Final Report

for

TRF Senior Research Scholar Program

(Program for Promoting Collaborative Research Network)

Program: Directed Exploratory Research in Basic Synthetic Organic Chemistry and Bioactive Natural Products

Submitted to: The Thailand Research Fund

by

Professor Dr. Vichai Reutrakul

and Research Team

Covering Period

September 2003 to March 2007

Contract no. RTA4680015

Final Report

Period : September 2003 – March 2007

Program : Directed Exploratory Research in Basic Synthetic Organic Chemistry and Bioactive Natural Products (Program for Promoting Collaborative Research Network)

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The Thailand Research Fund

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1. Collaborative Network

The collaborative network has work has been set up and research groups that are in the research network are as shown on Scheme 1. The collaborative activities are multidisciplinary and can be summarized as follows.

1.1 Directed Exploratory Research in Basic Synthetic Organic Chemistry

The research activities have been be carried out in collaboration with Professor Manat Pohmakotr and Dr. Chutima Kuhakarn, Mahidol University, Bangkok. This involved co-supervision of research students, extensive research consultations, the share of equipments and supplies and the use of TRF fund. The scope of research activities covered new synthetic methodologies and the total synthesis of bioactive natural products.

1.2 Drug Discovery from Bioactive Natural Products: The Search for Lead Structures

The research is interdisciplinary involving biodiversity, chemistry, pharmacology and toxicology. The program has been directed toward uncovering the lead structures from plants which could be developed into agents for the following therapeutic indications: antitumor, anti-HIV, anti-inflammatory, antimicrobial and for cholangiocarcinoma tumors. The collaborative activities can be summarized as follows.

1. Biodiversity

The survey, collection and identification of plants have been carried out in collaboration with Dr. Thawatchai Santisuk and Mr. Narong Nanthasaen. Royal Forestry Department, Bangkok. Research fund has been utilized for these activities.

2. Chemistry

Extractions, isolation and structure elucidation of pure compounds from plants have been carried out in cooperation with:

1. Dr. Patoomratana Tuchinda

Department of Chemistry, Mahidol University, Bangkok

2. Professor Vatcharin Rukachaisirikul

Department of Chemistry, Prince of Songkhla University, Hadyai, Songkhla

3. Dr. Thongchai Kruahong

Department of Chemistry, Rajabhat University Suratthani, Suratthani

The collaboration involved co-supervision of students, extensive research consultations, the use of spectroscopic equipment, supplies and provision of research fund.

3. Bioassays

1. Cytotoxic Assays

Collaboration with Dr. Smaisukh Sophasan, Professor Pawinee Piyachaturawat and Dr. Surawat Jariyawat; Department of Physiology, Mahidol University, Bangkok, has been on the cytotoxic assays with P-388, KB, COL-1, BCA-1 and LU-1. Rat glioma cell line (ASK) has also been used in the assays for cytotoxic and antimitotic potentials. Assays with additional human cancer cell lines KB-V(+VLB), KB-V(-VLB), LNCap, ZR-75-1 and *in vivo* hollow fiber assay have been carried out in cooperation with Professor John M. Pezzuto, Purdue Unversity, U.S.A. Professor John Pezzuto has now moved to the University of Hawai at Hilo. Contact with this research group has been maintained. These facilities are utilized for confirmatory bioassays.

The research involved graduate students, extensive research consultations and research support.

2. Anti-HIV Assays

The anti-HIV assay using reverse transcriptase enzyme (HIV-1-RT) and constructed virus (MC 99) have been carried out by Professor Chalobon Yoosook, Department of Microbiology, Mahidol University, Bangkok.

Collaboration involved graduate students, extensive research consultations and research support.

3. Anti-inflammatory Assay (Neutrophils)

Anti-inflammatory assay using neutrophils has been carried out by Dr. Payong Wanikiat, Department of Pharmacology, Facullty of Science, Mahidol University. The research involved graduate students technical staff and research support

4. Anti-inflammatory Assay and Preliminary Toxicology

Anti-inflammatory assay using EPP-induced rat ear edema model as the main assay has been carried out by Dr. Ampai Panthong, Department of Pharmacology, Chiangmai University, Chiangmai. The collaboration involved graduate students, extensive research consultations and research support.

Preliminary toxicological studies have been carried out by Dr. Ampai Panthong, Department of Pharmacology, Chiangmai University, Chiangmai. The research involved graduate students, extensive research consultation and research support.

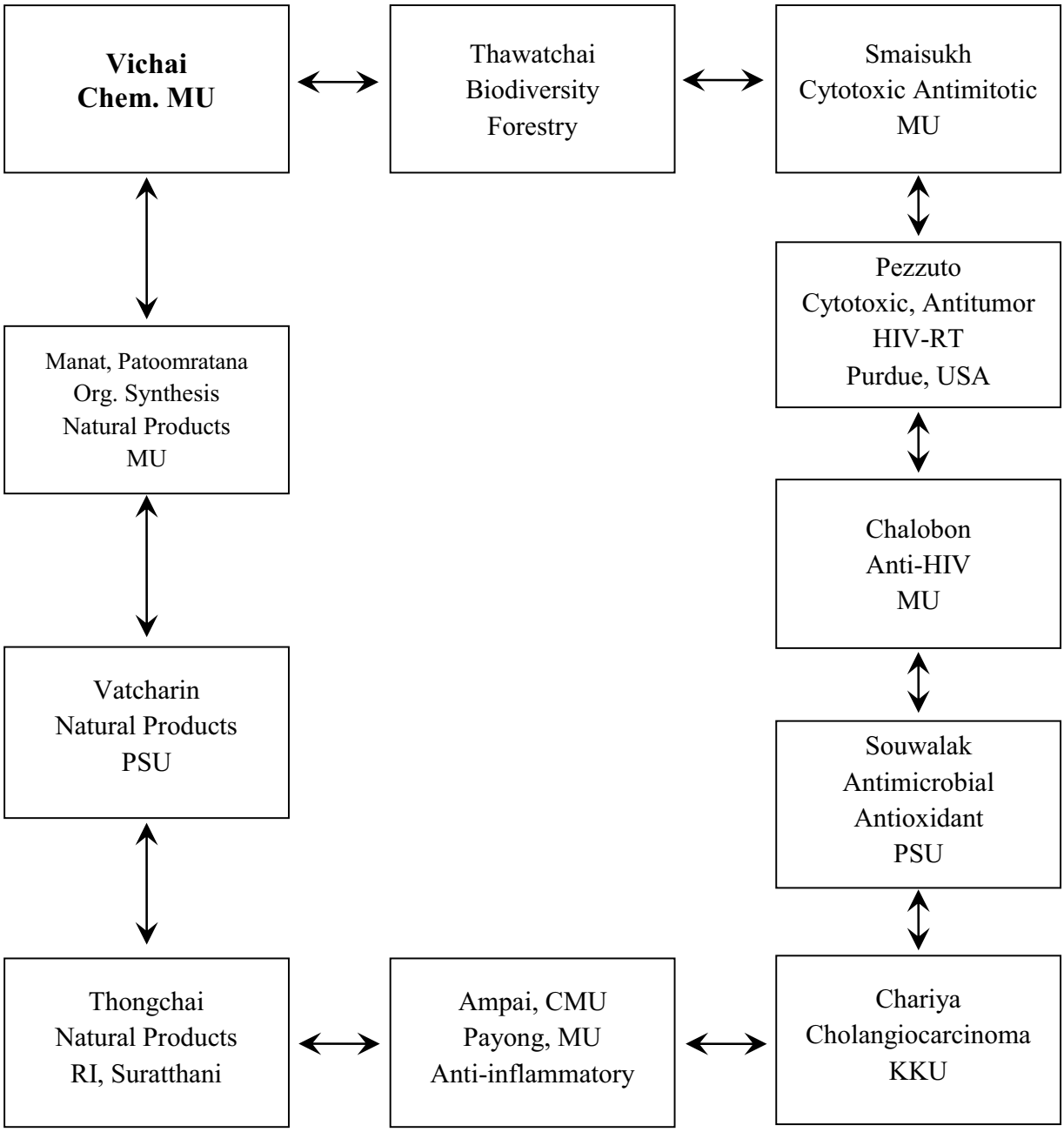
5. Antimicrobial Assay

A battery of antimicrobial assays has been set up by Dr. Sauwaluk Pongpaichit, Department of Microbiology, Faculty of Science, Prince of Songkhla University. The research involved the assay of extracts and pure compounds isolated from natural sources by graduate students and technical assistant.

6. Anti-cholangiocarcinoma Assay

A series of primary cholangiocarcinoma cancer cell lines has been utilized to assay for active extracts and pure compounds from natural sources. This type of cancer is prevalent in Northeastern Thailand and currently there is no effective drug to combat the disease. The facilities have been set up at Department of Microbiology, Faculty of Medicine, Khon Kaen University with Dr. Chariya Hahnvajanawong as the main investigator.

Scheme 1 Diagram of Collaborative Research Groups



MU = Mahidol University; PSU = Prince of Songkla University

KKU = Khon Kaen University CMU = Chiangmai Uniersity

RI = Rajabhat Institute, Suratthani

2. Acknowledgements

The research team wishes to thank The Thailand Research Fund for the generous financial support through The Senior Research Scholar Award for the period September 2003 to March 2007 (contract no. RTA4680015). The Principal Investigator (VR) wishes to express deep appreciation to all the investigators, students and technical staff of all the departments involved.

Finally, the research team wishes to thank: Departments of Chemistry, Physiology, Pharmacology and Microbiology; Faculty of Sciences, Mahidol University: Departments of Chemistry and Microbiology; Faculty of Sciences, Prince of Songkhla University: Department of Microbiology, Faculty of Medicine, Khon Kaen University: Department of Pharmacology, Faculty of Medicine, Chiangmai University: and finally, Rajabhat University, Suratthani: for the laboratory spaces and equipment for research.

3. Abstract

TRF Senior Research Scholar Program

(Program for Promoting Collaborative Research Network)

Project Code : **Contract no. RTA468005**

Program : **Directed Exploratory Research in Basic Synthetic Organic Chemistry and Bioactive Natural Products**

Investigators : **Vichai Reutrakul (PI),** Manat Pohmakotr, Chutima Kuhakarn, Patoomratana Tuchinda, Samaisukh Sophasan, Chalobon Yoosook and Payong Wanikiat (Mahidol University); Thawatchai Santisuk (Ministry of Natural Resources and Environment); and Souwalak Pongpaichit (Prince of Songkhla University); Chariya Hahnvajanawong (Khon Kaen University); Ampai Panthong (Chiangmai University); and Thongchai Kruahong (Rajabhat University, Suratthani).

E-mail (PI) : scvrt@mahidol.ac.th

Program Period : **September 2003 – March 2007**

Objectives :

The proposed TRF Senior Research Scholar Program has the following objectives.

1. Further fostering and strengthening the collaborative research network, among researchers in Thailand and abroad, which has been established during 1998-2002. New collaborators in the appropriate emerging related areas of research have been added.

2. Producing research scientists who will participate in the development of science and technology of the country.

3. Carrying out directed exploratory research in basic synthetic organic chemistry and bioactive natural products.

Methodology, Results and Discussions

New Synthetic Methodology and Total Synthesis

Exploratory research on *gem*-difluoromethylene building block led to the successful generation of difluorophenylsulfonylmethyl radical for the first time. Its chemistry demonstrated that this reactive species is equivalent to a *gem*-difluoromethylene radical. Attempt to generate a difluoromethyl carbanion from arythiobromodifluoromethanes by metal halogen exchange reaction led to the discovery of a novel α-arylsulfanyl-α-fluoro carbenoids. The species has been proven to undergo dimerization and addition of Grinard reagent. The difluoromethyl carbanion has been successful generated by the reaction of α,α-difluoro-α-phenylsulfanyl-α-trimethylsilylmethane with anhydrous tetra-*n*-butyl ammonium fluoride in tetrahydrofuran. The species can be trapped with carbonyl compounds leading to the synthesis *gem*-difluoroalkenes and *gem*-difluorinated α-hydroxesters and γ-butyrolactone. The results, vide supra, have been published in high impact factor journals. α,α-Difluorophenylsulfanyl carbocation has been successfully generated by the treatment of Lewis acids with bromodifluorophenylmethane. The chemistry of the species exhibited the synthetic equivalency of thioester cation and geminal carbonyl dication. The results will be submitted for a publication shortly. The overall results represented a major advanced in chemistry and the synthesis of *gem*-difluoro compounds.

Aspects of new synthetic methodology employing catalytic process have been explored. Samarium dienolated mediated stereoselective synthesis of anti-1,3-diol monoesters *via* aldol-Tischenko reaction has been demonstrated. A novel method involving direct catalytic asymmetric Mannich-type reaction *via* a dinuclear zinc catalyst for the synthesis of either *anti*- or *syn*-α-hydroxy-β-amino ketones has been investigated and the results have been published in the Journal of American Chemical Society (impact factor 8.58). Lanthanide triflates, in particular, ytterbium triflate are effective catalysts for the synthesis of (1-akyl-1-aryl) methyl phenyl sulfones from α-amidosulfones *via* the formation of N-acyliminium ions and for the efficient synthesis of 2,3-unsaturated glucopyranosides from glycals. Mild and selective oxidation of secondary alcohols has been accomplished using IBX/nBu$_4$N/CH_2Cl_2:H_2O system. The compounds synthesized by these high interesting new methodologies are very valuable intermediates for further synthesis of useful and bioactive compounds.

The program has also ventured into nanochemistry. A new technology employing spinning dish processing has been introduced. The production of nanosized β-carotene particles has been successful

and the results have been published in the Journal of American Chemical Society (impact factor 8.58).

The chemistry of the vicinal dianions derived from succinate esters has been extensively explored. The dianions have been utilized in the synthesis of furan derivatives, α-butyrolactones, (±)-thuriferic acid ethyl ester and its analogues, (±)-picropodophyllone and (±)-gmelinol. These naturally occurring compounds have been reported to exhibited wide ranging biological activities. (bis)Trimethyl silyloxy derivative of diethyl succinate and 2,5-(bis)Trimethylsiloxyfuran have been applied to the synthesis of γ-lactams, crucial intermediates for the synthesis of many biologically important natural products. α-Sulfinyl carbanions underwent cyclization to 1-azabicyclo [m.n.o] alkenes and 5-alkylidene 2-cyclopentenones.

The investigations in the new synthetic methodology and total synthesis have resulted in 18 publications in high impact factors journals.

Drug Discovery from Bioactive Natural Products: The Search for Lead structures.

An interdisciplinary research program aiming at the discovery of lead structures from naturally occurring sources involving biodiversity, chemistry and biology was undertaken. The bioassays for cytotoxic, anti-HIV, anti-inflammatory, antimicrobial, anti-oxidant and for cholangiocarcinoma cancer have been established and have been utilized to evaluate extracts and pure compounds.

Bioactive compounds from selected plants with cytotoxic, anti-HIV-1 and anti-inflammatory activities from the Garcinia genus including: *Mammea harmandii* (cytotoxic coumarins), *Garcinia speciosa* (anti-HIV-1 protostane triberpenes), *Cratoxylum arborescens* (anti-HIV-1 xanthone and triterpenes), and *Garcinia hanburyi* (cytotoxic, anti-HIV-1 and anti-inflammatory caged xanthones and triterpenes) have been identified. The novel caged xanthones are of particular interest as leads structures for antitumor and anti-inflammatory agents. New cycloartanes with anti-HIV-1 activity have been isolated from *Gardenia thailandica* and *Gardenia tubifera*. These compounds represent a novel class of cycloartanes with such biological activity. Plants from Euphorbiacea family have provided complex lead structures with wide ranging biological activities. *Phyllanthus taxodiifolius* and *Phyllanthus acutissima* yielded cytotoxic and anti-HIV lignans and triterpenes. A novel cyclic peptide with apoptotic activity in Caspase-3 deficient cancer cells at nanomolar concentrations has been identified from *Mallotus spodocarpus*. The compound provides a novel lead structure for further development. Active extract and pure compounds have been identified from *Polyalthia crassa*, *Ventilago*

harmandiana, *Ochna integerrima*, *Berleria lupulina* and *Clinacanthus nutans*. These new findings adds considerable knowledge on the biodiversity of these endemic plants.

A range of products with the trade name of Plaitanoids^{TM} have been launched. This invovation originated from the research work, in part, under the support of TRF Senior Research Program on a Thai plant *Zingiber cussumunar*. A range of cosmetics and spar products are commercially available.

Suggestion/Further Implication/Implementation

The research on synthetic organic chemistry led to the discovery of fundamental properties of α-substituted fluoro-radical, -carbenoid, -carbanion and - carbocation. New synthetic methodologies have provided technology for the synthesis of intermediates for further use in the synthesis of useful chemicals. The methods using dianions chemistry allow the convenient entry to bioactive natural products. These discoveries will provide synthetic chemists with new and fundamental technology for the synthesis of new useful chemicals and pharmaceutical intermediates. Program on the discovery of lead structures from natural sources have provided novel bioactive natural products with anti-tumor, anti-HIV-1 and anti-inflammatory activities. Caged xanthones would be a good candidate for further development as pharmaceutical products.

Keywords : Synthesis, bioactive natural products, anti-tumor, anti-HIV-1, anti-inflammatory

4. Executive Summary

The program: directed exploratory research in basic synthetic organic chemistry and bioactive natural products consists of two major sections i.e. exploratory research in new synthetic methodology, total synthesis; and discovery of bioactive lead structures from plants with anti-tumor, anti-HIV-1 and anti-inflammatory activities. Even though the funding of the program officially ended in March 2007, the research activities and outputs were extended until the early part of year 2009 as evidence from the publications. .

Directed exploratory research in basic organic chemistry

The investigation in new synthetic methodology and total synthesis cover the chemistry of *gem*-difluoromethylene compounds, total synthesis of natural products with dianion species and catalytic reaction involving samarium, zinc and lanthanides complexes.

Major advances have been achieved in the research aiming at the introduction of a *gem*-difluoromethylene moiety into organic molecules as a CF_2 "building block". Radical and carbanion species with *gem*-difluoromethylene group have been successfully generated from bromodifluorophenylmethane with a radial initiator and from α,α-difluoro-α-phenylsulfanyl-α-trimethylsilymethane with fluoride as a base, respectively. The introduction of CF_2 "building block" using both reactive species has been demonstrated. The bromodifluorophenylsulfanylmethane can serve as synthetic equivalent of *gem*-difluoromethylene diradical, whereas the α,α-difluoro α-phenylsulfanyl-α-trimethylsilylmethane is the synthetic equivalent of α,α-difluo-α-phenylsulfanylmethyl carbanion.

α-Arysulfanyl-α-fluoro carbenoids and α,α-difluorophenylsulfanyl carbocation have been generated from arylthiobromodifluoromethanes with Grignard reagent and bromodifluorophenylsulfanylmethane with Lewis acids respectively. The reaction of the carbenoids with elactrophiles and their dimerization have been demonstrated. The carbocation derived from the initially form α,α-difluorophenylsulfanylmethyl carbocation undergoes Friedel-Crafts type acylation with activated aromatic compounds yielding thioesters or/and benzophenones. Synthetic equivalencies of bromodifluorophenylsulfanylmethane as thioester cation and germinal carbonyl dication have been demonstrated.

