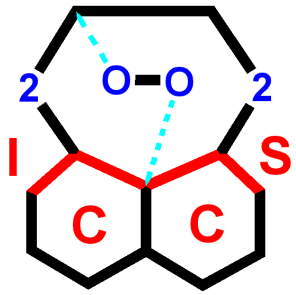
The Third International Symposium for Chinese Medicinal Chemists

第三屆世界華人藥物化學研討會 28-31 Dec 2002, Hong Kong

Program & Abstracts

The Hong Kong University of Science and Technology

ISCMC-2002



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The Hong Kong University of Science and Technology

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ACKNOWLEDGMENTS

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National Natural Science Foundation of China, Beijing
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Program & Abstracts, The Third International Symposium for Chinese Medicinal Chemists (ISCMC-2002)

Welcome

On behalf of the Hong Kong University of Science and Technology, I am pleased to extend a very warm welcome to all of you to *The Third International Symposium for Chinese Medicinal Chemists* (**ISCMC–2002**), which is the first symposium of this series in the Hong Kong Special Administration Region.

The International Symposium for Chinese Medicinal Chemists (ISCMC) is held every two years with the objective to provide a stimulating venue for exchanging scientific results and enhancing communication among the medicinal chemists in the Chinese Mainland, Taiwan, Hong Kong and overseas. The first and second symposia of ISCMC were held successfully in Taipei (July 19-23, 1998) and Chengdu (October 15-19, 2000). This year, HKUST together with colleagues from other local tertiary institutions, is honored to host the third symposium of this series in Hong Kong.

We have organized a comprehensive and exciting scientific program with distinguished scientists presenting their latest scientific findings and sharing their insights. This symposium promises a wealth of outstanding science in all aspects of medicinal chemistry with special focus on the studies of novel approaches to drug discovery and development, including chemical biology, bioinformatics, virtual screening, combinatorial chemistry, chirotechnology, and TCM related research. We hope that this symposium will provide us a unique opportunity to share the latest discoveries in medicinal chemistry and to explore potential research collaborations.

On behalf of the Organizing Committee, I sincerely hope that you will enjoy your stay at HKUST. I look forward with great pleasure to my own participation and to interacting with many scientists from the Chinese Mainland, Taiwan and overseas for a rewarding and successful meeting.

Nancy Ip
Chair, Organizing Committee

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The Third International Symposium for Chinese Medicinal Chemists
(ISCMC-2002)

28-31 December 2002
The Hong Kong University of Science and Technology

Day 1 (28 December 2002, Saturday)

14:00-21:00 pm	Registration [Academic Concourse]
18:30-21:00 pm	Welcome Reception [University Center, Tin Ka Ping Hall]

Day 2 (29 December 2002, Sunday)

9:00-9:30 am 9:30-10:15 am	[LTB] **Opening ceremony** **Plenary Lecture PL-1: Prof. Hung-wen Liu** *Studies of UDP-galactopyranose mutase from Escherichia coli. An unusual role of reduced FAD in its catalysis*	Chair: Prof. Chris C. K. Chang
10:20-10:40 am	Tea break	
	Session A-1 [LTB] Chair: Prof. Dawei Ma	*Session B-1* [LTC] Chair: Prof. Yun-Dong Wu
10:40-11:10 am	**Invited lecture IL-7: Prof. Xiao-Jiang Hao** *Bioactive compounds from Chinese medicinal plants*	**Invited lecture IL-23: Dr. Jun Xu** *HTS data mining and virtual library analysis*
11:15-11:45 am	**Invited lecture IL-8: Prof. Richard K. Haynes** *Hyperactive peroxidic antimalarials and questions on mechanism of action*	**Invited lecture IL-10: Prof. Hua-Liang Jiang** *Aspects of virtual screening in the cycle of drug discovery: Successful stories, prospects and challenge*
11:50-12:20 pm	**Invited lecture IL-11: Prof. Xiaoyu Li** *Immunomodulating natural products from Chinese herbs*	**Invited lecture IL-25: Prof. Michael M. Yang** *Integration of functional genomics and cell-based assays for drug discovery from traditional Chinese medicine*

Day 2 (29 December 2002, Sunday)

12:30-14:00 pm	Lunch [University Center, Bistro]	
	Session A-2 [LTB] Chair: Prof. Zong-Ru Guo	*Session B-2* [LTC] Chair: Prof. Peng George Wang
14:00-14:30 pm	**Invited lecture IL-1: Dr. Jianming Bao** *Pyrrolidine modulators of chemokine receptor activity*	**Invited lecture IL-5: Prof. Zhongwu Guo** *Glycopeptide synthesis with free oligosaccharides as phase tags*
14:35-15:05 pm	**Invited lecture IL-15: Prof. Dawei Ma** *Design and synthesis of matrix metalloproteinase inhibitors*	**Invited lecture IL-19: Prof. Lai-Xi Wang** *Bioorganic approaches to an effective HIV vaccine*
15:10-15:40 pm	**Invited lecture IL-18: Prof. Cherng-Chyi Tzeng** *Synthesis and anticancer evaluation of furoquinolines*	**Invited lecture IL-28: Prof. Biliang Zhang** *High-throughput synthesis for anti-HIV and anticancer drug Discovery*
15:45-16:05 pm	Tea break	
	Session A-3 [LTB] Chair: Prof. Zhen Yang	*Session B-3* [LTC] Chair: Prof. Zhihong Guo
16:05-16:35 pm	**Invited lecture IL-14: Dr. Kun Liu** *Small molecule insulin mimetics with potential utilities as anti-diabetic as well as anti-obesity therapies*	**Invited lecture IL-12: Prof. Chun-Hung Lin** *Synthesis of bioactive carbohydrates by glycosidic bond formation*
16:40-17:10 pm	**Invited lecture IL-24: Dr. Yao-Chang Xu** *From an idea to a clinical candidate: A search for new treatment of depression using selective 5-HT1A receptor antagonist*	**Invited lecture IL-16: Prof. Dehua Pei** *Enzymes for posttranslational protein modification as novel drug targets*
17:15-17:45 pm	**Invited lecture IL-21: Prof. Yan-Guang Wang** *Polymer-supported synthesis of heterocycles*	**Invited lecture IL-20: Prof. Peng George Wang** *Carbohydrate-based drug development*
17:50-18:10 pm	**Oral presentation OP-4: Dr. Jason Siu** *Studies towards the total synthesis of rapamicin*	**Oral presentation OP-3: Prof. Yong Gao** *Nanoparticle supports for biological and chemical applications*
18:30-20:00 pm	Dinner [China Garden, Ground Floor, Atrium]	
20:00-21:30 pm	Poster presentations [Academic Concourse] Chair: Prof. Wei-Min Dai	

Day 3 (30 December 2002, Monday)

9:00-9:45 am	[LTB] Chair: Prof. Henry N. C. Wong **Plenary Lecture PL-2: Prof. Tsann-Long Su** *Development of DNA topoisomerase II-mediated anticancer agent: AHMA derivatives*	
9:50-10:20 am	**Invited lecture IL-13: Prof. Guo-Qiang Lin** *Recent development in the carbon-carbon bond formation: Learn something from natural products*	
10:25-10:40 am	Tea break	
10:40-11:10 am	*Session A-4* [LTB] Chair: Prof. Li-He Zhang **Invited lecture IL-2: Prof. Ji-Wang Chern** *Design and synthesis of potential DNA double and triple helices stabilizing agents*	*Session B-4* [LTC] Chair: Yan-Guang Wang **Technical presentation TP-1: Dr. Vijay Gupta** *Highly efficient and automated microwave-assisted organic synthesis through coherent synthesis™*
11:15-11:45 am	**Invited lecture IL-4: Dr. Daniel T. W. Chu** *Recent advance in macrolide antibiotic research*	**Invited lecture IL-31: Dr. Xiao-Yi Xiao** *High throughput crystallography and structure-based drug discovery*
11:50-12:20 pm	**Invited lecture IL-29: Prof. Yi-Hua Zhang** *Design, synthesis and anti-inflammatory activity of α-substituted p-(methanesulfonylphenyl)propenoic acid and related compounds*	**Invited lecture IL-9: Prof. Ziwei Huang** *Protein-protein interactions: Mechanisms, medicinal chemistry, and implications for post-genomic drug discovery*
12:30-14:00 pm	Lunch [University Center, Bistro]	

Day 3 (30 December 2002, Monday)

14:00-14:30 pm	*Session A-5* [LTB] Chair: Prof. Dehua Pei **Invited lecture IL-3: Prof. Der-Hang Chin** *The action of apoprotein in the antitumor antibiotic neocarzinostatin*	*Session B-5* [LTC] Chair: Prof. Guo-Qiang Lin **Invited lecture IL-6: Prof. Zong-Ru Guo** *Design and synthesis of anti-diabetics based on PPAR-gamma structure and virtual screening of focused library*
14:35-15:05 pm	**Invited lecture IL-22: Prof. Zhen Xi** *DNA recognition and damage by small molecules at bulge site*	**Invited lecture IL-26: Prof. Zhen Yang** *Diversity-oriented synthesis and branched reaction pathway applied to natural product-like compounds*
15:10-15:40 pm	**Invited lecture IL-17: Prof. Ben Shen** *Natural product biosynthesis and prospects of engineering microorganisms for chemical structural diversity*	**Invited lecture IL-30: Dr. Jieping Zhu** *Development of novel multicomponent domino process for heterocycle synthesis*
15:45-16:05 pm	Tea break	
16:05-16:25 pm	*Session A-6* [LTB] Chair: Yi-Hua Zhang **Oral presentation OP-1: Prof. Zongwei Cai** *LC-MS application for high-throughput DMPK study in drug discovery*	*Session B-6* [LTC] Prof. Cherng-Chyi Tzeng **Oral presentation OP-5: Prof. Ming-Jung Wu** *Cytotoxicities and topoisomerase I inhibitory activities of 2-[2-(2-alkynylphenyl)ethynyl]benzonitriles, 1-aryl-3-decen-1,5-diynes, and their related bi-enediyne derivatives*
16:30-16:50 pm	**Oral presentation OP-2: Prof. Cheng-Bin Cui** *Chemical and biological properties of new cell cycle inhibitors and apoptosis inducers from Chinese medicinal herbs*	**Oral presentation OP-6: Prof. Ding-Yah Yang** *Mode of active of 4-hydroxyphenylpyruvate dioxygenase inhibition by triketone-type inhibitors*
16:55-17:15 pm	**Oral presentation OP-7: Prof. Lin Xia** *3D-QSAR study on 1-(substituted phenyl)-4-(2-substituted phenoxyethyl)piperazine analogues of α_1-adrenoceptor antagonist*	**Oral presentation OP-8: Prof. Zhihong Guo** *Biomimetic combinatorial synthesis of cyclic peptide libraries for drug discovery*
18:30-20:30 pm	Banquet [China Garden, Ground Floor, Atrium]	

Day 4 (31 December 2002, Tuesday)

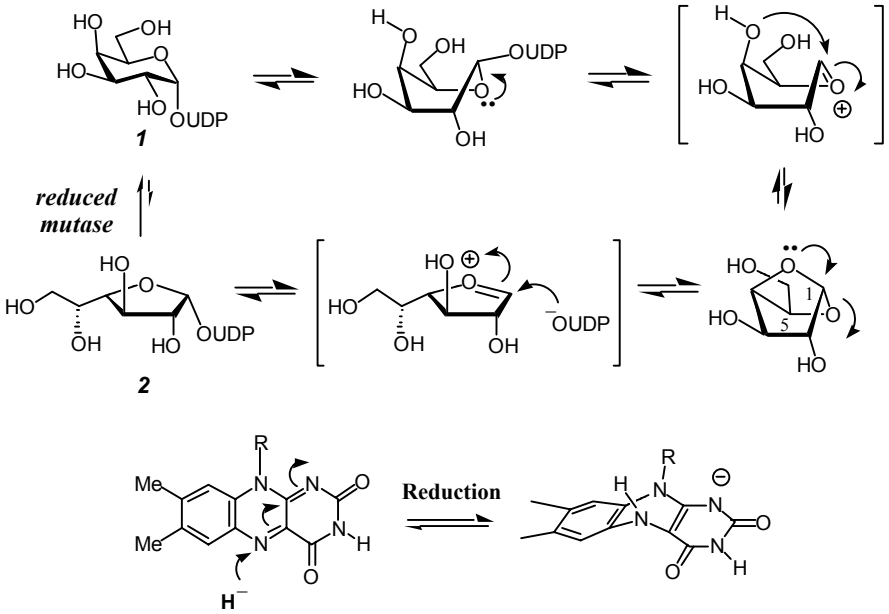
9:00-9:45 am	[LTB] Chair: Prof. Ji-Wang Chern **Plenary Lecture PL-3: Prof. Li-He Zhang** *Chemical syntheses and calcium release activities of N-1-glycosyl substituted cADPR mimics*
9:50-10:20 am	**Invited lecture IL-32: Prof. Yun-Dong Wu** *Theoretical study of secondary structures of peptides*
10:25-10:45 am	Tea break
10:50-11:20 am	[LTB] Chair: Prof. Richard Haynes **Invited lecture IL-27: Dr. Tao Ye** *Studies toward the total synthesis of pharmaceutically active marine natural products*
11:30-12:00 noon	[LTB] **Closing ceremony**
12:00-13:30 pm	Lunch [University Center, Bistro]
13:30-17:30 pm	Optional tours

Contents

PL-1. Studies of UDP-Galactopyranose Mutase from *Escherichia coli*. An Unusual Role of Reduced FAD in Its Catalysis

Zhishu Huang, Qibo Zhang, and Hung-wen Liu*
Division of Medicinal Chemistry, College of Pharmacy, and Department of Chemistry and Biochemistry, University of Texas, Austin, TX 78712, USA

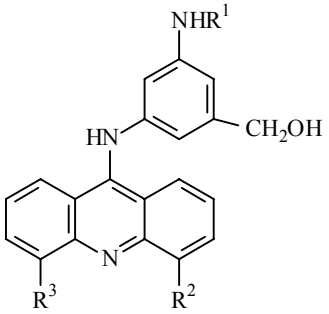
The galactofuranose moiety found in many surface constituents of microorganisms is derived from UDP-D-galactopyranose (UDP-Gal*p*, **1**) via a unique ring contraction reaction catalyzed by UDP-Gal*p* mutase. This enzyme, which has been isolated from several bacterial sources, is a flavoprotein where the FAD coenzyme is noncovalently bound. Since its catalysis does not appear to involve a redox mechanism, whether the enzyme-bound FAD plays an active role in the reaction mechanism has been obscure. To study this transformation, the corresponding *E. coli* mutase was purified and the ring contraction product, UDP-Gal*f* (**2**), was chemically synthesized. Using UDP-Gal*f* as the substrate, the preference of the reaction toward the pyranose product was confirmed. Interestingly, when the enzyme was reduced by sodium dithionite, its catalytic efficiency was increased by more than two orders of magnitude. A comparable rate enhancement was also noted when the flavin coenzyme was selectively reduced by photoreduction in the presence of 5-deazariboflavin under anaerobic conditions. Since mutase with either oxidized or reduced FAD is active, the change of the redox state in FAD appears to affect only the activity, but not the catalytic mechanism. It is conceivable that reduction of FAD may induce a favorable conformational change of the enzyme that may be more conducive to catalysis. It is also possible that the reduced flavin bears a higher electron density at N-1, which may then be used to stabilize the transiently formed oxocarbenium ion intermediates to facilitate catalysis. Whether structural effects, electronic effects, or some other mechanisms dictate the ability of FAD to enhance the rate of the mutase reaction is an interesting, albeit challenging question. Several experiments designed to address this question have been carried out and their results will be presented. This work has provided evidence indicating the active involvement of FAD in regulating the catalytic efficiency of this enzyme.



PL-2. Development of DNA Topoisomerase II-Mediated Anticancer Agents: AHMA Derivatives

Tsann-Long Su
Laboratory of Bioorganic Chemistry, Institute of Biomedical Sciences, Academia Sinica, Taipei 115, Taiwan

A series of DNA topoisomerase II (Topo II)-mediated anticancer 9-anilinoacridine derivatives, namely, 3-(9-acridinylamino)-5-hydroxymethylaniline (AHMA, **1**) derivatives, was designed and synthesized on the basis of the known metabolic pathway of *m*-amsacrine (*m*-AMSA). AHMA (**1**) is one of the representative compounds in the new 9-anilinoacridine generation. This agent possesses an intriguing chemical structure, where the substituents on the anilino ring are in the *meta* position to each other. Unlike *m*-AMSA, AHMA can avoid bio-oxidation to form quinonediimine, thus having a longer half-life in human plasma than *m*-AMSA. AHMA is a potent Topo II inhibitor and has superior antitumor efficacy than *m*-AMSA and VP-16 in mice bearing E0771 mammary adenocarcinoma, and B-16 melanoma.[1] Based on the drug's lipophilicity/hydrophilicity properties, drug-enzyme interactions or drug-DNA binding, a variety of AHMA derivatives by modifying the NH_2 and CH_2OH functions on the anilino ring and/or introducing substituent(s) on the acridine moiety were synthesized for antitumor studies. Among these compounds, AHMA-alkylcarbamates (**2**) were found to be more potent than their parent AHMAs.[2] Some of AHMA-alkylcarbamates have better antitumor efficacy than either *m*-AMSA or adriamycin in nude mice bearing human breast tumor MX-1 and its resistant tumor MCF-7/Ad xenografts with less toxicity towards the host. More recently, we have synthesized AHMA derivatives linked to DNA minor groove binding agents. Detailed structure-antitumor activity relationships, inhibitory effects against Topo II and DNA interaction of AHMA derivatives will be discussed.



1. AHMA $R^1 = R^2 = R^3 = H$ AHMA
2. AHMA-alkylcarbamates
   R^1 = COOR (R = alkyl group),
   R^2, R^3 = H, Me, $CONH(CH_2)_2NMe_2$

References:
1. Su, T.-L.; Chou, T.-C.; Kim, J. Y.; Huang, J.-T.; Ciszewska, G.; Ren, W.-Y.; Otter, G. M.; Sirotnak, F. M. Watanabe, K. A. *J. Med. Chem*. **1995**, *38*, 3226-3235.
2. Su, T.-L.; Chen, C.-H.; Huang, L.-F.; Chen, C.-H.; Basu, M. K.; Zhang, X.-G.; Chou, T.-C. *J. Med. Chem*. **1999**, *42*, 4741-4748.

PL-3. Syntheses and Calcium Mobilizing Evaluations of N^1-Glycosyl Substituted Stable Mimics of Cyclic ADP-Ribose[†]

Li-Jun Huang,[§] Yong-Yuan Zhao,[‡] Lan Yuan,[╫] Ji-Mei Min,[§] and Li-He Zhang[*, §]
[§]*National Key Laboratory of Natural and Biomimetic Drugs, Peking University, Beijing 100083, China [E-mail: zdszlh@mail.bjmu.edu.cn]*
[‡]*Department of Chemical Biology, School of Pharmaceutical Sciences, Peking University, Beijing 100083, China*
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[†]*J. Med. Chem.* **2002**, in press.

Ryanodine receptors, together with IP_3 receptors, represent a major pathway of Ca^{2+}-release from intracellular stores and have been shown to be involved in many physiological and pathological processes.[1] Cyclic ADP-ribose (cADPR, **1**), a novel cyclic nucleotide known since 1987,[2] has been attracting worldwide attention in recent years because of its potent calcium mobilizing activities in many systems, especially as a potential second messenger in cellular Ca^{2+} homeostasis.[3]

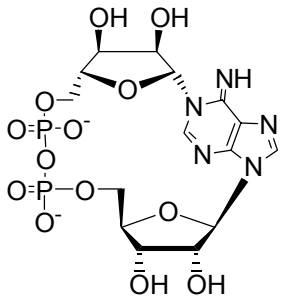
Due to their biological importance, many analogs with modifications at the adenosine unit have been synthesized from NAD^+ analogs using ADP-ribosyl cyclase and served as valuable research tools in the elucidation of the mechanism of cADPR action.[4] However, the analogs that can be obtained by enzymatic and chemoenzymatic methods are limited by the inherent substrate specificity of the enzyme. In fact, there is few analog modified at the N^1-ribosyl moiety of cADPR in contrast to many adenosine modified cADPR analogs by enzymatic method. Furthermore, in some cases the newly formed glycosidic bond is attached to the *N*-7 of the purine ring instead of the desired *N*-1 position.[5] In addition, cADPR can be readily hydrolyzed at the unstable N^1-glycosidic linkage to give ADP-ribose.[6] Therefore, to build up a structure-activity profile for the Ca^{2+} releasing ability of cADPR, it is urgently required to synthesize stable N^1-substituted cADPR mimics by means of chemical synthesis (Figure 1).

Recently, Matsudu and co-workers first described the synthesis of cyclic IDP-carbocyclic-ribose (cIDP-carboribose, **2a**), in which the 4'-oxygen in the N^1-ribosyl moiety is substituted by a methylene group.[7] In this study, we have designed a novel class of stable cIDPR mimics (**3**, **4a**, **4b**, **5a**, **5b**, **6**), in which the N^1-ribosyl moiety is replaced by different configurational glycosyl and the N^1-glycosyl linkage is shifted from N^1-$C_{1''}$ to the N^1-$C_{2''}$ position of furanose in order to improve the stabilization. The 3"-*O*-allyl and 8-bromo modifications have been included due to their anticipated increased cell permeability. Furthermore, in order to explore the role of N^1-glycosyl in the structural modifications, an N^1-acyclic analog has been synthesized in this study. These new cIDPR analogs will provide a greater understanding of ryanodine receptor function and could lead to novel therapeutic agents.

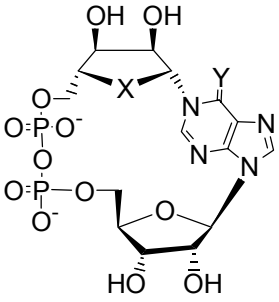
Rat brain microsomes was one of the first mammalian cell preparations in which cADPR and IP_3 were shown to trigger Ca^{2+} release independently of each other. The six novel cyclic nucleotide analogs (**3**, **4a**, **4b**, **5a**, **5b**, and **6**) were tested for their abilities to release calcium from rat brain microsomes and compared to authentic cADPR by using a cofocal laser-scanning microscope (CLSM). The dilution and all experiments were conducted at 17 °C. The cross-membrane property was tested with HeLa cells through the similar method. It is known that fluo-3 has a higher affinity for Ca^{2+} than other divalent cations. The increase in fluorescence intensity indicates more complexes formation between fluorescence dye and Ca^{2+}. In this study, the changes in the fluorescence intensity were used to monitor the changes

in free Ca^{2+} concentrations in rat brain microsomes and intact HeLa cells. The data shown are typical curves for at least two experiments carried out in duplicated using different rat brain microsomes and HeLa cells preparations. The concentrations of samples are measured according to the extinction coefficients of their UV spectra.

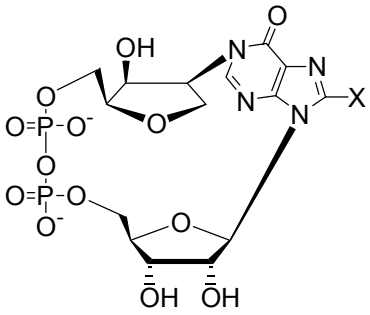
The results are consistent with the finding described above that mimics with different configurations at the N^1-glycosyl moiety retained the activities of induced Ca^{2+} release and 8-substituted mimics (**4b**, **5b**) facilitate the permeability of cell membrane. More interestingly, the N^1-acyclic analog **6** exhibited a strong potency to induce Ca^{2+} release in both of rat brain microsomes and intact HeLa cells (Figure 2). The data obtained from the experiments on HeLa cells showed that the extracellular cADPR mimics can increase the level of Ca^{2+} in intact cells, but it is still not well understood if the cellular Ca^{2+} level correlates with the level of cADPR mimics in cells or the cellular Ca^{2+} level is elevated from other unknown mechanisms. Although the mechanism is not clear, the N^1-glycosyl substituted mimics will be used as a tool for further investigation.



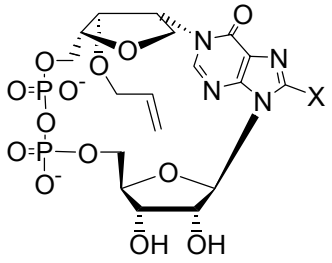
cADPR



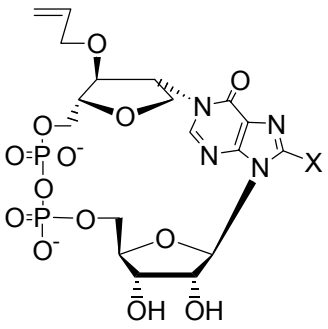
1: X = O, Y = NH
2a: X = CH_2, Y = O
2b: X = CH_2, Y = NH



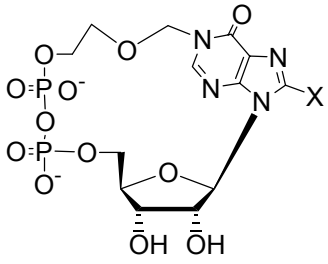
3: X = Br



4a: X = H
4b: X = Br



5a: X = H
5b: X = Br



6: X = Cl

Figure 1

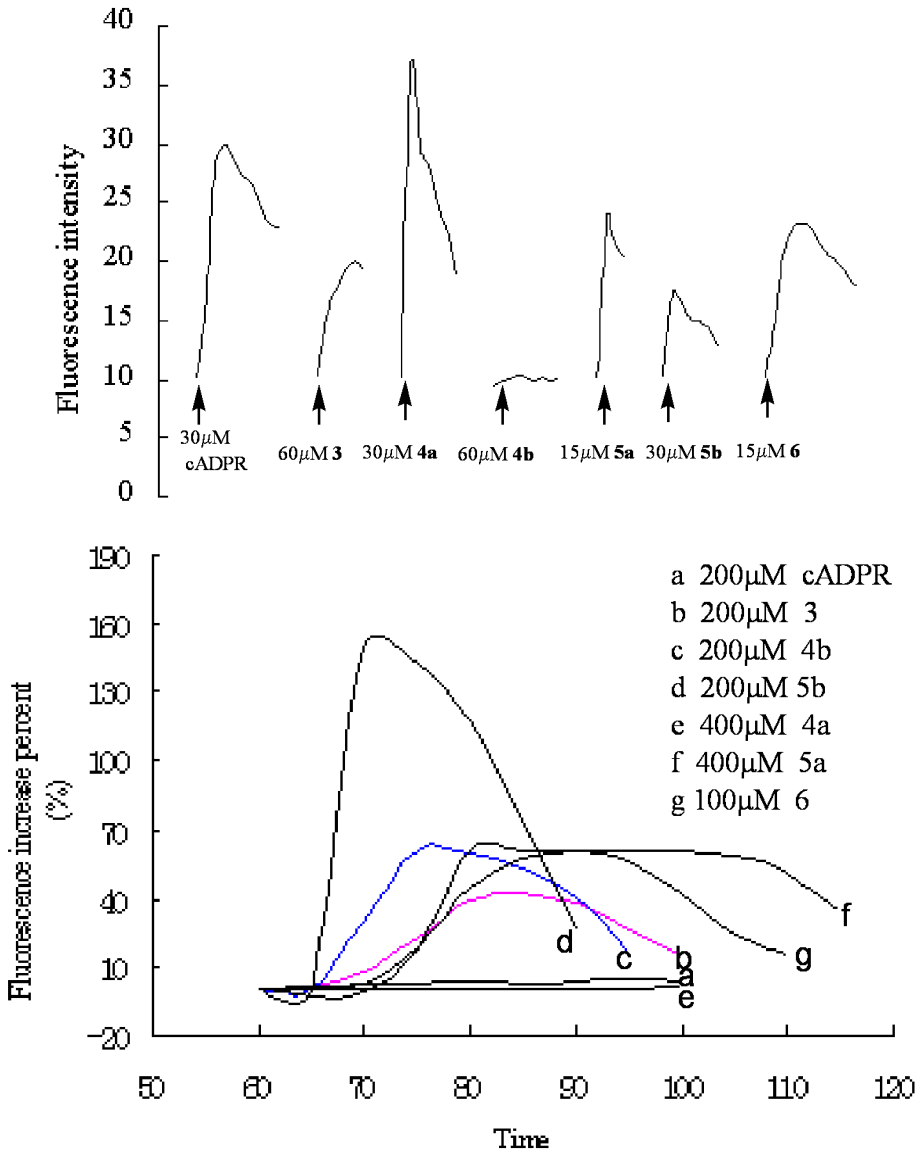


Figure 2

Acknowledgement. We thank the financial support from The National Natural Science Foundation of China.

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7. Shuto, S.; Shirato, M.; Sumita, Y.; Ueno, Y.; Matsuda A. *J. Org. Chem.* **1998**, *63*, 1986-1994.

IL-1. Pyrrolidine Modulators of Chemokine Receptor Activity

Jianming Bao, Robert Baker, Jennifer Chee, Frank Kayser, Christopher Forbes, Jill Johanson, Lei Meng, Shouwu Miao, Bruce L. Daugherty, George Eiermann, Yanfen Guan, Lorraine Malkowitz, John S. Mudgett, Stephen G. Pacholok, Marco P. Soares, Gloria C. Wolfe, Liwen Zhang, Tracey D. Klatt, Sherrie X. McCormick, Michael Forrest, Sander G. Mills, Malcolm MacCoss, Martin S. Springer, William H. Parsons, and Kathleen M. Rupprecht
Merck Research Laboratories, Merck & Co., Inc, Rahway, New Jersey 07065, USA

Chemokines are a superfamily of small molecular weight proteins (8-10 kD) which play a crucial role in immune and inflammatory reactions and in viral infection. Currently, about 50 chemokines have been characterized. These proteins are secreted by a wide variety of cells in response to injury, allergens, or invading microorganisms. Chemokines attract and activate leukocytes and possess activities on diverse cellular systems ranging from blood vessels to the central nervous system. Chemokines mediated these processes by binding to members of the G-protein-coupled superfamily of receptors which contain 7 transmembrane α-helices.

Eosinophils are major effector cells implicated in a number of chronic inflammatory diseases in humans, particularly bronchial asthma and allergic rhinitis. The chemokine receptor CCR3 was the third β-chemokine receptor characterized in an expanding family that numbers close to 20 to date. CCR3 has been shown to be highly expressed on the cell surface of eosinophils. Binding of eotaxin, a CCR3-specific chemokine, to CCR3 provides a potent mechanism for the accumulation of eosinophils into the airways in patients with asthma, and thus provides an attractive target for therapeutic intervention.

This presentation will focus on a new class of pyrrolidine antagonists for CCR3. The SARs relating to substituents at N1, C3 and C4 positions of the pyrrolidine ring will be discussed. Compounds with potent antagonistic activities in a number of functional assays, including eotaxin-induced calcium flux and eotaxin-induced release of reactive oxygen species have been identified. Several compounds with excellent *in vitro* activities have been also evaluated in *in vivo* assays.

IL-2. Design and Synthesis of Potential DNA Double and Triple Helices Stabilizing Agents

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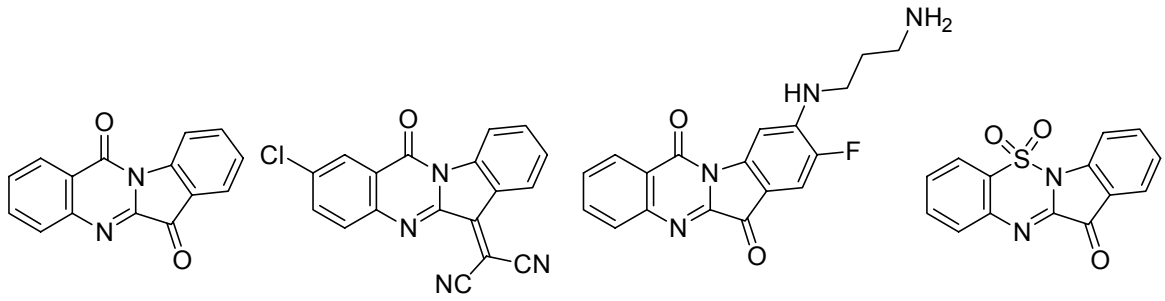
School of Pharmacy, College of Medicine, National Taiwan University, No. 1, Section 1, Jen-Ai Road, Taipei, Taiwan

Tryptanthrin (**1**), indolo[2,1-*b*]quinazolin-6,12-dione, and its derivatives were reported to show antimicrobial activity and inhibitory activity against tuberculosis.[1] The planar tetracyclic system is in common for some antitumor drugs such as camptothecin and ellipticine. In continuing our studies of quinazoline derivatives, we have designed and synthesized a series of tryptanthrin derivatives as potential anticancer agents, and some of them showed better cytotoxicity than tryptanthrin itself in many cancer cell lines. Importantly, **1** and **2** were found to be reversal agents of some anticancer drugs with different mechanisms. In addition, triple helix-forming oligonucleotide (TFOs) could interfere with the transcription and translation of DNA, consequently serving as therapeutic agents in antigene and antisense approaches, respectively. However, the use of TFOs has been hampered by the instability of the triple helices under physiological conditions. Up till now, the stabilization of triple helix formation has attracted intense interest for nucleic acid therapeutics in an antigene strategy. We integrated a long alkylamine side chain onto tryptanthrin to form **3**, in which indolo[2,1-*b*]-quinazolinone can interact with DNA through π–π stacking and hydrogen bond donors, and the alkylamine side chain offers binding with DNA via electrostatic interactions. Both computer modeling and thermal denaturation experiments revealed that **3** stabilized not only duplex DNA but also triplex DNA. On the basis of bioisosterism concept, 6-oxoindolo-[1,2-*b*]benzo[1,2,4]thiadiazine 12,12-dioxide (**4**) and its derivatives were designed and synthesized. This structurally novel planar skeleton ring system has never been reported previously, and it is not only a new series of heterocycles worthwhile to develop but also expected to have potential in anticancer activity.



