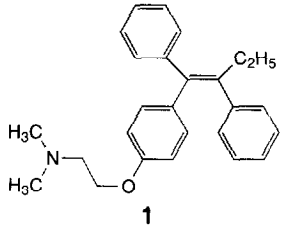
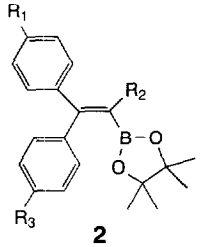
Combinatorial chemistry

Tamoxifen analogues

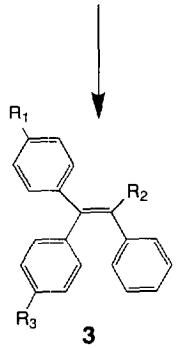
Tamoxifen (**1**) is used clinically to treat estrogen-dependent breast cancer. In the search for novel and possibly more-selective estrogen antagonists, a synthetic route has been devised and used to prepare a combinatorial library of 25 analogues [Brown, S.D. and Armstrong, R.W. *J. Org. Chem.* (1997) 62, 7076–7077]. The library synthesis employed five acetylenes, five aryl halides and a polymer-bound aryl iodide. The key to the success of this approach is the use of a resin-capture step that traps only the intermediate vinyl boronate (**2**) by Suzuki reaction with the solid-supported aryl iodide. This procedure is a simple but effective way to clean up the products of a solution-phase reaction. Other reaction by-products or intermediates lack the appropriate functionality to permit reaction with the solid-phase reagent and could subsequently be removed by washing the resin.



1



2



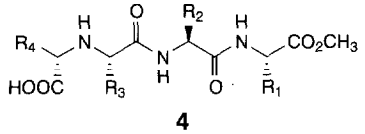
3

Another distinguishing feature of this library synthesis is the use of a silicon atom to tether the aryl iodide to the resin beads. The arylsilane was readily cleaved by a protodesilylation reaction under acidic conditions to give products (**3**) that carry no trace of the resin attachment site.

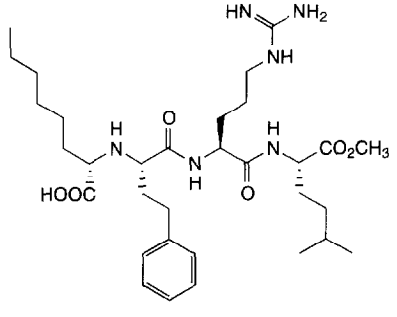
Matrix metalloproteinase library

Using TentaGel resin as the solid support, a combinatorial library of 20,000 compounds has been synthesized in the search for novel inhibitors of metalloproteinases [Esser, C.K. *et al. Bioorg. Med. Chem. Lett.* (1997) 7, 2639–2644]. The first two amino acids (designated W and X) used in the synthesis of the library compounds (**4**) were incorporated through a mix-and-split combinatorial technique to give mixtures of 200 components. The final two residues were added such that each of the final 100 mixtures contained a specific YZ sequence. Mixtures active in any particular assay were deconvoluted by the repeat synthesis and assay of the constituent 200 compounds.

This library has been tested in over 50 different biological screens, including assays for the inhibition of connective tissue degradation mediated by matrix metalloproteinases (MMPs). Compound (**5**) was found to be an inhibitor of MMP-3 with an IC_{50} value of 0.4 μM.



4



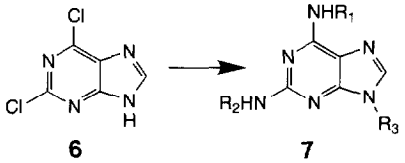
5

Purine kinase inhibitor library

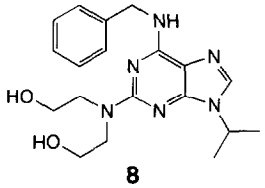
The progress of a cell through the process of mitosis is controlled by several serine and threonine kinases. These multiprotein complexes consist of cyclin (a regulatory protein) and cyclin dependent kinase (CDK). The synthesis of a purine library designed specifically to identify inhibitors of CDK2, a key kinase involved in mitosis, has recently been reported [Schow, S.R. *et al. Bioorg. Med. Chem. Lett.* (1997) 7, 2697–2702].

A library of 3,000 purines (**7**) was constructed both in mixtures and as individual components using solution-phase sequential displacement of chlorine atoms in 2,6-dichloropurine (**6**). Following substitution of the 6-chloro group, alkylation of the 9-position, under basic conditions, introduced a second site of structural diversity. The final step was the displacement of the 2-chloro moiety with amines under forcing conditions.

The library was screened against CDK2, and several active compounds (including **8**, IC_{50} = 0.5 μM) were identified for evaluation as potential antiproliferative agents.



6 **7**



8

Nick Terrett
Discovery Chemistry
Pfizer Central Research
Sandwich, Kent
UK CT13 9NJ
Tel: +44 1304 618451
fax: +44 1304 618422
e-mail: nick_terrett@sandwich.pfizer.com

1359-6446/98/$19.00. PII: S1359-6446(97)01147-1