UNITED NATIONS INDUSTRIAL DEVELOPMENT ORGANIZATION
INTERNATIONAL CENTRE FOR SCIENCE AND HIGH TECHNOLOGY

In cooperation with

Department of Chemistry, Moscow State University

UNIDO Workshop
on
Combinatorial Chemistry and Combinatorial Technologies

ABSTRACTS
of lectures

May 13-14, 2004, Moscow

Foreword

Combinatorial methods can be used whenever high numbers of compounds have to be prepared for testing. The pharmaceutical industry has passed through a remarkable transition in the last few years and much effort was done to identify novel targets in order to find new, therapeutically useful compounds by using the tools of combinatorial technology. Although the major pharmaceutical companies in Central Eastern Europe made the initial steps toward the introduction of the combinatorial approach in their research projects, still they are lagging behind the leading companies. The demand for new materials with defined functions, e.g. polymers, catalysts, pigments, liquid crystals, superconductors, thermo- and photochromic materials, to mention a few, has been increasing continuously. Combinatorial chemistry has a great potential to accelerate the process that leads to the discovery of such novel materials. Although main emphasis today is on use of combinatorial methods in pharmaceutical applications: the technique is suitable whenever a high number of compounds have to be prepared for testing. Additional fields include agro research, material research, etc. Most major pharmaceutical companies are active in the field, and it is generally accepted that the methods have high potential for the so-called lead finding and drug discovery process: the technology is expected to contribute to the reduction in time and costs.

A lack of co-ordinated effort in Russia and CIS countries has meant that combinatorial chemistry and combinatorial technologies have not been channeled into programs of industrial development. These are indeed vital to local enterprises if they are to remain competitive and economically viable in the coming decades, and for gaining expertise on application practice in combinatorial technology.

The International Centre for Science and High Technology (ICS) is an autonomous institution within the legal framework of the United Nations Industrial Development Organization (UNIDO), with headquarters in Trieste, Italy. The mandate of ICS relates to know-how transfer and technology transfer, and derives its justification from the perception that a competitive industrial and technological capability cannot be built-up without an adequate scientific knowledge and without participating in the development and utilization of new and advanced technologies.

Chemistry department of Moscow State University - the host of this event - flexibly reflects the above trends in the research area, teaching projects, and interaction with combichem-oriented business sector. This institution pioneered to open new speciality "Medicinal chemistry", and it is the birthplace of the special practical course on combinatorial chemistry (since 2001). Series of conferences devoted to combinatorial chemistry topics has been launched by MSU in 1999 (Zvenigorod) and continued in 2001 (University campus) and 2002 (Zelinskii institute of organic chemistry). This workshop is the next one in this line.

Local Organizers:

Prof. Academician **Valeriy V. Lunin**
Dr. **Eugene V. Babaev**

Contact address:
Dr. E. Babaev, Chemistry Department
Moscow State University, Moscow 119992
Tel.: +7-(095)-939-30-20
Fax : +7-(095)-932-88-46
E-mail: babaev@org.chem.msu.su

ICS-UNIDO

Professor **Stanislav Miertus**

Area of Pure and Applied Chemistry
ICS-UNIDO, Trieste, Italy
Tel: +39-40-9228114
Fax : +39-40-922 0068
E-mail : miertus@ics.trieste.it
Secretary: Emanuela Corazzi:
E-mail emanuela.corazzi@ics.trieste.it

ICS UNIDO Workshop on Combinatorial Chemistry & Combinatorial Technology
Moscow, Russia, May 13–14, 2004.

Solid Phase: a Common Motif for the Preparation of Peptides and Polycondensed Heterocycles

FERNANDO ALBERICIO
Barcelona Science Park, University of Barcelona, Barcelona, Spain

Recent years have witnessed constant changes in the pharmaceutical industry. Although the elucidation of the human genome followed by advances in functional Genomics and Proteomics has revolutionized our understanding of the molecular mechanisms that underlie many diseases, the industry faces a great challenge. To successfully produce drug candidates, it is necessary to improve the combined performance of *Docking*, *Combinatorial Chemistry*, and *High-Throughput Screening.*

Combinatorial Chemistry has brought about a revolution in many fields, among them medicinal and organic chemistry, and has itself undergone considerable evolution. In contrast to the emphasis placed upon the simultaneous preparation of thousands, if not millions, of compounds in its early days, *combinatorial chemistry* has been redirected towards the rapid and rational preparation of small-medium sized libraries of priority compounds.

