mixtures. Therefore, fine-tuning of the mixtures must guide the combinatorial synthesis scheme taking into account expected hit rates, thereby minimizing later deconvolution procedures (Barnes and Balasubramanian 2000). Employing mixtures instead of defined sets of compounds (vide infra) anticipates a significant decrease in time between synthesis and screening. For the process of lead development, this rather pragmatic and straightforward collection of information from screening mixtures is proposed to be advantageous. Taking into account the massive size of these screening libraries, other techniques might not be capable of handling it.

A major advancement in the field of combinatorial synthesis of peptide-like structures came with the solid supported synthesis from peptide-like backbone structure without further chemical manipulation by Kodadek and coworkers (2009). Using *N*-substituted glycine units (peptoids), the diversity of side chain chemistries on a peptide-like backbone presentation was explored. The side chain extends from the main chain nitrogen rather than the alpha carbon and allows preservation of favorable peptide conformations, while at the same time peptoids are protease resistant. Peptoids have been described in 1992 (Simon et al. 1992), but early attempts failed due to limited monomer supply and the resynthesis of smaller pools during the deconvolution process (Zuckermann and Kodadek 2009). Recently, advances in oligo-*N*-alkylglycine chemistry and screening technology enabled inexpensive screening of large peptoid libraries. One success story is the discovery of high affinity binders of the vascular endothelial growth factor receptor 2 (VEGFR2) (Udugamasooriya et al. 2008) (Fig. 3). Peptoids coupled to fluorescent

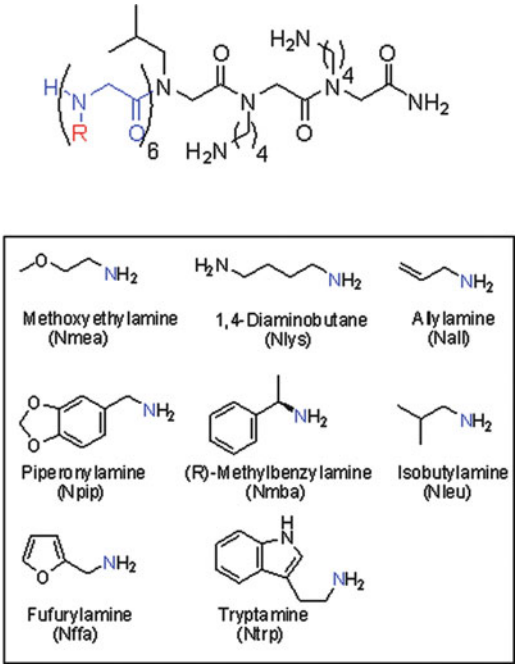

Fig. 3 Schematic representation of a peptoid library. General structure of a compound from a 250,000-membered peptoids library used by Udugamasooriya et al. (2008). The three *C*-terminal residues were fixed, while diversification was applied to the six N-terminal residues (drawn in *blue*). The main chain nitrogen is substituted with a combination of R-groups as depicted in the *box* (*blue nitrogens* represent the respective main chain nitrogen in the peptoids). Reprinted with permission from Udugamasooriya et al. (2008). Copyright © 2008 American Chemical Society