Developing combinatorial libraries provides access to high-quality diverse chemical compound collections that give scientists powerful tools to discover lead molecular structures with a wide range of physiological properties. The birth of combinatorial chemistry can be traced to the first sequential peptide synthesis on solid phase in the 1960s. The merits of using solid phase synthesis include the ability to use excess reagents to push reactions to completion and the easy purification of the resin bound product through filtration and washing. While solid phase peptide synthesis is highly developed and robust, the same cannot be said for every reaction on solid phase. The use of solid phase synthesis for non-peptide library production has a number of drawbacks associated with it. The additional steps required for attachment and removal of the linker as well as the inability to easily monitor reaction progress can make the process cumbersome. But most significantly the adaptation of standard solution reactions to solid phase methods entails additional and frequently difficult problems such as linker compatibility, points of substrate attachment and achieving efficient and complete reaction conversions. Multi-step synthesis of non-peptide libraries can be extremely difficult as the chemistry being used is often not as highly optimised as peptide synthesis and results in a poor quality of the final library. This has lead to the resurgence of solution phase chemistry as the preferred method of non-peptide library generation in industry but often exploiting variants of the solid phase principals. The advantages of using solution phase synthesis include the vast literature of reactions to draw from and the absence of extra steps associated with solid phase synthesis.

One major drawback of solution phase organic synthesis lies in the purification and isolation of the individual products particularly in library generation when multi-step synthesis is required. A number of approaches involving the use of solid supported reagents and scavenger resins have emerged to aid the purification bottleneck. These techniques mirror the advantages of solid phase synthesis, as the excess reagents used or reaction byproducts can be separated from the product by simple filtration. Solid supported reagents and scavenger resins can provide an easy means of work-up for a solution phase reaction thereby eliminating the need for further purification techniques. A key advantage of using solid phase synthesis is that an excess of reagents can be used to drive reactions to completion. If this approach is adopted for solution phase, the problem of how to remove the excess reagent must be solved.

Over the past 20 years combinatorial chemistry has proved to be an important tool for the generation of large numbers of compounds required for drug discovery programmes. This two-part article covers the history and current developments of scavenger strategies in combinatorial chemistry and organic synthesis.
For example, if a substrate B is reacted with an excess of A, then the product AB will be contaminated with the remaining excess of A. Removal of this excess reagent upon reaction completion can be achieved by employing a suitable scavenger resin. The scavenger resin is added and reacts with the excess A, resulting in A being covalently bonded to the resin. Filtration separates the solution of product AB from scavenger resin sequestered A (Scheme 1).

Probably the most important advantage in using a functionalised polymer as a scavenger to remove excess reagents or byproducts is the simplification of product work-up, separation and isolation. The need for complex separation, extraction and chromatographic techniques is replaced by simple filtration. With linear polymers, techniques such as precipitation, sedimentation and ultrafiltration can be used. In addition, resins provide the opportunity for automation and thus high-throughput synthesis.

The most important and obvious disadvantage is the additional cost in using a supported scavenger. This might be well offset by the potential advantages, particularly if the scavenger can be regenerated. In addition there is always a possibility that the desired product itself may undergo a side reaction with the scavenger. A report in the early 1980s lists dozens of polymeric reagents that have found applications as catalysts, protecting groups, substrate carriers, analysis (sensors), ion exchange, detection of reaction intermediates, chromatography, enzyme immobilisation and others. Polymeric phosphine reagents, sulfonium salts, halogenating agents, redox, acylating and alkylating reagents, and polymer bound nucleophiles can all be used, in principle, as scavengers as well as for organic synthesis. In two parts, this article will focus on scavenger strategies in combinatorial chemistry and organic synthesis over the past 25 years, including:

### Part 1
- Polymeric scavengers
- Reactive filtration

### Polymeric scavengers

In 1997, the concept of complementary molecular reactivity and molecular recognition was introduced as a method of purification for parallel solution phase combinatorial library generation. This technique is now more commonly known as scavenging and was proposed to remove excess reagents or byproducts in combinatorial library generation. Polymeric scavengers are typically electrophilic or nucleophilic in nature and are designed and used to sequester specific reagents. They are also known as ‘quenching agents’ or ‘sequestering agents’.