Combinatorial chemistry has introduced into modern programs of medicinal chemistry new concepts and tools, namely diversity, automation and an interdisciplinary approach to problem solving. Another hallmark of combinatorial chemistry has been the implementation of various tactics used in peptide synthesis. Thus small scale work, use of orthogonal protecting groups and perhaps of greatest importance, synthesis on solid-phase, are common features of many modern combinatorial synthetic chemistry laboratories.

Although *Combinatorial Chemistry* may be conducted in solution, the solid-phase mode is often the method of choice. Solid-phase has been validated for the synthesis of biopolymers (peptides, oligonucleotides, peptoides and other foldamers), and small but simple organic molecules. Thus, there is a call for the use of solid-phase mode for the preparation of natural products, which are perhaps the most important source of biologically active compounds, and, therefore constitute a unique platform for obtaining chemical diversity.

The first part of the presentation will cover the impact of the combinatorial approach to organic and medicinal chemistry, while the second portion will discuss examples of the solid-phase synthesis of libraries related to compounds with interesting therapeutic activity: Lamellarins and Kahalalides, which are heterocycles and peptides from marine origin with antitumoral activity.

ICS UNIDO Workshop on Combinatorial Chemistry & Combinatorial Technology
Moscow, Russia, May 13–14, 2004.

Teaching students the combinatorial chemistry

EUGENE V. BABAEV
Moscow State University, Chemistry Department, Moscow, Russia

The experience of organic chemistry chair of MSU in teaching undergraduate students the practical combinatorial chemistry course is overviewed.

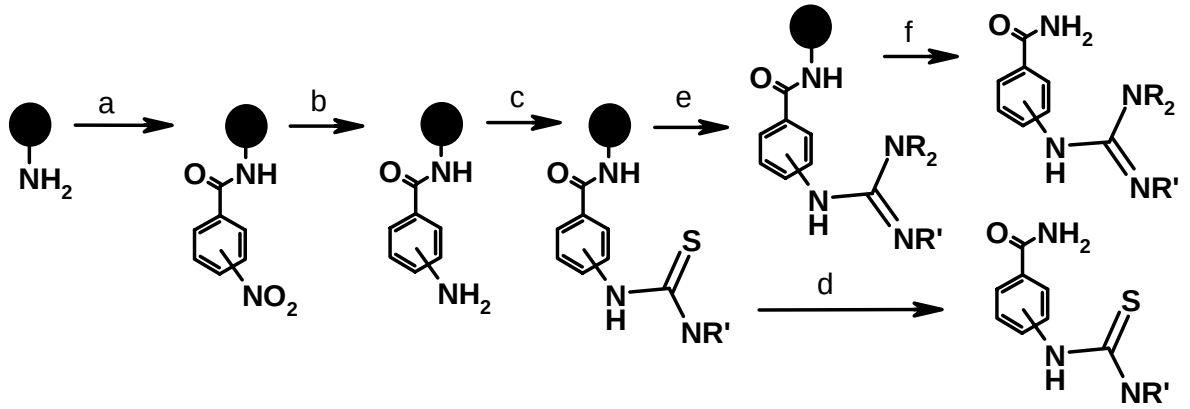
During the course the students get acquaintance with modern methodologies of combinatorial chemistry in several phases:

(1) General overview of methods and methodologies used in combinatorial chemistry
(2) Practical education on personal computers to create and manipulate with the chemical libraries (databases manual creation and modification, automatic generation of libraries from the subsets of building blocks)
(3) Practical task to prepare mini-library using solid phase or liquid phase parallel synthesis technique.
(4) Computer manipulations with the NMR spectra of the obtained compounds libraries.

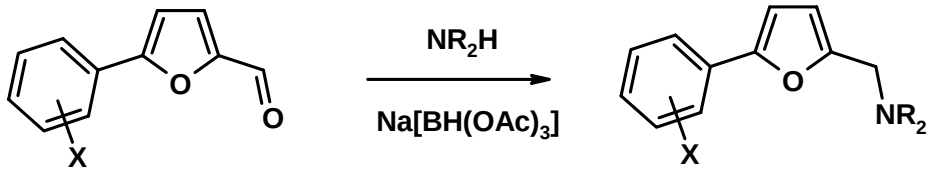
In our experience 3-4 teachers can perform

In the period 2001-2004 we have tried to vary the experimental tasks in order to find optimal and reproducible experimental protocols. As a result, two main protocols have been selected, tested and recommended for further use as educational tasks.

