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cc: Reporting
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INTERNATIONAL CENTRE FOR SCIENCE AND HIGH TECHNOLOGY

In co-operate with
Faculty of Pharmaceutical Sciences, Chulalongkorn University

Final Report
on

Opinion Leaders' Meeting
on
"Potential Applications of CC/CT/MD"
23 April 2001

and

Workshop
on
"Southeast Asian Countries on CC/CT: Natural Products and Technologies on Rapid Screening"
24-27 April 2001

Bangkok, Thailand

UNITED NATIONS INDUSTRIAL DEVELOPMENT ORGANIZATION

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1. Background

Natural products have long been and will continue to be extremely important as sources of medicinal agents and models for the design of novel substrances for treating mankind's diseases. However, despite many important past contributions from the natural products, still a great number of bioresources have never been described and relatively few have been surveyed systematically for biologically active chemical constituents. For example, the tropical forests of Southeast Asian countries are the forests that have been recognized as one of the world's major regions of complexity and species diversity but much of their biodiversity remains to be investigated. It is, therefore, highly expected that new natural products of valuable and pharmaceutically interesting materials remain to be discovered and developed.

Internationally, this research area of "Natural Products Drug Discovery" has been rapidly evolving as new technologies of combinatorial chemistry, combinatorial biosynthesis and combinatorial technologies are developed to accelerate the process. For developing countries, however, the introduction of these sophisticated and new methodologies are not easy since only limited resources are available. In addition, most of industrial research centers are not ready to invest in new technologies. It is on this background that the International Centre for Science and High Technology (ICS) aims to develop awareness in industrial and academic sectors of Southeast Asian countries regarding the importance for adopting combinatorial technologies in the pharmaceutical and other industrial fields.

ICS is an institution within the legal framework of the United Nations Industrial Development Organization (UNIDO), with headquarters in Trieste, Italy. The Centre mandate relates to know-how transfer and technology transfer from developed countries to developing countries, 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. For these reasons, ICS-UNIDO decided to hold this Southeast Asian Regional Workshop on "CC/CT: Natural Products and Technologies on Rapid Screening". The issue was also discussed and evaluated during the Opinion Leaders' Meeting on "Potential Application of CC/CT/MD". Both events took place at the Faculty of Pharmaceutical Sciences, Chulalongkorn University, Bangkok, Thailand on April 23-27, 2001.

2. Objectives

- To evaluate the state of the art of combinatorial chemistry and molecular design and their industrial applications in Southeast Asia
- To build awareness among industry and academic decision makers on a very rapid development of combinatorial chemistry, and its relevance for industry in the region
- To evaluate possible initiative (follow-up projects and feasibility studies) concerning CC/CT of industry and academia from Southeast Asian countries
- To set up a regional ICS-UNIDO network on Combinatorial Chemistry and Combinatorial Technology

3. Organization

The Meeting of Opinion Leaders on "Potential Applications of CC/CT/MD" and the Workshops on "Southeast Asian Countries on CC/CT: Natural Products and Technologies on Rapid Screening" were organized by the International Centre for Science and High Technology (ICS), United Nations Industrial Development Organization (UNIDO), in cooperation with the Faculty of Pharmaceutical Sciences, Chulalongkorn University, Bangkok, Thailand.

The Opinion Leaders' Meeting on "Potential Applications of CC/CT/MD" took place on April 23, 2001 and the Workshops on "Southeast Asian Countries on CC/CT: Natural Products and Technologies on Rapid Screening" took place on April 24-27, 2001 at Chulalongkorn University, Bangkok, Thailand

4. Funding

The funding used for the Meeting and Workshops was contributed by various sources :

The ICS-UNIDO approved contribution for both events was **US$ 25,000.**

The amount received from UNIDO on April 30, 2001 was **US$ 20,000**
(910,500 baht)

The actual expenditure from the ICS-UNIDO contribution was **US$ 20,379.46**

The final balance was **US$ 4,620.54**

The hosting country, Thailand, contributed **US$ 5,086.**

The actual expense from the UNIDO contribution was lower than expected, mainly because of the effort to reduce travelling cost of SEACs participants, and on bargaining for their self finance. In addition, the effort to rearrange for accommodation with good quality at cheaper price. A summary of the final budget is given in **Annex 1**.

5. Participation

The Meeting of Opinion Leaders on "Potential Applications of CC/CT/MD" consisted of 20 participants, 6 international experts and 14 Southeast Asian and Asian countries' representatives from academia, decision-makers and pharmaceutical industry on the relevance of combinatorial chemistry, combinatorial technologies and molecular modeling. The Workshops on "Southeast Asian Countries on CC/CT: Natural Products and Technologies on Rapid Screening " consisted of the same group of experts, Southeast Asian and Asian representatives, as well as 30 local scientists, researchers and industrialists (**Annexes 2-4**).

6. Materials

Each participant at the Meeting and at the Workshops received a bag with all the essential information concerning, lecture notes, program, list of participants, pen, notebook and the identification badge.

7. Opening Ceremony

On the Opinion Leaders' Meeting, **Dr. Wanchai De-Eknamkul**, Chair of the Secretariat Committee gave a report address on behalf of the Organizing Committee and **Dr. Kamchon Kittiyakawee**, Vice President of Chulalongkorn University gave an opening remark on behalf of Chulalongkorn University. Distinguished guests joining this first event included **Prof. Piazzardi Paolo**, Cultural Attache Ambasciata d'Italia. Thailand ; **Mr. Claudio Scaratti**, representative of UNIDO Regional Office in Bangkok. etc.

On the opening ceremony of the Workshops, **Dr. Kaisri Umprayn**, Chairman of the organizing committee, gave a report address on behalf of the Organizing Committee and **Dr. Usanee Yodyingyuad**, Vice President for Science and Technology Development Policy gave opening remarks on behalf of Chulalongkorn University.

8. Programs

The Agendas of the Opinion Leader's Meeting and of the Workshop are given in the **Annex 5**

9. Social Events

Welcome Party was organized for the international experts and Southeast Asian representatives by the Faculty of Pharmaceutical Sciences, Chulalongkorn University on Monday, April 23 at 07.00 - 09.00 pm.

Farewell Party was hosted by the organizer on Thursday, April 26 at 06.30 - 09.00 pm.

10. Detailed Report

First Event: Opinion Leaders' Meeting

Opening and Introductory Session

K. Kittiyakawee, Vice President of Chulalongkorn University, opened the Opinion Leaders' Meeting. **K. Umprayn**, Chairman of the organizer, introduced participants and **G. Fassina** (ICS-UNIDO, Scientific Advisor) described the mandate of ICS-UNIDO and gave an overview of the ICS-UNIDO activities in the Area of Pure and Applied Chemistry. He also illustrated the mission of ICS-UNIDO to be

undertaken to the benefit of the developing countries and countries in transition. The role of ICS-UNIDO in promoting projects aimed at establishing international co-operative links between academic and industrial partners was also addressed.

Session 1: CC/CT/MD as New Technologies for Drug Development

P. Seneci (ICS-UNIDO expert, NADAG Germany) gave a presentation on the impact of combinatorial technologies in industry. He provided the audience with background of solid phase synthesis being used in combinatorial chemistry. In principle, solid phase reaction must be easy to design, well assessed in solution, compatible with known supports and linkers, and offering several options of experimental protocols. This is particularly useful for developing a combinatorial library with the format of one bead-one compound. The solid phase synthesis can generate molecular diversity of both natural macromolecules (peptides, nucleotides, sugars) and small organic molecules. In these aspects, major coverage was given to the design, synthesis and the screening of synthetic libraries for the discovery of novel leads embedded with biological activity. Strategic aspects related to chemical diversity (CD) needed and embedded into primary libraries (lead discovery), and focused libraries (lead optimization) were thoroughly described. The possible CD sources include compound collection, solid-phase pool libraries, discrete libraries, natural products and virtual compounds. Finally, the trends of combinatorial technologies were given, including 1) multiple CD sources in an "evolutionary" screening collection, 2) extensive use of virtual facilities, 3) more small, high quality pure libraries of discretes, 4) less large, primary libraries and 5) screening of natural products by CC/CT.

T. Buss (Centre for Natural Product Research, Singapore) gave an overview on the impact of natural products on the modern pharmaceutical industry. A number of examples were given on the art of discovery in the past of pharmacologically active compounds used presently from higher plants and microorganisms. These included the discovery from the opium poppy of the analgesic morphine, antitussive codeine, antiarrhythmic papaverine and verapamil. In addition, the discovery of aspirin from white willow, antiasthmatic agents of ephedrine and its derivatives from Ma Huang, and anticancer taxol from Yew plant were also described. From microorganisms, the discovery and impact of various groups of antibiotics were presented. These included the groups of benzylpenicillin, cephalosporin, mevastatin, cyclosporin A, tacrotimus and rapamycin. Finally, emphasis was put on the importance of natural product screening as the single most successful drug discovery strategy to date. These natural product drugs have been directly responsible for doubling human's life span in the last century, half the top-selling pharmaceuticals and responsible for over US$ 32 billion sales (of US$ 63 billion total) in 1993. Moreover, forty-one significant new drugs derived from natural products have been marketed in the past 10 years, the most important ones are anticancer and anti-infective agents.

G. Fassina (ICS-UNIDO expert, Tecnogen, Italy) presented an overview of the bussiness-related aspects of CC/CT/MD. Emphasis was put on the aspects of economics and patenting. Nowadays, the introduction of combinatorial technologies and rationalizing the synthesis of compounds for random search of new activities has provided an unlimited source of new compounds capable of satisfying various needs.

The main advantage of this new technology is the speed in finding and optimizing useful leads. The disadvantage is the limitation in producing the variety of chemical structure. Fields of application of combinatorial technologies are the diagnostic, the down-stream processing, the catalysis, the new material sectors, and especially the identification of new macromolecules endowed with catalytic activity. Economically, the combinatorial business is increasing in the market captalization over time although with no clear leadership position enjoyed by any single company. A remarkable high number of patents have been filed by companies and research institutions in different aspects of combinatorial technologies. Many companies have patents that enable them to pursue unique chemistry to generate libraries of compounds, whereas many prefer not to file patent applications on their libraries but to keep them as trade secrets.

P. Seneci (ICS-UNIDO expert, NADAG, Germany) presented successful case studies of the use of CC/CT in obtaining biologically active natural products. The introduction described various possible available library formats, including decoration of a natural product-derived scaffold, construction of a natual product-inspired library, combinatorial biosynthesis and combinatorial biotransformations. The natural product taxol was first used as a successful case study in the presentation. The content involved the design and synthesis of a taxoid library using radiofrequency encoded combinatorial chemistry (Xiao et al., 1997, J. Org. Chem. 62, 6029). Radiofrequency encoded combinatorial (REC) chemistry is a recently developed nonchemical encoding strategy in library synthesis. Encoding chemical libraries of complex molecular structures like taxol can be constructed employing the noninvasive REC strategy and novel solid phase synthetic techniques, as demonstrated by the synthesis of the first 400-membered toxoid library in a discrete format and in quantities of multimilligrams per compound. Another case study presented was on the generation of solution-phase libraries of organic molecules by combinatorial biocatalysis. Combinatorial biocatalysis is a powerful methodology for synthesizing libraries of organic compounds in solution. The integration of biocatalysis with high-speed robotics represents a new avenue of biotechnology for the discovery of new molecules and biotransformation schemes. The versatility of this approach was demonstrated by the synthesis of diverse libraries from small organic precursors such as (2-endo, 3-exo)-bicyclo [2.2.2] oct-5-ene-dimethanol (BOD), 2,3-(methylenedioxy) benzaldehyde (MDB) and adenosine (ADS).

