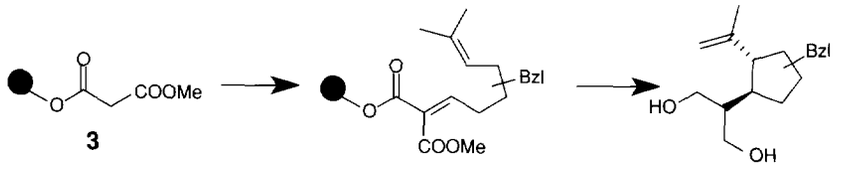

Stereoselective cycloalkane formation

Tietze, L.F. and Steinmetz, A. [*Angew. Chem. Int. Ed. Engl.* (1996) 35, 651–652] have demonstrated a two-component domino reaction leading to cyclopentane and cyclohexanes. A malonate functionalized polymer **3** was condensed with an aldehyde as a prelude to an ene rearrangement catalysed by zinc bromide. Following cleavage from the resin by diisobutylaluminium hydride reduction, this Knoevenagel–ene process generated cycloalkanes with high stereoselectivity.

Optimizing library design

In order to discover novel drug discovery leads, many companies are employing combinatorial chemistry to synthesize huge numbers of compounds for high-throughput biological assay. An alternative to this process is the iterative synthesis of fewer compounds, but using the results of each round of screening to dictate the compounds prepared in the subsequent rounds. The difficult question is how to use the results to design the next library. One way around this issue is to use computational genetic algorithms to design the structures. A recent paper from a group at Sterling-Winthrop [Singh, J. *et al. J. Am. Chem. Soc.* (1996) 118, 1669–1676] describes the strategies of selection, crossover and mutation used to optimize affinity and selectivity of peptides for stromelysin. The synthesis of 300 compounds through five generations was sufficient to identify peptides with improved activity.

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Emerging molecular targets

Human adenovirus protease

The three-dimensional structure of the human adenovirus protease has just been resolved to 2.6 Å by Dr. Walter F. Mangel and coworkers at Brookhaven National Laboratory (Upton, NY, USA). The human adenovirus causes acute upper respiratory, eye and intestinal tract infections. Such infections are common in children and are a leading cause of death in developing nations.

The new structure and previous studies suggest at least three different sites on the protease where drugs might act to inhibit proteolytic activity. One is the active site where the enzyme cleaves the viral precursor proteins to produce the protein species needed to form the assembled viron. The other two sites are binding regions for cofactors, which are essential for enzymatic activity, an unusual requirement for a viral protease. One cofactor is a short peptide whose binding site has been determined. The other cofactor is the viral DNA whose binding site remains to be determined [Ding, J. *et al. EMBO J.* (1996) 15, 1778–1783].

Mangel's group suggest that the presence of three sites of attack on the enzyme makes it highly likely that an inhibitory compound could be discovered. Moreover, simultaneous administration of compounds that bind at each site may overcome the problems of resistance that are common to antiviral agents. Thus, it is important to determine the site at which the viral DNA binds to the enzyme. The researchers are currently attempting to grow crystals in the presence of the viral DNA in order to answer this important question. In the meantime, the human adenovirus protease might prove to be an excellent candidate for high-throughput screening or rational drug design programs.

Proton-pumping ATPase and male contraception

An acidic environment in the vas deferens and epididymis is essential for the maturation of sperm and for maintaining their immobility and quiescent state prior to ejaculation. Previous studies implicated a carbonic anhydrase and a Na^+/H^+ exchanger in maintenance of this environment. However, Dr Sylvie Breton and coworkers at Harvard Medical School (Boston, MA, USA) and Woods Hole Marine Biology Laboratory (Woods Hole, MA, USA) report that high concentrations of a proton-pumping ATPase also line the luminal surfaces of the vas deferens and epididymis and suggest that the enzyme is important in maintaining this acidic environment. They also propose that the ATPase may be an effective target for a male contraceptive [*Nat. Med.* (1996) 2, 470–472]. A rise in pH resulting from inhibition of the ATPase could arrest the development of the sperm and trigger premature mobility, resulting in decreased fertility.

In the same issue, Dr Malcolm Potts (University of California, Berkeley, CA, USA) provides a discussion of the considerable political hurdles involved in the development of an oral male contraceptive [*Nat. Med.* (1996) 2, 398–399].

Egr-1 and vascular injury

The development of vascular occlusive lesions as a result of vascular injury is a complex process of vascular remodeling involving the coordinated effects of numerous growth factors that stimulate endothelial and smooth muscle cells. Such factors include platelet-derived growth factor A and B, human transforming growth factor-β1, tissue factor and urokinase-type plasminogen activator. Each of these growth factors may be induced in endothelial cells upon activation of specific transcription factors, but the key elements that regulate their coordinated expression upon vascular injury are not well understood.

Dr Levon M. Khachigian and coworkers from Brigham and Women's Hospital (Boston, MA, USA) report that the expression of these growth factors upon vascular injury may be coordinated by the transcription factor Erg-1 [*Science* (1996) 271, 1427–1431]. The authors found that expression of Erg-1 preceded the expression of each of the growth factors. Moreover, the gene for each growth factor has a binding region for Erg-1 in its promoter. If the authors are correct in their contention that the expression of Erg-1 is the trigger that leads to complex process of vascular remodeling, Erg-1 may emerge as an important target for the development of new compounds to combat vascular diseases.

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