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Combinatorial Chemistry: A Guide for Librarians

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Combinatorial Chemistry: A Guide for Librarians

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Abstract

In the 1980s a need to synthesize many chemical compounds rapidly and inexpensively spawned a new branch of chemistry known as combinatorial chemistry. While the techniques of this rapidly growing field are used primarily to find new candidate drugs, combinatorial chemistry is also finding other applications in various fields such as semiconductors, catalysts, and polymers. This guide for librarians explains the basics of combinatorial chemistry and elucidates the key information sources needed by combinatorial chemists.

Introduction

Most librarians who serve chemists or chemistry students are familiar with the six main disciplines of chemistry. These are:

Physical chemistry applies the fundamental laws of physics, such as thermodynamics, electricity, and quantum mechanics, to explain chemical behavior.

Analytical chemistry is the determination of the composition of materials, and the identifying of its constituents. Determining the amount of active ingredient and impurities in a pharmaceutical preparation is a clear example of analytical chemistry.

Organic chemistry - Carbon is a versatile element that readily combines with both itself and many other atoms to make a nearly limitless number of chemical compounds, millions have been recorded. Even though most carbon compounds have nothing to do with life, the chemistry of carbon and its compounds is known as organic chemistry. This misnaming of carbon chemistry

arose because the earliest known carbon containing chemicals, such as sugar, the acetic acid in vinegar, alcohol, soaps, and vegetable dyes were all derived from plants and animals. Most of the substances we see in everyday life are organic.

Inorganic chemistry is the study of noncarbon containing substances. However, some small and simple carbon containing compounds, where carbon does not significantly determine the substance's properties may be included. The materials used to construct nearly all the important parts in computers, such as the semiconductors in chips and the monitor screens are important applications of inorganic chemistry.

Biochemistry is the chemistry of life; the reactions and structures of substances in living organisms. Derived from and intertwined with biochemistry are the related disciplines, molecular biology which focuses on the role of molecular structures, primarily genes, and structural biology which seeks to relate the structure of substances such as proteins to their biological role.

Polymer Chemistry is the science of large molecules (macromolecules) that are formed by the joining of small simple molecules. Polymers are both naturally occurring and synthetic. Some polymers familiar to us are plastics, fabrics, paints, and rubbers.

In the late 1980s (Service 1997; Lebl 1999) a new field of chemistry called combinatorial chemistry arose. **Combinatorial chemistry** is an innovative method of synthesizing many different substances quickly and at the same time. Combinatorial chemistry contrasts with the time-consuming and labor intensive methods of traditional chemistry where compounds are synthesized individually, one at a time. While combinatorial chemistry is primarily used by organic chemists who are seeking new drugs, chemists are also now applying combinatorial chemistry to other fields such as semiconductors, superconductors, catalysts and polymers.

Why did chemists need to develop this new field of chemistry which is essentially a time saving shortcut to making new compounds, as opposed to the traditional method of making single compounds step by step?

The large pharmaceutical companies have vast collections of compounds synthesized by the traditional slow and consequently expensive methods (Borman 1999). They have already screened most of these for pharmaceutical activity. While natural products are a source for new drugs, most of the readily obtainable natural products have already been found (Baum 1994). They need another approach to make and test many more compounds easily and inexpensively. Also, new and small pharmaceutical companies without the benefit of such compound collections, need to compete with the established companies, and combinatorial chemistry is a way they can (Borman 1999).

Between 12 and 15 years and as much as $500 million are needed to develop a new drug, and bring it to market (Alper 1994; Brennan 2000; Zall 2001). Combinatorial Chemistry enables pharmaceutical companies to develop new candidate drugs in months instead of years (Brennan 2000). Because thousands of new compounds can be created and screened in days, hundreds of millions of dollars have been invested in this technique, and nearly all of the major pharmaceutical companies now have their own combinatorial chemistry departments (Plunkett & Ellman 1997). Numerous new drug discovery companies have been formed (Thayer 1996; Service 1997).

Compounds discovered with the help of combinatorial chemistry are in clinical trials (Service 1996;Plunkett & Ellman 1997). Combinatorial chemistry shows promise in developing anticancer drugs (Mort 2001). Once these benefits of combinatorial chemistry became apparent, inorganic and polymer chemists started applying these methods.

The Basics of Combinatorial Chemistry

Traditionally, chemists make compounds one at a time, step by step. If the synthesis of a compound requires numerous steps, the intermediate compounds are usually purified after each step. On the other hand, when chemists use combinatorial methods they will always be making many different compounds at the same time often in the same reaction vessel. The purification steps are usually faster and less complicated compared to the traditional methods. Here is a simple example of combinatorial chemistry:

Chemists often start a combinatorial synthesis with a batch of small plastic beads, each individual bead is about the size of a grain of sand. They attach small molecular building blocks to these beads stepwise.

