The Current Status of Heterocyclic Combinatorial Libraries

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I. Introduction

One of the fundamental objectives of organic and medicinal chemistry is the design, synthesis, and production of molecules having value as human therapeutic agents. Until 1920−1940, therapeutically useful compounds were usually identified and produced from plant, animal, or fermentation sources. The most dramatic of such synthetic discoveries was the synthetic production of penicillin, which has saved innumerable lives and decreased human suffering worldwide. The successes of organic and medicinal chemistry have fundamentally changed human therapeutics over the past 30−40 years by the steady design, preparation, and improvement of compounds that affect virtually all human medical conditions. While of immense importance, drug discovery approaches remained relatively static from 1945 to 1985. Typically, drug discovery involved the individual synthesis of hundreds to thousands of analogs of a weakly active lead compound in an attempt to enhance the original activity, bioavailability, and selectivity, while at the same time decreasing its toxicity. It has been estimated that, for each new drug approved, 1000 man-years of effort was required and 10 000 individual compounds had to be prepared by highly skilled medicinal chemists. The recent introduction of readily accessible synthetic combinatorial libraries (SCLs) of compounds has resulted in a fundamental shift in how drug discovery is carried out. This revolutionary concept enables hundreds to thousands of times more compounds to be synthesized and screened compared to traditional approaches.[1−5] For example, combinatorial chemistry allows a single chemist to synthesize all 1000 possible individual analogs of the quinazolinone pharmacophore **1** (Figure 1), with R^1, R^2, and R^3 each having 10 different functional groups, in 2−6 weeks. Using traditional approaches, this effort would take 10 medicinal chemists a full year to accomplish.

All of the underlying concepts used in SCLs have their origin in the field of peptide chemistry. Merrifield's solid phase synthetic approaches presented in 1963,[6] initially used and optimized for peptides, are the conceptual basis for all synthetic combinatorial approaches. Geysen's group and our laboratory made the first pragmatic innovations enabling the combinatorial synthesis of large compound arrays on pins and standard resins, respectively[7,8] in 1984/1985, and Fodor et al. first prepared combinatorial libraries on glass surfaces in 1990.[9] Major theoretical[10] and practical breakthroughs[11−13] in the combinatorial synthesis of mixtures occurred in 1986 and 1991, which further set the foundation for later advances. These approaches and concepts have now been broadly applied to the synthesis of heterocycles and other classical organic compounds.[4,5,14] This review traces the evolution and evaluation of combinatorial libraries of heterocyclic compounds and provides descriptions of the deconvolution strategies used for the identification of individual compounds from soluble libraries composed of mixtures of compounds.

A. Solid Phase Organic Synthesis

The primary focus of synthetic organic and medicinal chemists has been the synthesis of individual compounds using traditional solution chemistry approaches. While traditional approaches have been, and remain, highly successful, they involve purification of each intermediate compound in the synthesis, making them time-consuming and expensive, and ultimately yield a limited number of compounds (typically 25−100 compounds per year per chemist). Solid phase synthetic chemistry, first developed by

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Adel Nefzi was born in Tunis (Tunisia) in 1963. He studied chemistry at the University of Tunis and received his Ph.D. from the Institute of Organic Chemistry, University of Lausanne, in 1995, where he worked in the laboratory of Manfred Mutter. His doctoral work focused on pseudoprolines as a solubilizing, structure-disrupting protection technique for peptide synthesis. Following postdoctoral studies at Torrey Pines Institute for Molecular Studies, he is currently an assistant member working on the design and synthesis of small molecule and heterocyclic combinatorial libraries.

John M. Ostresh was born in Illinois in 1959. He received his B.A. in chemistry from Southern Illinois University in 1981. He received his M.S. in chemistry from the University of California, San Diego, in 1986. He is the Director of Chemistry at Torrey Pines Institute for Molecular Studies and is the coinventor of the "libraries from libraries" concept. His current research involves the development of small molecule combinatorial libraries.

Merrifield for peptides,[6] has been successfully employed over the past 30 years for the synthesis of peptides,[15−18] peptidomimetics,[19−23] oligonucleotides,[4,24] and oligosaccharides.[25−27] Since reactions on polymer supports enable chemical reactions to be driven to completion (often >99.8% yields per step) and are readily automated, combinatorial chemistry has been carried out primarily by solid phase synthesis.[28] The community of medicinal chemists has now embraced the power of these solid phase approaches. This understanding is leading to a renaissance in organic synthesis. As with many paradigm shifts, combinatorial chemistry is a consequence of, and a response to, a specific need. This is a need for new compound diversities, which in turn has been prompted by the explosion of new biological targets that continue to be identified through modern molecular biology methods.

The solid phase synthesis (SPS) of compounds other than peptides was first presented by Rapoport and Leznoff. Crowley and Rapoport studied the

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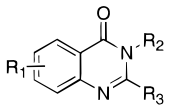

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Figure 1. Representation of a quinazolinone combinatorial library **1** having three positions of diversity, R_1, R_2, and R_3.

Dieckman cyclization on the solid phase.[29] Leznoff and co-workers reported the synthesis of natural products such as insect sex attractants and unsymmetrical carotenoides.[30−32] Both of these pioneers published reviews on the use of these approaches.[29,33] Since this early work, advances in solid phase chemistry have been focused primarily in the area of peptide synthesis. These broadly applicable approaches have virtually all stemmed from the need for, and importance of, peptides for basic research and drug discovery. The SPS tools available prior to 1990 have been extensively reviewed.[15] Winter recently reviewed the importance of the correct choice of supports for successful synthesis on solid supports.[34] Ellman's work[28,35−37] can be credited with alerting the pharmaceutical and medicinal chemistry community to the power of combinatorial solid phase synthetic approaches.

Early examples detailing the synthetic concepts and practical successes of combinatorial libraries made up of tens of millions of short peptides for the identification of lead compounds include work from this laboratory[11,38,39] on potential analgesics[40] and antibacterials[41,42] and studies by Owens and coworkers on the identification of HIV protease inhibitors[43] following the screening of peptide libraries.

Peptide combinatorial libraries have led to the identification of a wide range of bioactive peptides, including novel antibacterials,[41] potent agonists and antagonists to opioid receptors,[44−46] trypsin inhibitors,[47] compounds that inhibit melittin's hemolytic activity,[48] and antigenic peptides recognized by monoclonal antibodies.[49−52] Along with linear peptide sequences, our laboratory and other groups have also developed combinatorial libraries of cyclic peptides.[53−58] Potent endothelin antagonists were identified using a library of triamides by Terret and co-workers.[59] N-Substituted oligomers ("peptoids") have been synthesized by Simon and co-workers and have been shown to be quite stable to enzymatic hydrolysis.[60] In addition, peptoid libraries were shown to yield high affinity receptor ligands.[61]

B. Organic Reactions on the Solid Phase

Substituted heterocyclic compounds offer a high degree of structural diversity and have proven to be broadly and economically useful as therapeutic agents. The development of strategies for the synthesis of heterocyclic compounds on the solid phase is expanding as a greater understanding of how to successfully carry out such reactions is gained. Typically, combinatorial libraries containing several positions of diversity have been synthesized by the consecutive incorporation of multifunctional building blocks with orthogonal protecting groups. In the case of the first building block, the solid phase support has served as a protecting group for one functionality following incorporation. Upon deprotection of the orthogonal protecting group, subsequent building blocks were similarly incorporated until all positions of diversity were added. Since amide bond formation has been optimized thoroughly through the years, it has been used extensively in combinatorial synthesis.

A large number of functional groups can be derivatized using solid phase reactions, including amines, alcohols, aldehydes, ketones, and carboxylic acids. Many standard organic reactions have been adapted to solid phase chemistry. These include oxidation, reduction, nucleophilic substitution, nucleophilic addition, carbene insertion, Diels−Alder addition, condensations including Claisen and aldol, and catalyzed reactions such as Stille coupling, Suzuki coupling, and the Heck reaction for C−C bond formation.[62,63] A large variety of heterocyclic compounds has been synthesized via imine formation or using multicomponent condensation.

Imines are often used as intermediates in organic synthesis and are the starting point for chemical reactions such as cycloadditions, condensation reactions, and nucleophilic addition. The formation of imines via condensation of amines with aldehydes was first adopted for the reductive alkylation of resin-bound amino acids.[64−66] Imines have now been used as synthetic intermediates in the generation of a range of heterocyclic combinatorial libraries (Figure 2).

Multicomponent condensations such as the Ugi reaction[67] and the Biginelli condensation[68] are especially useful for the creation of diverse chemical libraries on the solid phase. Four-component condensation has been reviewed recently by Mjalli and

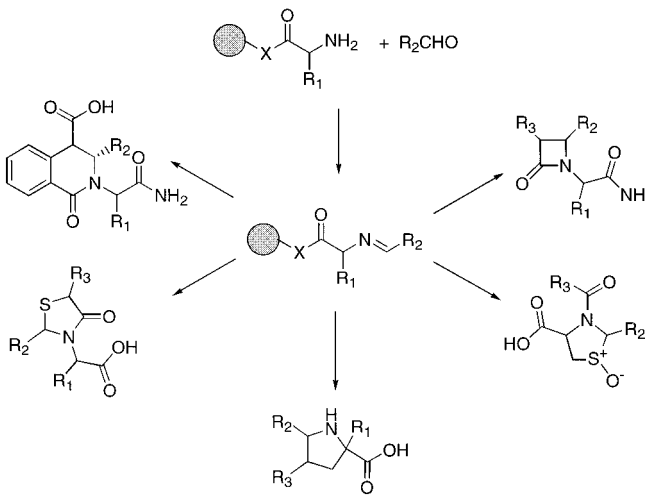


Figure 2. Imines as starting materials for the solid phase synthesis of heterocyclic compounds.

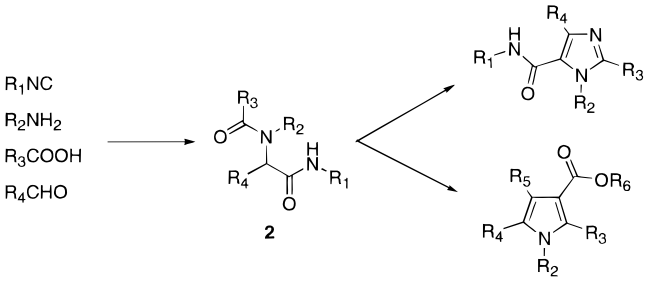


Figure 3. Multicomponent condensations on the solid phase.

Toyonaga for the synthesis on solid phase of small-ring heterocycles.[69,70] For example, the one-pot condensation of an amine and an aldehyde, followed by the addition of isocyanide and a carboxylic acid, provides a dipeptidomimetic *N*-alkyl-*N*-acyl-α-amino amide **2** (Figure 3) that can serve as a useful starting point for the synthesis of imidazoles and pyrroles, which are pharmaceutically acceptable compounds. In addition, the Biginelli dihydropyridine synthesis has been adapted recently to the solid phase by Wipf and Cunningham.[71] The importance of these multicomponent syntheses is that the adaptation to the solid phase has allowed the synthesis of single compounds versus multiple products in solution.

A partial list of the wide variety of reactions adapted to the solid phase are shown in Figure 4. A review of the recent literature involving solid phase organic reactions has been published by Hermkens and co-workers.[63]

II. Synthesis Methods

Two synthetic approaches, involving either the mixing of multiple resins or the use of mixtures of incoming reagents, are now widely used to incorporate multiple functionalities at diverse positions within an SCL.

A. Resin Mixtures

The "divide, couple, and recombine" (DCR) synthesis method,[11] also know as the "split resin" method,[12] was developed for use in the synthesis of peptide SCLs. This synthesis method, illustrated in Figure

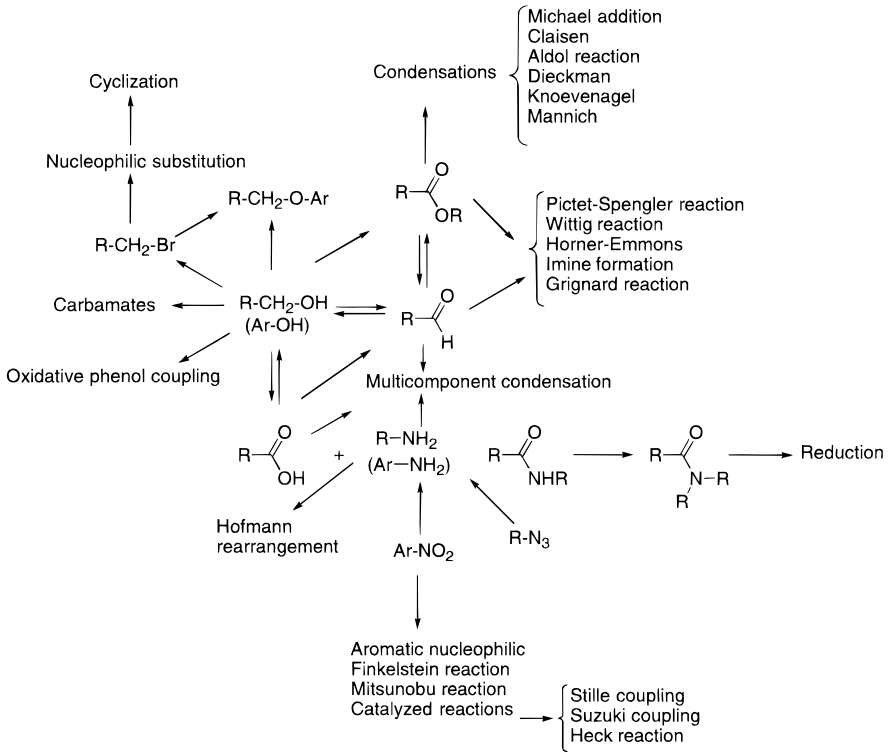


Figure 4. Nonexhaustive list of organic reactions adapted to the solid phase.

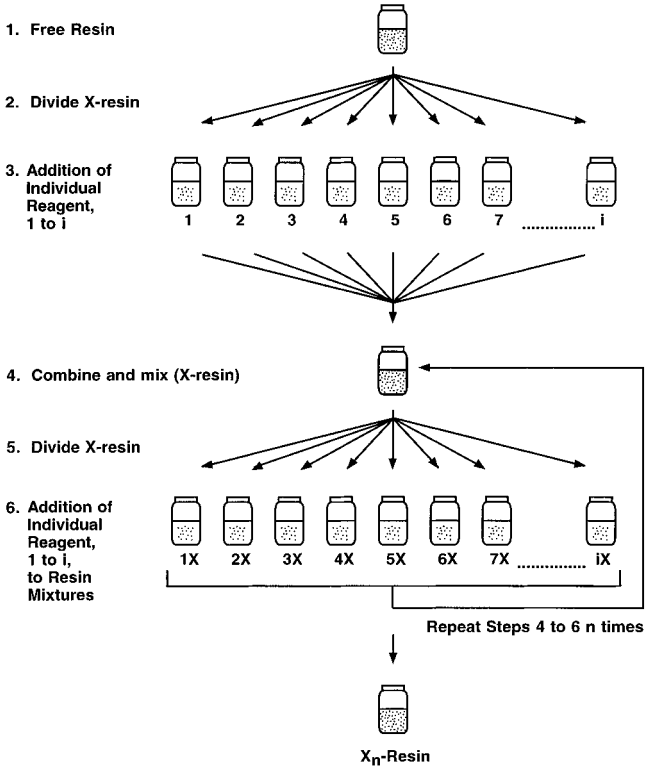


Figure 5. Illustration of the split-resin method of synthesis for combinatorial libraries.