![Scheme 1: Scavenger resins to assist in the removal of excess reagents](image1)

![Scheme 2: An early example of polymer scavenging of the allergen isoalantolactone](image2)

![Scheme 3: Multi-step synthesis using polymeric scavengers](image3)
In 1980, Frechet et al exploited the use of an insoluble polymer bound nucleophilic primary amine to selectively bind and remove α-methylene-g butyrolactone allergens from complex mixtures. Contact dermatitis results from an allergic reaction with sesquiterpene lactones, but these potentially harmful compounds can be effectively removed by scavenging. A dilute solution of the allergen such as isoalantolactone and scavenger polymer was stirred at room temperature for 24 hours to effectively remove typically >95% of the allergen (Scheme 2).

Solid supported nucleophiles and electrophiles have been used to simplify the work-up and purification of parallel non-peptide small molecule libraries. The authors prepared ureas, thioureas, amides, sulfonamides and carbamates utilising a nucleophilic scavenging agent to remove the excess isocyanate, acyl chloride or sulfonyl chlorides following simple filtration (Table 1, entry 1).


This work also demonstrated the use of an electrophilic polymer supported isocyanate to sequester an excess of secondary amine following alkylation with alkyl halides and epoxides (Table 1, entries 2, 3).

In the same report, multi-step sequences were carried out providing urea products in high purity and yield following the sequential use of polymer supported scavenger reagents (Scheme 3).

Table 1 The use of supported nucleophiles and electrophiles for purification of parallel non-peptide small molecule libraries

<table>
<thead>
<tr>
<th>entry</th>
<th>limiting reagent</th>
<th>excess reagent</th>
<th>scavenger</th>
<th>solvent/ temp.</th>
<th>representative product</th>
<th>yield (%)</th>
<th>purity (HPLC)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>R1R2NH</td>
<td>R3RCOCl²</td>
<td>NH₂</td>
<td>CH₂Cl₂/RT</td>
<td>(see text)</td>
<td>87%</td>
<td>94%</td>
</tr>
<tr>
<td>2</td>
<td>R1R2NH</td>
<td>R3</td>
<td>NCO</td>
<td>MeOH/RT</td>
<td>(see text)</td>
<td>94%</td>
<td>93%</td>
</tr>
<tr>
<td>3</td>
<td>R3O₂⁻</td>
<td>R1R2NH</td>
<td>NCO</td>
<td>CH₂CN/30-40°C</td>
<td>(see text)</td>
<td>96%</td>
<td>&gt;95%</td>
</tr>
<tr>
<td>4</td>
<td>R1NH₂</td>
<td>R2CHO</td>
<td>(see text)</td>
<td>(see text)</td>
<td>(see text)</td>
<td>73%</td>
<td>90%</td>
</tr>
<tr>
<td>5</td>
<td>R1R2NH</td>
<td>R3RCOCI</td>
<td>(10% HOAc-C₂H₅OH/RT)</td>
<td>(see text)</td>
<td>(see text)</td>
<td>82%</td>
<td>&gt;95%</td>
</tr>
</tbody>
</table>

a) typically 1.25-2-fold excess. b) piperidinomethyl polystyrene or other solid-supported base is added as an acid scavenger. c) acid chlorides or chloroformates. d) reaction was diluted with 2 volumes of CH₂Cl₂ prior to scavenging at room temperature.

e) X-halide, sulfonate ester. f) purity estimated by ¹H NMR.

Reactive filtration
Most commercial scavenging resins are available in bead form and are easily prepared, widely used and have good mechanical stability. However, drawbacks include size variations in the resin and slow
diffusion through the pores containing the reactive sites as well as handling challenges such as electrostatic charge that make automation difficult. Tripp et al developed a reactive filtration technique involving grafted macroporous polymer monolithic disks as an alternative to beads that can be used in the purification of combinatorial libraries. Polyethylene encased porous poly(chloromethylstyrene-co-divinylbenzene) disks were prepared by polymerisation in a cylindrical glass mold and cut to a disk format (Figure 1).