They like to use these plastic beads because they need only wash the beads to purify the intermediate compound between each step. To make this washing easier, the chemist often puts these batches of beads into chemically resistant porous bags resembling tea bags, or puts the beads into columns resembling coffee filters.

In this example we will start with eight of these tea bags in one container, although we could use any number of these bags. Each bag contains a spoonful of these small plastic beads. To keep track of these bags, each bag can simply be labeled with a pencil.

The chemist first attaches a small molecular building block to these beads by soaking them in a solution containing this building block. We will call this first building block molecule "a". At this point we have eight individual bags of beads with the first molecule, "a" attached to every bead

beads-a beads-a beads-a beads-a

beads-a beads-a beads-a beads-a

The beads are then washed to remove any excess "a" and any undesired reaction products.

The chemist then puts two of these bags in a vessel containing building block "b," two bags in another vessel with "c," two bags in a another vessel containing "d," and finally two bags in a vessel containing "e."

beads-a-b beads-a-c beads-a-d beads-a-e

beads-a-b beads-a-c beads-a-d beads-a-e

Here also, once this set of reactions is finished, the bags are washed, to remove undesired substances. A third round of reactions takes place in eight individual containers. A new and different building block is added to each container.

beads-a-b-f	beads-a-c-h	beads-a-d-j	beads-a-e-l
beads-a-b-g	beads-a-c-i	beads-a-d-k	beads-a-e-m

We now have eight different and clearly defined compounds. After all building blocks have been added, the bond between the plastic bead and the compound attached to it can easily be cleaved. Each of the compounds can now be tested for the desired activity. In this example we used the same building block only in the first position. Chemists always have the option of repeating the same building blocks. Even the compound a-a-a can be made if desired.

This example fulfills the requirement of combinatorial chemistry because the chemist made more than one substance at the same time. However, several reaction vessels were required. Chemists are always seeking to make even more compounds with the same amount of work involved in this example. Wherever possible they want to be able to make many different compounds in the same reaction vessel in a minimum number of steps.

Let us now look at a more sophisticated application of combinatorial chemistry. We will start here with three batches of beads, in three separate containers, one reacted with building block "a," one with "b," and one with "c."

beads-a	beads-b	beads-c
container #1	container #2	container #3

After this first reaction, the beads are washed and then mixed together in one vessel, then split among three separate containers.

beads-a	beads-a	beads-a
beads-b	beads-b	beads-b
beads-c	beads-c	beads-c
container#1	container #2	container#3

Now, building blocks "a" are added to container #1, "b" to container #2, and "c" to container #3. After these are allowed to react, each container has the following:

beads-a-a	beads-a-b	beads-a-c
beads-b-a	beads-b-b	beads-b-c
beads-c-a	beads-c-b	beads-c-c
container#1	container #2	container#3

All of the beads are again washed then mixed together and again split into three containers. Again, building blocks "a" are added to container #1, "b" to container #2, and "c" to container #3. After this set of reactions, each container has the following:

beads-a-a-a	beads-a-b-a	beads-a-c-a
beads-b-a-a	beads-b-b-a	beads-b-c-a
beads-c-a-a	beads-c-b-a	beads-c-c-a
	container #1	

beads-a-a-b	beads-a-b-b	beads-a-c-b
beads-b-a-b	beads-b-b-b	beads-b-c-b
beads-c-a-b	beads-c-b-b	beads-c-c-b
	container #2	

beads-a-a-c	beads-a-b-c	beads-a-c-c
beads-b-a-c	beads-b-b-c	beads-b-c-c
beads-c-a-c	beads-c-b-c	beads-c-c-c
	container #3	

Here in only three sets of reactions, never using more than three containers, we made all 27 possible combinations of compounds consisting of these three building blocks. In this still rather simple example, we stopped after three steps. Performing just one more round of this mixing and splitting would yield 81 distinct compounds. Note that after each round of reactions the contents were mixed together than split into separate containers. Hence this type of synthesis is called mix and split or split and mix.

In the first example using the tea bags, each tea bag produced only one compound. In this mix and split example each container has nine different compounds. In the field of combinatorial chemistry, a collection of several or many different compounds in the same container is called a library. This rather unusual use of the word library was adapted from the field of molecular biology where the term library defines a mixture that results when a large piece of genetic material (DNA or RNA) is cut into many small pieces, and the piece of genetic material with a sought after property is identified and isolated from the mixture.

Again looking at the above example of a combinatorial synthesis, suppose the contents of these three containers are tested for the desired activity, and only the contents of container #3 are active. How does the chemist know which of these nine compounds in this library contributed to the activity? The active compound has the structure ?-?-c, where the question marks represent building blocks "a," or "b," or "c."