G. Fassina (ICS-UNIDO expert, Tecnogen, Italy) presented a successful case study on the commercialization of a combinatorial product. The emphasis was on monoclonal antibody (Mab) products. Presently, production of Mabs by hybridoma technology or transgenic animals can be easily scaled up but purificaiton of immunoglobulins from crude feedstocks still poses several problems. Main difficulties are due to the low antibody concentration in all culture supernatants or milk of transgenic animals. The conventional purification method using immobilized protein A or protein G is expensive and time-consuming. A synthetic ligand (TG 19318) which is able to mimic protein A in the recognition of the immunoglobulin FC portion has been identified previously (Fassina et al., 1996, J. Mol. Recog. 9, 564-569). The application of this ligand in affinity chromatography for the down stream processing of antibodies has been fully characterized, examining the specificity and selectivity for polyclonal and monoclonal IgG derived from different sources. The results showed that Mabs derived from cell culture supernatants or ascites fluids were

both conveniently purified on TG 19318- affinity columns even from very diluted samples. The ligand is useful not only for IgG purification from different sources, but also from IgM, IgA and IgE isolation from sera or crude cell supernatants.

G. Terstappen (GlaxoSmithKline, Italy) presented a topic on the impact of high throughput screening in drug discovery. Based on bioinformatics analysis and an estimated 100,000 human genes, successful target classes comprehend about 6,500 proteins. These include 3,500 enzymes, 2,000 G-protein coupled receptors, 1,000 ion channels and about 150 nucleus receptors (Terstappon & Reggiani, *Trends Pharmacol. Sci.*,22, 2001) and thus indicating the huge potential for drug discovery. Not all of these biomolecules will become drug targets, and the selection of thee most relevant targets for a given disease is very important in current pharmaceutical research. The substantial increase in molecular targets has further increased the need to efficiently identify small molecules of lead compounds acting on these targets. Enormous advances in screening compounds in an efficient manner have been made through high throughput screening (HTS) which allows several hundred thousand compounds to be tested on a given target in a reasonably short time. A case study was given on biomolocular screening in order to identify agonists of Glutamate-Ca^{2+} Receptor (mGluR7) which is one of transmembrane's G-protein coupled receptors (GPCRs). The HTS was developed by coupling of rat mGluR7 to the luciferase reporter gene system which correlates to the level of intracellular cAMP. The HTS assay was performed in 96-well plates in the presence of $3x10^4$ mGluR7-Luc cells/well and compound to be tested. After being incubated for 4 hr at 37°C, luciferase substrate reagent was added and luminescence was measured using a betacounter. Using the optimized HTS assay, a diversity set of about 20,000 compounds was screened. Among these, only 71 compounds were confirmed positive with an EC_{50} < 10 μM, equivalent to the hit rate of 0.4%. The best compound was about 5000 fold more potent than LAP4, the most active agents known to date. This is the first example of the application of reporter gene technology to HTS for group II and III mGlu receptors.

Session 2: Potential Applications of CC/CT/MD in Southeast Asian Countries

S. Pummangura (Dean, Faculty of Pharmaceutical Sciences, Chulalongkorn University, Bangkok, Thailand) presented the application of CC/CT/MD in Thailand. Emphasis was put on natural products research. Natural products have long been and will continue to be extremely important as both sources of medicinal compounds, and models for the design of new pharmaceuticals. Thailand has an advantage in being located in the area that has a variety of forest types and aquatic habitats and therefore is rich in both biological and chemical diversity. Natural products research based on traditional methods have been carried out for some time in various research institutes and universities in order to discover biologically active compounds. Still, however, very little is known about the chemical diversity of Thai tropical plants and marine organisms. Therefore, it is reasonable to expect that new plant and marine sources of pharmaceutically and agrochemically interesting natural products remained to be discovered and developed in this country. Presently efforts are being made in order to fully utilize the abundant natural product resources. A list of more than fifty medicinal plants with impressive ethnobotanical

records has been promoted for common usage with intensive research studies. Marine natural products are also rapidly gaining acceptance as another source of medicinal agents. With bioassay-guided fractionation, an anticancer ET743 from a Thai *Ectienascidia* tunicate and an antimalarial ansamycin from a marine *Streptomyces* have been discovered. For new technologies, high throughput screenings and combinatorial technologies are just becoming available in Thailand. In the future, implementation of this mass screening technology with minimal amounts of test samples will greatly facilitate and make more efficient the process of natural products drug discovery in Thailand. For the area of combinatorial chemistry, the research on generating libraries of small organic molecules is essentially lacking in Thailand. This is partly due to a lack of specialist and the prime interest in the molecules of natural origins. For the discipline of molecular design, it is now fully recognized and integrated in the research process of some projects such as antimalarial drug research initiated by the National Science and Technology Development Agency.

P. Masters (Lynk Biotechnologies, Singapore) gave an overview of Lynk Biotechnologies Pte Ltd., which is one of Singapore's first biotech startups. Drug development is an expensive and lengthy process, usually spanning over decades. The probability of taking a drug lead from the pre-clinical stage to commercial sale is only about 1 in 250. With a patent life of 20 years, and an average interval of some 8-12 years between patent registration and commercial sale of products, companies are generally left with just 8-12 years to generate maximum returns on their investments. At Lynk, the company is able to speed up the process by reducing the time needed for lead development and optimization, plus identification of potential side effects during pre-clinical testing. Link's proprietary technologies include SM@RT™, and Receptomics™. The SM@ RT™ technology allows the design and development of unique small molecules, which are able to form strong, specific bonds with selected receptors, to permanently knock-out the receptor function. The Receptomics™ technology is utilized in the next stage involving high throughput proteomics screening, and advanced-mass spectroscopy technology. This technology allows to "fish" out and identify the target and subsequently the drug pocket on the target molecule. One case study was given on a search for anti-hypertensive compounds via adenosine receptor. A potent inhibitor LBT-2001 (Ki = 0.5 μM compared with Ki = 500 μM for cytidine) was found by an experiment on nucleoside transport protein knock-out. Information on LBT-2001 binding site and its docking to the binding site is also presented. Other case studies included computer aided design of histone deacetylase inhibitor and the study on serotonin receptor inhibitor.

E.P. Capareda (University of the Philippines Los Banos College, Philippines) presented the potential use of CC/CT/MD in the Philippines. Since the previous ICS-UNIDO workshop held at the University of the Phillipines Los Banos in 1999, there has been continued research in areas such as natural products chemistry and material science for which CC/CT/MD have much impact, particularly in the development of pharmaceuticals and agrochemicals. With the rich and diverse plant, animal and marine resources in the Philippines, there is active natural products research in almost all of the major academic institutions. Natural products are also being studied as potential pesticides, insecticides, herbicides and plant disease control agents. However, there is very little R&D work on natural products in industry although screening of essential oils for antimicrobial and antifungal activity have been done in a private pharmaceutical company. Much of the government support goes to

programs involving the development of herbal medicine whereas the Natural Products Society of the Philippines aims to the national program that is chemistry-based. The latter program envisions achieving its goals through four phases of work plan: Phase I: Massive Collection and Screening ; Phase 2: Correlation. Dereplication and Prioritization ; Phase 3: Persuit of Lead or Top Priority Bioactive Samples ; Phase 4: Production of Bioactive Natural Compounds and Synthetic Analogs. With new technologies, however, there is still very little research work in the area of CC/CT/MD in the Philippines.

U.D. Palanisamy (SIRIM BERHAD, Malaysia) gave a presentation on the current status of CC/CT/MD and natural products research in Malaysia. CC/CT/MD has only been recently identified as priority research areas under the 8th plan (2001-2005) of research program. Natural products R&D, on the other hand, has been on going in several academic and research institutes for a number of years. The use of CC/CT/MD techniques in the field of natural products is greatly lacking. There has been efforts to set up a National Center for Computational Science in Malaysia in order to create state-of-the-art facilities for academia, industry and the inventing community. Presently, initial seeding of the project is taking place in the form of the natural products information system whereas research using combinatorial chemistry for catalysis is being initiated by the University of Malaya. The recent Malaysian-Massachusetts Institute of Technology Collaboration Program (1998-2002) has been a tremendous success. This has encouraged the government to call out for more research on natural products. Several priority areas were identified for both short-term development program and long-term discovery program. The development program includes standardization of herbal materials, sustainable production of quality raw materials, development of value added products and efficient processing technologies. The discovery program includes enrichment of scientific data of Malaysian plants (eg. efficacy studies on selected disease targets: cancer, cardiovascular, infective, HIV, CNS, liver drugs) and development of platform technologies (eg. medium & high throughput screens for the selected disease targets, combinatorial chemistry, bioreactor technology, microassay technology and cell culture technology). Therefore, the use of CC/CT/MD techniques in the natural products R&D is identified as a long-term discovery programme.

Session 3: Recommendations

After the end of Session 2, there was a round-table discussion and recommendation participated by both the country-representatives and ICS-UNIDO experts. Two groups were set up for this session. One consisted of all Thai participants headed by **Dr. K. Umprayn** and three ICS-UNIDO experts, chaired by **Dr. P. Seneci** (Group I). The other group consisted of representatives of other Southeast Asian countries, Kuwait and the other ICS-UNIDO experts chaired by **Dr. G. Fassina** (Group 2). The results of the meetings are as follows :

Group 1: Recommendation from Thailand (Dr. Seneci, Chair)

Dr. K. Umprayn and **Dr. W. De-Eknamkul** pointed out that Thailand has a strong potential to develop and use the new technologies and to be a regional ICS-UNIDO network for training and workshop operation of CC/CT/MD. The strong

points of Thailand are the availability of relevant national policy, bioresources, human resources of various scientific areas, research grants, target tropical diseases and strategic regional location (the center of Southeast Asian Region). For the weak points, Thailand still lacks the know-how on bioassay technologies, acquisition of targets (enzymes, receptors, ion channels, target-expressed cell lines etc)., and collaborative research. If those weak points can be overcome by the support of ICS-UNIDO, the progress in using the new technologies for research in the academic institutes and industry and for regional training will be highly possible.

Dr. P. Seneci responded that the ICS-UNIDO supports for the needs of Thailand are possible in terms of granting research fellowships for researchers in Trieste, or in terms of finding donors to grant external fellowships to gain experience in well-established laboratories. Moreover, a support in terms of an international expert as advisor to Thailand is also possible. However, Thailand should develop a proposal indicating clearly the needs of support. According to his idea, the research fellowships and the appointment of advisor can be parts of a short-term plan whereas the establishment of the regional ICS-UNIDO network center can be put in the proposal as a long-term plan.