Following attachment of a free radical azo initiator, the polymerisation of 2-vinyl-4,4-dimethylazlactone was initiated from the surface (Scheme 4).

The use of these disks as scavenging filters to remove various amines from solutions in flow-through operations was demonstrated by effective removal of amines in a very short period of time from their solutions in a variety of solvents including alcohols and water (Scheme 5, Table 2).

There are two important requirements for monoliths in flow through systems (i) high permeability to allow high flow through rates and (ii) a high loading capacity. However, high permeability is usually obtained with large pore size which results in diminished loading capacity. This was overcome by grafting a functional polymer on to the surface of the monoliths with relatively large pore size which allowed for good permeability without compromising loading. Reactive filtration flow-through procedures remove the excess of undesired reagents from solutions in a short amount of time and complement solution phase combinatorial library generation.

An alternative to grafting is to polymerise the continuous phase of an internal phase emulsion. This technique produces a material called PolyHIPE which has a more open permeable structure and a high surface area (Figure 2). Monolithic polymer supports and scavengers were prepared via nucleophilic displacement of chloride in poly(4-vinylbenzyl chloride-co-divinylbenzene) PolyHIPE materials. Reactions of monolithic PolyHIPE with tris(2-aminoethyl)amine, 4-aminobutanol, tris(hydroxymethyl)aminomethane, morpholine and hexamethylenetetramine led to functionalised polymers with amino and hydroxyl functionalities with high degrees of conversion. 4-Chlorobenzoyl chloride was efficiently and rapidly scavenged from solution by the tris(2-aminoethyl)amine derivative of monolithic poly(4-vinylbenzyl chloride-co-divinylbenzene) PolyHIPE at ambient temperature.

Scavenging experiments used resin with 5.3mmol of NH/NH₂ groups per gram to sequester 4-chlorobenzyl chloride from solution; a

<table>
<thead>
<tr>
<th>AMINE</th>
<th>SOLVENT</th>
<th>AMOUNT SCAVENGED %</th>
</tr>
</thead>
<tbody>
<tr>
<td>benzylamine</td>
<td>tetrahydrofuran</td>
<td>74.7</td>
</tr>
<tr>
<td>phenethylamine</td>
<td>tetrahydrofuran</td>
<td>76.9</td>
</tr>
<tr>
<td>butylamine</td>
<td>dichloromethane</td>
<td>78.0</td>
</tr>
<tr>
<td>diethylamine</td>
<td>dichloromethane</td>
<td>90.1</td>
</tr>
<tr>
<td>3,5-dimethylaniline</td>
<td>tetrahydrofuran</td>
<td>47.6</td>
</tr>
</tbody>
</table>

Conditions. Reaction mixture: 0.2mmol of t-butyliisocyanate, 0.3mmol of amine, 1.5mL of solvent; porous disc 5x3mm diameter; grafted with 20% 2-vinyl-4,4-dimethylazlactone and 2% DVB; flow rate 3mL/h, residence time 8min.
3.35-fold molar excess of amino groups was used (Scheme 6).

After one-hour reaction time, the acid chloride was no longer detectable in the mixture. A similar experiment was performed under flow through conditions. A solution of 4-chlorobenzyl chloride in dichloromethane was passed through a column containing a mono(2-aminoethyl)amine derivative of vinyl benzyl chloride/divinylbenzene (VBC/DVB) PolyHIPE. At a flow rate of approximately 20mL/h and ambient temperature, 86.8% of the acid chloride was scavenged after the first pass-through of the solution, increasing to 98.5% after the second-pass through of the same solution. For comparison, the scavenging ability of a commercial trisamine resin (Argonaut PS-Trisamine, loading 3.1mmol/g NH/NH2 by elemental analysis) was found to be slower: 82% of acid chloride was scavenged after two minutes, 90% after 10 minutes and 99% after 30 minutes. These preliminary results indicate that highly permeable monolithic PolyHIPE supports are advantageous in solution phase organic synthesis. The monolithic format simplifies reagent transfer and other manipulations, furthermore flow-through procedures allow more rapid transformations.