Novel new synthetic catalytic processes have been uncovered. Samarium dienolate, generated from regioselective cleavage of a phenylsulfonyl activated cyclopropyl ketone with samarium (II)

iodide, underwent aldol-Tischenko reaction with both aliphatic and aromatic aldehydes to give *anti*-1,3-diol monoesters, an important synthon in many bioactive natural products. A direct catalytic asymmetric Mannich-type reaction via a dinuclear zinc catalyst is amendable for the synthesis of either *anti*-or syn-α-hydroxy-β-amino ketones, valuable synthetic intermediates for the synthesis of drugs and biologically active compounds. Lanthanide triflates have been employed catalytically for the syntheses of alkyl 2,3-unsaturated glucopyranosides and (1-alkyl-1-aryl)-methyl phenyl sulfones, classes of compounds which are very useful for the synthesis of bioactive natural products, *via* oxonium and N-acyliminium ions intermediates. Selective oxidation of secondary alcohols has been achieved by IBX/nBu_4NBr/CH_2Cl_2-H_2O system.

A new area of chemical nanotechnology research has been initiated. The success has been achieved in the production of nanosized β-carotene particles using spinning disk processing. The results are potentially applicable in the areas of pharmaceuticals and drug delivery.

The synthetic method utilizing vicinal dianions derived from diethyl succinated has been applied to the syntheses of furan derivatives, γ-butyrolactones, (±)-thuriferic acid ethyl ester and its analogues, (±)-picropodophyllone and (±)-gmelinol. These natural occurring compounds have been reported to exhibit wide ranging biological activities. The synthetic routes developed pave way for acquiring more of these compounds for further biological evaluations. (bis)Trimethylsilyloxy derivative of diethyl succinate and 2,5-(bis)trimethylsilyloxy furan have been employed for the synthesis of γ-lactones, crucial intermediates for the synthesis of biologically important natural products. The cyclization of α-sulfinyl carbanion derived from iminolactam gives rises to 1-azacbicyclo [m.n.o] alkenes framework which is an important structural assembly in a number of heterocyclic systems, especially alkaloids natural products possessing biological activities such as pyrolidine, indolizidine and quinolizidine alkaloids. The intramolecular acylation of α-sulfinyl carbanions with masked α,β-ansaturated esters provides intermediates which are precusors of 5-alkylidene-2-cyclopentenones , commonly encountered structural unit in a number of prostaglandins and various bioactive natural products.

The research results on the directed exploratory research in basic organic chemistry have been highly successful. A total of 18 publications in high impact factor journals have been achieved.

Directed exploratory research in bioactive natural products

The scope of the program falls within the drug discovery area with the focus on the discovery of lead structures from plants. The program is interdisciplinary involving biodiversity, chemistry and biology. The biological parts consist of a battery of bioassays for extracts, semi-purified fractions and pure compounds. Mechanistic and toxicological studies facilities and expertises are also available within the collaborative network. The bioassays cover: cytotoxic assays with cultured mammalian cell lines; anti-HIV-1 assays using reverse transcriptase enzyme (HIV-1-RT) and constructed virus (MC99); anti-inflammatory with EPP-induced rat ear edema and neutrophils activities; preliminary toxicology both with bacterial mutation and whole animal experiments; antimicrobial assay involving bacteria, yeasts and filamentous fungus; and cholangiocarcinoma assay using cultured primary cell lines established patient's cancer cell. These bioassays are valuable resources and vital to the development of lead structures. Plants selected for investigations are based on the results of screening assay, *vide supra*, of the extracts of plants collected from tropical forests. The plant collections were based on; ethnobotanical, information from data bases worldwide, long experience and information accumulated in our research over the past ten years. Special attention was given to rare and endemic plants. The structures of pure compounds were elucidated with modern spectroscopy, in particular, one and two dimentional NMR, LC-MS-MS and single x-ray diffraction analysis. All pure compounds were bioassayed for the biological activities. A total of 14 species of plants have been investigated in details. Cytotoxic caumarins were isolated *Mammea harmandii* (Guttiferae), Novel caged xanthones with cytotoxic, anti-HIV-1, anti-inflammatory and anticholangiocarcinoma were isolated from *Garcinia hanburyi* (Guttiferae). These compounds are good lead structures with potential for further pharmaceutical development. Triterpenes with anti-HIV-1 and anti-inflammatory activities were isolated from *Garcinia hanburyi*, *Garcinia speciosa* and *Cratoxylum arborescens* (all from Guttiferae). New cycloartanes with cytotoxic and anti-HIV-1 activities were isolated from *Gardenia thailandica* and *Gardenia tubifera* (both from Rubiaceae). The these type biological activities of cycloartanes have been demonstrated for the first time by our research group. Cytotoxic and anti-HIV-1 lignans were isolated from *Phyllanthus taxodiifolius* and *Phyllanthus acutissima* (both from Euphorbiaceae). Another Euphorbiaceae plant, *Mallotous spodocarpus*, yielded a novel cyclic peptide, with seven amino acids, with cytotoxic and anti-HIV activities at nanomolar concentrations. Mechanistic studies indicated that the peptide exerts strong anticancer activity *via* stimulation of multiple apoptotic path ways in caspase-3 deficient cancer cells. New styryl-lactones with cytotoxic activities were isolated from *Polyalthia crassa* (Annonaceae). A novel pyranonaphthoquinone with anti-HIV-1 activity was isolated from

Ventilago harmandiana. Preliminary toxicological evaluation of the compound indicated that it was non-mutagenic and non-toxic. The anti-HIV-1 flavonoid glycosides were isolated from *Ochna integerrima*. The discovery added to the knowledge on the biological activity of this endemic plant. The inhibition of neutrphils function of the extracts of *Barleria lupulina* and *Clinacanthus nutans* extracts (both from Acanthaceae) was demonstrated.

Continuous work on *Zingiber cassumnar* (Zingiberaceae) led to the development of a range of cosmetics products. The products with the brand name Plaitanoids^{TM}, which is now on the market. 18 publications in international journals with high impact factor have been achieved for the drug discovery program.

A total of 76 persons has been involved in the collaborative program, these include: 14 researchers including the principal investigator, 13 Ph.D. students (11 had graduated of which 7 were funded by the Royal Golden Jubilee Ph.D. program), 27 M.Sc. students (all graduated), 22 technician, research assistants and research associates.

The PI was invited to give a plenary lecture in Indonesia, (November 2006), an invited lectures in USA (December 2004), invited lectures at the meeting of TRF Senior Scholars and young TRF Grantees (October 2005 and 2006).

This Senior Research Scholar Program was selected as "The Outstanding Research Program on the Studies of Bioactive Compounds from Thai Medicinal Plants" for 2004. The PI was awarded "The National Outstanding Researcher Award" for 2005, chemical and pharmaceutical sciences, by The National Research Council of Thailand.

The exchanges of students and faculty members have also taken places. Seven Ph.D. students spent a year each at Stanford University (2 students), University of California at Santa Cruz (2 students) the University of Western Australia (1 student) Uppsala University (1 student) and Purdue University (1 student). Two faculty members Professor Barry M. Trost, Stanford University (1 week) and Professor Rebecca Braslau, University of California at Santa Cruz (1 week); visited collaborative laboratories and gave seminars as part of the collaborative seminar program. Two Ph.D. students from Stanford University (Mr. Zachary Ball) and University of California at Santa Cruz (Mr. Aaron Nilsen) spent two months each doing research at Professor Vichai Reutrakul's laboratories. One M.Sc. student (Miss Therese Landolski) from University of Uppsala carried out collaborative research at the PI's laboratory for 3 months during 2004.

In summary, the achievement highlights of the "Directed Exploratory Research in Basic Synthetic Chemistry and Bioactive Natural Products" are 35 Publications in international journals; 76 researchers, technicians, research assistants and research associates involved in the program; produced. 11 and 26 Ph.D. and M.Sc. graduates, respectively; Seven exchanged Ph.D. students from Thailand and 3 foreign students carried out collaborative research at PI's laboratories; two world renowned chemists, from Stanford University and University of California at Santa Cruz, visited PI's and collaborative laboratories and gave a series of cutting edge seminars; the PI was awarded the National Outstanding Researcher Award for 2005 by the National Research Council of Thailand; the program was recognized as "the Outstanding Research Program on Studies Bioactive Compounds from Thai Medicinal Plants" for 2004; a range of products under the brand name "Plaitanoids^{TM}" was launched. The collaborative program has exceeded the goal set in the program. The research activities and academic culture created will have a long lasting impact to personnel involved in the program and to the collaborative laboratories.

5. Description of Research: Details of Research Untaken

5.1 Introduction

The proposed TRF Senior Research Scholar Program has the following objective.

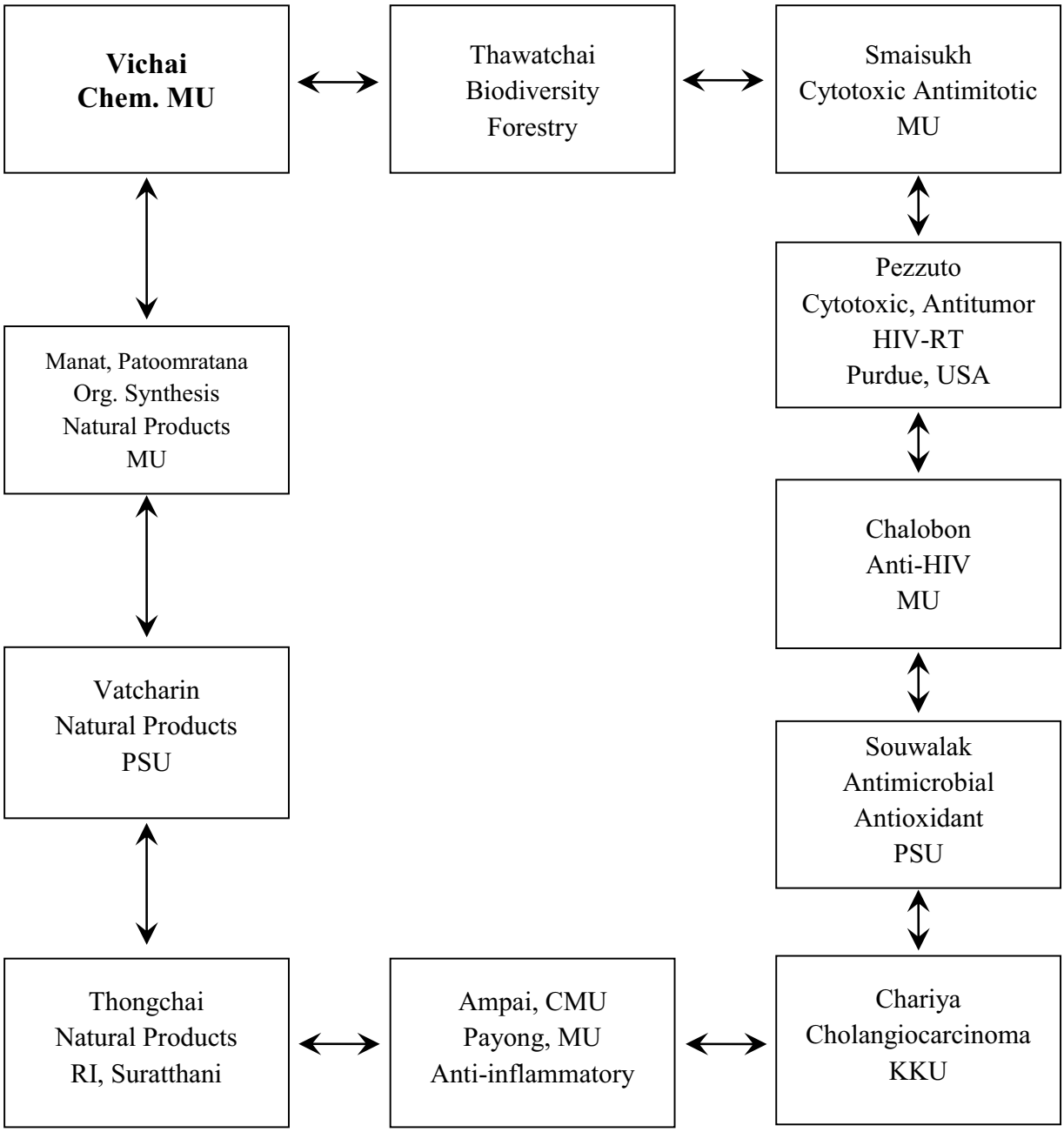
1. Further fostering and strengthening the collaborative research network, among researchers in Thailand and abroad, that has been established during 1998-2002. New collaborators in the emerging related areas of research will be considered when appropriate.

2. Producing research scientists who will participating in the development of science and technology of the country.3. Carrying out directed exploratory research in basic synthetic organic chemistry and bioactive natural products.

5.2 Collaborative Research Network

The collaborative research network as shown on Scheme 1 has been successfully established. Intensive collaborations among the three main groups i.e. biodiversity, chemistry and biodiversity led to high output of the program.

Scheme 1 Diagram of Collaborative Research Groups



MU = Mahidol University; PSU = Prince of Songkla University

KKU = Khon Kaen University CMU = Chiangmai Uniersity

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The highlight of the program is carry out high quality directed basic research couples with the high quality human resource development. The effort has met the expectation as indicated by the outputs, *vide infra*.

5.3 Directed Exploratory Research in Basic Organic Chemistry

The main theme of this section of the program is the development of new synthetic methodology for the synthesis of useful chemicals and the total synthesis of bioactive natural products. The results will provide the basic knowledge on new and improved methodology for the synthesis of useful chemicals and pharmaceuticals intermediates. The total of bioactive compounds will pave way for a systematic approach to drug development and acquire expertise in organic synthesis technology.

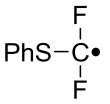
5.3.1 The systhesis of *gem*-difluoromethylene Compounds

The *gem* difluoromethylen Building Block

The investigation covered the chemistry and the synthetic applications of novel *gem*-difluoromethylene compounds **1** and **2**. The reactive intermediates; radical **3**, carbenoids **4**,

1

2



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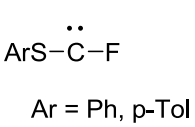

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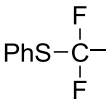

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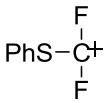

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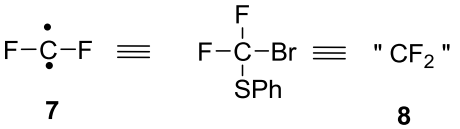
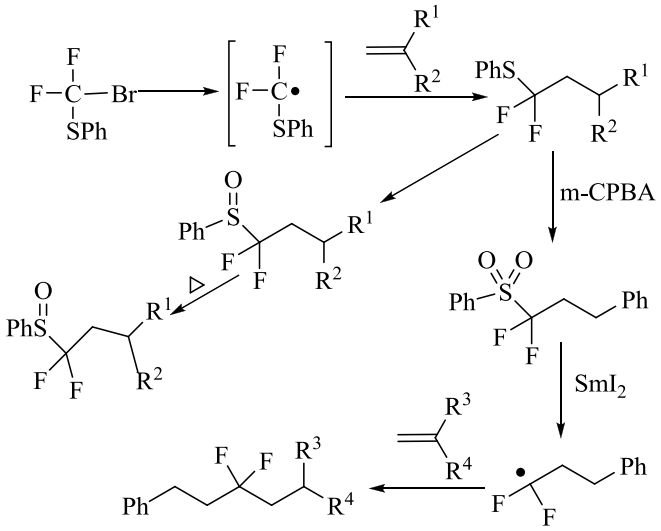


7 **8**

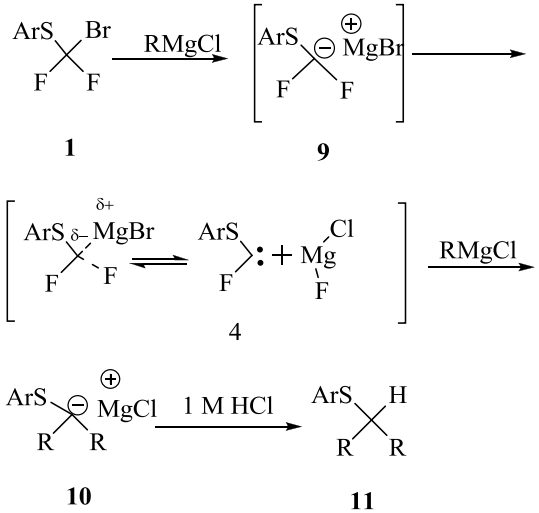
carbanion **5** and carbocation **6** have been successfully generated. The radical 3 reacted with olefins to give *gem*-difluoromethylene compounds. Further manipulation of these synthetic intermediates led to the convenient synthesis of *gem*-difluoroalkenes and products containing a midchain CF_2 group with manipulatable functionality. This work, demonstrated for the first time, the synthetic potential of compound 1 as a *gem*-difluoromethylene (CF_2, **8**) building block through the reaction of the radical 2 and as a synthetic equivalent of a-*gem*-difluoromethylene radical 7. The results are summarized in Scheme 2 and the work has been published in the **Journal of Organic Chemistry 2004, 69, 6913-6915**.

Scheme 2



The Grignard reagent **9**, generated from the bromine-magnesium exchange reaction of arylthiobromodifluoromethanes **1** with Grignard reagent**s** e.g. i-PrMgCl) proved to be unstable and decomposed to the carbene **4** which further reacted with with the Grinard reagents to give the carbaion 10.

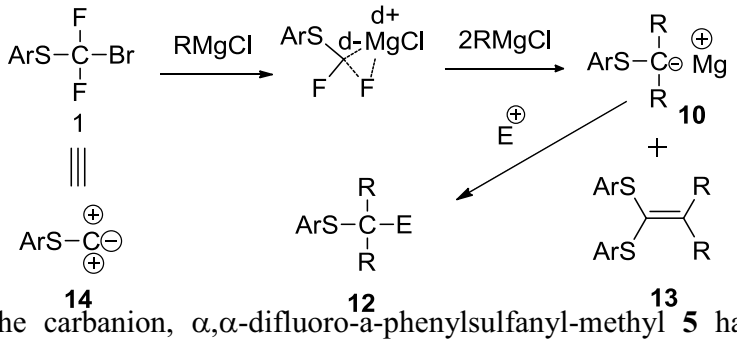
Scheme 3



1 **9** 4 **10** **11**

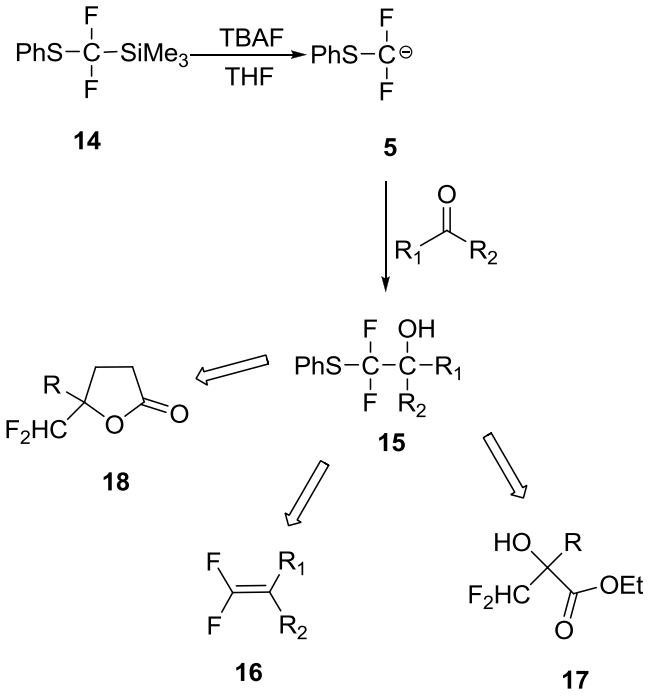
Compound **10** gave the sulfide **11** on work up. Trapping compound **10** with electrophiles gave alkyl aryl sulfides **12** and ketonedithioacetals **13**. The results of this novel discovery are summarized in Scheme 4. This novel discovery has been published in **Organic Letters 2004, 6,4547-4550**. Arylthiomethanes has been demonstrated for the first time to be equivalent to multipole synthons **14**.