5, involves the coupling of reactants to individual aliquots of resin followed by thorough mixing of the resin. This method allows the generation of approximately equimolar mixtures of compounds. Due to the statistical distribution of beads at each step, care should be used in determining the appropriate amount of resin to be used in the synthesis in order to ensure inclusion of all compounds in the library.[2,72] An important aspect to the DCR approach is that due to the physical nature of dividing and mixing the resin beads, each resin bead contains only one compound when the library is completed.[12]

B. Reagent Mixtures

A second synthetic approach, termed the "reagent mixture" method, generally uses a predefined ratio of reagents in excess to accomplish approximately equimolar incorporation of each reagent at a position of diversity.[73] The use of reagent mixtures requires a thorough knowledge of the mechanism and kinetics involved in the specific reactions being carried out. This method offers the advantage that a mixture of reagents can be readily incorporated at any position in a sequence. A large excess of incoming reagents is used such that pseudo-first-order reaction kinetics is observed. It is important that the relative reaction rates of the incoming reagents are approximately equal and relatively independent of the resin-bound reagents (i.e., similar nucleophilicity, no significant steric hindrance). We have found that this concept applies equally well to mixtures of incoming reagents such as aldehydes and carboxylic acids (unpublished results). We have recently applied the reagent mixture method to the synthesis of heterocyclic compounds, such as cyclic urea and cyclic thiourea libraries.[74]

A number of reports have been presented on the use of limiting reagents to accomplish the same result.[75,76] This method relies on initially reacting equal amounts of all reagents, equimolar relative to the resin, in order to obtain a resin-bound mixture. The reaction is then repeated using excess reagents in order to drive the reaction of the remaining unreacted sites to completion. Reasonable results can be obtained for the addition of one position of diversity. However, a major disadvantage to this

method is seen when incorporating more than one position of diversity. Incoming reagents can be preferentially consumed by particular resin-bound reactants whenever there are even small differences in reaction rates or relative reaction rates. Repetitive cycles using this method multiplies the problem, resulting in large deviations from equimolarity in the final products. We have successfully used the described reagent mixture approach for the synthesis of libraries of small organic molecules, such as cyclic ureas and thioureas,[74] while others in the field have predominantly used the resin mixing approach.

III. Deconvolution Methods

Three approaches are generally used for the structural deconvolution of active compounds from assay data using non-support-bound SCLs: iterative deconvolution,[11] positional scanning deconvolution,[38] and tagging.[77] Each approach has been used to identify individual active compounds in a wide variety of SCLs and assays.

A. Iterative Deconvolution Method

The iterative deconvolution method (Figure 6) is illustrated with a generic heterocycle containing four positions of diversity, designated OXXX (where O represents a defined position of diversity and X represents mixture positions).[11] The SCL is first screened to identify active mixtures. Since for each mixture within the library one position of diversity is defined, active mixtures suggest the importance of the functionality at that position. The remaining three positions are then identified sequentially through an iterative process of synthesis and screening.

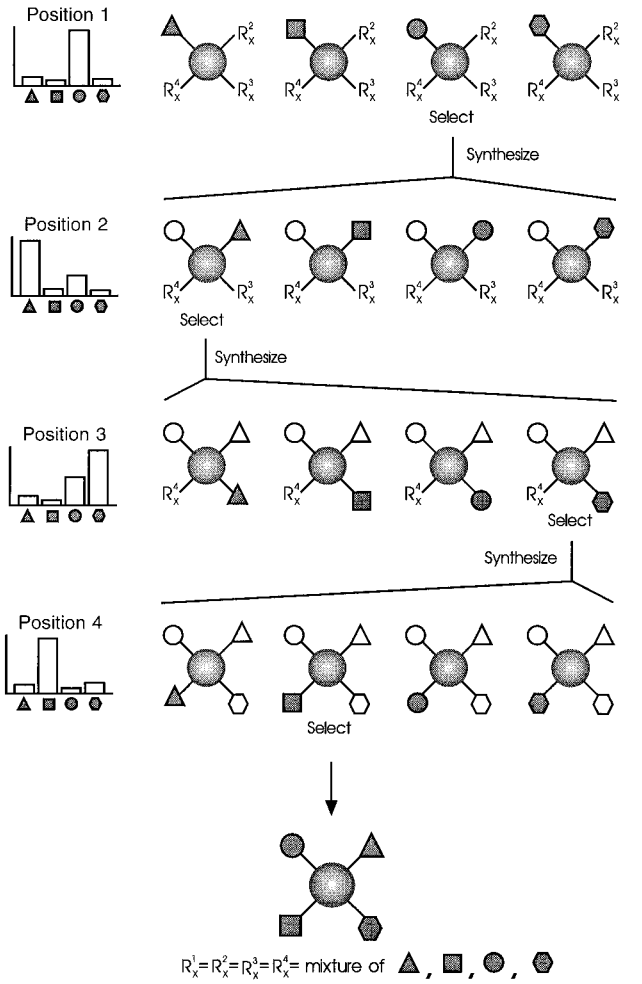


Figure 6. Generic representation of iterative deconvolution.

B. Positional Scanning Deconvolution Method

The positional scanning (PS) approach[38] is illustrated in the generic representation shown in Figure 7. It involves the screening of separate, single defined position SCLs to individually identify the most important functionalities at each position of diversity within a library. A complete PS-SCL having four positions of diversity consists of four sublibraries (designated OXXX, XOXX, XXOX, and XXXO), each of which has a single defined functionality at one position and a mixture of functionalities at each of the other three positions. The generic library shown contains 256 compounds ($4 \times 4 \times 4 \times 4 = 256$). The pooling of each sublibrary, which contain the same 256 compounds (4 mixtures of 64 compounds), would vary on the basis of the functionality at the defined position of that sublibrary. The structure of individual compounds can be determined from such a screening since each compound is present in only one mixture of each sublibrary. In theory, if

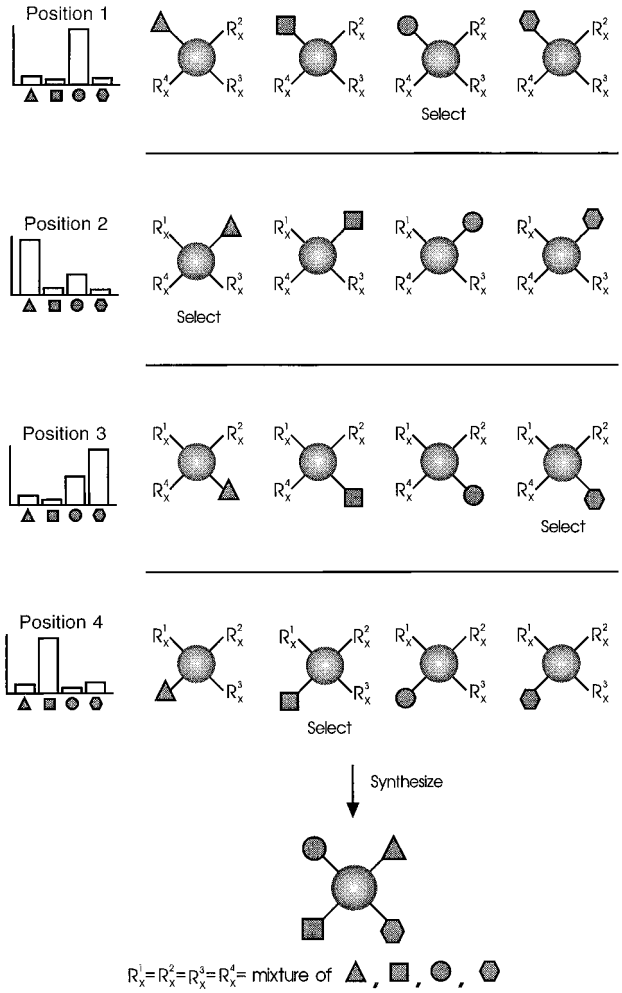


Figure 7. Generic representation of positional scanning deconvolution.

only one compound was active in the library, activity corresponding to that compound would be found in the one mixture of each sublibrary containing that compound. When considered in concert, the defined functionality in each mixture can then be used to identify the individual active compound responsible for the activity. In reality, the same result is seen, but the activity is generally due to the sum of more than one active compound. Anomalous results are seen if the activity is due to the sum of many weakly active compounds. PS-SCLs are generally prepared using the reagent mixture approach described above. Although the synthesis of PS-SCLs is theoretically possible with the DCR approach, in reality the labor involved makes the synthesis unfeasible. Freier and co-workers have performed a thorough examination of the theoretical and experimental aspects of iterative and positional scanning deconvolution.[78,79]

Déprez introduced a similar method of deconvolution termed orthogonal libraries.[80] In this method, instead of synthesizing sublibraries such that the number of libraries is equal to the number of positions of diversity, two sublibraries are synthesized in which compounds are pooled into mixtures based on two-dimensional matrices of the reagents used at each step. Libraries are synthesized such that each mixture in a sublibrary contains one and only one compound in common with each of the mixtures in the second sublibrary. A major advantage to this technique is that the resin splitting method can be used to prepare the library.

Since the resin mixing synthesis approach has been the method used for the synthesis of small organic molecule libraries, the iterative approach has been the primary deconvolution method used.

C. Tags

The concept of one compound per resin bead upon completion of a resin splitting synthesis can be exploited in the third approach to deconvolution of combinatorial libraries. In the tagging approach, an attached compound codes for the structure of interest (Figure 8). In general, resin linkers containing two orthogonally protected functional groups are used to allow the concurrent synthesis of both the library of interest and encoding compounds, which upon cleavage are sequenced or otherwise decoded to determine the structure of the compounds of interest. For each tagging approach, a compatible chemistry between the tags and compounds of interest has to be determined.

Kerr and Zuckermann described the alternating synthesis of peptides and compounds of interest using the resin splitting approach. Following screening of the resin-bound library, active compounds were determined by microsequencing of the resin-bound peptide.[81]

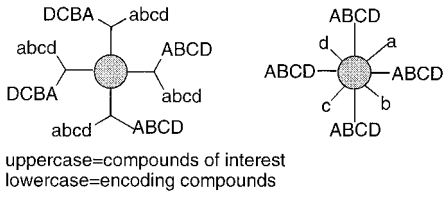


Figure 8. Generic representation of tagging strategies.

Lebl and co-workers described a similar scheme.[82] In addition, they have described the incremental release of small amounts of the library such that a solution-based assay can be used.[83]

Resin-bound assays were also used with the encoding scheme described by Ohlmeyer and co-workers.[84,85] Using a binary coding system, encoding polyhalobenzenes were added to a small amount of the available amine at each step of a split resin synthesis, which recorded both the reaction step and reagent used. The linker used for attachment of the tags could be photolytically cleaved and rapidly analyzed by electron capture gas chromatography. The major advantage of this method is that the encoding compounds are not oligomers.

Ni and co-workers[86,87] used secondary amines in a more chemically robust binary coding scheme. In this method, the secondary amines are incorporated using iminodiacetic acid. Following completion of the library, the tagging strand is hydrolyzed and the secondary amines dansylated and can be detected at sub-picomole levels using RP-HPLC.

Brenner and Lerner proposed the use of oligonucleotide tags.[88] The tag would be synthesized concurrently with the compounds of interest using the DCR approach. Following a resin-bound assay, structures could be determined using a panning strategy. Amplification of the the encoding oligonucleotide followed by sequencing would allow the structure and synthetic history of active compounds to be determined. This strategy was later reduced to practice by Nielsen and others in the same group[89] and independently by Needels and co-workers.[90]

Both Nicolaou[91] and Moran[92] described the use of encapsulated radio-frequency tags which, when combined with the split synthesis method, can be used to uniquely identify the synthetic history of each resin bead.

IV. Heterocyclic Compounds

A. Cyclic Compounds Containing One Heteroatom

1. Compounds Containing Nitrogen

a. Pyrroles and Derivatives. The synthesis of pentasubstituted pyrroles has been reported by Mjalli[69] using a multicomponent condensation. The condensation of a resin-bound amine to an aldehyde, followed by the addition of carboxylic acid and isocyanide, resulted in the formation of resin-bound *N*-alkyl-*N*-acyl-α-amino amides. Treatment with neat acetic anhydride or isobutyl chloroformate and triethylamine in toluene, followed by the addition of a series of acetylenic esters, provided the polymer-bound pentasubstituted pyrroles. The reaction proceeded via in situ cyclization of the intermediate via [3 + 2] cycloaddition with a variety of alkynes. An isomeric mixture of pyrroles in an approximately 4:1 ratio was obtained following release of the product from the resin with 20% TFA/DCM (Figure 9). The desired products were obtained in overall yield of 35−75% over eight steps, illustrating the power of solid phase synthesis.

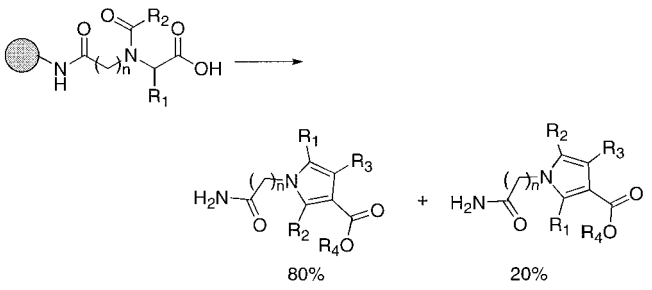
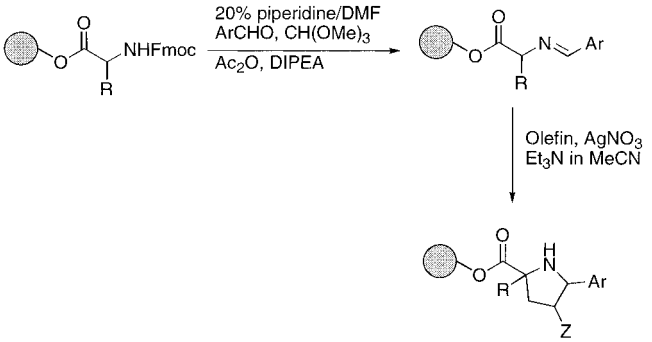
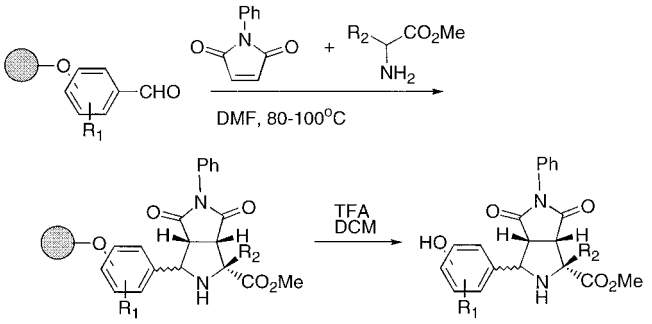


Figure 9. Solid phase synthesis of pyrroles via multicomponent condensation.