1 **2** **3** **4**

Reference:

1. Mitscher, L. A.; Baker, W. *Pure Appl. Chem.* **1998**, *70*, 365-371.

IL-3. The Action of Apoprotein in the Antitumor Antibiotic Neocarzinostatin

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Neocarzinostatin (Figure 1) is the first isolated enediyne antitumor antibiotics. Similar to other nine-membered enediynes, it consists of a single polypeptide chain (113 aa) and a small chromophore (MW 659) that exhibits the biological activity of the drug in inducing DNA cleavages. The apoprotein plays an important role as a stabilizer or carrier to protect and regulate the availability of the chromophore. The protein can also direct the cycloaromatization pathway of the enediyne ring (Scheme I). Understanding of the interaction between the apoprotein and its chromophore is important because it may strongly affect the drug activity. Here we intend to explore the basic protecting, regulating, and directing mechanisms[1,2] of this chromoprotein system at the molecular level.

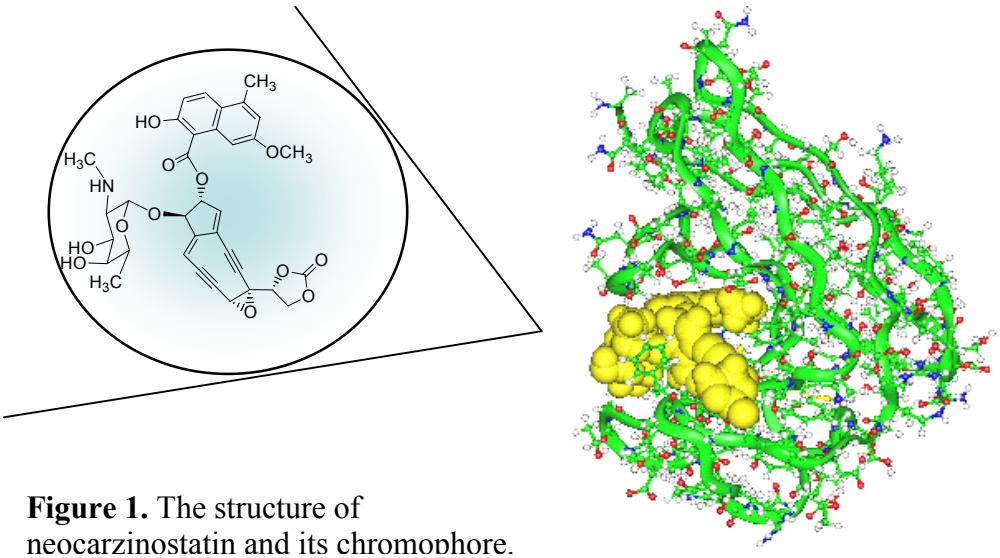
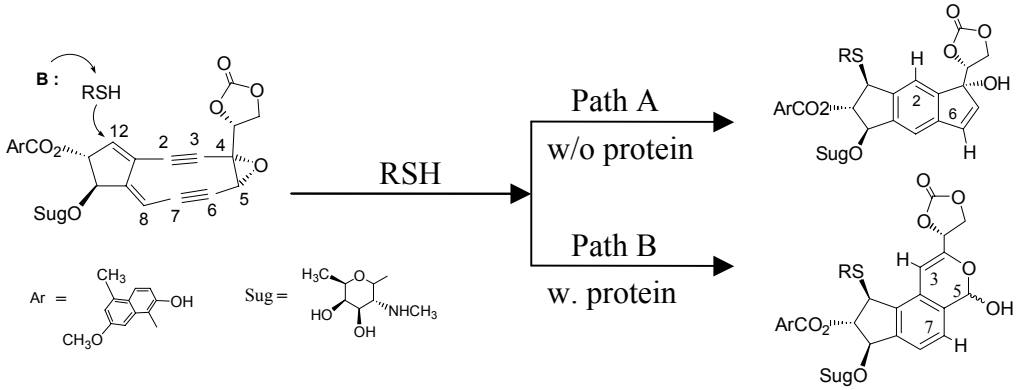


Figure 1. The structure of neocarzinostatin and its chromophore.



Scheme 1. The cycloaromatization of the neocarzinostatin chromophore

References:
1. Chin, D.-H. *Chem. Eur. J.* **1999**, *5*, 1084-1090.
2. Sudhahar, G. C. P.; Balamurugan, K.; Chin, D.-H. *J. Biol. Chem.* **2000**, *275,* 39900-32906.

IL-4. Recent Advance in Macrolide Antibiotic Research

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Emergence of bacterial resistance to macrolide antibiotics, particularly in gram positive bacteria, has been observed. Novel macrolides having C-4" carbamate functional groups and ketolides, the 3-keto derivatives of macrolide, were found to have activities against macrolide resistant strains. The medicinal chemistry, biological activity and bacterial resistance of macrolide/ketolide antibiotics will be discussed.

IL-5. Glycopeptide Synthesis with Free Oligosaccharides as Phase Tags

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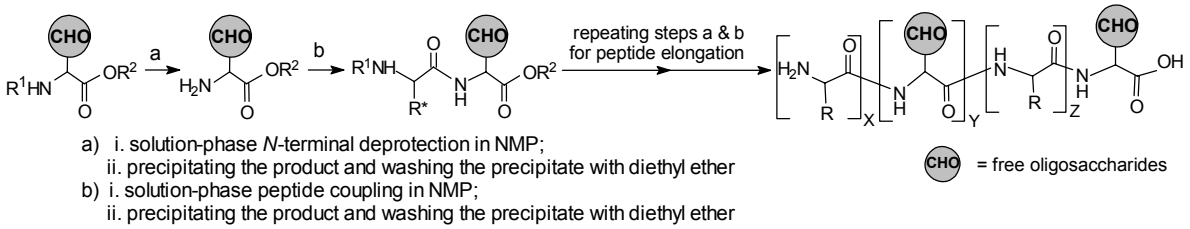
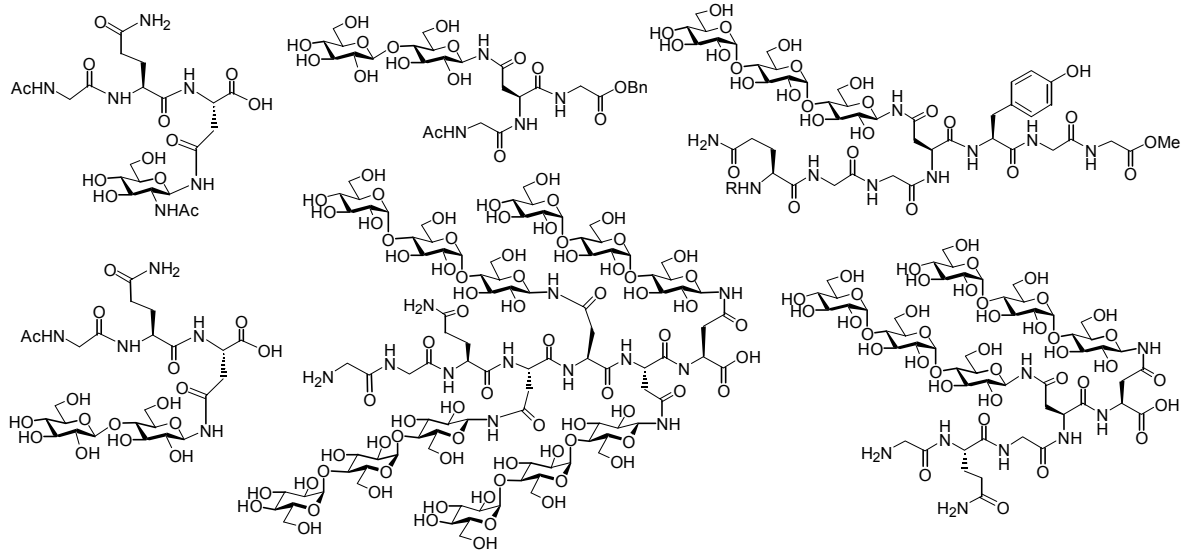
Glycopeptides play an important role in the biological world, and thus, synthetic glycopeptides with homogeneous and well-defined structures are in high demands. However, glycopeptide synthesis remains an important challenge in organic chemistry, despite that numerous valuable preparation approaches for them have been established during the past two decades. To develop a practical method for the preparation of glycopeptides containing acid- and/or reduction-liable carbohydrate and peptide chains, which are not easily achievable with the classic methods, we recently explored a new strategy that utilizes glycosylated amino acids with free oligosaccharides as the building blocks and "phase tags". While the reactions to achieve glycopeptide elongation were conducted in the homogenous solutions in *N*-methyl 2-pyrrolidinone (NMP), the reaction product of each step could be easily isolated by the precipitation method, namely, by adding a less polar solvent, such as diethyl ether, to the NMP solution and then isolating the precipitated product by filtration or centrifugation. The new strategy can take advantage of both solution-phase and solid-phase syntheses. It can also get around some serious problems in glycopeptide synthesis, which can often affect the glycopeptides, such as the final carbohydrate deprotection in most classic methods and the strongly acidic conditions used to retrieve glycopeptides from the polymer supports in traditional solid-phase synthesis.





IL-6. Design and Synthesis of Anti-diabetics Based on PPAR-gamma Structure and Virtual Screening of Focused Library

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Type II diabetes is a metabolic disorder characterized by hyperglycemia that causes chronic complications leading to renal failure, blindness and coronary artery disease. Hyperglycemia in type II diabetes is caused by an increase of insulin resistance and by impaired insulin secretion from the pancreas. It has been shown that peroxisome proliferator activated receptor-γ (PPAR-γ) located in nucleus is able to increase the insulin sensitivity, to promote the differentiation of lipocytes, and to retard complications.[1] Although some PPAR-γ modulators have been marketed as anti-diabetes II drug such as Pioglitazone and G-1262570, unsatisfactory efficacy and safety profile restricts their application.

Analyzing the binding feature of PPAR-γ to its modulators by docking operation and molecular simulation, and based on the knowledge of 3D-QSAR of PPAR-γ modulators, a pharmacophore model was derived,[2] featured by the presence of hydrogen bondings on one end, a hydrophobic fragment with a hetero-atom on the other end, and a flat moiety connecting the two terminals.

Guided by the combinatorial strategy, building blocks were selected from commercially available compounds with the following criteria: drug-like, pharmacophoric demand, feasibility and selectivity of synthetic reactions. These blocks are automatically connected with Project Library software and constitute a virtual and focused library with the capacity of over 1000 compounds. By means of computational virtual screening program DOCK4.0 each compound was matched with the binding pocket of PPAR-γ and the results were evaluated by the score system of shape and energies.[3] Thirty molecules with high scores and structural diversity were selected and synthesized. The activity of the compounds is being evaluated using receptor binding experiment, and the results are to be discussed.

References:
1. Willson, T. M.; Brown, P. J.; Sternbach, D. D.; Henke, B. R. *J. Med. Chem.* **2000**, *43*, 527-550.
2. Yi, X.; Guo, Z. *Acta Pharmaceutica Sinica* **2001**, *36*, 262-268.
3. DOCK [Computer Programme], Version 4.0, Regents of the University of California,1998.

IL-7. Bioactive Compounds from Chinese Medicinal Plants

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The chemical investigations on *Spiraea japonica* and its varieties have led to the report of 10 new atisane-type diterpenoids including two new glycosides and more than 30 new diterpene alkaloids of atisine- and hetisine-type. Some of those alkaloids such as spiramine Q significantly inhibited rabbit platelet aggregation induced by PAF and AA *in vitro* and *ex vivo*, and others like spiramine T exhibited protective effects on cerebral ischemia-reperfusion injury in gerbils. Parts of semisynthetic sulfur-containing atisane-type diterpenoids showed neuroprotective effects on cortical neurons. Some *O*-terpenoidal coumarins isolated from plants of the genus *Clausena* exhibited neuroprotective effects as well.

Nootropic agent, aniracetam was developed in Europe, and entered market this year. Clausenamide was a nootropic drug discovered from plant by Beijing Institute of Materia Medica. Our group designed and synthesized a series of molecules based on the studies on aniracetam and clausenamide. After screening, KMBZ-009 was found to be more active than aniracetam and clausenamide, and is eight times more active than aniracetam.

More natural products including *Euodia* alkaloids, diterpenoids of cleistanthadane-type, triterpene saponins having various biological activities such as anti-rice blast, antifungal and regulating the growth of plant endophytes were studied in our group.

IL-8. Hyperactive Peroxidic Antimalarials and Questions on Mechanism of Action

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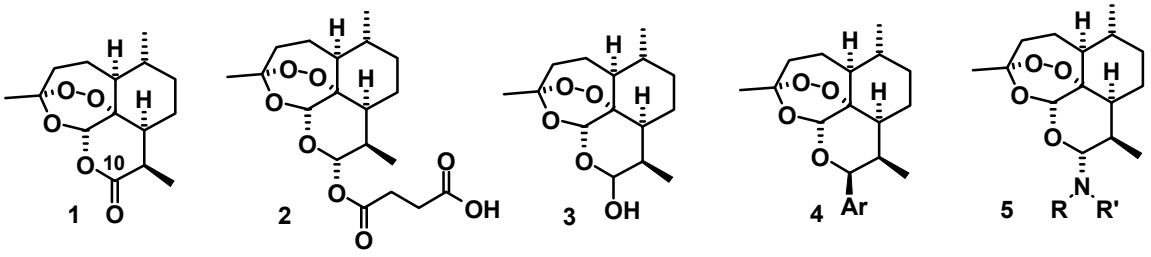
The use of qinghaosu (artemisinin) **1**, and its derivatives including artesunate **2** for treatment of malaria is thoroughly established. Work continues apace to develop new derivatives which do not display the disadvantages of artesunate, namely, instability to storage, short pharmacological half life ($t_{1/2}$ several minutes), and rapid hydrolysis *in vivo* to the *highly* neurotoxic[1] dihydroartemisinin **3**. To this end we have embarked on a program to prepare stable, non-neurotoxic derivatives, which do not provide dihydroartemisinin during metabolism,[2] including various aryl and amine substituted derivatives **4** and **5** (R, R' = alkyl) Some of these compounds display picogram/mL activities *in vitro* against *P. falciparum*, and sub-milligram/kg activities *in vivo* against *P. berghei* in mice.



The hyperactivity of these compounds raises questions as to the mechanism of action of this class of antimalarial, widely assumed to involve cleavage of the peroxide catalyzed by intraparasitic iron, either incorporated within hemin, or in the 'free' state, to generate C-centered free radicals which are supposed to alkylate malaria parasite proteins. We have previously provided arguments against 'C-centered' radical pathway based on considerations of redox chemistry and structure-activity relationships,[3] but nevertheless, more or less dogmatic assertions unfortunately continue to permeate the literature.[4] However, we have now conducted an examination of *both* the ferrous heme and 'free' iron(II) catalyzed decomposition of compounds **4** and **5**, which provides results which are decidedly incompatible with a radical pathway. We show that the very active compounds react sluggishly *either* with ferrous heme *or* with 'free' iron(II) under conditions which cause substantial decomposition of artemisinin. Details of these reactions are presented, and the lecture concludes with a discussion of a possible model of mode of action.

References:
1. Schmuck, G.; Haynes, R. K. *Antimicrobe Agents Chemotherapy* **2002**, *46*, 821-827.
2. Haynes, R. K. *et. al.* PCT Int. Appl. WO 2000004024 A1, 27 Jan 2000; Appl.: WO 1999-GB2267 14 Jul 1999; EP 1998-305596 14 Jul 1998.
3. Haynes, R. K. *Current Opinions Infect. Diseases* **2001**, *14*, 719-726.
4. For succinct summaries and espousal of the radical viewpoint, see: Wu, Y. *Acc. Chem. Res.* **2002**, *35*, 255-259.

IL-9. Protein-Protein Interactions: Mechanisms, Medicinal Chemistry, and Implications for Post-Genomic Drug Discovery

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Our laboratory is interested in exploring the fundamental mechanism of biological recognition in protein-protein and protein-ligand complexes and translating such basic knowledge into the discovery of new drugs. Two representative areas of research will be presented in this talk: Bcl-2 family proteins and chemokine receptors.

Bcl-2 family proteins play a key role in regulating apoptosis or programmed cell death and are implicated in the resistance of cancer cells to many of the currently available drugs. We have recently discovered and studied synthetic peptides and non-peptidic organic compounds that act as antagonists or agonists of the Bcl-2 family. Progress in using these molecules as leads to develop a new class of anticancer drugs and probes to study basic mechanism of Bcl-2-regulated signaling pathways will be discussed.[1] In another project, chemokine receptors such as CXCR4 are essential co-receptors required for the cellular entry of human immunodeficiency virus type 1 (HIV-1) and thus represent important targets for anti-HIV drug development. Recently we synthesized peptides and peptidomimetics as antagonists of CXCR4. Studies in using these CXCR4 antagonists to obtain surprising new insights into the mechanism of ligand-CXCR4 interaction and signal transduction and the implications of these studies for the development of new anti-HIV agents will be discussed.[2,3]

References:
1. Huang, Z. *Chemistry & Biology*, **2002**, *9*, 1059-1072.
2. Huang, Z. *Mini-Reviews in Medicinal Chemistry*, **2002**, *2*, 373-383.
3. Zhou, N.; Luo, Z.; Luo, J.; Fan, F.; Cayabyab, M.; Hiraoka, M.; Liu, D.; Han, X.; Pesavento, J.; Dong, C.; Wang, Y.; An, J.; Kaji, H.; Sodroski, J. G.; Huang, Z. *J. Biol. Chem.* **2002**, *277*, 17476-17485.

IL-10. Aspects of Virtual Screening in the Cycle of Drug Discovery: Successful Stories, Prospects, and Challenges

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The completion of the human genome suggests there are 30,000 to 40,000 genes and at least as many proteins. Many of these proteins are potential targets for drug intervention to control human disease or injury; popular estimates are in the range of 2000 to 5000. Discovering lead compounds that may be developed as new drugs against these new targets is an exciting and stimulating challenge for the medicinal chemists and pharmacologists. During the history of modern chemistry, organic chemists have synthesized and isolated from natural sources more than 16 million organic compounds. Among them less than 1% have been screened for drug discovery, about 7000 drugs have been found in this way. Therefore, we may believe that large numbers of new drugs, at least many active compounds, are hiding in this organic compound *mine*. However, how to mine this compound source is a hard task of our medicinal chemists. Collecting all these 16 million compounds and screening them randomly is unpractical, because it will cost billions of US dollars for one target. While a new computational method — virtual screening (VS) shows a dawning to solve this problem.

Virtual screening is a natural extension of molecular docking or three-dimensional (3D) pharmacophore based database searching (PBDS), capable of automatically evaluating very large databases of compounds. Two strategies have been used in virtual screening: (1) using docking approach to rank the databases if the 3D structures of the targets are available, and (2) using PBDS to identify potential hits from the databases if the 3D structures of the targets are unknown. Normally, these two approaches are used synthetically, because the later method can filter the compounds quickly and the former method can evaluate ligand-receptor binding more accurately.

VS by docking shows great promise. Doman *et al*. compared the performance of random high throughput screening (HTS) and molecular docking in searches for inhibitors of protein tyrosine phosphatase 1B (PTP1B) — a target for type 2 diabetes. The result indicated that docking enriched the hit rate by 1,700-fold over random screening. Li *et al*. demonstrated the high efficiency of docking in ranking hits by their DockCrunch project. They searched ACD-SC database (contains 1.1 million compounds at that time, now it has about 2.2 million compounds) using docking approach against the estrogen receptor. Among the 37 compounds selected from the virtual screening, 21 compounds show activity less than 300 nM, 14 compounds' activities are less than 100 nM and 2 are less than 10 nM.

Recently, we have parallelized the well-known program DOCK developed by Kuntz *et al.* in several types of supercomputers. This speeds up the database screening dramatically. Employing this approach, we have discovered a series of active compounds from the available databases MDL/ACD, MDL/MDDR, ACD-SC and our own database CNPD (Chinese Natural Produce Database) against several targets, such as tyrosine kinase, potassium ion channel, β-secretase, MMPs, and PPARγ. Targeting the ligand binding domain of PPARγ, we screened ACD-SC (2.2 million compounds) using above parallelized DOCK, 14 compounds with activity less than μM were tackled, and two of them show binding affinities higher than all the

launched PPARγ agonists. It is pleased that, aided by VS, we obtained these positive results only within 6 months. Taking the most active compounds as leading scaffolds, the focused libraries syntheses by combinatorial chemistry and crystal structures of the complexes determination by X-ray crystallography are being performed.

Nevertheless, VS are still facing many challenges. Most of the current docking methods such as DOCK and AutoDock have not considered the flexibility of targets (mostly proteins); there is no universal scoring function for ranking the binding affinity between small molecules and targets. Solving these two problems is the main task in developing new virtual screening methods based on docking. Combinatorial chemistry will produce more than 10^{200} compounds in the coming years. VS cannot finish the screening of such a large number of compounds in a short period even use the fastest supercomputer in the world. Therefore, integrating docking approaches with molecular diversity analysis is a tendency of VS development.

IL-11. Immunomodulating Natural Products from Chinese Herbs

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Traditional Chinese medicine always pays close attention to strengthening the patients resistance against illness. Modern scientific studies have shown that quite a few herbs are immunologically active. The active components studied by my group will be reviewed here briefly. *Astragalus mongholicus* Bunge was considered as a bioenergetics used widely in China. A polysaccharide APS has been isolated from the root of this herb which is a polymer of glucose and arabinos. APS increases the specific antibody formation as well as synthesis of RNA, DNA, and protein in mouse spleen. It also promotes significantly macrophage phagocytosis. *Acantopanax senticosus* Harms is used as a tonic and sedative agent. The polysaccharide PES isolated from it possesses significant immunoprotentiating activity and induces interferon production. *Achyranthes bidentata* Blume is widely planted in China. An oligosaccharide AbPS with MW 1360 was isolated from its root which composes 6 glucose and 3 mannose units. AbPS significantly enhanced the humoral responses and B lymphocyte proliferation and antagonized the immunosuppressive effects of cyclosporin A in mice. AbPS increased the production of TNF and activity of NK cells and revealed antitumor activity. In tumor patients treated with chemotherapy or radiotherapy, AbPS maintained peripheral WBC counts and improved their quality of life. PSP, the protein bound polysaccharide extracted from *Coriolus versicolor* has been well studied and developed as an anticancer drug in China. PSP promoted T cell proliferation and increased the ratio of CD4+/CD8+. Both animal and clinical tests showed PSP increased NK and LAK cells activities as well as anticancer cytokines IL-2, IL-6, IFN, and TNF productions so to induce tumor cell apoptosis. *Tripterigium wilfordii* Hook F. has been used for treatment of fever, chills, and inflammations. The triterpenoid is now used to treat rheumatoid arthritis, chronic nephritis, and various skin disorders with perfect results. Celastrol, a triterpene compound isolated from it was proved to be an identical immunosuppressor and inhibited free radical damage in experimental arthritis. Ginkgolide A, B and bilobalide from *Ginkgo biloba* extract (GBE) inhibited IL-1, TNF, and NO production in LPS stimulated rat microglia so to prevent the chronic inflammatory process in brain and protect PC12 cells against β-amyloid peptide induced apoptosis in neurodegenerative diseases.

IL-12. Synthesis of Bioactive Carbohydrates by Glycosidic Bond Formation

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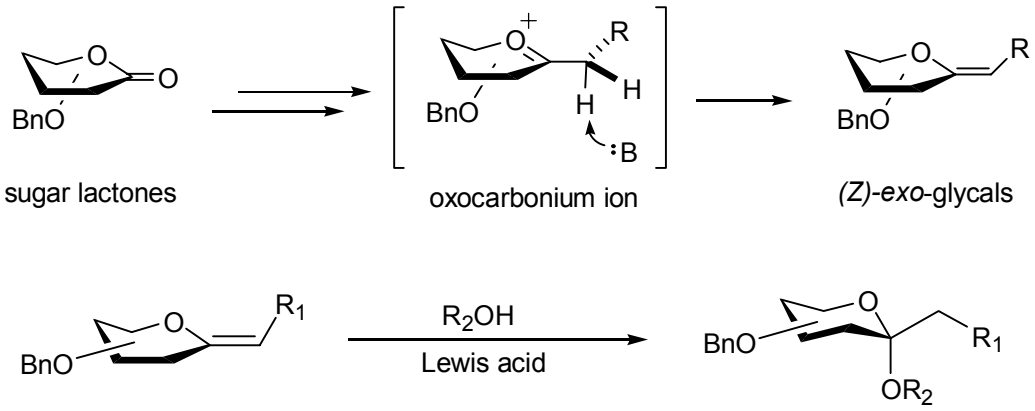
Institute of Biological Chemistry, Academia Sinica, No. 128 Academia Road Section 2, Nan-Kang, Taipei 11529, Taiwan

endo-Glycals are versatile building blocks in the preparation of numerous biomolecules and substrates for a variety of chemical transformations. The chemistry with regard to *exo*-glycals is less addressed in the literature. We will demonstrate the stereoselective synthesis of (*Z*)-*exo*-glycals from sugar lactones, as well as their reactivity and various applications. The most exciting result is the glycosylation reactions of *exo*-glycals. Recent progress will be presented on the stereoselectivity, choice of Lewis acid, the determination of the stereochemical configuration, and optimizations to achieve high yields.

Additionally, the enzyme reactions to produce Lewis antigens using a fucosyltransferase will be included.



IL-13. Recent Development in the C-C Bond Formation: Learn Something from Natural Products

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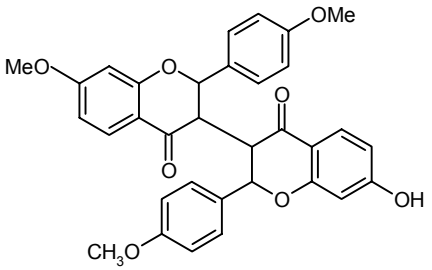
Natural Products have played a vital role in new drug discovery and in the development of organic chemical synthesis as well. As a consequence, the natural diversity provides us a great deal of interesting compounds either as the original sources or in the form of their derivatives for synthetic targets and for bio-screening tests. We have recently been involving in the structural elucidation and asymmetric synthesis of several natural products, which extended to several new developments of carbon-carbon bond formation in our group.

1. Synthesis of bioactive axial biaryls through Ullmann-type reaction

In our course of seeking the lead compounds in natural resources, we have isolated an unknown compound **1** from the plant *wikstroemia indica L.* which exhibits potential inhibitory effect against 15-lipooxygenase. In order to establish the stereochemistry of **1**, it is necessary to synthesize **1**. Thereby, preparation of the structurally related bibenzopheran **2**, which was isolated from *Aloe barbadensis*, was taken as the model for the synthesis of **1**. During the course of the total synthesis of bibenzopyran-4-ol, a modified Ullmann-type coupling reaction, shown in Scheme 1, was discovered and the extension of this homo-coupling condition to various α-iodo-α,β-unsaterated ketones or bromo-alkenes will be presented.



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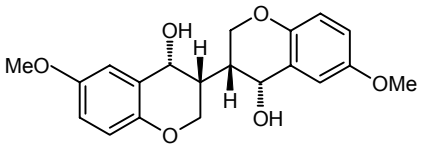

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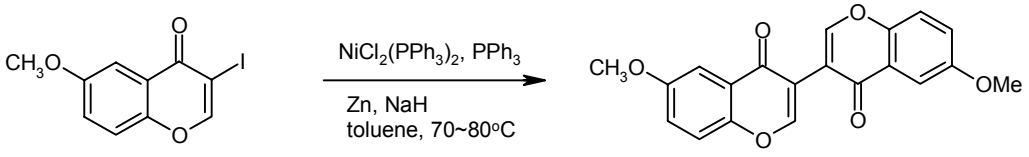
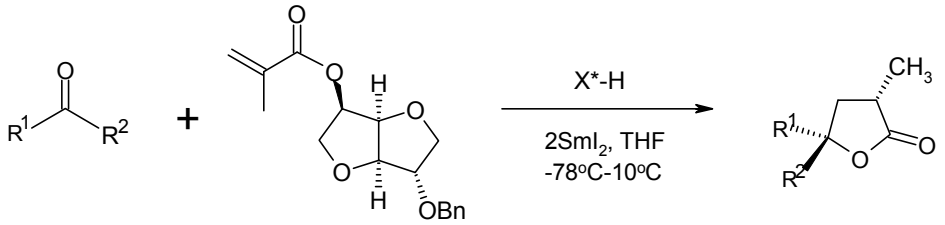


3 **4**

Scheme 1

2. SmI_2-mediated asymmetric synthesis of optically active α,γ-substituted-γ-butyrolactones

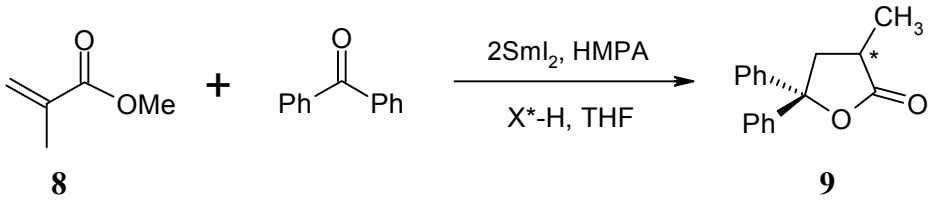
Compounds bearing the substituted γ-butyrolactone moiety are widespread in nature. Moreover, functionalized γ-butyrolactones are important intermediate for the synthesis of many organic compounds. The asymmetric synthesis of optically active α-methyl-γ-phenyl-γ-butyzolactone (Scheme 2) can be performed by using the SmI_2-mediated coupling of ketones (symmetrical and unsymmetrical ketones) with a chiral methacrylate derived from isosorbide.



Scheme 2

For example, when $R^1 = R^2 =$ Ph, the product was obtain in 95% ee, while (±)-saltam was used as the proton source to quench the reaction. Furthermore the stereochemistry of the two chiral centers in the butyrolactones **7** in Scheme 2 can be constructed in enantio-cotrolled manner by using different auxiliaries derivable from various sugars.

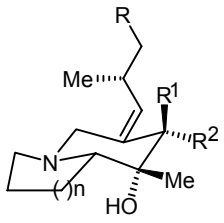
When optically active protected amides (X*-H) were used as the chiral proton source the above reactions were able to take place in the reagent-controlled manner (Scheme 3), giving the products **9** in up to 84% ee.



Scheme 3

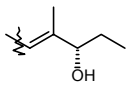
3. Studies on the stereoselective synthesis of pumiliotoxin A, allopumiliotoxin, and their analogues

A remarkable variety of alkaloids have been isolated in minute quantities from skin extract of frogs of the family *Dendrobatidae*, with the pumiliotoxin A and allopumiliotoxin classes as the representatives having the general structure **10** (n = 1).



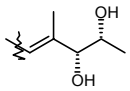
10 n = 1, 2

R =



$R^1 = R_2 =$ H: pumiliotoxin A **11**

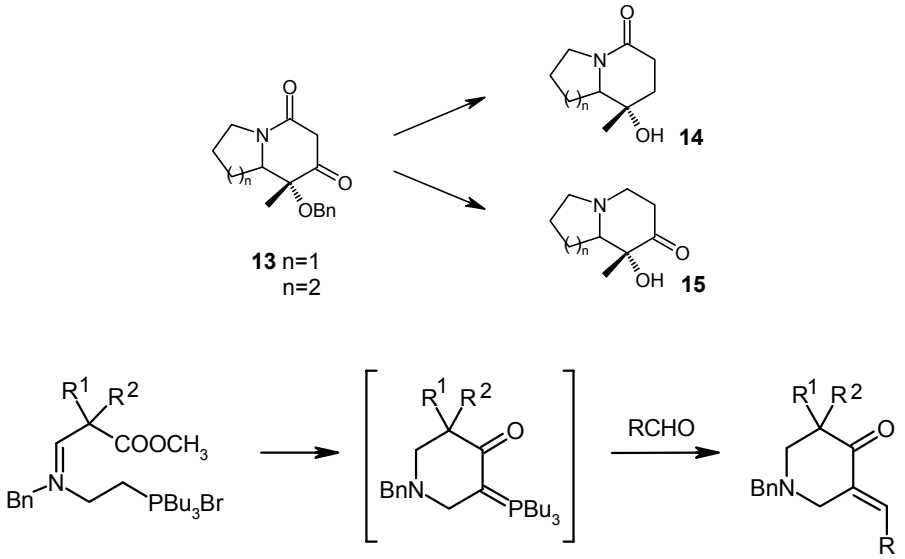
R =



R^1 = H, R^2 = OH: allopumiliotoxin 229B **12**

Recently, pharmaceutical studies of these compounds on cardiotonic and myotonic activities stimulate interest in this family of dendropatid alkaloids both in synthesis and in the studies of the relationship of structure-activities. We are interested in the establishment of a general synthetic way of **10** (n = 1) and its homo-derivatives (**10**, n = 2). Depicted herein is the synthesis of the common key intermediates **13**, **14**, **15** and a one-pot intermolecular

transylidation Wittig olefination. What shows in Scheme 4 provides a facil access to 3-alkylidene-piperiden-4-one, a common structural motif useful for the synthesis of **10**.



Scheme 4

Acknowledgement: The authors are grateful to the NSFC (Grant 297912045) and the Major Basic Research Development Program (Grant 2000077506) for the financial supports.

