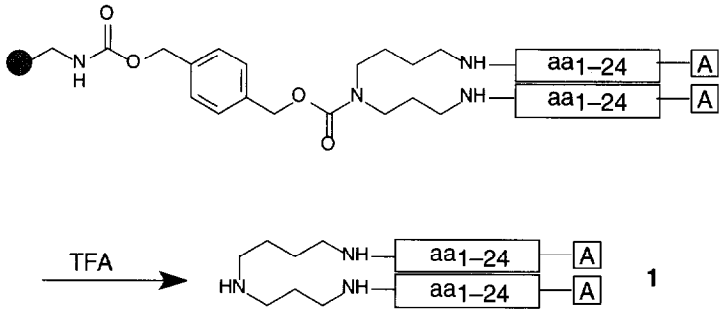
Combinatorial chemistry



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Combinatorial antiparasitic agents

Trypanosomal parasites are responsible for several tropical diseases including African sleeping sickness and Chagas' disease. A potential treatment of these infections is by inhibition of the parasitic enzyme trypanothione reductase. In a recent paper, Bradley, M. and coworkers [*J. Chem. Soc., Chem. Commun.* (1996) 941–942] have used a combinatorial library prepared by solid-phase synthesis to seek new inhibitors. The compounds synthesized were trypanothione analogues (**1**) that explored variation of the amino acid residues (aa_{1-24}) and acylating or sulphonylating groups (A). The secondary amine in the compounds was attached to the resin through a carbamate linker. Screening in solution was possible following acid-catalysed cleavage of the linker to regenerate the amine.

Purification of von Willebrand Factor

The glycoprotein von Willebrand Factor (vWF) has a key role in the blood coagulation cascade. However, the purification of vWF is difficult because it is a multimeric protein comprised of subunits with a range of molecular weights. A combinatorial approach has been used in a novel, efficient method for the purification of vWF [Carbonell, R.G. *et al. Bioorg. Med. Chem.* (1996) 4, 699–708]. A lead peptide (RLRSFY) that interacts with vWF was discovered through the screening of a phage-display library. Subsequent conservative modification of this peptide led to an optimized structure (RVRSFY) that has been immobilized on a solid support and used for the successful affinity purification of vWF.

'Universal' biphenyl library

The design and synthesis of a 'universal' library for drug discovery is eagerly sought by combinatorial chemists. Such a library should have the structural diversity that permits the generation of leads for essentially any biological target. Scientists at Sphinx pharmaceuticals have described the solid-phase synthesis of their universal library that explores the structural space around a rigid biphenyl template [Pavia, M.R. *et al. Bioorg. Med. Chem.* (1996) 4, 659–666]. The synthesis of the biphenyl core allows the display of three or four different ring substituents in a variety of spatial arrangements depending on the substitution pattern chosen, as illustrated by compound **2**. The synthetic route permitted independent functionalization of the two aromatic rings with the key biaryl forming step achieved by a modified Stille coupling.

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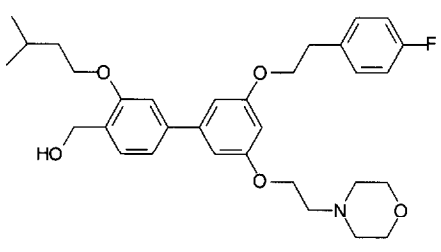

2

Emerging molecular targets

Vitronectin receptors and retinal neovascularization

The overgrowth of small blood vessels in the retina is a major cause of blindness associated with diabetic retinopathy, premature birth, senile macular degeneration and other ocular diseases. The primary trigger for the condition is believed to be hypoxia; upon an abrupt decrease of oxygen levels, various growth factors that induce vascularization are released in the retina. The vitronectin receptor, an $\alpha_v\beta_3$ integrin, has recently been identified as a marker of the angiogenic phenotype of endothelial cells. Thus, it seemed reasonable to Dr Hans-Peter Hammes (Jestus-Liebig Universität, Giessen, Germany) and his colleagues at Albert Einstein College of Medicine (New York, USA) and the Kerckhoff-Klinik (Bad Nauheim, Germany) to investigate the effects of vitronectin receptor antagonists on retinal neovascularization. They used a mouse model of proliferative retinopathy in which 7-day-old mice are exposed to an environment of 75% oxygen followed by an abrupt transfer to normal atmospheric oxygen. A fluorescein-labeled cyclic peptide antagonist of the vitronectin receptor, cyclic RGDfV, was injected subcutaneously. The cyclic peptide, which has previously been shown to block the adhesion of endothelial cells to a vitronectin-coated substratum, could be observed to accumulate in the retina by direct observation of the fluorescein label. Most importantly, the mice that received the vitronectin receptor antagonist exhibited a significant decrease in the level of retinal vascularization as compared to a control group that did not receive the antagonist [*Nat. Med.* (1996) 2, 529–533]. The authors suggest that vitronectin antagonists may prove to be highly useful in blocking the neovascularization associated with ocular diseases. Moreover, if vitronectin receptor antagonists were available that could be applied directly to the eye, retinal neovascularization might be prevented without the undesirable side-effects that would be expected to occur with systemic administration. The discovery of vitronectin receptor antagonists suitable for direct ocular administration sounds like a good opportunity for drug discovery groups.

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