Scheme 4



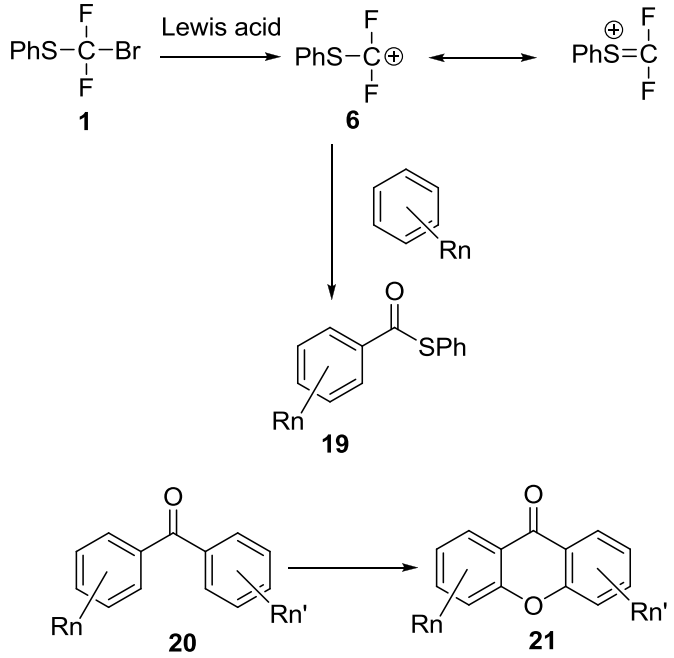
The carbanion, α,α-difluoro-a-phenylsulfanyl-methyl **5** had been successfully generated by the reaction of α,α-difluoro-α-phenylsulfanyl-α-trimethylsilylmethane **14** with tetra-n-butyl-ammonium fluoride (TBAF) in THF. Upon trapping the carbanion **5** with carbonyl compounds led to the corresponding adducts **15** which could be transformed into *gem*-difluoroalkenes **16**, *gem*-difluoromethylated-α-hydroxyesters **17** and γ-butyrolactones **18**, Scheme 5. The work was published in **Tetrahedron 2006, 62, 5973-5985** and **Tetrahedron 2007, 63, 9429-9436**.

Scheme 5



The α,α-difluorophenylsulfanylmethyl carbocation **6** has been generated from the precusor **1** with Lewis acids e.g. $AlCl_3$ and $SnCl_4$. The carbocation underwent Friedel Crafts type acylation with activated aromatic compounds yielding thioesters **19** or/and benzophenones **20**. The methodology had been applied to the synthesis of naturally occurring xanthone derivatives **21**, Scheme 6. The bromodifluorophenylsulfanylmethane **1** (Ar = Ph) had been demonstrated as the synthetic equivalent of thioester cation and germinal carbonyl dication. The results were summarized in a manuscript and will be submitted for a publication shortly.

Scheme 6

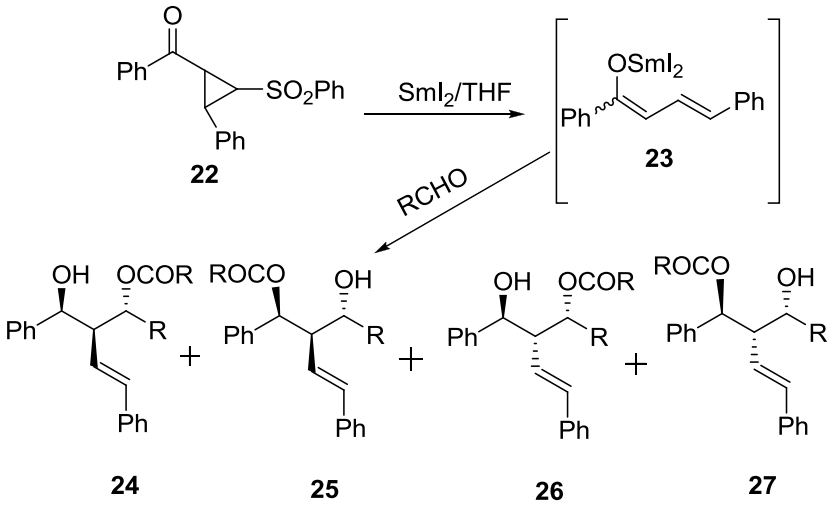


5.3.2 New Synthetic Methodology and Catalytic Reactions.

Aldol-Tischenko Reaction

The reaction of an (*E*)-samarium dienolate **23**, generated by the regioselective cleavage of a phenylsulfonyl activated cyclopropyl ketones **22** with samarium (II) iodide, with aliphatic and aromatic aldehydes give the 2-substituted anti-1,3-diol monoesters **24** to **27**, stereosectively, in good to excellent yields. The 1,3-diols moiety is the structural units found in many bioactive polyketides, macrolides and coalescing agents in paint industry. The results represent the first report of a dienolate in the aldol-Tishchenko reaction and also provide an optically active polyol with (*R*)-glyceraldehyde. The research, Scheme 7, has been published in **Tetrahedron Letters 2006, 47, 4753-4757**.

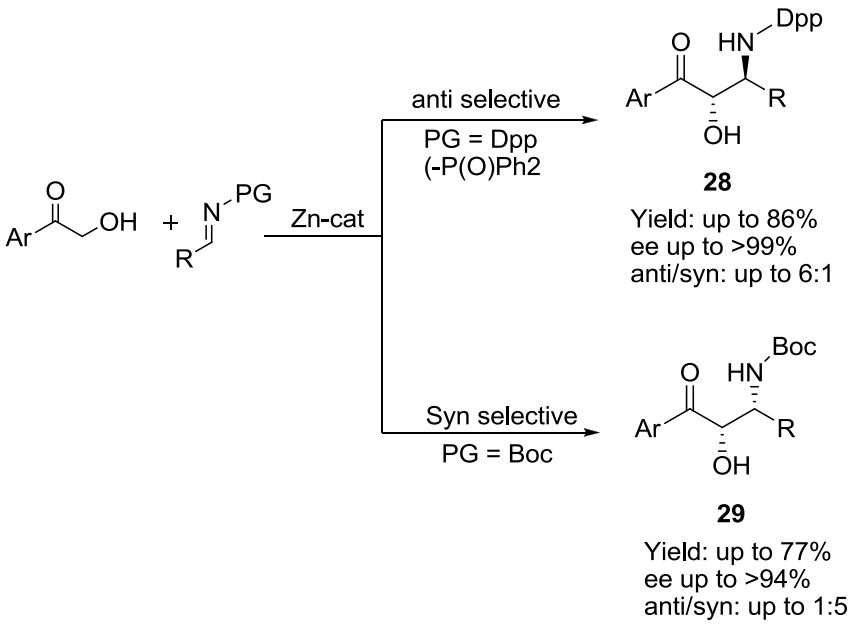
Scheme 7



Catalytic Asymmetric Mannich-type Reaction

The work on catalytic reaction led to a major success on the development of the direct catalytic asymmetric Mannich-type reaction *via* a dinuclear zinc catalyst for the synthesis of either *anti*- or *syn*-α-hydroxy-β-aminoketones. The work represents the first example of utilizing this reaction for the synthesis of *anti* **28** and *syn* **29** with excellent enantio selectivity. The results have been summarized , Scheme 7, and published in the **Journal of American Chemical Society 2006, 128, 2778-2779**.

Scheme 8



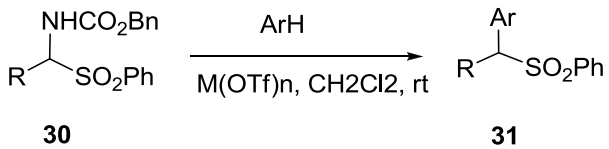
PG = Protecting group ; DPP = Diphenylphosphinoyl

Boc = tert - Butoxycarbonyl

Catalysis with Lanthanide Triflates

Ytterbium triflates catalyzed the generation of N-acyliminium ions from α-amidosulfones. The ions could be trapped with aromatic compounds to give (1-alkyl-1 aryl) methyl phenyl sulfones **31** in good yields. The synthesized intermediates are useful for transforming into substituted methane compounds. The transformations were summarized in Scheme 9 and has been published in **Tetrahedron Letters 2007, 48, 2467-2470**.

Scheme 9



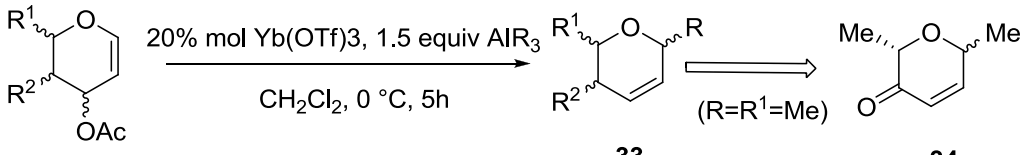
30 **31**

40-84%

R = allkyl, aryl
ArH = electron rich aromatics and heteroaromatics

The reaction of trialkylaluminum with glycals **32** in the presence of a catalytic amount of Ytterbium triflate led to the corresponding alkyl-2,3-unsaturated glycosides **33** in good to excellent yields. The reaction worked efficiently at zero degree celsius. The results represented a very mild method for the synthesis of glycosides which are important intermediates for the synthesis of biologically important natural products with glycal moiety. One of the glycal synthesized was converted to the enone **34** as an intermediate for the synthesis of bioactive pyranonaphthoquinones. The work, as summarized in Scheme 10, has been published in **Tetrahedron Letters 2009, 50, 6233-6235**.

Scheme 10



32 **33** **34**

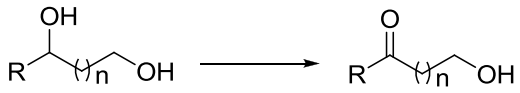
R = CH_3 and CH_2CH_3

R1 = H, CH_3, CH_2OAc, $CH_2OSi(Me)_2Bu^t$

R2 = Ac, $Si(Me)_2But$

A new method for selective oxidation of secondary alcohols using IBX/*n*-Bu_4NBr/CH_2Cl_2-H_2O system has been developed. The procedure could oxidize secondary alcohol selectively in the presence of primary alcohol. The work has been published in **Tetrahedron 2005, 61, 8995-9000**.

Scheme 11



R = Alkyl or Aryl

Chemical Nanotechnology

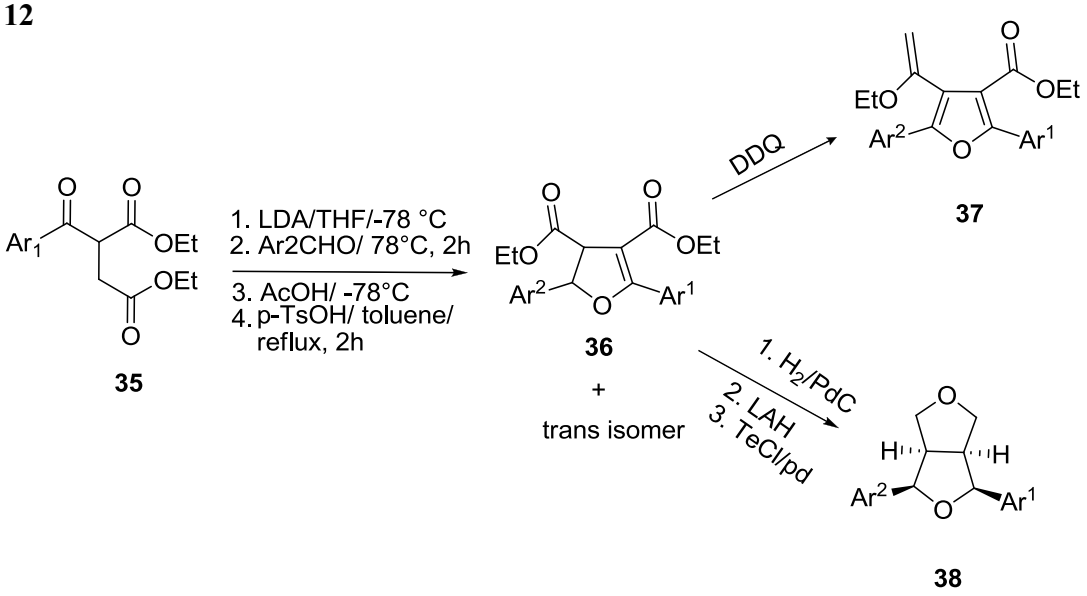
Conversion of low bioavailability of many biological active and pharmaceutical compounds into nanoparticles is one of the frontier research in solving the delivery problems of these molecules to the target sites. Exploratory research on production of nanosized β-carotene particles using spinning disk process technology with sulfonato-calix[4,5,6,8] arenes and α,β-cyclodextrins. The mean particle sizes for the calixenes are 42, 56 nm and 71.4 and nm, respectively, for each sulfonato-calix [5,6 and 4,8] arene, whereas the cyclodextrins form nanoparticles with a mean diameter of 71 and 68.5 nm, respectively. The results of this cutting edge research have been published in **The Journal of American Chemical Society 2006, 128, 13847-13853**.

Vicinal Dianions

The methodology involving the vicinal dianions of succinate derivatives has been developed as a four-carbon building blocks in organic synthesis.

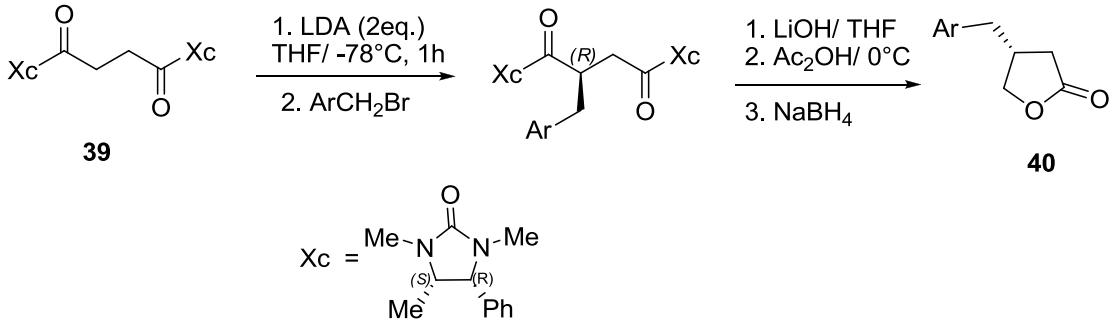
The preparation of functionalized-2,3-dihydrofurans **36**, furan **37**, and diaxial 2,4-diaryl-3,7-dioxabicyclo [3.3.0] octanes **38** has been achieved with vicinal dianions of diethyl α-aroylsuccinates **35** as shown in Scheme 12. The results have been published in **Tetrahedron Letters 2003, 44, 7937-7940**.

Scheme 12



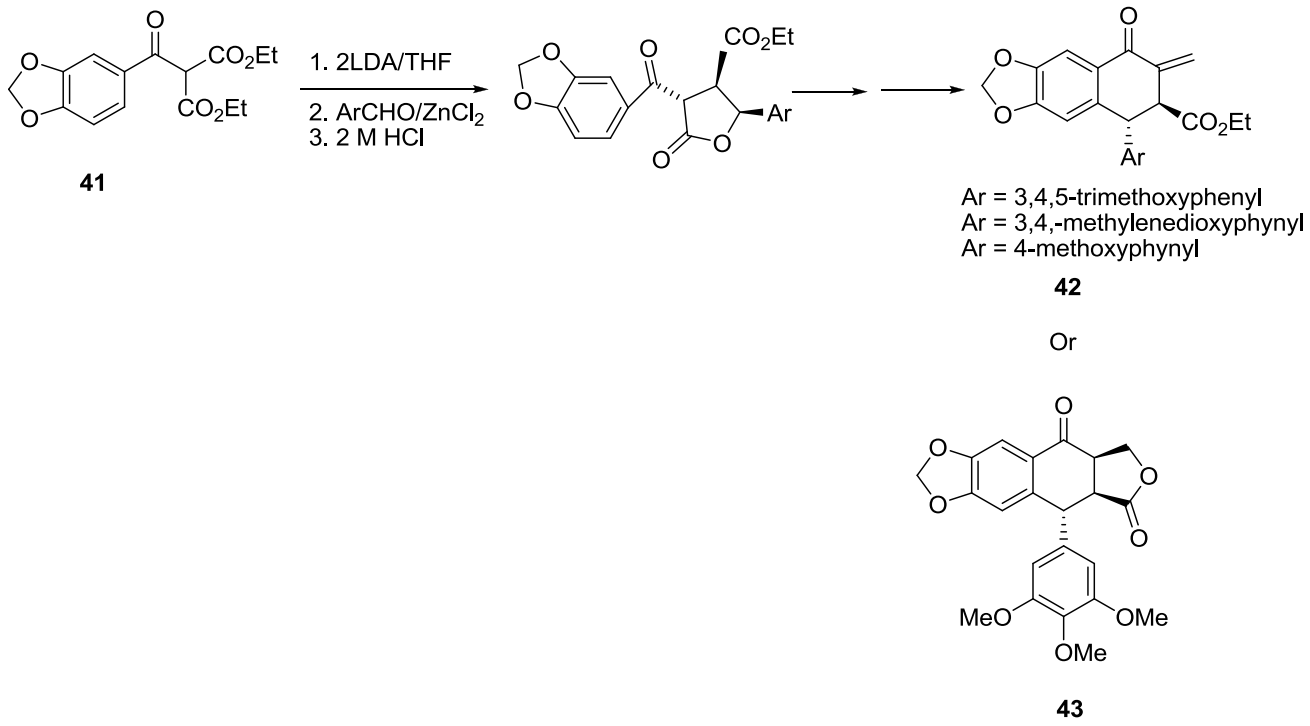
Chiral (R)-β-arylmethyl-γ-butyrolactones **40** have been synthesized by a highly diastereoselective alkylation of vicinal dianions of chiral succinic acid derivatives **39** as shown in Scheme 13. The work has been published in **Tetrahedron Letters 2004, 45, 4315-4318**.