Dr. W. De-Eknamkul asked whether it was possible that the fellowships allow the researchers to visit a number of laboratories in order to be able to learn more bioassay systems and the preparation of proteomic targets. This will help the new technologies to be transferred more rapidly.

Dr. T. Buss and G. Terstappen suggested that the starting point should concentrate on simple techniques and not necessary to be high throughput screening with sophisticated and robotic equipment and then observe the progress. The researchers who get the fellowships should also take with them some samples for studying the new combinatorial technologies. Moreover, the relationship between the Thai researchers and the host institutes or industry should be a two-way linkage. This means that research collaboration should also be put in the program.

Dr. K. Umprayn accepted the suggestion and added that for Thai pharmaceutical industry, standardization (by finger prints) of medicinal products are very important. He would like, if possible, to add this aspect into the proposal.

Dr. P. Seneci said that he did not mind if the proposal states clearly the relationship between the standardization of medicinal materials and the application of the new technologies in this area.

Summary :

Recommendations working group 1 headed by **P.F. Seneci**

(**Countries:** Thailand, both academic and industrial representatives)

Thailand expressed a strong interest to develop medium-high throughput assays for the screening of relevant targets for the region (tropical disease) and to use these MTS-HTS assays to screen their vast natural products' diversity. They **need soon the formation of young scientists**, especially in the field of biological assay

development and of natural products' isolation and characterization; they need assistance to select and identify institutions (private or public) where to send these fellows, and also to identify donors for fellowships to sustain the formation program. Within **medium timeframes**, Thailand indicated also a strong desire to host advanced practical courses on CC/CT applied to natural products, as part of the follow up activities related to the first event to be organized in India (see point 2). Within a **longer timeframe** they suggested the need for a CC/CT Research Centre in Thailand mostly focused on Natural Products' Research. As **preliminary actions**, we identified the need to write a follow-up proposal to be included as an Appendix in the Workshop Final Report and to identify 2-3 projects regarding natural products structures to be brought by the fellows to the above mentioned institutions. Profs. De-Eknamkul and Umprayn (Chulalongkorn University) agreed to be responsible for these preliminary actions. A proposal on a follow up program for Thailand is provided in **Annex 6**.

Group 2: Recommendation from SEACs (Dr. Fassina, Chair)

Recommendations: working group 2 headed by **G. Fassina**
(**Countries:** India, Nepal, Laos, Philippines, Indonesia, Malaysia, Kuwait)

All the countries, except Kuwait, have expressed a strong interest on application of CC/CT/MD on natural product research. A strong need for advanced practical courses has emerged, and India (**Dr. Raghavan**) expressed its availability to host such meeting at the IICT facility in Hyderabad follow Thailand (**Prof. Umprayn**) in further meeting (see below). The Kuwait representative (**K. Habib**) stated that its region (Emirates and Saudi Arabia) has focused interest on oil industry, and suggested the possibility to organize awareness meetings in the near future focused on application of CC/CT/MD on catalysis/new materials. Preliminary actions (hosting site selection, participating countries and number of participants, resource persons identification, evaluation of budget needs) have been scheduled in order to determine in short time the feasibility of such initiatives.

Second Event: Workshops on Southeast Asian Countries on CC/CT: Natural Products and Technologies on Rapid Screening

Combinatorial Technologies: Principles and Concepts

Dr. Giorgio Fassina (ICS-UNIDO expert, Tecnogen, Italy)

Drug discovery in the past has been based traditionally on the random screening of collection of chemically synthesized compounds or extracts derived from natural sources, such as microorganisms, bacteria, fungi of both terrestrial or marine origin. This approach is very time-consuming and expensive, and thus the pharmaceutical industry demands more rapid and cost effective approaches to lead discovery. The advent of new methodologies in molecular biology, biochemistry and genetics has led to the identification and production of an ever increasing number of enzymes, proteins and receptors involved in biological processes of pharmacological relevance and good candidates for the development of screening assay. Furthermore, the development of combinatorial chemistry has led to new processes for the generation of collection of structurally related compounds (libraries). These combinatorial approaches has revitalized random screening as a paradigm for drug discovery and has raised enormous excitement about the possibility of finding new and valuable drugs in short times and at reasonable costs.

Combinatorial Technologies in Pharmaceutical, Agricultural Industry and in Biotechnologies

Dr. Pierfausto Seneci (ICS-UNIDO expert, NADAG, Germany)

Combinatorial chemistry started in the late 80's-early 90's as solid phase chemistry for pharmaceutical purposes. The solid phase chemistry firstly applied to the synthesis of natural molecules (eg. peptides, nucleotides and saccharides) but subsequently applied to small organic molecules. A solid phase reaction must be easy to design ,well assessed in solution, compatible with known supports and linkers and offering several options of experimental protocols. This is particularly useful for developing a combinatorial library with the format of one bead-one compound. In the pharmaceutical research, its main objective is to develop new drugs with a known molecular target (eg. enzyme, receptor etc.), ligand fishing (identification of peptide sequence), drug design (exploitation of peptide-target interaction) and synthetic peptide combinatorial libraries (large number of peptides). For combinatorial libraries, there are two groups of molecular diversity. One is natural macromolecules which has limited diversity because the backbone is always the same and the other is small organic molecules which has high degree of diversity. These combinatorial technologies are now major areas of industrial interest, particularly in pharmaceutical research, veterinary/agriculture/food, diagnostics and affinity purifications. Details of combinatorial technologies used in these industries were given.

Biomolecular Screening in Drug Discovery

Dr. Georg C. Terstappen (GlaxoSmithKline, Italy)

High-throughput screening (HTS) has become the cornerstone for the identification of novel drug molecules for most pharmaceutical companies. HTS means testing as many compounds on a target as possible in the shortest period of time. It is a bioassay which chemistry (the molecule) meets biology (the target). Practically, HTS should be simple and easy to perform with low sample volume. No steps of filtration, centrifugation or transfer steps are involved and thus it allows screening of large numbers of compound libraries. Basically, two different types of

assays can be distinguished: functional cell-based assays and ligand-binding assays. Both types have similar high sample throughput but the cell-based assays generally have more pharmacological relevance than the ligand binding assays. An example was given on biomolecular screening showing identification of agonists of Glutamate-Ca^{2+} Receptor (m GluR7). A m GluR7 is one of transmembrane's G-protein coupled receptors (GPCRs). A HTS bioassay has been developed by coupling of rat m GluR7 to the luciferase reporter gene system which correlates to the level of intracellular CAMP. This HTS assay can be performed in 96-well plates in the presence of m GluR7-Luc cells and compound to be tested. After incubation, luciferase substrate is added and luminescence in measured using a betacounter. Another example was given on a functional assay using fluorescence image plate reader (FLIPR). In this case of cell-based assay, agonists and antogonists of m GluR5 signaling via Ca^{2+} increase can be identified using a biochemical reaction of Ca2+ sensitive fluorescence dyes. Practically, recombinant cells (in either 96- or 384-well-plate) are first loaded with calcium-sensitive dye, then cells are stimulated and fluorescence changes are measured. For study on ion channels, an example was given on functional fluorescence assay with voltage-sensor DiBAC for SK3 potassium channel. In this case, recombinant cells In 96- or 384-well microplates are loaded with the fluorescence dye DiBAC for 30 min in the presence of compounds tested for channel modulating activity. After channel activation, the decrease in cell fluorescence is measured (ex: 480 nm, em 520 nm). Another example was on the functional fluorescence assay using fluorescence resonance energy transfer (FRET) for studying sodium channel modulators. In this assay protocol, microplates containing cells with phospholipid anchored coumarin (CC 2-DMPE), compounds to be tested and oxonol dye (DiSBAC) are incubated before being transfered to voltage image plate reader (VIPR) with Na^+ addition for result reading. Finally, information on scintillation proximity assay (SPA) technology was presented. This is a "mix-and-measure" which makes binding assays homogeneous (i.e. no separation of unbound ligand by filtration or centrifugation is necessary). In principle, when a SPA bead containing scintillant binds to specifically radiolabeled ligand, it will cause luminescence which will be measured.

Screening Natural Product Samples for Drug Discovery

Dr. Tony Buss (Centre for Natural Product Research, Singapore)

The advantages of natural product screening for drug discovery are the compounds' chemical diversity and inherent biological activity. There remains an enormous reservoir of biological and, thus, chemical diversity waiting to be discovered. The basic process involved in natural products lead discovery consists of microbes fermented, dried plant material and fermentation broths extracted with solvent, crude extracts screened for biological activity, active samples ("hits") purified chromatographically and purified compounds characterized. In the area of natural product screening, the following issues should be considered: access to biological/chemical reservoir, compatibility with HTS, rate limiting and resource intensive, complex chemical structures impede lead optimization and the role of serendipity. Natural products with anti-hepatitis C Virus (HCV) activity, for example, have been screened by HCV protease assay. The assay is performed in 96-well plates using tritium labeled biotinylated substrate peptide (attached to streptavidin coated SPA bead) and HCV NS3 protease. After being incubated overnight, the plates are read by a betacounter. The samples with high cpm mean the ones with anti-HCV protease activity ("Hits"). Based on this protease assay, some metabolites from

Aspergillus ochraceus have been found to have the protease inhibitory activity, such as mellein, 4-hydroxymellein (IC_{50} 35 μM). Natural products with anti-malarial have been screened by Plasmepsin II protease assay. Plasmepsin II is an aspartic protease required to cleave haemoglobin and is essential for parasite survival and , thus, is a validated anti-malarial target. A fluorescent Plasmepsin FRET Assay was developed to measure the activity of this protease enzyme. Based on this assay, natural product "hits" have been found to be Pepstatin A, a peptide with MW 685.9, with IC_{50} ~ 10 pM and the alkaloid sanguinarine with IC_{50} ~ 12 mM. In the area of natural product screening, there is the need to increase productivity. The main obstacles are the slow process of purification and characterization, the presence of inappropriate activities of tannins, fatty acids and sulphated steroids, the effect of color quenching and the rate limitation of the modification of complex structures. These can be partly solved by preparing high quality samples (picfactionation) for screening, using LC/UV/MS for rapid dereplication, using automated HPLC for rapid purification, generating "bio-analogues", using combinatorial biosynthesis and culturing the "unculturables". The details of these issues were given in the presentation.

