Combinatorial Chemistry: Concepts, Strategies and Applications

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ABSTRACT

Combinatorial chemistry started with Merrifield's Nobel Prize winning invention- the solid-phase synthesis of peptides. By mid 1980s, solid phase techniques have been greatly refined so that it was possible to make huge numbers of peptides simultaneously in the same reaction vessel, using a few steps. Later, strategies and techniques of solution phase combinatorial synthesis have been developed as well. While solid phase synthesis makes it easier to conduct multi-step reactions and to drive reactions to completion, solution phase synthesis allows a much wider range of organic reactions. In its earliest form, the primary objective of combinatorial chemistry was to generate large "libraries"of molecules en masse – instead of synthesizing compounds one by one, as how synthetic organic chemistry has been practiced for the last 100 years- and how to find the most promising "lead" pharmaceutical compounds by high throughput screening of the libraries. Although combinatorial chemistry and combinatorial technology have been mostly applied to drug and agrochemical discovery, they can be powerful tools in the diagnostic, down- stream processing, catalysis and new materials sector.

INTRODUCTION

Combinatorial chemistry (**CC**) is a set of techniques for creating simultaneously a multiplicity of compounds and then testing them for various kinds of activity. It started in the early 1980s with solid-phase peptide synthesis, although it was not called combinatorial chemistry until the early 1990s. The solid phase synthesis of peptides- Merrifield's Nobel Prize-winning invention – depended on the use of consistent and reliable reaction conditions for peptide couplings, and the use of a polymeric solid phase to permit the simple separation of products from reagents. By mid 1980s, solid phase techniques have been so greatly refined that it was possible to make huge numbers of peptides as well as oligonucleotides

simultaneously in the same reaction vessel, using a few chemical steps. And thus, combinatorial chemistry was born. However, it is only after 1993 that some of the well-established strategies for these biopolymers have been applied to the more difficult task of synthesizing large numbers of small organic molecules with molecular weights of up to 500 or so – the class of compounds from which drugs are most often found.

The Impact Of Combinatorial Chemistry On Drug Discovery

At the beginning, the primary objective of combinatorial chemistry was to generate "libraries" of molecules en masse – instead of synthesizing compounds one by one, as how synthetic organic chemistry has been practiced for the last 100 years- and to find the most promising "lead" pharmaceutical compounds by high-throughput screening (HTS) of the libraries.

In the first phase of the drug discovery process, a medicinal chemist needs to find a lead compound – a structure with some degree of affinity for the biological target. Then the lead's structure is improved to yield a drug development candidate (Figure 1). Traditionally, the identification of new leads has been carried out by random screening of natural products, or proprietary and commercial collections. This approach has resulted in many important drugs, however the ratio of novel to previously discovered compounds has decreased with time. Moreover, the process is very time consuming and expensive. With the introduction of combinatorial chemistry, the new techniques that permit the rapid synthesis of thousands or even millions of new compounds for lead discovery, has revitalized random screening as a paradigm for drug discovery. The impact of combinatorial chemistry has swept through the pharmaceutical and biotechnology industries like a tidal wave, touching nearly all organizations engaged in pharmaceutical research and development (Borman 1997).

Combinatorial Synthesis

For the last 100 years, synthetic chemistry has been characterized by slow, steady and painstaking work. Combinatorial chemistry has permitted a level of chemical productivity not possible just more than 10 years ago by discarding many of the dearly held precepts of organic synthesis, for example, that all compounds and intermediates need to be fully purified and characterized.

The usual practice in organic synthesis is to make one compound at a time, in one reaction at a time. For example compound **X** would have been reacted with compound **Y** to give product **XY**, which would have been isolated after work-up and purified through crystallization, distillation or chromatography (Figure 2). In contrast to this approach, combinatorial chemistry offers the potential to make every combination of compound **X1** to **Xn** with compound **Y1** to **Yn**. The
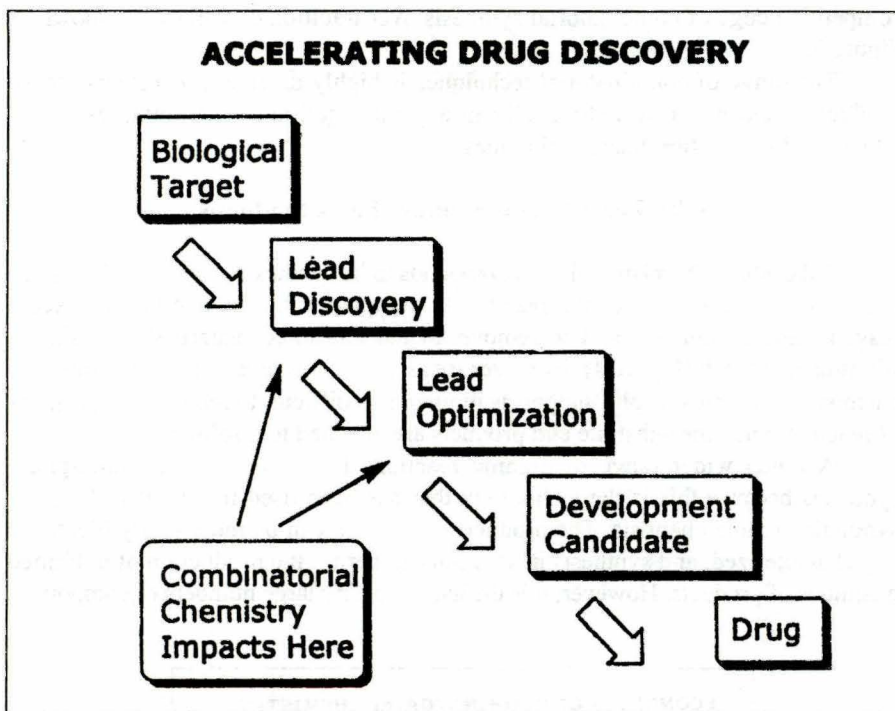
ACCELERATING DRUG DISCOVERY

Biological Target

Lead Discovery

Lead Optimization

Development Candidate

Drug

Combinatorial Chemistry Impacts Here

Figure 1. The key steps in the drug discovery process

Classical Organic Synthesis

$$X + Y \longrightarrow XY$$

Combinatorial Synthesis
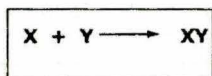
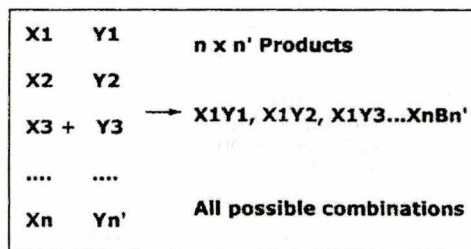| X1 | Y1 | n x n' Products |
X2	Y2	
X3 +	Y3	$\longrightarrow$ X1Y1, X1Y2, X1Y3...XnBn'
....	....	
Xn	Yn'	All possible combinations

Figure 2. Comparison between classical and combinatorial sysnthesis

competitive edge of combinatorial synthesis over traditional synthesis is shown in Figure 3.