(I). Solid phase synthesis: Multistep solid phase synthesis of substituted guanidines on Rink resin using Mimotopes Lanterns. The protocol (a) - (d) was reproduced from literature data, whereas the longer sequence (a) - (f) is our original finding:



(II). Liquid phase parallel synthesis: Obtaining of the library of amines by reductive amination of (hetero)aromatic aldehydes. This second task can be realized either in an "economical" way (no sophisticated equipment except parallel shakers; use of parallel chromatography) or with the use of the Buchi SynCore unit (parallel heating & shaking, parallel evaporation, parallel filtering). One example of the students' task is the following:



Attempts to arrange parallel biological screening of the samples prepared by students will be discussed.

ICS UNIDO Workshop on Combinatorial Chemistry & Combinatorial Technology
Moscow, Russia, May 13–14, 2004.

Combisyn™ Reactor For Parallel Organic Synthesis

M. B. BARU and A.V. IVASCHENKO

Chemical Diversity Research Institute, Ltd, Dolgoprudny, Russia

The problem of high-speed synthesis of small diverse libraries of pure compounds stays acute in hit-to-lead optimization process. Methods of combinatorial chemistry allow for rapid generation of novel compounds in large numbers. But for all that, the emphasis is shifted to assessment of diversity and purity of compounds obtained by means of high throughput synthesis. Chemical Diversity Labs achieved the goal of successful solution offering its helping hand to all chemical researchers around the globe.

Our latest advance is CombiSyn™ [1-3] - a family of original reactors for parallel organic synthesis. CombySyn™ reactors emerged out of efforts put by our skillful engineers, designers and highly qualified synthetic chemists into performance analysis of commercially available equipment for parallel synthesis to create a reliable, simple and effective instrumentation so needed to improve quality of synthetic processes. The basic idea of modularity maximizes flexibility and convenience of "custom-built" assembly to fit for every particular task. Individual reaction control makes it possible to study and select conditions for synthesis. Utilization of backflow condensers allows for application of volatile solvents. Central inert gas distribution system with direct passing-through allows reactions under an inert atmosphere with no need of magnetic stirrers. Proprietary magnetic stirring elements provide the most effective way of heterogeneous mixture agitation at high stirring speeds. Compatibility with standard laboratory magnetic stirrers and thermostats simplifies experiment performance. The temperature range may be varied from minus 30 to plus 250 degrees centigrade. It may also be expanded by application of special heat-transfers.

Now, in laboratories of Chemical Diversity Research Institute, there are more than one hundred CombiSyn™ of various modifications. Such reactions as nucleophilic and electrophilic substitution, amidation, oxidation, condensation, hydrogenation, multicomponent will successfully be carried out in CombiSyn™. Use of CombiSyn™ reactors allows to provide high-efficiency synthesis of combinatory libraries.

REFERENCES

1. Rus. Pat. №2180609
2. Rus. Pat. №2183135
3. http://www.combisyn.com/pages/products.phtml

ICS UNIDO Workshop on Combinatorial Chemistry & Combinatorial Technology
Moscow, Russia, May 13–14, 2004.

High-Throughput Analytical Methods for Library Characterization

GÁBOR DIBÓ
Eötvös Loránd University, Budapest, Hungary

A new paradigm in drug discovery is the combinatorial production of pools of compounds, so-called libraries, followed by high-throughput screening (HTS). The introduction of a new drug to the market requires 10–15 years and a budget of 6–800 million euros. Application of the combinatorial approach makes possible the significant reduction of both the time and the cost of the drug discovery process.

Our combinatorial chemistry group at the Department of Organic Chemistry, Eötvös Loránd University has pioneered combinatorial science since 1982 [1]. Currently, we apply our powerful split-mix synthesis strategy for random combinatorial synthesis [2] and the simple and elegant string synthesis strategy for the parallel synthesis of peptide libraries [3].