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IL-14. Small Molecule Insulin Mimetics with Potential Utilities as Anti-diabetic and Anti-obesity Therapies

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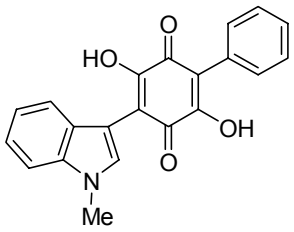
We recently reported the discovery of a hydroxyquinone anti-diabetic fungal metabolite which acted as an insulin mimetic in several biochemical and cellular assays. Based on this natural product lead, a series of 3,6-diaryl-2,5-dihydroxybenzoquinones were synthesized and evaluated for their abilities to selectively activate human insulin receptor tyrosine kinase (IRTK). 2,5-Dihydroxy-6-(1-methylindol-3-yl)-3-phenyl-1,4-benzoquinone (**1**) was identified as a potent, highly selective and orally active small molecule insulin receptor activator. A detailed SAR study was conducted around **1**, which will be discussed in the presentation. Compound **1** activated IRTK with an EC_{50} of 300 nM and did not induce the activation of closely related receptors (IGFIR, EGFR and PDGFR) at concentrations up to 30,000 nM. Oral administration of the compound to hyperglycemic db/db mice (0.1–10 mg/kg/day) elicited substantial to nearly complete correction of hyperglycemia in a dose-dependent manner. In ob/ob mice, the compound (10 mg/kg) caused significant reduction in hyperinsulinemia. A structurally related compound **2**, inactive in IRTK assay, failed to affect blood glucose level in db/db mice at equivalent exposure levels. The discovery of compounds with improved IR activating potency and selectivity as described in this report suggests that future efforts in this field may ultimately lead to a potential new therapy for NIDDM with a mechanism distinct from all other agents currently known.



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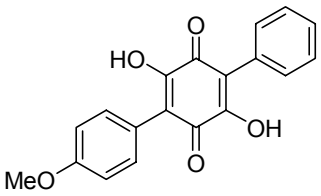

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Insulin has also been suggested to function as one of the adiposity signals to the brain for modulation of energy balance. We investigated the efficacy and feasibility of small molecule insulin mimetic compounds to regulate key parameters of energy homeostasis. The results indicated that activation of central and peripheral insulin signaling with small molecule insulin mimetic agents leads to beneficial effects on the control of body weight, food intake, adiposity, and insulin sensitivity. Thus, insulin mimetics hold potential as a novel anti-obesity treatment.

IL-15. Synthesis and Biological Activity of Matrix Metalloproteinase Inhibitors

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State Key Laboratory of Bioorganic and Natural Products Chemistry, Shanghai Institute of Organic Chemistry, The Chinese Academy of Sciences, 354 Fenglin Lu, Shanghai 200032, China

The matrix metalloproteinases (MMPs) are a structurally related class of enzymes that are responsible for the metabolism of extracellular matrix proteins. This family of enzymes includes the collagenases, stromelysins, and gelatinases. MMPs are necessary for tissue remodeling and the healing cascade. However, the aberrant expression of these zinc- and calcium-dependent enzymes has been linked to the accelerated breakdown of connective tissues associated with pathological disease states including arthritis, tumor invasion and metastasis, periodontal disease, and multiple sclerosis. Therefore, MMP inhibitors are expected to provide therapeutic agents for a number of disease states. However, since MMPs play a significant role in human physiology, the use of nonselective inhibitors might be expected to produce a variety of side effects. In fact, clinical studies using nonselective inhibitor Marimastat for treatment cancer have shown that this drug has a dose limiting side effect. The side effect is believed to be mechanism based and hypothesized to result from inhibition of MMP-1. Based on these results, much effort has been directed to the development of selective MMP inhibitors. In this lecture we will discuss our recent results.

IL-16. Enzymes for Posttranslational Protein Modification as Novel Drug Targets

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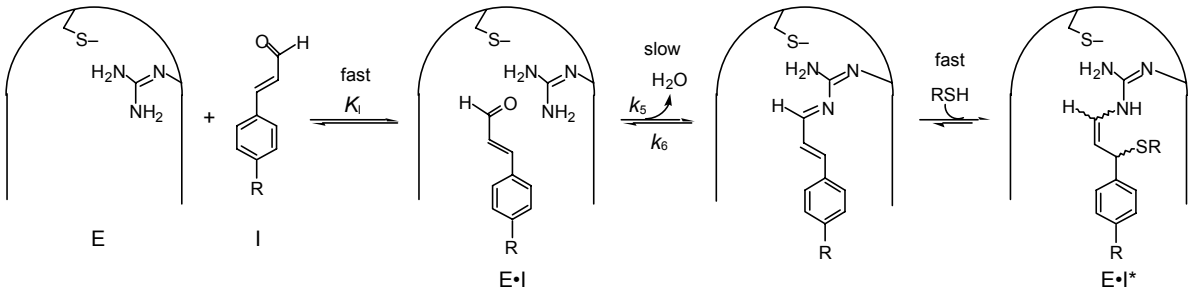
Protein tyrosine phosphatases (PTPs) are a large family of enzymes that catalyze the hydrolytic removal of the phosphoryl group from phosphotyrosyl (pY) proteins. PTP inhibitors provide potential treatment for a variety of human diseases/conditions such as diabetes and obesity as well as useful tools for studying the function of PTPs in signaling pathways. Essentially all of the PTP inhibitors reported to date are negatively charged pY mimetics. Unfortunately, these negatively charged molecules generally have poor membrane permeability and, therefore, have limited value as therapeutics. We have now found that certain aryl-substituted aldehydes (e.g., cinnamaldehyde) act as reversible, slow-binding inhibitors of modest potency against PTPs. Attachment of a peptide moiety to the *para* position of cinnamaldehyde (Cinn) resulted in inhibitors of substantially increased potency (e.g., K_I^* = 5.4 μM against PTP1B for Cinn-Gly-Glu-Glu). The mechanism of inhibition was investigated using inhibitors specifically labeled with ^{13}C at various positions and ^{1}H-^{13}C heteronuclear single-quantum coherence spectroscopy, in combination with site-directed mutagenesis. The results show that instead of forming a hemithioacetal with the active-site cysteine, as in cysteine proteases, the aldehyde inhibitor forms an enamine adduct between the aldehyde group of the inhibitor and the guanidine group of a universally conserved arginine in the PTP active site (Scheme 1). These aldehydes may provide a general, neutral core structure that can be further developed into highly potent and specific PTP inhibitors.



Scheme 1. Proposed mechanism of inhibition by cinnamaldehyde derivatives.

IL-17. Natural Product Biosynthesis and Prospects of Engineering Microorganisms for Chemical Structural Diversity

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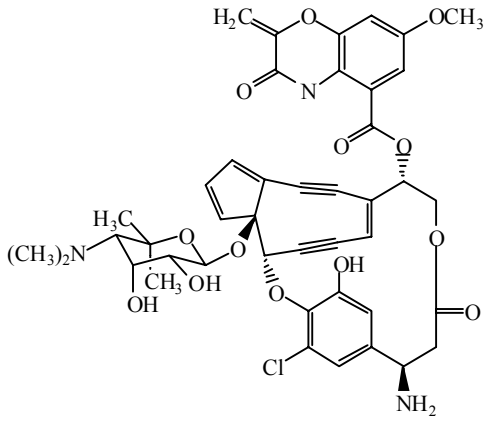
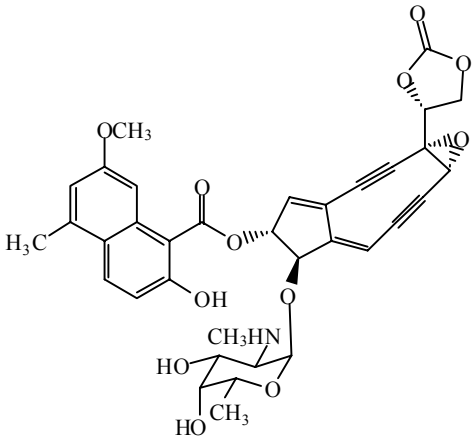
Division of Pharmaceutical Sciences, School of Pharmacy, and Department of Chemistry, University of Wisconsin, Madison, Wisconsin 53705, USA

Genetic manipulations of genes governing secondary metabolism offer a promising alternative to preparing complex natural products biosynthetically for drug discovery and development. The success of this approach depends critically on (1) the development of novel strategies for combinatorial manipulation of secondary metabolite biosynthesis gene clusters and (2) the continuous discovery and characterization of biosynthetic machinery that catalyzes novel chemistry. Examples from our current study on biosynthesis and engineering of the enediyne antitumor antibiotics, C-1027 and neocarzinostatin (NCS), will be presented to highlight the progress in this field. Cloning and characterization of C-1027 biosynthesis gene cluster from *Streptomyces globisporus* and the NCS biosynthesis gene cluster from *Streptomyces carzinostaticus* revealed (1) an iterative type I polyketide synthase that is distinct from any bacterial polyketide synthases known to date for enediyne core biosynthesis, (2) a general polyketide pathway for the biosynthesis of enediyne family of antibiotics, and (3) a convergent biosynthetic strategy for the C-1027 and NCS chromophores from diverse building blocks. Manipulation of genes governing C-1027 and NCS biosynthesis allowed us to produce new enediyne compounds in a predicted manner.



C-1027 chromophore



Neocarzinostatin chromophore

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IL-18. Synthesis and Anticancer Evaluation of Furoquinolines

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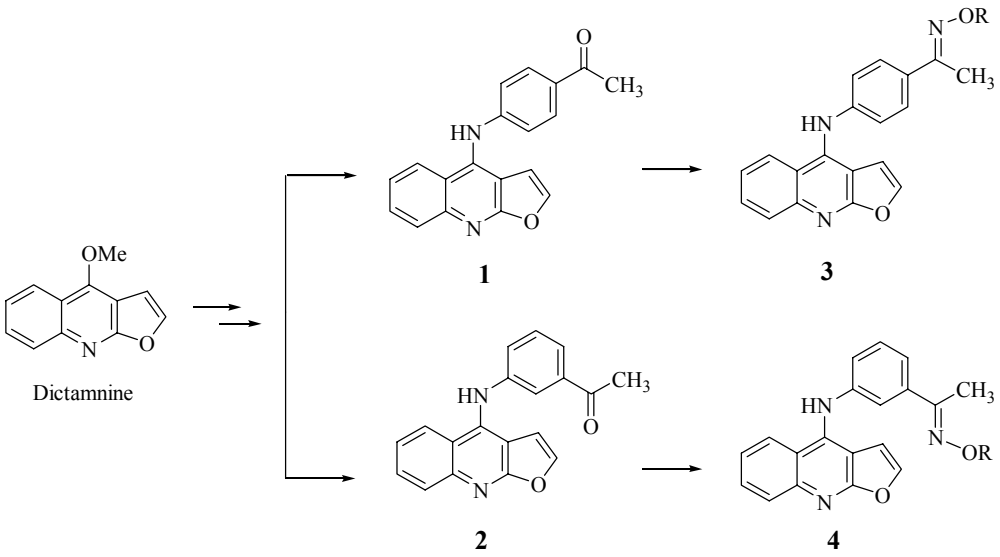
[b]*School of Pharmacy, Kaohsiung Medical University, Kaohsiung City 807, Taiwan*

Certain 4-anilinofuro[2,3-*b*]quinoline derivatives were synthesized from dictamnine, a natural alkaloid, and evaluated for their anticancer activity in the NCI's full panel of 60 human cancer cell lines.[1] 1-[4-(Furo[2,3-*b*]quinolin-4-ylamino)phenyl]ethanone (**1**) (mean GI_{50} = 0.025 μM), bearing an 4-acetylanilino substituent at C-4 position of furo[2,3-*b*]quinoline, was more active than its 3-acetylanilino counterpart **2** (mean GI_{50} = 5.27 μM) and both clinically used anticancer drugs, *m*-AMSA (mean GI_{50} = 0.44 μM) and Daunomycin (mean GI_{50} = 0.044 μM). Compound **1** was capable of inhibiting all types of cancer cells tested with a mean GI_{50} of less than 0.04 μM in each case except for the type of non-small cell lung cancer (average GI_{50} = 1.75 μM). On the other hand, the isomeric 4-anilinofuro[3,2-*c*]quinoline derivatives demonstrated a selective activity in inhibiting only certain melanoma and the renal cancer cells.



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IL-19. Bioorganic Approaches toward an Effective HIV Vaccine

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Institute of Human Virology, University of Maryland Biotechnology Institute, The University of Maryland, 725 West Lombard Street, Baltimore, MD 21201, USA

The expanding HIV epidemic urges the development of an effective HIV vaccine. For a successful vaccine, one of the following two immune responses should be elicited: broadly neutralizing antibodies and/or virus-specific cytotoxic T lymphocyte (CTL) responses. However, The design of an effective HIV-1 vaccine has turned out to be a formidable task. HIV-1 has evolved several mechanisms to evade the immune attack, including sequence variability of neutralizing epitopes, change of conformations, shielding of conserved epitopes through heavy glycosylations, and formation of compact glycoprotein complexes (envelope spikes) that hinder the accessibility of epitopes to immune response.[1,2] As a result, most HIV vaccines so far developed either are poorly immunogenic or raise antibodies only recognizing a narrow range of primary HIV isolates. Clearly, a successful strategy in developing an effective HIV vaccine relies on abilities to identify novel conserved epitopes on HIV that are accessible to neutralization and to design novel epitope-based immunogens that stimulate strong immune responses.

In this lecture, I will focus on two approaches toward an effective HIV-1 vaccine that are currently being pursued in my lab. These will include: 1) design and synthesis of novel multivalent gp41 peptides to duplicate the epitopes of the broadly neutralizing antibodies 2F5 and 4E10;[3,4] and 2) design and synthesis of novel clustered oligosaccharide constructs to duplicate the epitope of the broadly neutralizing antibody 2G12.[5] The conformational and immunological studies of the fully synthetic vaccines will be discussed.[6]

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IL-20. Carbohydrate-based Drug Development

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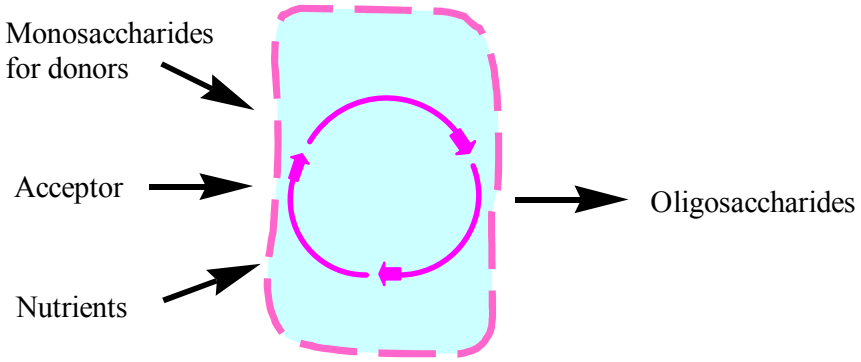
One of the obstacles in the development of carbohydrate-based pharmaceuticals is the difficulty and high cost of synthesizing complex carbohydrates. We have developed "superbug–superbeads" methods for large-scale synthesis of glycoconjuagates.[1] Our "superbug" approach makes use of engineered bacteria through fermentation to provide all the necessary enzymes along the biosynthetic pathway starting from monosaccharides to oligosaccharides. This approach relies on a single microbial strain transformed with a single artificial gene cluster of all the biosynthetic genes and uses the metabolism of the engineered bacteria to provide the necessary bioenergitics (ATP or PEP) to drive a glycosylation cycle.[2] For small to medium scale (mg to g scale) research laboratory need, cell-free *in vitro* enzymatic reactions catalyzed by all the necessary biosynthetic enzymes immobilized onto solid resins (superbeads) should be more versatile and easy to handle.[3] In summary, the biotechnology for mass production of glycoconjugates has matured to such a level that it can provide a variety of products at a fraction of current commercial prices. Thus, a number of biomedically significant complex carbohydrates have been produced for research and development in wide areas ranging from antimicrobial to anti-cancer reagents and from vaccines to nutriceuticals.



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IL-21. Polymer-Supported Synthesis of Heterocycles

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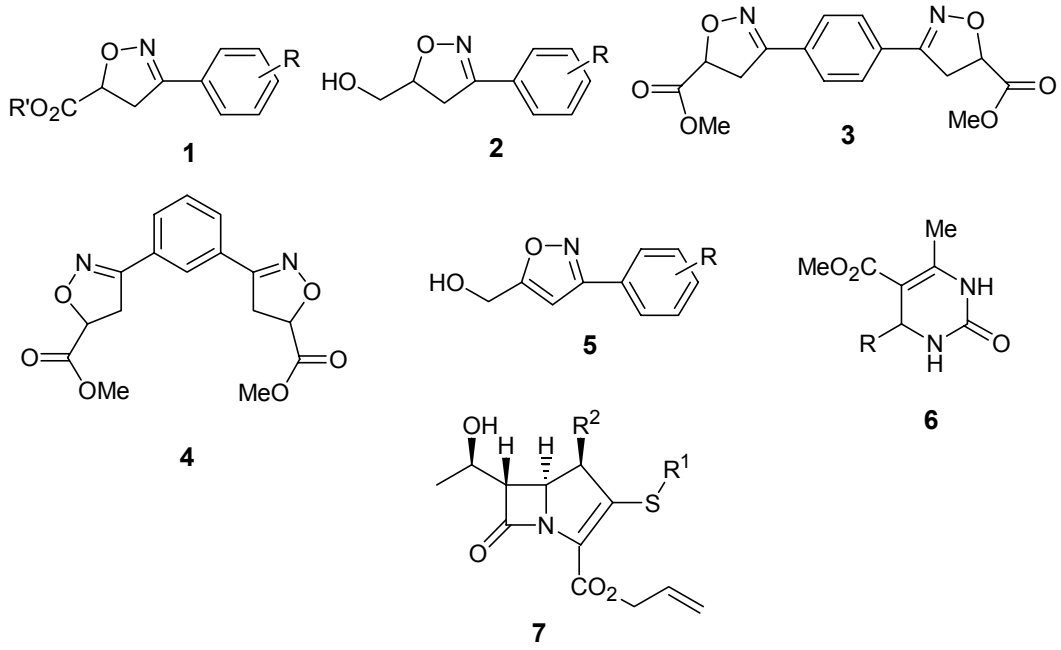
Combinatorial Chemistry of small molecules has generated a great deal of interest due to its impact on lead structure identification and optimization. In this field, polymer-supported syntheses including solid-phase synthesis and liquid-phase synthesis have been wildly used for the preparation of structurally diverse compound libraries. The liquid-phase synthetic approaches that utilize soluble polymers couple the advantages of homogeneous solution chemistry with those of solid-phase methods. In liquid-phase synthesis, the separation of the functionalized matrix could be easily achieved by either solvent or heat precipitation, membrane filtration or size-exclusion chromatography.

Heterocycle compounds such as isoxazoles, isoxazolines and 3,4-dihydropyrimidin-2(1*H*)-ones are versatile scaffolds for the synthesis of a wide variety of complex natural products and important pharmacophores in medicinal chemistry. The carbapenem class of β-lactam antibiotics has also exhibited potent and broad-spectrum antibacterial activities, and some of carbapenems have been clinically used. In this paper, we report the liquid-phase synthesis of isoxazolines (**1**–**4**), isoxazoles (**5**) and 3,4-dihydropyrimidin-2(1*H*)-ones (**6**) using soluble poly(etheylene glycol) (PEG) as support, and the solid-phase total synthesis of carbapenems (**7**) using chlorinated PS-DES-SiH resin as support.



Scheme 1

Acknowledgments: This work was financially supported by the National Natural Science Foundation of China (No. 29972037).

IL-22. DNA Recognition and Damage by Small Molecules at Bulge Site

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Nucleic acids can have richly diverse structures, including hairpins, knots, pseudoknots, triple helices, loops, helical junctions, and bulges. Such bulged structures in nucleic acids are of general biological significance. They have been proposed as intermediates in a multitude of processes including RNA splicing, frame-shift mutagenesis, intercalator induced mutagenesis, imperfect homologous recombination, as the binding site for the coat protein of bacteriophage, and in the ribosomal synthesizing machinery. Bulges have also been suggested as binding motifs for regulatory proteins involved with viral replication, including the TAR region of HIV-1. Additionally, the etiology of at least 14 human neurodegenerative genetic diseases has been attributed to genetic variations in the lengths of triplet repeats in genomic DNA (e.g. myotonic dystrophy, Huntington's disease, Friederich's ataxia, and fragile X syndrome). The unstable expansion of triplet repeats has been attributed to reiterative synthesis due to slippage and *bulge formation in the newly formed DNA strand*. As such, compounds capable of binding to bulges could have significant therapeutic potential. Despite these obvious ramifications, few previous attempts have been made to prepare compounds with affinity for bulged sequences. Success has been hindered by lack of an available substrate that can effectively mimic the base pairing involved at a bulged site, which may requires a unique wedge-shaped template.

In this report, we discussed our recent efforts in deciphering molecular mechanism of DNA damage and DNA bulge selectivity by small molecules such as enediyne antibiotic neocarzinostatin and its synthetic analogues. We also discussed the solution structures of a single base and a two-base DNA bulges complexed with either analog of the cleaving species (radical) of the drug. These structures clarify the mechanism of bulge recognition and cleavage by the drug and provide insights into the design of bulge-specific nucleic acid binding molecules. Our synthetic efforts to prepare bulge-specific, wedge-shaped, double-deckered molecules and their DNA bulge binding properties are also discussed.

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IL-23. HTS Data Mining and Virtual Library Analysis

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High throughput screening (HTS) has become an inseparable component in drug discovery. HTS produces great amount of data, and the related designs require the analyses of the great amount of the data, the analysis is usually called as data mining.

HTS data mining involves in information management (data base technologies) and information analysis (algorithms for knowledge extraction). When the size of a data set is small, many conventional information management systems, such as, Excel-like spreadsheets, can be used for processing. However, HTS data size is beyond the capacity of conventional information management systems and the traditional QSAR approaches. Therefore, new data management systems and data mining algorithms have to be introduced. The current achievements of HTS data mining technologies will be assessed. As the complementary component of HTS, VHTS (virtual HTS) technology will also be outlined. The techniques for virtual library generation and analyses are examined. Future directions to these fields are suggested.

IL-24. From an Idea to a Clinical Candidate: A Search for New Treatment of Depression Using Selective 5-HT_{1A} Receptor Antagonist

Yao-Chang Xu
Discovery Chemistry Research, Lilly Research Laboratories, Eli Lilly & Company, Lilly Corporate Center, Indianapolis, IN 46285, USA

Selective 5-HT_{1A} receptor antagonists have been hypothesized to have potential in the treatment of various psychiatric disorders including anxiety, depression, dementia, schizophrenia, and substance abuse. This presentation discusses the mechanism of selective serotonin reuptake inhibitor (SSRI) in curing the depression and its potential impact by the 5-HT_{1A} receptor antagonism. The author also describes the synthesis and characterization of a clinical candidate LY426965 along with major SAR investigation. LY426965 has a high affinity at cloned human 5-HT_{1A} receptors (K_i = 4.66 nM) and possesses little affinity for 45 other serotonergic and non-serotonergic receptors. Functionally, LY426965 did not stimulate [^{35}S]-GTPγS binding to cloned human 5-HT_{1A} receptors expressed in cell homogenates *in vitro* but did inhibit 300 nM 5-HT stimulated [^{35}S] GTPγS binding with a K_i value of 2.76 nM. *In vivo*, LY426965 blocks 8OH-DPAT-induced lower lip retraction, flat body posture and hypothermia in rats with ED_{50} values of 3.0, 2.0, and 2.4 mg/kg, p.o., respectively. A 20 mg/kg, p.o. dose of LY426965 fully blocks these 8OH-DPAT mediated effects for at least 8 hours. LY426965 also antagonizes the 8OH-DPAT-induced increase in rat serum corticosterone concentrations with an ED_{50} value of 9.2 mg/kg, p.o. In pigeons, LY426965 dose-dependently blocks the stimulus cue induced by 8OH-DPAT without being discriminated as similar to 8OH-DPAT. In electrophysiology studies, acute administration of LY426965 alone produces a slight elevation of the firing rate of 5-HT neurons in the dorsal raphe nucleus of anesthetized rats and greatly attenuates the inhibitory effect of fluoxetine on both the number of spontaneously active 5-HT cells per track and their firing rates. *In vivo* microdialysis studies show that LY426965 administration potentiates the fluoxetine-induced elevation of rat hypothalamic extracellular 5-HT concentrations beyond the increases produced by fluoxetine alone. These results show that LY426965 is a potent, selective, orally effective, and long-lasting antagonist of 5-HT_{1A} receptors, and potentially useful for depression when combined with an SSRI.

IL-25. Integration of Functional Genomics and Cell-based Assays for Drug Discovery from Traditional Chinese Medicine

Michael M. Yang
Applied Research Center for Genomic Technologies, City University of Hong Kong, Kowloon, Hong Kong SAR, China

Current drug discovery pipeline relies upon two critical aspects – combinatorial chemical library and high-throughput screening. The output of the pipeline is limited by the availability of drugable targets for screening, and the diversity of the compounds to be screened. By integrating state-of-the-art technologies such as biochips, cell-based assays, and bioinformatics, in combination with traditional Chinese medicine (TCM), we have established a functional genomics platform for disease gene identification and drug discovery. Our technology platform performs comprehensive DNA chip-based gene expression profiling to identify disease pathways that are targeted by effective TCM, and bioassay-based functional profiling to reveal the functions of the genes and drugs involved in these pathways. The combination of these technologies accelerates the identification of disease-related genes as potential drug targets, the understanding of action mechanisms and toxicology of TCM, and the discovery of new drug leads from TCM. In this presentation, we will focus on the combined use of obesity mouse model, 3T3-L1 preadipocyte/adipocyte cell-based assay, and human and mouse cDNA microarrays for screening drugs which can affect adipocyte differentiation.

IL-26. Diversity Oriented Synthesis and Branched Reaction Pathway Applied to Natural Product-like Compounds

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Darwin's theory of evolution through variation and natural selection anticipated the emergence of diversity and complexity in nature. However, this powerful concept has been applied to numerous other domains, including chemistry and leading to host of novel approaches such as combinatorial chemistry and high-throughput screening. Here we describe our recent efforts to synthesize complex compounds by diversity-oriented synthesis under palladium catalyst as a versatile tool for generating carbon-carbon bond reminiscent of natural product chemistry. That is, we have assembled in organized way different components, which are neither random nor repetitive so as to develop synthetic methods to create structural complexity, leading to branched reaction pathway where all variation could be imagined.

IL-27. Studies toward the Total Synthesis of Pharmaceutically Active Marine Natural Products

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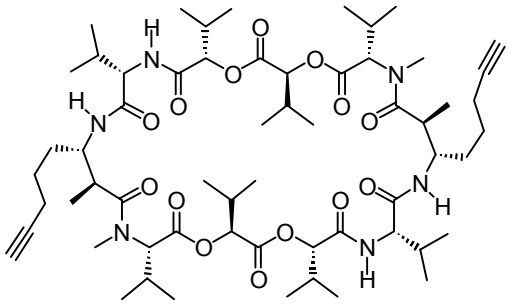
For more than two decades, there has been an ongoing quest to discover new drugs from the sea. Marine organisms are a rich source for natural products and many compounds that are derived from these organisms have generated interest both as challenging problems for structural elucidation and synthesis and for their cytotoxicities. Our research group has been involved in the total synthesis of marine natural products for past two years. Recently, we have completed the total synthesis of *ceratospongamide, yanucamide A, pitipetolide A* and *lyngbyabellin A*. The presentation will mainly focus on the synthetic studies of marine natural products *onchidin* (**1**)[1] and *apratoxin A* (**2**).[2]



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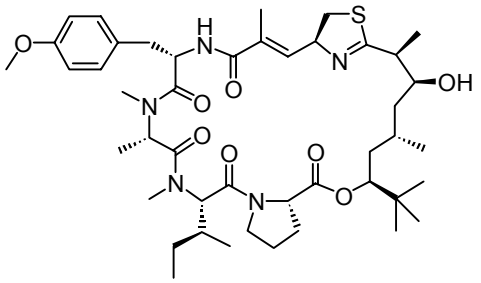

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Onchidin (**1**) was isolated from the pulmonate mollusc *onchidium* sp. assemblage collected off New Caledonia in 1994.[1] Due to the scarcity of the natural onchidin, the total synthesis becomes the only way to further study of it's pharmaceutically activities. The details of the total synthesis of *onchidin* will be presented.

Apratoxin A (**2**) was isolated from *Lyngbya majuscula* collected from Finger's reef, Apra Harbor, Guam in 2001.[2] *Apratoxin A* displays potent *in vitro* cytotoxicity against KB and LoVo cancer cell lines with an IC_{50} value of 0.52 nM and 0.36 nM, respectively. In contrast to most known potent anti-cancer natural products, *Apratoxin A* had no effect on the microfilament network, did not inhibit microtubule polymerization/depolymerization, and did not inhibit topoisomerase I. The cellular mode of action of *Apratoxin A* is, however, currently unknown. Progress towards the total synthesis of *apratoxin A* will be presented.

Acknowledgement. This work is supported by the Area of Excellence Scheme (established under the University Grants Committee of the Hong Kong Special Administrative Region), The University of Hong Kong, and The Hong Kong Polytechnic University.

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IL-28. High-throughput Synthesis for Anti-HIV and Anticancer Drug Discovery

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The encoding split-pool combinatorial synthesis on solid phase is the most powerful method to prepare chemical libraries. Recently, we have developed an encoding technology for high-throughput synthesis of small molecular libraries. The molecular tags are relatively small, chemically inert and highly sensitive. A high-throughput synthesis platform was established on the base of the encoding technology developed in our lab and the diverse chemical libraries can be synthesized by the platform for chemical genetic approach of biological systems.

RNA is a potential drug target because RNA plays an important role in living cell and many diseases caused by RNA viruses, including AIDS. So far, the only clinical successes in the field of target-directed AIDS treatment have been achieved with drugs against two key enzymes in the HIV life cycle: protease and reverse transcriptase. Despite development of a number of promising drugs and drug combinations, the success of AIDS therapy is significantly hampered by the development of drug resistance in viruses that escape the initial treatment. Such, the new attack strategies for AIDS are necessary to develop a new type of highly specific anti-AIDS drugs. HIV RNA should be another potential target for anti-AIDS drug discovery. We have prepared a glycopeptide-mimicking library by the encoding combinatorial synthesis and screened against HIV RNAs. Several interesting molecules are identified to inhibit the HIV RNA-protein interactions.

The reversible phosphorylation of proteins on serine or threonine residues preceding proline (Ser/Thr-Pro) is major cellular signaling mechanism. Recent identification of a novel prolyl isomerase Pin1 that specifically isomerizes only the phosphorylated Ser/Thr-Pro bonds in certain proteins. This post-phosphorylation mechanism may play an important role in cell growth control and diseases such as cancer and Alzheimer's. Pin1 might be a potential anti-cancer drug target. We have designed an unnatural peptide library based on the Pin1 structure. A library containing 4,000 members of molecules was synthesized by our high-throughput synthesis platform. A high affinity unnatural peptide tetramer was isolated to inhibit Pin1 isomerase. The small molecular library is developing for screening against Pin1 isomerase and we hope to identify small molecules to inhibit Pin1 as a possible anti-cancer drug candidate.

IL-29. Design, Synthesis, and Anti-inflammatory Activity of α–Substituted *p*-(Methanesulfonylphenyl)propenoic Acid and Related Compounds

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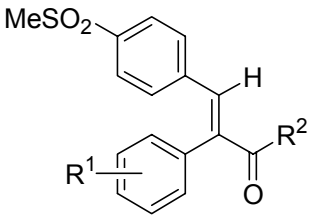
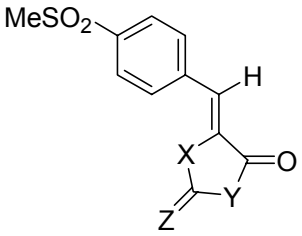
Seventy novel α-substituted *p*-(methanesulfonylphenyl)propenoic acid and related compounds (I–VI) were designed and synthesized on the basis of computer-aided drug design and by combining the structural features of *trans*-phenylpropenoic acid and Rofecoxib (RC), a tricycle type of COX-2 selective inhibitor, which entered market in 1999. The structures of I-VI were established by IR, ^{1}HNMR, MS, and elemental analysis. Anti-inflammatory activity of I–VI was evaluated in carrageenin-induced rat paw edema model. Twenty-one of them were as potent as Diclofenac (DC) and RC ($P > 0.05$). One compound was more potent than RC ($P < 0.05$). Gastrointestinal (GI) lesions of 8 active compounds were significantly less than DC ($P < 0.05$, $P < 0.01$) and comparable to RC and CMC-Na ($P > 0.05$).



R^1 = 2-Cl, 4-NO_2, 2,5-$(MeO)_2$-, etc.
I: R^2 = OH
II: R^2 = $OC_6H_4CH_2ONO_2$, OR-furoxan, etc.
III: R^2 = NHR, NHAr, etc.
IV: R^2 = N(R)OH
V: R^2 = N(R)CONR



VI: X = S, NH, NR
Y = NH, CH_2, O
Z = NH, S, O

The SARs of I–VI suggest that α–substituent be essential for anti-inflammatory activity. Preliminary QSARs were also analyzed and some useful information was obtained for further study on this type of compounds.

