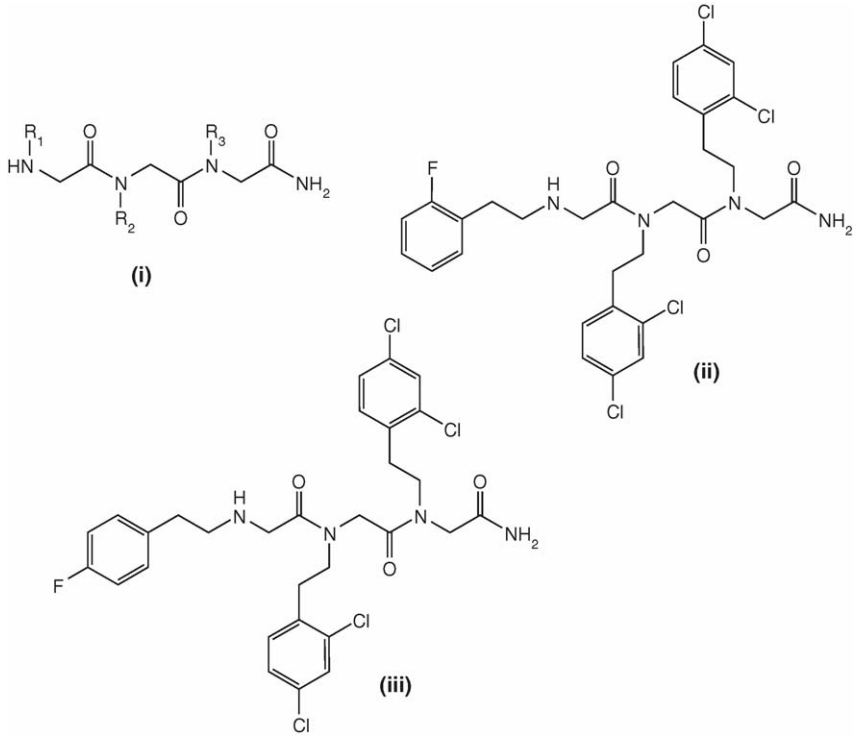
Peptoid positional scanning libraries for identification of multidrug resistance reversal agents

Peptoids, or *N*-alkylglycine oligomers, are non-natural compounds with wide-ranging biological activities. Of particular interest for drug discovery is the greater proteolytic stability and bioavailability they possess, compared with their respective peptide analogues, a corollary of their side-chains being nitrogen-bound rather than fused to α-carbons.

The modular approach to the synthesis of peptoids has been exploited previously in combinatorial library synthesis, for example the split-and-mix synthesis of derived peptoids has been used for the identification of new antibacterial compounds [1,2]. Previously, the modular composition of peptoids has also been used to synthesize and screen libraries of oligomers in a positional scanning format [3]. A single peptoid library in this format could be used, in principle, to identify hit compounds for multiple biological targets. One drawback with this particular approach was the propensity for side reactions to occur, responsible for low overall yields, attributable to when primary amines functionalized with tertiary amino moieties were used at the medial or C-terminal position of the trimer.

To obviate these problems, a new positional scanning library was envisioned [4]. In this work, a library of 5120 *N*-alkylglycine trimers (peptoids) were prepared in mixtures of either 256 or 320, depending on the sub-library synthesized. Synthesis was carried out on solid-phase Rink amide-linked AM RAM polystyrene resin (0.7 mmol/g, Rapp Polymer, Germany). The general structure of final compounds, cleaved from the resin by the use of trifluoroacetic acid, is depicted **(i)**. The synthesis of a 'reporter peptoid' containing three different 2-arylsubstituted ethylamines (to facilitate UV monitoring) was incorporated into the library construction sequence. The mass spectral analysis at different stages of the reporter synthesis indicated the presence of the expected peptoid fragments.

Multidrug resistance (MDR) to anticancer agents remains a major cause of treatment failure in cancer chemotherapy. MDR is the cross-resistance of tumour cell lines to several structurally unrelated chemotherapeutic agents – after exposure to a single cytotoxic drug. This phenomenon is often associated with overexpression of transmembrane glycoprotein (P-gp) encoded by the human MDR1 gene, which acts as a drug-efflux pump. This protein is thus considered a valid target for cancer chemotherapy. Screening of this peptoid library [general formula **(i)**] was carried out using an *in vitro* assay based on the accumulation of daunomycin on drug-resistant, P-gp overexpressing murine cell lines. Upon exposing library compounds to this assay several active mixtures were identified. These mixtures then underwent a deconvolution process to identify 20 active compounds. Upon re-screening, two peptoids, **(ii)** and **(iii)**, were identified that caused a higher intracellular accumulation of daunomycin than verapamil, at the same 5 μM dose. Cytotoxicity studies revealed that **(ii)** and **(iii)** decreased MDR in leukaemia cells >3-fold, presumably by blocking P-gp efflux.



1359-6446/06/$ - see front matter doi:10.1016/j.drudis.2006.05.008

The structural simplicity of these peptoids makes them amenable to structural manipulation, thus facilitating the optimization of lead molecules for drug-like properties. However, the high conformational flexibility of peptoids can generate selectivity problems because of unwanted off-target interactions. Synthesis of conformationally restricted analogues of these peptoids could amplify activity and remove off-target activity by 'freezing' the most active conformers. Thus, future work of this type is warranted.

1 Goodson, B. *et al.* (1999) Characterization of novel antimicrobial peptoids. *Antimicrob. Agents Chemother.* 43, 1429–1434
2 Ng, S. *et al.* (1999) Combinatorial discovery process yields antimicrobial peptoids. *Bioorg. Med. Chem.* 7, 1781–1785
3 Humet, M. *et al.* (2003) A positional scanning combinatorial library of peptoids as a source of biological active molecules: identification of antimicrobials. *J. Comb. Chem.* 5, 597–605
4 Masip, I. *et al.* (2005) Design and synthesis of an optimized positional scanning library of peptoids: identification of novel multidrug resistance reversal agents. *Bioorg. Med. Chem.* 13, 1923–1929

Paul Edwards
mepauledwards@fsmail.net