The range of combinatorial techniques is highly diverse, for instance, these products could be made individually in a parallel fashion or in mixtures, using either solid-or solution-phase techniques.

Solid-Phase Versus Solution-Phase Synthesis

Solid-phase chemistry allows compounds to be synthesized on a solid support, e.g. on resin bead, to force the reaction to completion by the addition of excess reagents and monomers, and to remove all the unwanted materials by a simple filtration and wash (Figure 4). However it has several disadvantages – the range of chemistry available on solid support is limited, it is difficult to monitor the progress of reaction when the substrate and products are attached to a solid phase.

A much wider range or organic reactions is available for solution-phase synthesis because this is the technology that has been used traditionally by most synthetic organic chemists. The products in solution can be more easily identified and characterized, and synthesis in solution can permit the production of unlimited quantities of products. However, it is difficult to purify large numbers of compounds
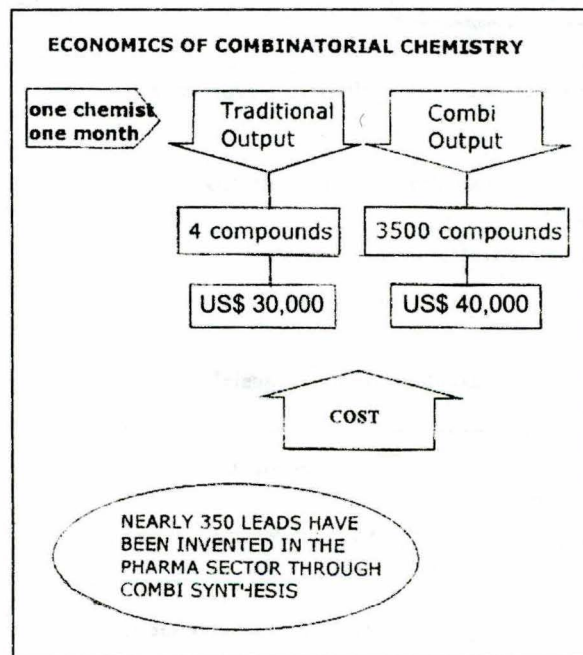
Figure 3. Competitive edge of combinatorial chemistry over traditional chemistry.
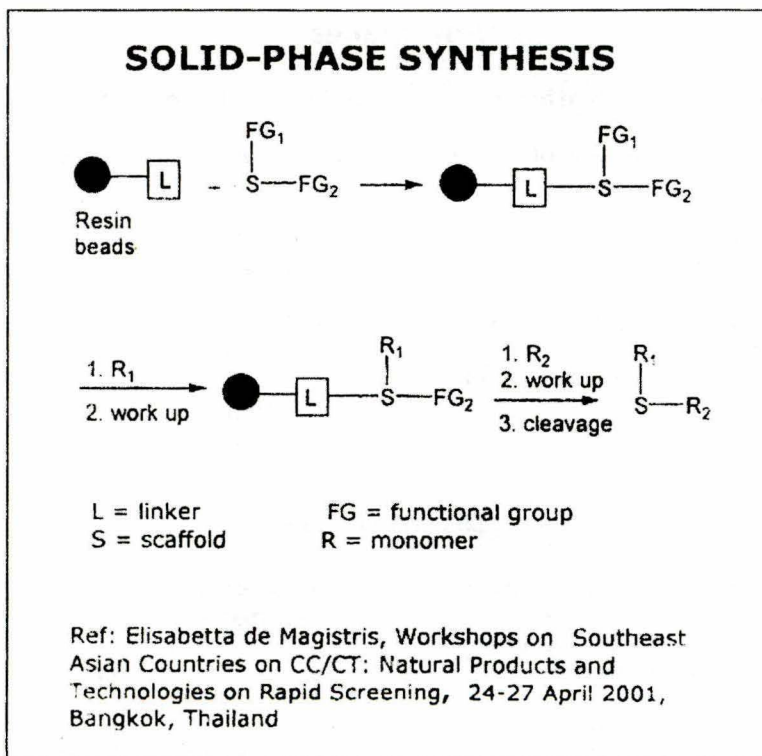
Figure 4. Solid-phase synthesis

without sophisticated automated processes and so the use of solution chemistry is restricted to short synthetic sequences using reliable chemistry. A comparison between solid-phase and solution-phase synthesis is presented in Figure 5.

Combinatorial Libraries: Formats

A combinatorial library is a single entity composed of many individuals (hundreds to millions) which can be prepared in many formats using many synthetic techniques. The library is tested for a specific activity and its active individuals, or "positives", are identified (Seneci, 1999). For example, a chemical library is a collection of chemical compounds generated for the purpose of speeding up the drug discovery process.

Combinatorial libraries can be made for a variety of purposes. For a specific application, a careful selection of the best available library format is often the key to the successful identification of positives from the library.

Advantages

Solid-Phase Synthesis

- large excess of reagents allowed

- multistep synthesis allowed

- easy work up/isolation

- mix and split possible

Solution-Phase Synthesis

- all organic reactions can be used

- no chemistry assessment

- no linker/cleavage chemistry

- unlimited product quantities

Disadvantages

Solid-Phase Synthesis

- time required for development

- additional steps for linkage/cleavage

- support and linker limit chemistry

- analytical monitoring of reactions still being developed

Solution-Phase Synthesis

- reactants cannot be used in excess

- automation of isolation and purification steps difficult

Figure 5. A comparison between solid-phase synthesis and solution-phase synthesis

Primary And Secondary Libraries

There are two main library formats: primary (diversity-based or unbiased) and secondary (focused or biased). Shown in figure 6 are the main features of and differences between the two formats. Primary libraries are usually prepared to identify one or more positives on an unknown target. Thus the library components have to be diverse as much as possible. This will eventually lead to a mild positive or a hit, out of the large library population. The structure of the hit is now the starting point for designing a secondary or biased library. Analogues of the hit will be prepared to understand the structure-activity relationships (SAR) of the

Combinatorial Library Formats

Primary: Hit	Secondary: Lead
• random	• focused
• solid phase	• solid/solution phase
• mix and split	• parallel synthesis
• > 10,000 compounds	• < 10,000 compounds
• < 1 mg/compound	• > 1 mg/compound
• biological assay on many targets	• biological assay on one target

Figure 6. A comparison between primary and secondary library formats

class of compounds. From this library a lead, a valuable molecule with a desired activity profile, will be the basis for a project potentially leading to a new marketable drug.

Primary libraries are typically large (>10,000 compounds) to span more diversity. They are prepared on solid phase as mixtures using the "mix and split" technique (other names: one-bead-one-compound, "Selectide", divide-couple-recombine) (Furka *et al.,* 1988, 1991) to increase productivity and to decrease the number of assays. On the other hand, secondary libraries are smaller (<10,000 compounds) and are prepared both on solid phase and in solution; they are finally obtained as discretes to obtain more reliable activity results on the analogues of the original hit. While primary libraries are normally tested on many assays to maximize the synthetic efforts by finding more hits on more targets, secondary libraries are tested only on the assay where their parent hit showed activity.