The generation of molecular diversity in combination with high-throughput screening has become the method of choice for the production of new pharmacological leads for chemical optimization. Due to the recent developments of synthetic organic chemistry, there is no technical difficulty in the production of large number of compounds. However, characterization and separation of such pool of compounds have been lagging behind the synthetic and screening methodologies. The chemical characterization of complex libraries represents a formidable challenge for the analytical chemists. This has lead to ultra-fast methods, miniaturization, multiple approaches, system automation and robust data handling/processing. Over the past few years, a plethora of sensitive, high resolution and high-throughput separation methods (SPE, HPLC, CE, PAGE) and spectroscopic techniques (FT-IR, NMR, MS) have been developed. However, by using conventional chromatographic and electrophoretic methods based on column technologies, the number of samples analyzed during a normal working day is confined to less than 100. Over-pressured layer chromatography (OPLC) is an instrumental planar chromatographic method introduced in the 1980s in Hungary. This technique allows the simultaneous separation of the same number of samples within minutes. Thus, daily analysis of hundreds of samples can easily be performed. The planar arrangement, intrinsically, allows multi-dimensional (MD) separation of complex mixtures of compounds with highly related structure [4]. Recently, the latest generation of the OPLC instrumentation (OPLC 50, Bionisis, France) has become commercially available.

This presentation will give a brief overview on the recent developments in high-throughput analysis (HTA) and will show the application of different modes of the OPLC technique for library analysis.

[1] Á. Furka: *Notarized Report,* **1982**. (in Hungarian).

[2] Á. Furka, F. Sebestyén, M. Asgedom, G. Dibó: *14th Int. Congress Biochem.,* Prague, **1988**; *Int. J. Peptide Prot. Res.* **1991,** *37,* 487–493.

[3] Á. Furka, J. W. Christensen, E. Healy, H. R. Tanner, H. H. Saneii, *J. Comb. Chem*. **2000**, *2*, 220–223; Á. Furka, G. Dibó, N. Gombosuren, *Curr. Drug Discov. Technol.* **2004,** *1*, in press.

[4] N. Gombosuren, E. Mincsovics, G. Dibó, *Int. Symp. Thin-Layer Chromatogr., Lyon, France*, **2003.**

Dynamic Combinatorial Chemistry

ALEXEY ELISEEV
Alantos Pharmaceuticals, Inc. Cambridge, USA

The major effort of today's combinatorial chemistry and high-throughput screening is focused on the synthesis and screening of libraries of individual compounds in a parallel fashion. Dynamic combinatorial chemistry (DCC) is an alternative approach, which allows one to combine synthesis and screening in a single step. DCC uses molecular building blocks to generate dynamic libraries — all possible structural combinations of the building blocks existing in a dynamic equilibrium. These special types of libraries are then refined via interaction with a biological target to produce (amplify) only those library components that bind tightly to the target. The addition of the biological target to the dynamic library promotes the formation of the best-binding constituents and minimizes the production of inactive compounds. Such an enrichment of the library with the best binders greatly simplifies identification of the active ligands from the large theoretical diversity of compounds. The ligands discovered in the dynamic library synthesis-screening can be optimized further, if necessary, into drug leads and ultimately clinical development candidates.

The presentation will primarily focus on the application of DCC to small molecule drug discovery. The following topics will be covered:

- DCC as a general approach to synthesis and screening of combinatorial libraries: advantages and limitations as compared to parallel techniques.
    - Examples of early examples of dynamic libraries. Bioactive peptides, inhibitors of carbonic anhydrase, lectins.
    - Basic reactions used in DCC. Examples of imine exchange, transesterification, aldol condensation, alkene metathesis.
    - Amplification effects in dynamic libraries. Thermodynamic vs. kinetic effects.
- DCC as emerging tool of drug discovery. Case study of neuraminidase inhibitors formed from *in vitro* virtual libraries.
- New developments in DCC and related approaches:
    - Tethering (Sunesis).
    - DCC with protein crystals (Astex).
    - Selective destruction (McGill).

Suggested Literature

1. A. Ganesan, *Angew. Chem. Int. Ed. Engl.* **37**, 2828-2831 (1998).
2. J. M. Lehn, *Chem. Eur. J.* **5**, 2455-2463 (1999).
3. J. M. Lehn, A. V. Eliseev, *Science* **291**, 2331-2332 (2001).
4. O. Ramström, J.-M. Lehn, *Nature Reviews, Drug Discovery* **1**, 26-36 (2002).

ICS UNIDO Workshop on Combinatorial Chemistry & Combinatorial Technology
Moscow, Russia, May 13–14, 2004.