Case Studies for HTS in Drug Discovery

Dr. Georg Terstappen (GlaxoSmithKline, Italy)

The first case study was given on the biomolecular screening in order to identify agonists of Glutamate-Ca^{2+} Receptor (mGluR7) which is one of transmembrane's G-protein coupled receptors (GPCRs). The HTS was developed by coupling of rat mGluR7 to luciferase reporter gene system which correlates to the level of intracellular cAMP. The HTS assay was performed in 96-well plates in the presence of $3x10^4$ mGluR7-Luc cells/well and each compound to be tested. After being incubated for 4 hr at 37°C, luciferase substrate reagent was added and luminescence was measured using a betacounter. With the optimized HTS assay, a diversity 2 set of about 20,000 compounds was screened. Among these, only 71 compounds were confirmed positive with an EC_{50} < 10 μm, equivalent to the hit rate of 0.4 %. The best compound was about 5000 fold more potent than LAP4, the most active agonist known to date. Similar study was also performed with another GPCR, namely pituitary adenylate cyclase activation peptide receptor (PACAP receptor). Again about 20,000 compounds of the same diversity set were screened in order to identify agonists of PACAP receptor. In this case, however, no hits have been identified. The third case study was given on the screening for SK3 potassium channel blocker. This lead discovery was studied sequentially from cloning of human SK3 potassium channel from human brain, transfection of CHO-K1 cells, functional selection of stable SK3 expressing cells, assay development and characterization, and assay optimization for HTS. In principle, the HTS was based on functional fluorescence assay with the slow membrane potential-sensitive dye (voltage-sensor) $DiBAC4_3$ (hyperpolarisation leads to extrusion of DiBAC and a decrease in cell fluorescence). In practice, the recombinant cells in 96 or 384 well microplates are first loaded with the fluorescence dry DiBAC for 30 min. Then, compounds that are tested for channel modulating activity are present during this incubation phase. After channel activation, the decrease in cell fluorescence is measured (ex: 480 nm ; em 520 nm) by FLIPR. Using this optimized HTS assay, a diversity (random) compound library was screened in comparison with a focussed compound set. It was found that the random library of 28,787 compounds got 62 hits or 0.2% hit rate, the focussed library of 15,374 compounds got 66 hits or 0.4%, whereas the substructure search of 257 compounds got 55 hit or 21% hit rate. In conclusion, since diversity HTS is not

yet delivering the number of new lead compounds for drug development that was expected, a clear need for increasing structural diversity can be anticipated. Thus, it is important to make the immense diversity, found in natural products, effectively amenable to HTS before it may be lost to drug discovery.

Drug Leads from Natural Products

Dr. Tony Buss (Centre for Natural Products Research, Singapore)

Cardiovascular disease is the major cause of death and disability in the developed countries, and hypercholesterolaemia is a major risk factor. Therefore, the decrease of body's biosynthesis of cholesterol is relevant to the reduced risk of the cardiovascular disease. Hydroxymethylglutary CoA (HMG CoA) reductase has been known as the enzyme catalyzing the rate-limiting step of the cholesterol biosynthetic pathway. Inhibition of this enzyme, however, will also lead to the biosynthetic inhibition of dolichol and ubiquinone which are necessary for the body. Therefore, the enzyme squalene synthetase (SQS) which catalyzes the step of the conversion of farnesyl diphosphate into squalene in the cholesterol biosynthetic pathway has been considered a good target to find its inhibitors. Based on the developed enzyme-based bioassay, a fungal culture filtrate of *Phoma* species was found to have inhibitory activity on the SQS function. Bioassay-guided fractionation led to the discovery of a chemical group of potent SQS inhibitors, namely squalestatins, with IC_{50} = 12 - 22 nM against rat SQS. The squalestatins are a family of natural products with at least 49 analogues and are present in a number of fungal species. This group of compounds is biosynthesized from benzoic acid, phenylalanine and S-adenosylmethionine. Studies on the structure- activity relationship have found the significance of various functional groups of the compound on the potency of their SQS inhibitor activities.

Computational Tools for CC/CT and Case Studies

Dr. Valerie Gillet (Prof., University of Sheffied, UK)

Computational tools are widely used in the chemical, pharmaceutical and agrochemical industries for rational drug design. These tools encompass not only quantum mechanics but also molecular mechanisms, minimisation, simulations, conformational analysis and other computer-based methods for understanding and predicting the behaviour of molecular systems. The important outline of computational tools for CC/CT are included in using computational tools to increase the effectiveness of high-throughput screening and combinatorial chemistry, high-throughput screening (virtual screening, diversity analysis, subset selection techniques and computer filters), and combinatorial library design (diverse libraries, target or focused libraries). Supply of compounds, with historical collections, compound acquisition programmes and combinatorial chemistry) is a crucial first step for this tool. It is well known that the cost of screening vast libraries is a serious issue, virtual screening can be used to choose compounds from external suppliers or to design combinatorial libraries. Obviously, the success of virtual screening strategies will depend on both the quality of information about target (enzyme active site, well-defined 3D pharmacophore, whole molecule properties, biological activities, etc.) and the quality of "fitting software. Statistical methods such as principal analysis are used to reduce the large number of molecular descriptors (log P, molecular weight, molar refractivity, 2D and 3D properties) for a set of compounds to a smaller set of crucial descriptors that computationally efficient methods are required. The visualization of large sets of data is facilitated by traditional program. Clearly, computational tools for CC/CT are very useful for discovery of new target molecules and elimination of time

wasted pursuing poor candidates. Another interesting techniques in computational tools for CC/CT, and case studies for the design of 2-aminothiazole library and cathepsin D library were given.

Biological Combinatorial Libraries and Case Studies

Dr. Giorgio Fassina (ICS-UNIDO expert, Technogen, Italy)

The presentation was on the application of genetic engineering for the preparation of biological combinatorial libraries. Biological methods for library preparation are mainly limited to peptide or oligonucleotide libraries. For peptide libraries methods are based on the construction of a pool of clones, each one expressing a different peptide on its surface. The peptides are fused to proteins normally expressed on the surface of the microorganism used. Phage display libraries are the most commonly used. Screening is accomplished by incubation of the target molecule, absorbed to a solid support, with the phage population. Phages will bind the target even after extensive washing steps. Target-bound phages are isolated and propagated by infection of *E. Coli* and subjected to an additional round of adsorption to the immobilized target. Similarly, oligonucleotide libraries can be screened for immobilized targets using the PCR methodology to expand the number of active sequences after each selection cycle. The construction of biological displayed libraries requires the introduction into a micro-organism of the genetic information necessary for the peptide synthesis. For the construction of a random peptide display library, it is necessary to synthesize pools of DNA fragments that are then inserted into specific vectors. The DNA fragments are chemically synthesized as a mixture of single-stranded degenerated oligonucleotides containing constant regions and one or more degenerated stretches of DNA. The DNA fragments to be cloned must be in a double-stranded form. This is normally done by annealing short oligonucleotides to a complementary constant region inserted during the synthesis and by enzymatically completing the complementary DNA strand. After compatible ends are prepared by restriction enzyme digestion, the fragments are ligated into an appropriate vector and then introduced into the microorganism. In order to be accessible to the target molecule, the peptides must be exposed to the medium and anchored to the viral coat or bacterial external membrane (through fusion of signal sequence at one end). The entire phage genome is usually used as a vector after specific modifications have been introduced. In this case, the library is constituted of viral particles displaying a number of peptide molecules equal to the number of fusion coat protein molecules. Alternatively, a defective phage vector, called phgemid can be created. In this case, phages will display a mixture of peptide-coat protein fusion and the corresponding wide-type coat protein. Compared to chemical libraries, biological display libraries have advantages on the possibility to use a library for many different selection processes, the easy propagation of the library and of the selected clones, and the possibility to build larger size libraries. On the other hand, a disadvantage is the fusion of peptides to a microorganism protein and, therefore, the binding site can be extended to the fusion protein or the fusion protein may influence the peptide conformation.

Combinatorial Technologies in Homogeneous and Heterogeneous Catalysis

Prof. Dr. K.V. Raghavan (Indian Institute of Chemistry Technology)

The primary goal in materials development for discovery of systems that meet a number of physical, chemical, and structural requirements is to screen new catalysts and optimal process conditions at high throughput rate. The integration of robotic

systems, reactor miniaturization, parallelism, high speed functionality techniques and informatics/simulation will bring new catalysts, processes and products to the market at lower cost and in limited time. Combinatorial catalysis, started from 1995, has become an attractive methodology in both organic chemistry and inorganic chemistry. Research pioneers in combinatorial technology in homogenous catalysis were 2 pyrrolidine methanol ligands, silver catalyst, enantio selective synthesis, dipeptide titanium complexes, etc. For research pioneers in heterogeneous catalysts were focused on transition metals (Pt, Ru, Os, Rh and Pd), metal impregnated mixed oxides and co-oxidation Pt, Ph, Pd catalysts, etc. Generally, combinatorial libraries employing homogenous catalyst and heterogeneous catalyst in the reactions were generated in solution, film and solid. However, activity profiles of new entities in catalysis is more difficult to observe than binding of normal combinatorial chemistry with receptor in pharmaceuticals. The area of combinatorial technologies in homogeneous and heterogeneous catalysis, while well developed in term of hardware for library generation and chemical reactions, still suffers from the limited availability of appropriate methodologies for screening and dedicated hardware. The concepts in combinatorial catalysis and the details of these technologies using both homogeneous catalysts and heterogeneous catalysts, and case studies were given in these workshops.

Combinatorial Technologies in Materials Science

Prof. Dr. K.V. Raghavan (Indian Institute of Chemistry Technology)

Combinatorial chemistry has expanded to materials design problems outside the drug field. It is well known that the kinds of problems, the desired outcomes, and the appropriate strategies are significantly different from those associated with conventional experimentation. Therefore, initial work has focused on development of robotic sample preparation, reactors, and sensors. The goals and strategies of combinatorial chemistry applied to materials development are quite different from those of the pharmaceutical arena such as synthesis, mixtures, and process variables, emphasis on broad coverage and synergy, experimental space metrics not know, and challenge is finding high order synergies of qualitative and mixture/process variables. The development in this methodology potentially offers significant advantages in speed and cost. By combining microchip and combinatorial technologies, thousands of distinct compounds or an entire continuous ternary-phase diagram can be formed. Measuring electrical impedance, optical, magnetic and structural properties may assess physical properties of the combinatorial material library. In these workshops, new strategies in combinatorial material science including some material library designs, finer aspects of combimaterial synthesis, high throughput screening and computational informational informatics for data handling were given. To understand this field, case studies in this section were also presented

Combinatorial Chemistry: Synthetic and Analytical Technologies

Dr. Elisabetta de Magistris (GlaxoSmithKline, UK.)

Combinatorial chemistry is very powerful tool for the generation of immense molecular diversities and new organic compounds in the scope of basic research and drug discovery. The essence of combinatorial chemistry is the ability to generate large numbers of chemical entities very quickly, and it reduces the time required to find and optimise lead compounds. In principle, combinatorial chemistry is compatible with both solution-phase and solid-phase synthesis to generate "combinatorial library". Fundamentally, the number of compounds containing all possible combinations of

monomers from combinatorial library is increased exponentially with the number of the reaction steps and the positions that could be varied. The majority of the compound libraries have been synthesized on a solid support. Compared with the reaction in solution phase, the solid support technique offers many advantages such as large excess of reagents allowed, multistep synthesis allowed, easy work-up/isolation procedures and synthesis automation easily obtainable. However, the solid support technique was limited to reaction-scale restriction (amount of the solid support and its loading), not "all" organic are directly transferable on solid support, extensive chemistry assessment, linker/cleavage chemistry, reactions that require a totally inert atmosphere, and selective deprotonation with 1 equivalent of base at $-78^{\circ}C$. Solution phase synthetic techniques have the advantage of unlimited product quantities and all organic reaction can be easily manipulated. However, in a solution-phase synthesis, isolation or purification of the reaction products away from the reaction (reactants, reagents and side products) may prove to be a difficult task.