Determining the structure of an active compound present in a mixture of compounds is termed deconvolution. In the above example, one way to find the active compound is to backtrack, and make all nine possible combinations of compounds that end with building block "c". Deconvolution is one of the major challenges of combinatorial chemistry and often its most time consuming step. Chemists have developed ingenious and elaborate methods to speed up this process. Sometimes they tag or encode some of the building blocks or the beads with a tracer they can later detect.

Another variation of combinatorial chemistry is known as parallel synthesis. Here all the products are synthesized in separate reaction vessels. Typically a plate with 96 individual wells is used, with beads attached to each well. Building blocks are added individually to the beads in each well. The advantage of parallel synthesis is that the composition of each compound is known, but generally, the split and mix procedure can generate many more compounds in the same amount of time.

These examples illustrate the main limitation of combinatorial chemistry. The simplicity of combinatorial chemistry is also one of its drawbacks. Only certain types of compounds can bind to plastic beads, and only a fairly limited number of reactions can be used in these repetitive steps. This means that only certain types of substances can be made using combinatorial chemistry. One of the challenges facing combinatorial chemists is to develop new reactions and new classes of substances that can be applied in simple and repetitive steps.

To overcome the limitation of the small number of reactions that can be performed on beads, chemists have developed methods of performing combinatorial chemistry in solution where a vast range of reactions can be performed. Other chemists have devised methods that combine the advantages of both the plastic bead method and the solution method (Han et al. 1995; Borman 1996; Service 1996). They use beads that dissolve in some solvents, but not in others. Here they perform a large range of reactions in solution then transfer the reaction mixture to a solvent where the beads are not soluble, so that the impurities can be removed by simply washing the now solid beads.

Still other chemists have combined molecular biology with combinatorial chemistry. They introduce different combinations of genes into microorganisms, turning each batch of microorganism into an individual bioreactor (Borman 1998).

After any combinatorial synthesis whether split and mix, parallel or solution, the products need to be tested or screened for the sought-after activity against the intended biological target, which could be an antibody, a receptor or other biological target molecule such as the Human Immunodeficiency Virus.

Combinatorial chemists can now create thousands of compounds in just days (Service 1997; Dagani 2000). They need rapid and inexpensive ways of screening such large numbers of compounds. Consequently they developed robotics and automated methods to help them with these screenings. This need to be able to rapidly screen huge numbers of compounds has spawned its own discipline known as high throughput screening. Combinatorial chemistry would not be manageable or efficient without it. Much automation has also worked its way into the synthesis steps.

The concepts of combinatorial chemistry were not invented by a pharmaceutical chemist. Rather they were invented by an inorganic chemist in the 1970's who was seeking new superconductors (Dagani 1999). This technique was not then adapted by chemists because efficient application of combinatorial chemistry required this automation and robotics, and such equipment was not available at that time.

Rarely will a combinatorial synthesis produce a useful drug. Instead a candidate compound will have to be modified by substantial traditional chemistry. The combinatorial product will lead the way to a new drug, hence the term for such preliminary products are lead compounds.

Searching the Combinatorial Chemistry Literature

As any new scientific specialty such as combinatorial chemistry evolves, matures and becomes familiar to many chemists, the terminology for this specialty will also evolve and mature. Rarely will a paper on one of the established disciplines actually mention the name of that discipline. For example, if you read specialty journals in biochemistry or physical chemistry, you will rarely find the words biochemistry or physical chemistry.

Consequently, many papers on combinatorial chemistry do not now use this term. Instead some authors consider the term "parallel synthesis" to be synonymous with combinatorial chemistry (Borman 1999). Other investigators may only use one word such as "combinatorial" or "combinatorially", or shorthand descriptions such as "mix and split", "split and mix", "split synthesis", or "high throughput" to describe their work. All of these various ways of saying combinatorial chemistry must be considered when searching the literature. Fortunately, the term "combinatorial chemistry" has been a controlled vocabulary index term in *Chemical Abstracts* since 1997, so most of the important literature in this field should be retrievable from *Chemical Abstracts* even when authors use a less standard way of describing their work.

The Journals Needed by Combinatorial Chemists

Most research areas in chemistry advance so rapidly that books are to some degree out of date as soon as they are published. Combinatorial chemists, as all research chemists, rely on scientific journals as their primary source of knowledge. While each of the long established disciplines of chemistry have their leading specialty journals, combinatorial chemistry is just beginning to develop theirs. Nearly all of the combinatorial literature appears in already established journals.

Since most combinatorial chemists are organic chemists seeking new drugs, we will examine the journals needed by these chemists, and separately examine the journals needed by inorganic and other combinatorial chemists. We cannot assume that these two different groups of chemists publish in and need the same journals. Fortunately,*Chemical Abstracts* is divided into 80 sections by discipline, and online searches can be restricted to any desired sections.

