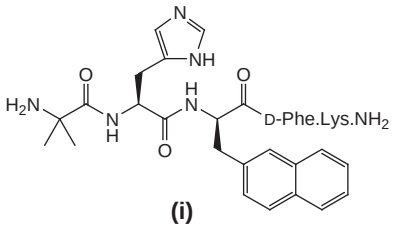
Combinatorial chemistry

Optimization of growth hormone secretagogues

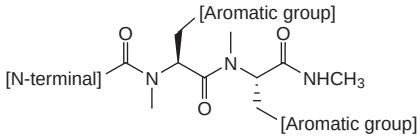
Several peptidic compounds have been discovered that have the ability to release growth hormone (GH) from the pituitary. Through this mechanism, these agents could offer the opportunity to treat several medical conditions including GH deficiency, osteoporosis and obesity. Several acylated dipeptides related to ipamorelin (**i**) have been investigated as GH releasers, and a recent



(i)

paper describes the use of combinatorial chemistry to investigate structure–activity relationships (SAR) in this series[1].

The 96 compounds in the library were individually synthesized on an *N*-methylated amine solid-phase support in a fashion that enabled variation of three positions of diversity (**ii**) and the generation of a terminal *N*-methylamide following trifluoroacetic acid-catalyzed cleavage. The *in vitro* GH-releasing



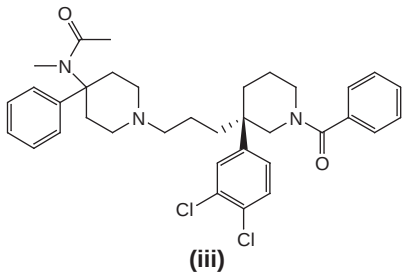
(ii)

properties of the purified products were determined in a rat pituitary cell assay, and full agonist potencies with EC_{50} values down to 1 nM were observed. It was notable that there was a distinct unpredictability in the SAR, in that some structural building blocks did not confer activity in a predictable manner. This very unpredictability emphasizes the advantages of making every compound in the combinatorial library, rather than relying on isolated compounds to develop the SAR.

1 Ankersen, M. *et al.* (1999) Demonstration of the strength of focused combinatorial libraries in SAR optimisation of growth hormone secretagogues. *Eur. J. Med. Chem.* 34, 783–790

Neurokinin-3 receptor antagonist SAR

The neurokinin-3 receptor is one of three receptors that binds the tachykinin or neurokinin family of peptides. Several non-peptide antagonists of the human receptor have been reported, and the use of combinatorial chemistry to optimize the antagonist, SR142801 (**iii**), has recently been disclosed[2].



(iii)

The 3-(3,4-dichlorophenyl)-3-propylpiperidine fragment was held constant while the amine and acylating group substituents were varied in an indexed (or orthoganol) combinatorial library. In total, 49 compounds were prepared using solution-phase methods in orthoganol pools of seven compounds. By screening the compounds while in these mixtures, it was possible to identify which of the peripheral groups made the greatest contribution to receptor affinity. These predictions were confirmed by the preparation and testing of six individual compounds, although the best compound discovered from this approach was still ≈30-times weaker than SR142801.

2 Raveglia, L.F. *et al.* (1999) Investigation of SAR requirements of SR 142801 through an indexed combinatorial library in solution. *Eur. J. Med. Chem.* 34, 825–835

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

Apoptosis in immature brain: a therapeutic approach to neuronal death

Neonatal hypoxic–ischaemic (HI) encephalopathy is an easily recognized clinical syndrome in 2–4 out of a 1000 full-term newborn infants that suffer asphyxia at, or shortly before, birth. Approximately 15–20% of such asphyxiated infants die during the newborn period and, of the survivors, 25% will exhibit permanent neurological deficits[1]. Experimental models of HI in the rat pup have been used for dose–response evaluations of a series of neuroprotective agents including free radical scavengers, excitatory amino acid antagonists and voltage-sensitive calcium channel blockers[2].

The regulation of cell number is an important function for the precise control of unwanted and dangerous cells. During development or after pathological conditions, apoptosis serves as a significant regulatory mechanism whereby the organism eliminates cells by the execution of death programs[3]. Initiation of apoptotic pathways begins with death-triggering signals, followed by an execution phase where activated cellular mechanisms stimulate multiple biochemical cascades. Finally, a destruction phase is entered where morphological changes occur and cellular breakdown begins. Several lines of evidence now indicate that apoptosis is an important mechanism in cell death associated with stroke, epilepsy and neurological disorders.

Many of the neuropathological characteristics of apoptosis have been

 1359-6446/00/$ – see front matter PII: S1359-6446(00)01521-X