IL-30. Development of Novel Multicomponent Domino Process for Heterocycle Synthesis

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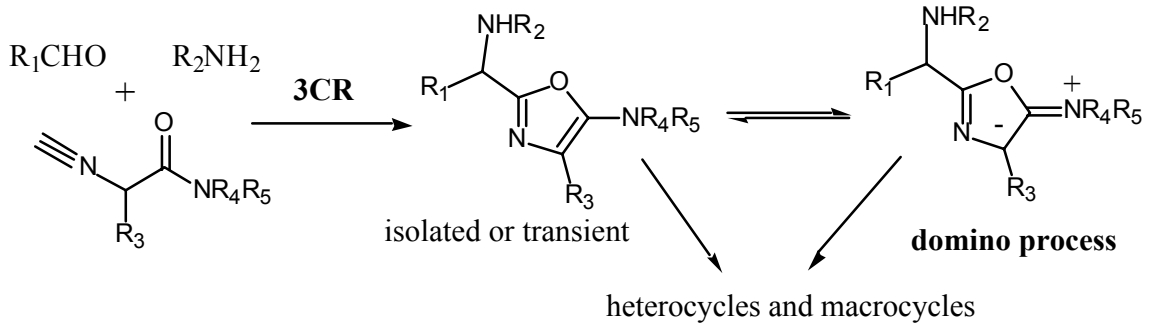
Being capable of combining three or more reactants together in a single ordered event to produce scaffolds that contain all inputs, multicomponent reaction (MCR) offers great possibility for molecular diversity per step and is becoming a cornerstone of high throughput syntheses.[1,2] We have been engaged in a research program aimed at the development of highly efficient synthesis of heterocyclic and macrocyclic compounds by combined use of multi-component reaction (MCR) and domino processes.[3] The guiding principle is to devise a novel multi-component synthesis of a heterocycle that is appropriately functionalized allowing it to be engaged in the subsequent domino process. In an ideal case, the heterocycle obtained by MCR should be poly-functionalized in such a way that different domino processes can be envisaged leading to completely different but biologically relevant cyclic scaffolds. We will present the development of a novel three-component synthesis of 5-aminooxazole and its subsequent transformations, either as isolated or as a transient intermediate, to poly-heterocycles and macrocycles.



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IL-31. High Throughput Crystallography and Structure-based Drug Discovery

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Structure-based drug discovery has historically been a slow, laborious process used in only a modest fraction of drug discovery programs in the industry. A high throughput technology platform developed at Syrrx systematically bypasses historical bottlenecks in the protein structure determination process. Deployed in a factory-like environment, Syrrx's automated systems enable the determination of protein structures more quickly, reliably, and economically than has been previously possible. This capability is used in combination with computational drug discovery methods and high-speed chemistry to accelerate drug discovery programs.

IL-32. Theoretical Study of Secondary Structures of Peptides

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Secondary structures such as α- and 3_{10}-helicies and β-sheets are ubiquitous in proteins.[1] They play vital roles in many biological functions. Peptides formed by non-natural amino acids, such as β-amino acids and amyloxy acids, also form variety of secondary structures. We have recently initiated a systematic theoretical study on understanding the secondary structures of peptides, and would like to present our progress in the following aspects: (1) The Conformational features of β-peptides;[2-5] (2) Secondary structures of oxa-peptides;[6-9] (3) The origin of cooperativity for the formation of α- and 3_{10}-helicies. We demonstrate that induced long-range electrostatic interaction is important for the cooperativity in the helices [10] (4) The cooperativity in the hydrogen bond network of β-sheets. We demonstrate that cooperativity in terms of enthalpy contribution in hydrogen bond network is not large in β-sheets.[11] (5) The origin of β-sheet-forming propensities and syn and anti preferences of β-sheets. By calculating the binding energy as a function of backbone pleating, we show that sidechain-induced peptide backbone pleating is critical to the β-sheet-forming propensities and syn and anti preferences of β-sheets.

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OP-1. LC-MS Application for High-Throughput DMPK Study in Drug Discovery

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A method of using liquid chromatography-mass spectrometry (LC-MS) for simultaneous determination of multiple drugs as well as their metabolites for *in vitro* and *in vivo* experiments was developed to support drug-metabolism and pharmacokinetic (DMPK) studies. The new approach offers significant increase in analytical throughput to meet challenge in drug discovery. *In vitro* metabolism study of α-1a antagonist for identifying lead candidates was supported by determination of metabolic rate and identification of drug metabolites using the LC-MS method. In combining with limited time-point pharmacokinetic study, greatly increased throughput was demonstrated for the *in vivo* screening and investigation of *in vivo-in vitro* correlation. In addition to the quantitative analysis of the parent drugs, the technique allowed simultaneous detection of major metabolites without having to re-analyze the animal plasma samples. For α-1a antagonists (Figure 1), major sites of the metabolism were identified as hydroxylation on the phenyl ring, piperidine *N*-dealkylation and *N*-demethylation. The metabolite identification confirmed the predicted metabolism-structure-relationship.

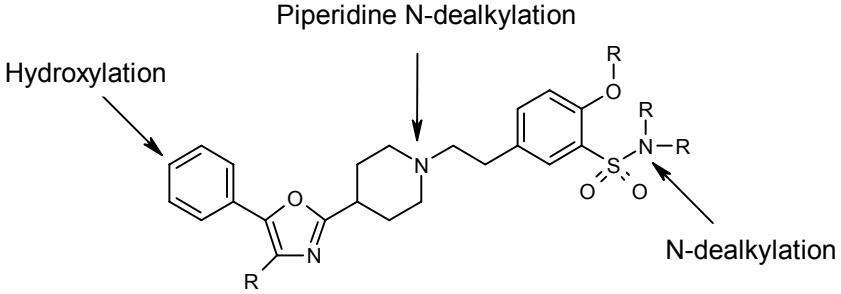

Figure 1. Relationship of structure and metabolism

The developed LC-MS method was also applied to the analysis of ginsenosides extracted from Chinese Ginseng (Figure 2). The high-throughput *in vitro* study revealed the cross-structural relationship of the ginsenosides and their metabolites. Thus, the designing of "cassette" groups for the study of multiple components must be conducted carefully in order to eliminate cross-interference problem during the LC-MS analysis.

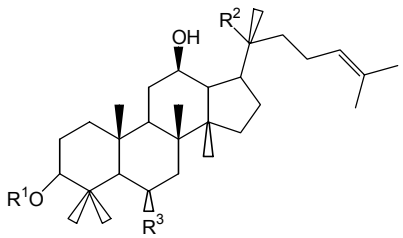

Figure 2. Structures of ginsenosides (R^1, R^2, R^3 = H, OH, CH_3 or sugar)

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OP-2. Chemical and Biological Properties of New Cell Cycle Inhibitors and Apoptosis Inducers from Chinese Medicinal Herbs

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Living cells in human body are in a dynamic balance between their proliferation and death. Human body controls the balance by switching "on" or "off" cell cycle and apoptosis to keep homeostasis at cellular level. Cell cycle and apoptosis are strictly controlled bioprocesses, and cell cycle is the sole pathway for cell proliferation, while apoptosis is a best way to eliminate unnecessary cells in physiological condition. Under normal condition, even some cancerous cells featured by DNA damage would be eliminated or repaired by the homeostatic system including the cell cycle and apoptosis processes. However, when the control process of cell cycle or apoptosis was deregulated, the undesired and unlimited proliferation of cancerous cells occurred, leading to an imbalance and subsequently to the generation of cancer. Therefore, chemical agents inhibiting cell cycle or inducing apoptosis might be useful to regulate the balance and thus possessed the potential to treat cancers. Thus, the screening of new cell cycle inhibitors and apoptosis inducers from Chinese medicinal herbs were undertaken for the discovery of new anticancer agents aiming at cancer chemotherapy.

Thousands of Chinese medicinal herbs, which are used for the treatment of cancer by Chinese people, were examined by evaluating their inhibitory effects on cell cycle and their inducing activity on apoptosis in mammalian tsFT210 cells. In addition, their effects on the growth and morphology of a fungus, *Pyricularia oryzae*, a useful model for screening anticancer agents, were also investigated. Then, chemical and biological investigations on bioactive compounds from several species of Chinese medicinal herbs were carried out. The bioactive compounds were isolated through a bioassay-guided separation procedure and their chemical structures were elucidated by modern spectroscopy. The inhibitory effects on cell cycle and the inducing activity on apoptosis in mammalian tsFT210 cells were evaluated systematically for the compounds obtained, and anticancer effects of some active compounds were also evaluated by both *in vitro* and *in vivo* tests. As a result, tens of the compounds including more than ten of new compounds from Chinese medicinal herbs were demonstrated to be new cell cycle inhibitors and apoptosis inducers, which were also chemically characterized to belong to polyphenolic, alkaloidal and terpenoidal compounds. Meanwhile, several of these potential agents were also demonstrated to exert remarkable anticancer activity both *in vitro* and *in vivo*. Furthermore, the mode of their action was also investigated by modern molecular and cellular biological means to demonstrate detailed mechanism of their action for several of these potential agents. In this presentation, the discovery, the chemical and biological properties of those new agents and their anticancer activities will be reported and discussed.

Acknowledgements. We thank Prof. H. Osada of RIKEN and Prof. T. Tsuruo of Tokyo University, for kind gift of tsFT210 and HCT-15 cell lines, respectively. This work was supported by NNSFC (No. 39825126) and the Ministry of Science and Technology (No. G1998051113), China.

OP-3. Nanoparticle Supports for Biological and Chemical Applications

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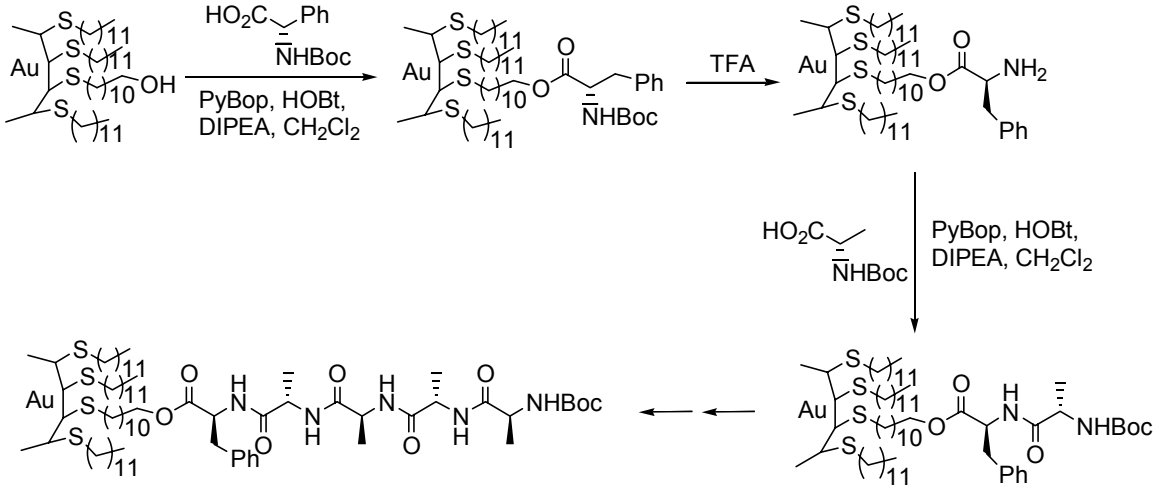
At the nanometer scale, the chemistry and physics of matter bridge between those of bulky materials and their constituent atoms due to confinement and quantum size effects, offering prospects of novel, and even size-dependent properties that have potential applications in biomedical and chemical sciences. Alkanethiolate/Au monolayer-protected clusters (MPCs) are of particular interest for biomedical applications owing to their stability, tunable solubility in aqueous and organic solutions, and relative ease of characterization. To improve their bio-specificity and expand application potentialities of these types of systems, biologically active molecules such as peptides and small ligand molecules are usually attached to Au nanoparticles.

Recently, our group has studied the peptide elongation process and Diels-Alder reactions for coating the surfaces of Au MPCs with peptides and small molecules. In our peptide elongation studies, a pentapeptide Phe-Ala-Ala-Ala-Ala was anchored onto the Au surfaces using the N-Boc chemistry strategy (Scheme 1). Our work has determined that the ee of each incorporated amino acid was maintained and an average coupling yield of 95% was achieved for each coupling step. HPLC analysis confirmed the high purity of our final peptide that was the only peptide molecule cleaved out of the Au surfaces.

We also carried out detailed kinetics studies of Diels-Alder reactions on the Au MPC surfaces. Diene Anthracene on Au MPCs was reacted with several dienophiles in organic solutions. Some surface-related kinetics were observed in our studies. We also synthesized a folate-labeled Au MPC that was utilized for labeling cancer cell lines with the assistance of transmission electron microscopy (TEM).



Scheme 1. Coating Au MPC surfaces with a pentapeptide via peptide elongation

OP-4. Studies towards the Total Synthesis of Rapamycin

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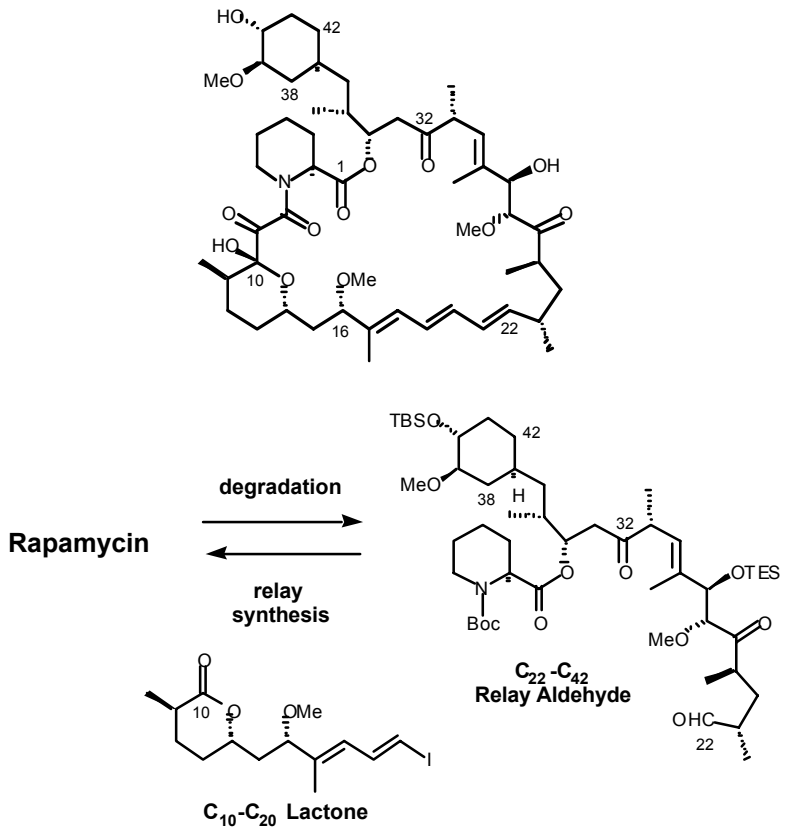
B. P. Whiffen Laboratory, Department of Chemistry, The University of Cambridge, Lensfield Road, Cambridge CB2 1EW, England

Rapamycin **1** is a remarkably potent immunosuppresant isolated from an Easter Island (*Rapa Nui*) soil sample containing the fungal strain *Streptomyces hygroscopicus*. Rapamycin **1** has an impressive architecture: its polyketide structure accommodates several challenging features including both lactone and lactam functionalities, 15 stereogenic centres, a conjugated *E*,*E*,*E*-triene, an isolated trisubstituted double bond and a masked 1,2,3-tricarbonyl unit. This plethora of structural complexity and its extraordinary biological activity present a fascinating challenge and opportunity to synthetic organic chemists. There has been four total synthesis of Rapamycin **1** to date. This presentation will describe the Ley group strategy towards Rapamycin **1** (a relay synthesis) and the synthesis of 2 advanced intermediates. With these two fragments in hand, our end game strategy will be outlined.

Figure 1. The structure of Rapamycin **1**



Scheme 1. Relay synthesis of Rapamycin **1**

References:
1. Ley, S.V.; Kouklovsky, C. *Tetrahedron* **1994**, *50*, 835.
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OP-5. Cytotoxicities and Topoisomerase I Inhibitory Activities of 2-[2-(2-Alkynylphenyl)ethynyl]benzonitriles, 1-Aryl-3-decen-1,5-diynes, and Their Related Bi-enediyne Derivatives

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[b]*National Research Institute of Chinese medicine, Taipei, Taiwan*
[c]*Graduate Institute of Natural Products, Kaohsiung Medical University, Kaohsiung, Taiwan*
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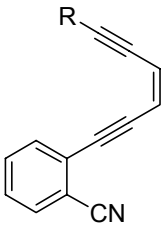
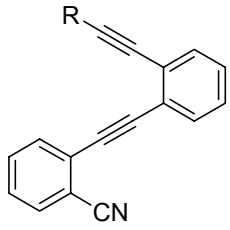
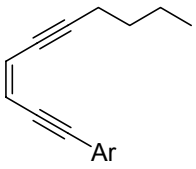
A series of acyclic enediynes, 2-(6-substituted-3-hexen-1,5-diynyl)benzonitriles (**1-5**) and their derivatives (**7-10**, **11-12**, **13-23**) were evaluated for their activities against several solid tumor cell lines and topoisomerase I. Compounds **1-5** show selective cytotoxicity with Hepa cells, and 2-[(6-phenyl)-3-hexen-1,5-diynyl]benzonitrile **5** reveals the most potent activity. Analogues **8-10** and **13-22** also have the same effect with DLD cells, 4-nitro-1-(3-(Z)-dodecen-1,5-diynyl)benzene **21** shows the highest activity among them. Moreover, 2-(3-(Z)-dodecen-1,5-diynyl)trifluoromethyl benzene **20** exhibits the strongest inhibitory activity with Hela cell line. Derivatives **9-10**, **18** and **23** display inhibitory activities with topoisomerase I at 87 μM. The cell cycle analysis of compound **5**, which induces a significant blockage in S phase, suggests that these novel enediynes probably undergo other biological pathways to give the cytotoxicity, except the inhibitory activity toward topoisomerase I.



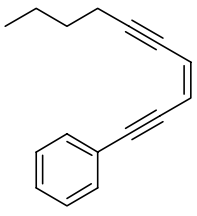
1: R = CH_2OTHP
2: R = $(CH_2)_3OTHP$
3: R = $(CH_2)_3CH_3$
4: R = $(CH_2)_4CH_3$
5: R = C_6H_5



7: R= CH_2OTHP
8: R= $(CH_2)_3OTHP$
9: R = $(CH_2)_3CH_3$
10: R = $(CH_2)_4CH_3$



13: Ar = *p*-ClC_6H_4
14: Ar = *p*-CNC_6H_4
15: Ar = pyridinyl
16: Ar = thienyl
17: Ar = pyrazinyl
18: Ar = *p*-$CF_3C_6H_4$
19: Ar = *m*-$CF_3C_6H_4$
20: Ar = *o*-$CF_3C_6H_4$
21: Ar = *p*-$NO_2C_6H_4$
22: Ar = *o*-$CH_3CO_2C_6H_4$
23: Ar = *p*-$CH_3COC_6H_4$



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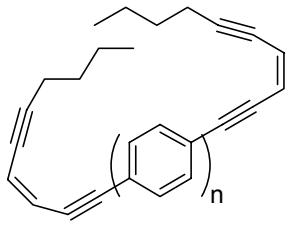

11: n = 1
12: n = 2

Chart 1. Structures of enediyne compounds **1-23**

OP-6. Mode of Action of 4-Hydroxyphenylpyruvate Dioxygenase Inhibition by Triketone-type Inhibitors

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A series of 2-(2-nitrobenzoyl)-cyclohexane-1,3-dione analogues (**1**-**9**) were designed, synthesized and evaluated for inhibition of 4-hydroxyphenylpyruvate dioxygenase (4-HPPD), a key enzyme involved in the catabolism of tyrosine which catalyzes the conversion of 4-hydroxyphenylpyruvate to homogentisate.[1] The correlations between the results of enzyme inhibition, ferric chloride tests, as well as the conformational analysis suggested that the tight binding between triketone-type inhibitors and 4-HPPD is likely due to chelation of the enzyme-bound ferric iron with the enol tautomer of 1,3-diketone moiety of the triketones. The presence of a 2-carbonyl group in the triketone is an essential structural feature for potent 4-HPPD inhibition. Modification of the 3-carbonyl group of triketone moiety to other functionality will reduce the overall planarity and thus prevent keto-enol tautomerization, resulting in a decrease or lack of inhibition activity.

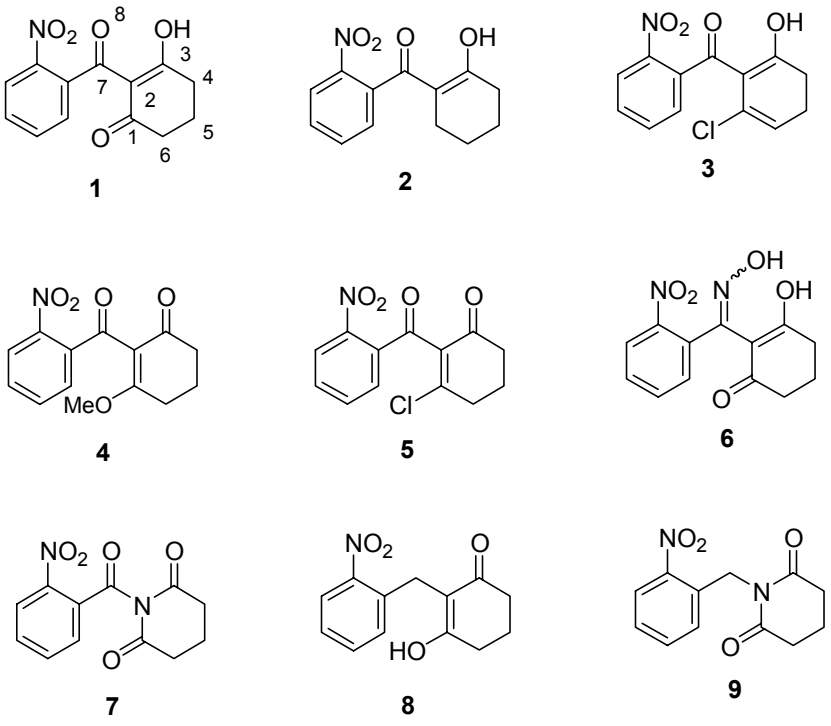

Figure 1. Compounds synthesized for SAR studies

Reference:

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OP-7. 3D-QSAR Study on 1-(Substituted phenyl)-4-(2-substituted phenoxyethyl)piperazine Analogues of α_1–Adrenoceptor Antagonist

Hao Fang,[a] Lin Xia,[a] Jianfeng Pei,[b] and Jiaju Zhou[b]
[a]*Department of Medicinal Chemistry, China Pharmaceutical University, Nanjing 210009, China*
[b]*Institute of Process Engineering, Chinese Academy of Sciences, Beijing 100080, China*

We have designed and synthesized a series of 1-(substituted phenyl)-4-(2-substituted phenoxyethyl)piperazine analogues which display good blocking activity to α_1 –AR in radioligand binding assays. Using the method of Comparative Molecular Field Analysis (CoMFA), we studied the 3D-QSAR on a Silicon Graphics O2 workstation with Sybyl 6.4 program. Conformational analysis was carried out with random search and partial atomic charges were calculated using MOPAC/AM1 program. The CoMFA model has good predictive ability that the coefficients of cross-validation (q^2) and non-cross-validation (r^2) are 0.689 and 0.998, respectively, and the value of variance ration F is 232.7. The coefficient contour plots of steric and electrostatic interactions from model are shown in Figure 1. The most potent compound, 1-[2-(2-methoxyphenoxy)ethyl]-4-(2-methoxyphenyl)piperazine, is shown in the background. It suggests that the contribution to activity from steric effect is 68.9%, and that from electrostatic effect is 31.1%. This model will help us design new compounds with better potency in the future.

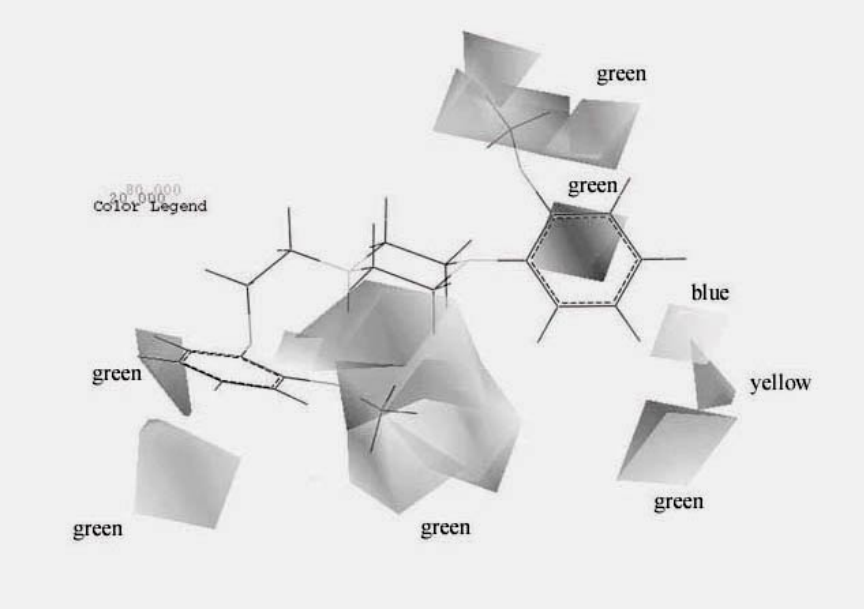

Figure 1. CoMFA STDEV*COEFF contour map

OP-8. Biomimetic Combinatorial Synthesis of Cyclic Peptide Libraries for Drug Discovery

Zhihong Guo
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Cyclic peptides are an appealing class of small organic molecules in drug discovery. In comparison with their linear counterparts, cyclic peptides are more stable *in vivo* and more pharmacogenic as a result of their reduced conformational mobility that allows presentation of diverse functionality in a defined and predictable manner. However, limited availability of diverse cyclic peptide libraries for biological screening hampers their application in biomedical research. To generate such libraries, we choose scaffolds of gramicidin S and tyrocidine A, two similar natural cyclopeptide antibiotics with a rigid β-pleated sheet conformation, for diverse presentation of functionality. Two novel methods have been developed to synthesize the scaffold-based combinatorial libraries. In a chemoenzymatic approach, enzymes in the biosynthesis of the natural products are utilized to cyclize the linear peptide precursors synthesized combinatorially on a solid support. In another biomimetic approach, the self-cyclizing capability of the linear biosynthetic precursors of the scaffold molecules and their analogues is exploited for combinatorial synthesis of the cyclic peptide libraries. Generation of these cyclopeptide libraries and their potential application in pharmaceutical research will be discussed.

PP-1. Two New Triterpene Esters from *Daphniphyllum oldhami*

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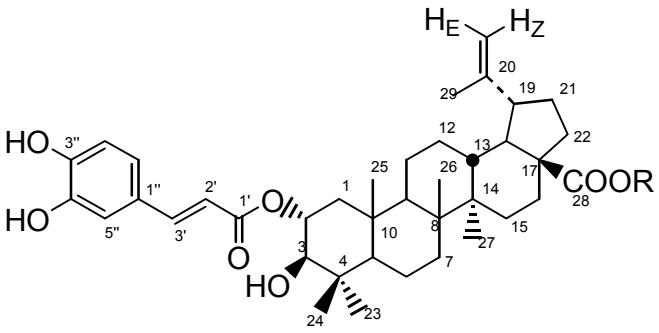
The shrub *Daphniphyllum oldhami* is widely distributed in southern China, where it has a number of folkloric uses, such as for the healing of wounds and as an antiinflammatory remedy.[1] A previous phytochemical investigation performed on the genus *Daphniphyllum* resulted in the isolation of alkaloids of the daphniphyline group[2] and antioxidant flavonoid.[3] But no any phytochemical investigation had been done on the species *D. oldhami.* On our search for plant-derived medicinal agents, the stems of *D. oldhami* collected from Guangdong Province, China, was chemically studied.



1: R = H; **2**: R = CH_3

Two new triterpene esters, 2-*O*-caffoeylalphitolic acid (**1**) and 2-*O*-caffoeylalphitolic acid methyl ester (**2**), together with two known triterpenes, betulin[4] and 28-hydroxyllupene,[5] were isolated from the EtOAc-soluble fraction of an EtOH extract of the plant. The immune activities of compounds **1** and **2** were tested, but both of them showed no significant bioactivity. Other bioassays of compounds **1** and **2** are currently being investigated. This communication deals with the isolation and the structural elucidation of new triterpene esters.

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PP-2. The New Compounds from *Carthamus tinctorius*

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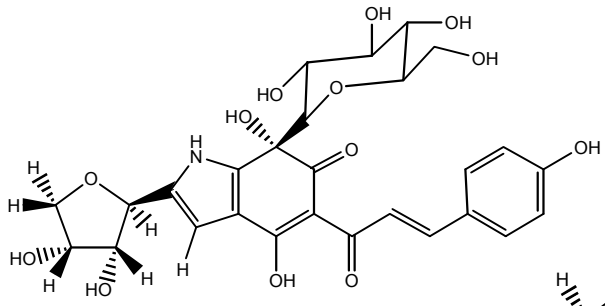
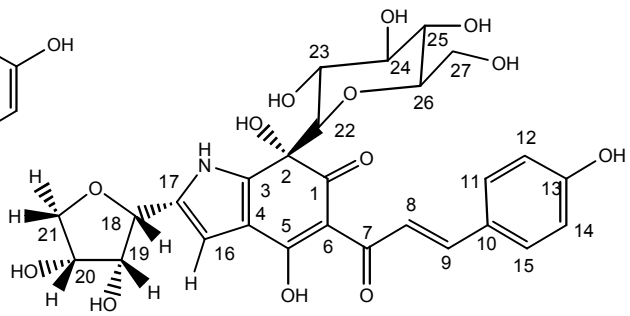
Shanghai Institute of Materia Medica, The Chinese Academy of Sciences, Shanghai 200031, China

Carthamus tinctorius L. belongs to the plant family *Compositae*, also called safflower. It is a traditional Chinese medicine widely used to treat gynaecological, cardiovascular, and cerebrovascular diseases over thousand years in China. During the course of our investigation, Cartomin (**1**) and Isocartomin (**2**), two novel semi-quinone charlcone compounds possessing a pyrrole *C*-glycoside were isolated together with a new cycloheptenone oxide derivative, Cartorimine (**3**), and two new flavonoids (**4**, **5**).

Their chemical structures were elucidated as follows:



1



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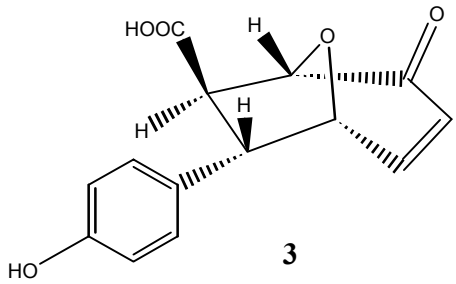
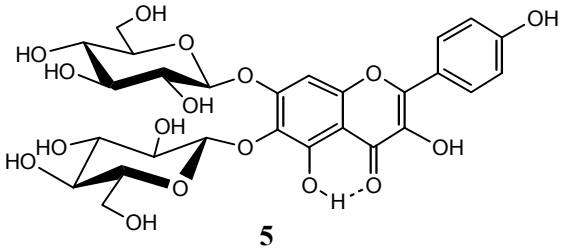


3



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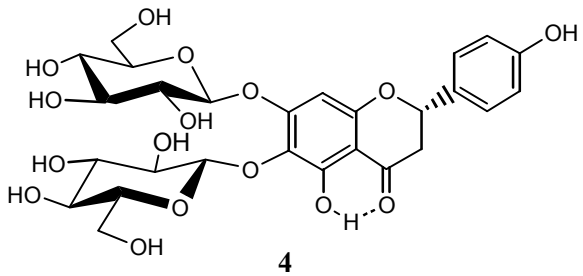

4

PP-3. Chemical Preparation of Ginsenoside Rg3 from *Panax* Plants

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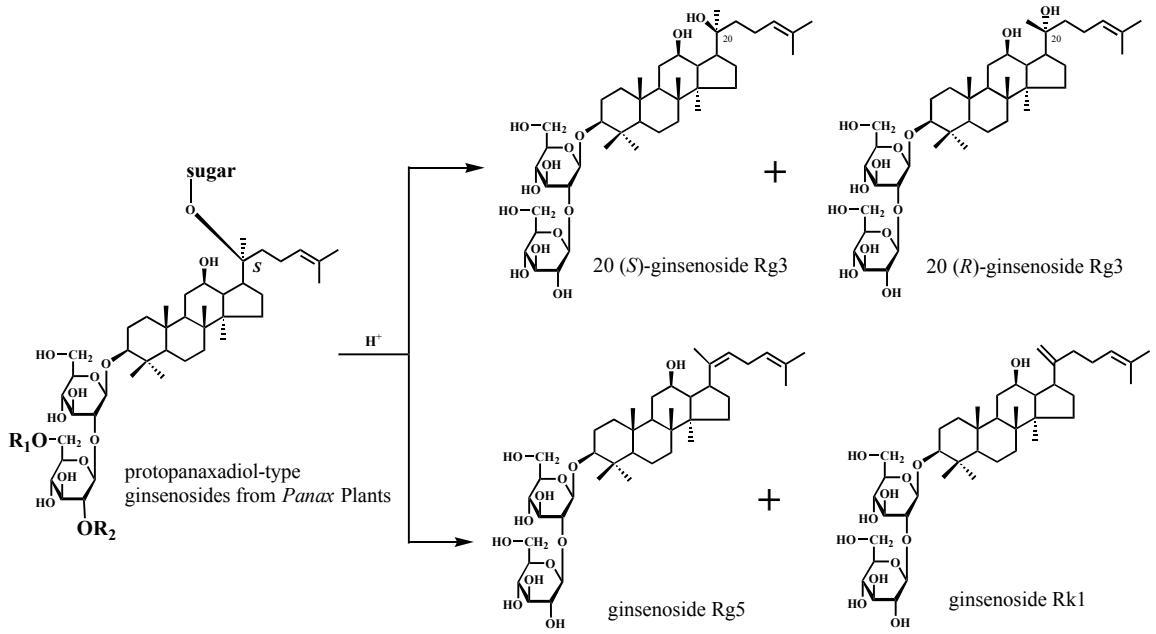
(20*R*)-Ginsenoside Rg3 is an anticancer Category-I new drug with anti-angiogenic activity which was approved in 2000 in China. It is present in ginseng root in a trace amount, and the procedures of its isolation and purification are complicated. This research aims at chemical preparation of Ginsenoside Rg3 from the total ginsenosides in *Panax* plant from the viewpoint of effective utilization of plant resources. Three plants belonging to family Araliaceae, i.e. *Panax ginseng*, *P. notoginseng*, and *P. quinquelifolium* were chosen as experimental materials. The total saponins extracted from the leaves and flowers of the above individual plant were hydrolyzed by several kinds of acids. The contents of (20*S*)- and (20*R*)-Ginsenoside Rg3 in the hydralates of the ginsenosides were determined by HPLC (ODS).[1] Ginsenoside Rk1 and Rg5 with anticarcinogenic effect[2] were also characterized from the hydrolates by means of LC/MS.



