specifically downregulated by **viii**. *In vivo*, compound **viii** was also found to prolong survival and decrease tumour growth rates in two xenograft tumour models. The dual action of the cationic porphyrin **viii** in decreasing both c-MYC protein levels and telomerase activity make this a worthwhile agent for further study.

4 Seimiya, H. *et al.* (2002) Telomere shortening and growth inhibition of human cancer cells by novel synthetic telomerase inhibitors MST-312, MST-295 and MST-199. *Mol. Cancer Therap.* 1, 657–665

5 Izbicka, E. *et al.* (1999) Effects of cationic porphyrins as G-quadruplex interactive agents in human tumor cells. *Cancer Res.* 59, 639–644

6 Grand, C.L. *et al.* (2002) The cationic porphyrin TMPyP4 down regulates c-*MYC* and human telomerase reverse transcriptase expression and inhibits tumor growth *in vivo*. *Mol. Cancer Therap.* 1, 565–573

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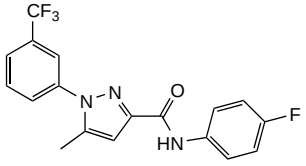
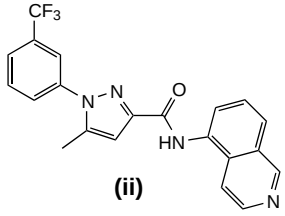
Combinatorial chemistry

Neuropeptide Y5 receptor ligands

Neuropeptide Y (NPY), a 36-amino acid C-amidated peptide, is abundantly expressed in the CNS and has been shown to robustly stimulate feeding. A family of six NPY receptor subtypes belonging to the superfamily of G-protein coupled receptors has been described in the literature ([1] and references therein). NPY Y1 and NPY Y5 are thought to be the most likely subtypes responsible for centrally mediated NPY-induced feeding responses. Antagonists at the NPY Y5 receptor are effective in reducing food intake in animal models of feeding [2]. Consequently, there has been an impetus to discover small-molecule NPY Y5 receptor antagonists to provide new treatments for obesity and other eating disorders [1]. A small library of 28 compounds was synthesized in solution in an attempt to elucidate SAR based on the pyrazole carboxamide lead **i** found from HTS. The library compounds were evaluated for binding affinity to the human NPY Y5 receptor. The assay used a stably transfected HEK293 cell line and measured competitive inhibition of binding of ^{125}I-PYY. One of the most potent compounds found was **ii**, which bound to the human NPY Y5 receptor with an IC_{50} value of 80 nM and was shown to inhibit cumulative food consumption by 43.2%, 2–6 hours after dosing in a fasting induced feeding model in rats. This work has produced an interesting set of compounds with affinity for the human NPY Y5 receptor, and further work in this area is warranted.



(i)



(ii)

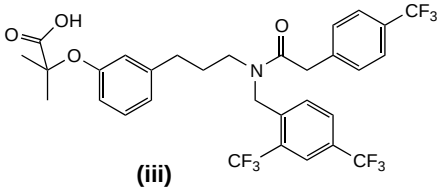
1 Kordik, C. P. *et. al.* (2001) Pyrazolecarboxamide human neuropeptide Y5 receptor ligands with *in vivo* antifeedant activity. *Bioorg. Med. Chem. Lett.* 11, 2287–2290

2 Criscione, L. *et al.* (1998) Food intake in free-feeding and energy-deprived lean rats is mediated by the neuropeptide Y5 receptor. *J. Clin. Invest.* 102, 2136–2145

PPARγ/δ dual agonists

The metabolic syndrome X, which consists of a clustering of several metabolic risk factors in a single patient, contributes significantly to increased mortality. The major components of this syndrome include dyslipidemia, insulin resistance, obesity and hypertension. Although established therapies are available to treat these risk factors individually (e.g. statins and fibrates for dyslipidemia, and metformin and glitazones for insulin resistance), no single drug can treat multiple risk factors of the metabolic syndrome X. Evidence suggests that the hyperlipidemic effects of the fibrate drugs and the antidiabetic effects of the glitazones are a result of activation of the α and γ sub-types, respectively, of the peroxisome proliferator-activated receptor (PPAR).

The PPARs are orphan receptors that belong to the nuclear hormone receptor superfamily of ligand-activated transcription factors. Identification of the metabolic syndrome X has therefore become one of the major efforts in the pharmaceutical industry. PPARδ is a recently discovered molecular target for the treatment of dyslipidemia. Hence, PPARγ/δ dual agonists could provide an efficient treatment for this syndrome by providing dual control of glucose and lipid metabolism [3]. A library of 480 compounds was synthesized on solid phase using SASRIN® resin. The library compounds were screened against all three human PPAR subtypes in a scintillation proximity assay (SPA) binding assay. One of the most potent compounds isolated was **iii**, which possessed a K_i value of 10 nM against hPPARγ, a K_i value of 5 nM against hPPARδ, and over 30-fold selectivity against hPPARα. This work has provided a novel potent PPARγ/δ dual agonist. Compounds with this dual receptor activity could provide a new approach to the development of drugs for the metabolic syndrome X.



(iii)

3 Liu, K. G. *et. al.* (2001) Identification of a series of PPARγ/δ dual agonists via solid-phase parallel synthesis. *Bioorg. Med. Chem. Lett.* 11, 2959–2962

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