The majority components in solid-phase technology are as follows:

a. The solid support that should be stable to a wide range of organic solvents and reagents.
b. The linker which connects the support to the scaffold or target molecule and should be cleavaged under mild conditions.
c. The scaffold or target molecule which should be synthesized in high yield and purity.

The field of peptide synthesis has driven the development of new solid-phase supports for organic chemistry. The supports used almost exclusively in combinatorial synthesis of small organic compounds are polystyrene based resins crosslinked with 1-2% divinylbenzene, and TG resins crosslinked with polystyrene and 3000-4000 polyethylene glycol. The most extensive range of linkers and derivatized resin for solid phase synthesis has been developed and various solid supports with linkers for carboxylic acids, for amines and alcohols were presented in this section. In addition, solid supports used in Mitsunobu reaction and Wittig reaction, commercially available solid/polymer-supported oxidants, examples of commercially available solid-supported scavengers, and some attractive organic reactions on solid-supports were awakened to the advantages and challenges of solid-phase synthetic strategies.

The example of chemical libraries, collection of chemical compounds prepared using combinatorial chemistry, is as follows :

a. Pool libraries can be created from a mix and split synthetic strategy (very high productive process, high number of compounds synthesized with high probability to find active molecules for a given biological target, iterative deconvolution process in order to find the active molecules with very time consuming step)
b. Discrete libraries (a single compound in a well, parallel synthesis methodology)
c. Encoded bead-based libraries based on radiofrequency signals and semiconductor memory devices using a multifunctional Microreactor (encoded mix and split synthesis: chemical encoding for oligonucleotides, oligopeptides, haloarene, secondary amines and isotopically labelled aminoacids; radiofrequency encoding for discrete libraries)

As a consequence, diversity analysis is an important aspect of library design. Analytical chemistry technologies are applied to identify compounds generated from combinatorial libraries. In the case of chemistry assessment (on bead analyses), analytical techniques are colorimetric assays (detection of free amines and thiols), IR (reaction monitoring), FT-IR (structural information), gel-phase NMR and nano probe MAS-NMR. HPLC, HPLC-MS, HPLC-ELS, CZE; MS; LC-NMR, LC-IR and CLND are very useful techniques for analysis the components from quality control of chemical libraries (on cleavage solution analyses). Considerable efforts have to be spent from the analytical side in developing new, more sensitive methodologies to detect very small quantities of compounds and possibly quantify them in order to increase biological assay data value. At present, combinatorial chemistry technologies are impacting more and more the drug discovery process. High throughput methodologies for compound physical/chemical and biometric properties estimation are also necessary and are being developed.

CC/CT in Natural Product's Research and Case Studies

Dr. Pierfausto Seneci (ICS-UNIDO expert, NADAG, Germany)

Natural products (NPs) can be obtained from bacteria, fungi, plants, terrestrial invertebrates and marine invertebrates. In 1994, 39% of approved drugs were NPs or their derivatives, and 60-80% of approved antibacterials and anticancer drugs were NPs or their derivatives. NP Libraries and CC Libraries are common in the processes of rational design, synthesis, screening, isolation, characterization, optimization/scale up, and possibly subjected to HTS. There are various library format of NPs: decoration of a NP-derived scaffold, construction of a NP-inspired library, combinatorial biosynthesis and combinatorial biotransformations. The decoration libraries are obtained by semi-synthetic modifications of a NP derived core structure possessing the characteristics of easy access (natural or synthetic), suitable diversity points, assessed chemical reactivity and selectivity, and intellectual property coverage. The examples of the decoration libraries were given of the core structures of L22 (an indole alkaloid), L24 and L25. For construction of a NP-inspired library, it can be done by using available precursors to build either a NP scaffold or a NP-like scaffold with simple synthetic scheme and suitable diversity points. The examples were given for the construction of β-lactams and balance libraries. For combinatorial biocatalysis, its characteristics are the unpredictable diversity available, mild reaction conditions, wide range of reactions and stereoselective/regioselective outcome. The examples were given for the combinatorial biocatalysis of various discretes of organic molecules from L30 structure by combinatorial reactions of halohydration, glycosylation, acetylation, and from L31 structure by lipase catalytic reaction. For combinatorial biosynthesis, it is a rational modification of known active molecules by the technique of genetic engineering. Genetically modified polyketide synthase enzymes were given as an example for this library format. For the session of case studies for CC/CT in NPs' research, the design and synthesis of a taxoid library was presented using radiofrequency encoded combinatorial chemistry (REC). REC is a recently developed nonchemical encoding strategy in library synthesis. Encoding chemical libraries of complex molecular structures like taxol can be constructed employing the noninvasive REC strategy and novel solid phase synthetic techniques, as demonstrated by the synthesis of the first 400-membered taxoid library in a discrete format and in quantities of multimilligrams per compound. Another case study was given on the synthesis of a sarcodictyin library on solid phase. This case started with the synthesis of chemical resins for loading of the sarcodictyin core on solid phase.

followed by the synthesis of various tethered sarcodictyin cores. The next step was loading of sarcodictyin cores to solid supports and followed by solid phase synthesis of sarcodictyin libraries. The last case study was on the CC and NPs: Teicoplanin aglycone as a molecular scaffold for solid phase synthesis of combinatorial libraries (P. Seneci et al. (1996) Tetrahedron Letters, 37, 6319).

Country and Institutional Report: Thailand

Dr. Wanchai De-Eknamkul (Chulalongkorn University, Bangkok, Thailand)

Thailand has various types of tropical forests which may support up to 12,000 species of vascular plants and 3,500 species of vertebrates. Many of the plant species have not yet been investigated chemically although a lot of ethnobotanical clues and ecological hints can provide a valuable short cut in harnessing the potential of Thai plants as sources of new pharmaceuticals and agrochemicals. Thailand started seriously considering about their bioresources just after the UN Earth Summit in 1992 in Brazil. A national policy on this issue was put in the 8th National Economic and Social Development Plan (1997-2001) and will also be in the 9th Plan (2002-2007). Thai strategy has been on the conservation and sustainable utilization of biological diversity. Based on the national policy, a number of relevant programs have been established, including Biodiversity Research and Training (BRT) program and Thailand Tropical diseases research (T-2) program. While BRT's ultimate goal is to assess the biodiversity remaining in Thailand and to investigate the present and potential benefits of biodiversity, T-2 emphasis is on research and development of medicinal products for tropical diseases research. In addition, natural products R&D have been carried out in a number of universities distributed all over the country and in a specific research institute, such as Chulabhorn Research Institute (CRI) which was established by Her Royal Highness Princess Chulabhorn, a natural products chemist. Generally the use of CC/CT in the field of natural products in Thailand is relatively lacking. This is due to the economic crisis occuring in Thailand during 1997-1999 that limited a transfer of know-how and technologies of this new field to Thailand. However, by analyzing the current status of natural products drug discovery, Thailand is considered to have strong points on the aspects of the availability of bioresources, human resources (chemists, biologists, biochemists, phytochemists, biotechnologists, etc.), research grants and target tropical diseases. These will be a strong base for further development of CC/CT/MD in Thailand. For the weak points, Thailand still lacks know-how on bioassay technologies, acquisition of targets (enzymes, receptors, ionchannels, targets-expressed cell lines, etc.), and collaborative research. Based on these situations, Thailand proposed needs of supports from ICS-UNIDO for both short-term and long-term program in this field. For the short-term plan, the emphasis is on research fellowships for training on bioassay systems and technologies as well as a linkage with the oversea institutions. For the long-term plan, Thailand aims to set up a regional ICS-UNIDO network on CC/CT and MD at the Faculty of Pharmaceutical Sciences of Chulalongkorn University.

Country and Institutional Report: Philippines

E.P. Capareda (University of the Philippines Los Banos College, Philippines)

Since the previous ICS-UNIDO workshop held at the University of the Phillipines Los Banos in 1999, there has been continued research in areas such as natural products chemistry and material science for which CC/CT/MD have much impact, particularly in the development of pharmaceuticals and agrochemicals. With

the rich and diverse plant, animal and marine resources in the Philippines, there is active natural products research in almost all of the major academic institutions. Natural products are also being studied as potential pesticides, insecticides, herbicides and plant disease control agents. However, there is very little R&D work on natural products in industry although screening of essential oils for antimicrobial and antifungal activity have been done in a private pharmaceutical company. Much of the government support goes to programs involving the development of herbal medicine whereas the Natural Products Society of the Philippines aims to the national program that is chemistry-based. The latter program envisions achieving its goals through four phases of work plan: Phase I: Massive Collection and Screening ; Phase 2: Correlation, Dereplication and Prioritization ; Phase 3: Pursuit of Lead or Top Priority Bioactive Samples ; Phase 4: Production of Bioactive Natural Compounds and Synthetic Analogs. With new technologies, however, there is still very little research work in the area of CC/CT/MD in the Philippines.

Country and Institutional Report: Malaysia

U.D. Palanisamy (SIRIM BERHAD, Malaysia)

CC/CT/MD has only been recently identified as priority research areas under the 8th plan (2001-2005) of research program. Natural products R&D, on the other hand, has been on going in several academics and research institutes for a number of years. The use of CC/CT/MD techniques in the field of natural products is greatly lacking. There has been efforts to set up a National Center for Computational Science in Malaysia in order to create state-of-the-art facilities for academia, industry and the inventing community. Presently, initial seeding of the project is taking place in the form of the natural products information system whereas research using combinatorial chemistry for catalysis is being initiated by the University of Malaya. The recent Malaysian-Massachusetts Institute of Technology Collaboration Program (1998-2002) has been a tremendous success. This has encouraged the government to call out for more research on natural products. Several priority areas were identified for both short-term development program and long-term discovery program. The development program includes standardization of herbal materials, sustainable production of quality raw materials, development of value added products and efficient processing technologies. The discovery program includes enrichment of scientific data of Malaysian plants (eg. efficacy studies on selected disease targets: cancer, cardiovascular, infective, HIV, CNS, liver drugs) and development of platform technologies (eg. medium & high throughput screens for the selected disease targets, combinatorial chemistry, bioreactor technology, microassay technology and cell culture technology). Therefore, the use of CC/CT/MD techniques in the natural products R&D is identified as a long-term discovery programme.