Scheme 1



Scheme 2



Murphy and co-workers reported the synthesis of pyrrolidine combinatorial libraries.[93] Starting from polystyrene resin-bound amino acids, the α-amino ester was condensed with aromatic and heteroaromatic aldehydes in neat trimethyl orthoformate to afford the resin-bound aryl imine. Pyrrolidine and pyrroline derivatives were obtained through cycloaddition of the 1,3-dipoles azomethine ylides to olefin and acetylene dipolarophiles (Scheme 1). A library of 500 compounds was reported. The screening of this library for in vivo inhibition of ACE led to the identification of 1-(3′-mercapto-2′(*S*)-methyl-1′-oxopropyl)-5-phenyl-2,4-pyrrolidinedicarboxylic acid 4-methyl ester as a potent ACE inhibitor that incorporates the mercaptoisobutyryl side chain.

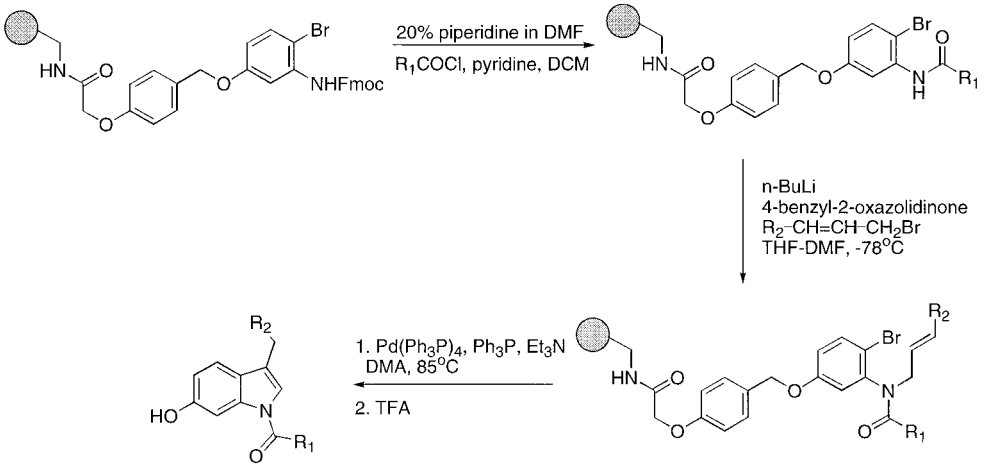
b. Proline Derivatives. Hamper and co-workers reported the solid phase synthesis of proline analogs via a three-component 1,3-dipolar cycloaddition of a resin-bound azomethine ylide[94] (Scheme 2). The attachment of hydroxybenzaldehydes to Wang resin via Mitsonubu coupling, followed by reaction with an α-amino ester and a maleimide, afforded the resin-bound proline analogs. The dipolar cycloaddition provides mixtures of diastereomers, which can be separated by HPLC.

c. Indoles. Mohan and Yun reported the solid phase synthesis of indole analogs via an intramolecular Heck reaction of polymer-bound aryl halides[95] (Scheme 3). The use of a variety of commercially available acid chlorides and allylic alkylating agents in the presence of lithium benzyloxazolidinone provided intermediates which were then subjected to Heck reaction conditions. The use of a catalytic amount of $Pd(Ph_3P)_4$ with Ph_3P and Et_3N in DMA at 85 °C under nitrogen for 5 h affords the desired indole analogs following cleavage from the resin.

d. *β*-Carbolines. First reported by Kaljuste and Unden,[96] the reaction of polymer-bound tryptophan with a variety of aldehydes and ketones under Pictet−Spengler conditions[97] has also been reported by Mayer and co-workers.[98] The *β*-carboline derivatives exhibited significant bioactivity.[99] Following incorporation of Fmoc-tryptophan, the condensation with an aldehyde or ketone under acidic conditions provided the *β*-carbolines in high yield and purity. The same strategy has been published by Yang and Guo[100] with the only difference being that Boc-tryptophan was used (Scheme 4).

e. Pyridines and Derivatives. Nitrogen heterocycles are important pharmacophores in drug design, especially pyridine derivatives, which are among the most frequently cited heterocyclic compounds. The pyridine structure is found in various therapeutic agents, including numerous antihistamines, as well as antiseptic, antiarrythmic, antirheu-

Scheme 3



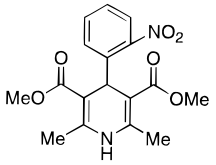


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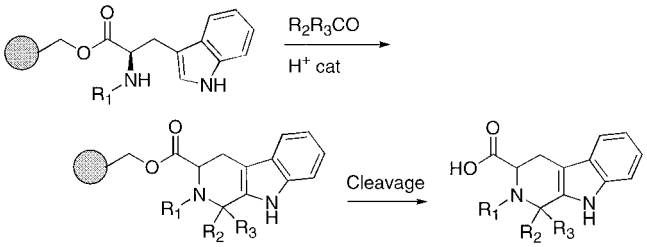
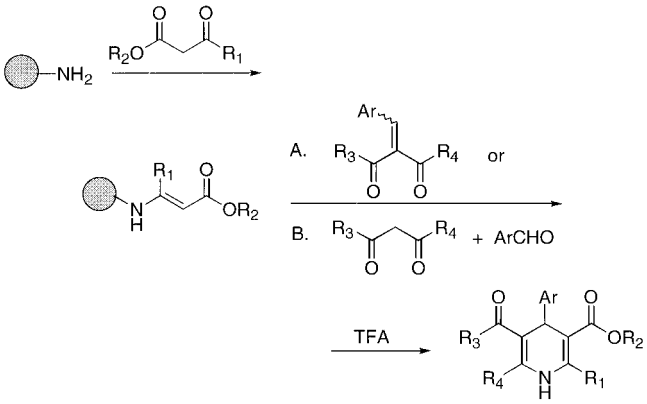
Figure 10. Structure of nifedipine (**3**).

Scheme 4



Scheme 5



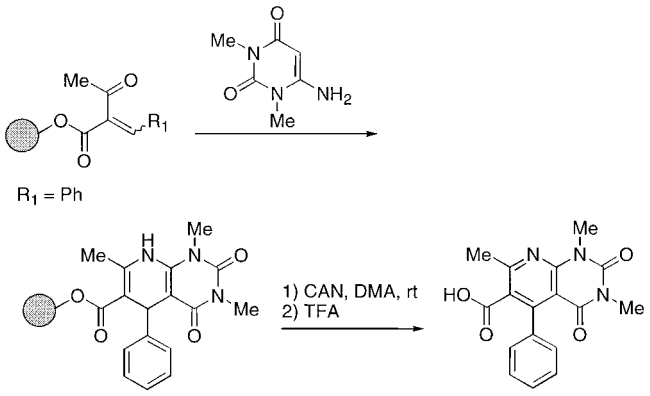
matic, and other pharmaceutical compounds.[101]

The dihydropyridine derivatives are also found in many bioactive compounds. They have been found to have vasodilative, antihypertensive, bronchodilative, hepatoprotective, antitumor, antimutagenic, and antibiotic properties. Examples of existing dihydropyridine therapeutics include the potent cardiovascular drugs nifedipine (**3**) (Figure 10), nitrendipine, and nimodipine.[102]

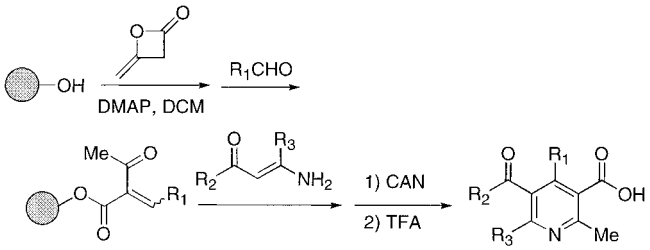
Gordeev and co-workers reported the solid phase synthesis of 1,4-dihydropyridines (DHP) derivatives.[103−105] Their strategy is based on a Hantzsch-type reaction. A support-bound enamino ester is generated by condensation of a β-keto ester with a resin-bound amine. Following treatment with an aldehyde, a second β-keto ester is added to generate a resin bound intermediate which, after cleavage with TFA, cyclized to provide the 1,4-dihydropyridine (Scheme 5, method B).

The same product can be obtained by treatment of the immobilized enamino ester with arylidene dicarbonyls (Scheme 5, method A). In a model study, Gordeev also described the solid phase synthesis of the calcium channel blocker nifedipine. The reaction of methyl acetoacetate with polystyrene-based acid-cleavable Pal or Rink amine resins led to the formation of the methyl aminocrotonate ($R_1 = R_2 = Me$), which was reacted with preformed methyl 2-(2-nitrobenzylidene)acetoacetic ester or directly with 2-nitrobenzaldehyde and methyl acetoacetate in pyridine to yield the resin-bound product. Many DHP

Scheme 6



Scheme 7



derivatives were synthesized following these steps: (1) preparation of the immobilized N-tethered enamino component, (2) condensation of the component with either 2-benzylidene β-keto ester or β-keto ester and aldehyde in pyridine, and (3) TFA cleavage to afford the desired DHP.

The development of DHP chemistry offers numerous opportunities for further chemical modification. The secondary amine group in DHP can be oxidized to pyridines or subjected to other transformations such as alkylations and acylations. O-Immobilized keto esters react with aldehydes to afford Knoevenagel derivatives. The Hantzsch-type-reaction with α-oxoenamines generate 1,4-dihydropyridines that are oxidized with ceric ammonium nitrate (CAN) to produce pyridine derivatives. By using 6-aminouracils as the α-oxoenamine component instead of the enamino−ketone component, this approach was extended for the synthesis of pyrido[2,3-*d*]pyrimidines[103−105] (Scheme 6). Another synthetic route for the synthesis of DHP derivatives is the coupling of diketene to hydroxy resin to yield a resin-bound keto ester. The Knoevenagel condensation of the immobilized ketoester with aldehyde affords the arylidene ester which, following treatment with an enamino ester, undergoes a Hantzsch-type condensation to yield DHP derivatives (Scheme 7). This example illustrates the inherent advantage of synthesis on a solid support. Excess reagents allow difficult reactions to be driven to completion and immobilized products are easily isolated following cleavage.

The solid phase synthesis of 4,5,6,7-tetrahydro-3*H*-imidazo[4,5-*c*]pyridines has been reported by Hutchins and Chapman. This synthesis was performed in parallel with the solid phase synthesis of tetrahydroisoquinolines[106] (Figure 11).

f. Isoquinolines and Derivatives. Isoquinoline derivatives are an important family of natural prod-

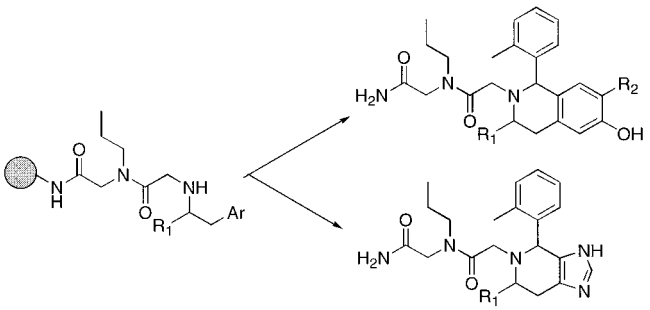


Figure 11. Synthesis of 1,2,3,4-tetrahydroisoquinolines and 4,5,6,7-tetrahydro-3*H*-imidazol[4,5-*c*]pyridines.

ucts. They have diverse biological activities such as bronchodilators, skeletal muscle relaxants, and antiseptics.[107] Goff and Zuckermann reported the solid phase synthesis of isoquinolinones by coupling a *trans*-4-bromo-2-butenoic acid (bromocrotonic acid) to a deprotected Rink amide linker.[108] Following S_N2 displacement of the bromine by a primary amine, the unsaturated monopeptoid was generated. The amine was then acylated by a substituted 2-iodobenzoyl chloride. An intramolecular Heck reaction on the solid phase[109] occurred using $Pd(PPh_3)_4$. The reaction was facilitated by the electron-withdrawing groups. Cleavage with 95% TFA in H_2O provides the (2*H*)-isoquinolinones. Isomerization has been observed due to a subsequent readdition of PdH. Elimination in the opposite direction gives the thermodynamically more stable isomer **4** (Scheme 8).

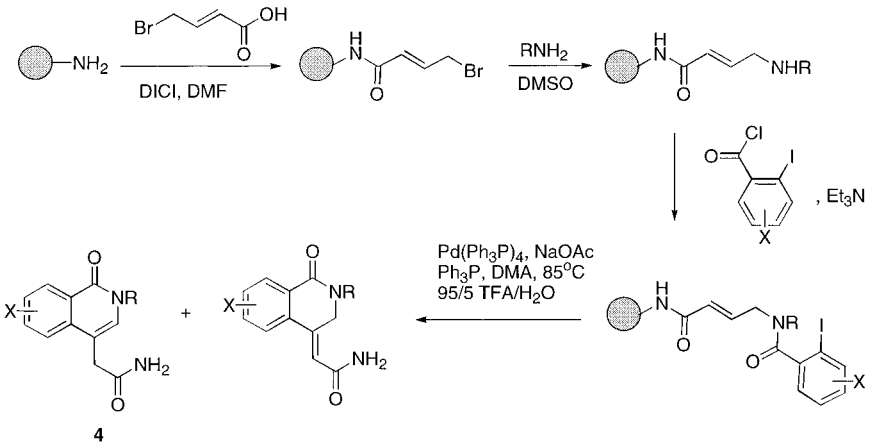
The solid phase synthesis of a 43 000 compound tetrahydroisoquinoline combinatorial library has recently been reported by Griffith and co-workers.[110] The library was synthesized using a three-step procedure. An imine was formed by reacting a substituted benzaldehyde with an MBHA resin-bound amino acid. Imine formation was driven to completion using trimethyl orthoformate as a dehydrating reagent. The treatment of the imine with homophthalic anhydride provided the desired tetrahydroisoquinoline. Isomerization to the more stable trans configuration was obtained following cleavage by treatment with 1 N NaOH. The tetrahydroisoquinoline library was prepared using the DCR method with MBHA resin, 11 amino acid building blocks, 38 aldehydes, and 51 amines. The library has been tested in a number of assays, including κ and μ opioid radioreceptor binding assays and in a σ radioreceptor binding assay. Using the "libraries from libraries" concept,[111,112] a second copy of the isoquinoline library was reduced in the presence of diborane to generate a second library having different physical and chemical properties (Scheme 9).