Scheme 13



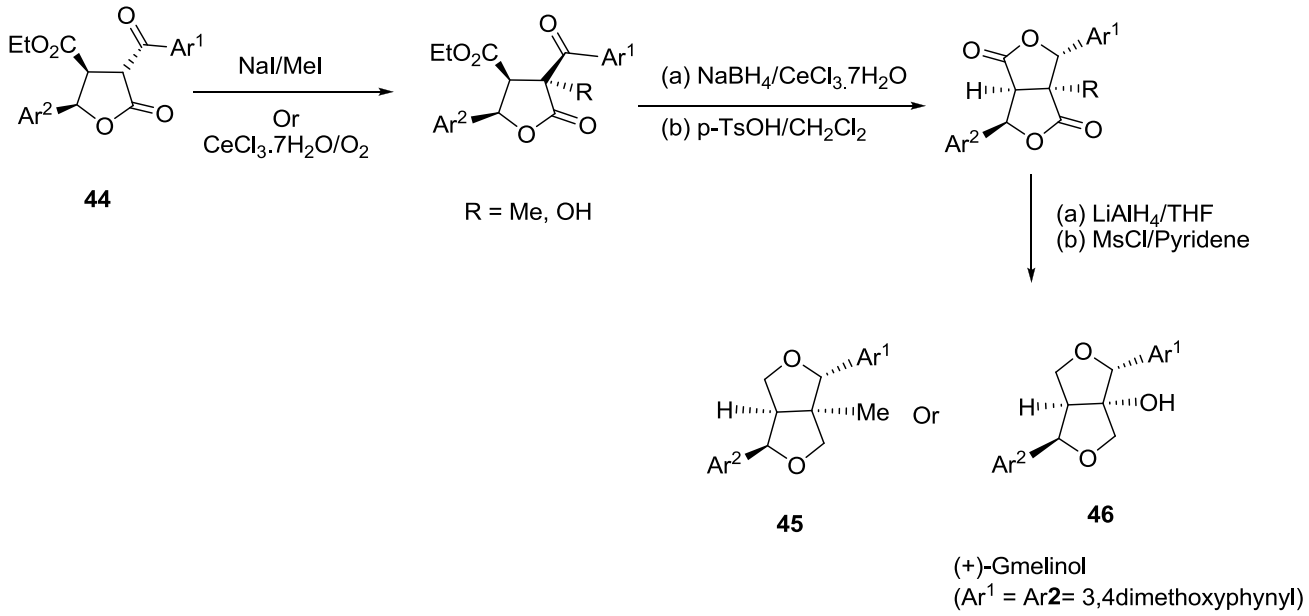
The α-aroylsuccinate esters **41** as the vicinal dianions have been utilized for the synthesis of natural products (±)-thuriferic acid ester, its analogues, **42** as well as (±)-picropodophyllone **43**, Scheme 14. These compounds have wide ranging biological activities including antineoplastic activity. The results have been published in **Tetrahedron 2005, 61, 5311-5321**.

Scheme 14



A general strategy for steroselective synthesis of 1-substituted *exo*, *endo*-2.6-diaryl-3,7-dioxabicyclo[3.3.0] octanes **45** including (±)-gmelinol **46** from (2,3-*trans*)-(4,5-*cis*)-α-aroylparaconic esters **44**, which are readily obtained from the reaction of vicinal dianions derived from α-aroylsuccinic esters with aromatic aldehydes has been developed. The synthetic sequence involved α-methylation or α-hydroxylation, reduction, bislactonization, and reduction followed by furofuran formation, Scheme 15. The work has been published in the **Journal of Organic Chemistry 2006, 71, 386-389**.

Scheme 15



44

R = Me, OH

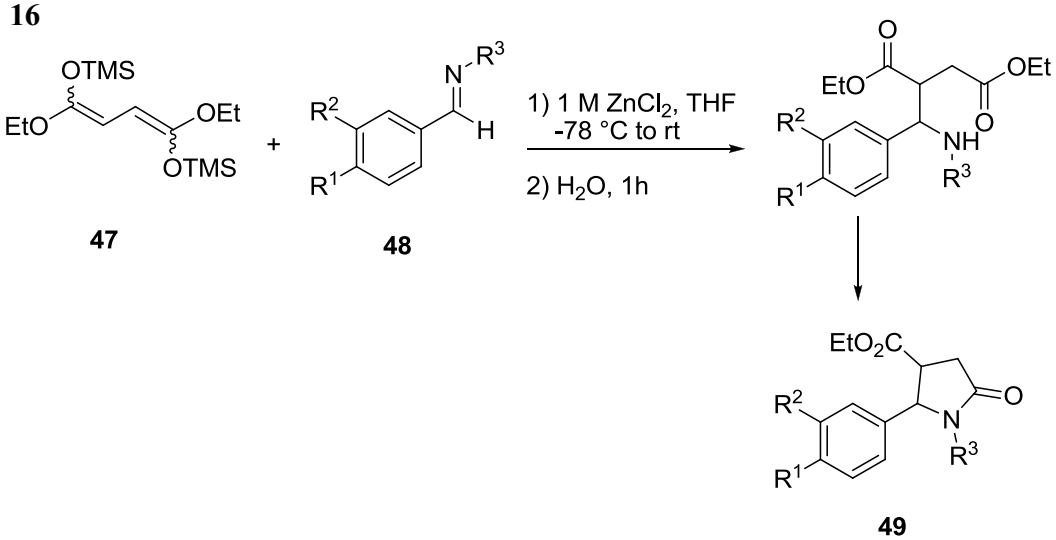
45 **46**

(+)-Gmelinol

(Ar^1 = Ar**2**= 3,4dimethoxyphynyl)

A four-carbon building block (bis)trimethylsilyloxy derivative **47** of diethyl succinate vicinal dianion reacted with imines **48** in the presence of zinc chloride *via* imino Mukaiyama-aldol type reaction to give β-carboethoxy-γ-lactams **49**, important subunit widely found in many classes of nitrogen heterocycles, Scheme 16. The research results have been published in **Tetrahedron 2007, 63, 4328-4377**.

Scheme 16

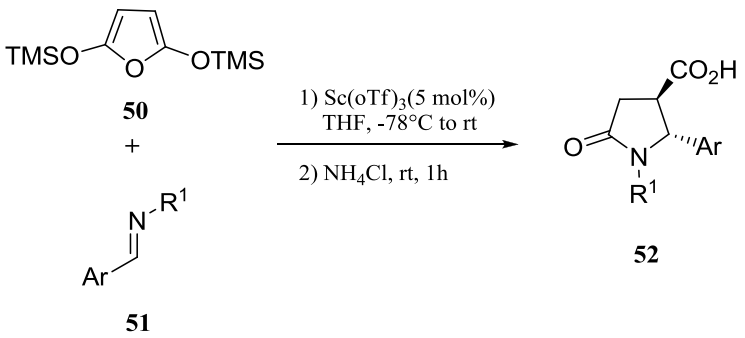


47 **48**

49

Mukaiyama-aldol type reaction of 2,5-bis(tri-methylsilyloxy) furan **50** with imines in the presence of catalytic amount scandium triflate yielded β-carboxy-γ-lactams **52** and their ethyl ester derivatives, Scheme 17, in high yield with high diastereomeric ratio. The γ-lactam unit is a prominent structural feature found in a number of biologically active natural products. The results were summarized in a publication in the **Journal of Organic Chemistry 2007, 72, 5016-5019**.

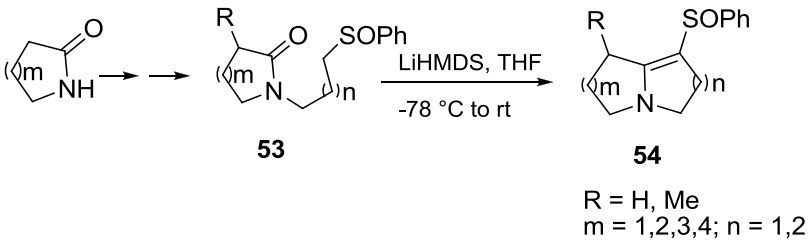
Scheme 17



α-Sulfinyl Carbanions

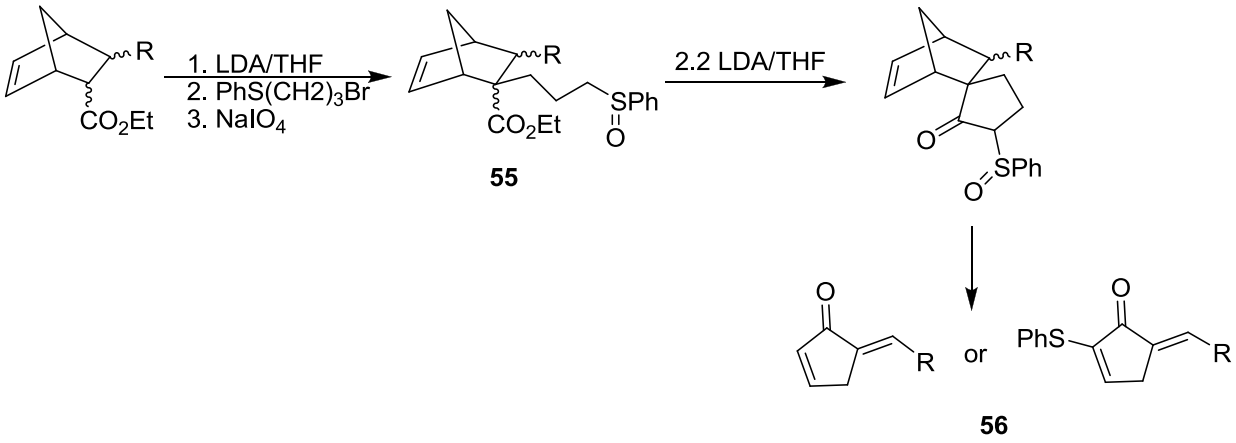
A general synthetic route based on the cyclization of α-sulfinyl carbanions derived from the corresponding sulfinyl lactams **53** has been developed for the synthesis of 1-azabicyclo [m.n.o] alkenes **54**, Scheme 18, which are important framework in a number of heterocyclic systems, especially alkaloid natural products. These included biologically active pyrolidine, indolizidine and quinolizidine alkaloids, and (-)-tuberostemonine. The summary of research has been published in **Organic Biomolecular Chemistry 2003, 1, 3495-3497**.

Scheme 18



Intramolecular acylation of α-sulfinyl carbanions with masked α,β-unsaturated esters **55** has been developed as a method for the synthesis of 5-alkylidene-2-cyclopentenones **56**, Scheme 19, which are structural unit found in a member of prostaglandins and various bioactive natural products. The results have been published in **Tetrahedron 2007, 63, 1806-1820**.

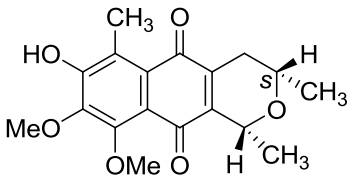
Scheme 19



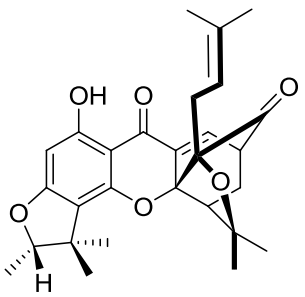
55 **56**

5.3.4 Research Work in Progress

In addition to the directed exploratory research in basic synthetic organic chemistry described in 5.3.1 to 5.3.3, the studies toward the total synthesis of biologically active pyranonaphthoquinone **57** and Sootepenseone **58** are being pursued.



57

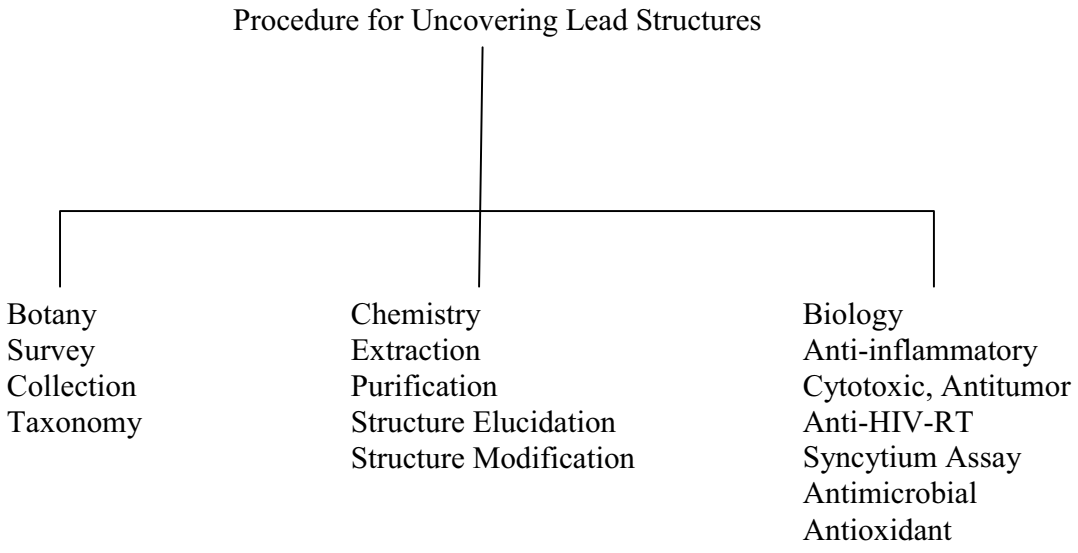


58 Sootepenseone

5.4 Directed Exploratory Research in Bioactive Natural Products: Drug Discovery from Bioactive Natural Products: The Search for Lead Structures

The program is directed toward uncovering the lead structures from plants which may be developed into agents for the following therapeutic indications: antitumor, anti-HIV, anti-inflammatory, antimicrobial and antioxidant activities. The research is interdisciplinary involving botany, chemistry, pharmacology and toxicology, Scheme 20.

Scheme 20



5.4.1 Botany: Survey, Collection and Taxonomy

The survey of biodiversity of Thai plants was carried out in collaboration with Forest Herbarium, Ministry of Natural Resources and Environment. Field trips were organized for the purpose of surveying and collecting plants for biological screening, covering various parts of Thailand which possesses different types of tropical forests. These include: hill evergreen and dry dipterocarp forests in the north; rain forest in central part of the country, dry evergreen and rain forests in the northeast; rain forests in the southern and the eastern parts. Plants were carefully selected based on information from databases worldwide, new plant species in specific genera that have been known to contain bioactive compounds, ethnomedical information and plants that are rare and endemic to Thailand. Experiences accumulated by the research team have been very valuable in conducting the field trips. Approximately 1 kg of each plant part was collected for initial extraction and biological screening. Three voucher specimens of each plant were collected and later on deposited at the Forest

Herbarium for future references,confirming the identification and assigning a BKF number. All specimens collected were systematically numbered which are used as the reference number for all research activities related to the plant. The taxonomic research aspects are an important component of the project. The taxonomic identification of plant is crucial for the research in determining the definite identity of the plant. Work on plant identification is divided into 3 main stages. The first stage is the preliminary identification during the field trip. The second stage is the confirmation of the identification at the Herbarium. The last stage of work is for those plants that are unknown or definite identification cannot be confirmed. This problem is a truly exciting taxonomic research. During the conduct of this project, several research problems of this type have been encountered.

5.4.2 Biological Bioassays

Bioassay results are one of the most important factors in deciding whether to proceed with the detailed investigation of a particular plant. Five main screening bioassays were employed i.e. cytotoxic, anti-HIV-1, anti-inflammatory, antimicrobial and antioxidant assays.

Cytotoxic Assay

Five mammalian cancer cell lines were employed i.e.

1. P-388: murine lymphocyte leukemia.
2. KB: human nasopharyngeal carcinoma
3. Col-2: human colon cancer
4. BCA-1: human breast cancer
5. Lu-1: human lung cancer

The cytotoxic and antimitotic assay using ASK: rat glioma cell line has also been established. Additional human cancer cell lines KB-V(+VLB), KB-V(-VLB), LNCaP,ZR-75-1 and *in vivo* hollow fiber assays are available in our collaborative laboratories (Professor John M. Pezzuto, University of Hawii, U.S.A.)

The cytotoxic assay for detecting anticholangiocarcinoma activity using the primary cancer cell lines from patients has also been established.

Anti-HIV-1 Assays

Two main assays employed are:

1. Reverse transcriptase enzyme (HIV-1-RT) assay.
2. Defective virus (MC 99) with transfected cell line (1A2) assay (syncytium assay). The HIV virus employed is similar to the wild type virus with the point mutation at ΔTat-Rev, rendering the non-infectious virus. The assay can be performed in a normal BSL-2 laboratory. Our previous assay results substantiated that the extracts tested exhibited similar activity toward the MC99 and wild type HIV viruses.

Anti-inflammatory Assay

The ethyl phenylpropiolate (EPP)-induced ear edema model in rat was employed; Male rats weighing 40-60 g were used. Ear edema was induced by topical application of EPP at a dose 1 mg/20 µl per ear to the inner and outer surfaces of both ears by means of an automatic microliter pipet. Test drugs were applied topically in volumes of 20 µl just before the irritant. The control group received vehicle only. Before and at 15, 30, 60 and 120 min after edema induction, the thickness of each ear was measured by vernier calipers. The percent inhibition of the edema formation of test substances was calculated.

A cell-based model using neutrophils was also employed to detect anti-inflammatory of extracts and isolated compounds

Antimicrobial Assay

The assay covered bacteria, yeasts and filamentous fungi.

Antioxidant Assay

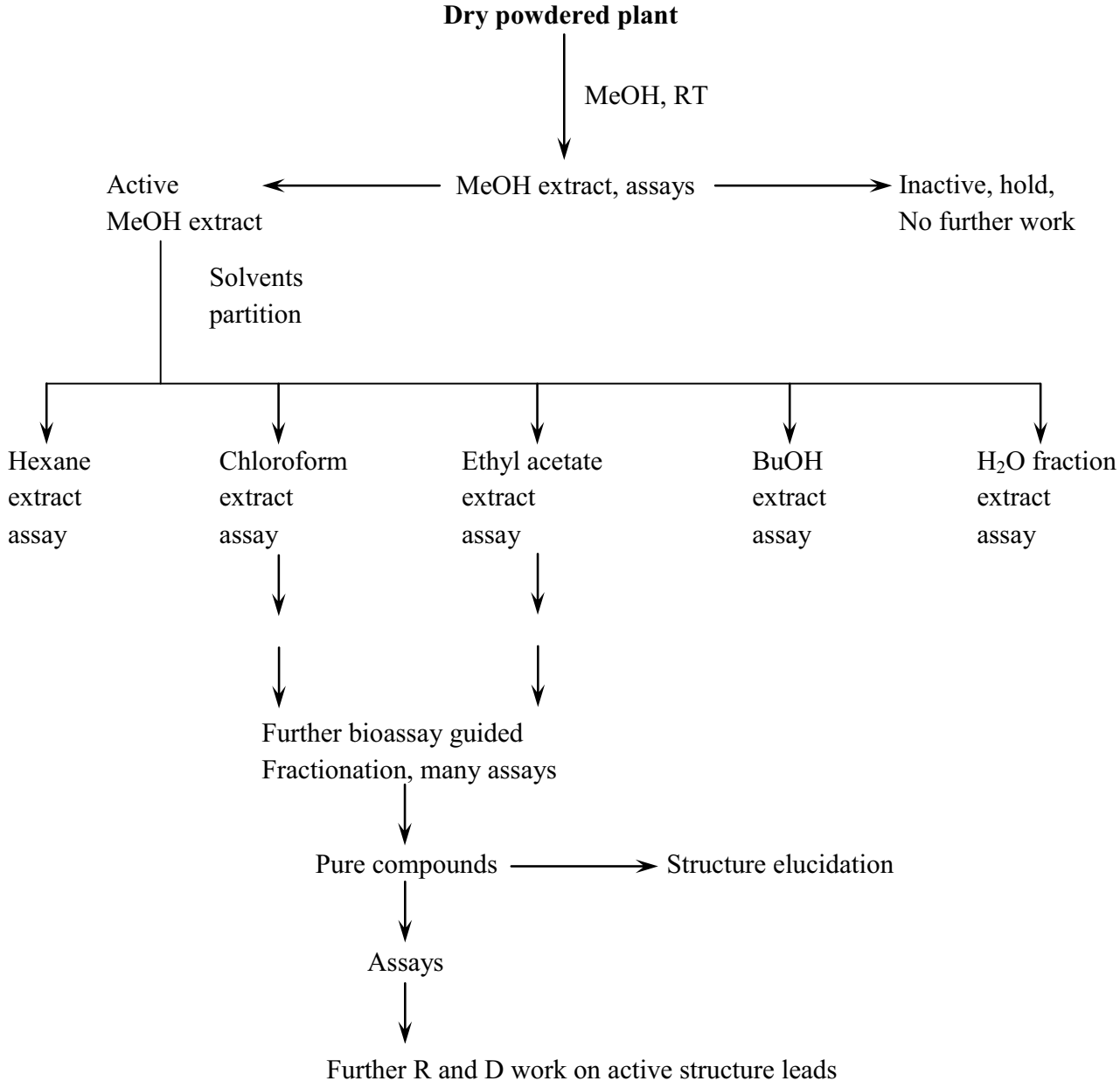
The tests used involved DPPH, hydroxyl and superoxide models. Preliminary toxicological studies using bacterial mutation and whole animal experiments have been established and employed for promising plant extracts and pure compounds.