Combinatorial Technologies in Biotechnology

GIOGRIO FASSINA
XEPTAGEN S. p. A. Pozzuoli (Napoli), Italy

The past decade has been signed by impressive advances in both areas of diagnostic and therapeutic medicine. While genomic, by identifying unknown genes, has enormously accelerated the discovery of new proteins related to these genes, combinatorial chemistry and combinatorial technologies (CCCT) have drastically speeded the process of drug discovery, by offering an unlimited source of molecular entities to be screened for a given activity. Combinatorial technologies can now be considered an integrated approach for a novel way of producing science, where chemistry, molecular biology, molecular design and screening are the essential components. The use of CCCT in the pharmaceutical industry is already well established, but other industrial sectors, such as the diagnostic and the biotech, are rapidly adopting combinatorial technologies in their research programs. In particular , the application of CCCT to the biotech sector has led already to extraordinary results, since this platform technology may be useful not only to gain basic information on biological systems important for the development of products or for the understanding of mechanisms of action of known substances, but more importantly to derive and accelerate new products development

ICS UNIDO Workshop on Combinatorial Chemistry & Combinatorial Technology
Moscow, Russia, May 13–14, 2004.

Introduction to Design of Combinatorial Libraries

GYÖRGY MIKLÓS KESERŰ
Computer Assisted Drug Discovery, Gedeon Richter Ltd., Budapest, Hungary

Combinatorial synthesis is clearly the main chemistry utility of the high throughput technologies applied in drug research. Early combinatorial technologies, such as split-and-mix synthesis was primarily used on peptides at the lead discovery phase of drug research programs. Nowadays, however, parallel synthesis – the methodology that produces pure compounds rather than mixtures - has become the ultimate methodology of combinatorial chemistry both in lead discovery and lead optimisation phases. Although the size of a discovery library remains important, now targeting, diversity, drug-likeness, synthetic feasibility and novelty of the synthesized compounds should be balanced. Although combinatorial chemistry suppliers still produce large libraries the drug research experience with combinatorial chemistry suggests that parallel synthesis of several hundreds or thousand potentially active compounds can be most effectively utilized at the lead optimisation phase. This goal can be achieved by the rational design of focused libraries that can be realized by automated synthesis. The lecture will focus on design strategies and methodologies of combinatorial libraries. Starting from the creation of virtual libraries several diversity descriptors will be introduced. Library design strategies will involve traditional diversity based approaches and several focusing strategies including design principles of target or target class specific libraries as well as ADMET focusing. Examples on ligand-based and structure-based virtual screening as well as neural network based approaches will be highlighted. The effectiveness of the focused approach will be demonstrated by an in-house case study of dopaminergic D3 library.

- György M. Keserű, László Molnár, István Greiner: A Neural Network Based Virtual High Throughput Screening Test for CNS Active Compounds. **Comb. Chem. & HTS** 3, 535 (2000).
- György M. Keserű, László Molnár: High throughput in silico prediction of blood-brain partitioning: a thermodynamic approach. **J. Chem. Inf. Comput. Sci.** 41, 120 (2001).
- Keserű, G. M.: A virtual high throughput screen for high affinity cytochrome P450cam substrates. Implications for in silico prediction of drug metabolism **J. Comput.-Aided Mol. Des.** 15, 649 (2001).
- László Molnár, György M. Keserű: A Neural Network Based Virtual High Throughput Screening of Cytochrome P450 3A4 Inhibitors **Bioorg. Med. Chem. Lett.** 12, 419 (2002).
- György M. Keserű, László Molnár: METAPRINT: a Metabolic Fingerprint. Application to Casette Design in ADME HTS **J. Chem. Inf. Comput. Sci.** 42, 437 (2002).
- Darvas F, Keserű G. M, Papp A, Dormán G, Ürge L, Krajcsi P.: In Silico and Ex silico ADME approaches for drug discovery. **Curr. Top. Med. Chem.** 2, 1287 (2002).
- Lobell M, Molnar L, Keserű G. M.: Recent advances in the prediction of blood-brain partitioning from molecular structure **J. Pharm. Sci.** 92 ,360 (2003).
- György M. Keserű: Prediction of hERG Potassium Channel Affinity by Traditional and Hologram QSAR Methods **Bioorg. Med. Chem. Lett.** 13, 2773, (2003).
- László Molnár, György M. Keserű, Ákos Papp, Zsolt Gulyás and Ferenc Darvas: A neural network based prediction of octanol–water partition coefficients using atomic5 fragmental descriptors **Bioorg. Med. Chem. Lett.** 14, 851 (2004).

Polymer Supported Combinatorial Synthesis of small organic molecules of Medicinal Interest

BIJOY KUNDU
Medicinal Chemistry Division, Central Drug Research Inst., Lucknow, India

The rapid automated synthesis of molecular diversity to fuel high-throughput screening for lead generation as well as the synthesis of directed libraries for subsequent lead optimization has evolved into effective strategy to accelerate drug discovery. Indeed during past decade combinatorial chemistry has provided access to greatly expanded chemical collections of drug-like compounds through the development of solid phase methods, which proceed in high yields and purities.