In general, primary libraries are used in the pharmaceutical industry for the exploratory phase to reduce the time needed for the identification of a positive on a poorly known target. Secondary libraries are used to speed up the SAR data acquisition through parallel synthesis of a large number of hit analogues.

Discrete And Pool Libraries

Libraries can be distinguished further into pool libraries, where the compounds are prepared as mixtures, and discrete libraries, where the compounds are prepared as individuals (Figure 7). Discrete libraries are made by the automation of classical organic synthesis to be able to handle many reaction vessels in parallel (up to tens

of thousands); the term parallel synthesis comes from this concept. Since discrete libraries require the handling of many reaction vessels, the number of individuals is limited to a maximum of few thousands, even with a high degree of automation. On the other hand, pool libraries are made by using the "mix and split" solid-phase technique. Pool libraries are theoretically in terms of numerousity, but the amount of each individual is much smaller, usually less than 1 mg of final compound.

Discrete libraries do not require structure determination since each library well contains a single compound and its structure is known through the position of the reaction vessel (spatial encoding). Pool libraries require the determination of positives from a library pool through various processes either related to the deconvolution of the library complexity or to the decoding of suitable tags anchored to the solid support.

Combinatorial Library Formats

Discrete Libraries (Parallel synthesis)

- smaller numbers (10s to 1000s)
- larger quantities (> mg each)
- no structure
- determination
- quality control

Pool Libraries (Mix and Split)

- larger numbers (1000s to ??)
- smaller quantities
- (<< 1 mg each)
- structure
- determination/decoding
- quality control

Figure 7. A comparison between discrete and pool libraries

Mix and Split Library Synthesis

This solid-phase technique was pioneered by Furka (Furka *et al.* 1988, 1991) and has been enthusiastically adapted by many others to prepare pool libraries. In the mix and split process, library compounds are synthesized on resin beads. A quality of the resin beads is divided into a number of equal portions and each portion is individually reacted with a different monomeric starting material. The coupling reaction is usually pushed to completion by the addition of excess monomer and coupling reagent; the excess is removed from the solid phase by subsequent washing. The different portions are recombined, the solid phase is thoroughly mixed, again divided into portions, and each portion is reacted with a new set of reagents giving a set of dimeric units as mixtures. This whole process may then be repeated as necessary (for a total of n times). The number of compounds

obtained arises from the geometric increase in products: in this case, X (monomers) raised to the power n (total number of coupling steps).

Illustrated in Figure 8 is the mix and split process for a simple example of a 3x3x3 library, giving 3 mixtures consisting of 9 compounds each. There are several ways of progressing these compounds to biological screening. Although the compounds can be tested while still attached to the beads (on-bead assay), a favored method is to cleave the compounds from the beads and to test them as a mixture in solution (solution assay). Activity in any given mixture (a sub-library) reveals the partial structure of active compounds within the a library, since the residue last coupled is unique to each mixture. Identification of the most active compounds can be achieved by the deconvolution of the most active mixtures in the library through further rounds of synthesis and screening.

The deconvolution of the 27 component library where the active structure is found to be the trimer YXY, is illustrated in Figure 9, How is it possible to identify the most active compound as the trimer YXY? Based on the bioassay, the mixture with Y at the terminal is the most active (Pot B found to be active). The library is then subjected to what is called "recursive" deconvolution (Erb *et al.* 1994) – the retained samples of the three different mixtures of the intermediate dimmers on resin are treated with Y to give all the nine compounds with Y at the terminal position, and the second position defined by being unique in each mixture. The most active mixture will thus define the middle portion of the most trimer to be residue X. Finally, the three individual compounds can be independently resynthesized and tested to reveal both the most potent compound and possibly some SAR data as well.

Parallel Solution Library Synthesis

Manual or automated approaches can be used for the parallel preparation of tens to hundreds of analogues of biologically active substrate. The products are synthesized using reliable coupling and functional group interconversion chemistry and are progressed to screening after removal of solvent and volatile by-products. A comparison of parallel and orthodox synthesis is presented in Figure 10.

Orthodox synthesis usually involves a multistep sequence, e.g. from the starting material **A** through to the final product **D**, which is purified and fully characterized before screening. Guided by the biological activity of the previous compound, the next analogue is then designed, prepared and screened. This process is repeated to optimize both activity and selectivity. In contrast, parallel analogue synthesis involves reaction of a substrate **S** with multiple reactant, **R1, R2, R3 ....Rn,** to produce a compound library of n individual product, **SR1, SR2, SR3 ....SRn.** This library is screened without purification, and with only minimal characterization of the individual compounds, using a rapid throughput screening technique. Any active compounds identified, are resynthesized on a large scale for purification, characterization, and screening by traditional methods. If biological
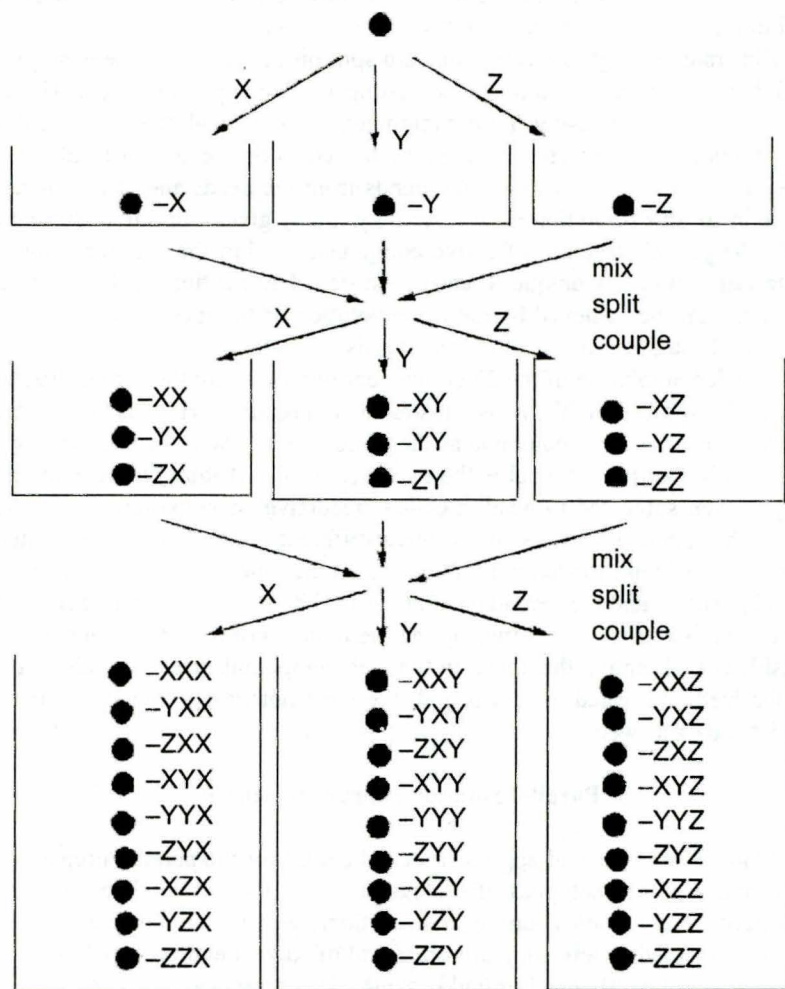
Figure 8. Mix and split library synthesis

activity is confirmed, the newly discovered leads and SAR are used to design new substrate templates. Further libraries are then prepared, again using the parallel analogue synthesis methodology, and this time, it is now focused on the new substrate. This process is thus a rapid and iterative fine-tuning similar to conventional lead optimization, only much faster and involving more analogues.