Meutermans and Alewood reported the solid phase synthesis of tetrahydroisoquinolines[113] using the Bischler−Napieralski reaction.[114] The synthetic route is illustrated in Scheme 10. The polystyrene resin-bound deprotected (L)-3,4-dimethoxyphenylalanine was acylated with acetic acid derivatives using HBTU as coupling reagent. The product obtained was then treated with $POCl_3$ under optimized conditions to afford a Bischler−Napieralski cyclization. The best results were obtained using 30 equiv of freshly distilled $POCl_3$ at 80 °C in toluene for 8 h. The desired dihydroisoquinoline was isolated following cleavage with HF in *p*-cresol and HPLC purification. To extend this strategy to the synthesis of tetrahydroisoquinolines, the dihydroisoquinoline was treated with $NaBH_3CN$ to reduce the resin-bound imine and yielded the desired tetrahydroisoquinolines.

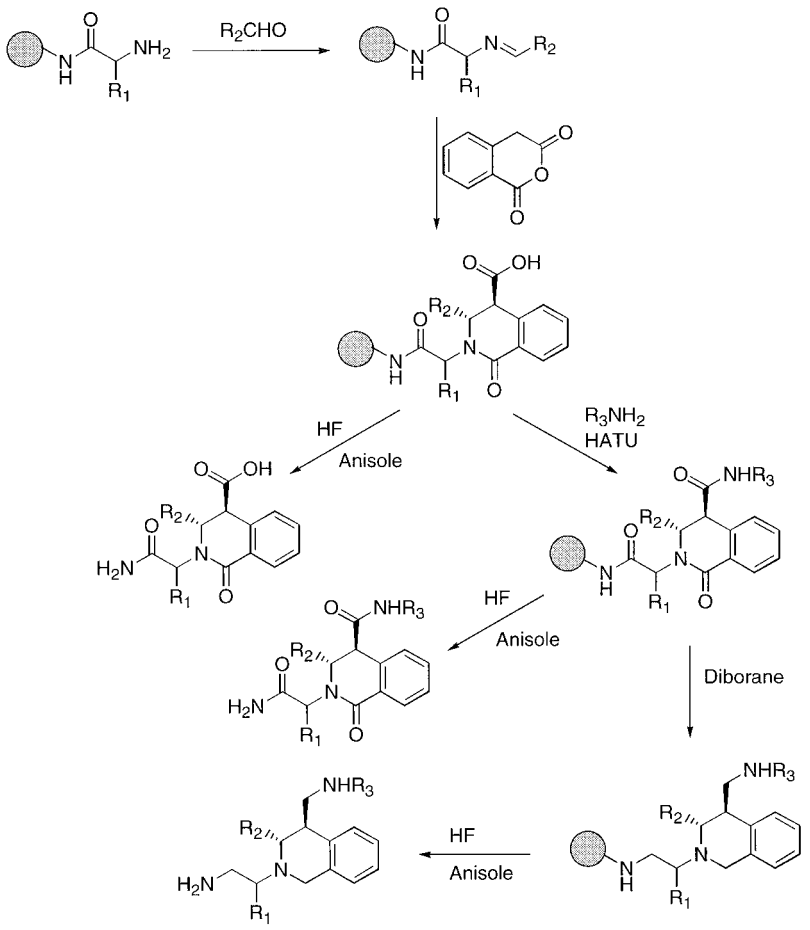
Hutchins and Chapman reported the synthesis of 1,2,3,4-tetrahydroisoquinolines and 4,5,6,7-tetrahydro-3*H*-imidazo[4,5-*c*]pyridines using substituted *m*-tyramines, histamines, and various aromatic, aliphatic, and heterocyclic aldehydes.[106] The cyclocondensation in pyridine of the resin-bound dipeptidomimetic with aldehydes led to the formation of an imine intermediate which, following heating, afforded the resin-bound tetrahydroisoquinolines. In the case of resin-bound substituted histamines, 4,5,6,7-tetrahydro-3*H*-imidazo[4,5-*c*]pyridine compounds were obtained using the same conditions for cyclization (Figure 11).

g. Quinolones. A solid phase approach for the synthesis of eight quinolones using the diversomer technology[115] has been reported by MacDonald and co-workers.[116] Quinolone derivatives have antibacterial and antibiotic properties. Transesterification of the β-keto ester (2,4,5-trifluorobenzoyl)acetic acid to *p*-(benzyloxy)benzyl alcohol resin (Wang resin) was achieved by heating the mixture in toluene with a catalytic amount of 4-(*N*,*N*-dimethylamino)pyridine (DMAP) at 110 °C for 72 h. Activation of the resin-bound β-keto ester was achieved with dimethylformamide dimethyl acetal for 18 h, followed by in situ

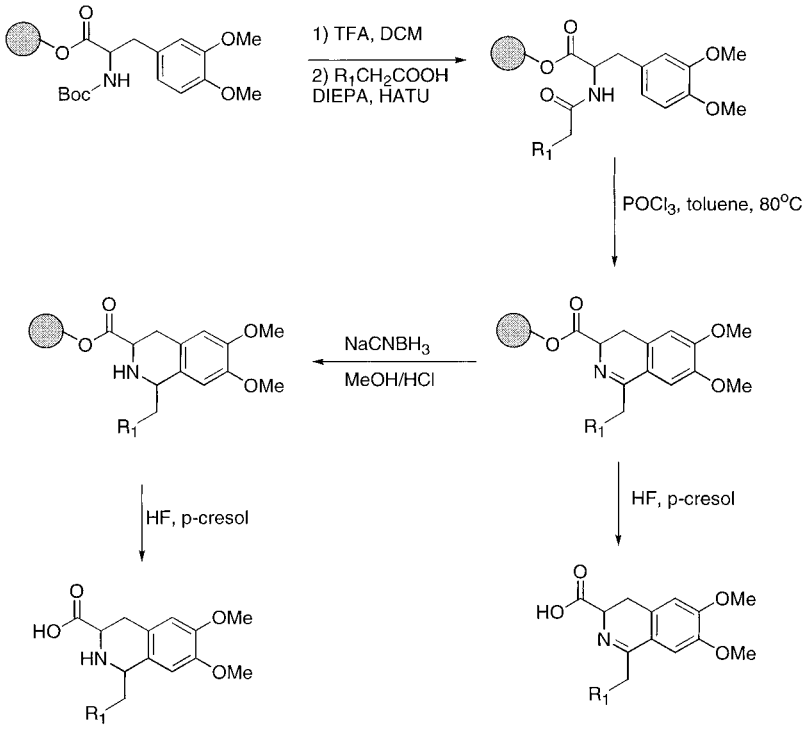
Scheme 8



Scheme 9



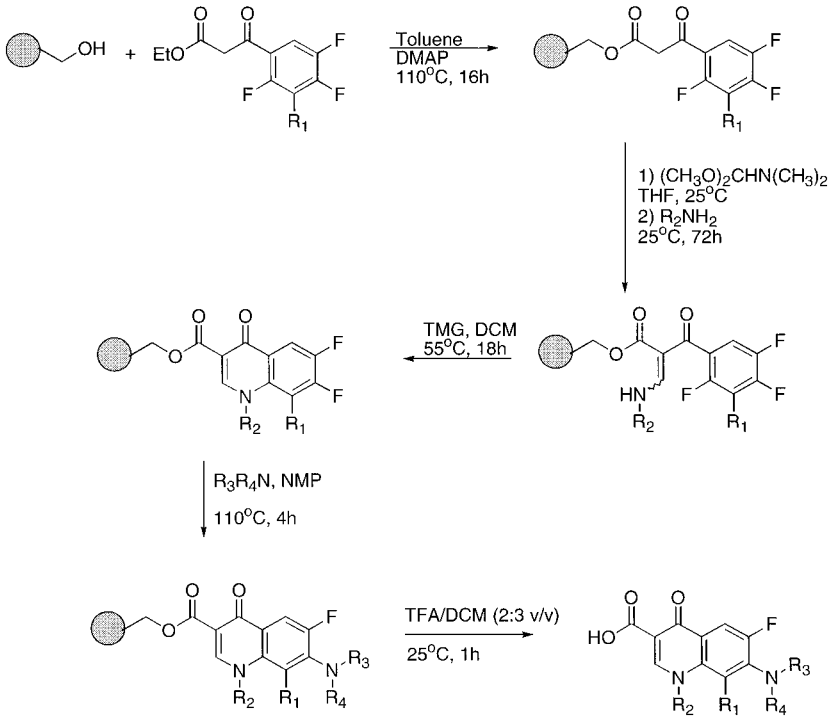
Scheme 10



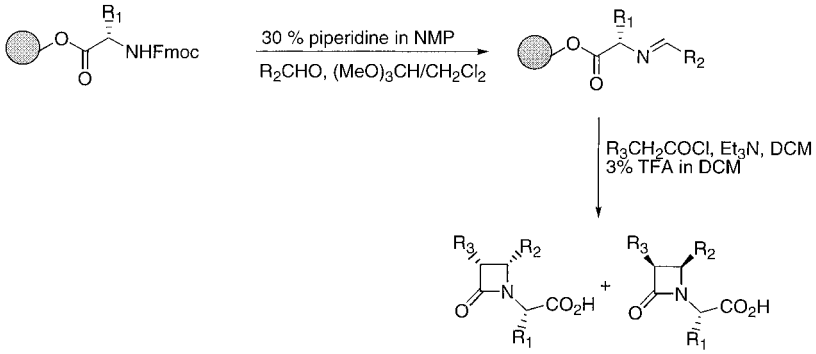
addition of a primary amine at 25 °C for 72 h. The resulting resin-bound enamide cyclized to the quinolone in a solution of tetramethylguanidine (TMG) and dichloromethane (DCM) at 55 °C. Nucleophilic substitution of the resin-bound ester was achieved by treatment with a variety of piperazines at 110 °C for 4 h. Finally, cleavage with 40% TFA/DCM afforded the desired quinolone (Scheme 11).

h. *β*-Lactams. Ruhland and co-workers reported the combinatorial synthesis of structurally diverse

Scheme 11



Scheme 12

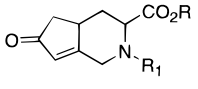


β-lactams[117](Scheme 12). Following removal of the Fmoc protecting group from resin-bound amino acids, a 10−15-fold excess of alkyl, aromatic, or α,β-unsaturated aldehydes in a 1:1 mixture of $(MeO)_3CH$/DCM was added to yield the resin-bound imines. The [2 + 2] cycloaddition occurred by addition of acid chlorides to a methylene chloride suspension of the imine resins in the presence of triethylamine at 0 °C. The reaction mixture was allowed to warm to room temperature with agitation for 16 h. The products were cleaved from the Sasrin support by treatment with a solution of 3% (v/v) TFA/DCM for 45 min. Due to the assymetric center of the amino acid, two cis-diastereoisomeric β-lactams were formed in ratios varying from 1:1 to 3:1 (based on ^{1}H NMR and HPLC). To demonstrate the utility of the solid phase synthesis of β-lactams, Gallop et al. generated 15 β-lactams using valine−Sasrin resin, five aldehydes (benzaldehyde, 2-furaldehyde, 2-pyridinecarboxaldehyde, 2-thiophenecarboxaldehyde, and β-phenylcinnimaldehyde), and three different acid chlorides (phenoxyacetyl, phtalimidoacetyl, and 4(*S*)-phenyloxazolidylacetyl chlorides). Most of the β-lactams were obtained in >80% purity following acidic cleavage.

i. Azabicyclo[4.3.0]nonen-8-one Amino Acid Derivatives. Bolton recently reported the solid phase synthesis of azabicyclo[4.3.0]nonen-8-one amino acid derivatives **5** via intramolecular Pauson−Khand cyclization. It was shown that this reaction proceeds efficiently and with a high level of asymmetric induction to provide bicyclic amino acid derivatives[118] (Figure 12).

2. Compounds Containing Oxygen

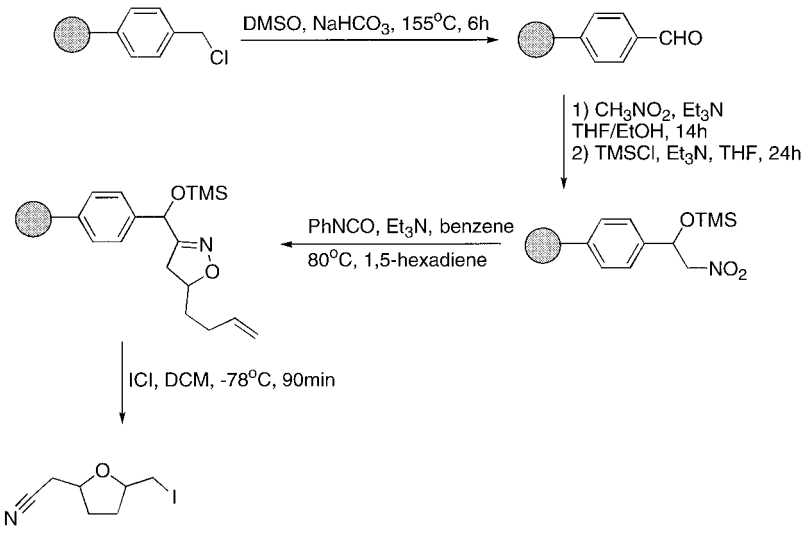
a. Furan and Pyran Derivatives. Beebe and co-workers reported the solid phase synthesis of 2,5-disubstituted tetrahydrofurans.[119−121] This group of compounds has important structural elements of many polymer antibiotics.[122,123] Merrifield support was oxidized to the aldehyde and condensed with nitromethane to yield the polymer-bound 2-nitro-1-phenylethan-1-ol. Following protection of the hy-



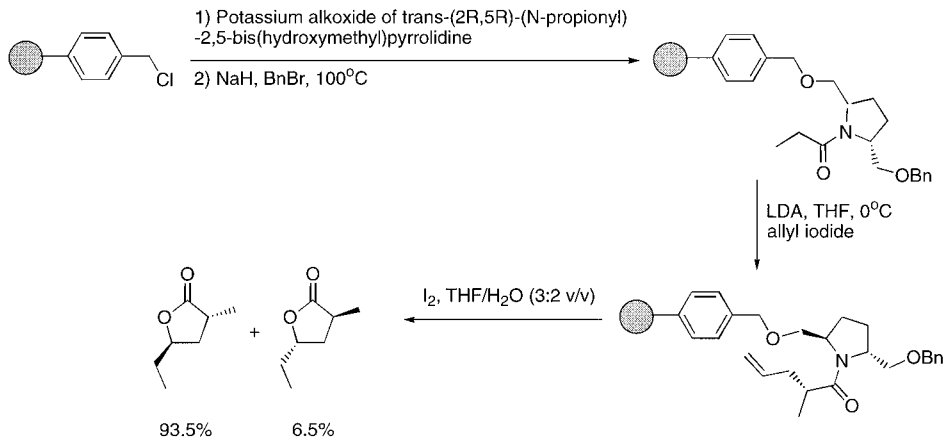
5

Figure 12. Structure of azabicyclo[4.3.0]nonene-8-one amino acid derivatives **5**.