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PP-4. Content Analysis and Antibacterial Activity of Flavonoids from *Trollius chinensis* Bunge

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Trollius chinensis Bunge (Ranunculaceae) is a Chinese folk medicinal herb growing widely in northern China. Its flower parts are traditionally used to treat upper respiratory infections, pharyngitis, tonsillitis, and bronchitis. Clinical efficacy in China for the treatment of upper respiratory infections was reported to be as high as 90%. Previous studies indicated that the crude aqueous extract of *Trollius* flowers possessed antibacterial activity with no observable side effects. In the present study, we analyzed the total flavonoids and flavonoid compounds purified from *T. chinensis* using HPLC method. We have found that the dried sample of *T. chinensis* contained 1.01% and 0.452% (w/w) of orientin and vitexin respectively. In addition, we have also isolated proglobeflowery acid for the first time from the flowers of *T. chinensis*. In our investigation, antibacterial activity of the crude extract, total flavonoids, as well as the purified flavonoid compounds, namely, orientin, vitexin and proglobeflowery acid from T. chinensis were examined using the microdilution method. The bacteria that we selected to screen were 4 Gram-positive and 5 Gram-negative strains, including *Bacillus subtilis* (ATCC6633), *Staphylococus epidermidis* (ATCC12228), *Staphylococus aureus* (ATCC6538), and *Micrococcus gutti* (ATCC9341). The results showed that antibacterial activities of T. chinensis mainly exhibited against Gram-positive strains, especially *Staphylococcus*. Table 1 shows the inhibitory effect of the total flavonoids and compounds isolated from *T chinensis* against *S. aureus* and *S. epidermidis*. The effects of the total flavonoids and purified flavonoid compounds isolated, e.g. orientin and vitexin, showed potent antibacterial activity against *S. aureus* and *S. epidermidis*. Proglobeflowery acid also possessed antibacterial activity, but its activity was relatively weak.

Table 1. The minimal inhibitory concentration (MIC, μg/mL) using the microdilution method

Extract and compounds	*S. aureus* (ATCC6538P)	*S. epidermidis* (ATCC12228)
Total flavonoids	50	25
Orientin	100	25
Vitexin	25	25
Proglobeflowery acid	200	200

Reference:
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PP-5. The Separation of an Active Component from *Momordica charantia L.* and Its Antiviral Investigation *in vitro*

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Momordica Charantia L., has brought about an increasing attention because of its various potential pharmaceutical values. For instance, it has hypoglycemic,[1] antiviral,[2] antidiabetic,[3] and antitumorigenic[4] function. It possesses some active components such as momordicoside (A, B, C, D, F_1, G, H, I, L), momordicin (I, II), momordica charantia lectins, α,β-momorcharin, momordica charantia inhibitor, ribosome inactivating protein, MAP30,[4] GAP31, and so on.

In our study, a component was separated from the fruit juice of *Momordica charantia L.* (Bitter gourd) using solid phase enriching followed by ion-exchange chromatography. A main component was prepared by HPLC, and verified by IR, ^{1}H NMR, ^{13}C NMR, and MS. Furthermore, by means of observing cytopathic effect (CPE), adopting MTT colorimetric assay for the assessment of cell viability, calculating virus inhibition rate and testing titers, the antiviral activities of the component were investigated *in vitro*. The investigation showed that the component can inactivate directly ADV (EC_{50}: 8.6 μg/mL; TI: 12.18), HSV-1 (EC_{50}: 11.1 μg/mL; TI: 6.8) and HSV-2 (EC_{50}: 8.9 μg/mL; TI: 8.5), but cannot inactivate directly CVB3. It can inhibit the multiplication of the above four viruses: ADV (IC_{50}: 13.4 μg/mL; TI: 7.82), HSV-1 (IC_{50}: 4.8 μg/mL; TI: 15.8), HBV-2 (IC_{50}: 3.2 μg/ml; TI: 23.7), CVB3 (IC_{50}: 35.4 μg/mL; TI: 2.96). Experimental results indicated that the component is a potential anti-viral agent.

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PP-6. The Glycoconjugate Is a Kind of Important Active Component in the Tonic Chinese Medicine

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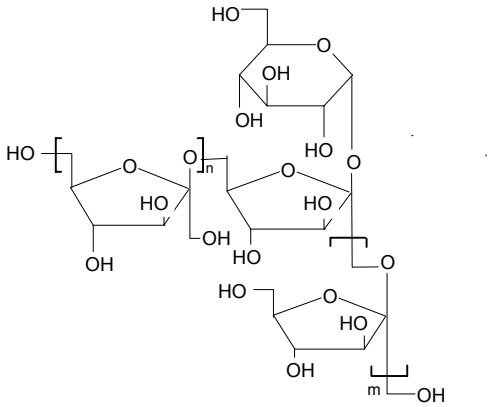
A number of research reports showed that the polysaccharide and the glycoconjugate possess functions of strengthening body's immunity, inhibiting lipid peroxidation, and protecting liver. These effects are identical with actions of medicinal herbs for nourishing *qi*, enriching the blood, strengthening *yang*, and nourishing *yin*. For example, *Panex ginseng* polysaccharide, *Astragalus membranaceus* polysaccharide and *Lycium barbarum* glycoconjugate were isolated from the corresponding nourished *yin* Chinese medicine; *Cistanche deserticola* polysaccharide and *Epimedium brevivornum* polysaccharide were isolated from the commonest strengthening *yang* Chinese medicine; and *Angelica sinensis* polysaccharide was isolated from traditional enriching blood Chinese medicine.

Achyranthan is a water-soluble polysaccharide which was isolated from the root of *Achyranthes bidentata*. It possesses effects of immunomodulation, protection of liver, and inhibition of tumor. *Achyranthes bidentata* has been found to possess actions of strengthening the tendons and bones, treating numbness of the waist and knee. These actions are relevant to immunoactivity. Up to now, over fifty-sixty polysaccharides and glycoconjugates have been isolated from tonic Chinese medicine. They are important effective components of tonic Chinese medicine.



Achyranthan (Abps)
m,n = 0~19, m+n = 2~19

PP-7. Bioactive Natural Products Formation by *Agrobacterium*-Plant Gene Transfer Method

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[c]*Institute of Materia Medica, The Chinese Academy of Medical Sciences, Beijing 100050, China*

The most widely used method for the introduction of new genes into plants is based on the natural DNA transfer capacity of *Agrobacterim tumefaciens*. Over the past decades, intensive studies on the production of biological active principles by this system have resulted in a reasonably progress in some traditional Chinese medicines.

This paper tries to compile some results in our research group during near past years, which show the importance and the potential of *Agrobacterium*-plant gene transfer system for a biotechnological production of biological active natural products. Main examples given are "Hairy-root culture of *Polygonium multiflorum* Thunb. and the production of its active constituents—anthraquinones" and "Crown gall culture of *Panax quinquefolium* L. and the identification of its ginsenosides".

Transformed hairy roots of *Polygonium multiflorum* Thunb. were obtained by the transformation of *Agrobacterium rhizogenes* R1601. It was clearly demonstrated that T-DNA of *Agrobacterium rhizogenes* Ri plasmid was integrated into the cells of hairy roots by the experiments of PCR amplification. Through the screen of basic medium and the research of growth curve of hairy roots, the optimum inoculum time was selected in 30 to 35 days in the optimum condition-MS medium. On the condition, the content of rhein was 2.55 folds higher in hairy roots than that of natural plants by means of HPLC.[1]

It was clearly demonstrated that the T-DNA in Ti plasmid of *Agrobacterium tumefaciens* C58 was integrated into the nucleus of plant cell of *Panax quinquefolim* by the experiments of paper electrophoresis. The strain of crown galls with fast growth and genetic and biochemical stability were selected in different hormone-free media. The optimal culture conditions of growth and accumulation of ginsenosides were achieved by using MS and White medium. The time course of crown gall growth and ginsenosides accumulation were investigated, and the result showed that the growth and ginsenosides content reached a maximum at 24th day and 28th day, respectively. The effects of some physical and chemical factors on the growth and ginsenosides saponins content were examined. The compounds of sponins from cultivated crown gall were analyzed qualitatively and quantitatively by means of TLC and HPLC, and the highest content of total saponion and ginsenoside Rb_1, Rg_1, and Re were 3.32%, 1.881%, 0.021%, and 0.194% (DW), respectively, which were 1.53, 1.48, 0.21, and 1.94 folds compared with those of natural plants respectively. The contents of total saponion and ginsenoside Rb_1, Re were 1.28, 3.76 and 0.33 folds compared with those of calli cultures.[2]

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PP-8. Phytochemical studies on *Juniperus przewalskii*

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[a]*Department of Chemistry, The Chinese University of Hong Kong, Shatin, N.T., Hong Kong SAR, China*
[b]*School of Chinese Medicine, The Chinese University of Hong Kong, Shatin, N.T., Hong Kong SAR, China*

Sabina przewalskii Kom. (*Juniperus przewalskii*) (Cupressaceae) is a folk medicinal plant used in the northwestern region of China for the treatment of bleeding and coughs. Little is known about the chemical and pharmacological properties of this plant. Investigation on this plant has been carried out with the aim of understanding the chemical composition of the plant and discovering natural products processing novel chemical structure. The plant materials are extracted and further separated into different fractions. The fractions are subjected to the chromatographic separation. A number of organic compounds have been purified and subjected to spectroscopic analysis. Selected compounds and fractions are tested for biological activities. The bioassay result shows that the ethyl acetate extract exhibits a hepatoprotective effect against menadione hepatotoxicity.

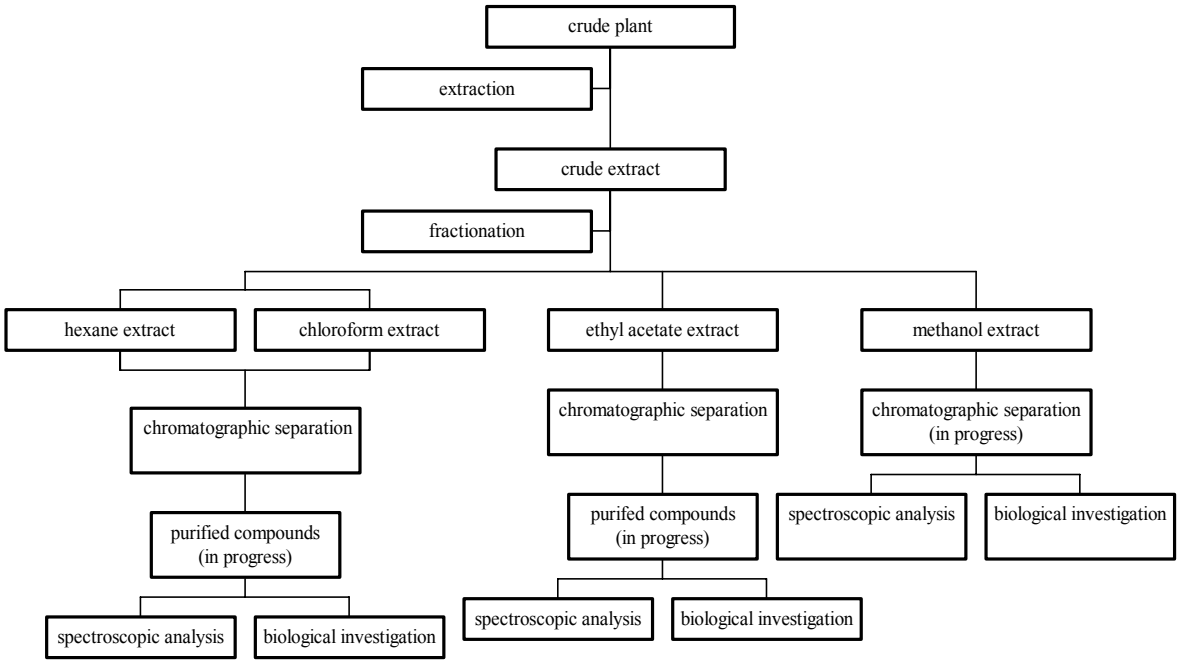

Figure 1. Methodology used for extraction and purification

PP-9. Inhibitory Effect of Naringin on Duck Hepatitis B Virus *in vitro* and *in vivo*

Xue-Long Deng, Paul Pui-Hay But, and Vincent E. C. Ooi
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Chronic hepatitis B virus (HBV) infection is highly contagious and may lead to more serious clinical consequences including liver cirrhosis and hepatocellular carcinoma (HCC). It is a major public health problem worldwide. The World Health Organization estimated that there are more than three hundred and fifty million chronic carriers of this virus and more than 1 million carriers worldwide die from cirrhosis and HCC each year.[1] Nucleoside analogue monotherapy is currently the conventional treatment, but it may never completely suppress hepadnaviral DNA synthesis because of catabolism, inefficient phosphorylation, and competition from endogenous nucleic acid precursors.[2] To identify new and more potent inhibitors of HBV replication is urgently needed. Traditional Chinese medicine (TCM) has long been used to relieve liver diseases such as hepatitis, jaundice, cirrhosis and hepatoma. Some herbal extracts have yielded molecules, often related to flavonoids, with proven antioxidative, antifibrotic, antiviral, or anticarcinogenic properties.

By using a primary duck hepatocyte (PDH) culture system infected with duck hepatitis B virus (DHBV) *in vitro* and living duck model *in vivo* with a dot blot hybridization method. A flavonoid, naringin isolated from *Citrus* species was found to have an effective inhibition on DHBV DNA replication. Administration of naringin with doses ranging from 25~100 μg/ml showed a potent inhibition on DHBV DNA *in vitro* and it's IC_{50} was 18.6 μg/ml. The result of a short-term antiviral assay *in vivo* showed that naringin at dose of 200 mg/kg/day was effective on total DHBV DNA replication in serum at five day's treatment.

The anti-reverse transcriptase (RT) activity assay showed that naringin at dose of 10^{-4} M, 10^{-5} M, and 10^{-6} M had an inhibition of 64%, 58%, and 48% on DHBV endogenous RT respectively.

An effect of naringin on DHBV RT genome from 1526th base pair (bp) to 1768th bp including domain B and C was performed with a PCR and DNA sequencing technique. The result showed that naringin at dose of 25~100 μg/ml had no effect on the primary structure of this fragment.

These antiviral assays revealed that naringin may partially account for the use of herb, *Citrus grandis,* in the treatment of HBV infection.[3] Naringin is a potent anti-HBV agent *in vitro* and *in vivo*.

Acknowledgment. This work is partially supported by a grand from Innovation and Technology Fund of Hong Kong SAR Government.

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PP-10. The Reactions of *Tanshinones* with Biogenic Amine Metabolites *in vitro*

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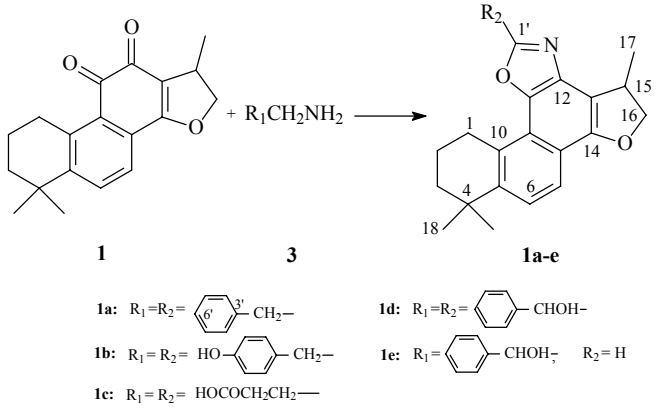
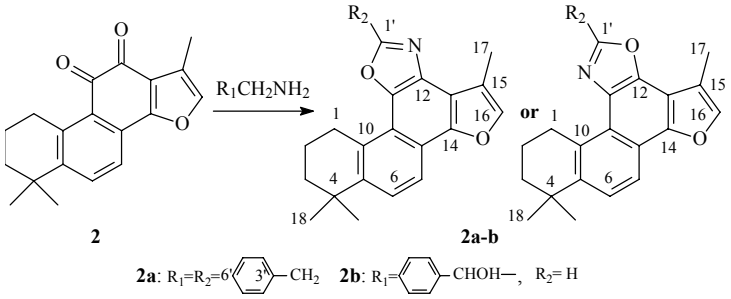
Hepatic encephalopathy (HE) is a serious neuropsychiatric complication of both acute and chronic liver disease. It was suggested that the abnormal high concentration of ammonia in plasma and cerebrospinal fluid and neurotransmission failure were responsible for HE. In our previous work, *cryptotanshinone,* a typical diterpenoid tanshinone from the traditional Chinese medicine *Salvia miltiorrhiza* Bunge, has shown property of reacting with aqueous ammonia. Further animal studies show *tanshinones* can decrease the ammonia concentration in plasma and alleviate the symptoms of HE.

In our attempt to explore the nature of the results, the interaction of typical *tanshinones* with the biogenic amine metabolites involved in the pathogenic pathways of HE, such as 2-phenylethylamine, tyramine, 4-aminobutyric acid, and 2-amino-1-phenylethanol, have been examined systematically. In this paper, we report the chemical reaction of *cryptotanshinone* (1) and *tanshinone IIA* (2) with biogenic amine metabolites mentioned above *in vitro*.



Scheme 1. Reactions of *cryptotanshinone* (**1**) with biogenic amines *in vitro*



Scheme 2. Reactions of *tanshinone IIA* (**2**) with biogenic amines *in vitro*

Acknowledgement. This work is sponsored by the Guangzhou City Science Foundation (2000-Z-021-01) and Guangdong Provincial Science Foundation (2KM04103S).

PP-11. *In Vitro* Metabolism of Ginsenoside Rg3 Using Rat S9

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Rg3, a ginsenoside from Red Panax *ginseng,* has been shown to have inhibitive activities of tumor metastasis in mice and *in vitro* tumor cell invasion.[1,2] Rg3 formula "Capsule Shen Yi" has been approved to be the first class Chinese medicine as a new anticancer drug in China. Pharmacokinetic study of Rg3 in human plasma after oral administration has been reported.[3] To our best knowledge, however, there is no report on the metabolite identification of Rg3.

We have established a method to study *in vitro* metabolism of Rg3. The method was carried out by incubating Rg3 with S9 fraction from rat liver, cofactors, and activator at 37 ^{o}C. The determination of metabolic rate of Rg3 and identification of its major metabolites were performed by using HPLC coupled with Quadruple-Time Of Flight (Q-TOF) mass spectrometry. The LC/MS results show that oxidation and hydroxylation are the major metabolic pathways under the incubation conditions. Intensive peaks of $[M+Na]^+$ ions were detected for both parent drug Rg3 and its metabolites by positive electrospray (ESI). LC/MS/MS technique provided accurate masses of both $[M+Na]^+$ and fragment ions, which were used to elucidate the structure of Rg3 (Figure 1). This information was extremely useful for the *in vitro* metabolite identification.

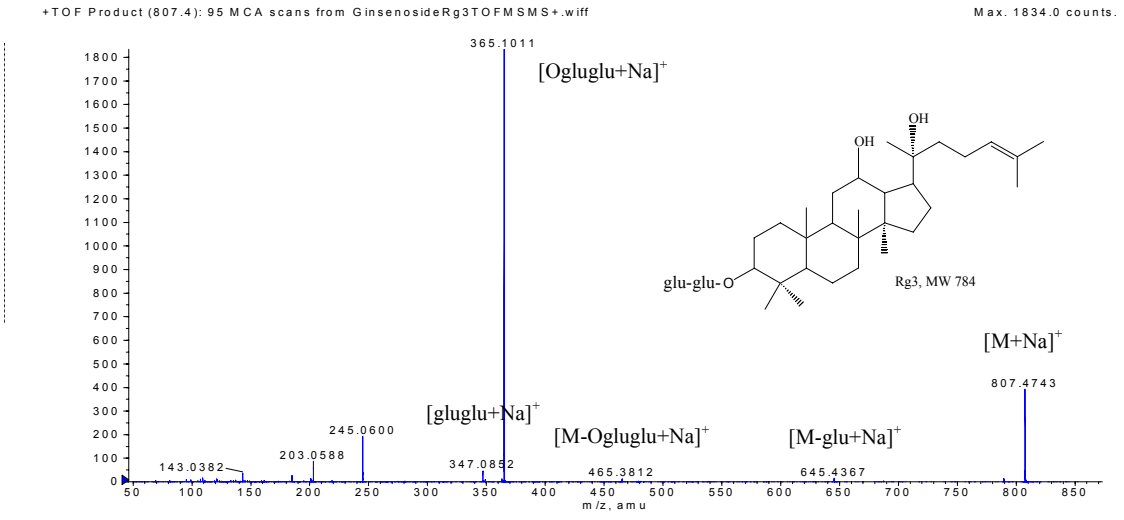

Figure 1. Structure elucidation of Rg3 from accurate mass determination of the parent and fragment ions

References:
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PP-12. The Effect of Gastrodia Extract on Enzyme Activity of MAO-B in Mice

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Gastrodia elata Blume is an important traditional Chinese medicine with wide pharmacological activities such as sedative action, immunity enhancement, and so on. According to literatrue, the clinical test proved that Gastrodia elata Blume was useful to treat Parkinson's disease. Our preliminary studies have showed that Gastrodia elata Blume could grow in intelligence and possessed antiaging action. The experiments confirmed that the enzyme activity of monoamine oxidase B (MAO-B) was positve correlation with age. The thinking activities ability in brain would descent and the organism would be aging constantly while the enzyme activity of MAO-B increased. In order **t**o explore the mechanism of action further, the effect of Gastrodia extract (GE) on enzyme activity of MAO-B in subacute aging model mice induced by *D*-galactose was observed in this paper.

Experimental drug preparation. Gastrodia elata Blume was provided by Wuhan Guoyao group Co. Ltd. According to the method of literatrue, the experimental solution (1 mL solution equivalent to 100 mg of crude drug) was prepared by the dried Gastrodia elata Blume and adjusted to pH 6-7 and sterilized.

Animal groups. Fifty-six Kunming mice (♀ & ♂, weighting 20±2 g, certificate No. 01-3052, provided by Wuhan biological products institute) were randomly divided into five groups: physiologic saline control, *D*-galactose model, experimental drug groups (lower, middle, higher dosage of experimental drug). *D*-galactose was injected subcutaneously in the model mice at dosage of 100 mg/kg. After GE was given (ip) for 30 days, the enzyme activity of MAO-B in brain was assayed.

Results. After GE was given at dosage of 0.25 g/kg, 0.5 g/kg, and 1.0 g/kg for 30 days, the enzyme activity of MAO-B in decreased significantly ($P < 0.01$) compared with *D*-galactose model group (Table 1).

Table 1. The effect of Gastrodia extract on enzyme activity of MAO-B in mice brain

groups	dosage	activity of MAO-B
	mL/kg	$U \cdot h^{-1} \cdot mg^{-1}$
physiologic saline control	–	4.290+0.797
D-galactose	100	10.282+1.899[a]
D-galactose +GE (lower dosage)	100+250	5.576+1.369[b]
D-galactose +GE (middle dosage)	100+500	4.917+1.066[b]
D-galactose +GE (higher dosage)	100+1000	4.366+1.012[b]

[a] $P < 0.01$ (compared with physiologic saline control group, T-test).
[b] $P < 0.01$ (compared with *D*-galactose model group, T-test).

Conclusion: GE could inhibit the enzyme activity of MAO-B in aging model mice brain induced by *D*-Galactose and delay biochemical damage.

PP-13. A New Combinatorial Concept: "Synergistic Therapy Library" (STL)

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Combinatorial chemistry, the integration of combinatorial synthesis and bioassay,[1] has been moving fast and almost involved all areas during the drug lead discovery process. Particularly, the new methods or concepts are practiced very well such as "dynamic library".[2] In this paper, we provide a new combinatorial concept, "Synergistic Therapy Library" (STL). A typical scaffold of STL is taxol and muramyl dipeptide (MDP) conjugates library that has been hypothesized to simultaneously supply chemotherapeutic and immunotherapeutic functions in one molecule. A representative new compound has been synthesized on solid support based on our published method.[3] A full molecular weight is identified by ESI-MS. The biological synergistic activities of this new compound are being evaluated.

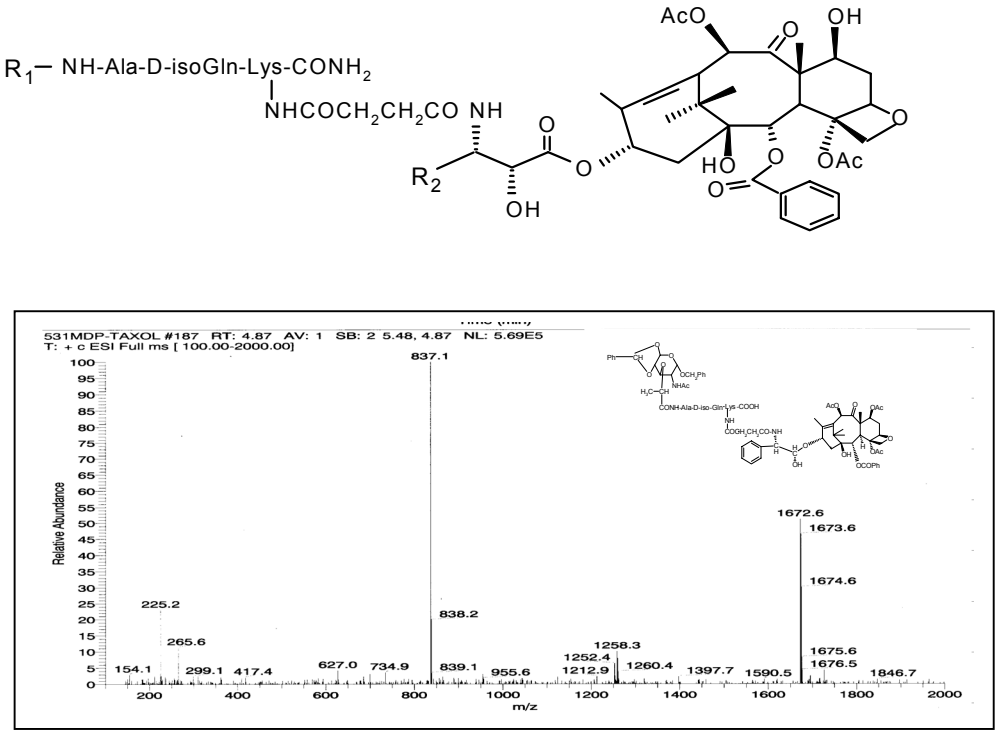

Figure 1. A representative STL scaffold and a synthesized typical compound. R_1 and R_2 represent variable positions

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PP-14. Asymmetric Synthesis of Unnatural (+)-Huperzine A by Palladium-Catalyzed Bicycloannulation

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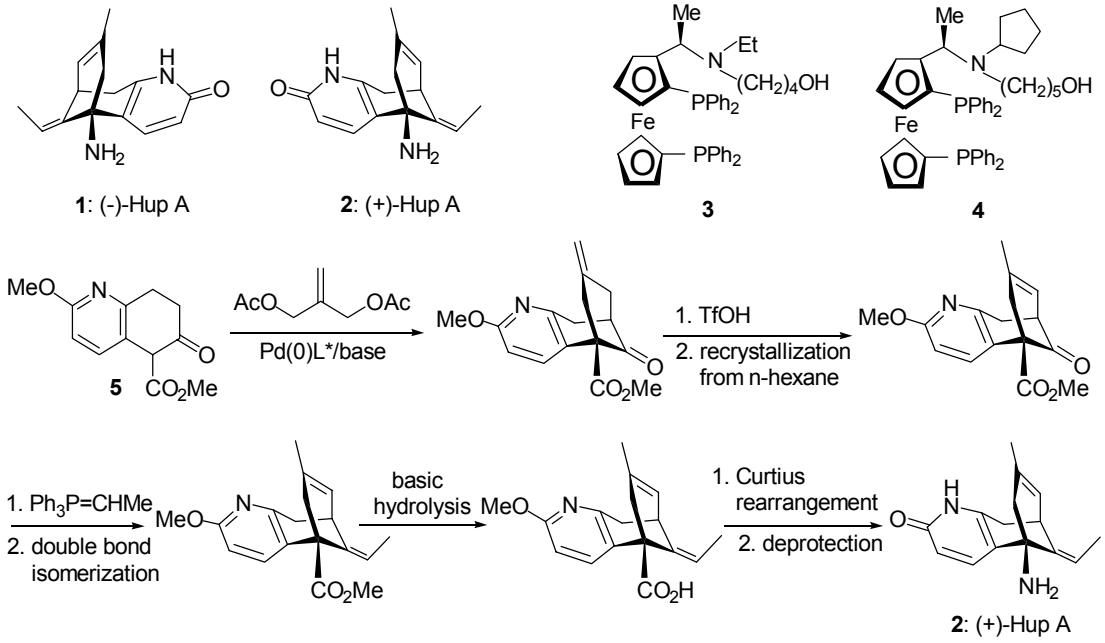
Natural (-)-huperzine A (Hup A, **1**), a Lycopodium alkaloid isolated from the Chinese traditional medicinal herb *Huperzia serrata*, is a potent inhibitor of acetylcholinesterase (AChE).[1,2] Clinical trials have demonstrated that Hup A could significantly improve memory deficiencies in patients of Alzheimer's disease (AD). Now, Hup A has been approved as a new drug for treatment of AD symptoms in China. We are interested in studying on synthesis of the enantiomeric unnatural (+)-Hup A (**2**) and its pharmacological activities, as well as structural biological studies of its complex with *Torpedo californica* AChE by X-ray crystallographic analysis.

We have achieved highly enantioselective total synthesis of (-)-Hup A by Pd-catalyzed bicycloannulation on β-keto-ester **5**, using new chiral ferrocenylphosphine ligangs, such as (*R,S*)-**3** and (*R,S*)-**4**, developed in our laboratory.[3] By using the enantiomeric chiral ligand of **3** or **4**, asymmetric synthesis of (+)-Hup A was performed according to the reaction sequence similar to the total synthesis of (-)-Hup A as shown in Scheme 1.



Scheme 1. Asymmetric total synthesis of unnatural (+)-Hup A

Acknowledgement: The work is financially supported by the National Natural Science Foundation of China.

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PP-15. Resolution of *N*-Methyl-3-phenyl-3-hydroxypropylamine and Crystal Structure Studies on Its Dibenzoyl-(*S*,*S*)-tartrate

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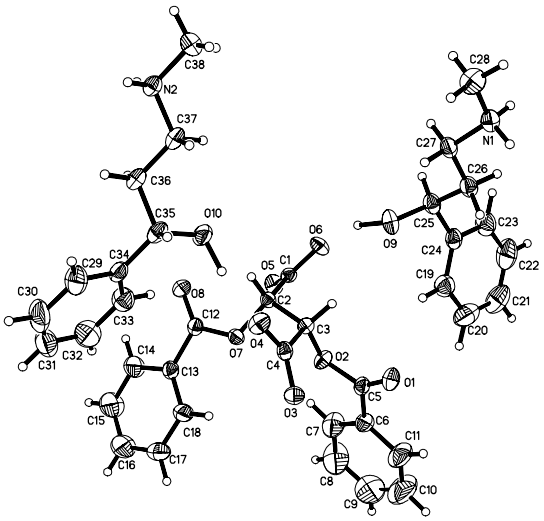
N-Methyl-3-phenyl-3-hydroxypropylamine **1,** an important intermediate of fluoxetine,[1-3] had been synthesized and resolved by using (–)-*O*,*O*'-dibenzoyl-(*S*,*S*)-tartarric acid. Di-[((*R*)-*N*-methyl-3-phenyl-3-hydroxy)propylammonium]-*O*,*O*'-dibenzoyl-(*S*,*S*)-tartrate **2** was obtained in the resolution of **1**. (*R*)-**1** and (*S*)-**1** were also obtained. Crystal **2** was characterized by IR spectroscopy, mass spectrum, NMR, X-ray diffraction. **2** crystallizes in the orthorhombic space group P2(1)2(1)2(1) with cell parameters a = 0.9269(19) nm, b = 1.3021(3) nm, c = 3.1043(6) nm, α = 90°, β = 90°, γ = 90°, V = 3.7469(13) nm^3, Z = 4. The lattice was composed of two (*R*)-*N*-methyl-3-phenyl-3-hydroxypropylammonium cations and a (–)-*O*,*O*'-dibenzoyl-(*S*,*S*)-tartarric acid anion. Anions and cations were arranged in separate stacks and they were linked via hydrogen bonds.

Name: Di-[((*R*)-*N*-methyl-3-phenyl-3-hydroxy)propylammonium]-*O*,*O*'-dibenzoyl-(*S*, *S*)-tartrate



MW: 688
Formula: $C_{38}H_{44}N_2O_{10}$
mp: 164–166 °C
$[\alpha]_D^{20}$: –46.0 (*c* = 1, CH_3OH)
Experimental solubilities: freely soluble in water, methanol, ethanol, acetone, etc.
IR: 3350, 1730, 1640, 1378, 1260, 1080, 720 cm^{-1}
^1H NMR (D_2O): δ 1.9-2.2 (CCH_2C), 2.63 (CH_3), 2.92-3.16 (NCH_2C), 4.64-4.84 (CCHOH), 5.65 (CO_2CHO), 7.27 ($PhCO_2$), 7.42-8.16 (PhC)
MS: 689 (M^+)

References:
1. Young et al., *US Patent*, 5708035.
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3. Wong, D. T.; Bymaster, F. P.; Engleman, E. A. *Life Science* **1995**, *57*, 411.