5.4.3 Chemistry: Extraction, Purification, Structure Elucidation and Structure Modification

The primary extraction of the dry powdered plants was carried out using methanol as the solvent. The solvent was evaporated, freezed dry and submitted for bioassays. The overall bioassay guided fractionation of extracts for the identification of possible lead structures is as shown in Scheme 21.

Scheme 21

Overall research plan for the isolation of pure bioactive compounds



The extracts that were active in bioassay were subjected to bioassay guided fractionation. The initial process involved the solvent partition of the crude active methanol extract. Solvents of increasing polarity were employed i.e. hexane, ethyl acetate and butanol. The four fractions, including the remaining aqueous layer were evaporated to dryness and freezed dry for bioassays. The

active fractions were purified by various techniques including flash column chromatography, medium pressure chromatography (MPLC), preparative layer chromatography (PLC), radial chromatography (chromatotron) and, in some cases, semi-preparative HPLC. The fractionations were monitored by both thin layer chromatography (TLC) and bioassays (with the main chromatographic fractions). The nuclear magnetic resonance (NMR) spectra of fractions were recorded where possible. The spectroscopic information is as important as bioassay results in following the active/interesting compounds during the isolation process.

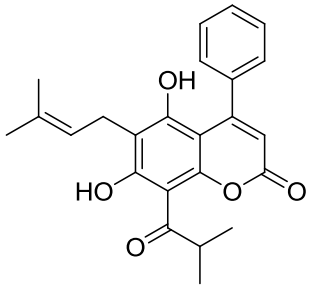
The structure elucidation of the pure compounds involved various modern spectroscopic techniques. The most important tool is high resolution nuclear magnetic spectrometer (NMR). The NMR techniques employed are both 1D and 2D, i.e. ^{1}H and ^{13}C, HMBC (heteronuclear multiple bond correlation), HMQC (heteronuclear multiple quantum correlation), DEPT (distortionless enhancement by polarization transfer), COSY (correlated spectroscopy) and NOESY (nuclear overhauser effect spectroscopy). Other spectroscopic techniques are UV (ultraviolet spectroscopy), IR (infrared spectroscopy) and MS (mass spectrometry, LC-MS-MS and EI-MS). In the case where pure compounds formed suitable crystals, single crystal x-ray diffraction analysis is utilized to finally confirm the molecular structure.

5.4.4 Research Results on Bioactive Natural Products

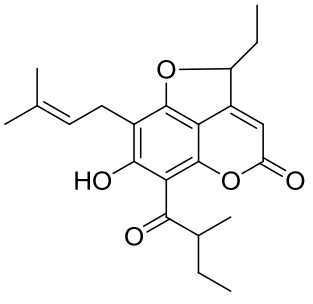
Plants from Guttiferae Family

Mammea harmandii

Two new naturally occurring coumarins, isomesuol **59** and mammearin **60**, together with nine known *Mammea coumarins* were isolated from the active ethyl acetate extract of the leaves and twigs of *Mammea harmandii*. Compound **59** showed cytoxicity against a panel of mammalian cancer cell lines. The results have been published in **Planta Medica 2003, 69, 1048-1051** and have added new information on this Thai plant.



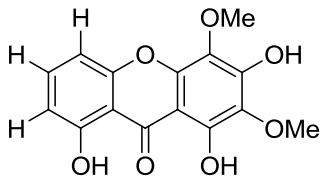
59



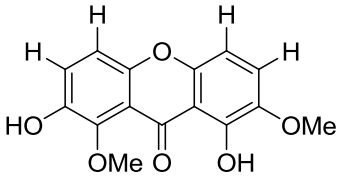
60

Cratoxylum arborescens

Two new xanthones 1,3,8-trihydroxy-2,4-dimethoxy-xanthone **61** and 1,7-dihydroxy-2,8-dimethoxy-xanthone **62** along with twelve known compounds consisting of xanthones, triterpenes, methoxyemodin, 3,4-dihydroxy benzoic acid and flavanoids glycosides have been isolated from the ethyl acetate extract with anti-HIV-1 activity of the leaves and twigs of *Cratoxylum arborescens*. Some isolated compounds showed anti-HIV-1 activities in the syncytium assay using $^{\Delta Tat/Rev}$MC99 virus and the 1A2 cell line system, and HIV-1 reverse transcriptase. The EC_{50} and IC_{50} values of the active compounds are in the range of therapeutic interest. This work represented the first report on the anti-HIV-1 activity of the plants. The results have been published in **Planta Medica 2006, 72-1433-1435**.



61

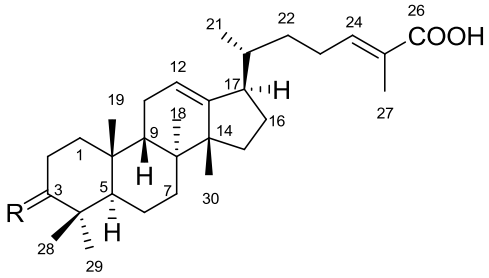


62

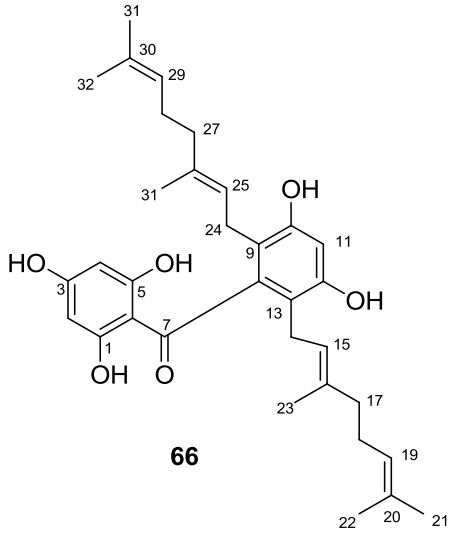
Garcinia speciosa

The ethyl acetate extract of the trunk bark and stems of *Garcinia speciosa* exhibited anti-HIV-1 reverse transcriptase assay. Bioassay guided fractionation of the extract yielded three new protostanes, garciosaterpenes A **63**, B **64** and C **65** together with a new digeranylbenzophenone, garciosaphenone **66**. The known compounds 8-desoxygartanin **67** (-)-epicatechin **68**, a mixture of achilleol A **69** and achilleol **70**, and stigmasterol were also isolated. Compounds **63** and **65** showed significant inhibitory activities (IC50 15.5 and 12.2 µg/ml, respectively) against HIV-1 reverse transcriptase and the syncytium assay (EC50 5.8 µg/ml with TI 3.4 and 37.0 mg/ml with TI 1.9, respectively. Compounds **66** was active in HIV-1 RT assay (IC50 23.9 g µg/ml), but toxic in the syncytium assay. This work represented the first report on the anti-HIV-1 activities of the protostane triterpenes. The results have been published in **Planta Medica 2003, 69, 1141-1146**.

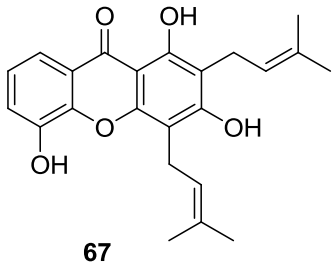
Scheme 22



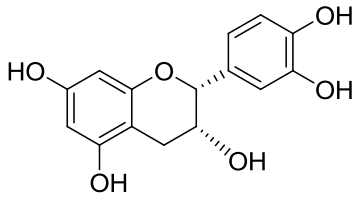
43 R = β-$OCOCH_3$, H
64 R = β-OH, H
65 R = O



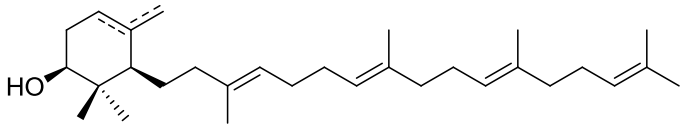
66



67



68



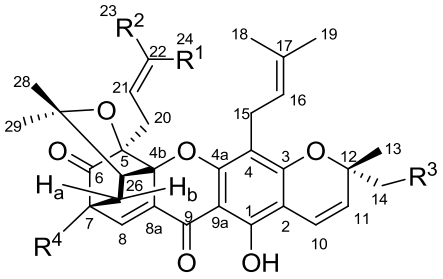
69 exocyclic double bond
70 endocyclic double bond

Garcinia hanburyi

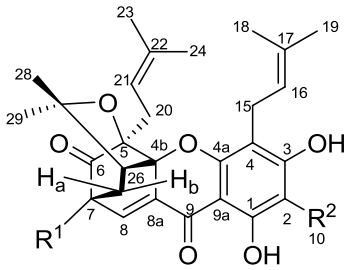
In Thai folklore medicine, gamboges, the yellow gum resin secreted from *Garcinia hanburyi*, is used for infected wound, pain and edema. The ethyl acetate extract of the gamboge and fruits exhibited wide ranging biological activities including: anti-inflammatory, analgesic and antipyretic activities using experimental animal models, cytotoxic and anti-HIV-1 activities. Bioassay guided fractionation of the ethyl acetate extracts of the resin and fruits of the *Garcinia hanburyi* gave three new caged xanthones, 7-methoxydesoxy-morellin **71**, 2-isoprenylforbesione **72** and 8.8a-epoxymorellic acid **73** together with nine known caged xanthones were isolated i.e. desoxymorellin **74**, isomorellin **75**, isomorellinol **76**, morellic acid **77**, gambogic acid **78** desoxygambogenin **79**, hanburin **80**, forbesione **81** and dihydroisomorellin **82**, Scheme 23. Most of the isolated compounds

showed significant cytotoxicities against a panel of mammalian cancer cell lines. Compound **73,** desoxymorellin **74**, gambogic acid **78**, hanburin **80**, forbesion **81** and dihydroisomorellin **82** exhibited anti-HIV-1 activity in the reverse transcriptase (RT) assay while the known compounds desoxygambogenin **79** and dihydroisomorellin **82** were found moderately active in the syncytium assay. This work represents the first report on the anti-HIV-1 activities caged xanthones.

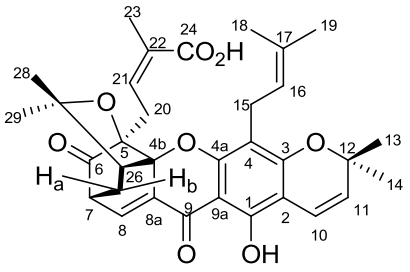
Scheme 23



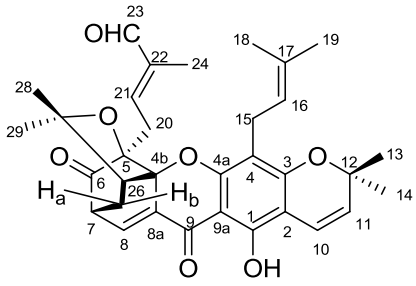
	R^1	R^2	R^3	R^4
71	CH_3	CH_3	H	OCH_3
74	CH_3	CH_3	H	H
75	CH_3	CHO	H	H
76	CH_3	CH_2OH	H	H
77	COOH	CH_3	Phenyl	H



	R^1	R^2
72	CH_3	Prenyl
79	CH_3	Geranyl
80	Prenyl	H
81	H	H



73



82

Bioassay guided fractionation of the extracts of leaves, twigs and resin of *G. hanburyi* led to the isolation of two new anti-HIV-1 and anti-inflammatory lupanes i.e. 2α-acetoxy-3β-hydroxy-19β-hydrogen-lup-20(29)-en-28-oic acid (2-acotoxyalphitolic acid) **83** and 2α-hydroxy-3β-acetoxy-19β-hydrogen-lup-20(29)-en-28-oic (3-acetoxyalphitolic acid) **84** together with the known betulinic acid **85**, betulin **86** and stigmasterol-3-0-β-D-glucopyranoside **87**, Scheme 24. All of the lupanes **83** to **86** displayed anti-HIV-1 activities in the anti-HIV-1 reverse transcriptase (IC_{50} values 16.3-116.9 μg/ml) and syncytium assays (EC50 5.6-73.6 mg/ml, SI 1.7-3.3). Moreover, compounds **83** to **86** exhibited anti-inflammatory activity in an ethyl phenylpropiolate (EPP)-induced ear edema model.

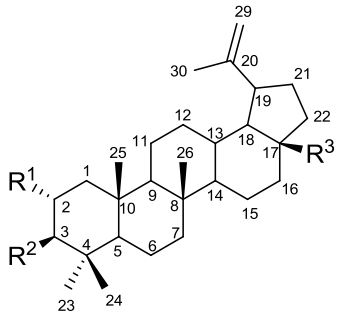
The caged xanthones and the terpenes are good lead structures for further drug development. The research on *G. hanburyi* have been published in:

Journal of Ethnopharmacology 2007, 111, 335-340

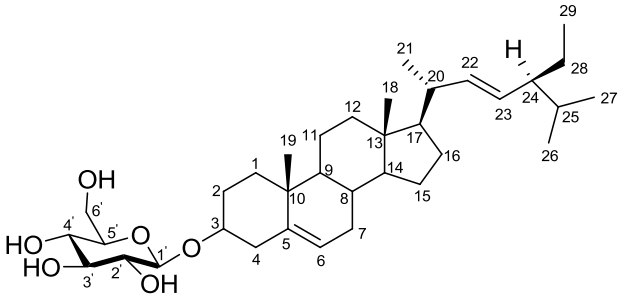
Planta Medica 2007, 73, 33-40

Planta Medica 2009, 75, 1-4

Scheme 24



	R^1	R^2	R^3
83	OAc	OH	COOH
84	OH	OAc	COOH
85	H	OH	COOH
86	H	OH	H



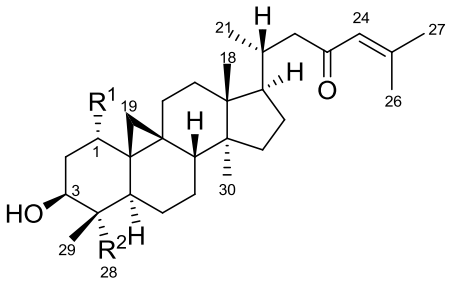
87

Plants from Gardenia Genus, Rubiaceae Family

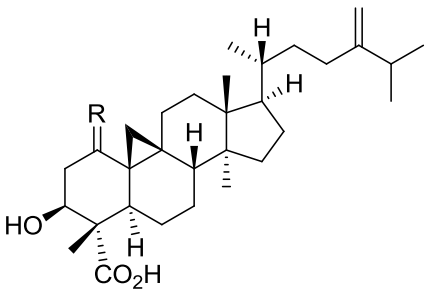
Gardenia thailandica

The anti-HIV-1 active chloroform extract of the leaves and twigs of the endemic plant, *Gardenia thailandica*, yield four cycloartanes i.e. Thailandiol **88**, gardenolic acid A **89**, quadrangularic acid E **90** and 3β-hydroxy-5a-cycloart 24(31)-en-28-oic acid **91**. In addition, 5-hydroxy-7,2',3',4',5',6'-hexamethoxyflavone **92**, 5,7-dihydroxy-2',3',4',5',6'-penlamethoxy-flavone **93**, 5-hydroxy-7,2',3',4',5'-penta-methoxyflavone **94** and 5,7-dihydroxy-2',3',4',5'-tetramethoxyflavone **95** were also isolated from the same source, Scheme 25. Compound **88** to **91** displayed anti-HIV-1 activities as determined by using the $^{\Delta Tat/Rev}$MC99 virus and 142 cell line system. The EC_{50} values determined by the syncytium assay ranged from < 7.8 to 110 μg/ml. They also exhibited moderate to high activities in reverse transcriptase (RT) assay; the IC50 values of compounds **88** to **91**, ranged from < 22.5 to 156.8 μg/ml. The work has been published in **Planta Medica 2004, 70, 366-370**.

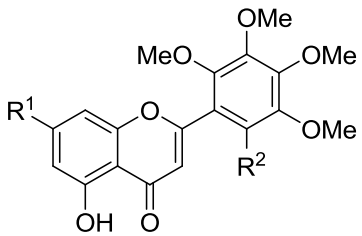
Scheme 25



88 R^1 = OH, R^2 = Me
89 R^1 = H, R^2 = COOH



90 R = O
91 R = H_2

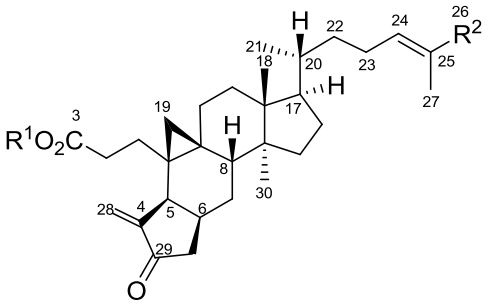


92 R^1 = R^2 OMe
93 R^1 = OH, R^2 = OMe
94 R^1 = OMe, R^2 = H
95 R^1 = OH, R^2 = H

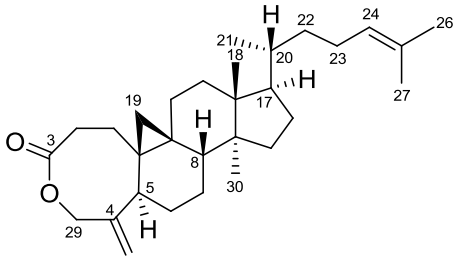
Gardenia tubifera

Bioassay guided fractionation of the hexane and chloroform extracts of the leaves and twigs of the endenmic plant, *Gardenia tubifera* led to the isolation of compounds with cytotoxic and anti-HIV activities: two new cycloartanes tubiferolide methyl ester **96** and tubiferaoctanolide **97**; two known cycloartanes coronalolide **98** and coronalolide methyl ester **99**; a new flavone 5,3',5'-trihydroxy-7,4'-dimethoxyflavone **100**, five known flavones **101** to **105**; and hexacosyl 4'-hydroxy-trans-cinnamate **106**, Scheme 26. Compounds **98**, **102**, **104** and **105** showed significant cytotoxic activity in a panel of mammalian cultured cell lines. Compounds **100** to **105** were found to be active in the $^{\Delta Tat/Rev}$MC99 syncytium assay. The work has been published in **Tetrahedron, 2004, 60, 1517-1523**. Both *Gardenia thailandica* and *Gardenia tubifera* gave novel cycloartanes with cytotoxic and anti-HIV activities. These results highlighted the important role of these type of lead structures for the development of therapeutic agents with the activities indicated.

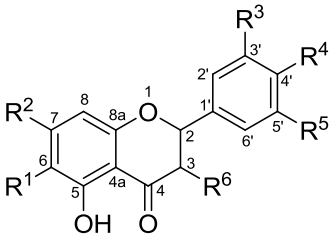
Scheme 26



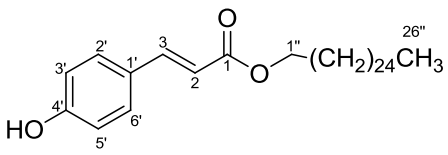
96 $R^1 = R^2 = Me$
98 $R^1 = H$, $R^2 = CHO$
99 $R^1 = Me$, $R^2 = CHO$



97



100 $R^1 = R^6 = H$, $R^2 = R^4 = OMe$, $R^3 = R^5 = OH$
101 $R^1 = R^2 = R^4 = R^6 = OMe$, $R^3 = R^5 = OH$
102 $R^1 = OMe$, $R^2 = R^4 = OH$, $R^3 = R^5 = R^6 = H$
103 $R^1 = R^4 = R^5 = OMe$, $R^2 = R^3 = OH$, $R^6 = H$
104 $R^1 = R^6 = H$, $R^2 = R^4 = R^5 = OMe$, $R^3 = OH$
105 $R^1 = R^2 = R^4 = R^5 = OMe$, $R^3 = OH$, $R^6 = H$



106

Plants from Euphorbiaceae Family

Mallotus spodocarpus

Mallotus spodocarpus is an endemic plant to Thailand. The people in the northeastern part of Thailand use this plant as a powder for skin whitening. The chloroform extract of the roots showed very strong anti-inflammatory and cytotoxic activity. The chloroform extract from the roots of *Mallotus spodocarpus* was investigated for anti-inflammatory and analgesic activities in animal models. In acute inflammatory models, the extract significantly inhibited ethyl phenylpropiolate-induced ear edema and carrageenin- and arachidonic acid-induced hind paw edema in rats. In the chronic inflammatory model using the cotton pellet-induced granuloma in rats, the extract exhibited inhibitory activity on the formation of granuloma. The extract also elicited pronounced inhibitory effect on acetic acid-induced writhing response in mice in the analgesic test. The results obtained suggest marked anti-inflammatory and analgesic activity of the extract.

Bioassay guide fractionation using cytotoxic assay led to the isolation of a 7-mer peptide, VR-3848. The compound exhibited cytotoxicity at 1 nanomolar range. VR-3848, has been shown to induce apoptosis at nanomolar concentrations in the leukemic Jurkat cell line. Apoptosis was associated with activation of caspases, release of cytochrome *c* from mitochondria, fragmentation of nuclear DNA, and externalization of phosphatidylserine on the cell surface. Overexpression of mitochondria-targeted Bcl-2 abrogated VR-3848-induced killing in this model. Primary human interleukin (IL)-2-activated T lymphocytes were considerably less sensitive to VR-3848-induced apoptosis as compared to Jurkat cells. VR-3848 thus holds the promise of being a potent and selective anti-cancer agent that deserves further exploration.

VR-3848 has also demonstrated strong anticancer activity *via* stimulation of multiple apoptotic pathways in caspase-3 deficient cells. The compound exhibited MCF-7 cancer cell growth through an activation of three related apoptotic pathways.

The results have been published in:

The Journal of Ethnopharmacology 2004, 90, 69-72

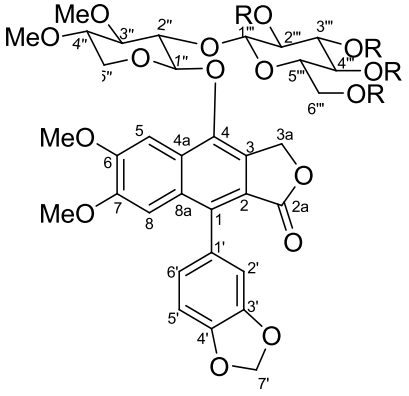
Cancer Letters 2004, 208, 171-178

Anticancer Research 2007, 27, 2473-2480

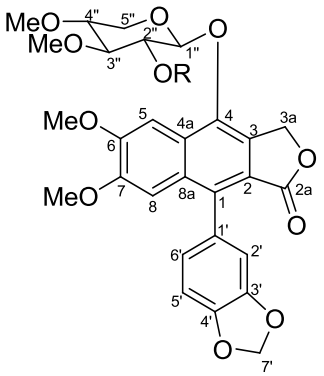
Phyllanthus taxodiifolius

Bioassay guided fractionation of the ethyl acetate extract of the aerial parts of *Phyllanthus taxodiifolius* with cytotoxic activity yielded four arylnaphthalide lignan glycosides: taxodiifoloside **107**, cleistanthoside A **108**, cleistanthin A **109** and cleistanthin A methyl ether **110**: together with a triterpene, glochidone, Scheme 27. Compounds **109** and **110**, as well as the derivatives **108a** and **109a** exhibited potent cytotoxic activities with GI_{50} value in the range of 10^{-7} to 10^{-9}M in a panel of cultured mammalian cancer cell lines. The new compound **107** showed moderate activity with GI_{50} of 10^{-6}M. Compounds **108** and glochidone were inactive in the assays. The work has been published in **Planta Medica 2006, 72, 60-62**.

Scheme 27



107 R = H,R' = Ac
108 R = R' = H
108a R = R = Ac



109 R = H
109a R = Ac
110 R = Me

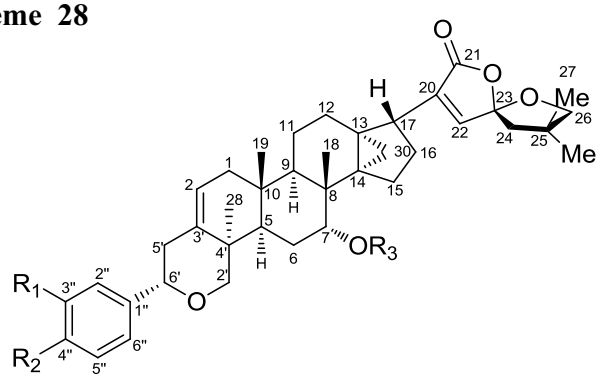
Phyllanthus acutissima

Bioactive dichapetalin-type triterpenoids and lignans were isolated from the methanol extract of the aerial parts of *Phyllanthus acutissima*. A total of twelve compounds were isolated: five new dichapetalin type triterpenoids acutissimatriterpene A to E, **111-115**; two new lignans, acutissimalignans A **116** and B **117**; two known lignans taiwanin C **118** and isogadian **119**; three known ellagic acid derivations 3,3',4'-tri-o-methylellagic acid **120**, 3'-mono-O-methylellagic acid 4-O-α-L-rhamnopyranoside **121** and 3,3',4'-tri-O-methylellagic acid 4-O-β-D-glucopyranoside **122**, Scheme 28. Structures and absolute configurations of compounds **111** and **115** were confirmed by single crystal x-ray diffraction analyses on the derivatives **111a** and **115b**, respectively. The absolute configurations of **113** (as **113a**), **115a** and **115c** were established by the correlation with their parent compounds.

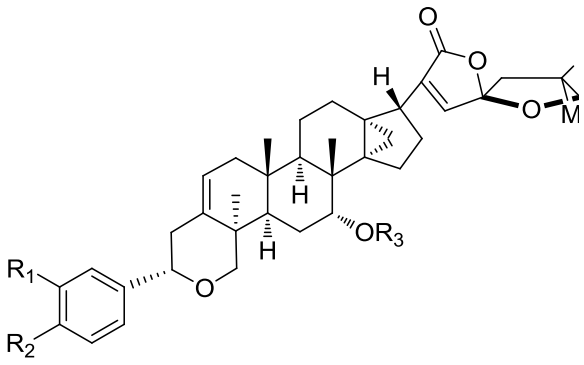
Compounds **111** to **121** were tested in the cytotoxic and anti-HIV-1 assays. When tested for cytotoxic effects against a panel of cancer cell lines, triterpenes **111** and **112** exhibited such activity only against the P-388 cell line, whereas triterpene **115** showed significant activities for the P-388, MCF-7, and Lu-1 cell lines. Lignan **116** was found active in all cell lines tested. Anti-HIV-1 activities were also evaluated employing cell-based cytotoxic and syncytium assays using $^{\Delta Tat/Rev}$MC99 virus and 1A2 cell line system, as well as HIV-1 reverse transcriptase (RT) assay. The cell-based assay for anti-HIV-1 activity revealed that all new compounds **111** to **117**, the known lignan **119** and the modified ellagic glycoside **121a** were active, while the lignan **118** and compound **121** were inactive. In the HIV-1RT assay, the known lignan **118** was most active (88.2% inhibition at 200 μg/ml), while triterpenes **111**, **112** and the modified ellagic acid glycoside **121a** were moderately active (>50 to 70% inhibition).

The results represented the comprehensive chemical and biological studies on the plant. It provided novel lead structures for cytotoxic and anti-HIV-1 activities. The work has been published in the **Journal of Natural Products 2008, 71, 655-663**.

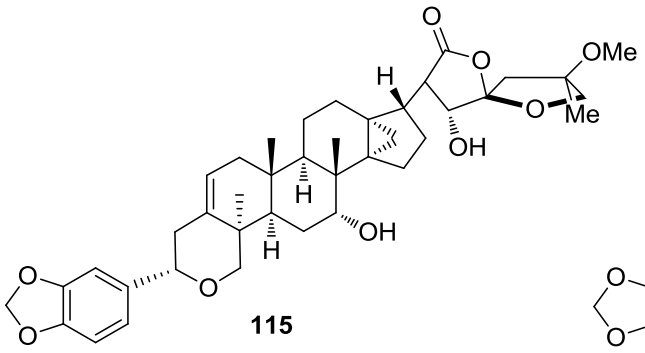
Scheme 28



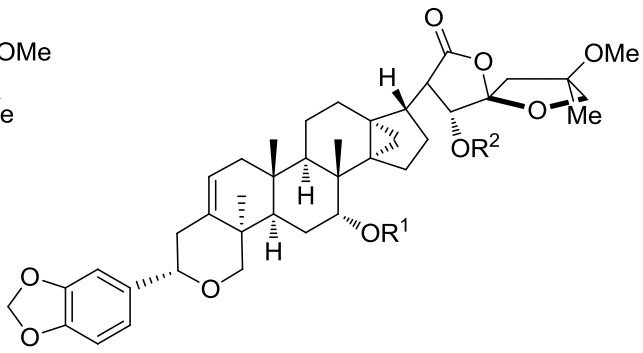
111 R1 , R2 = O-CH_2-O, R3 = H
111a R1 , R2 = O-CH_2-O, R3 = p-BrPhCO
112 R1 = R2 = R3 = H



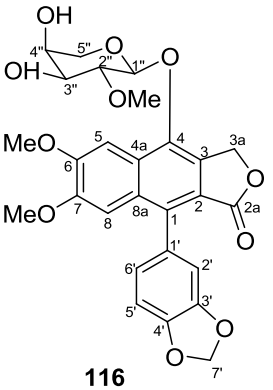
113 R1 , R2 = O-CH2-O, R3 = H
113a R1 , R2 = O-CH2-O , R3 = p-BrPhCO
114 R1 = R2 = R3 = H



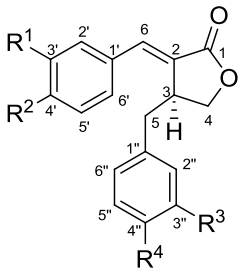
115



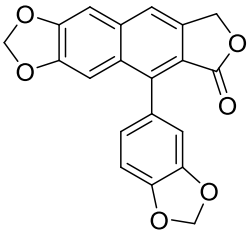
115a $R^1 = R^2 = H$
115b R^1 = H,R^2 = *p*-BrPhCO
115C $R^1 = R^2$ = *p*-BrPhCO



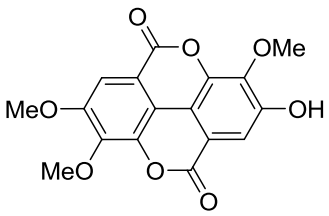
116



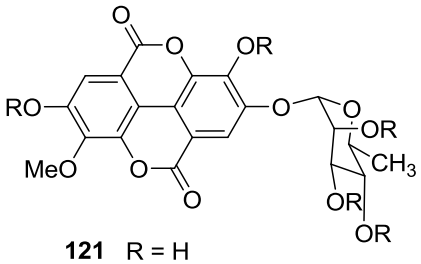
117 $R^1 = R^3 = OMe$, $R^2 = R^4 = OH$
119 R^1-$R^2 = R^3$-$R^4 = O$-CH_2-O



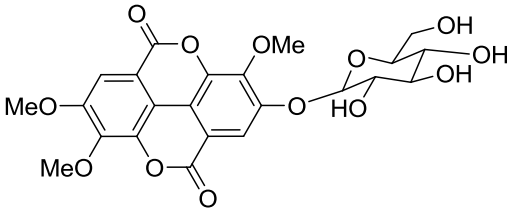
118



120



121 R = H
121a R = COMe



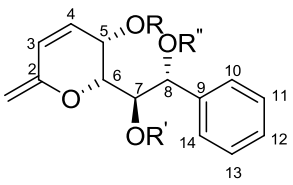
122

Plant from Annonaceae

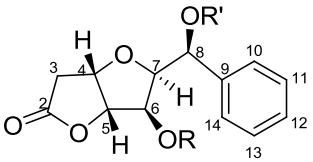
Polyalthia crassa

Bioassay guided fractionation of the cytotoxic ethyl acetate extract of the leaves and twigs of *Polyalthia crassa* gave eleven compounds; four new styryl-lactones, crassalactones **A 123**, **B 124**, **C 125** and **D 126**; seven known compounds (±)-3-acetylaltholactone **130**, (±)-altho-lactone **129**, aristolactam AII **131**, cinnamic acid, (±)-goniofafurone **128**, (±)-goniopypyrone **132**, and (±)-howiinol **A 127**, Scheme 29. The structure of crassalactone **D 126** was confirmed by single crystal x-ray diffraction analysis. Pure isolated compounds **123**, **124**, **125**, **126**, the alkaloid aristolactam **AII 131** were evaluated for cytotoxic effects against a panel of cultured mammalian cell lines. Compounds **123** and **126** showed broad cytotoxic activity for all cell lines tested, while compound **124** and **131** exhibited moderate cytotoxic effects only for the P-388 cell line. The results have been published in the **Journal of Natural Products 2006, 69, 1728-1733**.

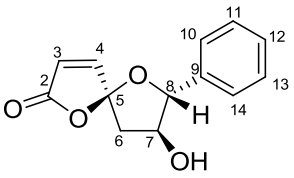
Scheme 29



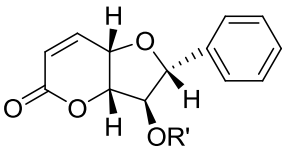
123 R = cinnamoyl, R' = R = H
127 R = R' = H, R" = cinnamoyl



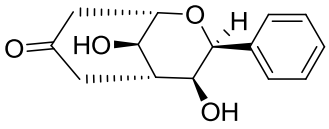
124 R = cinnamoyl, R' = H
125 R = H, R' = cinnamoyl
128 R = R' = H



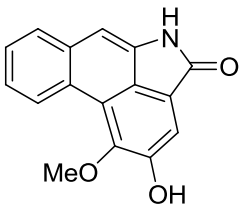
126



129 R = H
130 R = Ac



132



131

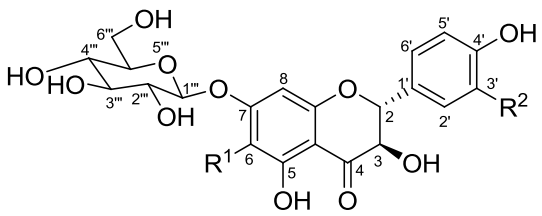
Plant from Ochnaceae

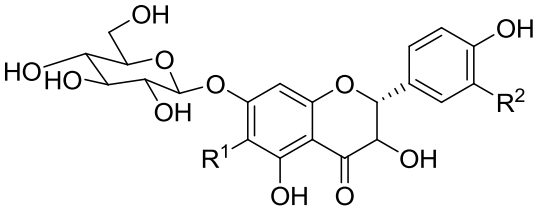
Ochna integerrima

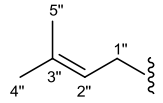
Ochna integerrima is the only species of this genus found in Thailand. Bioassay-guided fractionation of the anti-HIV-1 active ethyl acetate extract from the leaves and twigs of *Ochna integerrima* led to the isolation of twelve compounds: five new flavonoid glycosides **133** to **137**, Scheme 30: five known flavonoids ochnafavone **138**, ochnaflavone 7"-O-methyl ether **139**, 2",3"-dihydroochnaflavone 7"-O-methyl ether **140**, iriskumaonin methyl ether **141**, irisolone methyl ether **142** 6-γ, γ-dimethylallyltaxifolin 7-O-β-D-glucoside **143** and vitexin **144**. Compounds **133**, **135**, **136**, **137** and **143** showed anti-HIV-1 activities in the syncytium assay using the $^{\Delta Tat/Rev}$MC99 virus and the 1A2 cell line system with EC_{50} values ranging from 14.0-102.4 µg/ml. Furthermore the ochnaflavone **139** and **140** were very active; they exerted activities in the syncytium assay with EC_{50} values of 2.0 and 0.9 mg/ml, respectively, and likewise inhibited HIV-1 reverse transcriptase (RT) with IC_{50} values of 2.0 and

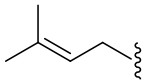
2.4 µg/ml, respectively. This work has identified potent and potentially valuable agents for anti-HIV-1 therapy. The results have been published in **Planta Medica 2007, 73, 683-688**.

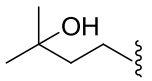
Scheme 30

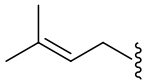


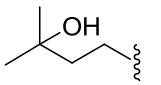


133 R^1 =  ; R^2 = H

134 R^1 =  ; R^2 = H

136 R^1 =  ; R^2 = OH

135 R^1 =  ; R^2 = OH

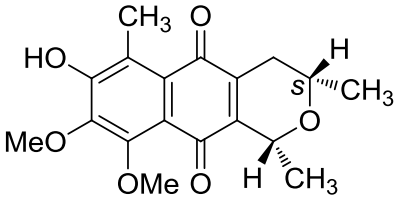
137 R^1 =  ; R^2 = OH

Plant from Rhamnaceae Family

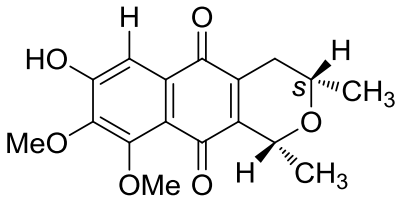
Ventilago harmandiana

Ventilago harmandiana is a climber endemic to Thailand. The interest in the plant is due to its reported use in traditional medicine for the treatment of diabetes as well as wound and chronic inflammation. The biological studies confirmed the alleged activities claimed in the traditional use of the plant. Methanolic extracts from the heart wood, stem bark, and stem wood of *Ventilago harmandiana* Pierre (Family Rhamnaceae) were assessed for anti-inflammatory effects using both acute and chronic inflammatory models. Analgesic and antipyretic activities of the extracts were also evaluated. It was found that all extracts possessed strong inhibitory effects on the acute phase of inflammation as seen in ethyl phenylpropiolate (EPP)- and arachidonic acid (AA)-induced ear edema as well as in carrageenin-induced paw edema in rats. The extracts elicited only weak inhibitory activity on cotton pellet-induced granuloma formation, a subchronic inflammatory model. In the analgesic test, all extracts exerted pronounced inhibitory activity in acetic acid-induced writhing response but showed only weak effects in the tail-flick test. The extract also showed excellent antipyretic activity on yeast-induced hyperthermia in rats. The results have been published in the **Journal of Ethnopharmacology 2008, 116, 234-244**.

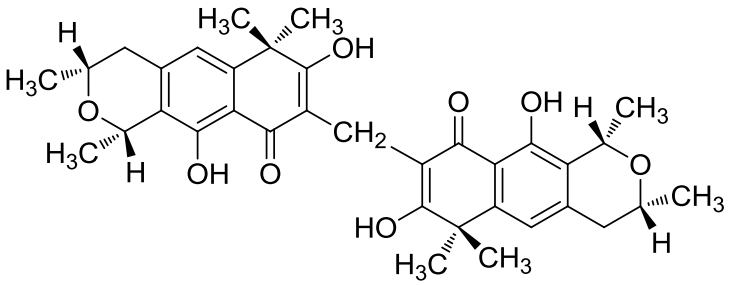
Bioassay-guided fractionation studies are on-going. A series of compounds such as pyranonaphthoquinones **57**, **145** and the dimer **146** have been identified. The total synthetic studies of compound **57** are on-going. The detailed biological evaluations of compound **57**, **145** and **146** are also on-going.



57



147



146

Plants from Acanthaceae Family

Berleria lupulina* and *Clinacanthus nutans

Both plants have been widely used in Thai traditional medicine *Berleria lupulina* has been used for diabetes, rheumatoid arthritis and snake bite. *Clinacanthus nutans* extract has been widely used as an anti-hepatitis and anti-herpes agent. Extracts from the leaves of both plants have been used as anti-inflammatory agents for the treatment of insect bites and allergic responses and as remedies for herpes simplex and varicella zoster virus lesions.

Our studies have been carried out on the methanol extracts of both whole plants for the anti-inflammatory effects and the inhibition of neutrophils responsiveness *in vivo* and cell based models, respectively. Both extracts induced powerful dose-dependent inhibitory effects in edema model in rats. There was a significant inhibition of myeloperoxidase (MPO) activity in the inflamed tissue

indicating that the anti-inflammatory effect of the extracts is associated with reduced neutrophils migration. Although both extracts did not affect neutrophils viability or apoptasis, treatment of neutrophils with extract concentration-dependently inhibited fMLP-induced chemotaxis, superoxide anion generation (SAG) and MPO and elastase release. These findings suggest that powerful anti-inflammatory properties of *Barleria lupulina* and *Clinacanthus nutans* extracts are mediated, in part, by inhibition of neutrophils responsiveness. Our work lends scientific basis for the anti-inflammatory activity of both plants. The results have been published in the **Journal of Ethnopharmacology 2008, 116, 234-244**.

5.4.5 Product and Innovation

A ranges product under the trade name of **Plaitanoids™** based on the research work; in part under TRF Senior Research Scholar Program; from PI's and other international research groups has been launched. The cosmetics and spar products are commercially available.

5.5 Assessment of Research Accomplished

5.5.1 Collaborative Research Network

The establishment of an effective collaborative research network as described in Scheme 1 has been achieved. The network activities both in the directed exploratory research in basic synthetic organic chemistry and bioactive natural products will be long lasting and the researchers within the network have been continuing the collaborative activities without the support from the TRF Senior Research Scholar Program. It is worth noting that a researcher within the network Professor Vatcharin Rukachaisirikul has been selected to receive a TRF Senior Research Scholar Award.

5.5.2 Directed Exploratory Research in Basic Organic Chemistry

The research program on basic organic chemistry has received excellent success. A total of **18 high quality papers** has been published in international journals with high impact factors. In addition, a manuscript has been submitted for a publication in an international journal, The results obtained included; chemistry of *gem*-difluoromethylene compounds, catalytic reactions with lanthanides and other transition metals, new technology on the preparation of nanoparticles and total synthesis of natural products.

5.5.3 Directed Exploratory Research in Bioactive Natural Products: Drug Discovery from Bioactive Natural Products: The Search for Lead Structures.

The research covered plants from the rain forest of Thailand. Plants with biological activities have been extensively studied. A total of **17** papers have been published in international journals with high impact factors. The pure compounds, lead structures and plant extracts with cytotoxic, anti-HIV-1 and anti-inflammatory activities have been isolated. Some of these compounds deserved further research and development.

A range of products under the trade mark , **Plaitanoids**^{TM}, derived from the research has been available commercially.

6. Research Outputs

6.1 Publications: Total 36 papers

6.1.1 Publications in International Journals on Directed Exploratory Research in Basic Synthetic Chemistry: 18 papers, 1 submitted.

Details of Publications in Synthetic Chemistry

1. Manat Pohmakotr,* Pornthep Numechai, Saisuree Prateeptongkum, Patoomratana tuchinda and **Vichai Reutrakul**, "A general synthetic route to 1-azabicyclo[*m.n.*0]alkenes *via* cyclisation base on α-sulfinyl carbanions", *Org. Biomol.Chem.*, **2003**, *1*, 3495-3497.
2. Manat Pohmakotr,* Arisara Issaree, Laddawan Sampaongoen, Patoomratana Tuchinda and **Vichai Reutrakul**, "Vicinal dianions of diethyl α-aroylsuccinates: preparation of functionalized-2,3-dihydrofurans and –furans, and diaxial 2,4-diaryl-3,7-dioxabicyclo[3.3.0]octanes", *Tetrahedron Letters, 44*, **2003**, 7937-7940.
3. **Vichai Reutrakul**,* Thanchanok Thongpaisanwong, Patoomratana Tuchinda, Chutima Kuhakarn, and Manat Pohmakotr*, "Difluorophenylsulfanylmethyl Radical and Difluoromethylene Diradical Synthons: *gem*-Difluoromethylene Building Block", *J. Org. Chem.* **2007**, *69*, 6913-6915.
4. Manat Pohmakotr,* Winai Leawsuwan, Patoomratana Tuchinda, Palangpon Kongsaeree, Samran Prabpai, and **Vichai Reutrakul***, "α-Arylsulfanyl-α-fluoro Carbenoids: Their Novel Chemistry and Synthetic Applications", *Org. Lett.*, **2004**, *6*, 4547-4550.
5. Manat Pohmakotr,* Darunee Soorukram, Patoomratana Tuchinda, Samran Probpai, Palangpon Kongsaeree and **Vichai Reutrakul**, "Highly diastereoselective alkylation of vicinal dianions of chiral succinic acid derivatives: a new general strategy to (*R*)-β-arylmethyl-γ-butyrolactones", *Tetrahedron Letters* **2004**, *45*, 4315-4318.
6. Manat Pohmakotr,* Taweechote Komutkul, Patoomratana Tuchinda, Samrarn Prabpai, Palangpon Kongsaeree and **Vichai Reutrakul***, "Syntheses of (±)-thuriferic acid ethyl ester, its analogues and (±)-picropodophyllone", *Tetrahedron*, **2005**, **61**, 5311-5321.
7. Chutima Kuhakarn,* Krisada Kittigowittana, Manat Pohmakotr and **Vichai Reutrakul**, "IBX/*n*-Bu_4NBr/CH_2Cl_2-H_2O: a new mild system for selective oxidation of secondary alcohols", *Tetrahedron* **2005**, *61*, 8995-9000.

8 Barry M. Trost,* Jaray Jaratjaroonphong, and **Vichai Reutrakul***, "A Direct Catalytic Asymmetric Mannich-type Reaction via a Dinuclear Zinc Catalyst: Synthesis of Either *anti*- or *syn*-α-Hydroxy-*β*-Amino Ketones", *J. Am. Chem. Soc.* **2006**, *128*, 2778-2779.

9. Natthinee Anantachoke, Mohamed Makha,* Colin L. Raston,* **Vichai Reutrakul**, Nigel C. Smith, and Martin Saunders, "Fine Tuning the Production of Nanosized *β*-Carotene Particles Using Spinning Disk Processing", *J. Am. Chem. Soc.* **2006**, *128*, 13847-13853.

10. Manat Pohmakotr,* Attapol Pinsa, Tipwan Mophuang, Patoomratana Tuchinda, Samran Prabpai, Palangpon Kongsaeree, and **Vichai Reutrakul***, "General Strategy for Stereoselective Synthesis of 1-Substituted *Exo*,*Endo*-2,6-Diaryl-3,7-dioxabicyclo[3.3.0]octanes: Total Synthesis of (±)-Gmelinol", *J. Org. Chem.* **2006**, *71*, 386-389.

11. Manat Pohmakotr,* Kanhokthron Boonkitpattarakul, Winai Leawsuwan, Suwatchai Jarussophon, Nongnaphat Duangdee, Patoomratana Tuchinda and **Vichai Reutrakula***, "α,α-Difluoro-α-phenylsulfanylmethyl carbanion equivalent: a novel *gem*-difluoromethylenation of carbonyl compounds", *Tetrahedron* **2006**, *62*, 5973-5985.

12. **Vichai Reutrakul**,* Jaray Jaratjaroonphong, Patoomratana Tuchinda, Chutima Kuhakarn, Palangpon Kongsaeree, Samran Prabpai and Manat Pohmakotr*, "Samarium dienolate mediated stereoselective synthesis of *anti*-1,3-diol monoesters via aldol-Tishchenko reaction", *Tetrahedron Letters* **2006**, *47*, 4753-4757.

13. Manat Pohmakotr,* Nattawut Yotapan, Patoomratana Tuchinda, Chutima Kuhakarn, and **Vichai Reutrakul***, "Highly Diastereoselective Synthesis of *β*-Carboxy-*γ*-lactams and Their Ethyl Esters via $Sc(OTf)_3$-Catalyzed Imino Mukaiyama-Aldol Type Reaction of 2,5-Bis(trimethylsilyloxy) furan with Imines", *J. Org. Chem.* **2007**, *72*, 5016-5019.

14. Manat Pohmakotr,* Sirinporn Thamapipol, Patoomratana Tuchinda and **Vichai Reutrakul***, "Intramolecular acylation of α-sulfinyl carbanions with masked α,β-unsaturated esters: a general strategy to 5-alkylidene-2-cyclopentenones", *Tetrahedron* **2007**, *63*, 1806-1820.

15. Chutima Kuhakarn, Kassrin Tangdenpaisal, Palangpon Kongsaeree, Samran Prabpai, Patoomratana Tuchinda, Manat Pohmakotr* and **Vichai Reutrakul***, "Lanthanide triflate catalyzed generation of *N*-acyliminium ions from α-amido sulfones: the synthesis of (1-alkyl-1-aryl)methyl phenyl sulfones", *Tetrahedron Letters* **2007**, **48**, 2467-2470.

16. Manat Pohmakotr,* Nattawut Yotapan, Patoomratana Tuchinda, Chutima Kuhakarn and **Vichai Reutrakul**,* "Stereoselective synthesis of β-carboethoxy-γ-lactams via imino Mukaiyama aldol-type reaction of 1,4-bis(trimethylsilyloxy)-1,4-diethoxy-1,3-butadiene", *Tetrahedron* **2007**, *63*, 4328-4337.

17. Manat Pohmakotr,* Duanghathai Panichakul, Patoomratana Tuchinda and **Vichai Reutrakul***, "*gem*-Difluoromethylation of α- and γ-ketoesters: preparation of *gem*-difluorinated α-hydroxyesters and γ-butyrolactones", *Tetrahedron* **2007**, *63*, 9429-9436.

18. Pramchai Deelertpaiboon, **Vichai Reutrakul***, Suwatchai Jarussophon, Patoomratana Tuchinda, Chutima Kuhakarn, Manat Pohmakotr, "Efficient sysnthesis of alkyl 2,3-unsaturated glucopyranosides from glycols mediated by ytterbium(III) triflate-trialkyl aluminum", *Tetrahedron Letters* **2009**, *50*, 6233-6235.

19. Chutima Kuhakarn, Nakin Surapanich, Siriporn Kamtonwong, **Vichai Reutrakul*** and Manat Pohmakotr, "α,α-Difluorophenylsulfanylmethyl carbocation as the synthetic equivalent of thioester cation and geminal carbonyl dication†", *Organic and Biomolecular Chemistry* **2010**, Submitted.

6.1.2 Publication in International Journals on Bioactive Natural Products: Drug Discovery: The Search for Lead Structures: 17 papers

Details of Publications Bioactive Natural Products

20. **Vichai Reutrakul**, Pornsiri Leewanich, Patoomratana Tuchinda, Manat Pohmakotr, Thaworn Jaipetch, Samaisukh Sophasan, Thawatchai Santisuk "Cytotoxic coumarins from *Mammea harmandii*", **Planta Med. 2003, 69, 1048-1051 (Impact Factor 2.289).**
21. Vatcharin Rukachaisirikul, Phanruethai Pailee, Assdhawut Hiranrat, Patoomratana Tuchinda, Chalobon Yoosook, Jittra Kasisit, Walter C. Taylor, **Vichai Reutrakul**, "Anti-HIV-1 protostane triterpenes and digeranylbenzophenone from trunk bark and stems of *Garcinia speciosa*", **Planta Med. 2003, 69, 1141-1146 (Impact Factor 2.289)**.
22. Wanlaya Uthaisang, **Vichai Reutrakul**, Chongkon Krachangchaeng, Prapon Wilairat, Bengt Fadeel*, "VR-3848, a novel peptide derived from *Euphobiaceae*, induces mitochondria-dependent apoptosis in human leukemia cells", **Cancer Letters 2004, 208, 171-178 (Impact Factor 3.741).**
23. Sopapan Intahphuak, Ampai Panthong*, Duangta Kanjanapoth[a], Tawat Taesotikul, Chongkon Krachangchaeng, **Vichai Reutrakul**, "Anti-inflammatory and analgesic activities of *Mallotus spodocarpus* Airy Shaw", **J. Ethnopharmacology 2004, 90, 69-72 (Impact Factor 2.322).**
24. Ampai Panthong*, Duangta Kanjanapothi, Tawat Taesotikul, Apithai Phankummoon, Kanda Panthong, **Vichai Reutrakul**, "Anti-inflammatory activity of methanolic extract from *Ventilago harmandiana* Pierre", **J. Ethnopharmacology 2004, 91, 237-242 (Impact Factor 2.322)**.
25. Patoomratana Tuchinda, Aroonchai Saiai, Manat Pohmakotr, Chalobon Yoosook, Jittra Kasisit, Chanita Napaswat, Thawatchai Santisuk, **Vichai Reutrakul**, "Anti-HIV-1 cycloartanes from leaves and twigs of *Gardenia thailandica*", **Planta Medica 2004, 70, 366-370 (Impact Factor 2.289)**.
26. **Vichai Reutrakul**,* Chongkon Krachangchaeng, Patoomratana Tuchinda,* Manat Pohmakotr, Thaworn Jaipetch, Chalobon Yoosook, Jittra Kasisit, Samaisukh Sophasan, Kulawee Sujarit and Thawatchai Santisuk, "Cytotoxic and anti-HIV-1 constituents from leaves and twigs of *Gardenia tubifera*", **Tetrahedron 2004, 60, 1517-1523 (Impact Factor 3.219)**.

27. Patoomratana Tuchinda,* Bamroong Munyoo, Manat Pohmakotr, Pongchan Thinapong Samaisukh Sophasan, Thawatchai Santisuk, and **Vichai Reutrakul**, "Cytotoxic styryl-lactones from the leaves and twigs of *Polyalthia crassa*", **J. Nat. Prod. 2006, 69, 1728-1733 (Impact Factor 3.159)**.

28. Patoomratana Tuchinda[1], Anawat Kumkao[1], Manat Pohmakotr[1], Samaisukh Sophasan[2], Thawatchai Santisuk[3], **Vichai Reutrakul**[1], "Cytotoxic arylnaphthalide lignan glycosides from the aerials parts of *Phyllathus taxodiifolius*", **Planta Medica 2006, 72, 60-62 (Impact Factor 2.289)**.

29. **Vichai Reutrakul**, Waraporn Chanakul, Manat Pohmakotr, Thaworn Jaipetch, Chalobon Yoosook, Jittra Kasisit, Chanita Napaswat, Thawatchai Santisuk, Samran Prabpai, Palangpon Kongsaeree, Patoomratana Tuchinda, "Anti-HIV-1 constituents from leaves and twigs of *Cratoxylum arborescens*", **Planta Med. 2006, 72, 1433-1435 (Impact Factor 2.289)**.

30. Sukathida Ubol, Jarin Kramyu, Promsin Masrinoul, Chongkon Kachangchaeng, Prapadsorn Pittayanurak, Samaisuk Sophasan and **Vichai Reutrakul**, "A novel cycloheptapeptide exerts strong anticancer activity *via* stimulation of multiple apoptotic pathways in caspase-3 deficient cancer cells", **Anticancer Research 2007, 27, 2473-2480 (Impact Factor 1.414)**.

31. Ampai Panthong*, Pinpaka Norkaew, Duangta Kanjanapothi, Tawat Taesotikul, Natthinee Anantachok, **Vichai Reutrakul**[b], "Anti-inflammatory, analgesic and antipyretic activities of the extract of gamboges from *Garcinia hanburyi* hook f.", **J. Ethnopharmacology 2007, 111, 335-340 (Impact Factor 2.322).**

32. **Vichai Reutrakul**, Natthinee Anantachoke, Manat Pohmakotr, Thaworn Jaipetch, Samaisukh Sophasan, Chalobon Yoosook, Jittra Kasisit, Chanita Napaswat, Thawatchai Santisuk, Patoomratana Tuchinda, "Cytotoxic and anti-HIV-1 caged xanthones from the resin and fruits of *Garcinia hanburyi*", **Planta Med. 2007, 73, 33-40 (Impact Factor 2.289)**.

33. **Vichai Reutrakul**, Niwat Ningnuek, Manat Pohmakotr, Chalobon Yoosook, Chanita Napaswad, Jitra Kasisit, Thawatchai Santisuk, Patoomratana Tuchinda, "Anti-HIV-1 flavonoid glycosides from *Ochna integerrima*", **Planta Med. 2007, 73, 683-688 (Impact Factor 2.289)**.

34. Payong Wanikiat,*, Ampai Panthong, Pacharawan Sujayanon, Chalobon Yoosook, Adriano G. Rossi, **Vichai Reutrakul**, "The anti-inflammatory effects and the inhibition of neutrophil responsiveness by *Barleria lupulina* and *Clinacanthus nutans* extracts", **J. Ethnopharmacology 2008, 116, 234-244 (Impact Factor 2.322)**.

35. Patoomratana Tuchinda,* Jittra Kornsakulkarn, Manat Pohmakotr, Palangpon Kongsaeree, Samran Prabpai, Chalobon Yoosook, Jitra Kasisit, Chanita Napaswad, Samaisukh Sophasan, and **Vichai Reutrakul**, "Dichapetalin-type triterpenoids and lignans from the aerial parts of *Phyllanthus acutissima*", **J. Nat. Prod. 2008, 71, 655-663 (Impact Factor 3.159)**.

36. **Vichai Reutrakul**, Natthinee Anantachoke, Manat Pohmakotr, Thaworn Jaipetch, Chalobon Yoosook, Jittra Kasisit, Chanita Napaswa, Ampai Panthong, Thawatchai Santisuk, Samran Prabpai, Palangpon Kongsaeree, Patoomratana Tuchinda, "Anti-HIV-1 and anti-inflammatory lupanes form the leaves, twigs, and resin of *Garcinia hanburyi*", **Planta Med. 2009, 75, 1-4 (Impact Factor 2.289)**.

6.2 Product, Innovation, Award and News

Product: 1

Plaitanoids^{TM}, a range of cosmetics and spa products are commercially available.

This Senior Research Scholar Program was selected as "The Outstanding Research Program on the studies of Bioactive compounds from Thai Medicinal Plants" for 2004.