Scheme 13



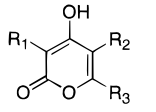
Scheme 14



droxyl group with trimethylsilyl chloride, the dehydration of the nitro group was performed in the presence of phenyl isocyanate to generate the resin-bound nitrile oxide. The nitrile oxide underwent a 1,3-dipolar cycloaddition with 1,5-hexadiene to afford the resin-bound isoxazole. Following an electrophilic cyclization with iodine monochloride, the desired 2,5-disubstituted tetrahydrofuran was obtained (Scheme 13).

The preparation of hydroxypyranones **6** on the solid phase has been reported[124] (Figure 13). Acylation of resin bound β,δ-dioxo ester with *N*-methoxy-*N*-methylamides followed by cyclative cleavage yielded the desired products. The preparation of tetrahydrohydroxypyranones has also been reported.[125]

b. γ-Butyrolactones. Starting from Merrifield resin, Kurth and co-workers reported the enantioselective solid phase preparation of γ-butyrolactones.[126−127] The optically active 3,5-disubstituted-γ-butyrolactone was prepared following a three-step process consisting of N-acylation, C_α-alkylation, and subsequent iodolactonization (Scheme 14). A resin-bound pyrrolidine was converted to *Z*-enolate, which following treatment with LDA and allyl iodide provided the C_α-alkylated resin. Iodolactonization of the resin-bound pentenamide moiety was achieved by treating a THF/H_2O (1.5:1) suspension of this resin with iodine for 3 days. The γ-butyrolactones were obtained in a 93.5:6.5 ratio following filtration and washing of the resin with ether.



6

Figure 13. Structure of pyran derivatives **6**.

3. Compounds Containing Sulfur

a. Sulfolenes. In earlier environmental research for the removal of sulfur dioxide from waste or flue gases, Nieuwstad and co-workers studied the reversible binding of sulfur dioxide by polymer-bound 1,3-diene acceptor systems.[128] Using divinylbenzene/styrene copolymers as the solid support, a number of immobilized 1,3-dienes were prepared (Scheme 15). These were able to bind sulfur dioxide by the formation of the corresponding sulfolene systems. Liberation of sulfur dioxide occurred by heating the polymer-bound sulfolene.

Scheme 15

B. Cyclic Compounds with Two or More Heteroatoms

1. Compounds Containing Multiple Nitrogens

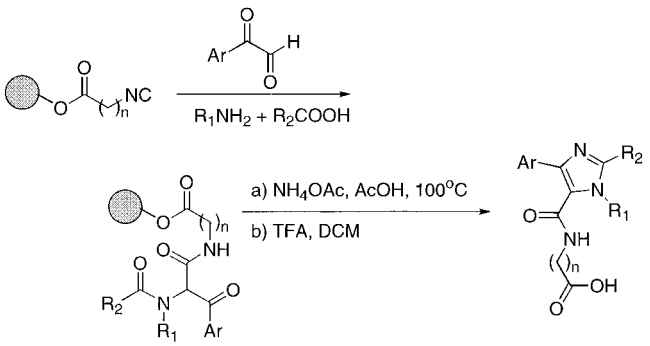
a. Imidazoles and Derivatives. Similar to the strategy reported for the synthesis of pyrroles, Mjalli and Toyonaga have shown that the condensation on solid support of an aldehyde with a 1,2-dione provides imidazole derivatives with three positions of diversity.[69] A fourth position of diversity can be introduced by adding a primary amine to the mixture, as shown (Scheme 16). By linking either the amine or the aldehyde to the Wang resin support, the synthesis of imidazole derivatives was performed by heating in AcOH at 100 °C for 4 h in the presence of a diketone with either the amine or aldehyde and ammonium acetate. The use of α-keto aldehydes in a four-component condensation reaction resulted in the synthesis of *N*-alkyl-*N*-acylamino ketone-based libraries, which were converted to highly substitued imidazoles. The condensation of aromatic ketoaldehydes, amines, and carboxylic acids to a resin-bound isocyanide provided the resin-bound keto diamides. When heated with ammonium acetate in acetic acid at 100 °C, tetrasubstituted imidazoles are obtained that can be cleaved from the polymer support in the presence of 10% TFA in DCM.

Recently, Phillips and Wei developed a solid phase synthesis of benzimidazoles by treatment of polymer-bound *o*-flouoronitro aromatic compounds with amines to afford an *o*-nitroaniline, which was then reduced with $NaBH_4Cu(acac)$[129] (Scheme 17). The cyclization was achieved with an aryl imidate. Cleavage was carried out with TFA.

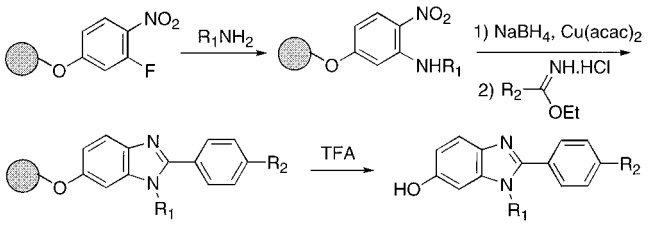
The possibility of using a gel-phase ^{19}F and MAS ^{19}F and ^{13}C NMR for monitoring the progress of nucleophilic substitution on aromatic rings was demonstrated by Shapiro and co-workers.[130]

b. Pyrazole Derivatives. Marzinzik and Felder reported the solid phase synthesis of functionalized pyrazoles.[131] A four-step reaction sequence, including a Claisen condensation, an α-alkylation, and a cyclization of a β-diketone with monosubstituted hydroxylamines, was described that generated a variety of highly functionalized pyrazoles (Scheme 18).

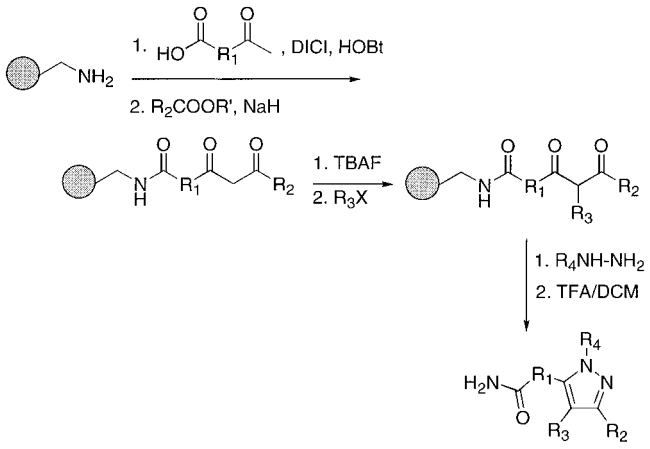
Scheme 16



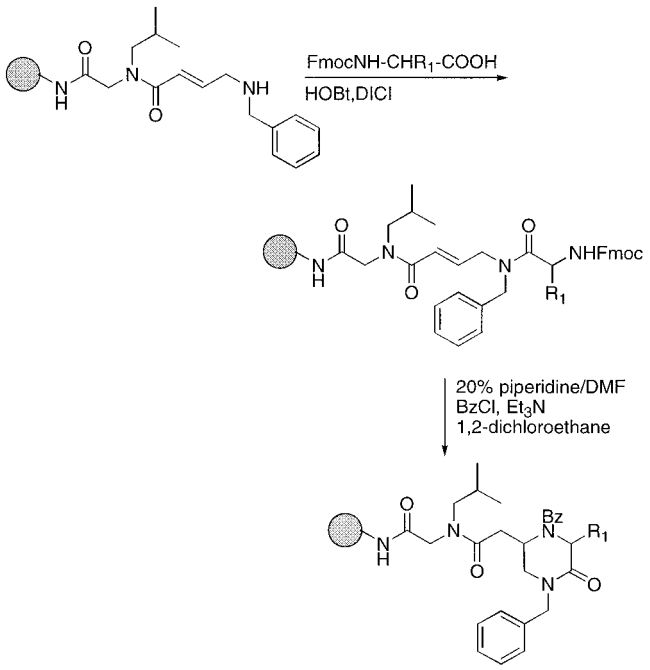
Scheme 17



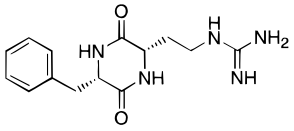
Scheme 18



Scheme 19



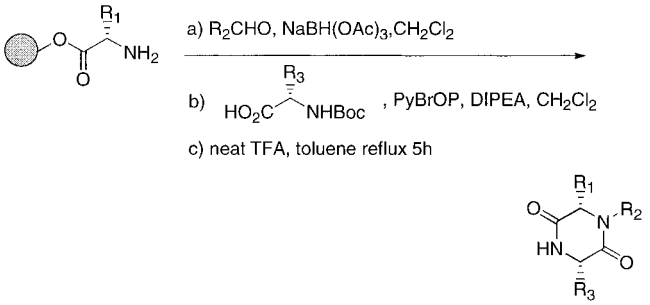
c. Piperazine Derivatives. Goff and Zuckermann reported the synthesis of 2-oxopiperazine by intramolecular Michael addition on the solid phase.[132] They were interested in synthesizing structurally constrained peptides containing cyclopropyl amino acids via treatment of unsaturated resin-bound dipeptoids using the Corey cyclopropanation reagent (dimethylsulfonium methylide). Instead of cyclopropane peptoids, they obtained an interesting family of constrained cyclic peptoids. After characterization of the products, they developed a simplified method to prepare the cyclic products. The coupling of resin-bound unsaturated dipeptoids with a variety of Fmoc-L-amino acids and DICI/HOBt affords tripeptioids, which, following treatment with 20% piperidine in DMF, were acylated with benzoyl chloride/Et_3N in 1,2-dichloroethane. Following treatment with 95% TFA in H_2O, a diastereomeric ratio of monoketopiperazines was obtained (Scheme 19). Rather than benzoyl chloride, phenyl isocyanate or bromoacetic acid and amine could be used.



7

Figure 14. Structure of diketopiperazine incorporating (*S*)-norarginine **7**.

Scheme 20



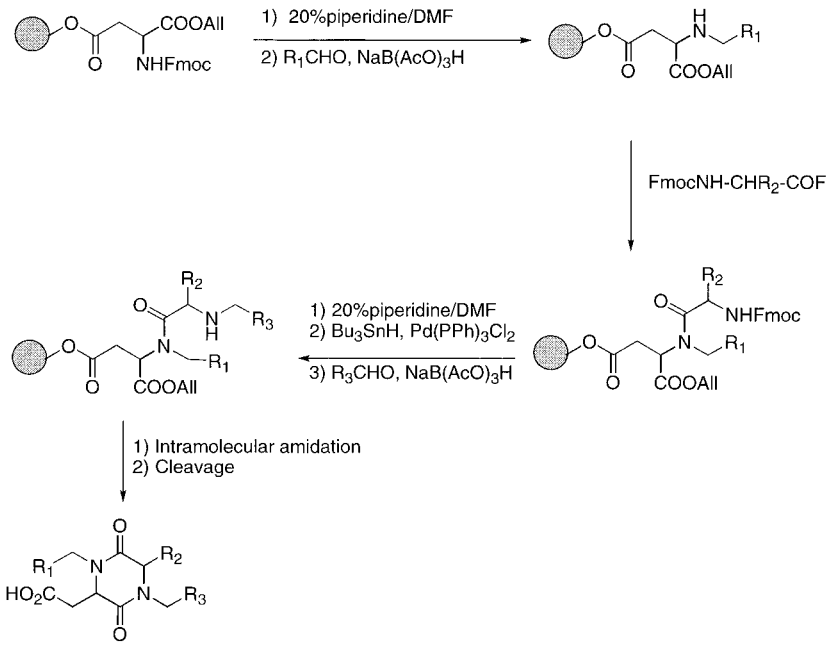
Gordon and Steele developed a strategy for the solid phase synthesis of diketopiperazines based on reductive amination of a support-bound amino acid with an aldehyde[133] (Scheme 20). The resulting secondary amine was then coupled with Boc amino acids employing PyBrop as activating agent. Following TFA treatment, cyclization to obtain the desired product was accomplished by heating at reflux in toluene. Using the DCR approach, a total of 1000 compounds was synthesized. Several DKPs were identified having significant biological activity, including affinity for the neurokinin-2-receptors.

Recently, Kowalski and Lipton have used this strategy for the solid phase synthesis of a diketopiperazine catalyst containing the unnatural amino acid (S)-norarginine.[134] The cyclic dipeptide **7** (Figure 14) composed of L-phenylalanine and L-norarginine has been shown to catalyze the enantioselective Strecker synthesis of (*S*)-phenylglycine derivatives from N-substituted aldimines and hydrogen cyanide.

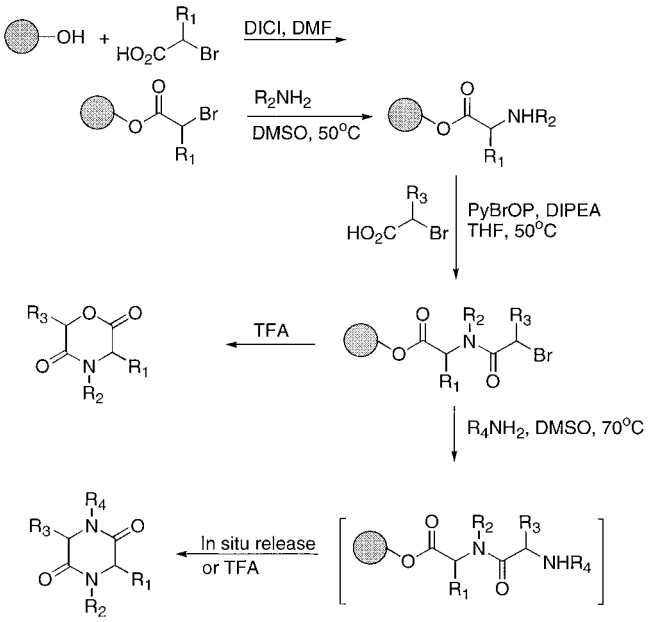
A similar approach has been published by Krchňák and co-workers.[135] This involved the coupling of the side chain carboxyl group of Asp, Glu, or Ida to the resin (Scheme 21). Following deprotection of the α-amino group, the first position of diversity was introduced by reductive alkylation of the polymer-supported amino group using a variety of aldehydes in trimethyl orthoformate with sodium triacetoxyborohydride as the reducing agent. The resulting secondary amine was then acylated with an amino acid. This reaction was difficult to perform in high yield, contrary to the results previously reported by Gordon and Steele,[133] even by highly activated protected amino acid fluorides. Following removal of the N-protecting group, a second reductive alkylation was accomplished by employing the same conditions. The desired dioxypiperazine ring was easily obtained upon mild activation of the free carboxylic group using the conventional coupling reagents DICI/HOBt. Using the diamino acid, Krchňák et al. were able to extend the diversity at R_3 (amino group) by acylating or alkylating the amino group or by attaching a second diketopiperazine ring.