Our institute has embarked on a program for the development of capability on targeted drug research by initiation and strengthening of facilities in the area of combinatorial chemistry. Several libraries based on lead molecules, heterocyclic structures and natural product-like structures have been generated using solid-phase strategies[1-4]. The details of our studies will be discussed.

References

1. Solid phase synthesis of 2-aminoquinazolin- based derivatives G. K. Srivastava, A. P. Kesarwani, R. K. Grover, T. Srinivasan, R. Roy and B. Kundu **J Comb Chem.** 5, 769, 2003.
2. Solid-phase synthesis of quinaxolines on S. K. Singh, P. Gupta, S. Dugeineni and B. Kundu**. SynLett** 2147, 2003.
3. Solid phase synthesis of 3,5 disubstituted Oxazolidin-2-ones. S. K. Rastogi, G. K. Srivastava, S. K. Singh, R. Grover, R. Roy and B. Kundu **Tetrahedron Lett.** 43, 8327, 2002.
4. Template-directed approach to solid-phase combinatorial synthesis of Furan-based libraries. P. Gupta, A. Pathak and B. Kundu. **Tetrahedron** 58, 10469, 2002.

ICS UNIDO Workshop on Combinatorial Chemistry & Combinatorial Technology
Moscow, Russia, May 13–14, 2004.

Introduction to ICS-UNIDO Activities with Focus on CC/CT Programs

STANISLAV MIERTUS
ICS-UNIDO, Area Science Park Trieste, Italy

The ***International Centre for Science and High Technology (ICS)*** is an institution within the legal framework of UNIDO(United Nations Industrial Development Organization) with the headquarters located in Trieste, Italy in the AREA Science Park. The Centre's mandate relates to the transfer of know-how and technology in favor of developing countries, and is justified by the perception that a competitive industrial technological capability cannot be built-up without adequate scientific knowledge and commitment to a sustainable development approach based on new and environmentally friendly technologies. In the present Work Programme the ICS's activities focus on specific sectors within the areas of:

- ***Pure and Applied Chemistry***
- ***Earth, Environmental and Marine Sciences and Technologies***
- ***High Technology and New Materials***

The main tools for the implementation of the Work Programme of the **ICS Area of Pure and Applied Chemistry**, are the following:

- ***Organization of Training Events (EGMs, Training Courses and Workshops)***
- ***Information Packages, Publication Activities and Networking***
- ***Fellowships and on Job Training Schemes***
- ***Development of Project Proposals and participation of ICS in international projects and initiatives***

Considering that sustainable development depends upon the harmonization of economic growth and environment conservation and protection, the ICS area of **Pure and Applied Chemistry** has identified as priority fields in its work programme the following themes, which are of key relevance to economic and industrial development as well as environmental protection:

- ***Catalysis and Sustainable Chemistry***
- ***Environmentally Degradable Plastics***
- ***Remediation Technologies***
- ***Combinatorial Chemistry and Technologies***

Combinatorial Chemistry and Combinatorial Technologies

These technologies, combined with Molecular Modeling and Design, have a strong impact on the development of new chemicals (pharmaceutical industries, agro-chemicals, new materials). Developing countries need to get acquainted with and gain expertise in combinatorial technologies to help local enterprises remain competitive and economically viable in the coming decades. Combinatorial chemistry and combinatorial technology have a potential influence not only on industrial growth, but also on environment protection. In fact, by optimizing industrial processes and production, with the lowering of relevant costs, less amounts of waste and by-products are created.

As well as the full range of training activities, capacity building and development of project proposals, effort is being invested in developing an expertise unit on molecular modelling internal to ICS. The aim is to satisfy a number of requests from developing countries (India, Malaysia, Southern Africa, Latin America, Central and East Europe, etc.) for training young researchers and technologists in this field. The capacity of this unit will also allow ICS to carry out feasibility studies and demonstration projects.

All awareness and capacity building activities (workshops, training courses, etc.) are organized at a regional (or sub-regional) level. Targeted regions are Asian, African, CEE and Latin American and Mediterranean countries. A host country, to represent the region, is selected by analysing the problems and needs of the area during the Expert Group Meetings organized under each subprogramme.