**Ion exchange scavengers for product purification**

Solid phase extraction is a purification technique that temporarily sequesters the product or byproduct to the solid phase. Normal phase, reverse phase and ion exchange chromatography are all variants of solid phase extraction. Ion exchange resins provide a useful method of purification for the separation of ionic compounds.
Cationic and anionic resin washes using ion exchange resins are readily automated with conventional liquid handling robotics for high throughput sample purification. This was exploited for preparation and purification in the parallel synthesis of a library of amide analogues (Scheme 7). More than 225 analogues were prepared by this automated procedure in an average yield of 75% and an average HPLC purity of 90%.

A related report describes the use of ion exchange resins as scavengers for parallel solution phase amide libraries. The authors investigated the use of nine different basic ion exchange resins in the purification of amides derived from acid chlorides and found that Amberlite IRA-68, a weakly basic resin, provided products of highest purity (>99%) following the reaction, the excess acid chloride was quenched with water and the basic ion exchange resin absorbed the resulting carboxylic acid from solution leaving behind the pure amide product (Scheme 8).

A solid phase extraction method using Dowex 1x8-400 format anion exchange resin was used for the capture of carboxylic acids in a 96-well parallel array. For example, a reaction between compounds A-X and Y-B-CO₂H in the presence of suitable coupling reagents resulted in a mixture containing the product A-B-CO₂H as well as reagent and X-Y byproducts (Scheme 9).

Addition of the anion exchange resin extracted the carboxylic acid from the mixture to give the resin bound A-B-CO₂⁻ (II). The non-ionic impurities were easily removed by filtration and solvent washing of the resin. The purified product A-B-CO₂H was then obtained after treatment of the resin (II) with a volatile solvent acid such as HCO₂H. A 12-membered carboxylic acid test library was prepared utilising the Stille coupling and purified using the DOWEX 1x8-400 formate resin to give products in an average (1H NMR determined) yield of 49% and an average HPLC purity of 95% (Figure 3).

Incompatible functional groups such as acids and bases can co-exist in the same reaction vessel when used in resin format. This is believed to be possible because of the relative isolation of the functional sites within the bead. The authors demonstrated this with the parallel Moffat oxidation of hydroxyethylamines to ketones using an amine encoded diimide (Scheme 10). A simple filtration provided the ketone products with no detection of starting material or reagent byproducts by spectroscopic analysis.

Polystyrene DVB supported derivatives of tris(2-aminoethyl)amine and methyl isocyanate can be...
used to quench excess reactants from crude reaction products of the solution phase parallel synthesis of ureas, thioureas, sulfonamides, amides and pyrazoles (Scheme 11). The products were isolated by a single filtration followed by solvent evaporation. The mechanical simplicity of this methodology allows the rapid parallel purification of crude reaction products, single compounds or mixtures, obtained via solution phase combinatorial chemistry. Since these resins are expensive, they are particularly useful for small-scale work where the labour, solvent and silica gel savings are considerable.

A PSQ methodology was used for the parallel preparation and purification of dihydropyridones and a subsequent ‘libraries from libraries’ approach gave aminopiperidines. The dihydropyridone scaffold was assembled via a solution phase acid catalysed hetero Diels-Alder reaction. The procedure reported by Affymax for imine library synthesis was used. An equimolar mixture of aldehyde and primary amine was stirred for one hour in triethylorthoformate and the solvent was evaporated. After evaporation, the resulting imines were used directly in the Lewis catalysed hetero Diels-Alder reaction with Danishefsky’s diene. The polymer supported polyamine removes the byproduct diene and any unreacted imine giving crude product yields of 50-95% and purities of 80-95% (Scheme 12).