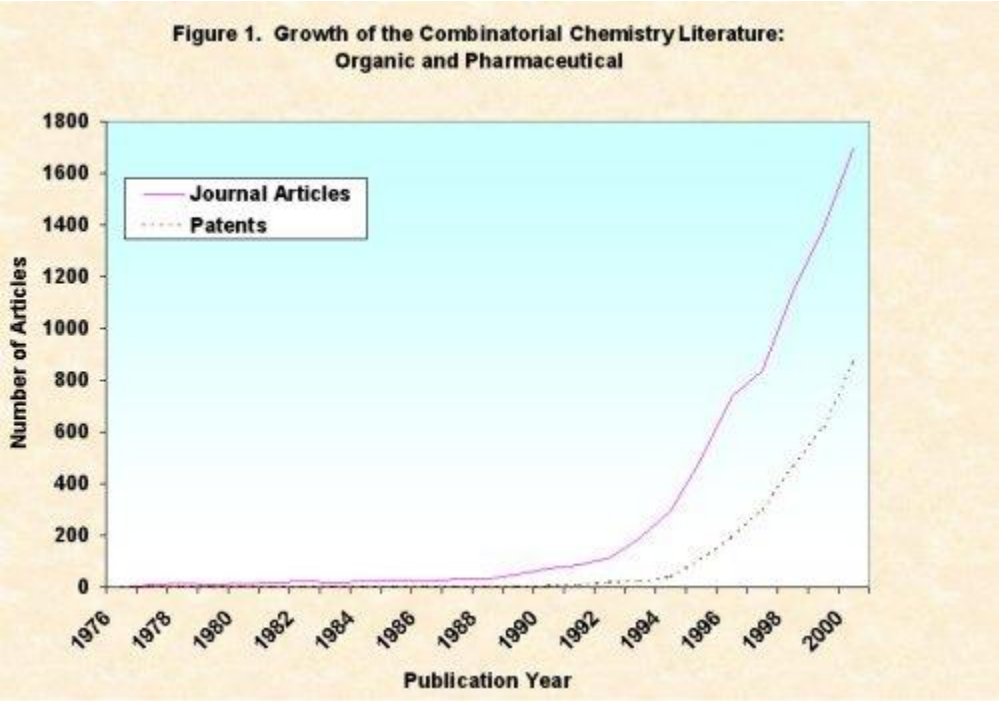
The data for the figures and tables below were gathered from *Chemical Abstracts*online. To obtain the data for organic and pharmaceutical chemistry, the searches described below were restricted to all of the biochemistry sections (sections 1-20), all of the organic chemistry sections (sections 21-34), section 63 (Pharmaceuticals), section 64 (Pharmaceutical Analysis), and section 80 (Organic

Analytical Chemistry). To obtain data for other applications of combinatorial chemistry, searches were restricted to all of the other remaining sections of *Chemical Abstracts*.

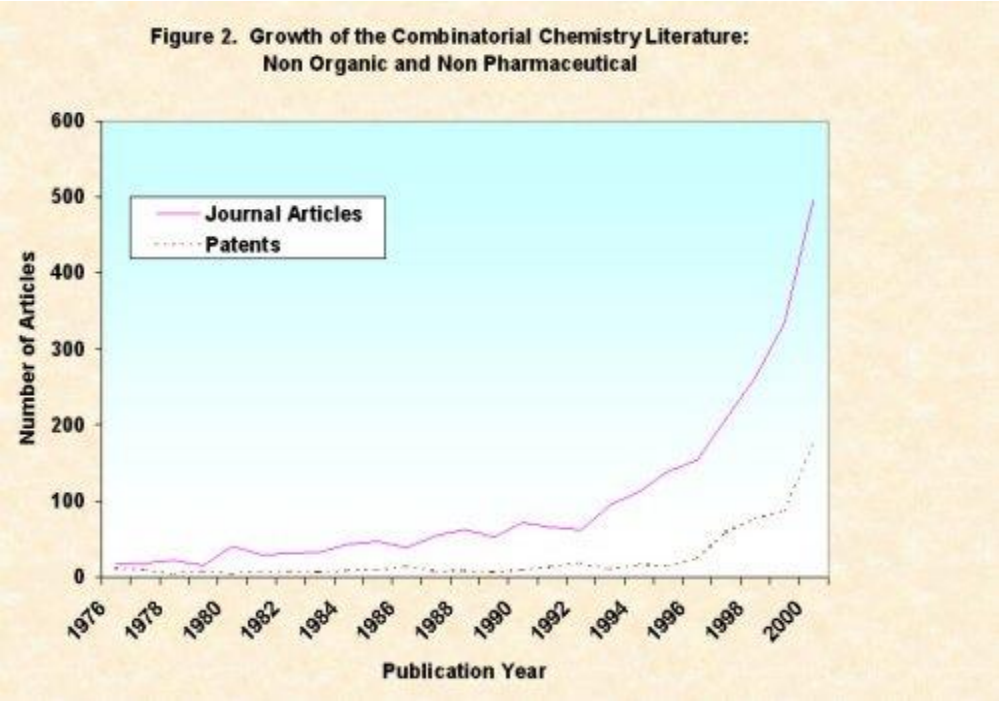
Figures 1 (organic and pharmaceutical chemistry) and 2 (all other fields of chemistry) show the continuously expanding growth in the literature of combinatorial chemistry. To obtain these figures, titles, abstracts and index terms in *Chemical Abstracts* online were searched for all of the various terms combinatorial chemists employ to describe their work. The captions to these figures detail the exact search strategy.