Country and Institutional Report: Nepal

Purusotam Basnet (Pokhara University, Nepal)

Nepal, in spite of its small size (147,575 sq km) contains more than 7000 plant species and among them, about 700 are supposed to be of known medicinal value. Many of such plants have never been screened for biological activities or subjected to chemical analysis. Therefore, it is very important to carry on screening of these plants to explore medicinal resources. Moreover, Nepal contains 48 ethnic dialects. Each ethnic group has carried on a unique healing tradition for centuries and passed them on from generation to generation. Slowly, such local healing traditions are on the edge of extinction. It is very urgent to investigate such human-experienced knowledge to

find the evidence-based medicine. Therefore, the CC/CT would be an ideal program to be launched. For the infrastructure, there is already enough manpower in Nepal to conduct CC/CT. However, CC/CT has not started in Nepal. Basic infrastructure such as transportation and communication are already far better than in the past. Many more Nepalese scientists living abroad can also be attracted to such research program. Currently, Nepal has five universities. The oldest university, Tribhuvan University, is established in 1959. All other universities are recently established, not more than 10 years old. Among these universities, Kathmandu Universtiy has been launching graduate program on Pharmaceutical Sciences since 1995, whereas Tribhuvan University has started since last year and Pokhara University is making preparation for this year. Therefore, the young generation with the pharmaceutical science background is expanding. They have common thinking that research is necessary for better health and economy, especially to explore Himalayan medicinal resources. Attempts have been done to establish a Research Center for Himalayan Medicinal Resources. The aims and goals of the Center are: revitalization of local healing tradition, preservation of rare Himalayan medicinal herbs, development of herbal medicinal resources and products, promotion of sustainable use of medicinal resources and environment protection, cultivation and propagation of medicinal resources to support rural economy. On this regard, CC/CT would be very ideal program to fulfill our goals, although it is very expensive for us to establish such high technology.

Country and Institutional Report: Kuwait

K. Habib (Department of Advance Systems, KISR, Kuwait)

The Kuwait Institute for Scientific Research (KISR) founded in 1967 is a center for applied research for development in the country. Two of the major goals of KISR is to conduct research for the advancement of the country's industry, and for the protection of its environment and natural resources, and to be up-to-date with scientific and technological advancements. KISR has undertaken many challenging projects, including: development of new advanced technologies to improve industrial efficiency, particularly in the oil sector, identification of better methods for managing and protecting the country's environment and investigation of new technologies for enhancing food production in the country in order to achieve sustainable systems that contribute to particular food security. However, the use of CC/CT/MD techniques in the field of natural products is generally lacking.

Country and Institutional Report: Laos

Dr. Outhip Sounthavong (National University of Laos, Laos)

The Department of Pharmacy has developed its curriculum, which aims to improve and produce qualified pharmacists. In order to achieve the goal and objectives of the Faculty of Medical Sciences, there is a need to develop a number of components of curriculum, teacher's competency, textbooks and facilities, and other significant items. Pharmacognosy and Phytochemistry are the main items that need to be considered and will be implemented. Since 1996, the Department of Pharmacy had printed two new textbooks of Pharmacognosy and two new handbooks of Phytochemistry. Currently, it is still at the beginning of the period of improving the practice on technical screening of the natural product in our department. But chemical reagents and instruments are not sufficient. Therefore, we use only TLC and UV lamp to screen and identify natural products. The current teaching of CC is only in theory.

This opportunity to learn about CC and CT from this workshop would help to improve our future intervention on this matter.

Country and Institutional Report: Indonesia

Syahrial Tahir (Centre for Research of Drug and Food Control, Indonesia)

The Centre for Research of Drug and Food currently is a new organization which has been established since April 19, 2001. The objects of the establishment of this center are as follows: to establish the drug and food research laboratory, to enhance possibility of developing the new compound of local natural resources and to establish network information with any regional, and international institution concerning the drug and food research program of each local natural resources. The development of the Indonesian's local natural products research has been performed by several universities and government institutions. One of the research work on the local natural resource has been done by Gajah Mada University, Yogyakarta. The Faculty of Pharmacy has worked on isolation, structural modification and molecule design and screening (in vitro) of some active substances and new substances (in vivo) which have the pharmacological activity. The research usually takes long period of time with expensive cost. The technologies of rapid screening application of CC/CT/MD are needed. Using this Opinion Leader's Meeting on Potential Applications of CC/CT/MD and Workshop. Indonesia would like to establish and develop the information network with regional and international institutions which develop the research of local natural resource.

Conclusions of Both Workshop Events

Since natural products have extreemly impact in SEACs, and highly expected that these bioresources will be valuable to be searched and developed. On behalf of Faculty of Pharmaceutical Sciences, Chulalongkorn University, we wish to thank ICS-UNIDO for giving our faculty the opportunity to organized for both "Opinion Leaders' Meeting" and workshop on "SEACs on CC/CT: Natural Products and Technologies on Rapid Screening". For the detail of the workshops, most participants understand more for an important role of CC/CT and also recognized that international experts presentations including case studies related to CC/CT were most useful. From the ICS-UNIDO evaluation form indicated that the topics of both rapid screening of NPs and combinatorial synthesis were of particular interests among the participants. The expansion of specific topic into detail will be useful, such as combinatorial systhesis and bioassay technologies, etc. In addition, more detail of recommendations were given from participants. All international experts, supported the discussion on different cases during the meeting and also during round table discussion, these make participants understand more clearly case by case of their lectures. Presentation of opinion leaders and country / institutional reports will inform current status for the application of CC/CT in their countries. At the last the round table discussion and recommendation for future actions of ICS-UNIDO was also carried out. The exchange idea between SEACs representatives show vision and process vision in order to carry out of CC/CT in this region. In summary the objectives for both events were met and the workshops found to be success.

11. Assessment of the Workshop

Assessment was performed by the questionnaire distributed to the participants. The results are summarized as follows:

A. Organization	**Excellent**	**Very Good**	**Good**	**Fair**	**no response**
- Information process	15 %	41 %	41 %	3 %	0 %
- Annoucement	12	50	35	3	0
- Scientific program	18	50	23	0	9
- Lecture/Workshop	21	47	29	0	3
- Working groups	3	24	53	3	17
- Case studies	21	53	26	0	0
- Time spent	12	59	23	3	3
	Balanced		**Unbalanced**		**no response**
- Student scientific knowledge	41 %		47 %		12 %
B. Duration of programme	**Just right**	**Too long**	**Too short**		**no response**
- Number of days	68 %	26 %	3 %		3 %
- Length of working days	47	47	0		6
C. Training facilities & Hotel	**Excellent**	**Very Good**	**Good**	**Fair**	**no response**
- Lecture/training rooms	38 %	44 %	15 %	0 %	3 %
- Breaks/refreshments	24	50	24	0	2
- Hotel accommodation	29	6	6	0	59
- Meals at the hotel	29	3	15	0	53
D. Organizer's response to participants needs					
- Organizer's response	18	50	29	0	3
E. Overall programme organization	12	59	24	0	5
F. Would you recommend to others from your institution		**Yes**	**Maybe**	**No**	**no response**
		88 %	6 %	0 %	6 %
G. Evaluation of Lectures and Speakers	**Excellent**	**Very Good**	**Good**	**Fair**	**no response**
- Course material	18 %	62 %	15 %	0 %	5 %
- Resident Lecture presentation	9	35	21	0	35
- International lecture presentation	21	65	3	0	11
- Ability of lectures to answer specific question	26	47	21	0	6

According to the filled questionnaires, most participants found the lectures given by international experts most useful. The topics of both rapid screening of natural products and combinatorial synthesis were of particular interests among the participants. Various case studies presented by the experts were well received. The overall programme consisted of good combination of content although some participants would like to have each specific topic be expanded into detail, such as combinatorial synthesis and bioassay technologies. Detailed recommendations from the participants are given below.

12. Recommendations from participants

(The answers were from all filled questionnaires)

1. Which part of the activity do you find most useful?

- Chemical synthesis of combinatorial hybrids, characterization and purification of organic synthetic hybrids.
- Discussion on personal/information networking.
- Lectures and case studies in general.
- Using the combinatorial technologies to build up chemical libraries.
- Synthetic and analytical techniques in CC.
- Organic synthetic libraries, characterization/purification, and natural products research
- High throughput screening (biological assay)
- Information presented by all international experts
- All activities
- lectures
- Seminar on case studies
- Combinatorial chemistry (for my institute) and CC-CT-MD (for universities. I will distribute copies of all handouts)
- Computational tools for CC/CT
- Screening natural product samples for drug discovery and drug leads from natural products
- Case studies
- Discussions with the technical experts
- Lectures/case studies
- Lectures
- Discussions and interaction of experts with participants
- CC/CT principle & concept, screening of natural products, and computer tool for CC/CT
- Drug discovery from natural products
- Case studies along with the lecture
- Lecture and round table discussion on chemical synthesis of organic combinatorial libraries
- Combinatorial technologies applied to natural products, both lectures and case studies
- Computational tools for CC/CT and CC/CT in natural products' research
- Natural products chemistry in the drug development process
- Screening natural products for drug discovery & HTS in drug discovery
- All program activities are useful
- Case studies: good to excellent examples
- All examples and answers to questions

2. Which part of the activity do you think should be expanded

- Case studies
- Chemical synthesis of organic combinatorial libraries and combinatorial material science
- Drug discovery from natural products
- CC/CT on natural products

- Just right combination
- Computational chemistry
- Case studies
- Screening natural product samples for drug discovery
- Drug leads from natural products
- Case studies
- Lectures related to discovery of bioactive compounds
- None
- Activities and case studies of natural products in real situation such as prescreening, organic synthesis libraries, opinion leaders' meeting and country reports
- Experiments to facilitate needs of this kind of research and details to approach
- Practical training on chemical synthesis of organic combinatorial libraries and HTS
- Computational tools and natural products' research
- Natural products library and use of combinatorial techniques on it
- HTS in drug discovery
- Computational chemistry
- Round-table discussions
- Reactions on insoluble support, and drug leads from natural products

3. Which part of the activity do you think should be dropped?

- None
- CC/CT on material science should be separated to another section. It is still useful but not for participants of this workshop
- The combination of the program was just right but time spent should be shortened a little bit
- None
- Each session is just fit to each other
- None
- Should combine round-table discussion with questions after lecture
- Shorten a day
- All are very important but it should be cut down in some extent
- None
- Combinatorial technologies in material science
- Those parts which is only relevant to industry or only industry can afford
- None
- Combinatorial technologies in material science

4. Any other suggestions for future improvements to the programme?

- Improvements of the section of "case study". They should include the research projects of speakers, not only from the literatures
- Presenters had too much material for presentation and thus the time was too long
- Training or demonstration of some technologies in the lecture should be included

- There should be an announcement for the programme at least 3 months in advance. It should have more participants in the workshops
- The program should be separated into small groups of chemistry, biology and pharmacology so that each group can have the intensive course of each field
- There should be laboratory work on rapid screening with emphasis on specific and problematic discussions of each region
- Organization of the program needs to be prepared and needs more time to invitate more people to attend
- Case studies 60%
- Questions after each lecture should be included in the round table discussion
- Probably scheduling of lectures such that it is not like a "marathon" session
- Speakers should have power point presentations, not overheads
- Lectures should be organized in a sequential manner (step by step) which will focus on main topic of the workshops. We cannot get all information of every aspect at the same time.
- Spread the schedule
- Emphasis more in depth for each parts
- Focus on specific area for longer time period
- Scientific programme was set up in a short notice. Therefore, it was difficult to be announce or distributed to a large population. So, this kind of workshops should be announced about 5-6 months in advance.
- Experts attending this workshop should be expanded to many fields
- Both education and industry have certain limitation. The program which can carry both together would be more beneficial
- Practical workshops should be incorporated into the program
- None
- Should minimize the outline and make it more specific to the application

5. Do you think that the topics/tools you studied during the course could be used by industries in your country? If so, how? If not, why not?