Nicolaou et al also reported a ‘libraries from libraries’ approach for the creation of diverse natural product like libraries of benzopyrans. An initial primary benzopyran library was generated using a solid phase split and pool synthesis and a directed sorting technique (Scheme 13). This primary library was organised into a 96-well format after cleavage resulting in one compound per well. A suitable epoxidising agent (volatile DMDO) was then added to each well to give the corresponding epoxides which were subsequently reacted with various nucleophiles including alcohols and amines to generate a second library of ring opened epoxides. Any unreacted excess nucleophiles were then scavenged, for example the excess amine was removed with a polymer bound isocyanate while excess alcohols were readily evaporated. A third generation library was possible via derivatisation of the ring-opened epoxides upon reaction with electrophiles. This included acetylation of the resulting secondary alcohol, with scavenging of the excess acetylating agent with polymer bound tris(2-aminoethyl)amine. Another derivative involved the resulting secondary amine (formed from reaction of the epoxide with a primary

Scheme 10: The parallel Moffat oxidation of hydroxyethylamines using an amine-encoded diimide

Scheme 11: Pyrazole synthesis with polymer-supported quenching purification (PSQ)
amine) and isocyanate, the excess of which was scavenged with a polymer bound tris(2-aminoethyl)amine. The scavenger resins were removed by filtration and the products obtained after concentration.

Taddei et al developed a soluble supported scavenger for sequestering alcohols, thiols, triphenylphosphine and triphenylphosphine oxide (Scheme 14).

Trichlorotriazine was reacted with MeO-PEG-OH (Mw 5000) to give a PEG-dichlorotriazine (PEG-DCT) that was used as a soluble electrophilic scavenger20. PEG-DCT was added at the end of reactions to completely remove nucleophilic reagents or byproducts. The reaction was considerably faster than with Wang resin-based systems (45min vs 12h). After precipitation of the polymer with diethyl ether, the desired product was isolated by filtration and evaporation. A disadvantage is that the PEG loading is low (0.2mmol/g), but the trichlorotriazine component is quite cheap.

Marsh et al developed novel high loading scavenger resins functionalised with triazine dendrimers (Figure 4)21. These resins gave comparable efficiency in acid chloride scavenging to commercial resins at significantly lower concentration due to the increase in the number of active functional groups.

These methods are suitable for medicinal chemistry applications. In 2002, Maltais et al reported the parallel solution phase synthesis of a new family of type 3 17ß-hydroxysteroid dehydrogenase inhibitors that were purified via polystyrene-based scavenger resins (methylisocyanate, piperidinomethyl, aminomethyl) (Scheme 15)21.

Sequestration enabling techniques
In some cases, it is difficult to remove reagents from solution phase reactions since a suitable scavenger does not exist or the reagent does not have an appropriate functionality. Further functionalisation can be used to convert the reagent into a form that can be scavenged with an ion exchange resin.

Parlow et al demonstrated the use of tetrafluorophthalic anhydride as a sequestration enabling reagent (SER) (Scheme 16)22. This allows for the derivatisation of moderately reactive amines and subsequent sequestration by basic scavenger resins. For example, aniline was reacted with the electrophiles benzyl chloroformate, benzoyl chloride, benzenesulfonyl chloride and phenylisocyanate. Tetrafluorophthalic anhydride was added to the reaction mixture after 24 hours. The polyamine scavenger resin was then added to sequester the
carboxy tagged aniline derivative, the excess SER, excess electrophiles and byproduct HCl. Following filtration and evaporation the products were obtained in high purity. A drawback with tetrafluorophthalic anhydride is its slow rate of conversion with electron-deficient anilines.

The use of ‘catch-and-release’ strategies for the preparation of heterocycles is accompanied by a cyclisation-cleavage step. Parts of the linker can become part of the product which is released into solution. A gel-type polystyrene-sulfonyl-hydrazide resin which was originally developed for carbonyl scavenging can also serve as a linker for carbonyl compounds in the solid phase synthesis version of the Hurd-Mori reaction for 1,2,3-thiadiazole synthesis (Scheme 17)\(^2\)3. A recent review describing rapid purification methods for combinatorial libraries also provides a useful list of scavenger resins and sequestration enabling reagents\(^2\)4. In the forthcoming Part 2 of this article, alternatives to traditional scavenging methods will be introduced. These include new resins, the use of polymeric and fluorous scavenger reagents and applications of microwave technology for accelerating scavenging reactions.