These data points were obtained during July 2001 in the free search preview of the CAPLUS database at http://stnweb.cas.org. The following search statement was used to obtain the data points for the number of journal articles published each year:

(combinatorial? or high throughput or parallel synthes!s or split synthes!s or mix(1A)split) and j/dt and NNNN/py and (bio or org or 63 or 64 or 80)/cc,sx. NNNN is the four digit year. For patents, the term p/dt was substituted for j/dt.



(combinatorial? or high throughput or parallel synthes!s or split synthes!s or mix(1A)split) and j/dt and NNNN/py not (bio or org or 63 or 64 or 80)/cc,sx. NNNN is the four digit year. For patents, the term p/dt was substituted for j/dt.



This jump in the number of combinatorial chemistry papers starting in the late 1990s is not an artifact caused by the introduction of the term combinatorial chemistry as a*Chemical Abstracts* controlled vocabulary term in 1997. Searches of MEDLINE and SciSearch, two databases having no index term for combinatorial chemistry, and BIOSIS, which is just beginning to apply combinatorial chemistry as an index term, show this same rapid expansion of the literature in this field.

Figures 1 and 2 reveal that patents as well as journal literature are a significant source of new information in combinatorial chemistry. While any experienced searcher can readily retrieve nearly all of the journal articles in any area of chemistry, by searching*Chemical Abstracts*, several different and intricate patent databases must be searched to insure that all patents in any area are retrieved (Simmons & Kaback 1996). Nancy Lambert, among many others, has cautioned that in many situations it is best to turn to patent searching experts (Shrode 1997).

Librarians need to know which journals contain the majority of this large and growing literature. Table 1 reveals the top 25 journals in organic and pharmaceutical combinatorial chemistry. The data in this table were gathered using a search strategy similar to the one used in Figure 1. These 25 journals contain 35% of the total journal literature in organic and pharmaceutical combinatorial chemistry.

Tables 3, 4 and 5 use different strategies for determining the journals most needed by combinatorial chemists working in organic or pharmaceutical chemistry. Journals that appear in at least two of these tables are in **bold type**.

Table 1. The Top 25 Journals in Combinatorial Chemistry: Organic and Pharmaceutical	
Journal	**Percentage of total number of Journal articles**
Tetrahedron Letters	3.96

Proceedings of the National Academy of Sciences	3.11
Analytical Biochemistry	1.98
Journal of the American Chemical Society	1.97
Bioorganic & Medicinal Chemistry Letters	1.89
Journal of Biological Chemistry	1.80
Analytical Chemistry	1.72
Journal of Chemical Information and Computer Sciences	1.65
Journal of Combinatorial Chemistry	1.55
Journal of Organic Chemistry	1.55
Journal of Medicinal Chemistry	1.20
Journal of Biomolecular Screening	1.19
Nucleic Acids Research	1.16
Molecular Diversity	1.07
Current Opinion in Chemical Biology	1.01
Angewandte Chemie, International Edition	0.98
Biochemistry	0.98
Journal of Molecular Biology	0.94
Chemistry & Biology	0.89
Genome Research	0.89
BioTechniques	0.81
Journal of Immunology	0.80
Molecular and Cellular Biology	0.78
Tetrahedron	0.77
Combinatorial Chemistry & High Throughput Screening	0.76

The STN CA file was searched during July 2001 using the following strategy:

s (combinatorial? or high throughput or parallel synthes!s or split synthes!s or mix(1A)split) and j/dt and (bio or org or 63 or 64 or 80)/cc,sx.
analyze l1 1- jt
set line 250
display l2 jt 1-25.

Similarly, Table 2 lists the top 25 journals for all other areas of combinatorial chemistry. These 25 journals contain 35% of the total journal literature in these areas of combinatorial chemistry.

Table 2. The Top 25 Journals in Combinatorial Chemistry: Non-Organic and Non-Pharmaceutical	
Journal	**Percentage of total number of journal**

	articles
Proceedings of SPIE-The International Society for Optical Engineering	7.69
Journal of Vacuum Science & Technology, B	2.58
Computers & Chemical Engineering	2.25
Review of Scientific Instruments	1.97
AIP Conference Proceedings	1.45
Nuclear Instruments & Methods in Physics Research, Section A	1.36
Nuclear Instruments & Methods in Physics Research, Section B	1.36
Conference Record of the IEEE Photovoltaic Specialists Conference	1.22
Fluid Phase Equilibria	1.22
Industrial & Engineering Chemistry Research	1.22
Microelectronic Engineering	1.17
Journal of Chemical Physics	1.12
Materials Research Society Symposium Proceedings	1.08
Angewandte Chemie, International Edition	0.98
Applied Physics Letters	0.98
AIChE Journal	0.89
Applied Optics	0.89
Proceedings - Electrochemical Society	0.89
Solid State Technology	0.84
Nuclear Physics B	0.75
Macromolecules	0.66
Journal of the American Chemical Society	0.61
Analytical Chemistry	0.56
Journal of Physical Chemistry	0.56
Journal of Vacuum Science & Technology	0.56

The STN CA file was searched during July 2001 using the following strategy:

s (combinatorial? or high throughput or parallel synthes!s or split synthes!s or mix(1A)split) and j/dt and NNNN/py not (bio or org or 63 or 64 or 80)/cc,sx.
analyze l1 1- jt
set line 250
display l2 jt 1-25

Another way to find the journals most needed by researchers in a specific discipline is to examine the citation patterns of the leading journal in that discipline (Barnett 1993). A new journal,

the *Journal of Combinatorial Chemistry*, published by the American Chemical Society since 1999, can now be expected to publish the most important papers in combinatorial chemistry, because most chemists have traditionally viewed this society's journals as the most prestigious place to publish. No other chemical society currently publishes a combinatorial chemistry journal.

Moreover, the other journals dedicated to combinatorial chemistry have published fewer papers than the *Journal of Combinatorial Chemistry*. At this time there are only two other journals devoted exclusively to combinatorial chemistry, *Combinatorial Chemistry & High Throughput Screening* (published by Bentham) and *Molecular Diversity* (published by Kluwer). Both the Bentham and Kluwer journals appeared earlier than the *Journal of Combinatorial Chemistry*, yet as of July 2001 *Chemical Abstracts* contains 133 and 110 references from the Bentham and Kluwer journals respectively, and 217 references from the American Chemical Society journal. Another journal, *Biotechnology and Bioengineering* has, since 1998, devoted some of their issues to combinatorial chemistry. 53 papers have appeared as of July 2001.

What journals do authors of papers in the *Journal of Combinatorial Chemistry* consult? Of the 217 papers listed from this journal in *Chemical Abstracts* as of July 2001, 190 are in organic or pharmaceutical chemistry using the same criteria as above. There are only 27 papers in this journal covering the other areas of chemistry, not enough for a meaningful citation pattern analysis.

Table 3 shows the top 25 journals cited by authors of papers published in the *Journal of Combinatorial Chemistry* dealing with organic and pharmaceutical chemistry from its inception in 1999 to July 2001.

Table 3. The 25 Journals Cited Most Frequently in the *Journal of Combinatorial Chemistry*	
Percentage of *Journal of Combinatorial Chemistry* papers containing a citation to the indicated journal	
Journal of Combinatorial Chemistry	97.32
Journal of the American Chemical Society	71.46
Tetrahedron Letters	68.78
Journal of Organic Chemistry	67.32
Angewandte Chemie, International Edition	55.85
Tetrahedron	54.63
Journal of Medicinal Chemistry	47.32
Chemical Reviews (Washington, D. C.)	46.59
Bioorganic & Medicinal Chemistry Letters	37.07
Proceedings of the National Academy of Sciences	34.39
Science	32.20
Current Opinion in Chemical Biology	26.34
Accounts of Chemical Research	25.61
Synlett	20.24
Nature	20.00

Chemical Communications	20.00
Synthesis	19.76
Molecular Diversity	19.76
Journal of the Chemical Society. Chemical Communications	17.56
Organic Letters	17.07
Chemistry & Biology	16.34
Drug Discovery Today	15.37
Journal of Chemical Information and Computer Sciences	15.12
Analytical Chemistry	14.88
Bioorganic & Medicinal Chemistry	14.39

STN was searched during July 2001 using the following strategy:

file CA
s 1520-4766/isn and (bio or org or 63 or 64 or 80)/cc,sx
file scisearch
s l1<cit>
analyze l3 1- rwk
display l4 1-100 rwk

Many combinatorial chemists choose to publish in journals other than the *Journal of Combinatorial Chemistry*; they will very likely cite papers from this journal in their list of references. We can use the citation feature in the *Chemical Abstracts* database to see who is citing the *Journal of Combinatorial Chemistry*. Table 4 lists the journals that have cited this journal at least four times. Here also, the citation analysis is limited to organic and pharmaceutical chemistry.

Table 4. The Journals Most Frequently Citing the *Journal of Combinatorial Chemistry*

Journal Title	Number of articles citing the *Journal of Combinatorial Chemistry*
Journal of Combinatorial Chemistry	64
Tetrahedron Letters	44
Organic Letters	34
Journal of the American Chemical Society	18
Journal of Organic Chemistry	13
Angewandte Chemie, International Edition	12
Current Opinion in Chemical Biology	12
Journal of Chemical Information and Computer Sciences	12
Current Opinion in Drug Discovery & Development	9

Journal of Medicinal Chemistry	9
Bioorganic & Medicinal Chemistry Letters	6
Chemical Reviews (Washington, D. C.)	6
Combinatorial Chemistry & High Throughput Screening	6
Journal of the Chemical Society, Perkin Transactions 1	6
Analytical Chemistry	5
Tetrahedron	5
Annual Reports in Medicinal Chemistry	4
Chemical Communications (Cambridge)	4
Chemistry--A European Journal	4
Frontiers of Biotechnology & Pharmaceuticals	4
Synlett	4

The STN CA file was searched during July 2001 using the following strategy:

s j comb chem/rwk and (bio or org or 63 or 64 or 80)/cc,sx
analyze jt l1 1-
set line 250
display l2 jt 1-25

Combinatorial chemistry has grown to such an extent that there are now departments, and research groups that incorporate the terms "combinatorial" or "high throughput" as part of their corporate name. Searching *Chemical Abstracts* for the journals where such groups publish revealed 88 journal articles, 84 of which are in organic and pharmaceutical chemistry according the same criteria employed above.

These 84 papers are from 38 distinct research groups and include 279 authors. The four papers from research groups in other areas of chemistry are not a big enough sample to analyze. Table 5 shows the 15 journals from these organic and pharmaceutical research groups containing two or more papers.

Table 5. The Journals In Which Combinatorial or High Throughput Groups Publish: Organic and Pharmaceutical

Journal Title	Number of Papers
Tetrahedron Letters	17
Bioorganic & Medicinal Chemistry Letters	6
Journal of Medicinal Chemistry	6
Journal of Combinatorial Chemistry	4
Combinatorial Chemistry & High Throughput Screening	3

Journal of the American Chemical Society	3
Chemistry & Industry (London)	2
Current Opinion in Drug Discovery & Development	2
Journal of Biological Chemistry	2
Journal of Organic Chemistry	2
Methods in Molecular Biology	2
Molecular Diversity	2
Organic Letters	2
Journal of the Chemical Society, Perkin Transactions 1	2
Tetrahedron	2

The STN CA file was searched during July 2001 using the following strategy:

s (combinatorial or high throughput)/cs and (bio or org or 63 or 64 or 80)/cc,sx and j/dt
analyze l1 1- jt
set line 250
display l2 jt 1-

The different approaches used to obtain lists of the major combinatorial chemistry journals in Tables 1,3,4, and 5 yield nearly the same results, there is extensive overlap. Any of these four approaches will reveal the leading combinatorial journals for organic and pharmaceutical chemists.

The titles in these tables are mostly the very familiar titles that nearly every chemistry library subscribes to. Except for a few specialized titles, libraries will not have to acquire many new journals when a combinatorial chemistry research group becomes established. Even most of the journals appearing in only one of these tables such as*Science*, *Nature*, *Biochemistry*, and the *Journal of Molecular Biology*, are titles already subscribed to by nearly any science library.

Books

Searches of the Library of Congress online catalog, OCLC-World Cat, and Books in Print online, revealed 57 books devoted to combinatorial chemistry, and the related areas of parallel synthesis, split synthesis and high throughput screening. Another 39 books contain a chapter or section on combinatorial chemistry. Because of this small number, librarians may be tempted to collect all of them.

Few of these books provide an overview of combinatorial chemistry. More than three-quarters of these are subject specific monographs or conference proceedings, which means that they may not cover topics relevant to chemists at your institution. Perhaps some of these books are by authors whose work is already known to the chemists in your organization. Often chemists know that their work is so new, it cannot yet be in any book.

One way to compare the relative importance of journal articles to books is to see how frequently authors cite each of these formats. A representative sample of journal articles, the 100 most recent research papers in the *Journal of Combinatorial Chemistry*contain 3226 literature citations. Only 5.4% of these citations are to books. A comparable analysis of research papers in the field of structural biology yielded similar results, 4.1% of the literature citations were to books (Lascar & Mendelsohn 2001), reinforcing that research scientists in life science related fields rely primarily on journals, not books.

For all of these reasons, any selection of books in combinatorial chemistry should be done in consultation with the chemists you serve.