Workers from Glaxo-Wellcome (Bailey *et al.,* 1996) prepared a typical solution-phase library of twenty 2-aminothiazoles as individual compounds using
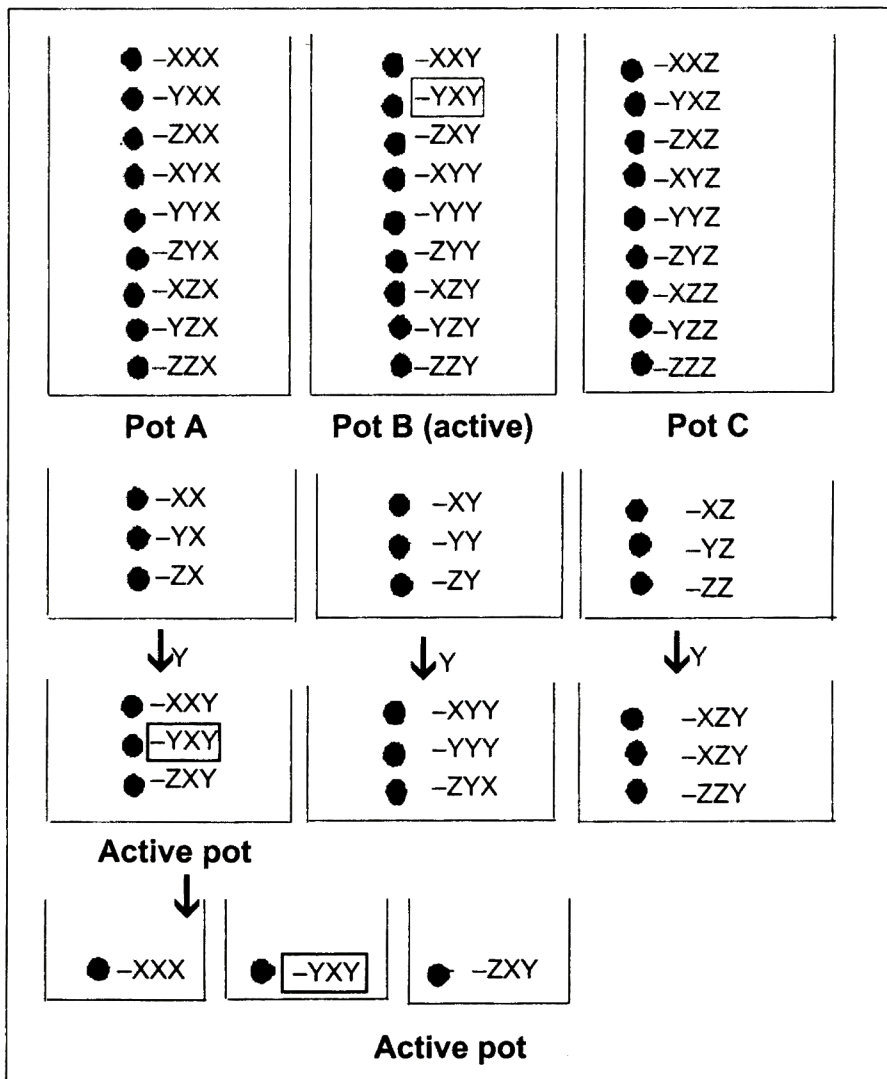
Figure 9. The identification of the most active sequence in a library through iterative resynthesis and screening (Terrett, 1998).

the reliable and traditional Hantzsch synthesis in 4 x 5 grid of one dram vials (Figure 11). The compounds were prepared by mixing five thioureas separately with four α-bromoketones (5 x 4 compounds), using a liquid dispensing robot to transfer the solutions. The reaction mixtures were heated at 70°C for 5 h and then quenched with dimethylamine. After the completion of the reaction, the DMF

Figure 10. A comparison between orthodox and parallel analogue synthesis. Adapted from Terrett (1998).

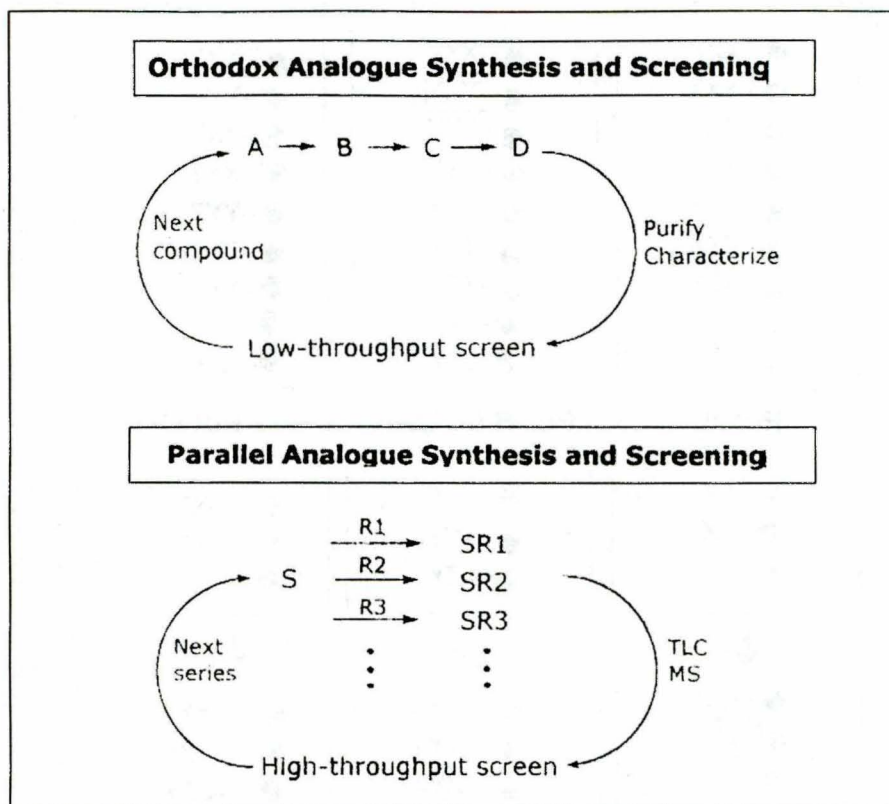solvent was removed by blowing a stream of nitrogen gas into each vial at ambient temperature for about 24 h. LC-MS showed that the principal component of all products had a molecular ion corresponding to the expected thiazole. High resolution MS and NMR confirmed the structures of the products. Within this set of twenty compounds, the known anti-inflammatory compound, fanetizole was synthesized – a clear demonstration of the value of this technique in drug discovery.

