CHIMIA 51 (1997) Nr. 11 (November)

Chimia 51 (1997) 826–831

ISSN 0009–4293

Identifying Novel Leads Using Combinatorial Libraries: Issues and Successes

Michael R. Pavia[a]*, **Sean P. Hollinshead**[b], **Harold V. Meyers**[a], and **Steven P. Hall**[b]

Abstract. Chemically generated libraries of small, non-oligomeric compounds are being widely embraced by researchers in both industry and academia. There has been a steady development of new chemistries and equipment applied to library generation so it is now possible to synthesize almost any desired class of compound. However, there are still important issues to consider that range from what specific types of compounds should be made to concerns such as sample resynthesis, structural confirmation of the hit identified, and how to best integrate this technology into a pharmaceutical drug discovery operation. This paper illustrates our approach to new lead discovery (individual, diverse, drug-like molecules of known structural identity using a simple, spatially addressable parallel synthesis approach to prepare Multiple Diverse as well as Universal Libraries) and describes some representative examples of chemistries we had developed within these approaches (preparation of bis-benzamide phenols, thiophenes, pyrrolidines, and highly substituted biphenyls). Finally, the manuscript concludes by addressing some the present concerns that still must be considered in this field.

Recent advances in genomics and molecular biology are supplying the pharmaceutical industry with large numbers of novel biological targets. The industry is responding by making use of high-throughput screening technologies coupled with compound libraries to rapidly identify and optimize ligands for these targets [1][2]. Clearly, chemically generated screening libraries are being widely embraced by researchers in both industry and academia. Today, the vast majority of efforts in the field are devoted toward the preparation of small, non-oligomeric compounds, the historically preferred drug molecule. There has been a steady development of new chemistries and equipment applied to library generation so it is now possible to synthesize almost any desired class of compound using these methodologies, and additional methods and chemistries are being reported on a weekly basis.

However, it is becoming increasingly clear that simply being able to synthesize any type of molecule is not sufficient. There are important issues to consider that range from what specific types of compounds should be made to concerns such as sample resynthesis, structural confirmation of the hits identified, and very importantly, how to best integrate this technology into a pharmaceutical drug discovery operation.

This paper will illustrate our approach to new lead discovery and describe some representative examples of our approaches and chemistries. Finally, we conclude by addressing some of the present concerns that still must be considered.

First, the ground rules for our discovery program (*Fig. 1*): We decided early on to prepare individual molecules of known structural identity using a parallel synthesis approach. The individual chemical reactions are carried out *via* multistep organic synthesis in a spatially addressable and parallel format so that one single and well-defined compound is prepared at each synthesis site and multiple syntheses are carried out simultaneously in multimilligram quantities. This approach allowed us to avoid the issues inherent in synthesizing and screening mixtures of compounds and allowed us to prepare sufficient quantity of each compound to allow for evaluation in multiple assays over a period of years.

Our target focus was selected to be molecules with low molecular weights (generally <600 amu) to afford the best chance of oral bioavailability and to be 'drug-like' (non-peptide or oligomeric).

Finally, we decided to pursue parallel array synthesis primarily using 96-well commercial microtiter plates and to apply automation to only select operations. As a result we were successful in developing a low-cost, simple approach that can be easily utilized by our combinatorial chemists and can also be easily transferred to traditional medicinal chemistry labs.

Our basic reaction vessel (*Fig. 2*) [3] consists of a commercially available polypropylene 96-deepwell plate which was modified for filtration by drilling a small hole in the bottom of each well, then placing a porous polyethylene frit into the bottom of each well. An aluminum plate clamp was made as a two-piece assembly, consisting of a solid base clamp fitted with four removable corner stainless steel studs, and a frame clamp which fits atop the plate and is secured with wing nuts. An inert gasket was utilized on the base clamp to prevent leakage of well contents. Additional pieces of equipment have been developed as needed and these needs have primarily been driven by new chemistry requirements. As stated earlier, we decided to apply automation only to select tasks that would free the chemists for more productive endeavors and also assure consistency in repetitive procedures. Among the procedures that are currently being automated on a routine basis are liquid transfer (solvents and reagents), solid transfer (reagents and resins), filtration, solid-phase extraction, and several analytical procedures.

Our initial efforts in preparing combinatorial libraries were focused almost exclusively on solid-phase organic chemistry, or carrying out the synthetic transformation while the product is attached onto

**Correspondence*: Dr. M.R. Pavia[a])
[a]) *Sphinx Pharmaceuticals*
A Division of *Eli Lilly & Company*
840 Memorial Drive
Cambridge, MA 02139, USA
[b]) *Sphinx Pharmaceuticals*
A Division of *Eli Lilly & Company*
615 University Drive
Durham, North Carolina 27707, USA

CHIMIA 51 (1997) Nr. 11 (November)

an insoluble polymer support. Solid-phase synthesis has many advantages over traditional solution-based methods. For example, large excesses of starting materials can be employed to drive reactions to completion without fear of complicating the workup procedure; simple filtration and resin washing are typically sufficient for removal of unreacted starting materials and reaction by-products. The relative site isolation of the resin-bound species can inhibit many types of intermolecular side reactions and help to stabilize reactive intermediates. Resin-bound materials tend to be air- and moisture-stable and are easily manipulated. Nevertheless, solid-phase synthesis also possesses many disadvantages. Solid-phase reactions are more difficult to monitor by conventional techniques. Typically, a large quantity of resin produces only a small amount of final product, serving to complicate analysis in many cases; increasing the loading capacity of a resin to circumvent this problem frequently leads to a concomitant decrease in the effective site isolation. Reactions are frequently significantly retarded on solid phase, and heterogeneous reagents cannot be employed. Many resins, particularly cross-linked polystyrene, display significant swelling and shrinking properties which can severely affect reaction rates and site accessibility; frequently, the optimal solvent for resin swelling is not the optimal solvent for the desired reaction. However, many of these disadvantages are being addressed with promising results. In addition, the range of organic reactions which has been successfully employed on solid phase continues to expand, making this a very powerful method.

We have recently begun to take advantage of a complimentary approach to solid-phase chemistry which largely circumvents the disadvantages discussed above but maintains many of its advantages. This involves carrying out library construction in solution but using either polymer-supported reagents to effect reaction or using polymer-bound scavengers to remove impurities and/or unwanted reactants or products. We now routinely make use of both solid-phase organic chemistry as well as solution-based methods depending on the particular chemistries involved. Between the two methods we have successfully carried out nearly one hundred different organic reactions in library format.

With a simple and economical procedure for carrying out library synthesis and a broad range of chemistries available to our researchers, we will next discuss our lead discovery efforts. We have approached the problem of lead discovery from two different, but complimentary approaches (*Fig. 3*), the Multiple Diverse Scaffold Approach and the Universal Library Approach. In both approaches we find a central scaffold portion of the molecule. We have selected these scaffolds to possess 'drug-like' properties and to have several sites for attachment of diversity elements. Diversity elements are those groups that are primarily responsible for selectively binding to the biological target of interest and as a group possess a broad range of physiochemical properties.

In the Multiple Diverse Scaffold Approach we have assembled a large collection of structurally diverse scaffolds. To date we have designed and synthesized over forty scaffolds with unique properties and diversity element orientations (examples of the preparation of three scaffold types are illustrated in the *Schemes 1–3*). For any given scaffold, the attachment points for the diversity elements remain constant and the identity of the diversity elements is changed. We commonly make use of a diversity element set containing over 1500 members. While the identity, and hence the properties, of the diversity elements is easily changed, in order to change the relative geometry of the diversity elements we are forced to change to a different scaffold.

In the Universal Library Approach we designed a versatile class of molecules which allows for the rapid display of mul-

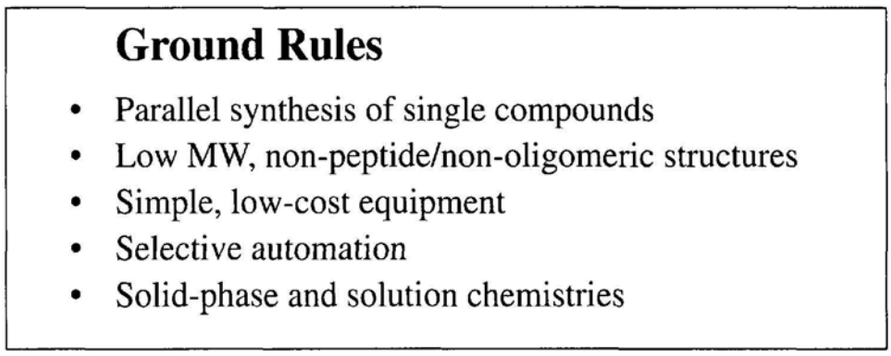


Fig. 1. *Ground rules*

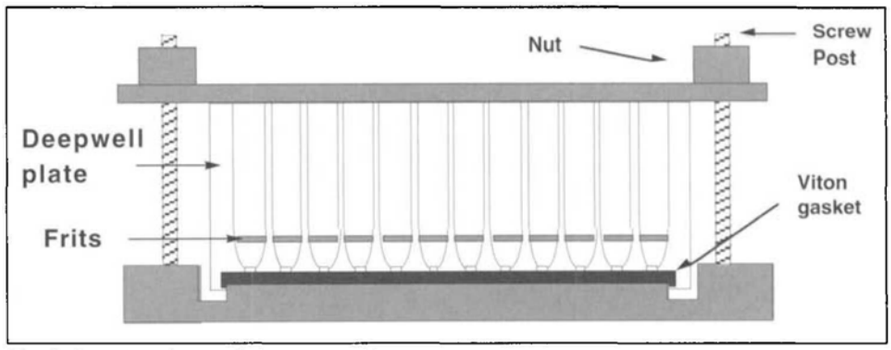


Fig. 2. *Reaction plate and clamp assembly*

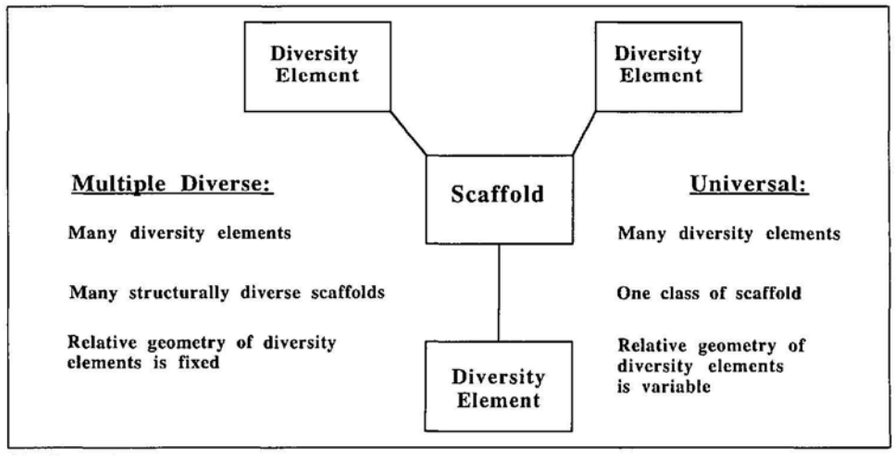


Fig. 3. *Lead generation strategies*

tiple diversity elements in large numbers of spatial arrangements using one general class of scaffolds. The relative geometry of the diversity elements are changed simply by changing the substitution patterns of the diversity elements around the scaffold. Additional modifications can be made that result in facile changes in the size, shape, and physical properties of the target molecules.

In designing specific libraries to be prepared within these two general approaches we make extensive use of computational analysis. This method is complimented by the medicinal chemistry intuition of our chemists, and of course the ongoing collection of biological test results helps to guide and refine our efforts.

Examples

Four specific library examples will now be described in more detail to illustrate the types of scaffolds and chemistries which can be prepared using our methodology. The first three examples illustrate the Multiple Diverse Scaffold Approach and the final example will illustrate the Universal Library Approach.

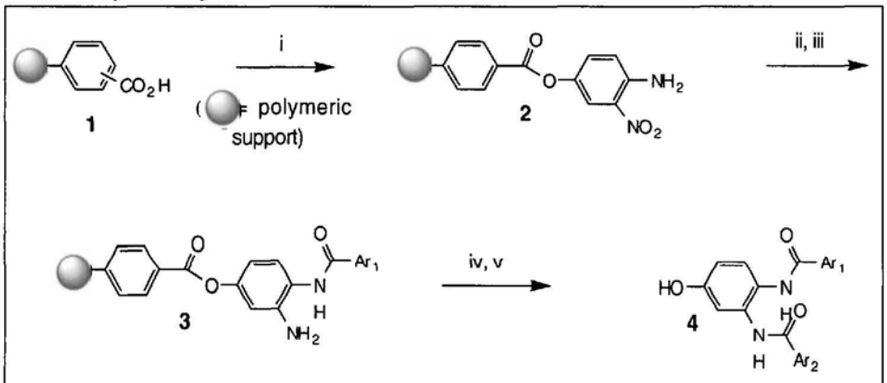
Example 1: 'Bisbenzamide phenols' (*Scheme 1*) [3]. The procedure for synthesizing this class of compounds will be described in detail and is illustrative of our general procedures. The scaffold 4-amino-3-nitrophenol was selected to allow a facile site of resin attachment (the OH group) and two differentiated sites for acylation (the amino group and the second site 'protected' as a nitro group). In addition to simple acylation reaction, it was also demonstrated that sulfonylation and isocyanation are also feasible chemistries to provide the corresponding sulfonamides and ureas, considerably increasing the diversity of the library.

We selected a solid-support linker that would maintain its integrity across the range of anticipated reaction conditions but which would be readily cleaved at any time under mild conditions to maintain the integrity of the scaffold and its attached functional groups. This strategy would enable us to characterize and monitor reactions and products in solution at each synthetic step if desired. Hence, the benzoate ester proved to be a satisfactory linker group, and could be cleaved readily under basic conditions but demonstrated negligible cleavage during the synthetic process.

A batch synthesis preparation was used to prepare multigram quantities of resin-bound monoacylated scaffolds (**3**, *Scheme 1*). The triply differentiated scaffold, 4-amino-3-nitrophenol was coupled to carboxylated polystyrene resin **1** (DIC, pyridine, catalytic DMAP in DMF, 25°, 24 h) through the OH group with excellent chemoselectivity. Subsequent acylation reactions were performed with acid-chloride derivatives (4 equiv.) and excess pyridine in CH_2Cl_2 (25°, 24 h). Aromatic nitro-group reduction was found to proceed smoothly on resin (5 equiv. of 2M $SnCl_2{\cdot}2H_2O$ in DMF, 25°, 5 h). This procedure afforded multigram quantities of benzanilide resins **3**.

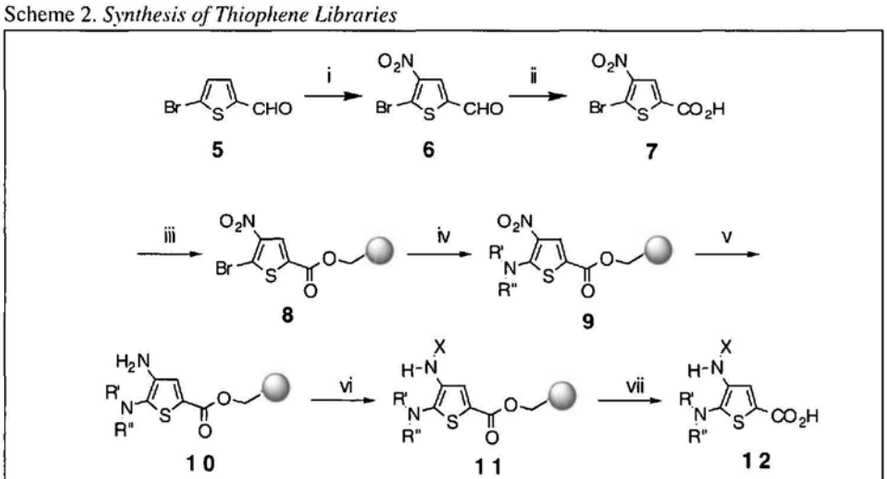
The benzanilide resins were loaded into plates for the second acylation and the appropriate reagents added (acid-chloride derivatives (8 equiv.), excess pyridine and catalytic DMAP in CH_2Cl_2 (25°, 24 h)). Once a plate was loaded the wells were sealed with strip caps then agitated to facilitate chemical reaction. Resins were washed after each synthetic step by allowing them to soak in solvent for a short period, then removing the solvent by suction. A typical washing protocol employs alternating DMF and MeOH (3 cycles), then a final CH_2Cl_2 rinse. The use of K_2CO_3 in MeOH generally gave good cleavage results. After cleavage, solution libraries were obtained by filtration into racks of 96 microdilution tubes. Phenoxide libraries were acidified (HCl/Et_2O or TMF) directly in the microdilution tubes, and solvents were removed *in vacuo* with a speedvac (*Savant*). Phenolic libraries **4** processed as described are suitable for

Scheme 1. *Synthesis of 'Bisamide Phenols'*



i) 4-amino-3-nitro-phenol, DIC, pyridine, DMAP, DMF ii) Ar_1-COCl, pyridine, DMAP, CH_2Cl_2 iii) 2M $SnCl_2{\cdot}2H_2O$, DMF iv) Ar_2-COCl, pyridine, DMAP, CH_2Cl_2 v) NaOMe, MeOH/THF

Scheme 2. *Synthesis of Thiophene Libraries*



i) KNO_3, HNO_3, 0° (45–50%) ii) NaH_2PO_4, H_2O_2, $NaClO_2$, MeCN-H_2O (94%) iii) Merrifield resin, Cs_2CO_3, DMF iv) R'R"NH, DMF, r.t. v) $SnCl_2.2H_2O$, DMF vi) electrophile, pyridine, DMAP, CH_2Cl_2 vii) NaOH, THF, MeOH

CHIMIA 51 (1997) Nr. 11 (November)

analytical work, direct biological screening, and storage.

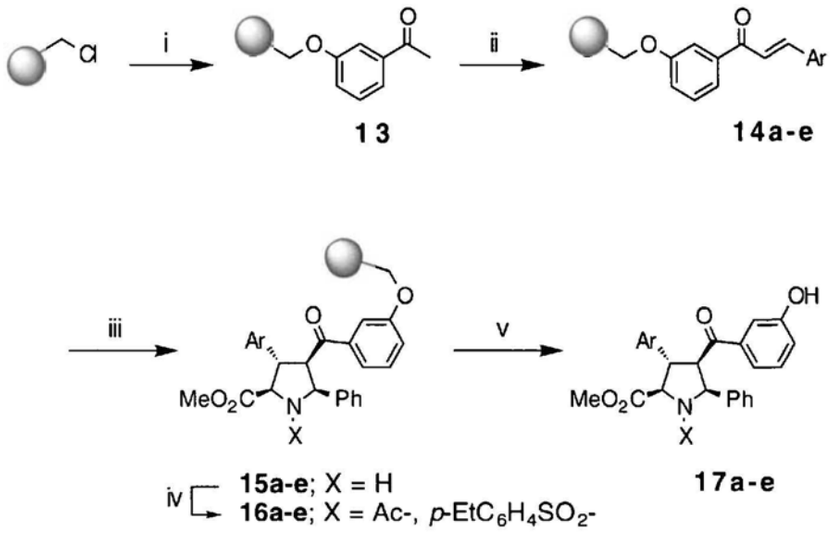
A randomly chosen subset of wells from each plate was directly analyzed by LC and ^{1}H-NMR. Thin-layer chromatography was conveniently performed on every well, providing a rapid qualitative assessment regarding the synthetic outcome. The average estimated purity per well was 82%, though approximately two thirds of the wells were essentially one component by TLC. Compound quantities typically ranged from 3–9 mg per well, and purity ranged from 68–82%.

Preparation of this phenol library represented one of the earliest examples of preparing large non-peptide libraries in a 96-well format. While the chemistry is quite simple, we now had a basic protocol which would allow us to develop more complex and synthetically useful transformations. Furthermore, even using this simple chemistry we were able to identify additional unique scaffolds that displayed the two acyl groups in different orientations. This expanded library is referred to as a 'diamino-alcohol super library'.

The synthesis of two additional scaffolds within the Multiple Diverse Approach will now be described. These two examples were selected to illustrate two unique methods for scaffold preparation. In the first example, a thiophene library, the scaffold is prepared first in solution. The library was then prepared *via* nucleophilic substitution and acylation reactions. In the second example involving the preparation of highly functionalized pyrrolidines, the scaffold was synthesized from various diversity element-containing building blocks *via* sequential carbon-carbon bond forming reactions.

Example 2: A thiophene library (*Scheme 2*) [4]. Nucleophilc aromatic substitution is a convenient method of introducing functionality into a molecule and, when coupled with the potential for utilizing N, S, and O nucleophiles, provide an attractive approach for the preparation of libraries containing diverse functionality. We employed a heterocyclic scaffold containing suitable electron-withdrawing groups (a NO_2 substituent) to facilitate the nucleophilic aromatic substitution reaction, which could subsequently be converted to a functional group for introduction of additional diversity. The scaffold of choice was 5-bromo-4-nitrothiophene-2-carboxylic acid (**7**) which was readily prepared from commercial 5-bromo-2-thiophenecarboxaldehyde (**5**) by nitration and subsequent oxidation.

Scheme 3. *Synthesis of Pyrrolidines*



i) 3-hydroxyacetophenone, Cs_2CO_3, NaI, DMF ii) ArCHO (12 equiv.), NaOMe (0.5M solution in MeOH, 12 equiv.), THF iii) $PhCH{=}NCH_2CO_2Me$, LiBr, DBU, THF iv) acylating agent, py, DMAP, CH_2Cl_2 v) TFA, CH_2Cl_2

	Ar
a	*p*-C_6H_4OMe
b	*p*-C_6H_4Br
c	*o*,*p*-$Cl_2C_6H_4$
d	1-naphthyl
e	*p*-Ph-C_6H_4

The scaffold was immobilized onto *Merrifield* resin (Cs_2CO_3/catalytic NaI in DMF). Subsequent treatment with a variety of aliphatic amines in DMF afforded an ambient temperature nucleophilic substitution of the bromo group to yield the corresponding 2-amino-substituted thiophenes **9** (under the same reaction conditions, anilines (R' or R" is aryl) were unreactive). Reduction of the NO_2 group ($SnCl_2{\cdot}2H_2O$ in DMF) allowed for introduction of additional diversity elements by reaction with electrophiles (sulfonyl chlorides, iso(thio)cyanates, *etc.*) under standard acylation reaction conditions (catalytic DMAP, pyridine, CH_2Cl_2) to afford **11**.

The final products **12** were conveniently cleaved from the resin by treatment with NaOH in THF/MeOH. This chemistry was successfully applied to the synthesis of a 1152-membered library from 32 individual amines and 36 electrophiles.

Example 3: A pyrrolidine library [5]. The final example of the Multiple Diverse Scaffold Approach is the preparation of highly functionalized pyrrolidines *via* 1,3-dipolar cycloaddition reaction on a solid support. The mild reaction conditions required for this chemistry and the ability to construct multiple bonds in a single transformation made this a highly attractive reaction for the solid-phase synthesis of heterocyclic compounds.

In our route (*Scheme 3*), 3-hydroxyacetophenone was coupled to chlorinated *Wang* resin (Cs_2CO_3/NaI in DMF) to afford **13**. For the condensation with aldehydes, NaOMe (0.5M solution in MeOH with THF as a co-solvent) was found to be the base of choice. Typically 12 equiv. of both aldehyde and NaOMe (0.5M in MeOH) were added to resin (pre-swelled in an equal volume of THF) to afford the required enones **14**. The enones were subjected to standard 1,3-dipolar cycloaddi-

CHIMIA 51 (1997) Nr. 11 (November)

tion reaction conditions with the N-metallated azomethine ylid in the presence of DBU and a *Lewis* acid (LiBr). High regio- and diastereoselectivity was observed to afford the desired products **15**.

The resulting pyrrolidines could also be conveniently reacted with acid chlorides and sulfonyl chlorides as shown in the *Table*. Cleavage from the resin (TFA-CH_2Cl_2) yielded the highly functionalized crude pyrrolidine **17**, which could be purified by chromatography or crystallization.

The three scaffolds illustrated herein represent the diverse nature of structures that can be prepared under the Multiple Diverse Scaffold Approach. For each scaffold a new synthetic route must be designed to place the diversity elements in geometrically unique positions within diversity space. An alternate approach termed the Universal Library Approach was also tested.

The Universal Library Approach: In this approach to lead generation we wished to design a scaffold which would allow diversity element display in a variety of spatial orientations by simply changing the substitution pattern of the diversity elements. A major challenge was to select a structural class of 'drug-like' target molecules of sufficient generality to allow a wide variation in substitution patterns. The biphenyl scaffold was selected as our initial class of target molecules. This drug-like scaffold allows for facile introduction of three or four functional groups in a large number of spatial arrangements simply by altering the substitution pattern on each aromatic ring. Furthermore, we have built into our design a simple method of changing the biphenyl scaffold to easily change the size, shape, and physical properties of the final products. It is important to note that the final products contain a pendant Me group since we desired not to have an invariant OH or COOH group in our final product. We wish to display important functional groups in space and do not wish to be biased by a strongly interacting invariant functional group.

The biphenyl molecules described herein are synthesized by a combination of solution- and solid-phase chemistries (*Scheme 4*) [6]. The scaffold is functionalized with appropriate side chains on the solid support using the *Mitsunobu* reaction and the final products are then cleaved from the solid support for subsequent modification and testing.

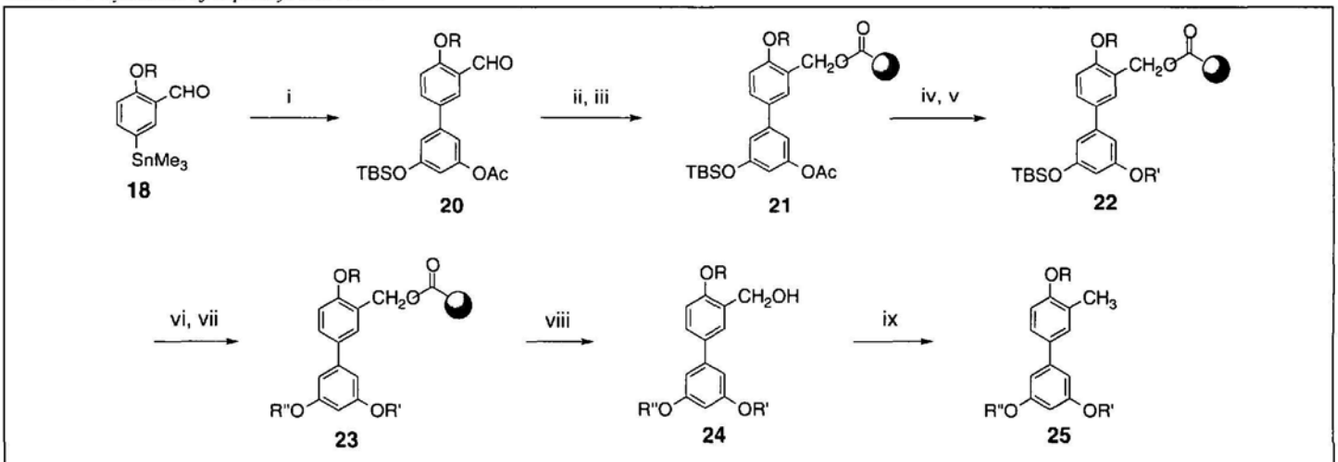
Stannylated 'A-ring' **18** and the differentially protected 'B-ring' **19** were prepared as previously described. The formation of the doubly protected biphenyl scaffold **20** was accomplished utilizing modified *Stille* conditions. By this route, multigram quantities of each unique biphenyl could be obtained after silica-gel chromatography. Prior to attaching the doubly protected biphenyl scaffolds to the solid support, reduction of the aldehyde functionality was necessary ($LiAlH(O\text{-}t\text{-}Bu)_3$ in THF). Carboxylated polystyrene resin was converted to the acid chloride and subsequent attachment of the biphenylmethanols onto the resin occurred in greater than 90% yield to afford **21**. Phenolic acetate removal from the resin-bound biphenyls was accomplished with a solution of 20% piperidine in CH_2Cl_2, and these resin-bound deprotected biphenyl-phenols were loaded into the 96-well plates. Functionalization of the free phenolic OH group was accomplished using *Castro* conditions for the *Mitsunobu* reaction to afford **22**. Removal of the phenolic *t*-butyldimethylsilyl group was accomplished under standard conditions, and further functionalization of the remaining free phenolic OH group was accomplished using a second cycle of *Mitsunobu* chemistry to afford **23**.

Table. *Yields of Purified Products Following Resin Cleavage*

Product	Ar	Acylating agent X	Yield[a])
17a	*p*-C_6H_4OMe	AcCl	45
17b	*p*-C_6H_4Br	AcCl	32
17c	*o*,*p*-$Cl_2C_6H_4$	*p*-$EtC_6H_4SO_2Cl$	68
17d	1-napthyl	*p*-$EtC_6H_4SO_2Cl$	31

[a]) % yields are for purified products and are calculated from acetophenone resin **1** and are unoptimized.

Scheme 4. *Synthesis of Biphenyl Libraries*



i) $Pd_2(dba)_3$, LiCl, TFP, NMP, 3-acetoxy-5-(t-butyldimethylsiloxy)-1-iodobenzene (**19**) ii) $LiAl(O\text{-}tBu)_3H$ iii) Et_3N, acid chloride resin iv) Piperidine v) 96-well format; R'OH, sulfamide ylide, CH_2Cl_2/toluene vi) TBAF, HOAc, THF vii) 96-well format; R"OH, sulfamide ylide, CH_2Cl_2/toluene viii) NaOMe, THF/MeOH; HCl ix) Et_3SiH, TFA

CHIMIA 51 (1997) Nr. 11 (November)

Cleavage of the biphenyl library from the solid support was accomplished by saponification (NaOMe in MeOH/THF). The resulting solutions were acidified, and the free biphenyl-methanols **24** were collected by gravity filtration into a 96-well plate. Post cleavage modification of the benzylic alcohol stub was accomplished by reduction with a solution of triethylsilane and TFA in CH_2Cl_2 for 12 h. Volatile components were removed to afford the free 'biphenyl-methanes' **25**.

In order to evaluate the chemical efficiency of the parallel synthesis procedure, random sampling of both the hydroxymethyl-biphenyls and the methyl-biphenyl derivatives was performed and quantified by TLC, HPLC, ^{1}H-NMR, and MS. Based on these analyses, average purity of the desired compounds within the library was estimated to be >50%.

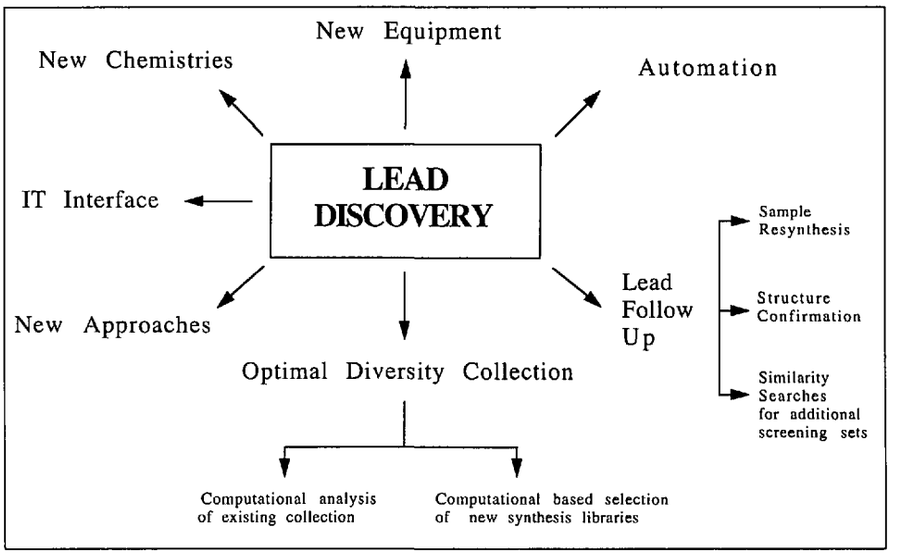


Fig. 4. *Lead discovery*

Conclusion

We have demonstrated a variety of conceptual approaches to lead generation along with a wide variety of chemistries to prepare structurally diverse classes of molecules. This diverse library is routinely being screened against a collection of biological targets of interest. Both approaches have been successful in identifying active compounds with binding affinities ranging from low-nanomolar to micromolar in a majority of the assays carried out. Furthermore, the wide range of chemistries now available to us, including the use of solid-bound reagents and scavengers, have been very useful for optimization of these leads and is routinely being utilized by our colleagues in medicinal chemistry.

Combinatorial chemistry has given us the ability to more rapidly and effectively identify novel leads for a variety of biological targets. However, there is a continuing need to further develop the technology and to integrate it with other aspects of drug discovery. Some of these needs are illustrated in *Fig. 4*.

We need to continue to develop chemistries suitable for library synthesis. Advances in adapting solution chemistry to solid-phase organic synthesis must continue. The creation of novel cleavable linkers for tethering reaction components to supports and improvements aimed at identifying novel solid supports to improve reaction yields and product loading will all contribute to this effort. An expanded scope of reactions that can occur with solution techniques using solid-bound reagents and scavengers as well as increasingly effective parallel purification schemes are also needed. In short, soon we will have the ability to make nearly any class of molecule we wish using these rapid techniques.

New and improved equipment is being developed to allow us to carry out reactions under many of the conditions utilized in a standard organic chemistry laboratory (these include heating, cooling, controlled atmosphere, hydrogenation, *etc.*). Improved generations of automated instrumentation is also being developed. Furthermore, progress is likely to continue to drive combinatorial technologies and instrumentation towards miniaturization.

In the area of computational analysis we continue to test and develop improved methods of library design and analysis of diversity space. As we achieve a better understanding of diversity space analysis, a reasonable goal will be to attempt to prepare libraries designed to rapidly explore diversity space with a limited number of structural motifs and effectively identify a chemical lead for many biological targets of interest. With the creation of so much chemical and biological data, new data-handling tools to process, keep track, and interpret results are being developed.

And finally, let's not forget some of the more mundane problems such as confirmation of the structure of active compounds and their resynthesis and secondary assay evaluation.

To date many of us have tended to separate combinatorial chemistry from mainstream medicinal chemistry. Combinatorial library approaches will not displace these older methods, but will need to be integrated with them. It is therefore important that our medicinal chemistry colleagues be adequately trained in the use of library technology for rapid structure-activity work. Finally, we need to jointly apply structure- and mechanism-based drug design with library design to achieve the best results.

For this new paradigm to achieve optimal success, all of the various disciplines including chemistry, molecular biology, genomics, screening, engineering, computational science, and information technology must work together effectively. Only in this manner will the exciting recent successes seen with combinatorial chemistry continue to multiply in the future.

We would like to thank all of our colleagues at both *Sphinx* and *Lilly*, especially Drs. *Stephen Kaldor* and *Marty Haslanger* for their efforts and support.

Received: May 28, 1997

[1] M.A. Gallop, R.W. Barrett, W.J. Dower, S.P. Fodor, E.M. Gordon, *J. Med. Chem.* **1994**, *37*, 1233.

[2] E.M. Gordon, R.W. Barrett, W.J. Dower, S.P.A. Fodor, M.A. Gallop, *J. Med. Chem.* **1994**, *37*, 1385.

[3] H.V. Meyers, G.J. Dilley, T.L. Durgin, T.S. Powers, N.A. Winssinger, H. Zhu, M.R. Pavia, *Molecular Diversity* **1995**, *1*, 13.

[4] S.P. Hollishead, submitted, 'Application of Solid Phase Reactions to a Novel Thiophene Scaffold'. Presented (in part) at the Fall 212th National ACS Meeting, August 25–30, 1996, Orlando, FL.

[5] S.P. Hollinshead, *Tetrahedron Lett.* **1996**, *37*, 9157.

[6] M.R. Pavia. M.P. Cohen, G.J. Dilley, G.R. Dubuc, T.L. Durgin, F.W. Forman, M.E. Hediger, G. Milot, T.S. Powers, I. Sucholeiki, S. Zhou, *Bioorg, Med. Chem.* **1996**, *4*, 659.