Scott and co-workers developed a novel route to a diketopiperazine library using α-bromocarboxylic acids and a range of amines[136] (Scheme 22). Displacement of a resin-bound bromide by a primary amine was followed by the acylation of the resin-bound secondary amine with an α-bromo carboxylic acid. The best results for the acylation step were achieved using THF as the solvent and PyBrop as the activating agent in the presence of DIEA. Treatment of the resin-bound bromide with a primary amine displaced the bromine and cyclized the remaining structure to afford the diketopiperazine. Two routes to cyclization were observed: intramolecular cyclization could occur directly under the reaction conditions to afford the desired diketopiperazine or the cyclization could be induced with TFA. The authors found that the cyclization via in situ release was influenced by the nature of R_1 and R_3. Using the DCR method, a library of 22 540 DKPs was prepared.

Scheme 21



Scheme 22



Dankwardt and co-workers recently developed the solid phase synthesis of aryl and benzyl piperazine derivatives.[137] Nitro-activated aryl fluorides were reacted with a large variety of N-substituted piperazines to provide aryl piperazine derivatives **8** of high purity (Figure 15). When using electron-withdrawing groups such as the trifluoromethyl group, incomplete reaction was obtained. However, benzyl chlorides and bromides gave good yields.

d. Benzodiazepines. Benzodiazepines are an important group of therapeutic agents.[138−140] The first efforts to prepare libraries of this type were focused on the synthesis of the seven-membered rings 1,4-benzodiazepin-2-one (**9**) and 1,4-benzodiazepine-2,5-dione (**10**) (Figure 16). One of the most interesting aspects of the benzodiazepines is their striking anticonvulsant properties in a variety of experimental models of epilepsy.[138] All known 1,4-benzodiazepines have the same profile of broad pharmacological activity, including antianxiety, sedative/hypnotic, anticonvulsant, and muscle-relaxing actions and tranquilizing properties. The benzodiazepines are

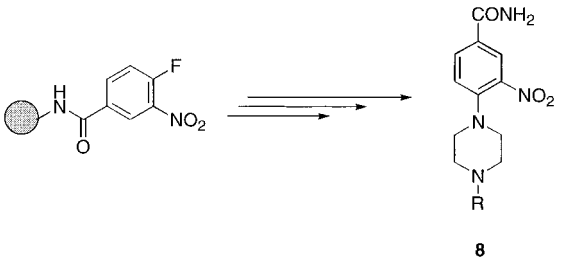


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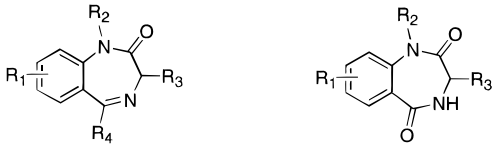
Figure 15. Synthesis of arylpiperazines **8**.



9 **10**

Figure 16. Structures of benzodiazepin-2-ones **9** and benzodiazepine-2,5-diones **10**.

also well-absorbed following oral administration. Many benzodiazepines drugs bind extensively to plasma and tissue proteins. The use of benzodiazepine in therapeutic applications has increased exponentially over the last 20 years. Benzodiazepines are now the most commonly prescribed group of drugs.[138]

Bunin and co-workers reported the synthesis of benzodiazepines from amino acids, two aminobenzophenones, and a variety of alkylating agents.[35] A range of Fmoc-protected aminobenzophenones were first synthesized in solution and then linked to the solid support. Following piperidine deprotection, a range of Fmoc amino acid fluorides was coupled and deprotected. The cyclization to benzodiazepine derivatives occurred under acidic conditions (5% AcOH). The generated resin-bound anilide was alkylated, and the desired products were obtained following treatment of the resin with TFA (Scheme 23).

Plunkett and Ellman employed the Stille reaction to generate 2-aminoaryl ketones on the solid support.[141] These were transformed to the desired diazepines following acylation of the amino group and cyclization. Following the coupling of [[2-(4-biphenylyl)isopropyl]oxy]carbonyl (Bpoc)-protected (aminoaryl) stannane to a solid support, a range of different acid chlorides was coupled under catalytic conditions. Following Bpoc deprotection and by utilizing the same conditions described earlier, a series of benzodiazepines was synthesized.

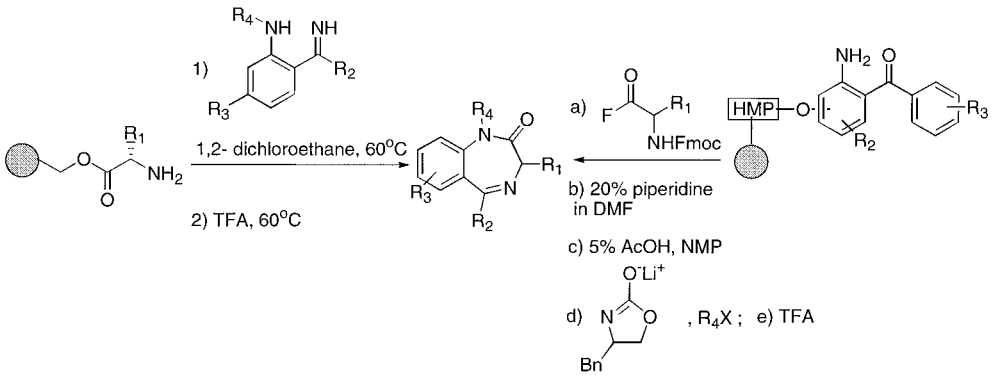
Dewitt and co-workers[115,142] reacted 2-aminobenzophenone imine to commercially available α-amino acids on Wang resin. The trans-imidation was followed by intramolecular cleavage leading to the desired benzodiazepine. Starting with 5 different amino acids and 8 different benzophenone imines, 40 benzodiazepines were produced in 9−63% yield (2−25 mg of material).

Starting from a support-bound N-alkylated glycine, Goff and Zuckermann reported the synthesis of 1,4-benzodiazepine-2,5-diones.[143] Following acylation of the N-alkylated glycine (peptoids) with bromoacetic acid and displacement of the bromine with an α-amino ester, the resulting secondary amine was acylated with a substituted o-azidobenzoyl chloride. Treatment with tributylphosphine gave the iminophosphorane, which upon heating at 125 °C cyclized to afford the resin-bound benzodiazepines. The desired product was removed from the resin by treatment with TFA (Scheme 24).

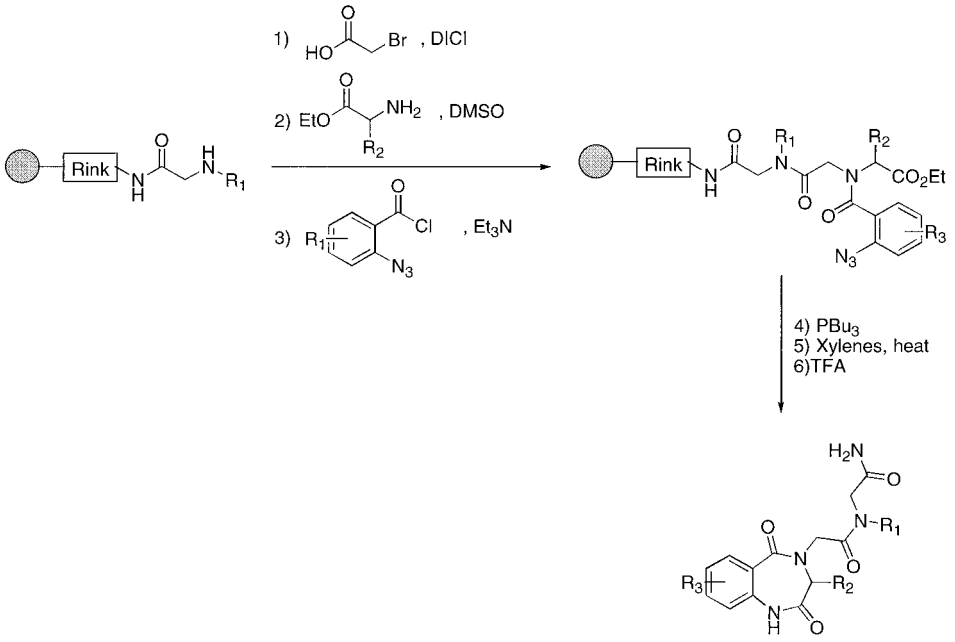
Boojamra and co-workers developed a method for the synthesis of 1,4-benzodiazepine-2,5-diones.[144] An amino ester was reductively aminated with an aldehyde derivatized support. The secondary amine was then acylated with anthranilic acid. The resulting amide was treated with the lithium salt of acetanilide to yield the cyclic product, which was then alkylated in situ. Treatment of the resin with TFA afforded the desired benzodiazepines (Scheme 25).

Moroder and co-workers recently developed a new method for the generation of benzodiazepines from peptide precursors.[145] A series of N^{α}-(2-aminobenzoyl)-*N*-alkylamino acid peptides were synthesized. The general tendency of these peptides to undergo

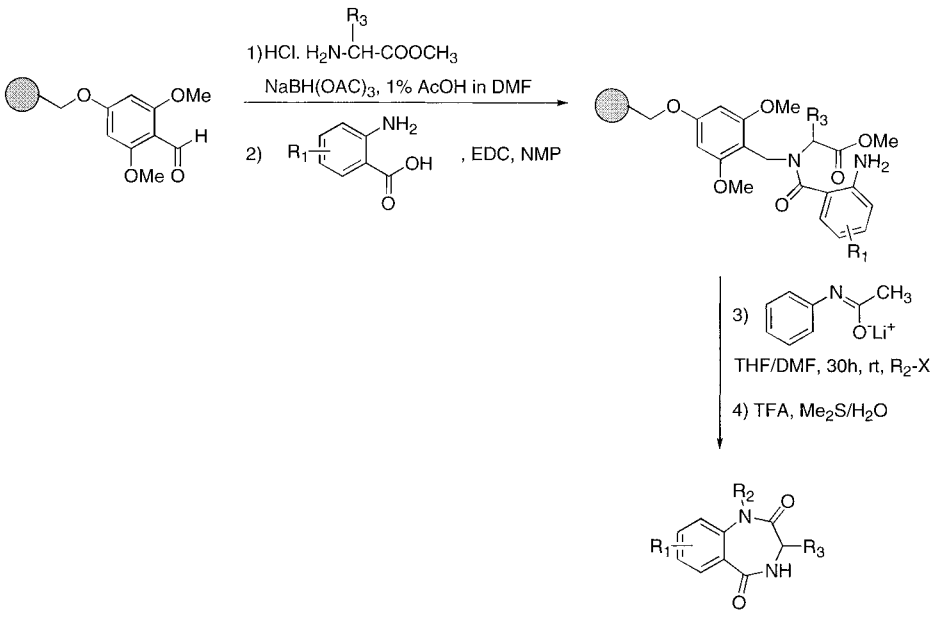
Scheme 23



Scheme 24



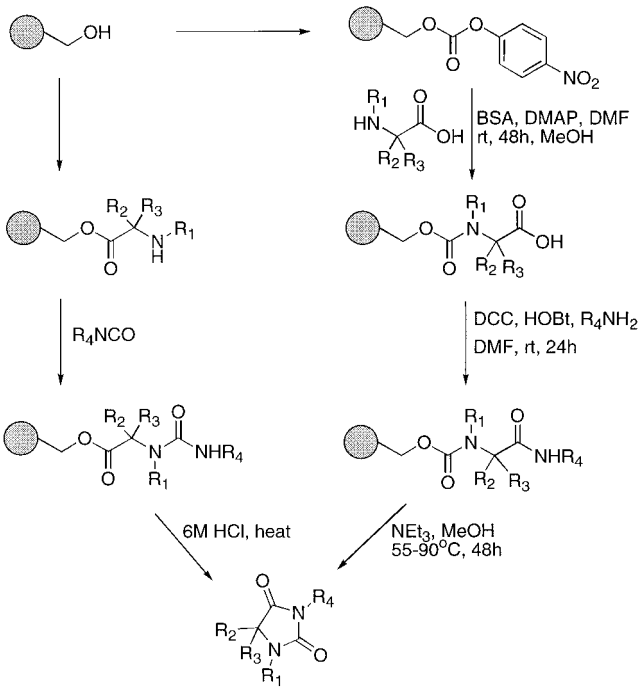
Scheme 25



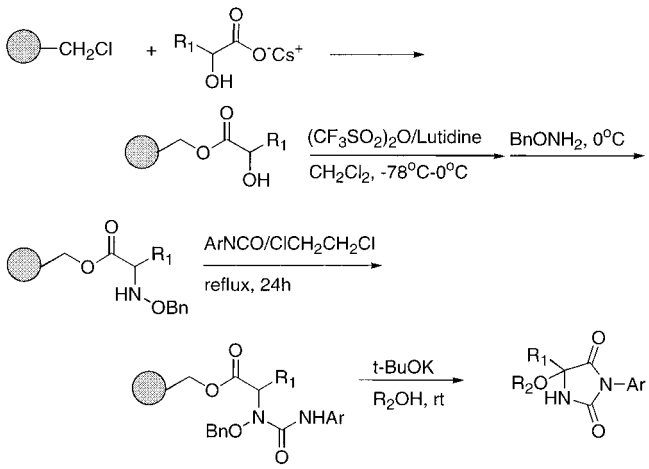
acid-catalyzed cyclization to 1,4-benzodiazepine-2,5-diones was investigated.

e. Hydantoins and Derivatives. Dewitt and coworkers also reported the synthesis of 40 hydantoins using the diversomer approach,[115,142] following condensation of a variety of isocyanates to Wang resin-bound amino acids. The cyclative cleavage leading to the hydantoin product occurred by heating the

Scheme 26



Scheme 27

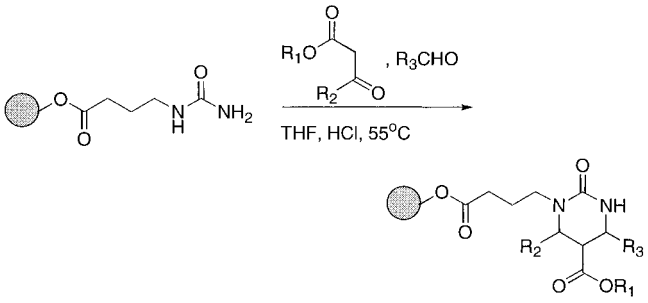


resin-bound urea in 6 M HCl (Scheme 26).