PP-16. Synthesis of (*S*)-(–)-Propranolol Hydrochloride via Asymmetric Dihydroxylation of Naphthyl Allyl Ether Using a Soluble Polymer- Supported Ligand

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β-Adrenergic blocking activity of (*S*)-(–)-propranolol (**1**) is 98 times as high as that of its *R* enantiomer. Sharpless asymmetric dihydroxylation (AD) reaction has been used in the enantioselective synthesis of (*S*)-(–)-propranolol.[1] However, the high cost as well as the high toxicity of the chiral osmium catalyst has restricted its use in industry. We have synthesized a simple soluble polymer-bound cinchona alkaloid-derived ligand DHQD-PHAL-OPEG-OMe for AD reactions (**Figure 1**).[2] Application of this ligand to the synthesis of (*S*)-(–)-propranolol proved to be very effective (**Scheme 1**).

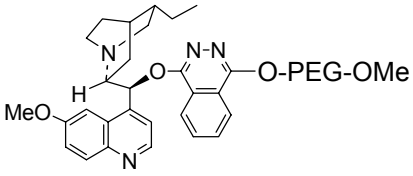
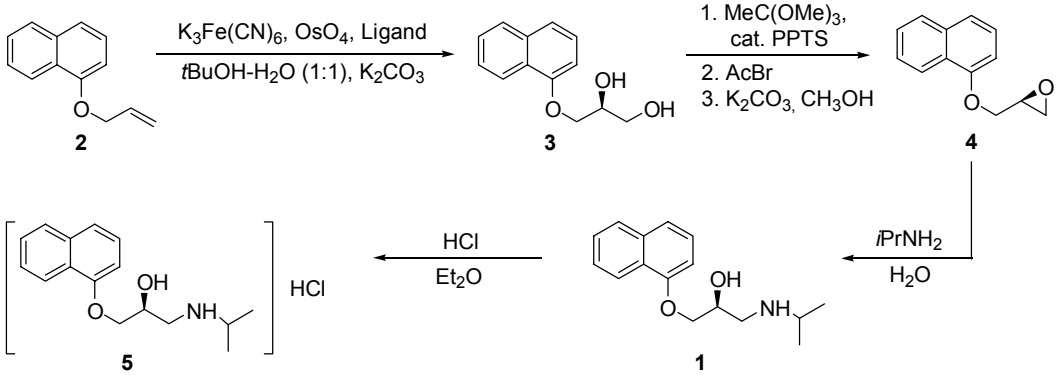


Figure 1. Chemical structure of DHQD–PHAL–OPEG–OMe



Ligand = DHQD-PHAL-OPEG-OMe, PPTS = pyridinium *p*-toluenesulfonate

Scheme 1. Synthetic route to (*S*)-(–)-propranolol hydrochloride

When the AD reaction of naphthyl allyl ether **2** was finished, the ligand was recovered by extraction with CH_2Cl_2 and precipitation upon addition of Et_2O followed by filtration. The filtrate was concentrated to provide the crude (2*S*)-3-(1-naphthyloxy)-1,2-propanediol (**3**, 90% ee by HPLC analysis), which was directly used in the next step. The diol **3** was converted into (2*S*)-3-(1-naphthyloxy)-1,2-epoxypropane (**4**) by a simple one-pot procedure via the acetoxonium ion.[3] The crude epoxide **4** was further transformed into (*S*)-(–)-propranolol hydrochloride (**5**) by a reported procedure.[4] The overall yield was 42.2%.

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1. Wang, Z. M.; Zhang, X. L.; Sharpless, K. B. *Tetrahedron Lett.* **1993**, *34*, 2267-2270.
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PP-17. Reactions of Racemic Naproxen and Ketoprofen with *threo*-(1*S*,2*S*)-2- Amino-1-(4'-nitrophenyl)-1,3-propanediol Derivatives

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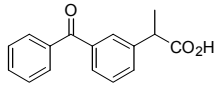
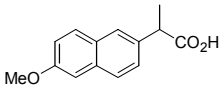
α-Arylpropanioc acid is one of important types of non-steroid anti-inflammatory chiral drugs**.** Similar to most of α-arylpropanioc acids, two enantiomers of naproxen and ketoprofen possess different physiological activity. It has been known, (*S*)-naproxen is 28 times more potent than (*R*)-naproxen; (*S*)-ketoprofen possesses extensive anti-inflammatory activity, and the (*R*)-isomer was used as a drug for treatment of periodontitis. For the preparation of (*S*)-naproxen and (*S*)-ketoprofen, a number of approaches have been reported. However, those preparative methods either need expensive chiral inductors, or are not easy to carry out. Therefore, development of a new, inexpensive preparation has important significance.

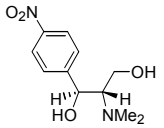
threo-(1*S,*2*S*)-2-Amino-1-(4'-nitrophenyl)propane-1,3-diol (ANP), as a by-product in production of chloromycetin, is one of the least expensive artificial chiral materials available, and, it is possible to undertake extensive structural modification due to its polyfunctional groups. We have prepared conveniently and chemoselectively cyclocondensation products of *threo*-(1*S,*2*S*)-ANP with ketones[1] and successfully applied to chiral separation of racemic ibuprofen[2] and preparation of enantiopure 1,1'-bi-2-naphthols. We explored possibility of application of *threo*-(1*S,*2*S*)-ANP derivatives to enantiomeric separation of racemic neproxen and ketoprofen. Thus, we examined reactions of racemic neproxen and ketoprofen with *threo*-(1*S,*2*S*)-ANP cyclohexanone condensate (namely, 4-aza-3-hydroxymethyl-2-(4'-nitrophenyl)-1-oxaspiro[4,5]decane, CHANP) or *threo*-(1*S,*2*S*)-2-dimethylamino-1-(4'-nitrophenyl)propane-1,3-diol (DMANP). For example, racemic ketoprofen reacted with CHANP in an equimolar ratio in Et_2O at room temperature to give a mixture of white diastereomeric ketoprofen derivatives in 79% yield, mp 82-84 °C. Racemic naproxen reacted with CHANP in a 2:1 molar ratio in Et_2O at room temperature to give white diastereomeric naproxen derivatives in 56% yield, mp 130-132 °C. Similar reaction of racemic naproxen and DMANP gave diastereomeric derivative in 88% yield. The solid was recrystallized in *i*-PrOH, and then decomposed by acidification to offer (–)-naproxen of 54.5% ee. The product enriched (*R*)-naproxen reacted with DMANP again, enantiomeric purity was upgraded to 65% ee.



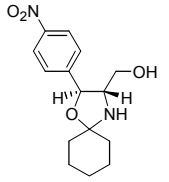
ketoprofen



naproxen



threo-(1*S*,2*S*)-DMANP



threo-(1*S*,2*S*)-CHANP

Acknowledgement. This work is supported by the National Natural Science Foundation of China (Project 29972033) and the Key Science Research Foundation of Hubei Province (Project 98IP1305).

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1. (a) Shan, Z.; Wan, B.; Wang, G. *Zhongguo Faming Zhuanli,* C.N. CN 00114346.8 (**2000**). (b) Shan, Z.; Wan, B.; Wang, G. *Helv. Chim. Acta* **2002**, *85*, 1062-1068.
2. (a) Shan, Z.; Wan, B. *Zhongguo Faming Zhuanli,* C.N. CN 01106592.3 (**2001**). (b) Shan, Z.; Wan, B. *Zhongguo Faming Zhuanli,* C.N. CN 01114245.6 (**2001**).

PP-18. Preparation of Enantiopure 1,1'-Bi-2-nanphthols *via threo*-(1*S*,2*S*)-2-Amino-1-(4'-nitrophenyl)-1,3-propanediol Cyclohexanone Condensate

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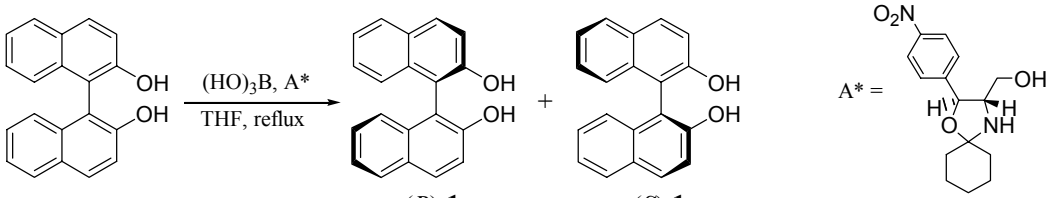
Enantiopure (*S*)-(–)- and (*R*)-(+)-1,1'-bi-2-naphthol are very important chiral ligands and auxiliaries, and have been extensively used in stoichiometric and catalytic asymmetric reactions. As far as the preparative method for optically active 1,1'-bi-2-naphthol is concerned, fractional recrystallization of diastereomers, resolution using enzymes or microorganisms, enantioselective inclusion complexation, and asymmetric oxidative coupling have become important approaches. However, these preparations utilized expensive resolving agents or chiral inductors, or are not easy to carry out, or the period of preparation is long; from the practical point of view, they are all not economical. *threo*-(1*S*,2*S*)-2-Amino-1-(4'-nitrophenyl)-1,3-propanediol (ATP), a "chiral waste" in the production of chloromycetin, is one of the least expensive artificial chiral materials available. In consideration of that reactions of 2,2'-dihydroxy-1,1'-biaryl and boric acid or its ester tend to form an ionic spirocyclic boron complex in the presence of an amine,[1] we recently explored possibility of preparation of enantiopure 1,1'-bi-2-naphthols *via* the formation of an ionic boron complex using *threo*-(1*S*,2*S*)-ATP or its derivative as a resolving agent, and found an economic, practical preparative method for both enantiomers of 1,1'-bi-2-naphthol.

A 2:1:1 mixture of racemic 1,1'-bi-2-naphthol, boric acid and *threo*-(1*S*,2*S*)-2- amino-1-(4'-nitrophenyl)-1,3-propanediol cyclohexanone condensate (CHANP, **3**)[2] was allowed to reflux in THF or CH_3CN for several hours to offer a white precipitate of bis[(*R*)-1,1′-bi-2-naphthol]boric acid CHANP derivative, which has been characterized by IR, ^{1}H NMR and MS. The precipitate gave massy, colorless transparent crystals of (*R*)-(+)-1,1'-bi-2-naphthol of 100% ee in *ca*. 65% yield after acidification and "kinetically" crystallization in toluene. The solution separated from the precipitate was evaporated and the residue was recrystallized in toluene to give (*S*)-(–)-1,1'-bi-2-naphthol of 100% ee in almost same yield.



rac-**1** (*R*)-**1** (*S*)-**1** (1*S*,2*S*)-**3**

Acknowledgement. This work is supported by the National Natural Science Foundation of China (Project 29972033) and the Key Science Research Foundation of Hubei Province (Project 98IP1305).

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2. Shan, Z.; Wan, B.; Wang, G. *Helv. Chim. Acta* **2002**, *85*, 1062.

PP-19. Enantioselective Hydrolysis of Various Racemic α-Substituted Arylacetonitriles Using *Rhodococcus* sp. CGMCC 0497

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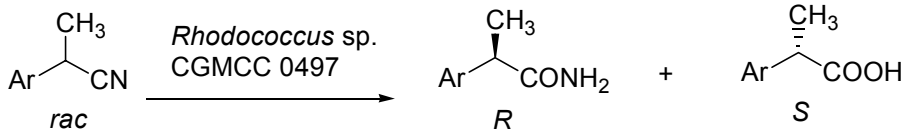
α-Arylpropionic acids are related to the non-steroidal anti-inflammatory drugs called profen. The claim that (*S*)-(+)-isomer may have advantages over the racemate has prompted frantic efforts to examine all profens for racemic switch potential. We here report the enantioselective hydrolysis of racemic α-substituted arylacetonitriles by *Rhodococcus* sp. CGMCC 0497[1] (pH 7.0, 30°C; Scheme 1) to the corresponding (*R*) amides and (*S*) acids with excellent enantiomeric excess in most cases (Table 1).[2]



Scheme 1.

Table1. Enantioselective hydrolysis of nitriles by *Rhodococcus* sp. CGMCC 0497

substrate	Ar	time	(*R*) amide		(*S*) acid	
		(h)	yield (%)	Ee (%)	yield (%)	Ee (%)
1	C_6H_5	3	42	97	48	96
2	4′-$NO_2C_6H_4$	5.5	47	86	44	90
3	2′-$OMeC_6H_4$	34	65	34	28	91
4	3′-$OMeC_6H_4$	10	42	>99	49	>98
5	4′-$OMeC_6H_4$	5	43	100	50	98
6	2′-ClC_6H_4	30	45	50	46	55
7	3′-ClC_6H_4	12	43	>99	48	97
8	4′-C C_6H_4	7	46	>98	48	>98
9	4′-FC_6H_4	4	45	>99	47	>98
10	4′-BrC_6H_4	5	45	>98	46	96
11	4′-IC_6H_4	3.5	42	>99	50	97
12	4′-$CH_3C_6H_4$	7	47	99	46	100
13	2′-naphthyl	24	52	69	40	98
14[a]	6′-MeO-2′-naphthyl	32	52	75	43	99

[a]The product **14c** is the known anti-inflammatory drug (*S*)-Naproxen.

References:
1. Wu, Z.-L.; Li, Z.-Y. *Biotechnol. Appl. Biochem.* **2002**, *35*, 61-67.
2. Wu, Z.-L.; Li, Z.-Y. *Tetrahedron: Asymmetry* **2001**, *12*, 3305-3312.

PP-20. Total Synthesis of (±)-Lycoramine: A Novel Route to the Galanthamine Skeleton

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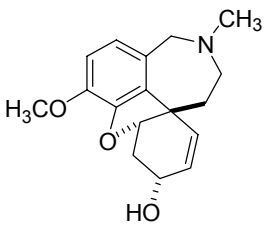
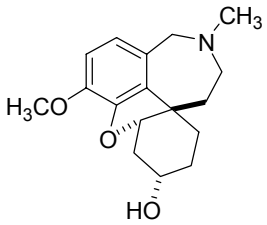
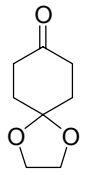
Galanthamine, an *Amaryllidaceae* alkaloid, possessing potent anti-acetylcholinesterase activity is currently used in clinic for the treatment of Alzheimer's disease. However, the production of galanthamine by isolation from natural sources is limited. Thus, it is desirable to develop a convergent and practical synthetic route for galanthamine. Herein, we demonstrate a novel approach towards the construction of the galanthamine skeleton by a total synthesis of (±)-lycoramine from cyclohexanedione monoethylene ketal (**1**) and isovanillin (**2**). The key step was the construction of the critical spiro quaternary carbon in compound **4** via a Pd-catalyzed cyclization of **3**.



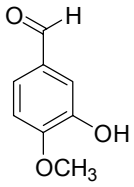
(-)-**galanthamine**



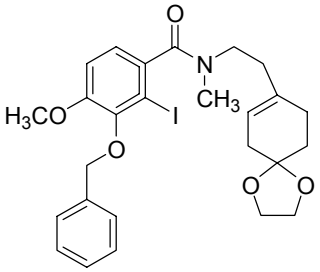
(±)-**lycoramine**



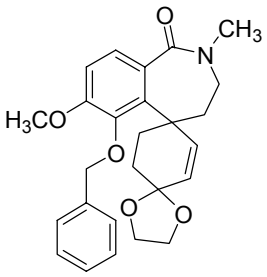
1



2



3



4

PP-21. Synthesis of 3-[4'-Acyl-2'-(1''-methoxy-1''-methylethyl)morpholin-3'-yl]-benzonitriles as Novel Potassium Channel Openers

Mei-Shan Lin[a,b] ( ), Chen-Yu Cheng[a] ( ), and Ling-Wei Hsin[a*] ( )
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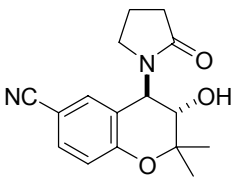
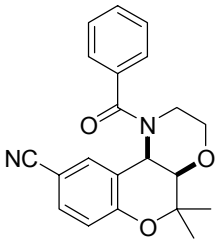
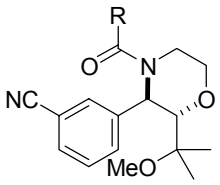
ATP-sensitive potassium channel openers (KCOs) such as cromakalim have been shown to be effective in alleviating urinary incontinence. However, a lack of tissue selectivity has limited its clinical potential. Previous work in this laboratory has determined that compound **1**, a rigid analog of cromakalim, is a bladder-selective KCO ($IC_{50,\ bladder}$ = 8.15 μM, $IC_{50,\ portal\ vein}$ = 34.5 μM). In an effort to develop potent and selective KCOs, a novel structural class of KCOs (**2** & **3**) was designed by opening the benzopyran ring of **1** to afford the 3-(morpholin-3'-yl)-benzonitrile skeleton. The synthesis and pharmacological activity of these novel ligands will be discussed.



cromakalim



1

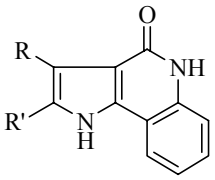


2: R = $OC(CH_3)_3$
3: R = C_6H_5

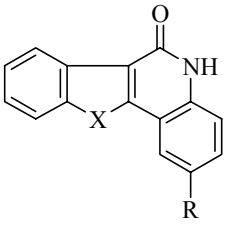
PP-22. Synthesis and Cytotoxic Activity Evaluation of Indolo-, Pyrrolo-, and Benzofuro- Quinolin-2(1*H*)-ones and 6-Anilino-indoloquinoline Derivatives

Yeh-Long Chen,* Chao-Ho Chung, I-Li Chen, Po-Hsu Chen, and Haw-Yaun Jeng
School of Medicinal and Applied Chemistry, Kaohsiung Medical University, Kaohsiung 807, Taiwan

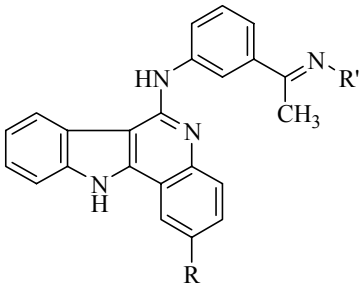
Certain indolo-, pyrrolo-, and benzofuro- quinolin-2(1*H*)-ones **4a**,**b**, **6**, **8**, **16a-c** and 6-anilinoindoloquinoline derivatives **10a**,**b**, **11a**,**b**, **12a**,**b** have been synthesized and evaluated *in vitro* against a 3-cell lines panel consisting of MCF7 (breast), NCI-H460 (lung), and SF-268 (CNS). Those active compounds **4a**,**b**, **6**, **8**, **10a**,**b**, **11a**,**b**, **12a**,**b** were then evaluated in the full panel of 60 human tumor cell lines derived from nine cancer cell types.[1] The results have shown that cytotoxicity decreases in the order of 6-anilinoindoloquinolines > indoloquinolin-2(1*H*)-ones > pyrroloquinolin-2(1*H*)-ones > benzofuroquinolin-2(1*H*)-ones. Among them, 1-[3-(11*H*-indolo[3,2-*c*]quinolin-6ylamino)phenyl]ethanone oxime hydrochloride (**11a**) and its 2-chloro derivative (**11b**) were most active, with mean GI_{50} values of 1.70 and 1.35 μM, respectively. Both compounds **11a**,**b** were also found to inhibit the growth of SNB-75 (CNS cancer cell) with a GI_{50} value of less than 0.01 μM, and, therefore, were selected for further evaluation for *in vivo* antitumor activity.



6: R = C_6H_5, R' = H
8: R = R' = C_6H_5



10a: X = NH, R = H
10b: X = NH, R = Cl
12a: X = O, 2-OCH_3
12b: X = O, R = 3-OCH_3
12c: X = O, R = 4-F

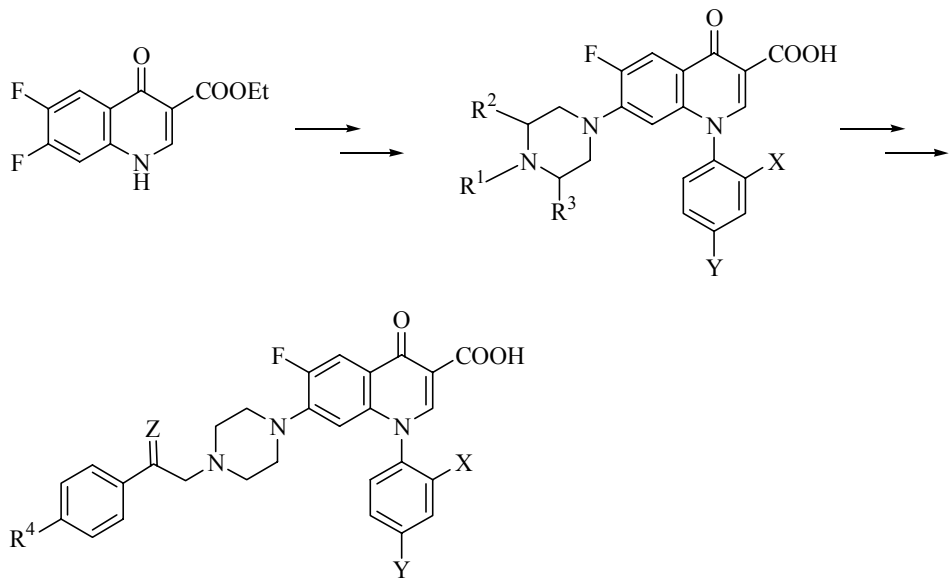


11a: R = H, R' = OH
11b: R = Cl, R' = OH
12a: R = H, R' = OCH_3
12b: R = Cl, R' = OCH_3

PP-23. Synthesis and Anti-mycobacterium Activity of 1-Arylquinolones

Jia-Yuh Sheu, Yeh-Long Chen, and Cherng-Chyi Tzeng
School of Medicinal and Applied Chemistry, College of Life Science, Kaohsiung Medical University, Kaohsiung 807, Taiwan

Several of the fluoroquinolone antibacterial agents, such as norfloxacin, ofloxacin, ciprofloxacin, and temafloxacin, have been examined as potential chemotherapeutics for *Mycobacterium tuberculosis* infection. These fluoroquinolones show good penetration into macrophages where they are both concentrated and retain a high degree of activity. This property is particularly important since it is well-known that surface-associated lipids of mycobacteria form a transport barrier when compared to the cell wall of true bacteria. However, a systematic study to optimize the fluoroquinolones against tuberculosis (TB) infection has not been undertaken. We have recently synthesized a number of 1-arylquinolone derivatives and evaluated for their antibacterial activity.[1] Some of them were found to be more potent anti-TB agents than norfloxacin and ciprofloxacin.

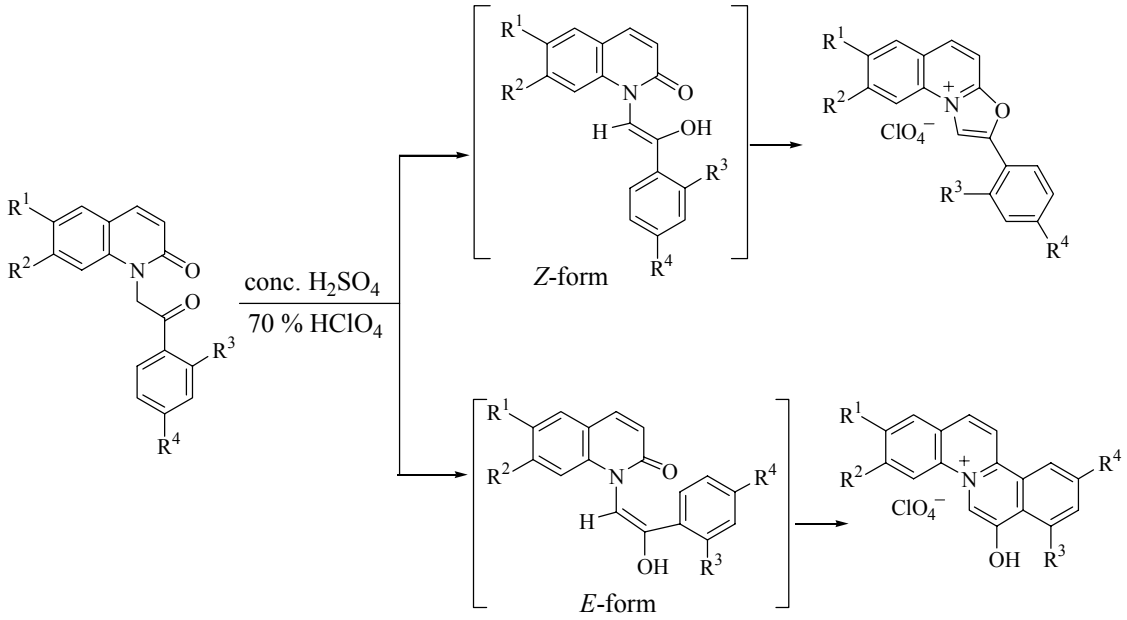


Reference:
1. Chen, Y. L.; Fang, K. C.; Sheu, J. Y.; Hsu, S. L.; Tzeng, C. C. *J. Med. Chem.* **2001**, *44*, 2374-2377.

PP-24. Synthesis of Potential Anticancer Dibenzo[*a,f*]quinolizinium and 2-Phenyloxazolo[3,2-*a*]quinolinium Perchlorates

I-Li Chen, Yeh-Long Chen, and Cherng-Chyi Tzeng*
School of Medicinal and Applied Chemistry, Kaohsiung Medical University, Kaohsiung 807, Taiwan

Among the possible dibenzoquinolizinium tetracyclic quarternary aromatic compounds, we were particularly interested in dibenzo[*a,f*]quinolizinium series because of its structural similarity to both anticancer dibenzo[*a,g*]quinolizinium alkaloid such as coralyne and deoxythalidastine and benzo[*c*]phenanthridine alkaloid such as nitidine and fagaronine. However, only two papers have appeared so far describing the preparation of this novel skeleton through the photochemical method. The present report describes acid-catalyzed ring cyclization of 1-[2-oxo-2-(4-methoxyphenyl)ethyl]-2(1*H*)-ones (R^4 = OMe) to form dibenzo-[*a,f*]quinolizinium salts *via* an *E*-form intermediate. On the other hand, certain 2-phenyl oxazolo[3,2-*a*]quinolinium perchlorates were synthesized by acid-catalyzed ring cyclization of 1-[(2-oxo-2-phenyl)ethyl]-2(1*H*)-ones (R^4 = H or Me) *via* the *Z*-form intermediate.

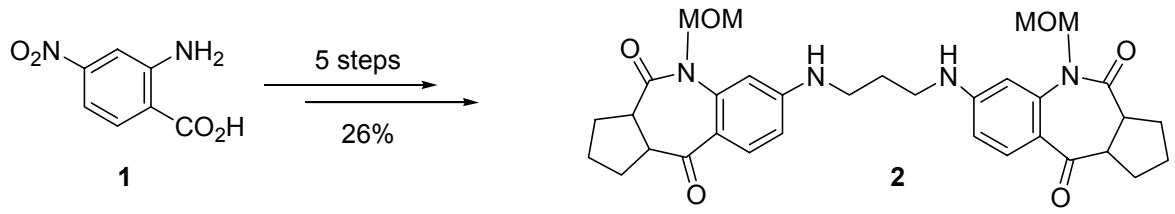


PP-25. Design and Synthesis of MOM-protected 8-Aminopyrrolo[2,1-*c*][1,4]benzodiazepine Crosslinking Agents

Jeh-Jeng Wang,*[a] Ping-Syh Tsai,[b] and Wan-Ping Hu[a]
[a]*School of Chemistry, Kaohsiung Medical University, Kaohsiung City 807, Taiwan*
[b]*Department of Chemical Engineering, National Kaohsiungl University of Applied Sciences, Kaohsiung City 807, Taiwan*

Pyrrolo[2,1-*c*][1,4]benzodiazepines (PBDs) are a group of potent, naturally occurring antitumor antibiotics produced by *Streptomyces* species. The cytotoxic and antitumor effects of these compounds are believed to arise from modification of DNA, which leads to inhibition of nucleic acid synthesis and production of excision-dependent single- and double-strand breaks in cellular DNA. These antibiotics have been proposed to covalently bond to N2 of guanine to form a neutral minor groove adduct.

In this presentation, we report a new class of PBD analog precursors based upon crosslinking two molecules of MOM-protected PBD with amino group attached at C8 positions. 8-(Propylamino)-10-methoxymethyl-pyrrolo[1,4]benzodiazepine-5,10-dione DIMER (**2**) was obtained in 25% overall yield from 4-nitroanthranilic acid.

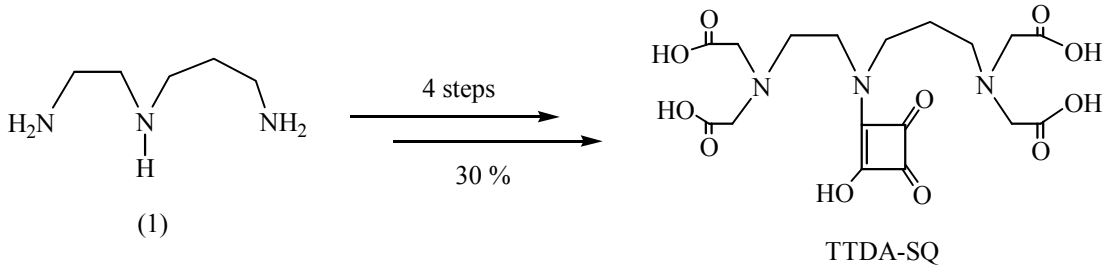


1 **2**

PP-26. Design and Synthesis of a Novel Ligand 6-(2-Hydroxy-3,4-dioxo-1-cyclobutenyl)-3,6,10-triazadodecane-3,10-tetraacetic Acid (TTDASQ) for MRI Contrast Agent

Tsan-Hwang Cheng , Ming-Hung Ou, and Yun-Ming Wang*
School of Chemistry, Kaohsiung Medical University, 100 Shih-Chuan 1st Road, Kaohsiung City 807, Taiwan

The development of contrast agents for magnetic resonance imaging (MRI) has become of great interest since this technique is a very powerful tool in medical diagnosis. In this report, we designed and synthesized a novel ligand 6-(2-hydroxy-3,4-dioxo-1-cyclobutenyl)-3,6,10-triazadodecane-3,10-tetraacetic acid (TTDA-SQ, Scheme 1) for MRI contrast agent, and the overall yield was 30% from *N*-(2-aminoethyl)-1,3-propanediamine (**1**). The structure of TTDA-SQ was confirmed by 400 MHz ^{1}H and ^{13}C NMR and elementary analysis.



Scheme 1

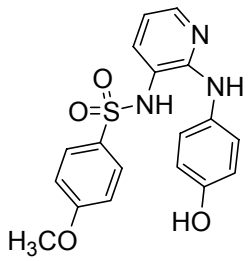
PP-27. Design and Synthesis of Carbazolylbenzenesulfonamide Derivatives as Potential Targeting Cell Cycle Inhibitors

Grace Shiahuy Chen (陳香惠),[a] Kuan-Yu Chen (陳冠妤),[a] Yu-Lin Leu (呂玉玲),[a] Chi-Yen Chang (張琦艷),[b] Jang-Yang Chang (張俊彥),[b] and Ji-Wang Chern (陳基旺)*[a]

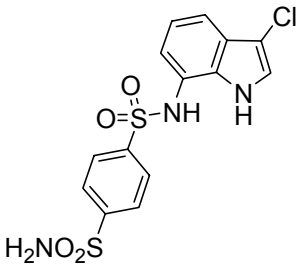
[a]*School of Pharmacy, College of Medicine, National Taiwan University, No. 1, Section 1, Jen-Ai Road, Taipei, Taiwan*

[b]*Division of Cancer Research, National Health Research Institutes, Taipei, Taiwan*

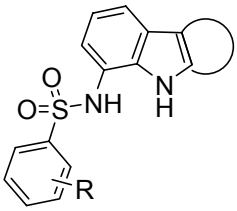
Intact components of cell cycle arrest checkpoints are potential targets for novel antineoplastics.[1] Many antitumor agents act at multiple steps in the cell cycle. The sulfonamide derivatives have been shown to possess diverse biological activities such as antibacterial, insulin releasing, carbonic anhydrase inhibitory, and antihyroid. Various sulfonamide drugs were reported to interact with many kinds of cellular protein targets. The first antitumor sulfonamide, **E7010**, was found to cause cell cycle arrest and apoptosis in M phase and to demonstrate good antitumor activity.[2] Interestingly, the same group reported that the other related series of antitumor sulfonamides, *N*-(7-indolyl)benzenesulfonamides such as **E7070**, showed prominent antitumor activity targeting in G1 phase not in M phase.[3] In the course of our study, we designed and synthesized a series of carbazolylbenzenesulfonamides **I** as novel potential antitumor agents in which the hydrophobicity may be expected to be increased by expanding the 2 and 3 positions of **E7070**. It was hoped that these compounds could serve as new cell cycle inhibitors. The preliminary cytotoxicity assays of the target compounds exhibited potentiality against many cancer cell lines. More importantly, our designed carbazolylbenzenesulfonamide derivatives are almost all more potent than the corresponding indole derivative.



E7010
Targeting M phase



E7070
Targeting G1 phase



I
Potential cell cycle inhibitors

References:

1. Shapiro, G. I.; Harper, J. W. *J. Clin. Invest.* **1999**, *104*, 1645-1653.
2. Yoshino, H.; Ueda, N.; Niijima, J.; Sugumi, H.; Kotake, Y.; Koyanagi, N.; Yoshimatsu, K.; Asada, M.; Watanabe, T.; Nagasu, T.; Tsukahara, K.; Iijima, A.; Kitoh, K. *J. Med. Chem.* **1992**, *35*, 2496-2497.
3. Owa, T.; Yosihino, H.; Okauchi, T.; Yoshimatsu, K.; Ozawa, Y.; Sugi, N. H.; Nagasu, T.; Koyanagi, N.; Kitoh, K. *J. Med. Chem.* **1999**, *42*, 3789-3799.

