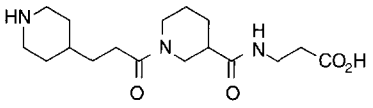
Combinatorial chemistry

Platelet fibrinogen receptor antagonists

Antagonists of the platelet fibrinogen receptor (GPIIb/IIIa) exhibit therapeutically useful inhibition of platelet aggregation. A key paper from workers at the R.W. Johnson Pharmaceutical Research Institute describes the solid-phase synthesis of libraries of such antagonists related to their lead compound, RWJ50042 (**1**) [Hoekstra, W.J. *et al. Bioorg. Med. Chem. Lett.* (1996) 6, 2371–2376]. Because the lead compound contains two strategically placed amide bonds, the synthesis of these analogues lends itself perfectly to a solid-phase combinatorial library approach, and thus analogues were synthesized in parallel linked to a 2-chlorotrityl resin through the amine.



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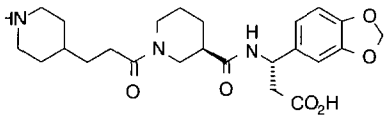
Although monomer variation gave a total of 288 (6 × 4 × 12) possible analogues, a 'concurrent refinement process' was used to pick out increasingly optimal sets for subsequent evaluation and in fact just over 200 compounds were made. The study led to several potent compounds including (**2**), and the number of new active antagonists produced allowed rapid assessment of critical *in vivo* properties including oral absorption, plasma half-life and duration of action.



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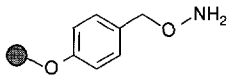
Matrix metalloproteinase inhibitors

Hydroxamic acids are metal-chelating groups that have an important role in the design of inhibitors of matrix metalloproteinases. A number of peptide hydroxamic acids have been prepared on solid-phase by chemists from British Biotech Pharmaceuticals [Floyd, C.D. *et al. Tetrahedron Lett.* (1996) 37, 8045–8048]. A novel linker for the generation of hydroxamates on Wang resin was developed by the conversion of the resin hydroxyl into an O-linked hydroxylamine (**3**). Tripeptides were built on the hydroxylamine using standard Fmoc synthetic procedures and cleavage from the resin under acidic conditions followed by flash chromatography gave products in greater than 80% yield.



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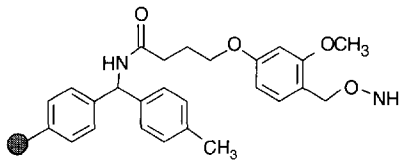
A second novel linker (**4**) was also produced that was more sensitive to acidic conditions and could be cleaved with greatly reduced concentrations of trifluoroacetic acid. Products generated have been submitted for screening against collagenase, stromelysin and gelatinase, and the new linkers are being used in the automated combinatorial synthesis of further matrix metalloproteinase inhibitors.



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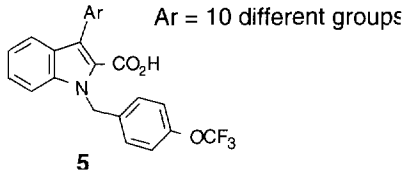
Combinatorial technology patents

The explosion in the use of combinatorial synthesis for drug discovery has been followed by the filing of many patents protecting both libraries and new synthesis technology. This complex field has recently been described in an excellent review by Christopher Newton [*Expert Opin. Ther. Pat.* (1996) 6, 827–835]. The review lists all of the major combinatorial chemistry patents published up to the middle of 1996 with a brief description of the main claims. As Dr Newton indicates, although several companies and institutions have patented strategies that involve vast numbers of compounds, the validity of such claims has yet to be tested in a court of law. Meanwhile, the majority of the major pharmaceutical companies continue only to file patents to protect series of compounds that they believe are commercially valuable. One exception to this is a SmithKline Beecham patent claiming small-molecule interleukin-8 receptor antagonists [SmithKline Beecham Pharmaceuticals, WO 96/18393]. Exemplification of the invention is in part achieved by the synthesis of combinatorial mixtures of ten compounds such as **5**, where each component is characterized by mass spectrometry. Newton remarks that the progress of this patent will be watched with some interest.



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Monitoring solid-phase chemistry using FTIR

Combinatorial chemistry relies primarily on the use of solid-phase synthesis for library production as the resin beads used give a handle for the separation of products from excess reagents. However, chemists have always found it difficult to determine how rapidly chemistry proceeds on solid-phase. A recent paper from Sandoz describes the use of single-bead FTIR as a method for determining the time course of solid-phase reactions [Yan, B. *et al. J. Org. Chem.* (1996) 61, 7467–7472].

By removing beads from a reaction at various time-points, washing the beads and observing the IR spectrum of a single flattened bead, it was possible to ascertain the pseudo-first order rate constant for the displacement of a resin-bound benzyl chloride with potassium acetate. It was found that the rate of this reaction on solid-phase is much faster than the rate of similar solution-phase reactions, possibly as a consequence of the high local concentrations of reactant in the resin bead.

The Sandoz group also demonstrated that reactions in the interior and on the surface of a resin bead proceed at comparable rates, and that reactions on TentaGel resin proceed no faster than the same reactions on Wang resin beads.

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