Combinatorial Technologies In Natural Products Research

To date, natural products screening is still the single most successful drug discovery strategy. A large number of microbial and plant extracts and other less common natural sources, have been screened and have provided a highly diverse and innovative chemical structures and varied biological activities. Around 40% of the top-20 selling drugs in 1997 were natural products; 30% of the new chemical
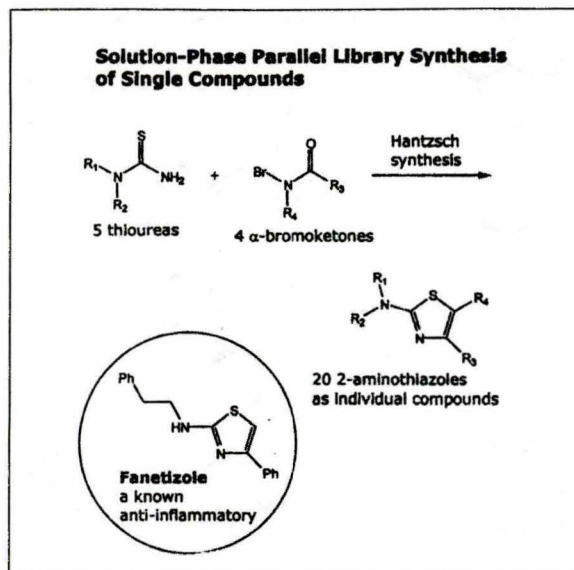
Figure 11. A solution-phase library of single compounds prepared by researchers from Glaxo-Wellcome

entities introduced in the market 1992 and 1996 were natural products; and 60-80% of the approved antibacterials and anticancer drugs in 1994 were natural products or natural products derivatives. Current commercial evidence also supports the case for natural products. Of the 20 best-selling non-protein drugs in 1999, nine (simvastatin, lovastatin, enalapril, pravastatin, atorvastatin, augmentin, ciprofloxacin, claritomycin and cyclosporin) were derived from or developed as the result of leads generated by natural products (Figure 12). These drugs have a combined annual sales of >16 billion US dollar (Harvey, 2000).

According to Seneci (2001) from Nucleotide Analog Pharma AG, Germany, "It may thus appear strange, and even irrational, that the interest towards natural products has reduced in the past years." Seneci goes on by enumerating the reasons behind this: the enormous efforts often necessary to isolate the active principles and to identify their structures, and worse, the frequent isolation of known compounds, determined only at the end of the tedious discovery process. In addition, the boom encountered recently by synthetic combinatorial chemistry has generated the wrong feeling that large libraries of synthetic molecules will be able to fulfill the needs of drug discovery in terms of quantity and diversity of structures. However, it is quite obvious that natural products and synthetic combinatorial chemistry are complementary and their correct use will significantly increase the degree of success of drug discovery. Natural products research should learn lessons from synthetic combinatorial chemistry. The technologies that have been developed for producing large synthetic combinatorial libraries and their high-throughput
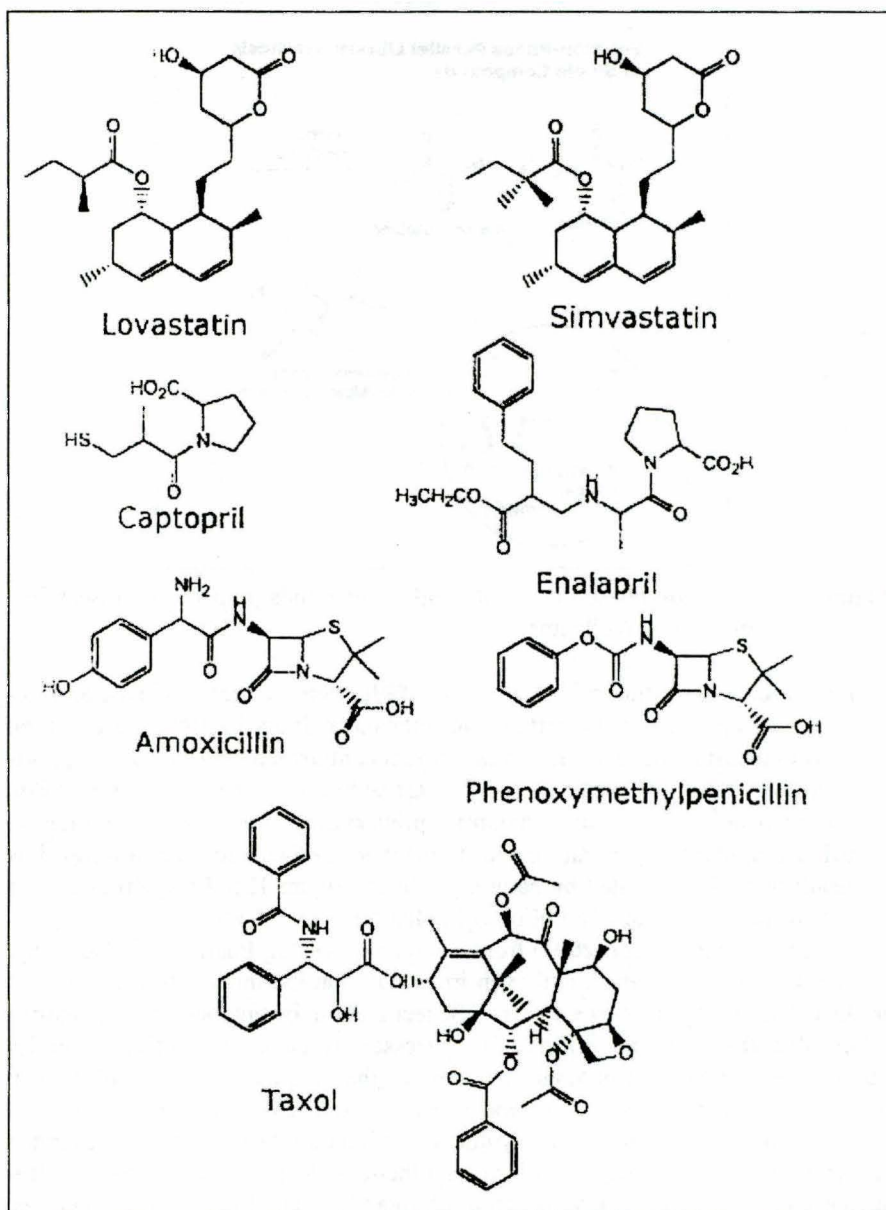
Figure 12. Some of the current best-selling drugs derived from natural products.

screening should also be applied to natural products research. There are several combinatorial trends in natural products research: synthetic combinatorial natural products-based libraries, combinatorial biosynthesis, combinatorial biocatalysis.