A lack of co-ordinated effort in developing countries has meant that CC/T and MD have not been channelled into programmes of industrial development. Developing countries (some African countries, Argentina, Brazil, China, India, Indonesia, Malaysia, Mexico, Philippines, Thailand, etc.) and countries of Central and East Europe are strongly aware of their need to take up combinatorial technologies. These are indeed vital to local enterprises if they are to remain competitive and economically viable in the coming decades, and for gaining expertise on application practice in combinatorial technology. Expert Group Meetings have been recently organized within the subprogramme in CC/T and MD.

ICS UNIDO Workshop on Combinatorial Chemistry & Combinatorial Technology
Moscow, Russia, May 13–14, 2004.

Methodologies and Strategies in Combinatorial Investigation Applied to Heterogeneous Catalysis: Key Issues of Data Management

CLAUDE MIRODATOS
Institut de Recherches sur la Catalyse – CNRS, Villeurbanne, France

Over the past five years, combinatorial chemistry applied to heterogeneous catalysis has been dealt with in more and more articles, reviews and patents. This methodology remains very controversial, however. Today, within universities as well as within public and private research centres, attitudes toward combinatorial methods run the gamut from fascination to scepticism. As such, "combinatorial catalysis" is too often mistaken for a random, undisciplined mixing of various chemicals. On the contrary, the combinatorial approach embodies conventional catalysis, micro mechanics, robotics, analytical methodology and information technology.

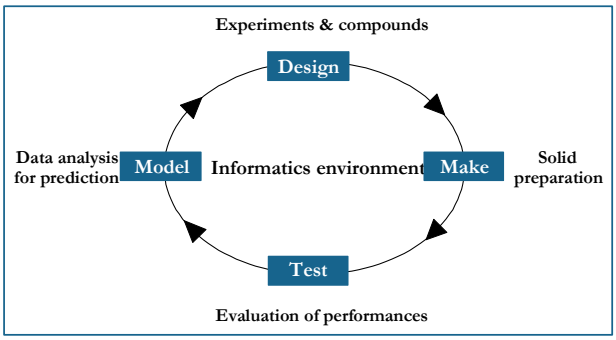


Figure 1 : Basic principle of the combinatorial approach applied to catalysis: iterative loop up to achievement of new product or process specification

Today, High Throughput Technologies (parallel reactors, robots for catalysts synthesis) are rapidly evolving but technical development is still required for specific applications. The major bottleneck with HTT resides in the treatment of huge volumes of data produced by the sequential combi-loops (Figure 1), which needs to be processed and interpreted in a **fast** and **efficient way**. All operations aimed at storing large quantities of diverse data in addressable locations, analysing this data with a battery of statistical methods and algorithms and then using this feedback to **design catalyst libraries** or to generate **fundamental knowledge**, collectively referred to as 'data management', are **still** in their **infancy** for combinatorial catalysis

This presentation will focus on this key issue of the combinatorial research, providing solutions developed in Academia. Various cases studies will be presented, including data base development, choice of search strategies and adapted software tools (DoE, NN).

References :

1. A. Holzwarth, P. Denton, H. Zanthoff and C. Mirodatos, **Combinatorial approaches to heterogeneous catalysis: strategies and perspectives for academic research,** Catalysis Today, 2441, 2001, 1-10.
2. D. Farrusseng, L. Baumes, C. Hayaud, I. Vauthey, P. Denton, C. Mirodatos, **The combinatorial approach for heterogeneous catalysis: a challenge for academic research. Strategies and perspectives.** Principles and Methods for Accelerated Catalyst Design, E. Derouane et al., Eds., NATO Science Series, Kluwer Academic Publishers, 2002**,** pp. 469-479.
3. D. Farruseng, L. Baumes, C. Mirodatos, **Data management for combinatorial heterogeneous catalysis : methodology and development of advanced tools.** in High-Throughput Analysis: A Tool For Combinatorial Materials Science, Radislav A. Potyrailo and Eric J. Amis, Eds, Kluwer Academic/Plenum Publishers, 2003, pp. 551-579.

Combinatorial Chemistry in Urals Region

MAXIM A. MIRONOV
Urals State Technical University, Russia

Combinatorial chemistry started developing in Urals region beginning from 2000. All work in this field can be divided into three parts:

A. Use of combinatorial methods in basic researches for the finding of new chemical reactions, optimization of the well-known synthetic methods, creation of new catalysts.
B. Creation of new technologies for the parallel synthesis and purification of organic compounds.
C. Teaching students combinatorial chemistry in course of training of high-level personnel for the regional industry.