The research on *Garcinia hanburyii* was publicized in Thairath News Paper on 11 January 2004.

6.3 Seminars and Meetings

6.3.1 Invited Lectures

Plenary Speaker, Indonesia, November, 2006

Invited Speaker, U.S.A., December, 2004

Invited Speaker, TRF Senior Scholars and Young TRF Grantees, October, 2005 and October 2006.

6.3.2 Seminars

The senior Scholar Research Program involved lectures by Professor Barry Trost, a world renown organic chemistry, from Stanford University during 14-19 December 2003, 16 December 2003, 6 hours lectures at Mahidol University on Allylic Alkylation, An Enabling Synthetic Methodology with the Emphasis on Palladium and Molybdenum.

17 December 2003, Prince of Songkhla University on "Crafting Chiral Space for Chiral Recognition in a Catalytic Synthetic Reaction".

18 December 2003, Burapha University on "New Strategies for the Synthesis of Complex Bioactive Targets".

6.4 Personnel Involved in the Program

6.4.1 A total of 76 persons has been involved in the program

1. Investigators including PI 14
2. Ph.D. Students 13
3. M.Sc. Students 27

4. Students Graduated

   Ph.D. 11

   M.Sc. 27

5. Research Associates, Technical Assistants,

   Research Assistants 22

6. Exchange Students

   From Thailand to U.S.A., Sweden, Australia

   Stanford University Ph.D. 2

   University of California at Santa Cruz Ph.D. 2

   Purdue University Ph.D. 1

   Uppsala University Ph.D. 1

   University of Western Australia Ph.D. 1

   From U.S.A., Sweden to Thailand

   Stanford University Ph.D. 1

   University of California at Santa Cruz Ph.D. 1

   Uppsala University M.Sc. 1

6.4.2 A List Research Team.

6.4.2.1 The main investigators in the collaborative research network are as follows.

1. Vichai Reutrakul, Principal Investigator (PI)
   Department of Chemistry
   Faculty of Science, Mahidol University (MU)
   Rama 6 Road, Bangkok 10400
2. Manat Pohmakotr, Investigator
   Department of Chemistry
   Faculty of Science, Mahidol University (MU)
   Rama 6 Road, Bangkok 10400
3. Patoomratana Tuchinda, Investigator
   Department of Chemistry
   Faculty of Science, Mahidol University (MU)
   Rama 6 Road, Bangkok 10400

4. Chutima Kongkittingam Kuhakarn Investigator
Department of Chemistry
Faculty of Science, Mahidol University (MU)
Rama 6 Road, Bangkok 10400
5. Samaisukh Sophasan, Investigator
Department of Physiology
Faculty of Science, Mahidol University (MU)
Rama 6 Road, Bangkok 10400
6. Chalobon Yoosook, Investigator
Department of Microbiology
Faculty of Science, Mahidol University (MU)
Rama 6 Road, Bangkok 10400
7. Payong Wanikiat, Investigator
Department of Pharmacology
Faculty of Science, Mahidol University (MU)
Rama 6 Road, Bangkok 10400
8. Vatcharin Rukachaisirikl, Investigator
Department of Chemistry
Faculty of Science
Prince of Songkhla University (PSU)
Hadyai, Songkhla 90110
9. Souwalak Pongpaichit Investigator
Department of Microbiology
Faculty of Science
Prince of Songkhla University (PSU)
Hadyai, Songkhla 90110
10. Thongchai Kruahong Investigator
Department of Chemistry
Faculty of Science and Technology
Rajabhat Institute Suratthani (RI, Suratthani)
Surat-Nasan Road, Suratthani 84100

11. Chariya Hahnvajanawong, Investigator
Department of Microbiology
Faculty of Madicine, Khon Kaen University (KKU)
Khon Kaen 40002

12. Ampai Panthong, Investigator
Department of Pharmacology
Faculty of Madicine, Chiangmai University (CMU)
Chiangmai 50202

13. Duangta Kanjanapothi
Department of Pharmacology
Faculty of Madicine, Chiangmai University (CMU)
Chiangmai 50202

14. Thawatchai Santisuk
Herbarium
Royal Forestry Department (Forestry)
Ministry of Natural Resources and Environment
Bangkok 10900

6.4.2.2 Graduate Students and Research Assistants in the Program

1. Department of Chemistry, Mahidol University, research in organic synthesis and bioactive natural products

Organic Synthesis

Ph.D. Students

1. Miss Thanchanok Thongpaisalwong (graduated 2005)
2. Mr. Suwatchai Jarussophon (graduated 2004)
3. Mr. Jaray Jaratijaroonphong (graduated 2006)
4. Mr. Pramchai Deelertpaiboon
5. Mr. Sopanat Kongsriprapan

M.Sc. Students

1. Miss Jariya Buajarern (graduated 2003)
2. Miss Siriporn Kamtonwong (graduated 2004)
3. Mr. Apiwat Chompoosor (graduated 2005)

4. Miss Kassrin Tangdenpaisal (graduated 2006)
5. Miss Darunee Soorukram (graduated 2003)
6. Miss Tipwan Mophoung (graduated 2003)
7. Mr. Taweechote Komutkul (graduated 2004)
8. Miss Arisara Issaree (graduated 2004)
9. Miss Saisuree Prateepthongkum (graduated 2004)
10. Mr. Winai Ieawsuwan (graduated 2004)
11. Mr. Attapol Pinsa (graduated 2005)
12. Mr. Krisada Kittigowittana (graduated 2005)

Bioactive Natural Products

Research Associate

1. Dr. (Miss) Thavorn Jaipetch

Ph.D. Students

1. Miss Pornsiri Leewanit (graduated 2005)
2. Miss Phanruethai Pailee (graduated 2006)
3. Mr. Bamrung Munyoo (graduated 2006)
4. Ms. Chongkon Krachangchaeng (graduated 2003)
5. Miss Natthinee Anatachole (graduated 2007)
6. Mr. Niwat Ningnuek (graduated 2007)
7. Mr. Suksit Nobsathian (graduated 2009)

M.Sc. Students

1. Miss Saidanee Wangpathanapanich (graduated 2003)
2. Miss Arunchai Saiai (graduated 2003)
3. Mr. Anawat Khumkhaos (graduated 2005)
4. Miss Suchada Buasuntorn (graduated 2007)
5. Miss Waraporn Chanakul (graduated 2007)
6. Miss Janchai Poonlaphdecha (graduated 2005)
7. Miss Jittra Kornsakulkarn (graduated 2007)
8. Miss Pubpha Benchathewan (graduated 2007)
9. Miss Siriporn Saepou (graduated 2007)

Technicians and Research Assistants

1. Miss Suttiporn Chaichana
2. Ms. Patcharin Poochaiwatananonth
3. Miss Prapadsorn Pittayanurag
4. Mr. Peradhama Thiemthieprat
5. Mr. Samreang Buntheang

2. Department of Physiology, Faculty of Science, Mahidol University.

Cytotoxic Assay

Staff

1. Dr. Samaisukh Sophasan

Research Associate

1. Dr. (Ms.) Kulawee Sujarit

Technicians

1. Miss Chonlada Sapeeya
2. Miss Chonticha Sornsong
3. Miss Sudatip Plangsorn
4. Mr. Suphatra Sae-Sim

3. Department of Microbiology, Faculty of Science, Mahidol University.

Anti-HIV Assays

Technicians, under the supervision of Dr. Chalobon Yoosook

1. Miss Jitra Kasisit
2. Miss Chanita Napasawadhi

4. Department of Chemistry, Faculty of Science, Prince of Songkhla University.

Bioactive Natural Products

Technicians, under the supervision of Dr. Vatcharin Rukachaisirikul

1. Mr. Somsak Saelim

5. Department of Chemistry, Faculty of Science and Technology, Rajabhat Institute Suratthani

Bioactive Natural Products

Research Assistant, under the supervision of Dr. Thongchai Kruahong

1. Miss Pootchana Predasukd

6. Department of Pharmacology, Faculty of Medicine, Chiangmai University.

Anti-inflammatory and Preliminary Toxicology

Ph.D. Student, under the supervision of Dr. Ampai Panthong and Duanta Kanjanapothi

1. Miss Sopapan Intaphueak (graduated 2004)

M.Sc. students, under the same supervisors

1. Miss Pinpaka Norkaew (graduated 2003)
2. Miss Wanicha Supradijaporn (graduated 2004)
3. Miss Siriporn Somya (graduated 2006)

7. Department of Pharmacology, Faculty of Science, Mahidol University.

Anti-inflammatory assay (neutrophils)

Research Assistant under the supervision of Dr. Payong Wanikiat

1. Miss Monthakarn Chaiyodwong
2. Miss Nontakarn Sricharoen

8. Department of Microbiology, Faculty of Science, Price of Songkla University.

Antimicrobial assay

Staff

1. Dr. Souwaluk Pongpaichit

Technician

1. Miss Thitapawan Nangpeng

9. Department Biochemistry, Faculty of Science, Prince of Songkhla University.

Antioxidative assay

Research Associate

1. Dr. Nongporn Towatana

Technician

1. Miss Pratum Ritthisunthorn

10. Department Microbiology, Faculty of Medicine, Khon Kaen University.

Anticholangiocarcinoma assay

Staff

1. Dr. Chariya Hahnvajanawong

M.Sc. Students

1. Miss Punsa Koryaiklang (graduated 2003)

2. Miss Porada Petchsuk (graduated 2003)
3. Miss Arpa Surapitoon (graduated 2005)

11. Herbarium

Royal Forestry Department

Biodiversity

Research Associates in collaboration with Dr. Thawatchai Santisuk

1. Mr. Narong Nanthasaen

7. Publications, Products Brochure and News.

7.1 Publications

7.2 Products Brochure

Plaitanoids™

สมุนไพรเป็นมรดกของชาติที่ถูกนำมาประยุกต์ใช้ควบคู่กับวิถีชีวิตของคนไทยมายาวนาน ไม่ว่าจะนำมาใช้ในการบำบัดรักษาโรคภัยไข้เจ็บหรือบำรุงสุขภาพให้แข็งแรง สมุนไพรตัวหนึ่งที่พบมากในประเทศไทยและนำมาใช้ในการบรรเทาอาการปวดเมื่อยกล้ามเนื้อ เคล็ดขัดยอก และผิวหนังอักเสบ รวมทั้งช่วยในการรักษาฝี หนอง สิว แมลงสัตว์กัดต่อย และรักษาโรคเกี่ยวกับทางเดินหายใจ คือ **"ไพล"**

ด้วยคุณประโยชน์ของสมุนไพร **"ไพล"** ทางด้านการแพทย์แผนไทยดังกล่าว ประกอบกับข้อมูลการวิจัย เกี่ยวกับสมุนไพร **"ไพล"** ของ **ศ.ดร.วิชัย ริ้วตระกูล** แห่งมหาวิทยาลัยมหิดล และเมธีวิจัยอาวุโส สำนักงานกองทุนสนับสนุนการวิจัย (สกว.) ที่ได้ทำการศึกษามานานกว่า 30 ปี รวมทั้งงานตีพิมพ์ในวารสารนานาชาติ ทำให้สำนักงานนวัตกรรมแห่งชาติ (NIA) ได้ทำการบุกเบิกและริเริ่มที่จะนำสมุนไพร **"ไพล"** มาพัฒนาเป็นสมุนไพรแห่งชาติ โดยได้ระดมความรู้ทางด้านวิชาการในการวิจัย **"ไพล"** จากโครงการพัฒนาบัณฑิตศึกษาและการวิจัยทางเคมี (PERCH) และประสานงานกับภาคเอกชนโดยมี

บริษัท โควิก เคมท์ อินเตอร์เนชั่นแนล (ประเทศไทย) จำกัด

เป็นแกนนำกลุ่มบริษัทเอกชนต่างๆ ซึ่งประกอบด้วย

บริษัท ดอกบัวคู่ จำกัด
บริษัท เอสซีติก คลินิก จำกัด
บริษัท เฮอร์เบิล อินโนเวชั่น จำกัด
บริษัท เดอะมิเดิลเวย์ วัน เวิลด์ จำกัด
บริษัท อดินพ จำกัด
และบริษัท เอส.ซี. อาร์ตทิสตรี้ จำกัด

รวม 7 บริษัท ซึ่งได้พัฒนาสมุนไพร **"ไพล"** จนเกิดขึ้นเป็น

Plaitanoids™

สนับสนุนโดย สำนักงานนวัตกรรมแห่งชาติ

NIA PERCH

KOVIC

Plaitanoids™ เป็นเครื่องหมายการค้า (Trademark) ของส่วนประกอบที่มีกลุ่มสารออกฤทธิ์พวก arylbutanoids เช่น DMPBD หรือ (*E*)-1-(3',4'-Dimethoxyphenyl)-butadiene และ Terpinen-4-ol ซึ่งได้มาจากเหง้าของ ***"ไพล"*** (*Zingiber cassumunar* Roxb.)

ผลิตภัณฑ์ภายใต้ชื่อ *Plaitanoids™*

Plaitanoids™ Essential Oil
Plaitanoids™ Liquid Extract
Plaitanoids™ Powder Extract

สารออกฤทธิ์ใน *Plaitanoids™*

กลุ่มที่ 1

Plaitanoids™ Essential Oil สารสำคัญ คือ สารในกลุ่ม Terpinen-4-ol ซึ่งมีฤทธิ์ในการต่อต้านการอักเสบและการติดเชื้อ และสารในกลุ่ม (*E*)-1-(3',4'-Dimethoxyphenyl)-butadiene = DMPBD ซึ่งมีฤทธิ์ในการบรรเทาอาการปวดเมื่อยและต่อต้านการอักเสบ

กลุ่มที่ 2

Plaitanoids™ Liquid Extract และ Plaitanoids™ Powder Extract สารสำคัญ คือ สารในกลุ่ม เคอร์คิวมินอยด์ (CURCUMINOIDS) มีคุณสมบัติช่วยบำรุงผิว ทำให้ผิวขาว ปกป้องผิวจากอนุมูลอิสระ และลดการอักเสบ นอกจากนี้ยังพบสารอนุพันธ์บางตัวในสารสกัดไพลที่มีฤทธิ์ลดการอักเสบได้ดีกว่า "ไคโคฟีนอล" สูงถึง 20-30 เท่า จึงเหมาะสำหรับใช้ในผลิตภัณฑ์ลดการอักเสบ รักษาสิว ผลิตภัณฑ์สปา ผลิตภัณฑ์บำรุงผิว ชะลอริ้วรอยเหี่ยวย่น ผลิตภัณฑ์ทำให้ผิวขาว และยังพบสารสำคัญใน ***"ไพล"*** อีกไม่น้อยกว่า 32 ตัว ซึ่งได้มีการค้นคว้าทดลอง และวิจัย โดยมีข้อมูลเชิงวิชาการสนับสนุนในการพัฒนาผลิตภัณฑ์นี้มากกว่า 39 ผลงานวิจัย

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7.3 News

ไทยรัฐ
ประจำวันเสาร์ที่ 11 มกราคม 2547

"รงทอง" ต้านเอดส์- "คองดึง" ลดมะเร็ง

● รุกวิจัยผลิตเป็นยาฝีมือคนไทย ● ติงอุดมฯ ไร้มาตรฐานประเมิน

ศ.นพ.เกษม วัฒนชัย องคมนตรี บรรยายพิเศษ เรื่อง "ยุทธศาสตร์การวิจัยเพื่อเพิ่มขีดความสามารถในการแข่งขันของประเทศ" ในการประชุม "นักวิจัยรุ่นใหม่พบเมธีวิจัยอาวุโส" ว่า การบริหารงานวิจัยต้องเป็นการบริหารยุทธศาสตร์เพื่อรับการเปลี่ยนแปลง แต่ไทยยังเน้นการบริหารแบบงานประจำ โดยส่งแค่รองนายกรัฐมนตรีดูแล จึงจำเป็นต้องสร้างความเข้าใจให้ทุกส่วน รวมถึงประชาชนเข้าใจถึงความสำคัญของงานวิจัย ทั้งนี้องค์กรที่ไม่มีผู้รอบรู้คือองค์กรที่ไร้สมอง ซึ่งเท่าที่ทราบบางมหาวิทยาลัยไม่ทำวิจัยเลย ทั้งที่หน้าที่แรกของมหาวิทยาลัยคือหาความรู้แล้วถ่ายทอด ไม่ใช่แค่สอนโดยอาศัยความรู้เก่าๆ และเปิดรับนักศึกษาเยอะๆ จบง่ายๆ ที่ผ่านมาอุดมศึกษาไทยไม่มีมาตรฐานกลางชาติในการประเมินเกณฑ์ขั้นต่ำ แม้แต่สาขาแพทยศาสตร์ก็ไม่มี รวมถึงสาขาอื่นๆ ที่สอนกันเองประเมินกันเอง

ผู้สื่อข่าวรายงานว่า ในที่ประชุมมีการนำเสนอผลงานวิจัยที่หลากหลาย ของนักวิจัยที่ได้รับทุนสนับสนุนจากสำนักงานกองทุนสนับสนุนการวิจัย (สกว.) อาทิ ศ.ดร.วิชัย ริ้วตระกูล จากภาควิชาเคมี คณะวิทยาศาสตร์ มหาวิทยาลัยมหิดล เมธีวิจัยอาวุโส ซึ่งค้นพบ "รงทอง" มีคุณสมบัติในการยับยั้งเชื้อโรคเอดส์ โดยระบุว่า ต้นรงทองเป็นพืชที่พบมากในแถบเอเชียตะวันออกเฉียงใต้ ในไทยพบมากที่ จ.จันทบุรี ซึ่งจากการทดสอบคุณสมบัติของสารในต้นรงทอง จนได้สารอนุพันธ์ใหม่ มีชื่อว่า GAMBOGIC ที่มีฤทธิ์ฆ่าเซลล์มะเร็ง ฆ่าเชื้อเอดส์และฆ่าเชื้อแบคทีเรียได้ดีมาก ขั้นต่อไปคือการทดสอบพิษวิทยาและทดสอบในสัตว์

ส่วน ส.ดร.สมศักดิ์ รุจิรวัฒน์ หน.ห้องปฏิบัติการเภสัชเคมี สถาบันวิจัยจุฬาภรณ์ ซึ่งทำวิจัยเรื่อง "การวิจัยและพัฒนาสารที่ใช้เป็นยา และกระบวนการสังเคราะห์ยาต้านมะเร็งแบบใหม่" กล่าวว่า จากการวิจัย "ต้นดองดึง" พบสารโคลชิซีน Colchicine ซึ่งเมื่อนำมาปรับเปลี่ยนโครงสร้างใหม่แล้วนำไปทดสอบฤทธิ์กับมะเร็งท่อน้ำดีพบว่า สารที่สังเคราะห์ขึ้นบางตัวมีฤทธิ์ยับยั้งการแบ่งเซลล์ได้ดีกว่าสารตัวแม่ถึง ๓๐ เท่า นอกจากนี้ยังพบสารลาเมลลารินในผลิตภัณฑ์ธรรมชาติกลุ่มหนึ่ง สามารถยับยั้งการแบ่งเซลล์มะเร็งและบำบัดการดื้อยาของเซลล์มะเร็งได้ ทั้งนี้คณะผู้วิจัยได้พัฒนากระบวนการสังเคราะห์สารกลุ่มลาเมลลารินใหม่ ด้วยวิธีทางเคมีอินทรีย์ทำให้ได้สารถึง ๘๐٪ ที่สำคัญคือลดขั้นตอน ซึ่งทั้งสองสารยังต้องใช้เวลาในการผลิตเป็นยา.