Synthetic Combinatorial Natural Products-Based Libraries

A specific class of synthetic combinatorial libraries in which biologically active natural products are either built during the synthesis or are used as scaffolds to be decorated, has recently emerged and has gained considerable attention in pharmaceutical research. The biological information contained in the natural scaffold increases the probability of discovering novel active structures. For example, yohimbinic acid, an natural alkaloid was decorated using a monomer set of 36 L-α-amino acids (R1) and a monomer set of 22 carboxylic acids (R2), to give 792 compounds as 22 pools of 36 compounds (Atuegbu *et al.* 1996) (Figure 13). The commercially available natural scaffold is known to posses a wide range of biological activities. The possibility of expanding the two monomer sets makes such a primary library a likely source for new biologically active analogues.

Another example is the construction of a library based on taxol, a potent anticancer drug (Figure 14). The noninvasive radiofrequency encoded (REC) strategy and novel solid-phase synthesis techniques were employed for the synthesis of this first ever 400-membered taxoid library in a discrete format and in quantities of multimilligrams/member (Xiao *et al.* 1997).

Analytical Evaluation Of Libraries And Structure Determination Of Identified Hits

A novel approach to analytical chemistry (and a new way of thinking by analytical chemists!) is required in order to keep pace with the demands of combinatorial chemistry. There are two areas which need be addressed: the monitoring of completeness of reactions during the synthesis of libraries, and the determination of the structures of the products.

Colorimetric Analysis

The completeness of solid-phase reactions is easily monitored when the main concern of the combinatorial chemist is the consumption of available amino groups. A quantitative assessment of chemical conversion can be done by the reaction with ninhydrin and determination of the resulting blue chromophore at 570 nm (Sarin *et al.,* 1981). A non-destructive method for the determination of amine-containing resin can be achieved by treating with a picric acid solution to form an amine salt, washing, and treatment with a base such as pyridine to liberate the picric acid which is then measured photometrically (Gisin, 1972).
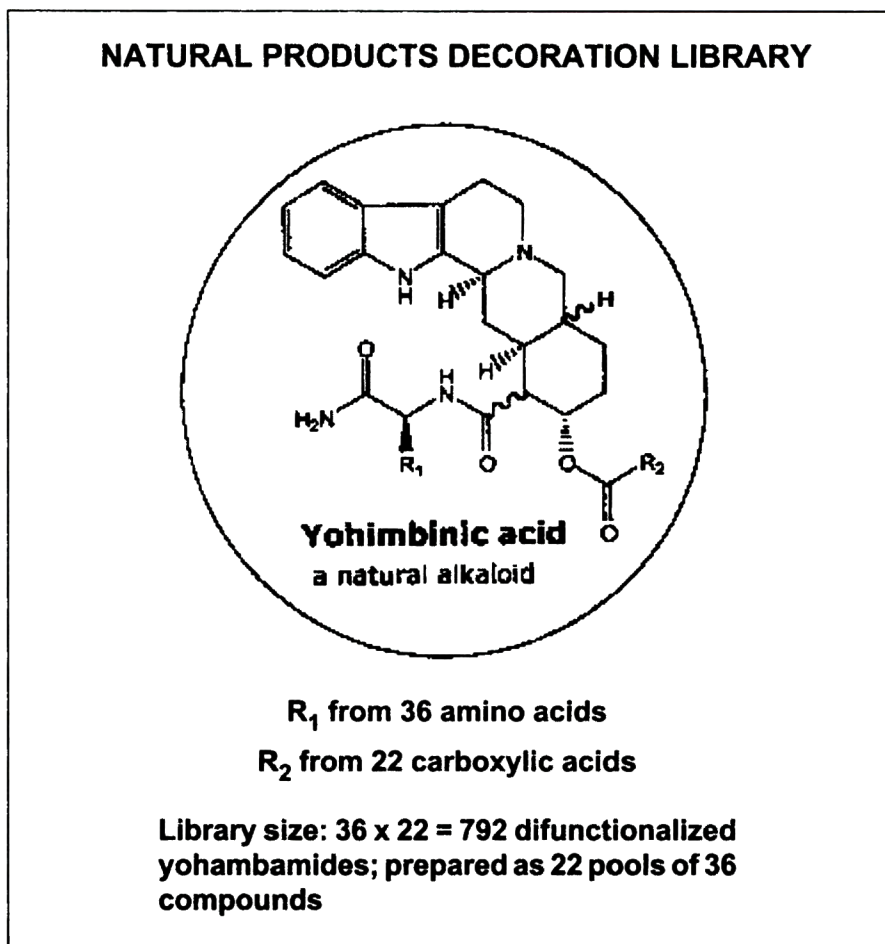
Figure 13. Decoration of yohimbinic acid

FT-IR On Bead

Fourier transform infrared (FT-IR) spectroscopy is a powerful technique for the monitoring of reactions on solid phase. It is possible to follow the extent of a reaction on solid phase by observing the appearance or disappearance of critical diagnostic absorption peaks; the intensity of the absorption signal can also be used as a marker for the degree of chemical conversion from starting materials to products. More recently the preferred method for analysis of libraries is FT-IR microspectroscopy whereby a single resin bead is extracted from the reaction mixture, washed with solvent, dried, and then located through an IR microscope

Figure 14. A library based on taxol, a potent anti-cancer drug

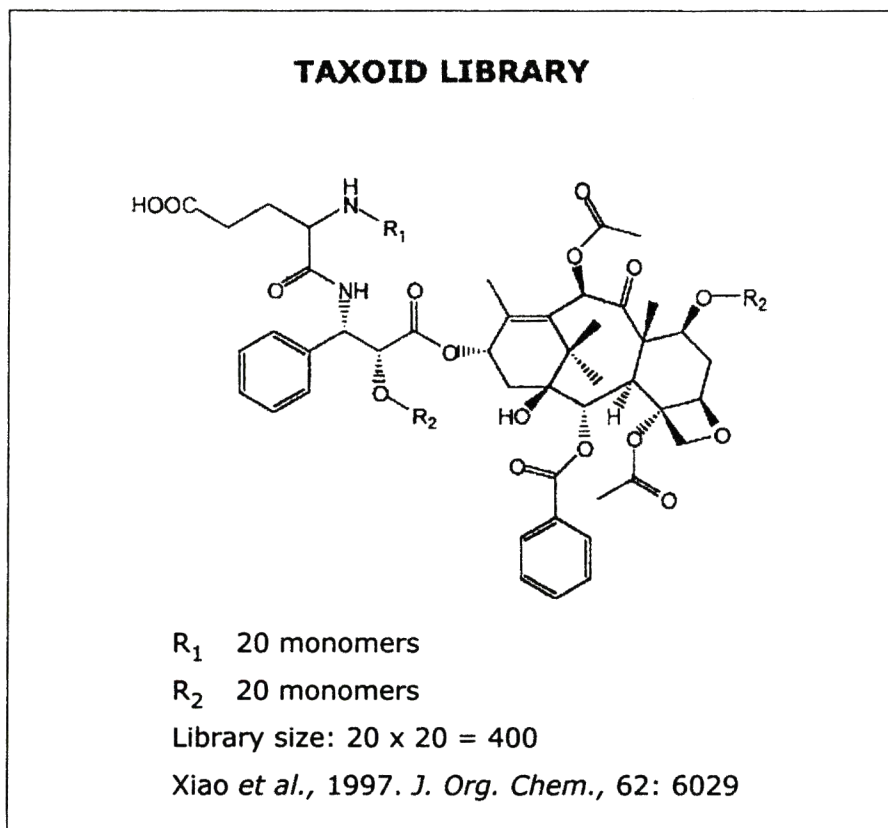(Yan *et al.*, 1995). The microscope is used to focus the IR radiation to allow the spectrum to be recorded in either reflectance or transmission mode. The beads examined are routinely 100 μm in diameter and contains around 400-800 picomoles of material.

Solid Phase NMR: Magic Angle Spinning NMR (MAS NMR)

The majority of NMR work has been done on samples in solution, thus the analysis of compounds while still attached to resin beads presents new challenges for the technique. The limited mobility of the polymeric support and also of the attached compounds leads to broad and poorly resolved signals. This has been overcome by using phase NMR techniques where the resin beads are swollen with to maximize compound mobility. However, the technique is limited by the very low sensitivity of the very small quantities of material on the bead. Large quantities of resins (several hundred milligrams) are required and acquisition times of several

hours are required. The advent of magic angle spinning (MAS) NMR has allowed high resolution ^{13}C and ^1H spectroscopy using smaller quantities of resins and shorter acquisition times. The use of MAS, which removes line broadening by spinning the sample about the magic angle (54.7° relative to the static magnetic field), and a nanoprobe has made possible the measurement of high-resolution proton spectra in solid-phase synthesis.

Mass Spectrometry

Mass spectrometry is used in combinatorial chemistry for monitoring of solid-phase products and reactions and for the identification of active compounds from libraries. IR and NMR, MS is a destructive technique that necessarily requires the cleavage of the compound being examined from the solid phase, but it is very sensitive technique that is able to produce data from picomole to fentamole quantities of compound. Three MS techniques have been very useful for analysis of combinatorial library samples: MALDI-TOF-MS, TOF-SIMS and ESI-MS.

Matrix-assisted Laser Desorption/Ionization Time-Of-flight
Mass Spectrometry (MALDI-TOF-MS)

This is a new technique that uses laser energy to desorp and ionize nonvolatile materials, such as peptides, intact from a matrix. High sensitivity allows the detection of fentamole compound quantities.

Imaging Time-Of-flight Secondary Ion Mass Spectrometry
(TOF-SIMS)

This technique offers mass accuracy of the order of ±0.01 atomic mass units, and thus can be used to distinguish between products of the same nominal mass. It also allows the ready identification of active peptides in a large combinatorial library by the examination of a single bead bearing the active compound (Brummel *et al.*, 1994).

Electrospray Ionization Mass Spectrometry (ESI-MS

In combination with capillary electrophoresis (CE), this technique has been used to determine the purity of a library mixture (Dunayevskiy *et al.*, 1996). It has also been shown to be useful in the measurement of binding constants – it is therefore able to identify compounds from within a combinatorial mixture that preferentially binds to a protein target.

Emerging Applications Of Combinatorial Chemistry And Combinatorial Technologies

In principle, any type of combinatorial library is used to speed up the discovery of novel active compounds – these compounds may not only be drug candidates, but also agrochemicals, new materials, catalysts, or polymers among others. Thus, although combinatorial chemistry and combinatorial technologies have been so far mostly applied to drug and agrochemical discovery, they can also be very powerful tools in the diagnostic, down-stream processing, catalysis and new materials sectors (Figure 15).

Combinatorial Material Science

The official birth of combinatorial material sciences is placed around mid 1990s (Xiang *et al.,* 1995), but it is only in the last four years that this field became popular among materials scientists.

Combinatorial technologies are ideally suited to boost the discovery of new materials. The synthesis of large, primary material library is very important for the identification of novel composites with interesting properties (hits). Focused materials libraries can then be used to optimize the combination and relative percentage of known active materials.

Most of the reported synthesis of materials science libraries involving solid reagents have used thin film deposition techniques, however solution-phase techniques have also been used successfully for some applications. Researchers at Symyx synthesized and screened a 25,000-meter inorganic library for luminescent materials; luminescent red phosphors and blue-white emission composites were identified from this library (Danielson *et al.,* 1997, 1998). A research group at Bell Laboratories has developed a new technique called continuous composition spread (CCS) for the synthesis of capacitors library, which was screened using scanning mercury-probe electrode (van Dover *et al.,* 1998 1999). The Materials Science Division at Berkeley has reported the synthesis and screening of a 256-member material library of ferroelectric materials for microwave applications (Chang *et al.,* 1998). Researchers from Sintef Applied Chemistry reported the preparation of zeolite arrays via hydrothermal synthesis (Corma, 1997).

Combinatorial Catalysis

Combinatorial catalysis is a methodology where large diversities of chemically and physically different materials libraries are prepared, processed and tested for activity and selectivity in a high-throughput fashion (Senkan, 2001). The use of combinatorial approaches have resulted in the discovery of superior catalytic materials in a matter of hours and days, as opposed to the months and years required using traditional methods. Combinatorial methods can also significantly
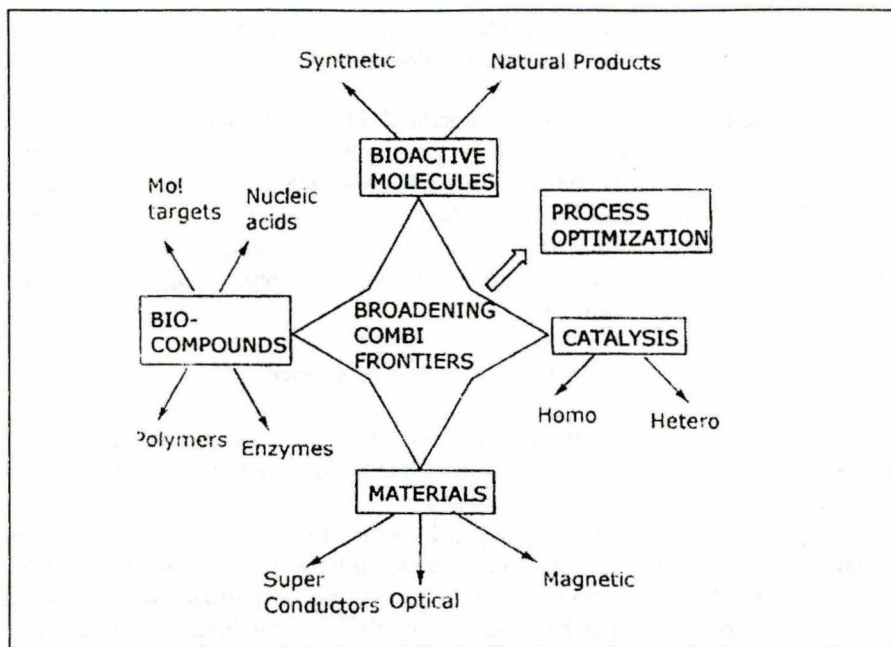
Figure 15. The emerging applications of CC/CT (Raghavan, 2001)

contribute to the understanding of catalytic function by increasing the chances of discovering totally new and unexpected catalytic materials, and by expediting the recognition of trends and patterns of structure-activity relationships.

New catalyst discoveries are routinely occurring in a number of laboratories. Some examples of homogeneous as well as heterogeneous combinatorial catalysis research are shown in Figures 16 and 17.

Information Sources For Combinatorial Chemistry

Combinatorial chemistry represents a real breakthrough, not only in the number of compounds synthesized and screened, but also in the exponential growth of publications and patent applications. Shown in Figure 18 is a listing of information sources for combinatorial chemistry (Nakayama, 2000).

Combinatorial Chemistry in The Philippines

In 15-17 July 1998, Dr. Norma Fajardo, then deputy director of the Institute of Chemistry, UP Los Baños attended a meeting on "Combinatorial Chemistry, Combinatorial Technologies and Molecular Design" in Trieste, Italy, sponsored by UNIDO and ICS (The International Centre for Science and High Technology. The

RESEARCH PIONEERS IN COMBI CATALYSIS

HOMOGENEOUS

(1995)
| University of California, Berkeley, USA | • Homogeneous catalysis
 • Parallel synthesis
 • 2 Pyrrolidine methanol ligands | • 11 Ligands
 • 2 Substrates
 • No purifications |

(1996)
| Texas A&M University, USA | • Assymetric C-H Insertion

 • Silver catalyst | • 96 candidates

 • Microliter plate format |

(1996)
| Boston College USA

 Yamaguchi University, Japan | • Enantioselective synthesis
 • β-cyanohydrin
 • synthesis Dipeptide titanium complexes | • Basic building blocks:
 2 amino acids aldehyde |

Figure 16. Research pioneers in combinatorial homogeneous catalysis (Raghavan, 2001)

mandate of ICS relates to the transfer of know-how and technology in favor of developing countries, which is justified by the perception that a competitive industrial technology capability cannot be built-up without adequate scientific knowledge and commitment to a sustainable development approach utilizing new and environment friendly technologies (Miertus, 1999). In that meeting, Dr. Fajardo presented a paper on the current state of combinatorial chemistry (CC), combinatorial technologies (CT) and molecular design (MD) in the Philippines. She used the survey on the state of chemical sciences in the country commissioned by NAST in 1998 as a major

RESEARCH PIONEERS IN COMBI CATALYSIS

HETEROGENEOUS

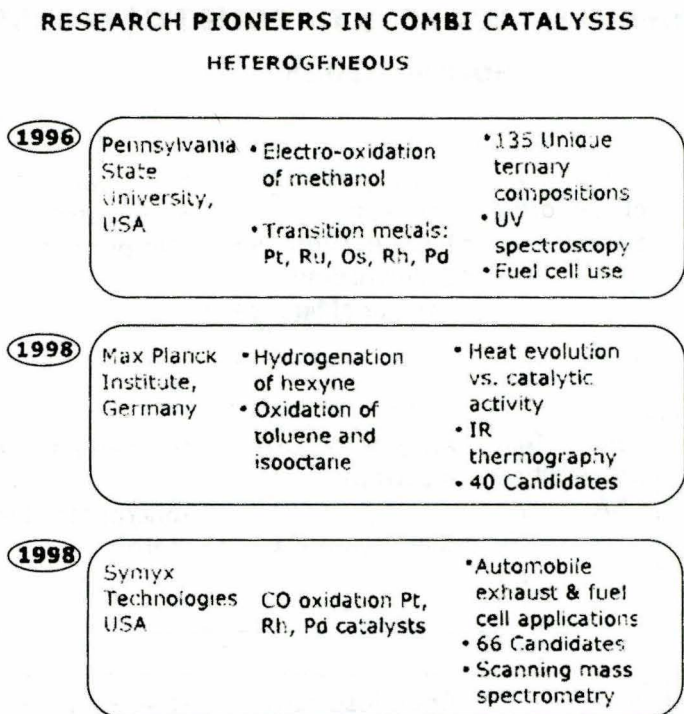| (1996)	Pennsylvania State University, USA	• Electro-oxidation of methanol • Transition metals: Pt, Ru, Os, Rh, Pd	• 135 Unique ternary compositions • UV spectroscopy • Fuel cell use
(1998)	Max Planck Institute, Germany	• Hydrogenation of hexyne • Oxidation of toluene and isooctane	• Heat evolution vs. catalytic activity • IR thermography • 40 Candidates
(1998)	Synyx Technologies USA	CO oxidation Pt, Rh, Pd catalysts	• Automobile exhaust & fuel cell applications • 66 Candidates • Scanning mass spectrometry

Figure 17. Research pioneers in combinatorial heterogeneous catalysis (Raghavan, 2001)

basis of her report (she was one of those involved in the study). The NAST study showed that no work involving CC/CT/MD was being done in the Philippines. Nevertheless, as an offshoot of that meeting, The Southeast Asian Regional Workshop on Combinatorial Chemistry and Combinatorial Technologies, sponsored by UNIDO and ICS and the Institute of Chemistry, UPLB, was held on 19-23 April 1999, at UP Los Baños. There were 27 selected participants representing academia, industry and government institutions from Hong Kong, India, Malaysia, Philippines, Taiwan, Thailand, Vietnam, together with world-recognized experts. There were 16 participants from the Philippines representing a good mix from academia (9), industry (4), government research institutions (3). The aim of the workshop was primarily to generate awareness of and interest in CC/CT/MD among the different participants. Among other reasons, because of the good showing of the group from IC, UPLB, which organized the workshop, ICS-UNIDO identified the Philippines as the ideal site for a proposed network center for CC/CT/MD in Southeast Asia. Since that time, proposals for the establishment of the center and for a combinatorial project

INFORMATION SOURCES IN COMBICHEM

WEBSITES

Combichem.net Homepage
http://www.combichem.net

Homepage has press releases
& product highlights

Combinatorial Chemistry Net Links
http://chemistry.miningco.com/education/chemistry/msub33.htm

compilation of articles, journals, software

Combinatrorial Chemistry/Organic Synthesis
http:pubs.acs.org/pin/combi.html

ACS sponsored advertised product showcase

Official Combinatorial Index Website
http://www.5z.com/divinfo

commercial sites (products),
scientific sites (literature & related links)

Figure 18. A selection of World Wide Web sites on combinatorial chemistry (Nakayana, 2000)

based on natural products have been made. All these plans are just waiting to take off, however big hurdles (infrastructure, logistics, lack of support and interest, etc.) need to be overcome.

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