- Yes, when some supports (money) and experts in this field are available
- No for industries now but yes for academic institutions
- Yes, I think that HTS is very useful for basic research. It makes research more convenience and shortening time to do the research.
- Yes, but it takes time and need a lot of research work
- No. Because there are very little activities of R&D in our pharmaceutical industry. It is, however, very useful for R&D in universities
- Yes, it is the beginning of research of which data can be obtained and utilized more effectively. It is very useful
- I think so, because they have R&D department especially in the government industries (drugs, vaccines) and the private industries (drugs, traditional drugs and cosmetics)
- No. Because of the limited budget and we have only small drug's industries
- At the moment, no. Because there is hardly any R&D in this area, but there is a lot of potentials
- Yes, but to make the industries know precise concept of CC/CT in terms of implement or investment in natural products drug discovery.

- Not in the near future because the industrial sector in Thailand spends only small part of budget for research
- Quite difficult to use in industry owing to limitation of expert scientists in this field and limitation of budget to have sophisticated equipment.
- Yes. Because there are interest in natural products and screening of herbs in Thailand
- In Nepal also. Pharmaceutical and agro-industries are growing fast. It means CC/CT/MD or HTS are the tools for faster development.
- Yes, in the future but not right now. Because the lack of CC/CT background, knowledge and need to be trained.
- Not now. Because chemical industry in Thailand is quite weak. It may be useful, however, in not very far future. However, for my company, a combination of rapid screening technique can be applied for finding useful crude herbal extract and the medicinal activities of medicinal herbs (i.e. natural products)

6. **Can you suggest any programme and future activities which ICS could pursue in order to help with the technological and scientific advancement of your country?**

- Training program, study-visit program, problem-solving and consultation from the experts (lecturers) in this field should be set up
- I would like to have programme which is involved in chemical synthesis of new chemical entities
- Workshops with practical parts
- Computer modeling of drug design
- About bioassay system and the acquisition of targets (such as enzymes, receptors, ion channel, cells, etc.) for the bioassays
- Hands-on courses
- New researches in tropical diseases (broad research area)
- Group training 6-8 persons (universities, industries and government sector). National/regional workshops in our country
- I would like to develop the phytochemistry in laboratory for teaching and screening about natural products in my country, and would like to train our teachers oversea
- Hands-on training on LTS/MTS and combinatorial synthesis
- To conduct hands-on training in this field
- Funding (fellowships) to selected scientists to observe and learn the whole process (in conceptual point of view) and then be back as trainers to organize the workshop. Grant fellowship to academic institute which already implement these technologies to learn specific know-how.
- Solid phase synthesis (in detail) and natural products screening
- Scholarship funding such as fellowship and expertise to help setting up the laboratories in Thailand. Also, budget should be provided for some expensive equipment
- I think that in Thailand, we need the know-how of extraction and synthesis in the industrial scale so that we can be sure that after drug discovery, we can produce it commercially.
- Energy optimization in manufacturing process and how to manage recycling waste in our country

- I would like to divide the activities into phases. In the initial phase, we should pass the knowledge of CC/CT to young people (through education). At the same time, the research or program should be launched or induced to launch by research institutions or industry.
- Practical part should be incorporated in the workshops
- Should have workshops in the specific field, i.e. combinatorial chemistry, computational chemistry and high throughput screening etc.
- Semi-synthesis of natural products

7. Do you think you have benefited from participation in this course/workshop? If so, how? and your institution?

- Yes, I have benefit from participation in this course/workshop. I hope I will use some ideas for my institution to produce something concerning it.
- Yes, personal contacts are most useful
- Yes, start thinking again about combinatorial chemistry and solid phase synthesis in the lab, and expand CT/CC in the drug design course of graduate programs
- Yes, this program give me some basic knowledge by using high technology which I did not know before
- Yes, I got a lot of knowledge about CC/CT which can apply to my work.
- Yes, I have learn the new technology that should be applied to my work, especially the HTS and CC
- Yes, I gain knowledge on CC/CT on various aspects
- I absolutely get benefit from this workshop. I obtain a lot of new ideas and technologies.
- Yes, I got better understanding about the CC/CT
- Yes, I learn many new things today
- I think these workshops bring the meaningful benefit to the development of knowledge, information technology especially for researchers, and university instructors
- Yes, I do. I think many information from this workshop will improve my teaching and my work in the future
- Yes, I have established some contacts for possible collaboration and have gained technical knowledge. This will help me/guide me in preparing possible research proposals for research in this area.
- Yes, I learn new technology for drug development
- Yes, meeting people
- Yes, I will inform my institution about these CC/CT and try to obtain grant from the government in order to implement about CC/CT
- Yes, this kind of workshops help to expand the concept of new technology in research and Thailand can convey this to our natural plant extract technology.
- Yes, I will try to use the new technologies such as solid-phase and solid supported reactions in my research work
- Creating the new ideas and all the documents received is very interesting for our natural product synthesis in the future.
- Yes, very much. Personally, I was in a stage to develop the syllabus for university students in Pharmaceutical Sciences. Therefore, this new field of science seems to be introduced to our university

- Yes, very much. I understand and can see the picture of CC/CT clearer.
- Yes, for the very least, exposure to CC/CT from some experts is great. Perhaps we may involve ourselves in a project with CC/CT
- Yes, but it may be looked ahead for some years

8. **How do you intend to disseminate the information you have acquired during the activity once back in your own country?**

- Short written report will be circulated
- Try to use CC/CT in the drug design research as much as the facilities, equipment, hard + software allowed
- I will give lecture relating to the course/workshop to my colleagues
- Distribute the information of CC/CT to the staff of my institute.
- Give a seminar and write scientific article
- Give a lecture on this topic to students
- Introduce some of these materials into the lecture involved
- Through notes, memos and lectures
- I will establish network information with university and industries
- By reporting, meeting and teaching in my faculty
- Conduct "mini" - echo seminar
- Make handouts available
- By inform other scientists in this field through seminar/workshop by local experts involved in this field.
- I will put the copies of the handouts in libraries and write a report about the workshop
- The documents are very useful for our company in research and development of new products
- I would like to pass this knowledge on CC/CT to our students who will be future manpower for the industry
- Perhaps a meeting format

Final Comments

- I would like to have more participants attending the conference which will make lecturer to be back to Thailand again in the future conference.
- We hope this programme will be continued in the future
- Some time must be put in the schedule of activities for some sight-seeing so that the participants will not have to skip the lectures and the program will not be too tiring. A few speakers went overtime with their talks.
- Handouts should be given before each lecture to enable following during talk
- Appreciate all ICS experts to put a lot of effort to give information to all participants in terms of awareness and implementation of these high technologies
- Please continue to arrange this type of workshop in depth again in order to make it possible to set up at least a research lab in this country
- Please follow up the case studies of CC/CT by teaching our university students

- In several developing countries in Asia, maybe infrastructure for such high technology is not enough yet. But ICS should launch the program CC/CT in coming decades, not next year.
- Prof. Tony Buss's lectures on natural products were the highlight of this workshop. This lecture was clear and exemplified with involvement of CC/CT to his research

13. Conclusion and follow-up

It was concluded that both ICS-UNIDO events (the meeting and the workshop) have been successful for awareness building in South East Asian Countries in fields relevant to Combinatorial Chemistry and Combinatorial Technologies. The importance of CC/CT especially in the better exploitation of naturally occurring compounds and biotechnology in these countries was evidenced. It was agreed to further develop this programme in Thailand and neighboring countries. Therefore, several proposals on follow-up activities have been discussed and are indicated in a preliminary form in the **Annex 6**. **Dr. Umprayn** (in tight cooperation with ICS-UNIDO) will organize a follow-up meeting before September 2001 (involving both academy and industry) in order to define a detailed follow-up plan.

Annex 1
Budget for the Opinion Leaders' Meeting and Workshop

ICS-UNIDO contribution

	planed in USD	Realized
Accomodation for 8 invited international lectures	2,061	1,542.00
Accomodation for 7 invited participants from SEACs	1,764	1,383.86
Meals (for all attendees)	2,900	2,273.48
Travel of 7 invited international lectures	7,800	7,092.66
Travel of 5 invited participants from SEACs	3,500	1,685.00
Travel of local participants	2,000	1,950.00
Living expenses (breakfasts,dinners) for 8 IEs and 7 SEACs	2,700	2,217.46
Local transport to and from the hotel to the institute and coaches for site visit	250	165.00
Publication of Proceedings/Special Issue of Journal	2,070	**2,070.00
Sub total of ICS-UNIDO contribution	**25,000**	**20,379.46**

**Reserve for publication of Proceeding/Special Issue of Journal to be distributed in SEACs and some Asian countries

Contributions of the hosting institution (and other co-sponsoring organizations)

Conference hall	400	486.00
Fax/Telephone/Post	600	350.00
Training materials	1,000	900.00
Secretariat	2,000	1,900.00
Publication of workshop abstract	500	500.00
Reception and meal for SEACs and Asian participants (self finance)	500	350.00
Reception and farewell	1,000	650.00
Sub total of local contribution	**6,000**	**5,086.00**
GRAND TOTAL(ICS-UNIDO contribution+Local contribution)	**31,000**	**25,037.12**

Annex 2 List of International Experts
Of the
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and
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Annex 5

Tentative Programme

First Event: Opinion Leaders' Meeting

1 day

April 23 (Monday):

8.00-8.45	Inauguration: Local Representatives/Committee
8.45-9.00	Programs and Activities of ICS-UNIDO: Prof. Miertus
9.00-9.45	Impact of CC/CT in Industry (including a Case Study): Speaker 1
9.45-10.30	The impact of Natural Products in Modern Pharmaceutical Industry (including a Case Study): Speaker 3
10.30-10.45	*Coffee Break*
10.45-11.30	Business-related Aspects of CC/CT/MD: Economics, Patenting, Financing: Speaker 4
11.30-12.00	Round Table Discussion
12.00-13.00	*Lunch*
13.00-13.30	Natural Products and CC/CT. Successful Case Studies: Speaker 1
13.30-14.00	A Successful Case Study: Commercialization of a Combinatorial Product: Speaker 4
14.00-14.30	Potential Applications of CC/CT/MD in Thailand: Local Opinion Leader
14.30-14.45	*Coffee Break*
14.45-15.30	Impact of High-Throughput Screening in Drug Discovery (including a Case Study): Speaker 2
15.30-15.50	Potential Applications of CC/CT/MD in Singapore: Local Opinion Leader
15.50-16.10	Potential Applications of CC/CT/MD in Hong Kong: Local Opinion Leader
16.10-16.30	Potential Applications of CC/CT/MD in India: Local Opinion Leader
16.30-16.50	Potential Applications of CC/CT/MD in the Philippines: Local Opinion Leader
16.50-17.10	Potential Applications of CC/CT/MD in Malaysia: Local Opinion Leader
17.10-18.40	Round Table Discussion and Recommendations for Future Actions (Structured as 50 minutes of Working Groups, then 30 minutes of reporting by WG leaders, then 10 minutes for the formalization of recommendations)
18.40-19.00	Closing Remarks: Profs. Miertus and Umprayn

