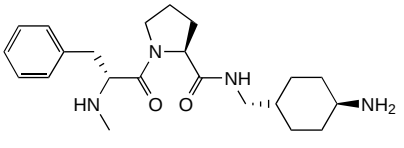
Combinatorial Chemistry

Library of thrombin inhibitors

As thrombin is a key mediator in the blood coagulation system, inhibition of this enzyme is a popular target for the therapy of several thrombogenic diseases. Following the discovery of a potent thrombin inhibitor (**1**, K_i = 5 nM) that failed to achieve significant blood levels upon oral administration to dogs or rats, a group from Merck have made a library of analogues in the attempt to improve the pharmacokinetics [Brady, S.F. *et al. J. Med. Chem.* (1998) 41, 401–406].

A solid-phase synthetic approach was developed that allowed the synthesis of compounds where the *N*-methyl-D-Phe residue was replaced with a range of carboxylic amides. The inhibitor template was linked through the right-hand amine to Wang resin by a carbamate bond, and the left-hand amine was derivatized by reaction individually with carboxylic acids chosen from commercial catalogues and in-house samples. Cleavage from the resin using TFA allowed solution screening of the final products.

Following the synthesis of a total of 200 analogues, a potent and selective compound (**2**, K_i = 1.5 nM) was identified. This compound subsequently demonstrated good efficacy and oral bioavailability in several animal models including a rat model of arterial thrombosis.



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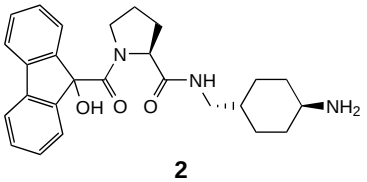

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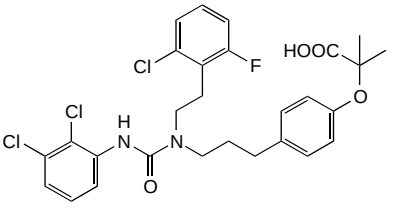
Library-derived PPAR ligands

The peroxisome proliferator-activated receptors (PPARs) are members of a family of ligand-activated transcription factors that recognize steroid hormones, retinoids, thyroid hormones and other ligands. Three receptor types have been identified, and whilst the physiological functions of PPARα and PPARγ are known, PPARδ is currently an orphan receptor with no known function. Recent work has used combinatorial libraries to find potent and selective inhibitors of the PPARδ receptor [Brown, P.J. *et al. Chem. Biol.* (1997) 4, 909–918].

Based on the premise that the phenoxyisobutyric acid group of the known fibrate class of lipid-lowering drugs would bias library components towards the PPAR receptors, a library of 480 compounds was prepared on SASRIN resin. To aid efficiency in both synthesis and screening, the library was prepared in 160 mixtures each of three components. Each well contained the three compounds generated from a mixture of three fibrate monomers combined with a unique carboxylic acid and isocyanate. Active mixtures in a cell-based reporter gene assay against each of the three human PPAR receptors were deconvoluted by resynthesis of the individual compounds.

This study identified the first high-affinity PPARδ ligand, GW 2433 (**3**),



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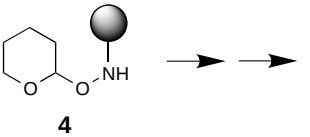
with an EC_{50} value of 160 nM. The corresponding radiolabelled analogues will be an important tool for the discovery of further potent and selective ligands of the PPARδ receptor.

Hydroxamate synthesis on solid phase

The hydroxamic acids are a class of compounds with potential for pharmacological activity against a wide range of biological systems including antibacterial, antifungal and anticancer targets. In particular the high affinity of the hydroxamate group for metal ions makes it a favourite choice for the design of metalloproteinase inhibitors. The wide utility of this functional group has made it a target for library synthesis, and a recent paper describes an effective solid-phase approach to these compounds [Ngu, K. and Patel, D.V. *J. Org. Chem.* (1998) 62, 7088–7089].

The principle of this approach was to attach an O-protected hydroxylamine to the solid phase, and use the tether as a nitrogen protecting group. The hypersensitive acid-labile tris(alkoxy)-benzyl ester linker was used with either allyl or THP protection on the oxygen.



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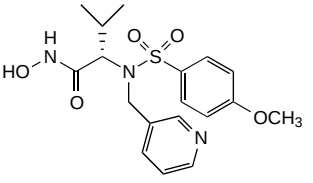

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The latter system (**4**) was successfully used in the synthesis of the Ciba-Geigy broad-spectrum matrix metalloproteinase inhibitor CGS 27023A (**5**, K_i = 43 nM against stromelysin) in an overall chemical yield of 66%.

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