The presentation will be focused on two original combinatorial techniques that develop in laboratory of combinatorial synthesis at the Urals State Technical University.

1. A simple and eco-friendly protocol for the chemical libraries production will be discussed. This protocol involving multi-component reactions in aqueous solutions is amenable to the automated synthesis of the combinatorial libraries with a broad scope of structural and chemistry diversity.
2. A new method for the search of multi-component reactions that allows us to discover new chemical reactions will be presented. Several of these new reactions have been used for production of chemical libraries. In addition the problems, which appear in connection with the screening of chemical libraries in the region, will be discussed.

Other part of presentation will be devoted to teaching students combinatorial chemistry at the university. During two years (2003-2004) we give a course of combinatorial chemistry, which includes lectures and practical training.

In summary, different aspects of the combinatorial investigations at the university and Urals region in all will be discussed. We hope that our experience will be useful for other regional universities.

ICS UNIDO Workshop on Combinatorial Chemistry & Combinatorial Technology
Moscow, Russia, May 13–14, 2004.

Microwave Applications in Combinatorial Chemistry and High Throughput Synthesis

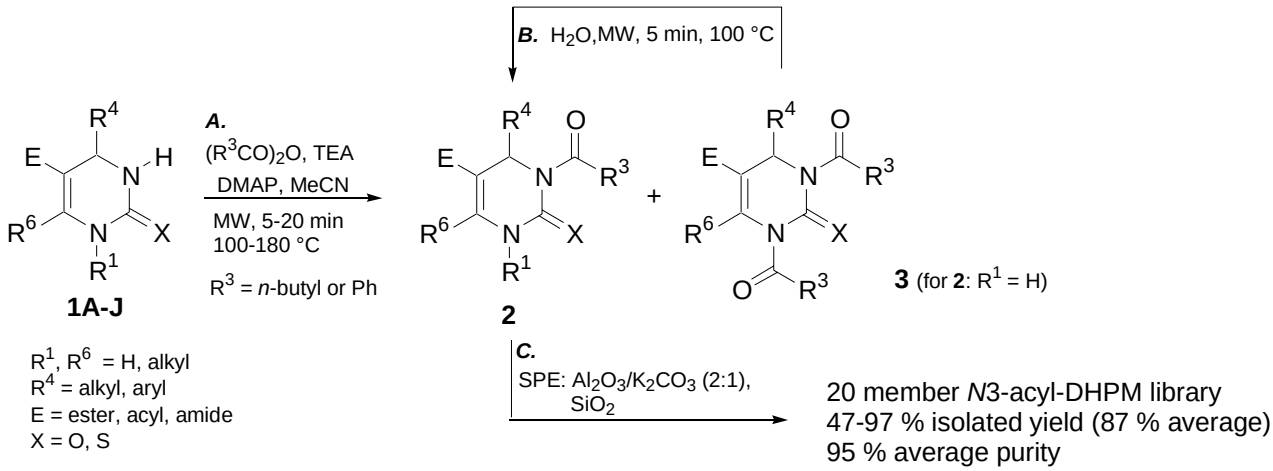
C.OLIVER KAPPE, ALEXANDER STADLER*
Institute of Chemistry, Department of Organic & Bioorganic Chemistry, Karl-Franzens University Graz, Graz, Austria

The interest and importance of Microwave irradiation towards organic synthesis applications has been dramatically increased in the last decade. Since the beginning of microwave mediated organic synthesis in the late 1980s featuring simple domestic microwave ovens, the available equipment has been improved, allowing a broad range of chemical reactions being carried out under microwave heating.

After a short introduction in Microwave theory this lecture will give a brief historical abstract on the development of suitable microwave instruments. An overview of the nowadays applicable instrumentation, featuring both multimode batch reactors and monomode instruments, will be given and a literature-based review of important microwave mediated model reactions in organic synthesis is presented.

Furthermore, the effectiveness of microwave irradiation towards combinatorial applications, e.g. solid phase synthesis is outlined, illustrated by several examples over the years. In this context variations of microwave equipment, dedicated for combinatorial purpose are introduced.
In addition some recent results from the Kappe group on the use of microwaves towards combinatorial chemistry and high throughput synthesis will be highlighted.

Finally an outlook with respect of the future needs of microwave users regarding scale up properties will be given.



Scheme 1. High Throughput Preparation of a Library of N3-acylated DHPMs[1]

SPONSORING ORGANIZATIONS: