and M2 (K_i = 350 nM and 250 nM, respectively) [8]. Interestingly, the dimethylpyridine amide of compound **vii** existed as a mixture of four slowly equilibrating rotamers, separable by chiral HPLC. Modifications to the pyridine amide were, thus, examined to reduce M1/M2 binding and simplify the chemical analysis of the product. Pyrimidine (**viii**) exists a mixture of two rotamers, due to symmetry, and yields improved activity in cell culture (IC_{50} = 0.5 nM, HIV cell entry). In addition, muscaranic receptor binding appears to be attenuated somewhat (K_i (M2)= 456 nM, K_i (M1) 575 nM) over compound **vii**. This compound also showed good absorption (F = 97% and 50% in rat and dog, respectively), exposure (AUC = 22,700 ng mL h^{-1} and 4710 ng mL h^{-1}; C_{max} = 1490 ng mL^{-1} and 340 ng mL^{-1} in rat and dog, respectively) and half-life ($T_{1/2}$ = 22 h and 8 h in rat and dog, respectively). These results suggest the potential advantage of using a symmetrical pyrimidine moiety, such as that found in compound **viii** and SCH-D, in place of the unsymmetrical pyridine N-oxide of compound **vii** and SCH-C.

5 Ross, T. *et al.* (1999) Role of chemokine receptors in HIV-1 infection and pathogenesis *Adv. Virus Res.* 52, 233–267

6 Liu, R. *et al.* (1996) Homozygous defect in HIV-1 co-receptor accounts for resistance of some multiply-exposed individuals to HIV-1 infection. *Cell* 86, 367–377

7 McCombie, S. W. *et al.* (2003) Piperazine-based CCR5 antagonists as HIV-1 inhibitors. III: synthesis, antiviral and pharmacokinetic profiles of symmetrical heteroaryl carboxamides *Bioorg. Med. Chem. Lett.* 13, 567–571

8 Tagat, J. R. *et al.* (2001) Piperazine-based CCR5 antagonists as HIV-1 inhibitors. II. Discovery of 1-[2,4-dimethyl-3-pyridinyl)carbonyl]-4-methyl-4-[3(*S*)-methyl-4-[1(*S*)-[4-(trifluoromethyl)phenyl]ethyl-1-piperazinyl]-piperidine N1-oxide (Sch-350634), an orally bioavailable, potent CCR5 antagonist. *J. Med. Chem.* 44, 3343–3346

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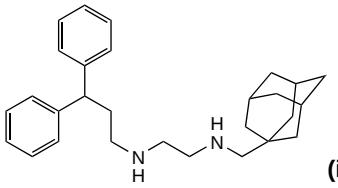
Molecules

Antituberculosis agents

Tuberculosis (TB) is the primary cause of human deaths that are attributable to a single etiologic agent, with almost three million deaths per year a result of infection with *tubercule bacillus*. Current chemotherapy consists of two phases: an intensive two-month period of daily therapy, followed by a four-month continuation phase. In most patients, sputum is cleared of live bacteria within two months of commencing oral therapy, but the full six-month course is required to prevent relapse after therapy is discontinued. Many decades of poor patient compliance with this prolonged and complex regimen has had two consequences: first, treatment of the disease is often unsuccessful and, second, there is an expanding epidemic of drug resistance that threatens TB control programs worldwide. One route that could decrease the length of treatment would be to improve the potency of the current anti-tuberculosis agents. This strategy would enable higher effective dosing of patients and could improve the therapeutic effect of the agent by maintaining the drug concentration above the minimum inhibitory concentration (MIC) for longer periods of time, or by enhancing the ratio of the peak:trough concentration to the MIC.