Speaker 1:	Dr. Pierfausto Seneci - Director of Chemistry, NAD AG, Germany
Speaker 2:	Dr. Georg Terstappen - Site Head, System Research - GlaxoSmithKline, Italy
Speaker 3:	Dr. Tony Buss - Director, Centre for Natural Product Research, GSK/CNPR, Singapore
Speaker 4:	Dr. Giorgio Fassina - Research Director, TECNOGEN SpA, Italy
Speaker 5	(only for Event 2, see below): Dr. Elisabetta de Magistris - GSK, Italy
Speaker 6	(only for Event 2, see below): Dr. Valerie Gillet - University of Sheffield, UK
Speaker 7	(only for Event 2, see below): Prof. Raghavan - Pune, India

Second Event: Workshop

4 days

April 24 (Tuesday):

8.30-9.00	Introduction. Participants, etc.: Profs. Miertus and Umprayn
9.00-9.15	Programs and Activities of ICS-UNIDO: Prof. Miertus
9.15-10.15	Combinatorial Technologies. Principles and Concepts: Speaker 4
10.15-10.30	*Coffee Break*
10.30-11.30	Combinatorial Technologies in Pharmaceutical. Agricultural Industry and in Biotechnologies: Speaker 1
11.30-12.00	Round Table Discussion
12.00-13.00	*Lunch*
13.00-14.00	HTS, MTS and LTS in Drug Discovery: Speaker 2
14.00-15.00	Screening Natural Products Samples for Drug Discovery: Speaker 3
14.45-15.15	*Coffee Break*
15.15-16.00	Case Studies for HTS in Drug Discovery: Speaker 2
16.00-17.30	Drug Leads from Natural Products: Speaker 3
17.30-18.00	Round Table Discussion

April 25 (Wednesday):

8.30-9.30	Computational Tools for CC/CT: Speaker 6
9.30-10.15	Case Studies for Computational Tools in CC/CT: Speaker 6
10.15-10.30	*Coffee Break*
10.30-11.30	Biological Combinatorial Libraries: Speaker 4
11.30-12.00	Round Table Discussion
12.00-13.00	*Lunch*
13.00-13.45	Case Studies for Biological Combinatorial Libraries: Speaker 4
13.45-14.45	Combinatorial Technologies in Homogeneous and Heterogeneous Catalysis: Speaker 7
14.45-15.30	Case Studies for Homogeneous and Heterogeneous Catalysis: Speaker 7
15.30-16.00	Round Table Discussion
16.00-16.30	*Coffee Break*
16.30-17.30	Combinatorial Technologies in Materials Science: Speaker 7
17.30-18.15	Case Studies for Materials Science: Speaker 7
18.15-18.45	Round Table Discussion

April 26 (Thursday):

8.30-9.30	Chemical Synthesis of Organic Combinatorial Libraries: Speaker 5
9.30-10.30	Characterization and Purification of Organic Synthetic Libraries: Speaker 5
10.30-10.45	*Coffee Break*
10.45-11.30	Case Studies for Organic Synthetic Libraries, Synthesis: Speaker 5
11.30-12.00	Round Table Discussion
12.00-13.00	*Lunch*
13.00-13.45	Case Studies for Organic Synthetic Libraries,

	Characterization/Purification: Speaker 5
13.45-14.15	Round Table Discussion
14.15-15.15	CC/CT in Natural Products' Research: Speaker 1
15.15-15.45	*Coffee Break*
15.45-16.45	Case Studies for CC/CT in NP Research: Speaker 1
16.45-17.30	Round Table Discussion

April 27 (Friday):

9.00-10.30	Country and Institutional Reports 1-3
10.30-11.00	*Coffee Break*
11.00-12.00	Country and Institutional Reports 4-5
12.00-13.00	*Lunch*
13.00-14.00	Round Table Discussion: Future Actions
14.00-14.30	Workshop Evaluation, Closing Remarks: Profs. Miertus and Umprayn

Annex 6
Proposal on
A Follow-Up Program :
Development of Combinatorial Technologies for Natural Products R&D in Thailand

Presented by Dr. Kaisri Umprayn
Faculty of Pharmaceutical Sciences, Chulalongkorn University
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1. Rationale

The tropical forests of Southeast Asian countries, especially Thailand, have long been recognized as one of the world's major region of origin and diversity of plant and animal species. It is generally accepted that there are numerous complex ecological webs that together contribute to the energetics of the tropical forest ecosystems. It is also known that biochemicals produced by plants, insects and herbivores play very important roles in balancing these ecosystems. Therefore, the tropical forest can be viewed as a huge factory producing an anormous diversity of biochemicals and offers an excellent source for screening and identifying naturally ocurring chemicals with particular biological activities. Presently, very little is known about the natural products available in Thai tropical forests. This situation makes it difficult to assess the economic significance of the natural chemicals with respect to their application and utilization as pharmaceuticals and agrochemicals.

Thailand has had a clear policy on the conservation and sustainable utilization of biodiversity since 1992. This issue has been in the 8th National Economic and Social Development Plan (1997-2001) and will be continued in the 9th Plan of the next five-year period (2002-2007). The main strategy of Thailand is on the idea of extractive reserves which represent a conservational compromise, with incentives for long-terms forest preservation derived from the sustainable harvesting of forest products. With this strategy, a program called Biodiversity Research and Training Program (BRT) has been established since 1996 with its ultimate goal of assessing the biodiversity ramaining in Thailand and to investigate the present and potential benefits of biodiversity for human life. During the last five years, many areas of Thailand have been investigated for all classes of organisms. Information has been being accumulated on new species and new records which lead to more updated taxonomic classification of various groups of organisms. In addition, Thailand has established another program called Thailand Tropical Diseases Research Program or T-2. The emphasis of T-2 is on research and development of medicinal products for tropical diseases. The target diseases include : malaria, enteric infections, helminthic infections, dengue haemorrhagic fever, hepatitis, tuberculosis and HIV-related infections. Obviously, the discovery of new medicinal agents from natural products has been the major activities for the researchers involved in these diseases. For universities, the research on natural products have also been carried out by a number of laboratories. The topics of study are based on the interest of each research group.

Generally the use of CC and CT in the field of natural products in Thailand is relatively lacking. This is due to the economic crisis occuring in Thailand during 1997-1999 that limited a transfer of know-how and technologies of this new filed to

Thailand. However, by analyzing the current status of natural products drug discovery, Thailand is considered to have strong points on the aspects of the availability of bioresources, human resources (chemists, biologists, biochemists, phytochemists, biotechnologists, etc.), research grants and target tropical diseases. These will be a strong base for further development of CC/CT/MD in Thailand. For the weak points, Thailand still lacks know-how on bioassay technologies, acquisition of targets (enzymes, receptors, ionchannels, targets-expressed cell lines, etc.), and collaborative research.

It was very fortunate that the ICS-UNIDO Southeast Asian Regional Workshop on CC/CT : Natural Products and Technologies on Rapid Screening was held last month during April 24-27, 2001 at Chulalongkorn University, Bangkok, Thailand. The workshop led to a stimulating, enlighting and exciting experience for most of the Thai participants and left them very enthusiastic to get start on this area of research. There were a lot of positive responses from the participants based on the evaluation questionnaires. However, there were a number of comments suggesting that the training should have had practical or hands-on sections in the program to make the workshop more complete. To this aspect, we think that Thailand, because of its central location in the region and its potential to develop in this area of new technologies, is in a position to establish a regional ICS-UNIDO network for the future training on CC/CT.

Based on these situations, Thailand would like to propose needs of supports from ICS-UNIDO for both short-term and long-term program in this field. For the short-term plan the emphasis is on research fellowships for training on bioassay systems and technologies as well as a linkage with the oversea institutions. For the long-term plan, we aim to set up a regional ICS-UNIDO network on CC/CT and MD in the Faculty of Pharmaceutical Science of Chulalongkorn University.

2. The objectives of the follow-up program

2.1 To develop the human resource of Thailand in the areas of combinatorial technologies, especially the bioassay systems related to disease targets.

2.2 To have an international expert to supervise Thailand for the long-term development of these new technologies

2.3 To establish a regional network training-center of ICS-UNIDO for further development of human resource in Southeast Asian countries

2.4 To have a collaborative research with the well-established research groups in either research institutions or pharmaceutical industry in this field

3. Workplan

The follow-up program activities to be carried out are as follows :

3.1 Assignment of an international expert by ICS-UNIDO to supervise the follow-up program. The name of the expert should be first proposed to Thailand for background considering before the officinal appointment.

3.2 Allocation of at least 3-4 fellowships to Thailand to allow 3-4 potential researchers to earn experience from the well-established laboratories. Among these fellowships, one should be trained for bioassay systems, one

for combinatorial synthesis or biosynthesis, one for the training on complete technology (short-time) and possibly the other one for training on purification of monoclonal antibodies for diagnostic purposes.

3.3 Support of various basic equipment involved in the fellowship program if possible. The equipment should be able to transport to Thailand after the end of the fellowship so that research and further training can be perform readily in Thailand.

3.4 Establishment of ICS-UNIDO network training center in Thailand for carrying out research and training in the areas of CC, CT, HTS. This activity will be closely supervised by the expert. It would be much more appropiate if there is a research collaboration between the expert's laboratory and the Center in Thailand. Emphasis of the project will be on "Drug Discovery from Thai Natural Products"

3.5 Organizing workshops by the ICS-UNIDO network Center in Thailand for a series of training on high technologies and new techniques for the Southeast Asian region

4. Time Schedule

This program will cover about 4 years with the following time schedule

Activity/year	1	2	3	4
4.1 Expert Appointment	↔			
4.2 Research & Training Fellowships	←	———	———	——→
4.3 Equipment support	←	———	→	
4.4 ICS-UNIDO Network Center Establishment		←	———	——→
4.5 Organizing Workshops and Training			←	·····

5. Institutional Capabilities

Since 1991, the Faculty of Pharmaceutical Sciences, Chulalongkorn University in Bangkok has been a network of UNIDO as "Pharmaceutical Technology Service Centre". This widely known locally as "UNIDO Centre" has been very successful in raising the status of Thai pharmaceutical industry. The Centre is now in cooperation with the Thai Pharmaceutical Manufactering Association (TPMA) and the Thai FDA in order to achive the goal. Presently, the Centre has a wide range of equipment both originally supported by UNIDO and subsequently purchased additionally by the Centre. The Centre has experienced in organizing workshops and training for transfer of know-how and technologies to the private industry.

Because of its strong base, the UNIDO-pharmaceutical Technology Service Centre potentially be expanded to the activities of know-how transfer of CC/CT/MD technologies to the regional Southeast Asian Countries. In terms of human resource, the Faculty of Pharmaceutical Sciences, Chulalongkorn University has faculty member who are medicinal chemists, pharmacognosists. These staff can help the Centre to fulfil the objectives of regional ICS-UNIDO network center.