PP-28. A Practical Approach to the Total Synthesis of Benzofuran Skeleton Natural Product. Application to XH-14, Obovaten, and Ailanthoidol

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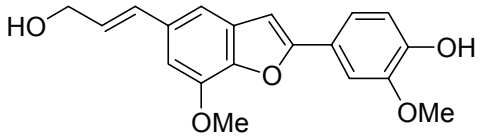
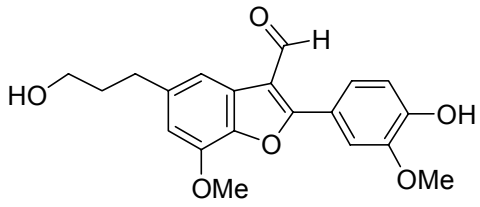
School of Pharmacy, College of Medicine, National Taiwan University, No. 1, Section 1, Jen-Ai Road, Taipei, Taiwan

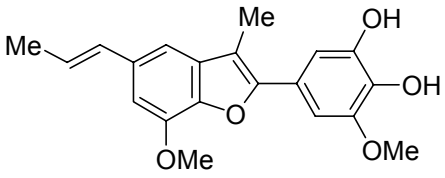
Lignans have been reported to possess a variety of biological activities. However, especially for the benzofuran skeleton ones, the biological activities have not been well established yet due to insufficient natural abundance. In the course of our interest in the synthesis of benzofuran derivatives for biological studies and in view of the pharmacological interest of lignans, we provide an approach, starting from vanillin, toward the syntheses of ailanthoidol (**1**), XH-14 (**2**), and obovaten (**3**). 1-Bromo-2,3-dimethoxy-5-(5',5'- dimethyl-1',3'-dioxan-2'-yl)benzene, prepared from vanillin, was coupled with substituted benzaldehyde to furnish carbinol. The corresponding alkyne was obtained *via* Covlin rearrangement of the corresponding ketone, which was obtained from oxidation of the previous alcohol. The substituted diphenylalkyne was then treated with mercury acetate to construct benzofuran skeleton, which could afford different intermediates *via* either reduction or halogenation and/or carbonylation. Elongation of the side chain at 5-position of this series of intermediates and then undergoing further necessary reactions shall provide the desired target compounds.



1, Ailanthoidol



2, XH-14



3, Obovaten

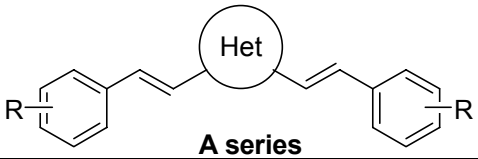
PP-29. Design, Synthesis, and Biological Evaluation of Heterocycle-Conjugated Styrene Derivatives as Inhibitors of Protein Tyrosine Kinases and Free Radical Scavengers

Shin-Yu Lai (賴信羽),[a] Chien-Shu Chen (陳建樹),[a] Pei-Shuang Hsu (徐佩霜),[a] Cheng-Yu Tsai (蔡正昱),[a] Chuen-Wang Fang (方春旺),[b] Ming-Jai Su (蘇銘嘉),[b] Chia-Lin Kao (高佳麟),[a] and Ji-Wang Chern (陳基旺)*[a]

[a]*School of Pharmacy, College of Medicine, National Taiwan University, No. 1, Section 1, Jen-Ai Road, Taipei, Taiwan*

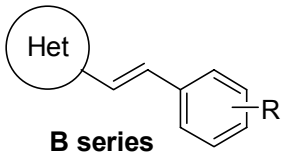
[b]*Department of Pharmacology, College of Medicine, National Taiwan University, Taipei, Taiwan*

In our efforts to develop protein tyrosine kinase (PTK) inhibitors as potential antitumor agents, two series of heterocycle-built-in push-pull molecules, A and B series, were designed and synthesized on the basis of two natural PTK inhibitors, curcumin and piceatannol. The inhibitory activities against $p59^{fyn}$, HER2, $p56^{lck}$, and EGFR (epidermal growth factor receptor) tyrosine kinases were evaluated. In general, the compounds in A series displayed broad and moderately potent inhibitory activity with the most potent members being the pyridine derivatives **12** and **14**. The compounds in the B series were relatively less active against HER2 and EGFR than the other two kinases. Overall, **12** and **22** were the most potent inhibitors of EGFR tyrosine kinase with the IC_{50} values of 0.44 and 0.39 μM, respectively. As effective PTK inhibitors, **5**, **9**, and **10** were found to have significant antiproliferative activity against the NCI 60 human cancer cell lines. In view of the antioxidant properties of a number of polyphenolic phytochemicals including curcumin and piceatannol, compounds bearing the 3,4-dihydroxystyryl moiety were evaluated for their free radical scavenging activity using DPPH method and found to be more potent than the natural antioxidant curcumin. The substitution of 3-dimethylaminopropoxy or 3,5-dibromo-4-hydroxy on the benzene ring led to a great loss in radical scavenging activity. The results of antioxidation assays showed that the three strong DPPH radical scavengers **5**, **9**, and **10** could protect LDL completely from copper-induced oxidation.



A series

Compd	Het	R
5	4-pyron-2,6-diyl	3,4-diOH
6	4-pyron-2,6-diyl	3-OMe-4-OH
7	4-pyron-2,6-diyl	3-OH-4-OMe
8	4-pyron-2,6-diyl	4-O$(CH_2)_3NMe_2$
9	2-pyron-4,6-diyl	3,4-diOH
10	1,3,4-thiadiazol-2,5-diyl	3,4-diOH
11	1,3,4-thiadiazol-2,5-diyl	4-O$(CH_2)_3NMe_2$
12	pyridin-2,6-diyl	3,4-diOH
13	pyridin-2,6-diyl	3,5-diBr-4-OH
14	pyridin-2,4-diyl	3,4-diOH
15	pyridin-2,4-diyl	3,5-diBr-4-OH



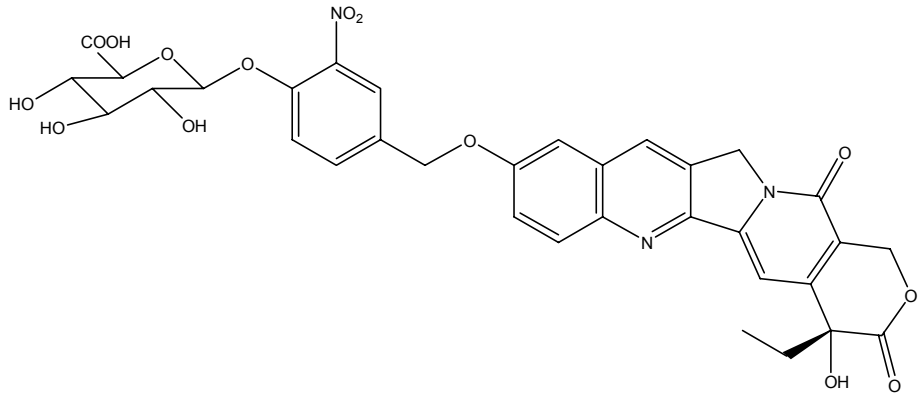
B series

Compd	Het	R
16	pyridin-4-yl	3,4-diOH
17	pyridin-4-yl	3,5-diBr-4-OH
18	quinolin-4-yl	3,4-diOH
19	quinolin-4-yl	3,5-diBr-4-OH
20	quinolin-2-yl	3,4-diOH
21	quinolin-2-yl	3,5-diBr-4-OH
22	8-OH-quinolin-2-yl	3,4-diOH
23	8-OH-quinolin-2-yl	3,5-diBr-4-OH

PP-30. Design and Synthesis of Water-Soluble Glucuronide Prodrug of Camptothecin for Cancer Therapy

Yu-Lin Leu (呂玉玲),[a] Yih-Jang Wu (吳奕璋),[b] and Ji-Wang Chern (陳基旺)*[b]
[a]*Chia-Nan University of Pharmacy and Science, Tainan, Taiwan*
[b]*School of Pharmacy, College of Medicine, National Taiwan University, No. 1, Section 1, Jen-Ai Road, Taipei, Taiwan*

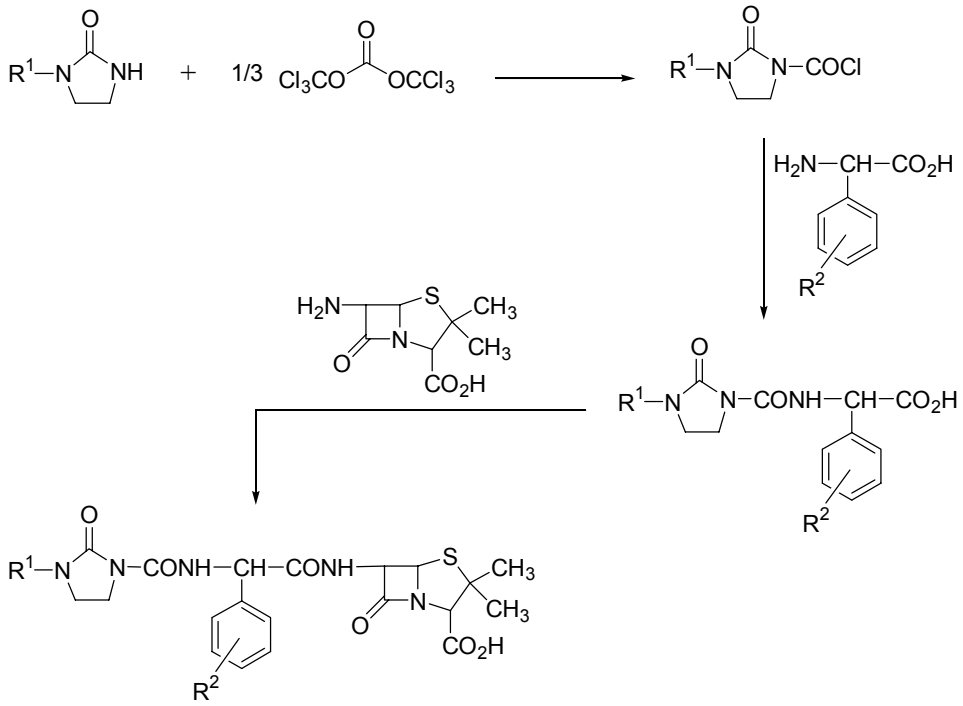
Glucuronide prodrug of 10-hydroxycamptothecin was designed and synthesized. This prodrug was stable in both aqueous solution and human plasma, in which 10-hydroxycamptothecin was connected to glucuronic acid by an aromatic spacer *via* an ether linkage. This prodrug was over 60 times more soluble than 10-hydroxycamptothecin in aqueous solution at pH 4.0, and it was 10-20 fold less toxic than 10-hydroxycamptothecin against several human tumor cell lines. The simultaneous addition of both β-glucuronidase and this prodrug to tumor cells resulted in a cytotoxic effect equal to that of 10-hydroxycamptothecin alone. This result demonstrated that this glucuronide-based prodrug could be activated by β-glucuronidase to release 10-hydroxycamptothecin through a spontaneous 1,6-elimination reaction. This prodrug may be useful for prodrug monotherapy of tumors that accumulate β-glucuronidase in extracellular lysosomal as well as for antibody-directed enzyme prodrug therapy of cancer.



PP-31. A Novel Synthesis of Penicillin Compounds

Wei-ke Su* ( ) and Bi-Bo Yang ( )
College of Pharmaceutical Sciences, Zhejiang University of Technology, Hangzhou 310014, China

We have investigated a novel synthesis technology of penicillin compounds of the following general formula **A** or their sodium salts. The whole synthesis route is given in Scheme 1.[1,2] In the first step, we have prepared 3-substituted 1-chlorocarbonyl-imidazolidin-2-ones using bis(trichloromethyl)carbonate (a stable solid; mp 79-80 °C and bp 205-207 °C; only slight decomposition to phosgene occurs at its boiling point), instead of phosgene, a very toxic gas.[3] The notable advantages of this technology are operational simplicity and environmental amiability. It greatly meets the demands of green chemistry.



A R^1 = H, CH_3SO_2, CH_3CO etc.
R^2 = H, *p*-Cl, *p*-CH_3 etc.

Scheme 1.

References:
1. Su, W.-K. CN Appl. 02107657.X, 22 March 2002.
2. Su, W.-K. CN Appl. 02107659.6, 22 March 2002.
3. Su, W.-K.; Zhang, Y.-M. *J. Chem. Res.(S)* **2000**, *9*, 440-441.

PP-32. Synthesis and Anti-anxiety Activity of 2',6-Disubstituted Flavone Derivatives

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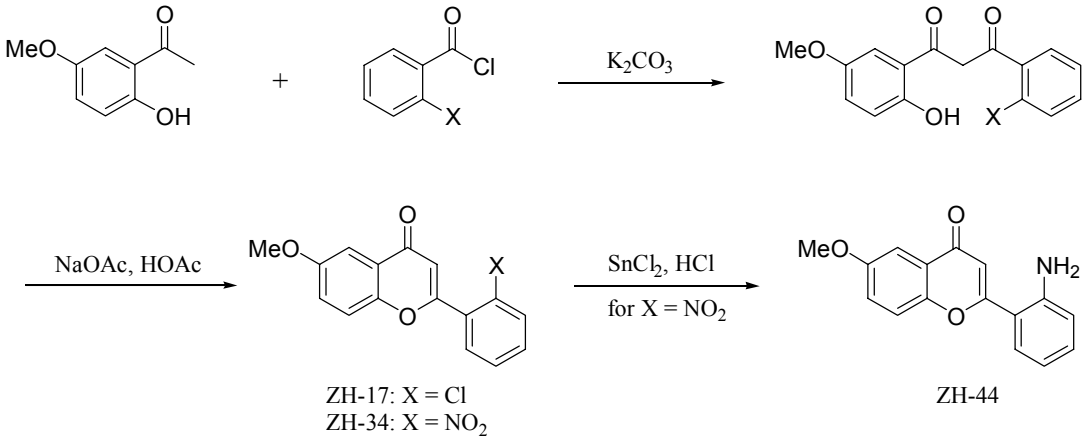
[b]*Department of Biochemistry, The Hong Kong University of Science and Technology, Kowloon, Hong Kong SAR, China*

The naturally occurring flavonoids exhibit various biological activities such as antitumor activity, anti-inflammatory activity, and cardiovascular activity and so on.[1] Some new flavone derivatives with anti-anxiety activity were isolated from some Chinese traditional medicines.[2] In order to study the structure-activity relationships of flavone derivatives, some 2',6-disubstituted flavone derivatives were synthesized, characterized, and evaluated. The target flavone derivatives were synthesized as shown in Scheme 1. Anti-anxiety activity *in vitro* of the target compounds were screened as shown in Table 1.



Scheme 1. Synthesis of the target compounds

Table 1. Affinities of flavone derivatives for $GABA_A$ receptor benzodiazepine binding-site

No.	Compound	IC_{50} (μM)	Ki (μM)
ZH-17	2-(2'-chlorophenyl)-6-methoxyflavone	>100	>100
ZH-34	2-(2'-nitrophenyl)-6-methoxyflavone	>100	>100
ZH-44	2-(2'-aminophenyl)-6-methoxyflavone	1.30	1.30
	diazepam	0.012	0.0095

References:

1. Harborne, J. B. *Flavonoids* (Chinese Edition), Beijing:Science Press, 1983:Beijing, p322.
2. Wang, H.Y. *Doctoral Dissertation*, Shenyang Pharmaceutical University, 2002.

PP-33. Synthesis, Characterization, and *in vitro* Antitumor Activity of Bis(butoxycarbonylmethyl)(4,7-diphenyl-1,10-phenanthroline-*N*,*N*')tin Dibromide

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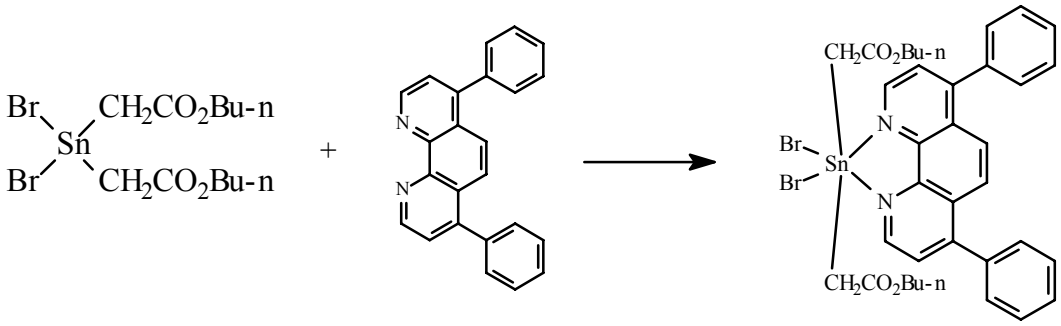
Since Crowe reported that diorganotin dichloride complexes have some interesting antitumor properties,[1] a large number of organotin compounds have been tested and many show reproducible antitumor activity in mice.[2] We have reported that the antitumor activity of a series of bis(alkoxycarbonylmethyl)tin dibromide complexes against two human tumor cell lines, WiDr and MCF-7 is lower compared to cisplatin.[3] This paper describes the synthesis, characterization of a new bis(alkoxycarbonylmethyl)tin dibromide complex, bis(butoxycarbonylmethyl)(4,7-diphenyl-1,10-phenanthroline-*N*,*N*')tin dibromide. This complex is synthesized as shown in Scheme 1. Antitumor activity *in vitro* of the target complex is higher than that of cisplatin against the above two human tumor cell lines as shown in Table 1.



Scheme 1. Synthesis of the target complex

Table 1. ID_{50} values in ng/mL obtained for the complex against two human tumor cell lines

Complex	WiDr	MCF-7
$Br_2Sn(CH_2COOBuN)_2$·4,7-diphenyl-1,10-phenanthroline	390	240
Cisplatin	620	850

References:
1. Crowe, A. J.; Smith, P. J.; Atassi, G. *Chem. Biol. Interact.* **1980**, *32*, 171.
2. Hu, C.; Wang, S.; Tan, R. *Chin. Pharma. J.* **1992**, *27*, 455.
3. Zhang, Z.; Pan, H.; Hu, C.; Fu, F.; Sun, Y.; Willem, R.; Gielen, M. *Appl. Organomet. Chem.* **1991**, *5*, 183.

PP-34. Studies on Total Synthesis and Anticancer Activities of Methyl Protodioscin

Mao-Sheng Cheng,[1]* Qian-Li Wang,[1] Quan Tian,[1] Zhen Yang,[2] and Xin-Sheng Yao[1]
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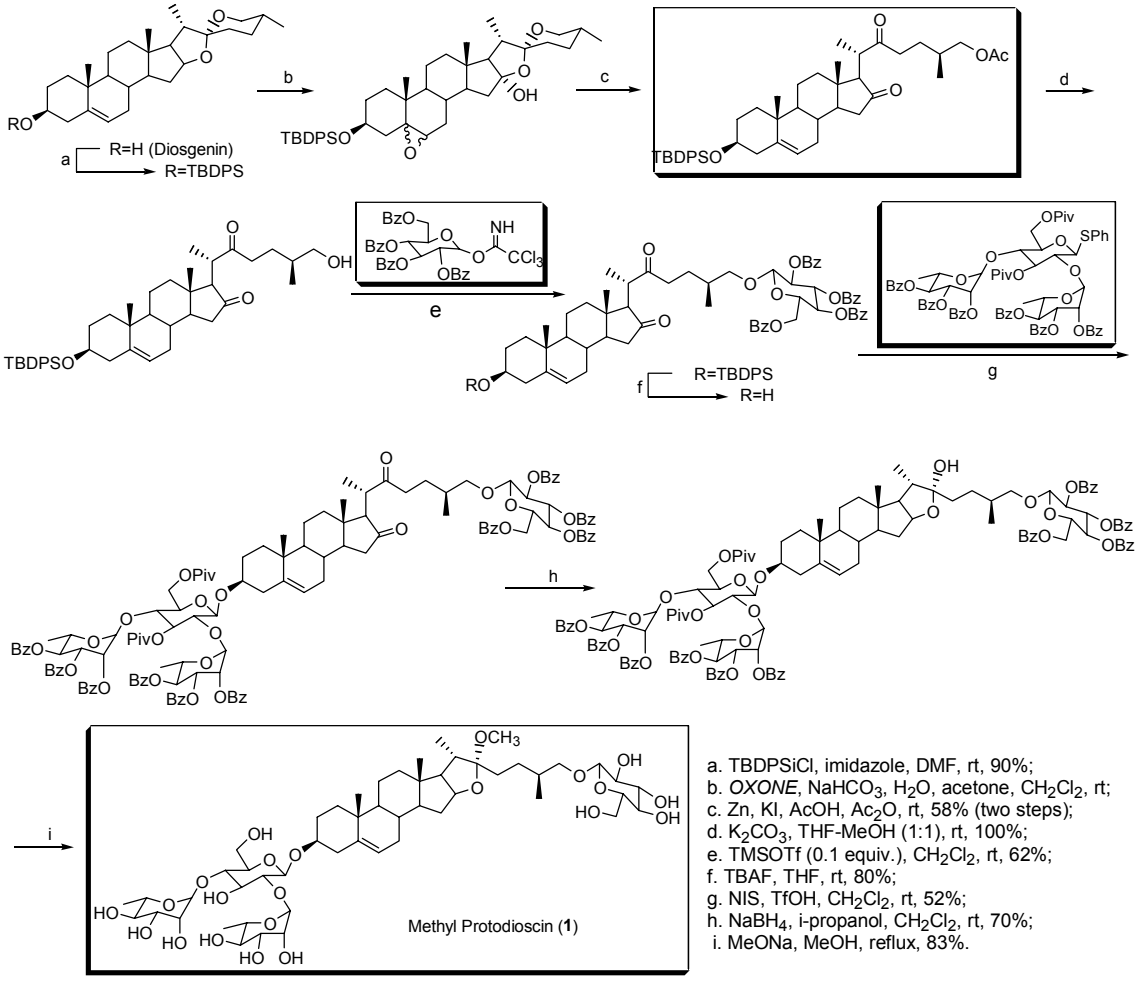
By repeated bioactivity-guided isolation, fourteen steroidal saponins, including Methyl Protodioscin (**1**), were isolated from Dioscoreaceae and tested for anticancer activities with a panel of 60 human cancer cell lines at NCI. Six compounds gave good activities in vitro and Methyl Protodioscin was the best one. After comparing with some known anticancer compounds, NCI suggested that there might be some new mechanisms involving in these compounds.[1,2] In order to get sufficient sample for further studies, we have achieved breakthrough on the synthesis of Methyl Protodioscin after two years effort. We now report the first synthesis of this compound from diosgenin in 9 steps in an overall yield of 7.8%.



Acknowledgement. This work is supported by the National Natural Science Foundation of China (Project No. 30028023).

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1. Hu, K.; Dong, A. J.; Yao, X. S.; Kobayashi, H.; Iwasaki, S. *Planta Medica* **1996**, *62*, 573-575.
2. Narayana, V. L. (Drug Synthesis & Chemistry Branch, National Cancer Institute) personal communication, June 11, 1998.

PP-35. Synthesis of WB_{852} and Its Analogues as Glutathione Depleting Agents

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The GSH-depleting agent IMEXON has striking anti-tumor effect *in vivo* and *in vitro*, which indicates that GSH-binding agents might be developed as new type of apoptosis-inducing and apoptosis-enhancing agents of tumor cells.[1] WB_{852}, one of the representatives of 2-alkylaminomethyl-5-(*E*)-alkylidene cyclopentanone hydrochlorides **I**, was an effective apoptosis-inducing agent in leukemia cells. The mass spectrum of a GSH adduct of WB_{852} indicated that the mechanism of action for WB_{852} and its analogues may proceed via an elimination–Michael addition process. The process can be illustrated as Figure 1.[2]

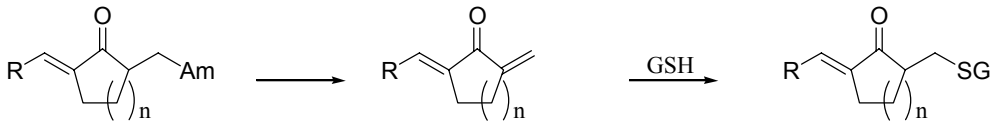
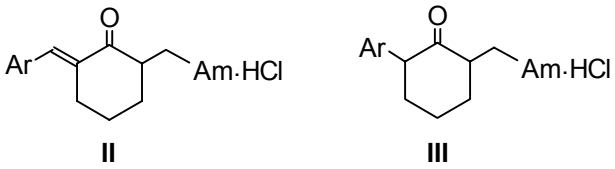


Figure 1. Reaction between WB_{852} analogues and glutathione

WB_{852} was supposed to induce tumor cells apoptosis through binding cellular GSH, decreasing intracellular GSH and generation of oxidative stress. In order to strengthen the design principle, a series of WB_{852} analogues **II, III** was designed and synthesized (Figure 2). The study of their GSH-binding abilities and quantitative structure-activity relationships are in progress.



Ar: C_6H_5; 2-CH_3O-C_6H_4-; 3-CH_3O-C_6H_4-; 4-CH_3O-C_6H

Am: $N(CH_3)_2$; –N⟨ ⟩; –N⟨ ⟩.

Figure 2. Chemical structures of WB_{852} analogues

References:
1. Dvorakova, K.; Payne, C. M.; Tome, M. E. et al. *Biochemical Pharmacology* **2000**, *60*, 749.
2. Chen, H. T.; Ji, Z. Z.; Wong, L. K. et al. *Bioorg. Med. Chem.***1994**, *2* 1091.

PP-36. Design and Synthesis of Imidazotetrazinones as Prodrugs of Temozolomide

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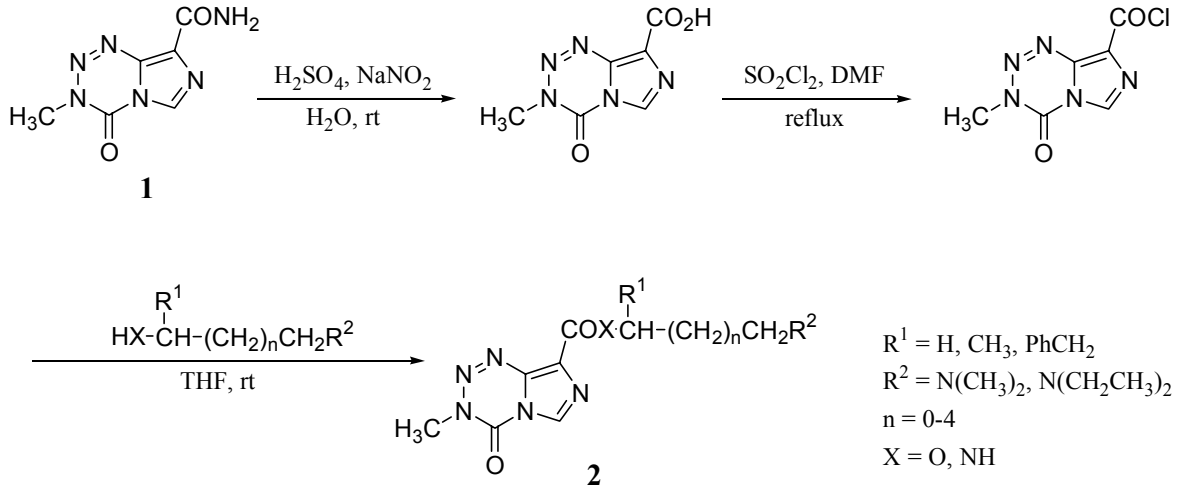
School of Pharmaceutical Engineering, Shenyang Pharmaceutical University, Shenyang 110016, China

Temozolomide **1**, is an novel anticancer drug to treat patients with metastatic malignant melanoma and primary brain tumors. Its anticancer activity is largely attributed to the methylation of DNA which is dependent upon formation of methyldiazonium cation. The latter attacks at the middle guanines of runs of three or more consecutive guanine on DNA.[1] The clinic trials have confirmed that **1** is a well tolerated orally available DNA-methylating agent and its activity is highly schedule-dependent.[2] But the hydrophilia of **1** is so poor that its development in clinic is limited. To improve its hydrophilia, a series of novel imidazotetrazinones **2** were designed and synthesized as prodrugs of **1**, whose chemical structures were characterized by IR, ^{1}H NMR, ^{13}C NMR, and MS. The synthetic route of the novel compounds is depicted as Scheme **1**. Antitumor activity test and SAR study of the target compounds are in progress.



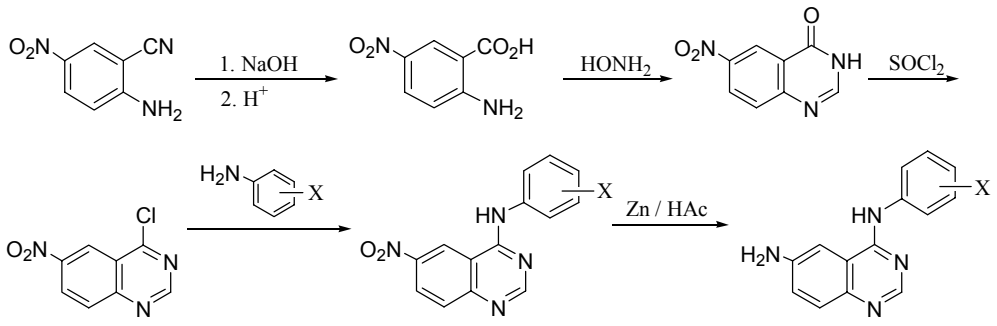
Scheme 1

References:
1. Clark, A. S.; Deans, B.; Stevens, M. F. G. *et al*. *J. Med. Chem*. **1995**, *38,* 1493-1504.
2. Stevens, M. F. G.; Hickman, J. A.; Langdon, S. P. *et al*. *Cancer Res.* **1987**, *47*, 5846-5852.

PP-37. Synthesis and Anticancer Effects of 6-Nitro-4-anilinoquinazolines and 6-Amino-4-anilinoquinazolines

Xiao-Li Sun,[a] Zhi-Hong Liu,[a] Sheng-Yong Zhang,[a] and Li-Bo Yao[*b]
[a]*Department of Chemistry,* [b]*Department of Biochemistry and Molecular Biology, The Fourth Military Medical University, Xi'an 710032, China*

The tyrosine kinase inhibitors of the epidermal growth factor receptor (EGFR) such as 6-nitro-4-anilinoquinazolines and 6-amino-4-anilinoquinazolines have been synthesized (Scheme 1**)**. The synthesized 4-anilinoquinazoline compounds have been rudimentarily screened by MTT method with A431 tumor cell line, which overexpresses EGFR, as model. The anticancer activity of 6-amino substituted inhibitors *in vitro* was higher than that of 6-nitro substituted ones (see Table 1). However, the difference of anticancer activity between the two series of quinazolines was much less than that of their inhibition on purified EGFR tyrosine kinase.[1] The reason why 6-nitro-4-anilinoquinazolines had anticancer activity *in vitro* was that 6-nitro might be transformed into effective metabolites through endocellular cytochrome oxidation-reduction system.



Scheme 1. Synthetic route of 6-amino-4-anilinoquinazolines

Table 1. Anticancer effect of 6-amino-4-anilinoquinazolines and 6-nitro-4-anilinoquinazolines against A431 cell line

m-	*p*-	6-amino-4-anilinoquinazolines		6-nitro-4-anilinoquinazolines	
		IC_{50} (μM)	IC_{90} (μM)	IC_{10} (μM)	IC_{90} (μM)
Br	H	1.41	79.4	17.4	N
Cl	H	1.5	151.4	22.38	N
Cl	F	1.99	81.28	12.02	N
H	Br	12.6	74.1	21.38	N
H	Cl	7.9	85.1	24	N

Reference:
1. Rewcastle, G. W.; Denny, W. A.; Zhou, H.; Cody, D. R.; McMichael, A.; Fry, D. W.; Bridges, A. J. *J.Med. Chem.* **1995**, 38, 3482-3487.

PP-38. Design, Synthesis and Evaluation of Small Molecules of MDM2 Blocker Based on the Structure of P53-MDM2 Complex

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Institute of Materia Medica, Peking Union Medical College & Chinese Academy of Medical Sciences, Beijing, 100050, China

The mdm 2 oncoprotein is a cellar inhibitor of the p53 tumor suppressor. It can bind the transactivation domain of p53 and downregulate its ability to activate transcription, resulting in tumor development. The interface relies extensively on van der Waals contacts and steric complementarity between the mdm 2 cleft and hydrophobic face of the p53 α helix as these interactions are augmented by two intermolecular hydrogen bonds—between Phe^{19}(p53) and Leu^{54} (mdm2), Trp^{23}(p53) and Gln^{72}(mdm2).[1] Theoretically, blockade of the mdm2-p53 interaction can recover the normal functions of p53. Based on the crystal structure of mdm2-p53 complex, a series of small molecules with the flexible backbones as mdm2 inhibitors were designed and synthesized. Thirty of them were chosen for the evaluation and IC_{50} are listed in Table 1.

Table 1. IC_{50} (μM) of the molecules in several cell lines.

	HT1080	A549	NCI-H446	HCT-8	MG-63	GLC-82	EC9706	MKN-45
2	8.66	0.24	/	5.95	1.07	54.31	0.77	/
3	6.40	/	/	6.69	/	/	/	/
4	5.37	/	/	2.56	16.2	44.02	/	/
6	8.20	/	54.89	20.0	/	/	/	/
7	24.07	18.2	/	/	70.0	/	0.09	/
10	/	/	/	46.3	/	/	/	/
11	/	/	/	9.92	/	/	/	/
12	/	/	/	4.48	/	/	/	/
13	/	/	4.84	4.76	/	/	0.13	/
14	/	/	7.86	13.9	/	/	17.66	/
15	/	/	/	28.2	/	/	/	/
16	24.90	/	/	11.3	/	38.23	/	/
18	18.95	0.44	/	9.49	16.5	18.08	0.08	/
19	24.36	/	/	/	/	7.17	/	/
20	/	0.55	/	/	/	/	0.25	/
22	32.11	1.67	/	/	/	/	/	/
23	/	7.79	/	/	/	/	/	/
26	/	1.68	/	/	/	/	0.31	/
31	22.92	0.40	/	8.96	/	/	0.015	/

Acknowledgement. This work is supported by the NSFC and National Key Basic Research Program.