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Combinatorial Chemistry

Scheme 16: The use of tetrafluorophthalic anhydride as an SER

Scheme 17: 1,2,3-Thiadiazoles prepared via ‘Resin Capture’ of ketones

References
The loading capacity is of considerable importance when choosing a scavenger resin for purification as higher loadings allow the use of less reagent which minimises cost. Therefore the search for higher loading alternatives that are cheap and easily handled has become increasingly important. Furthermore the majority of polymeric scavenger reagents consist of reactive functional groups linked to poly(styrene-divinylbenzene) that require suitable solvents to swell the resin to access the reactive sites. Solvents with good swelling properties include DMF, dichloromethane and THF. Now a number of alternative resins exist that can be used with a broad spectrum of solvents.

Alternatives to polystyrene-based scavengers include ROMPGEL scavengers. Arnauld et al reported a ring-opening metathesis (ROM) polymer supported anhydride as a selective high-loading scavenger for amines and hydrazines. The ROMPGEL polymer is readily synthesised from commercially available and inexpensive materials. Ureas, thioureas, amides, sulfonamides, carbamates, imines and hydrazones were obtained in high purity and yield after sequestration of the excess amine by the ROMPGEL scavenger (Scheme 1).

Another report uses a macroporous, highly crosslinked poly(styrene-divinylbenzene) as a base matrix for solid phase scavengers (Scheme 2). This matrix is superior to Merrifield resins when non-wetting solvents such as acetonitrile are used. A 12-membered test library of sulfonamides was generated in high purity.

Bradley et al developed a route for the large scale preparation of magnetic, chloromethylated functionalised polystyrene-based resin beads for solid...
phase synthesis and reaction scavenging\textsuperscript{3}. The beads compared favourably with the standard Merrifield in several reactions and showed the same swelling properties. The magnetic beads were used as scavengers in the preparation of sulphonamides and were removed from solution with a small array of magnets.

Most recently, functionalised silica gels have proved to be attractive alternative scavengers. Modified silica gels produced by Silicycle (www.silicycle.com) and HP (combizorb) show a broad solvent compatibility, do not swell and are considerably less expensive than traditional polystyrene based scavengers. Amino silica gel has been used to remove excess acyl chloride in the synthesis of 2,9-disubstituted guanines (Scheme 3)\textsuperscript{4}.

Macquarrie et al prepared high loading amino and diamino functionalised silica gels that were easily synthesised and used to efficiently scavenge a range of electrophiles including phenylisocyanate, benzene sulfonyl chloride and benzoyl chloride (Schemes 4, 5)\textsuperscript{5}.

Other silica-based scavengers included thiols, isocyanates, epoxides, triamines, imidazoles, dimethyl amine, isothiocyanates, silane, pyridine, acid chloride, sulfonyl chloride, imine, sulphonamide and diol. A caveat is that scavengers of this type do not resist aqueous base (at pH>12).

Polyaromatic Scavenger Resins (PAHSR)

The development of a chemically relatively inert pyrene anchor with a reactive scavenger attachment allowed unreacted reagents and impurities to be removed from a reaction by adsorption of the PAHSR to charcoal and simple filtration (Scheme 6)\textsuperscript{6}. However, during this research the authors became aware of a sensitivity to the pyrene reagent that caused allergic dermatitis that was enhanced by sunlight.

Atom transfer radical polymerisation (ATRP) provides a method for the controlled synthesis of polymers. One drawback however is the contamination of the polymer by ligand/metal when standard homogenous catalysis is used. Wilcox et al developed ‘Precipitons’ for copper catalyst removal in ATRP (Scheme 7, Figure 1)\textsuperscript{7}. Precipitons are E/Z-isomerisable compounds that can be attached to a reactant. After the reaction is complete, they can be isomerised to cause precipitation of the attached product. Nitrogen ligands bearing Precipitons were prepared and used in ATRP. After polymerisation was complete, the polymer solution was exposed to UV light to precipitate the Precipiton lig-
and CuBr complex. However, the ligand in this system cannot be reused or recycled, further work to recycle the Precipiton would provide an attractive method for the removal of metals from ATRP systems.