Drugs that affect the cell wall of the bacteria are known to have concentration-dependent cidal effects *in vitro* that might be achievable *in vivo* with enhanced potency. In an effort to discover more clinically effective treatments for *Mycobacterium tuberculosis*, the high throughput synthesis of libraries of potential inhibitors was undertaken [1]. Several large libraries of compounds were synthesised in mixtures of ten on rink acid resin (Novabiochem; http://www.novabiochem.com). A total of 63,238 compounds were synthesised and, from this set, several active mixtures were identified. Some of these mixtures were deconvoluted and the activity of single compounds was determined in an assay of the minimum inhibitory concentration, and a bioluminescent reporter strain assay that produces light in response to inhibition of cell wall synthesis by ethambutol. Several potent analogues were obtained upon deconvolution, with compound **i** being one of the most potent, possessing an MIC value of 0.5 mM. This work has delivered inhibitors with many unique structural features that suggest further routes for optimisation and, thus, further work in this area is warranted.



(i)

1 Lee, R. E. *et. al.* (2003) Combinatorial lead optimisation of [1,2]-diamines based on ethambutol as potential antituberculosis preclinical candidates. *J. Combi. Chem.*, 5, 172–187

Piperidines targeting the nociceptin receptor

The nociceptin/orphanin FQ (N/OFQ) receptor (NOP, previously named ORL-1) was discovered by several research groups in 1994, through cDNA expression cloning techniques. Its endogenous ligand nociceptin (N/OFQ), a novel heptadeca neuropeptide, was subsequently isolated from brain and identified in 1995. This discovery generated considerable interest, due to the important role of classical opioid receptors in the CNS. Although the NOP receptor is a member of the G-protein coupled receptor superfamily, with about 47% identity to the classical opioid receptors [MOP (μ), DOP(δ) and KOP (κ)], native opioid peptides and synthetic agonists that are selective for MOP, DOP or KOP receptors do not show significant affinity for the NOP receptor. Using nociceptin (N/OFQ) and its peptide analogues, a number of *in vivo* experiments have demonstrated that N/OFQ modulates a variety of

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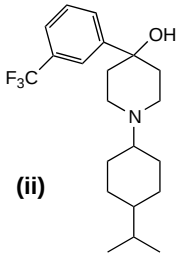
biological functions, such as food intake, memory processes, cardiovascular functions, locomotor activity and control of neurotransmitter release at peripheral and central sites. N/OFQ is involved in modulating pain mechanisms at the level of the spinal cord and N/OFQ might also be relevant in the treatment of CNS disorders, such as anxiety and drug abuse.

The search for small molecule N/OFQ agonists and antagonists has been reviewed recently [2]. Two libraries, totalling 348 compounds, were synthesised as singletons in solution and several active compounds were obtained. These compounds were screened and their K_i values were measured by examining their binding to the human NOP receptor expressed in recombinant HEK-293 cells. A set of 25 compounds were then designed, based on these library hits, to further optimise potency. From this optimisation study, several active compounds were obtained, with one of the most potent being compound **ii**, which possessed a K_i value of 12 nM against ORL-1. This work has generated rapid SAR and identified novel and potent agonists and antagonists of ORL-1, some of which could be used as the basis for the design of even more potent and selective ORL-1 agonists or antagonists in the future.



(ii)

2 Chen, Z. *et. al.* (2003) Design and parallel synthesis of piperidine libraries targeting the nociceptim (N/OFQ) receptor. *Bioorg. Med. Chem. Lett.* 13, 3247–3252

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Our new Monitor section...

From January 2004, our **Monitor** section is changing. This updated section will still bring you the hottest developments in the fields of medicinal chemistry, antiviral and antitumour molecules, combinatorial chemistry and drug delivery, but will now incorporate our **News in brief** and **People** sections.

This will now also include hot topics from recent publications in the fields of genomics and proteomics, neuroscience, gene therapy, cancer biology, new targets and mechanisms, bioinformatics, as well as business developments, new appointments and awards.

If you have any comments or suggestions regarding the new look **Monitor**, please contact Steve Carney (s.carney@elsevier.com) or Joanne Clough (j.clough@elsevier.com).