When searching these online book catalogs one must keep in mind that the term combinatorial does not only apply to chemistry. Combinatorial is an established term in mathematics where it defines the analysis of various kinds of mathematical combinations. There are even journals dedicated to combinatorial mathematics. To keep retrieval manageable when searching these large book catalogs, the term combinatorial should be combined with other keywords such as, chemistry, synthesis, libraries, drug, or catalyst, using the plural forms of these keywords where appropriate.

Combinatorial Chemistry on the World Wide Web

Combi-Web Consortium -- The Web Portal for Combinatorial Chemistry ({http://www.combi-web.com/}) is the merged product of four key sites in this field. Among the vast amount of information listed here are all the different types of world wide web based sources that should fulfill the web based information needs of practitioners in this field. This site lists guides to publications, patents, news, events, meetings, reviews, product guides, and discussion groups. Anyone interested in combinatorial chemistry should be able to benefit from this site.

Another portal, a smaller one, to consider is the Royal Society of Chemistry's**Combinatorial Chemistry Network**, {http://www.chemsoc.org/networks/ccn/}. It has much overlap with the Combi-Web Consortium.

Elsevier has mounted on Chemweb, its vast chemistry web site (http://www.chemweb.com/) a product they call **Combinatorial Chemistry: an Online Journal** ({http://www.sciencedirect.com/science/journal/14643383}). This is a searchable database consisting primarily of articles appearing in and accepted for publication in several Elsevier journals. The abstracts are viewable for free, but full-text access requires subscriptions to the individual journals.

Conclusion

Combinatorial chemistry is a new field of chemistry that employs novel concepts and techniques to rapidly synthesize and screen large numbers of compounds. Researchers in this field rely predominantly on journals rather than books. Fortunately for library collections, except for a few specialized journals, nearly all the literature in this field appears in the well-known journals that most chemistry libraries already own. Two world wide web portals provide convenient access to the abundant web based information sources in combinatorial chemistry.

References

Alper, J. 1994. Drug discovery on the assembly line. *Science* 264(5164):1399-1401.

Barnett, P. 1993. Defining, collecting and searching the neurochemistry literature.*Science & Technology Libraries* 13(3/4):39-56.

Baum, R.M. 1994. Combinatorial approaches provide fresh leads for medicinal chemistry. *Chemical & Engineering News* 72(6):20-26.

Borman, S. 1996. Combinatorial chemists focus on small molecules, molecular recognition, and automation. *Chemical & Engineering News* 74(7)29-54.

_____. 1998. Biosynthesis combinatorially. *Chemical & Engineering News*76(37):29-30.

_____. 1999. Reducing time to drug discovery. *Chemical & Engineering News*77(10):33-48.

Brennan, M.B. 2000. Drug discovery: Filtering out failures early in the game.*Chemical & Engineering News* 78(23):63-73.

Dagani, R. 1999. A faster route to new materials. *Chemical & Engineering News*77(10):51-60.

_____. 2000. Materials a la combi. *Chemical & Engineering News* 78(20):66-68.

Han, H., Wolfe, M.M., Brenner, S. & Janda, K.D. 1995. Liquid-phase combinatorial synthesis. *Proceedings of the National Academy of Sciences of the United States of America* 92(14):6419-6423.

Lascar, C & Mendelsohn, L.D. 2001. An analysis of journal use by structural biologists with applications for journal collection development decisions. *College & Research Libraries* 62(5):422-433.

Lebl, M. 1999. Parallel personal comments on "classical" papers in combinatorial chemistry. *Journal of Combinatorial Chemistry* 1(1)3-24.

Mort, M. 2001. Enlisting combichem to fight cancer. *Modern Drug Discovery* 4(2):28-32.

Plunkett, M.J. & Ellman, J.A. 1997. Combinatorial chemistry and new drugs.*Scientific American* 276(4):68-73.

Service, R. F. 1996. Combinatorial Chemistry hits the drug market. *Science* 272(5266) 1266-1268.

_____. 1997. High-speed materials design. *Science* 277(5325):474-475.

Shrode, F.G. 1997. Science and Patent Sessions at Online World, Sept.16, 1997 Washington, D.C. *Issues in Science and Technology Librarianship* Fall 1997 [Online]. Available: http://www.istl.org/97-fall/conference1.html [February 20, 2002].

Simmons, E.D, & Kaback, S.M. 1996. Patents, Literature. In: *Encyclopedia of Chemical Technology* Fourth Edition Volume 18 (ed. by J.I. Kroschwitz & M. Howe-Grant), pp. 102-156. New York: John Wiley & Sons.

Thayer, A.M. 1996. Combinatorial chemistry becoming core technology at drug discovery companies. *Chemical & Engineering News* 74(7):57-64.

Zall, M. 2001. The Pricing Puzzle. *Modern Drug Discovery* 4(3):36-42.