Ligands 3 and 5 were successfully used to remove CuBr. Upon completion of the polymerisation, the solution was cooled and exposed to UV radiation for two hours. The precipiton ligand precipitated and remained complexed with the Cu catalyst. The precipitated product can be isolated by decantation, filtration or sedimentation. The copper content of the polymer solution was determined by UV spectroscopy and indicated no detectable copper based on the lack of absorbance at 680nm.

**Fluorous quenching scavenger protocols**

The fluorous phase can be regarded as a third phase that is immiscible with both aqueous and most organic phases. Organic compounds are typically not soluble in fluorous solvents but can be rendered soluble by the incorporation of a fluorous tag. The purification is based on a fluorous/organic liquid-liquid extraction. Curran et al reported the use of a fluorous amine scavenger in the automated solution phase parallel synthesis of a small library of ureas (Scheme 8). The
Ureas were synthesised from organic amines and excess isocyanates. The fluorous amine scavenger sequesters the excess isocyanate and the resulting adduct is soluble in the fluorous phase that can be removed by a fluorous-organic extraction. The urea products were obtained in high yields and purities.

Natural products remain a significant source of promising lead structures for drug development. In recent years, an expansion of the structural diversity pool by preparation of libraries of natural products or natural product-like molecules has become a major focus of libraries of combinatorial chemistry. Wipf et al devised an efficient synthetic strategy for the preparation of 6-compound mixture combinatorial libraries that incorporated important structural elements of the marine natural product Curacin A. Fluorous trapping was used to streamline purification of the heterogenous multicomponent reaction products after the diversification step of the library synthesis to provide structurally defined mixtures. Subsequent biological testing warranted synthesis of the individual components with identification of some of the most potent synthetic curacin A analogues to date (Scheme 9).

**Scheme 8:** Fluorous quenching scavenger protocols for the purification of solution phase parallel urea libraries

**Figure 1:** Precipitons for copper catalyst removal in ATRP
Microwave-assisted scavenging protocols

As scavenging techniques often require long reaction times due to the heterogeneous nature of the reaction conditions any technology that can speed up the process is of considerable interest. Surprisingly, there are relatively few reports of the use of microwave technology used in conjunction with scavenging techniques. However Kappe et al recently reported the solution phase synthesis of Nß-acylated dihydropyrimidines utilising microwave heating in both the synthesis and purification (scavenging) steps (Scheme 10). After microwave promoted acylation with excess anhydride in sealed vessels at 130-180°C in 10 minutes, the authors examined the use of polymer supported amine scavenging reagents to remove any remaining excess anhydride and bisacylated byproduct. The polymer bound diamine 6 and silica based diamine 7 were found to be similar in efficiency with the main advantage being the reduction in time required for excess anhydride quenching from 4-6 hours to 5-7 minutes.

Conclusion

While solution phase combinatorial chemistry is far from being optimised, the key to further improvements in efficiency is not to abandon it altogether but to combine the advantages of solution phase with those of the solid phase. Both the preparation stage, the planning of the synthetic strategy and the procurement and weighing of reagents, as well as the reaction workup stage are serious bottlenecks in high throughput synthesis. Due to the importance of purification techniques both for combinatorial chemistry and natural product synthesis, the development of general scavenging strategies will undoubtedly continue to be refined. This will involve the development of...
higher loading, cheaper solid supported scavengers of alternative materials and physical forms. In conjunction with accelerated technologies including microwave protocols, the use of scavengers will ensure that purification of compounds will no longer be a major bottleneck in drug discovery projects.

Acknowledgement

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**Scheme 10: Microwave assisted scavenging**

![Scheme 10: Microwave assisted scavenging](image)

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