A hydantoin library of 800 compounds has been reported by Dressmann and co-workers.[146] In this approach, 20 different amino acids and over 80 primary amines were incorporated. Selected amino acids were attached via their N-terminal to (hydroxymethyl)polysterene resin using a carbamate linker (Scheme 26). This enabled the free acid resin-bound intermediates to be generated, which could then be converted to their corresponding amides using standard carbodiimide coupling reactions and excess primary amine. A cyclative cleavage occurred following treatment of the resin-bound intermediate with excess triethylamine in MeOH under reflux for 48 h.

Recently, a general method for the solid phase synthesis of 5-alkoxyhydantoins has been reported by Hanessian and Yang[147] (Scheme 27). They first developed the general synthesis in solution. Since high yields were obtained, they extended their protocol to a synthesis on solid support. An α-hydroxy acid was linked to Merrifield resin via its cesium salt.

Scheme 28



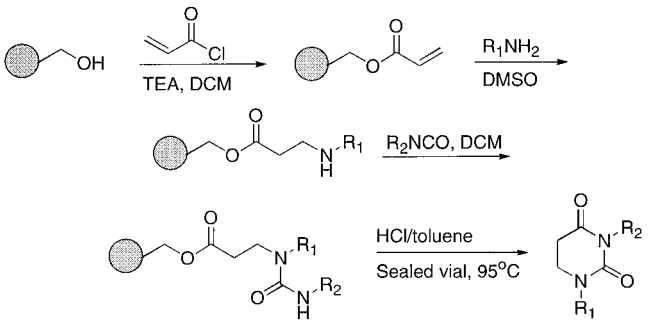
After treatment with trifluoromethanesulfonic acid anhydride in the presence of lutidine in dichloromethane, the polymer-bound α-hydroxy ester was transformed to an *N*-(benzyloxy)amine by in situ addition of *O*-benzylhydroxyamine. Following condensation in refluxing dichloromethane of aryl isocyanates to the resin-bound α-amino acid derivative, the resulting urea was treated with potassium *tert*-butoxide in an alcoholic solution. After a cyclative cleavage, this led to the desired 5-alkoxyhydantoin. The purity of the final product ranged from 89 to 96%.

f. Dihydropyrimidines and Derivatives. The dihydropyrimidine synthesis is a promising multicomponent condensation and could be highly relevant to combinatorial chemistry. Wipf and Cunningham have developed a solid phase protocol that provides the dihydropyrimidines in excellent yield and purity[71] (Scheme 28). The attachment of a γ-aminobutyric acid derived urea provided a resin-bound ester linkage. The subsequent Biginelli reaction[68] with 4 equiv of β-keto esters and aldehydes was performed at 55 °C in THF in the presence of catalytic HCl. The dihydropyrimidines were easily isolated by simple filtration in high yields. This protocol for Biginelli condensation on the solid phase offers a convenient alternative for the parallel synthesis of dihydropyrimidine libraries.

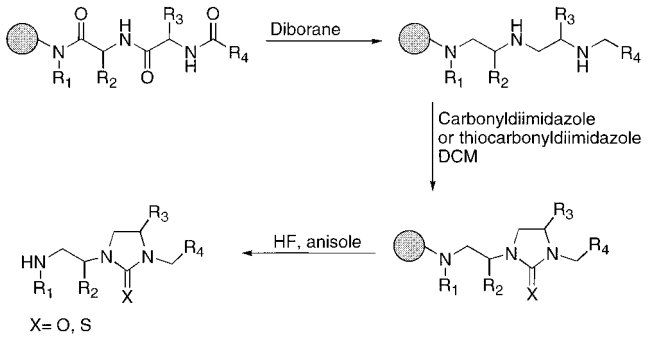
The approach used by Kolodziej and Hamper is similar to that reported for the formation of hydantoins from resin-bound α-ureido esters. The synthesis of a series of 1,3-disubstituted-5,6-dihydropyrimidine-2,4-diones was reported on the solid phase starting from commercially available amines and isocyanates.[148] Treatment of acrylate esters of Wang resin with primary amines afforded the N-substituted β-amino esters after Michael addition. Following treatment with isocyanate, the β-ureido ester was cyclized under acidic conditions to give the 5,6-dihydropyrimidine-2,4-dione. Consistent cyclization of the ureido esters occurred following treatment of the resin with acidic solutions at 95 °C (Scheme 29). A mixture of the β-ureido ester and the cyclized product was obtained when the polymer ester-bound compounds were treated with TFA at room temperature.

g. Cyclic Ureas and Thioureas. Many biologically active compounds contain cyclic ureas, including inhibitors of human immunodeficiency virus (HIV) protease and HIV replication.[149] We have approached the design and solid phase synthesis of cyclic ureas and thioureas using modified dipeptides as starting material. Thus, to synthesize the modi-

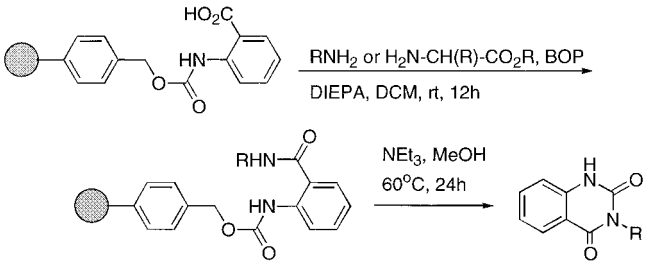
Scheme 29



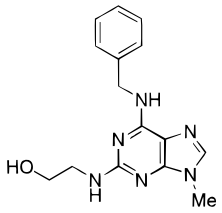
Scheme 30



Scheme 31



fied dipeptide, N-alkylation was performed on an amide-linked resin-bound N-tritylated amino acid using lithium *tert*-butoxide in THF, followed by the addition of the alkylating agent (methyl iodide, benzyl bromide, etc.) in DMSO.[21] Following removal of the Trt protecting group with 2% TFA in DCM, the second amino acid was added using traditional peptide chemistry. The resulting dipeptide was acylated with one of a wide range of available carboxylic acids to obtain the acylated dipeptide. Scheme 30 shows that reduction of the amide groups using diborane in THF at 65 °C generates two secondary amines.[112] Cyclization to obtain the five-membered cyclic ureas and cyclic thioureas was carried out using carbonyldiimidazole and thiocarbonyldiimidazole in anhydrous DCM.[74] The desired products were obtained in excellent yield and purity



11

Figure 17. Structure of olomoucine **11.**

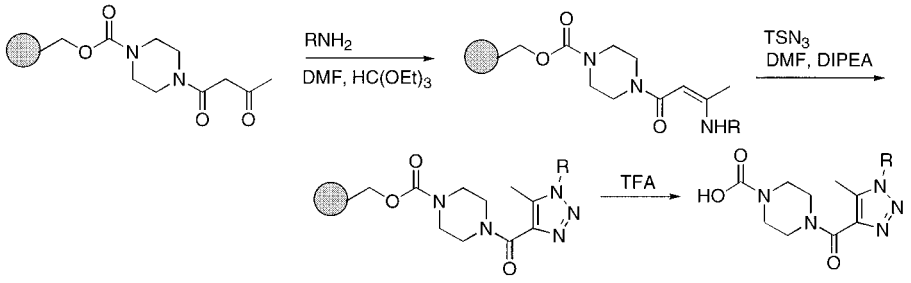
(>90% by HPLC) following cleavage from the resin with anhydrous HF. The cyclization step has also been successfully carried out using triphosgene and thiophosgene. Using this approach, two libraries of 250 000 cyclic ureas and 250 000 thioureas were prepared. The strength of this approach is that well-characterized peptide libraries can be prepared with the confidence that the yields and deconvolution approaches, iterative or positional scan, can also be used for the resulting heterocyclic library.

h. Quinazolines. Gouilleux and co-workers reported the solid phase synthesis of chiral 3-substituted quinazoline-2,4-diones.[150] Starting from hydroxymethyl polystyrene resin-bound anthranilic acid via an urethane linker, an amine compound (or C-terminal protected amino acid) was coupled using Bop and DIEA. The anthranilic amide generated was treated with an excess of NEt_3 in methanol at 60 °C for 24 h to afford the 3-substituted quinazoline-2,4-diones in high-purity (Scheme 31).

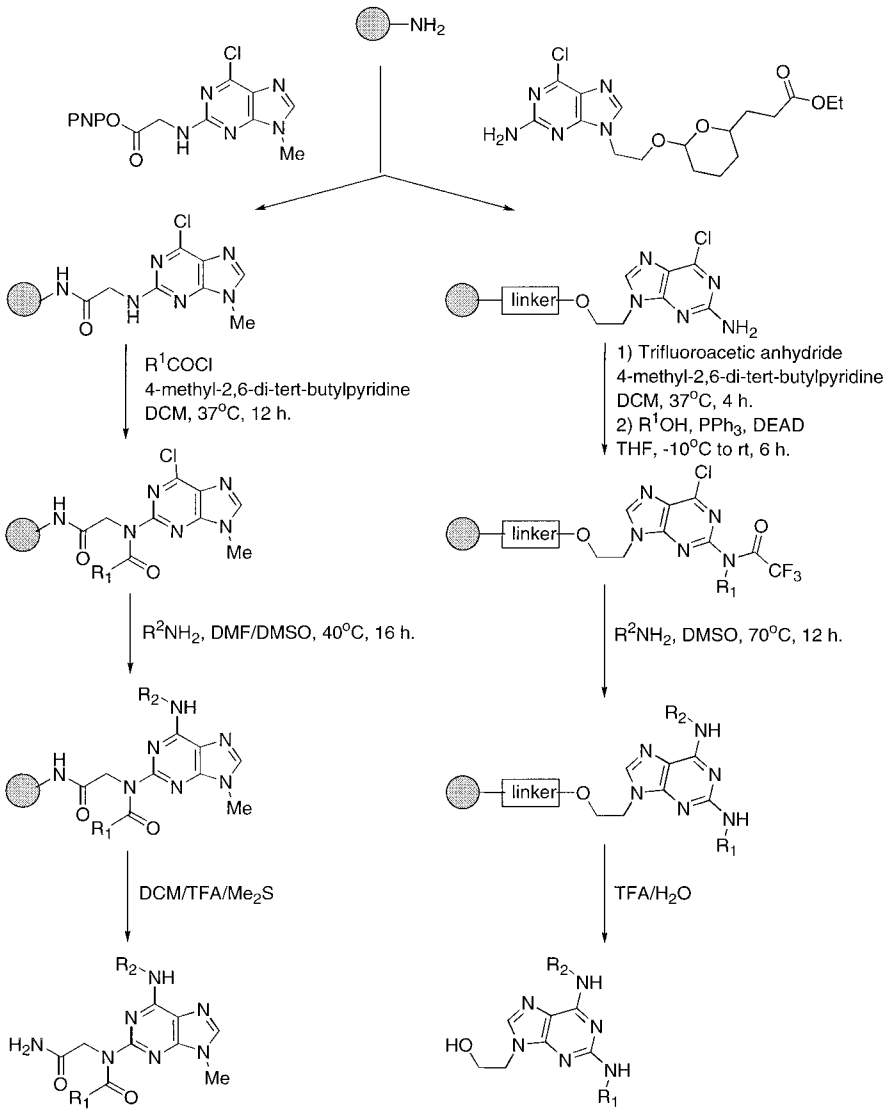
i. Triazoles. Recently, the solid phase synthesis of 1,2,3-triazoles has been reported by Zaragoza and Petersen.[151] In the presence of triethyl orthoformate, the condensation of primary aliphatic amines with a resin-bound 3-oxobutyramide resulted in 3-amino-2-butenoic acid amides (Scheme 32). The cyclization occurred after treatment with tosyl azide in the presense of a tertiary amine. Following removal of solvents, the treatment of the resin-bound 1,2,3-triazoles with TFA in DCM yielded the triazole TFA salts in good purity. Using electron-rich benzylic amines, mixtures of products were obtained. The stability of the intermediate carbocations could give rise to solvolysis of the initially formed triazoles during the acidolytic cleavage.

j. Purine Derivatives. Using Geysen's pin apparatus, Norman and co-workers reported the solid phase synthesis of libraries containing purine derivatives.[152] The purine ring system is a key structural element of the substrates and ligands of many biosynthetic, regulatory, and signal transduction proteins including cellular kinases, G proteins, and

Scheme 32



Scheme 33

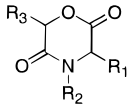


polymerases. A relatively selective inhibitor, olomoucine **11** (Figure 17), was identified that competitively inhibits CDK2/cyclin A with an IC_{50} of 7 μM. The synthesis of soluble olomoucine analogs was performed by attaching the purine scaffold to the solid support by either a glycinamide at the C-2 position or a hydroxyethyl substituent at the N-9 position (Scheme 33). In the first case, diversity was achieved by acylating the exocyclic nitrogen using an acid chloride in the presence of 2,6-di-*tert*-butyl-4-methylpyridine. A second site of diversity was obtained by the nucleophilic aromatic substitution of chloropurine derivatives by primary and secondary amines. In the case of attachment to the support at the N-9 position, diversity was achieved by acylation of the C-2 amino group with trifluoroacetic anhydride followed by alkylation under Mitsunobu conditions to afford the trifluoroacetamide derivatives. The treatment of the resin bound chloropurines with primary amines resulted in a nucleophilic substitution of the aromatic ring accompanied by aminolysis of the trifluoroacetamide. The resulting purine alcohols were cleaved from the support using 90:10 trifluoroacetic acid:water.

2. Compounds Containing Nitrogen and Oxygen

a. Diketomorpholines. Using the same approach previously described for the solid phase synthesis of diketopiperazines, a library of diketomorpholines **12** (Figure 18) has been also prepared by Scott and co-workers.[136] The cyclization of resin-bound bromides to diketomorpholine was induced by treatment with TFA. Initial cleavage from Wang resin afforded an acyclic bromo acid, which was followed by intramolecular displacement of the bromine by the carboxylate to afford the diketomorpholines. The diketomorpholine library synthesized using the DCR method consisted of 980 compounds (7 acids × 20 amines × 7 acids).

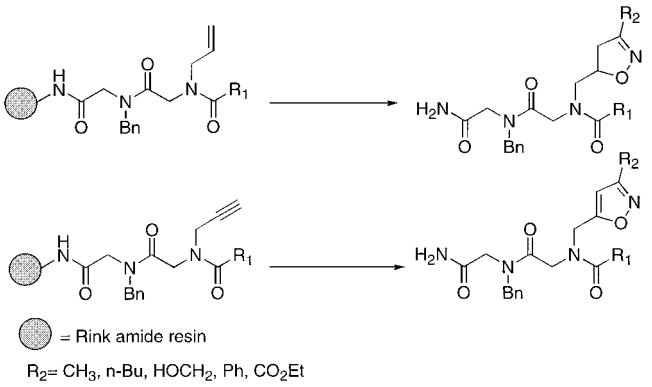
b. Isoxazoles and Isoxazolines. Yedidia and Leznoff reported the solid phase synthesis of isoxazole derivatives via 1,3-dipolar cycloaddition.[153] A divinylbenzene−styrene copolymer was reacted with



12

Figure 18. Structure of diketomorpholines **12**.

