Matrix metalloprotease inhibitors

Matrix metalloproteases (MMPs) are a large family of zinc-dependent endoproteases involved in the remodelling of connective tissue. The enzymes can be divided into four main groups: collagenases, gelatinases, stromelysins and membrane type MMPs. Abnormal expression and regulation of this group of enzymes has been directly implicated in the development of a number of pathological conditions including rheumatoid arthritis, cancer invasion and metastasis. A combinatorial approach using positional scanning techniques has been used to identify agents with activity against a number of pathologically important MMPs (Solid-phase synthesis and biological screening of N-α-mercaptoamide template-based matrix metalloprotease inhibitors, J. F. Lynas et al., Combinatorial Chemistry & High Throughput Screening, 3, (2000), 37-41). A small library of 40 compounds were individually synthesised on Rink amide AM solid support using a positional scan of twenty amino acids at position Xxx of (i) and (ii) respectively. Several of the compounds synthesised provided reasonably potent compounds for MMP-1 or MMP-8 over other MMPs tested. For example (i) with Xxx = Trp had an IC$_{50}$ for MMP-1 of 50 nM, and selectivities of between 3 and 79 fold over MMPs 2, 3, 8 and 9. Whereas (ii) with Xxx = Nva, possessed an IC$_{50}$ value of 240 nM against MMP-8, and selectivities of between 0.5 and 16 fold over other MMPs tested. By screening these compounds it was possible to identify which peripheral groups made the greatest contribution to binding. This work has allowed identification of alternate pharmacophores which might be used to focus the design and development of new libraries of MMP inhibitors with enhanced selectivity for individual species.

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Selective dopamine D$_4$ ligands

Hyperactivity of the dopaminergic system has long been linked to the etiology of schizophrenia. Several dopamine receptor subtypes have been discovered which can be divided into "D$_1$-like" (D$_1$, D$_5$) or "D$_2$-like" (D$_2$, D$_3$, D$_4$). Typical antipsychotics effectively block both the D$_4$ and D$_2$ receptors. It is hypothesised that D$_4$ blockade imparts the neuroleptic effect of the typical antipsychotics and the D$_2$ blockade is responsible for the unwanted extrapyramidal side effects. Thus a selective D$_4$ antagonist would represent an effective treatment for schizophrenia. The use of combinatorial chemistry in the discovery of novel inhibitors selective for D$_4$ over D$_2$ is described in a recent paper (A solution-phase combinatorial synthesis of selective dopamine D$_4$ ligands, J. P. Williams and K. Lavrador, Combinatorial Chemistry & High Throughput Screening, 3, (2000), 43-50).
A library of 332 individual oxadiazolylpiperidines based on the core motif (iii) was prepared in solution, and the products purified by preparative LC-MS using mass triggered sample collection. One of the most potent and selective compounds (hD₄ vs. hD₂) isolated from this library was (iv) which possessed a Kᵰ of 5 nM against human D₄, with better than 50 fold selectivity over human D₂. The authors have combined combinatorial synthesis with automated purification to deliver, in only one round of synthesis, a new series of selective dopamine D₄ ligands based on the 1,2,4-oxadiazole bioisostere of the ester group.

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