The Tetrahedron journals carry a wide diversity of papers in combinatorial and solid-phase chemistry. This month *Combinatorial Chemistry - An Online Journal* includes several papers describing useful advances in library chemistry, both in solution and on resin support, as well as some useful library analysis methods and two examples of library applications.

**Solid-phase library chemistry**

In this month’s issue, a new method for the synthesis of \( \alpha \)-amino acids on solid-phase is described (Barbaste *et al*., *Tetrahedron Letters*, 1998, 39(35), 6287-6290). N-Acetyl dehydroalanines, bound to Wang resin through the Mitsunobu reaction have been derivatised by the Michael addition of nucleophiles including 1,2,4-triazole and pyrazole. 4-Hydroxyquinolin-2(1H)-ones have been prepared on solid-phase from Wang resin-linked cyanoacetic acid (Sim *et al*., *Tetrahedron Letters*, 1998, 39(35), 6399-6402). Acylation with isatoic anhydrides and heating generated hydroxyquinolinones in a concomitant cyclisation and cleavage step. An automated approach has been used to prepare a library of benzimidazoles on solid-phase from 4-fluoro-3-nitro benzoic acid (Mayer *et al*., *Tetrahedron Letters*, 1998, 39(37), 6655-6658).

In the synthesis of combinatorial libraries it is sometimes necessary to change the protecting group on solid-phase bound monomers. A facile one-step conversion of N-Fmoc to N-Boc carbamates has been achieved in high yield using potassium fluoride with either \( t \)-Boc-S-2-mercapto-4,6-dimethylpyridine or \( di-t \)-butyl carbonate (Furlán and Mata, *Tetrahedron Letters*, 1998, 39(35), 6421-6422). Another paper demonstrates that diimide reduction of olefins on solid support is readily possible using sulphonylhydrazide in DMF (Lacombe *et al*., *Tetrahedron Letters*, 1998, 39(38), 6785-6786).

Armstrong’s group continue to publish novel variants and library applications of the multicomponent condensation reaction (Kim *et al*., *Tetrahedron Letters*, 1998, 39(39), 6993-6996). A 96-member library of acylated dipeptides generated using Ugi chemistry and further derivatisation using Grignard cleavage of a Weinreb type amide linker have been prepared on Rink resin.

The intramolecular ruthenium-catalysed ene-yne metathesis reaction has been successfully carried out on solid phase (Heerding *et al*., *Tetrahedron Letters*, 1998, 39(38), 6815-6818). Using a ‘mix and split’ approach, a library of over 4200 isoiindoline products have been prepared.

**Solution-phase library chemistry**

A solution-phase approach to the multi-milligram synthesis of perhydrooxazin-4-ones is described (Panunzio *et al*., *Tetrahedron Letters*, 1998, 39(36), 6585-6588). The key step is a hetero Diels-Alder cycloaddition of aldehydes with trimethylsilyloxyazadienes, and
HPLC and LC-MS were used to confirm that in most cases the six-membered product had been formed.

Dehydroamino acids have been prepared in a solution-phase three component synthesis based on the Passerini reaction (Kim et al, *Tetrahedron Letters*, 1998, 39(39), 7031-7034). A library of compounds were developed that could be used to probe the binding of the related azinomycin structures. The Ugi five-centre-three-component reaction based on L-homoserine has been used to prepare a library of N-carbamoylmethyl-α-aminobutyrolactones in solution (Park et al, *Tetrahedron Letters*, 1998, 39(39), 7109-7112). The key step of the reaction is the intramolecular addition of the homoserine hydroxyl onto an activated lactone to give the desired butyrolactone products.

Soluble polymers have been used as the support for 1,3-dipolar cycloadditions (Moore and Norris, *Tetrahedron Letters*, 1998, 39(39), 7027-7030). Alkynes attached to polyethylene glycols were reacted with azidosugars to give triazoles freed from the polymer through a borohydride reduction.


### Solid-phase linkers

A library of peptidic aldehydes has been prepared on polystyrene-supported triphenylphosphonium bromide (Hall and Sutherland, *Tetrahedron Letters*, 1998, 39(36), 6593-6596). Wittig chemistry generated an olefin linker that was ultimately ozonolysed to give aldehyde products.

An acyl hydrazide linker has been developed as an acid and base stable group for the generation of carboxylic acids, esters or amides from solid-phase (Millington et al, *Tetrahedron Letters*, 1998, 39(39), 7201-7204). The key step in the cleavage is copper (II) catalysed oxidation of the hydrazide, followed by nucleophilic attack onto the carbonyl with water, alcohols or amines. If used in the opposite sense, the linker offers the opportunity for the traceless generation of aromatic products.

### Library scaffolds and monomers

‘RECAP’ (resin activation/capture approach) technology has been used to produce the N-acyl-2-substituted dihydro-4-pyridone template (Chen and Munoz, *Tetrahedron Letters*, 1998, 39(38), 6781-6784). Staring with 4-hydroxyxpyridine loaded onto Wang resin, acylation and Grignard addition gave the desired products. Synthetic selectivity is achieved as only the pyridones could subsequently be cleaved under acidic conditions.

### Library analysis

Combustion elemental analysis is presented as a reproducible and accurate way of quantifying organic compounds on polystyrene or TentaGel resins (Yan et al, *Tetrahedron Letters*...
Letters, 1998, 54(39), 11755-1766). A peptoid synthesis has been monitored by this method and it was shown to be as accurate as well-established photometric techniques.

Three fluorinated linkers have been developed that allow the monitoring of solid-phase synthesis by gel-phase 19F NMR spectroscopy (Svensson et al, Tetrahedron Letters, 1998, 39(39), 7193-7196). The linkers are fluorinated equivalents of linkers commonly used for solid-phase synthesis and coupling and cleavage reactions could be efficiently monitored.

**Library applications**

Oligomannopeptoids ranging in size from the dimer to the hexamer have been generated through a solid-phase synthetic approach (Yuasa et al., Bioorganic & Medicinal Chemistry Letters, 1998, 8(16), 2139-2144). Although this solid-phase route is unlikely to be used for combinatorial chemistry, it has been demonstrated for this small library that the compounds mimic oligomannosides in their binding to concavalin-A.

A solid-phase combinatorial chemistry approach to a library of isoxazolythioamides related to leflunomide is described (Albert et al., Bioorganic & Medicinal Chemistry Letters, 1998, 8(16), 2203-2208). These compounds have been used in an investigation of potential immunosuppressant activity.