Scheme 34



propiolic acid or phenyl propionic acid to give the polymer-bound propiolate and polymer-bound benzyl phenyl propiolate. The treatment of those derivatives with benzonitrile oxide, generated in situ from α-chlorobenzaldoxime, at 0 °C in THF yielded the corresponding polymer-bound benzylisoxazoles.

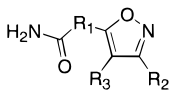
Using the same approach, the synthesis of a series of isoxazoles and isoxazolines on the solid phase has been reported by Pei and Moos via [3 + 2] cycloaddition of alkenes and alkynes with highly reactive nitrile oxides[154] (Scheme 34). The cycloaddition reactions of resin-bound peptoids were carried out in toluene at 100 °C or in DCM/H_2O at room temperature depending on the precursors of the nitrile oxides. Benzaldehyde oxime and various nitroalkyl compounds were selected as nitrile oxide precursors. The nitrile oxides were generated in situ by reacting the nitroalkyl compounds with phenyl isocyanate and triethylamine, or by oxidizing the oximes with sodium hypochlorite in the presence of triethylamine. The side reactions reported in solution chemistry were not seen in the solid phase synthesis due to the washing of the resin. High purity of the final products was reported.

The solid phase synthesis of isoxazolines and tetrahydrofuroisoxazolines via cycloaddition chemistry has also been reported by Beebe and co-workers.[120,121] The electrophilic cyclization of these compounds affords the corresponding substituted cyclic ethers.

Similar to that described for pyrazoles, Marzinzik and Felder reported the solid phase synthesis of functionalized isoxazoles **13**.[131] A four-step reaction sequence similar to that outlined in Scheme 18 was described, except monosubstituted hydroxylamines were used instead of monosubstituted hydrazines (Figure 19).

3. Compounds Containing Nitrogen and Sulfur

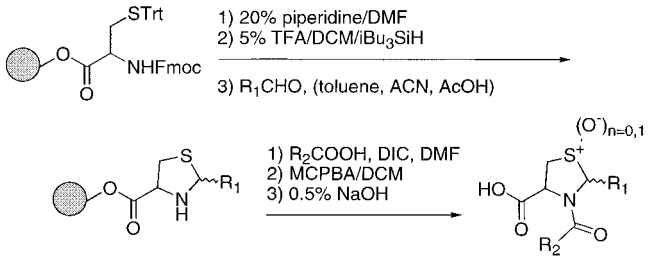
a. Thiazolidines. Patek and co-workers reported an elegant method for the synthesis of a number of *N*-acylthiazolidines.[155] The condensation of aldehyde to free (mercaptoalkyl)amine resulted in imine formation. Following cyclization, the acylated thiazo-



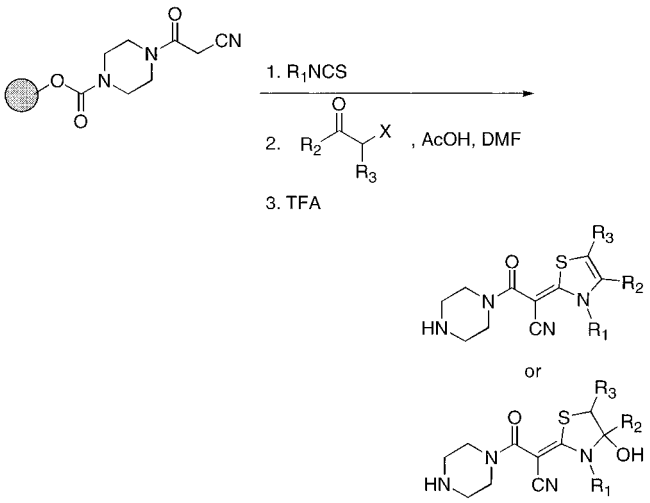
13

Figure 19. Structure of isoxazole derivatives **13**.

Scheme 35



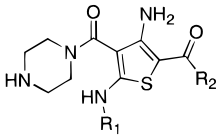
Scheme 36



lidine was obtained. Acylation increases the stability of the ring to acidolysis, but is cleavable with 20% TFA. The factors influencing the stability of acylated thiazolidine hetorocycles have been studied by Mutter and co-workers.[156,157] To increase the stability of the ring, the thioether was oxidized to sulfoxide using MCPBA (Scheme 35).

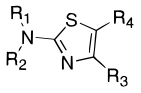
b. Dihydrothiazoles. The solid phase synthesis of substituted 3-aminothiophenes and 2-methylene-2,3-dihydrothiazoles has recently been reported by Zaragoza.[158] The reaction of resin-bound (cyanoacetyl) piperizine with aliphatic or aromatic isothiocyanates in the presence of DBU, followed by S-alkylation with α-halo ketones under slightly acidic neutral conditions, resulted in intermediates. The treatment of the intermediates with TFA yielded the 2-methylene-2,3-dihydrothiazoles of unknown configuration (Scheme 36). The treatment of the intermediates with DBU in DMF following acidolytic cleavage of the resin with TFA yielded the 3-aminothiophene derivatives **14** (Figure 20). Generally, no thiophenes have been obtained when using aliphatic halo ketones, except 3-bromo-1,1,1-trifluoro-2-propanone, which led to a clean thiophene formation.[158]

Recently, Bailey and co-workers have described the solution phase synthesis of combinatorial libraries of 2-aminothiazoles **15** via an adaptation of the Hantzsch synthesis. Use of a dipolar aprotic solvent (DMF)



14

Figure 20. Structure of aminothiophenes **14**.



15

Figure 21. Structure of thiazoles **15**.

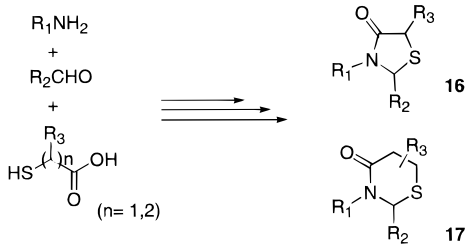


Figure 22. General procedure for the synthesis of thiazolidinones **16** and metathiazanones **17**.

and removal of the solvent using a nitrogen stream yielded the 2-aminothiazoles in excellent yield[159] (Figure 21).

c. 4-Thiazolidinones and 4-Metathiazanones. Holmes and co-workers reported the solution and polymer-supported synthesis of 4-thiazolidinones **16** and 4-metathiazanones **17** (Figure 22) derived from amino acids.[160] A three-component condensation of an amino acid ester or a resin-bound amino acid (glycine, alanine, *β*-alanine, phenylalanine, and valine), an aldehyde (benzaldehyde, *o*-tolualdehyde, *m*-tolualdehyde, *p*-tolualdehyde, and 3-pyridinecarboxaldehyde), and an α-mercapto carboxylic acid led to the formation of five- and six-membered heterocycles.

The reaction proceeds through the intermediate imine. Amino acids were chosen as the source of primary amine with the carboxylic acid function serving as the site of attachment to the support. The condensation of the support-bound amine with several aldehydes and mercaptoacetic acids in a one-pot reaction for 2 h at 70 °C with removal of water afforded the desired 4-thiazolidinones. To assure a complete reaction, Holmes et al. routinely employed from 15 to 25 equiv of reagent solution relative to the resin loading. Reactions were monitored by ^{13}C NMR analysis of the support. The reaction was driven to near completion through the use of higher concentrations of both aldehydes (0.75 M) and mercaptoacetic acid (2.0 M). Solid phase condensations to generate 4-metathiazanones using mercaptopropionic acid were less successful. The presence of a chiral center in the amino acid led to mixtures of the two possible diasteriomeric thiazolidinones.

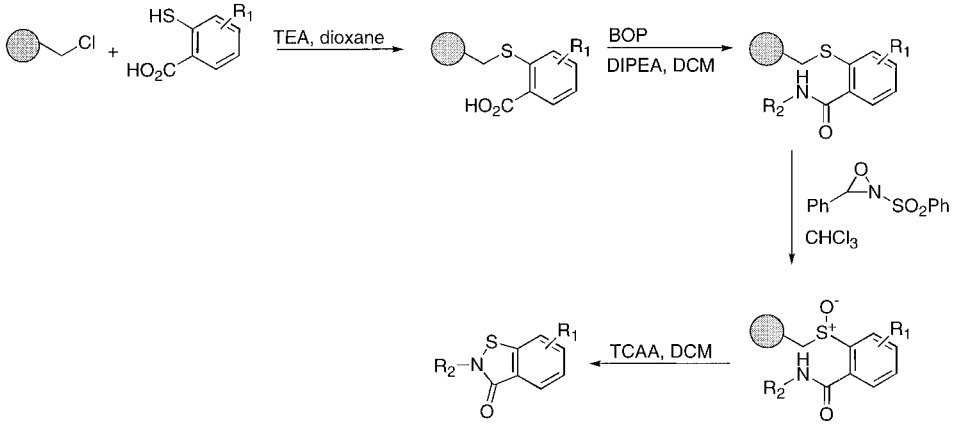
The identification of cyclo-oxygenase-1 inhibitors from 4-thiazolidinone combinatorial libraries has recently been reported by Look and co-workers.[161] The deconvolution analysis of 4-thiazolidinone libraries led to the identification of a compound that is as potent as the commercially available Cox-1 inhibitors ibuprofen and phenylbutazone.

d. Benzisothiazolones. Schroeder and co-workers reported the synthesis of benzisothiazolones.[162] The coupling of 2-carboxythiophenol to Merrifield chloromethylated resin afforded the resin-bound sulfide. The coupling of amine or hydrazide to the carboxylic acid group using BOP activation yielded the corresponding amide. To avoid overoxidation, selective mono-oxidation of the sulfide link was achieved by limited expossure to *N*-(phenylsulfonyl)-3-phenyloxaziridine. Activation of the resulting sulfoxide-bound products with trichloroacetic acid anhydride afforded, after cyclative cleavage, the desired benzisothiazolones in up to 60% yield (Scheme 37).

V. Conclusion

While change is a constant element in scientific research, at times an advance occurs which not only greatly exceeds the anticipated pace of change, but also cuts across and profoundly affects many other scientific disciplines. Such events result in major shifts in both conceptual understanding and day-to-day efforts. The introduction of combinatorial chemistry has produced such a paradigm shift. The broadly applicable concepts and tools encompassed by combinatorial chemistry accelerate advances within the originating discipline, namely synthetic organic and medicinal chemical research and discovery. Combinatorial chemistry, however, also catalyzes the acceleration of many other scientific disciplines. Thus, the availability of tens of thousands to millions of compounds in formats that can be rapidly screened in any existing assay system necessitates more efficient and cost-effective screening approaches to accommodate the large numbers of compounds. This, in turn, promotes the need for more efficient data handling approaches that can be used to facilitate computer-assisted design capabilities. The shear number of data points that can now be generated

Scheme 37



accelerates advances in biochemistry, molecular biology, bacteriology, etc. This is evident in submicroassay approaches, illustrated by the Affymax "chip" technology, which permits as many as 65 000 individual compounds to be synthesized and analyzed on the surface of a 1 cm × 1 cm silicon chip. Such data-acquiring ability greatly increases our understanding of structure−activity relationships and, in turn, adds strength to the computer-assisted design of new molecules. It can be expected from the current successes that the ability to synthesize and densely search the molecular space of therapeutically important receptors will permit not only highly active analogs of existing pharmacophores to be identified but, through the use of combinatorial variance of synthetic reaction conditions, allow the identification of entirely new synthetic approaches to novel pharmacophores. Combinatorial chemistry and synthetic approaches can be expected to rapidly lead to more active, more specific, safer, and less expensive therapeutics.

Except for a few noted laboratories, all organic combinatorial libraries synthesized to date have been prepared as individual compound arrays, tagged, resin-bound one bead/one compound arrays, or mixtures from which individual compounds are identified by successive iterative steps. We believe the two approaches that will predominate in combinatorial chemistry are the synthesis of individual compound arrays by robotic systems and the synthesis of mixtures of compounds for deconvolution using the positional scanning approach. This is due to the thoroughness of information obtained when all compounds in a given class are examined individually in a rapid manner, which is possible using individual compound arrays. Positional scan, on the other hand, addresses the combined pressures of economics and time constraints and the fact that not all assays are available in a conventional high throughput format.

While sometimes jaded by the pace of change, the global scientific community is clearly excited by and responding to the opportunities inherent in the revolutionary scale of combinatorial approaches to basic research and drug discovery. The past 10 years will be seen as the first decade of a new era in basic research and drug discovery brought about by the constantly accelerating growth of combinatorial chemistry and related approaches.

VI. Acknowledgments

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VII. Glossary

ACN	acetonitrile
AcOH	acetic acid
Bn	benzyl
Boc	*tert*-butoxycarbonyl
BOP	benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate
Bpoc	[(biphenylylpropyl)oxy]carbonyl
Bz	benzoyl
CAN	ceric ammonium nitrate
DBU	1,8-diazobicyclo[5.4.0]-undec-7-ene
DCC	*N*,*N*′-dicyclohexylcarbodiimide
DCM	dichloromethane
DCR	divide, couple, recombine
DHP	dihydropyridine
DICI	*N*,*N*′-diisopropylcarbodiimide
DIPEA	diisopropylethylamine
DKM	diketomorpholine
DKP	diketopiperazine
DMA	dimethylacetamide
DMF	dimethylformamide
DMSO	dimethyl sulfoxide
Fmoc	(9-fluorenylmethoxy)carbonyl
HATU	azabenzotriazolyl-*N*,*N*,*N*′-tetramethyluronium hexafluorophosphate
HBTU	2-(1*H*-benzotrizol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate
HIV	human immunodeficiency virus
HOBT	1-hydroxybenzotriazole
HPLC	high performance liquid chromatography
LDA	lithium diisopropylamide
MBHA	4-methylbenzhydrylamine
MCPBA	3-chloroperbenzoic acid
MeOH	methanol
NMP	*N*-methylpyrrolidinone
NMR	nuclear magnetic resonance
PAL	5-(4-[(Fmoc-amino)methyl]-3,5-dimethoxyphenoxy)valeric acid
PS-SCL	positional scanning synthetic combinatorial library
PyBOP	benzotriazol-1-yloxytrispyrrolidinophosphonium hexafluorophosphate
PyBroP	bromobispyrrolidinophosphonium hexafluorophosphate
SASRIN	super acid sensitive resin
SCL	synthetic combinatorial library
SN	nucleophilic substitution
SPOS	solid phase organic synthesis
SPS	solid phase synthesis
TCAA	trichloroacetic anhydride
THF	tetrahydrofuran
TFA	trifluoroacetic acid
TMG	tetramethylguanidine
Trt	trityl

VIII. Bibliography

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