Reference:
1. Kussie, P, H.; Gorina, S.; Marechel, V. et al. *Science* **1996**, *274*, 948.

PP-39. Anti-*Pneumocystis carinii* Activity of Conformationally Restricted Analogues of Pentamidine

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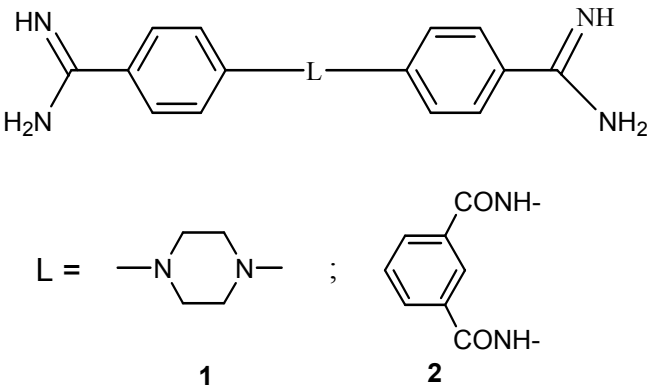
We have recently reported on the potent in vitro anti-*Pneumocystis carinii* activity of several conformationally restricted analogues of pentamidine,[1,2] including *N*,*N*'-bis(4-amidinophenyl)piperazine **1** and *N*,*N*'-bis(4-amidinophenyl)1,3-benzenedicarboxamide **2,** the structures of which are shown below. As an extension of this work aimed at studying the effect of restricting the conformational flexibility of pentamidine analogues on anti-*Pneumocystis carinii* activity, we have synthesized a series of nineteen new analogues of compounds **1** and **2**, in which the bis-amidinium groups have been modified in the majority of the compounds. The structure-activity relationships of this new series of compounds will be presented.



1 **2**

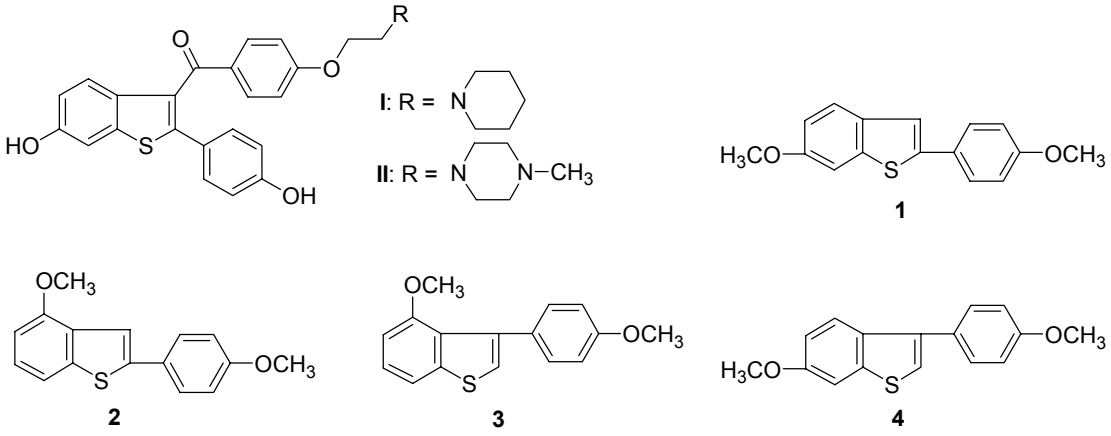
References:
1. Tao, B.; Huang, T. L.; Zhang, Q.; Jackson, L.; Queener, S. F.; Donkor, I. O. *Eur. J. Med. Chem*. **1999**, 34, 531-538.
2. Huang, T. L.; Tao, B.; Quarshie, Y.; Queener, S. F.; Donkor, I. O. *Bioorg. Med. Chem. Lett*. **2001**, 11, 2679-2681.

PP-40. Study on Synthesis of a Novel Raloxifene Analogue

Qingjiang Liao ( ) and Hua Xiang ( )
China Pharmaceutical University, Nanjing 210009, China

Raloxifene (**I**)[1,2] was a selective estrogen receptor modulator (SERM) which induces both estrogen-agonistic effects on bone and lipid metabolism or estrogen-anatagonistic effects on uterine endometrium and breast tissue, respectively, for postmenopausal women. In order to obtain a better lipid-water distribution coefficient, we have synthesized a novel Raloxifene analogue (**II**) by introducing 1-methylpiperazine into the basic ether side chain. The chemical structure of (**II**) was established by IR, NMR, and MS.

6-Methoxy-2-(4'-methoxyphenyl)benzo[b]thiophene (1), which is an important intermediate for synthesis of **II**,[2] was prepared by polyphosphoric acid (PPA) induced cyclization and rearrangement. Another three isomers **2**-**4** were also isolated and separated from the mother liquor; their chemical structures were established by spectroscopic analyses. Compounds **3** and **4** were reported for the first time. After using methanesulfonic acid, instead of PPA, the yield of **1** was increased in this improved synthesis. All of the reaction products from these two synthetic methods were compared and checked by HPLC.

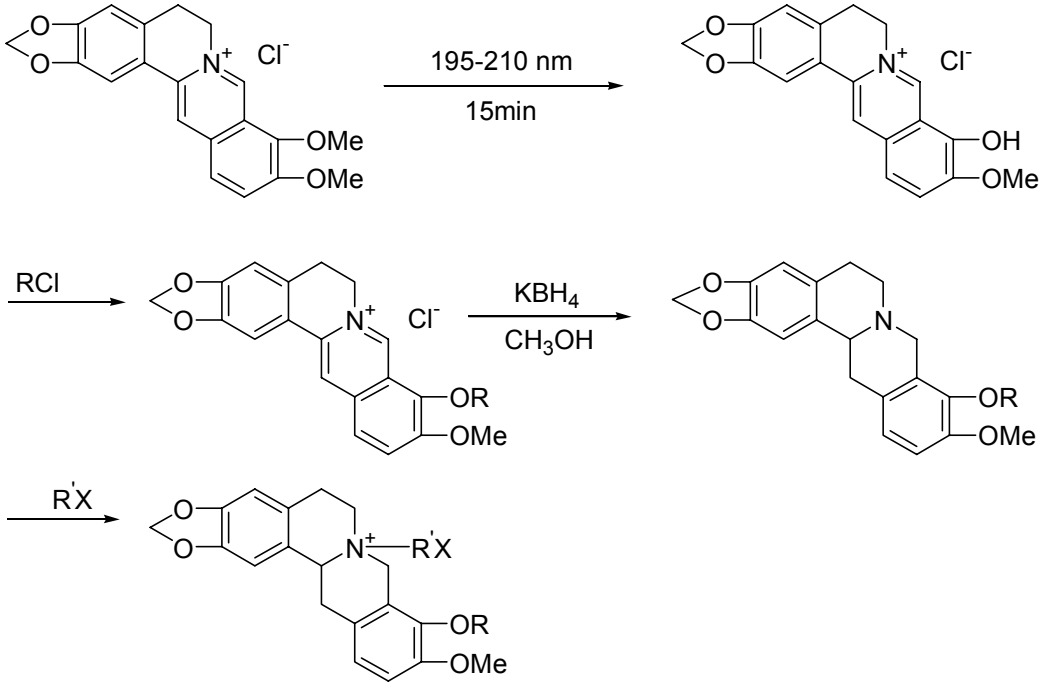


References:
1. Bruce, H. M.; Cohen, F. J. *Drugs* **1999**, *57*, 653-663.
2. Jones, C. D.; Jevnikar, M. G.; Pike, A. J.; Peters, M. K.; Black, L. J.; Thompson, A. R.; Falcone, J. F.; Clemens, J. A. *J. Med. Chem.* **1984**, *27*, 1057-1066.

PP-41. Synthesis and Antiarrhythmic Activity of Protoberberin Quaternary Ammonium Compounds

Can Zhang and Wen-Long Huang
New Drug Research Center, China Pharmaceutical University, Nanjing 210009, China

We have designed and synthesized a series of protoberberine quaternary ammonium compounds, by using berberine as the lead.[1] The structures were confirmed by IR, ^{1}H NMR, MS, HRMS. The results of preliminary pharmacological test showed that II_1 (R = -$COCH_3$, R' = -$CH_2C_6H_4Cl$, X = Cl, 10 mg/kg), II_3 (R = -$COCH_3$, R' = -$CH_2C_6H_4NO_2$, X = Br, 10 mg/kg), II_4 (R = -$COCH_3$, R' = -$CH_2C_6H_5$, X = Cl, 2.5, 5, 10 mg/kg), II_8 (R = -$COC_6H_4CH_3$, R' = -$CH_2C_6H_4Cl$, X = Cl, 2.5 mg/kg), II_9 (R = H, R' = -$CH_2C_6H_4Cl$, X = Cl, 2.5, 5, 10 mg/kg) have prophylaxis on the aconitine-induced arrhythmia. Moreover, II_9 has the most significant action, with $ED_{50(VF)}$ of 1.03×10^{-6} mol/kg.



R = -$COCH_3$, -$SO_2C_6H_5$, -SO_2CH_3, -COC_6H_5, -$COC_6H_4CH_3$, H, -COC_6H_4Cl, -$COC_6H_4NO_2$
R' = -$CH_2C_6H_4Cl$, -$CH_2CH_2OC_6H_4COOEt$, -$CH_2C_6H_4NO_2$, -$CH_2C_6H_5$, -CH_2CONH_2
X = Cl, Br

Scheme 1. Synthetic Method

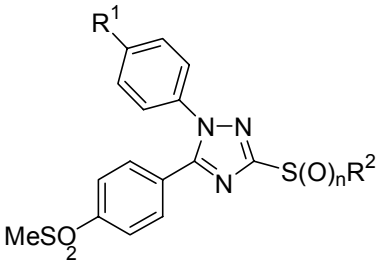
Reference:
1. Iwasa, K.; Kamigauchi, M.; Ueki, M.; Taniguchi, M. *Eur. J. Med. Chem*. **1996**, *31,* 469-478.

PP-42. Studies on Synthesis and Biological Activity of Nonsteroidal Anti-inflammatory Drugs

Jinyi Xu ( ),* Hequan Yao ( ), Xiaoming Wu ( )
China Pharmaceutical University, Nanjing 210009, China

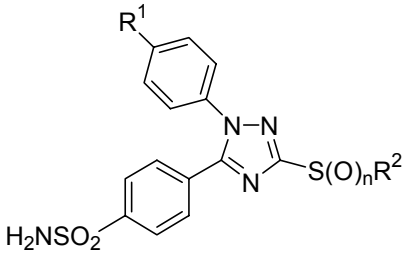
Nonsteroidal anti-inflammatory drugs (NSAIDs) are among the most widely prescribed medications with their uses limited by significant toxicity, particularly in the gastrointestinal tract and kidney. The studies of the cyclooxygenase (COX) have showed that there are two COX subtypes, designated as COX-1 and COX-2. It has been thought that the side effects of classical NSAIDs come from the inhibition of COX-1, while the therapeutic effects come from the inhibition of COX-2.

Selective COX-2 inhibitors have been developed as new NSAIDs, which bind specially to COX-2 and display the profiles of good potent activities and low side effects. Based on the lead compound Celecoxib and the SAR of molecular modeling study, three series of 1,2,4-trizoles derivatives were designed by application of the principle of bioisosterism and hybrid approach. Twenty-one compounds were synthesized with the aim that some new NSAIDs could be discovered.



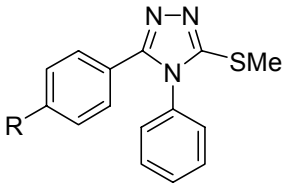
I

R^1 = H, Me; R^2 = Me, Et; n = 0-2



II

R^1 = H, Me; R^2 = Me, Et; n = 0, 2



III

R = $MeSO_2$-, H_2NSO_2-

All the target compounds have not been reported, while IR, ^{1}HNMR and MS spectra supported their structures. The preliminaries in vitro pharmacological tests indicate that seven compounds (I_f, I_g, I_h, II_a, II_e, II_f, III_a) exhibit certain potency, in which compound II_f exhibits a good potency. The deep going pharmacological studies are under investigation. The structure-activity relationship studies have been performed which could provide some useful suggestions for further research.

PP-43. Synthesis and Inhibitory Effects on Inducible Nitric Oxide Synthase of Isothiourea Derivatives

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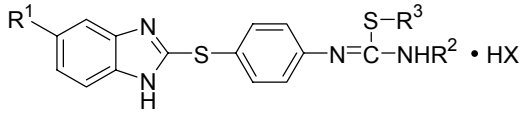
On the basis of the structure-activity relationship of NOS inhibitors and our research work in the past, in order to obtain compounds which possess isoform-selective and high active inhibitors of iNOS, a series of isothiourea derivatives (Figure 1) which contain 5-methoxy (or chloro)-benzimidazole-2-mercapto group have been designed and synthesized (Scheme 1). The reaction conditions for synthesis of the intermediates and target compounds have been improved and good yields were obtained. All the structures of new compounds are identified by IR, ^{1}HNMR, MS, and elemental analysis.

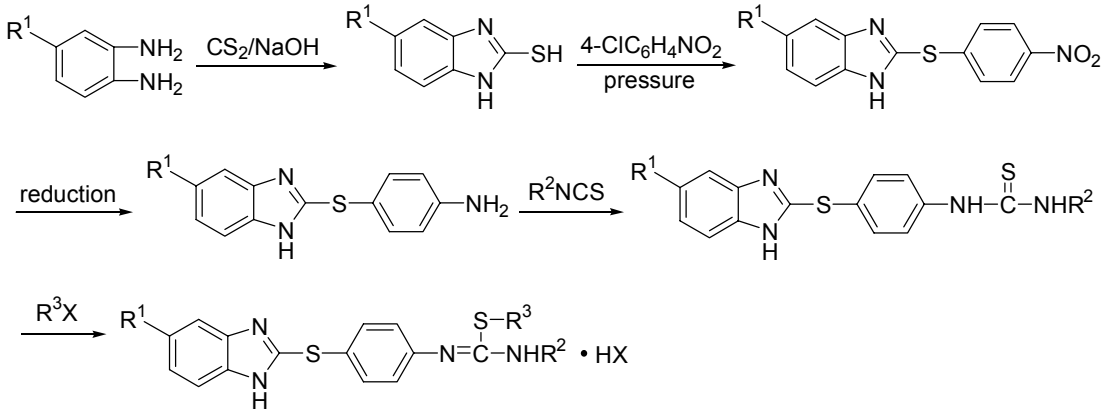
The inhibitory effects on iNOS of target compounds were evaluated. The results showed that all compounds have the ability to inhibit iNOS. Among these, the inhibitory effects on iNOS of compounds **I_7~I_{13}** (R_1 = OCH_3, R_2 = CH_3 or $CH_2CH_2CH_3$ or C_6H_5, R_2 = CH_3 or C_2H_5 or C_4H_9 or CH_2Ph) are stronger than aminoguanidine. Further investigations are in progress.



I

R^1 = OCH_3, Cl; R^2 = H, CH_3, $CH_2CH_2CH_3$, C_6H_5;
R^3 = alkyl ($C_{1\sim4}$), allyl, (un)substituted benzyl; X = Cl, Br

Figure 1. Structures of target compounds



Scheme 1. Synthetic route of target compounds

Reference:
1. Shearer, B.G.; Lee, S.; Oplinger, J. A.; Frick, L.W.; Garvey, E. P.; Furfine, E.S . *J. Med. Chem.* **1997**, *40*, 1901-1905.

PP-44. Novel Acetylcholinesterase Inhibitors for Alzheimer's Disease

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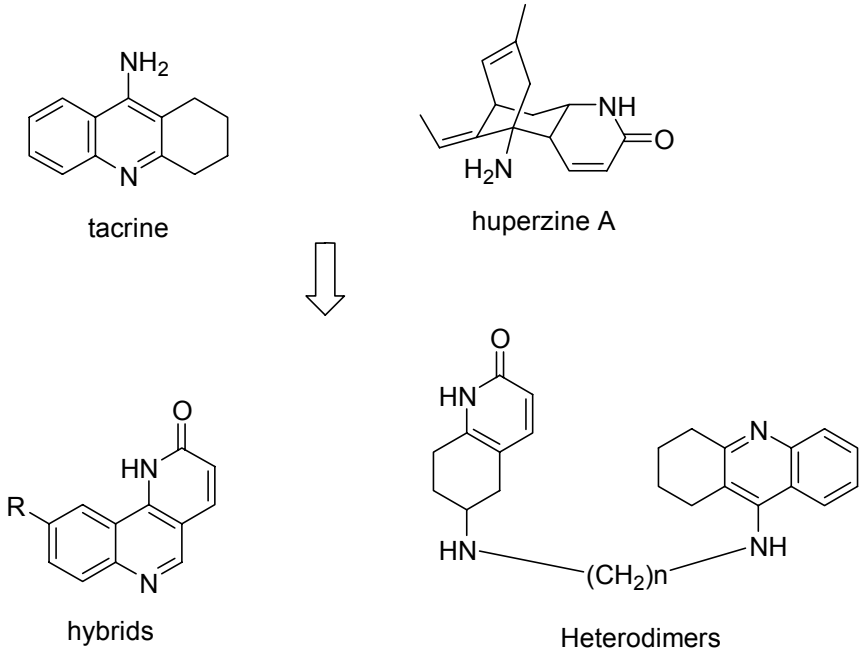
The Alzheimer's disease is a progressive neurodegenerative disorder that affects millions of old people. Acetylcholinesterase (AChE) inhibitors, such as tacrine (Cognex) and donepezil (Aricept), have been used to treat patients with Alzheimer's disease by enhancing the central cholinergic neurotransmission. Huperzine A, which was isolated from Chinese medicine (*Huperzia serrata*), has been found to be a potent and selective acetylcholinesterase inhibitor. Prompted by the success of hibridization and dimerization strategies to improve the potency and selectivity, we have designed and synthesized some novel potential acetylcholinesterase inhibitors. The syntheses of these compounds and their AChE activities will be presented and discussed.



PP-45. A New Synthesis of Epristeride, a Potent Human 5α-Reductase Inhibitor

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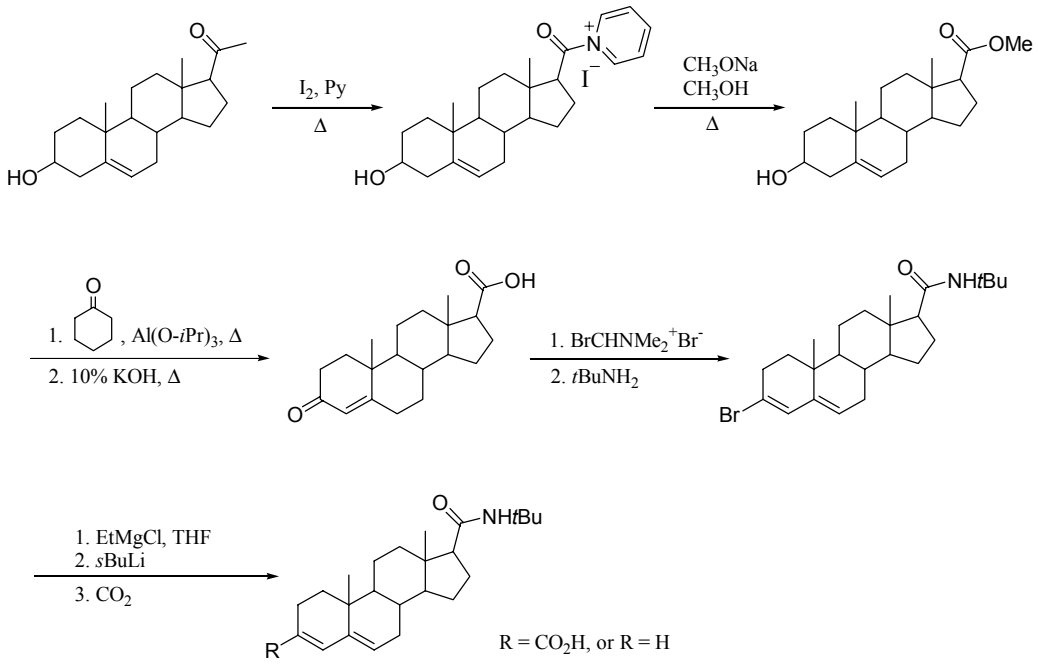
Benign prostatic hyperplasia (BPH) is an age-related, progressive disease characterized by a benign enlargement of the prostate gland which affects a large fraction of men over 50 years of age. It has been well established that growth of the prostate is stimulated by androgens, and it now appears that 5a-dihydrotestosterone (DHT) plays a primary role in the trophic support of this organ. The studies have demonstrated selective retardation of prostate growth by inhibition of human steroid.

5α-Reductase (SR), an enzyme responsible for the conversion of testosterone (T) into DHT. Thus, selective inhibition of SR could offer an alternative therapy for BPH. As an inhibitor of 5α-reductases for treatment of BPH, Finasteride (trade name Proscar) has been available in USA since 1992. And Epristeride (SK&F105657) is a potent uncompetitive inhibitor of DHT which belongs to a family of 3-androstene-3-carboxylic acids and is being clinically evaluated for the treatment of BPH.

Epristeride was synthesized by Holt and co-workers using an eight-step procedure starting from prognenolone. We have successfully improved the synthesis of epristeride by designing an efficient six-step process shown as follows:



Scheme 1. Modified synthetic route of epristeride

References:
1. Holt, D. A.; Levy, M. A.; Oh, H. J.; Erb, J. M.; Heaslip, J. I.; Brandt, M.; Lan-Hargest, H. Y.; Metcalf, B. W. *J. Med. Chem.* **1990**, *33*, 943-950.
2. Rasmusson, G. H.; Reynolds, G. F.; Utne, T.; Jobson, R. B.; Primka, R. L.; Berman, C.; Brooks, J. R. *J. Med. Chem.* **1984**, *27*, 1690-1701.
3. Mewshaw, R. E. *Tetrahedron Lett.* **1989**, *30*, 3753-3756.

PP-46. Synthesis of Oleanolic Acid Glycoconjugates

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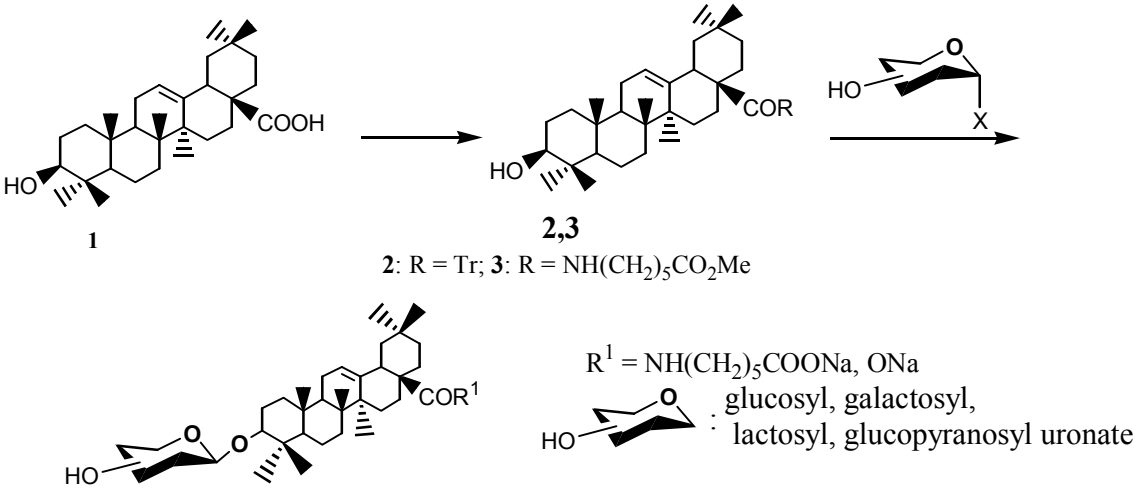
We have synthesized eight new glycoconjugates (*D*-glucose, *D*-galactose, *D*-lactose and *D*-glucuronic acid) of oleanolic acid through a facile approach. Firstly, oleanolic acid was converted into methyl *N*-(3-hydroxylolean-12-en-28-oyl)-6-aminohexanoate **2** and trityl oleanolate **3** as acceptors.



Scheme 1

D-glucose, D-galactose and D-lactose were converted into benzoyl group protected glycosyl trichloroacetimidates and D-glucuronic acid was converted into methyl (tri-*O*-acetyl-α-D-glucopyranosyl bromide)uronate as donors. Then, the coupling of the sugar moieties with 3-OH of **2** and **3** was carried out under the corresponding conditions. Finally, the protecting groups were removed to obtain target products. The structures of all target products were characterized by IR, ^{1}H NMR, ^{13}C NMR, DEPT, COSY, HMQC, and HRMS. Preliminary pharmacology results have showed that oleanolic acid lactoside has hypoglycemic activity.

References:
1. Chao-mei, M.; Nakamura, N.; Hattori, M. *Chem. Pharm. Bull.* **2000**, *48*, 1681.
2. Li, Y.-H.; Hisashi, M.; Masayuki, Y. *Bioorg.c & Med. Chem.* **1999**, *7*, 1201.
3. Masayuki, Y.; Toshiyuki, M.; Masashi, K.; Hisashi, M.; Osamu, M.; Johji, Y.; Nobutoshi, M. *Chem. Pharm. Bull.* **1996**, *44*, 1212.

PP-47. Discovering Potent Agonists of the Endothelial Target for Acetylcholine (ETA) via an Method Based-on Molecular Diversity and Pharmacophore

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Cardiovascular diseases are leading cause of mortality in the world. Over the past decades, considerable information has become available concerning the roles of the endothelium in maintaining the functions of cardiovascular system since Furchgott and Zawadzki discovered that acetylcholine (ACh) induced endothelium-dependent relaxation required an intact endothelium. The loss of vasodilator function in response to ACh testing is a marker of endothelial dysfunction and is closely related to a lot of cardiovascular diseases such as hypertension, heart failure, hypercholesterolemia, and atherosclerosis. The properties of the endothelial target for ACh (ETA) are unique and different from muscarinic (M) receptors.[1]

Herein, we report a simple but efficient approach based-on molecular diversity and pharmacophore for discovering selective lead compounds for biological targets or processes which are not yet fully elucidated. The method involves: (1) based upon the similarities and discrepancies between EPA and M receptors, the pharmacophores of all reported agonists of M receptors are dissected and simplified; (2) a collection of chain derivatives is designed and synthesized by coupling the above-obtained pharmacophores at a willing of increasing or reducing with a set of flexible linkers; (3) the collection of chain derivatives is screened to identify the pharmacophores for ETA agonists and their proper combinations not agonizing M receptors; (4) an initial "three-point" model is proposed by the structure-activity relationship analysis and the structural indexes of representative compounds obtained by quantum calculation; (5) a new collection of compounds is designed and synthesized by application of the proposed structural model and addition of auxiliary binding groups; (6) the new collection of compounds is screened to identify the selective potent agonists.

After the first round of synthesis and screen of 34 diverse compounds, two types of lead compounds were discovered. The first type is substituted α-amino-acetonitrile or acetate. The second round of 54 compounds were designed and synthesized by application of the structural model of the first type of lead compounds and bioisostere rule and addition of auxiliary groups. After screening, 6 potent selective agonists of ETA were found. After further pharmacological studies, 2 candidate compounds were identified, of which DMHPPP is of activities of antithrombosis, and PPVP antiatherosclerosis.

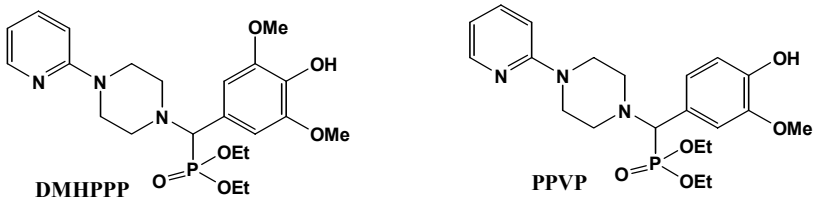

Figure 1. Structures of two candidate compounds discovered from this study

1. Shan, L.-M.; Wang, H. *Life Sci.* **2002**, *70,*1285-1298.

PP-48. Synthesis and Biological Activity of Selenium Daunorubicin Derivatives

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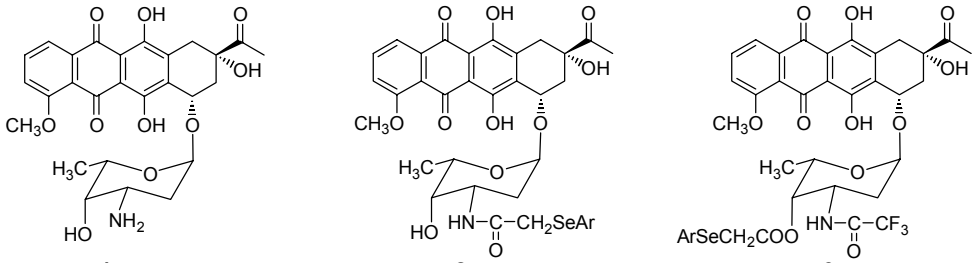
Daunorubicin **1** is clinically useful anthracycline antitumor agent. However, its clinic uses are hampered by a number of undesirable side effects, especially serious cardiotoxicity.[1] This stimulated the search for new anthracycline derivatives with improved pharmacological profiles.[2] Selenium now has been recognized as an essential nutrient substance and its deficiency can result many diseases in human body, such as cancer[3] and cardiovascular disease.[4] On the other hand, selenium can be a chemopreventive agent to remedy and retard cancers[4] and the reports on the synthesis and biological activity of 3′- or 4′-selenium daunomycin derivatives have not been reported so far. Therefore, we synthesized the 3′-(2-selenoaryl) acetamido daunomycin **2a~c** and 4′-(2-selenoaryl) acetoxy-N-trifluoroacetyl daunomycin **3a~c** and evaluated their activities against human stomach cancer SGC-7901 and human leukaemia HL60 *in vitro* (Table 1).



1 **2** **3**

Table 1. Cytotoxicity of new compounds **2a~e** and **4a~e** against tumor cells

Compds	Ar	IC_{50} (μg/mL)[a]	
		SGC-7901[b]	HL60[c]
2a	C_6H_5	>100	>100
2b	*p*-$CH_3C_6H_4$	18.2	>100
2c	*m*-MeC_6H_4	6.3	>100
4a	C_6H_5	91.1	1.6
4b	*p*-$CH_3C_6H_4$	>100	1.0
4c	*m*-MeC_6H_4	>100	1.2
1	-	0.23	0.08

[a]Activity against tumor cells were measured by MTT assay.
[b]SGC-7901, human stomach cancer. [c]HL60, human leukaemia.

References:
1. Llefark, S. K. *Cancer* **1973**, *32*, 302-314.
2. Elena, B. *J. Med. Chem*. **1997**, *40*, 4013.
3. Combs, Jr, G.F.; Gray, W. P. *Pharmacol. Ther*. **1998**, *79*, 179-192.
4. Rayman, M. *Lancet* **2000**, *356*, 233-41.

PP-49. Study on Synthesis of 17α-Estradiol Derivatives with Alkaline Side Chain on 3-Poisition

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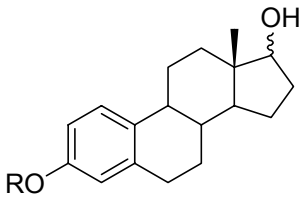
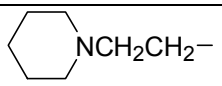
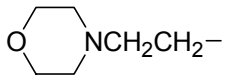
Since the aged population continues to grow dramatically worldwide, the effective management of postmenopausal osteoporasis, heart disease, and other disease associated with loss of estrogen after menopause will remain a major healthcare challenge.

Although some non-steroidal compounds were demonstrated to exert estrogen-agonist effects in some tissues and estrogen-antagonist effects in others. They have high affinity binding to the estrogen receptor. Estrogen has beneficial effects on skeletal and cardiovascular systems. Several reports suggest that hormone replacement therapy (HRT) may decrease the incidence of Alzheimer's disease among older, postmenopausal women. Estrogen has also been shown to favorably affect cerebral blood flow, potentially decreasing the incidence of vascular-related dementia in the elderly.

We synthesized the estrodiol derivatives with basic side chain on 3-position, and hope that the configuration at 17-hydroxy group will affect their activities without the undesirable effects of estrogen. The pharmacological effects will be measured.



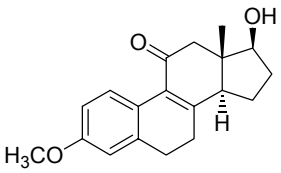
Compound	Configuration	R
1	17-α	
2	17-β	
3	17-α	
4	17-β	
5	17-α	$(C_2H_5)_2NCH_2CH_2-$
6	17-β	
7	17-α	H_3C-
8	17-β	

References:
1. Denton, R.; Dupont, S.; Kim, P.; *et al. J. Bone Miner Res.*, **1997**, *12*, 34.
2. Kuiper, G. G. J. M; Carlsson, B.; Grandien, K.; *et al. Endoc.* **1997**, *138*, 863-870.
3. Henderson, V. W.; Paganimi-Hill, A.; Emanuel, C. K.; *et al. Arch. Neurol*, **1994**, *51*, 896-900.

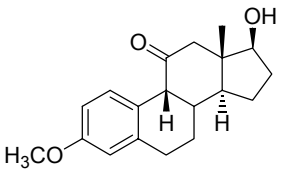
PP-50. Study on Synthesis of Estradiol Derivatives with Different Configuration on 14-Position

Ling-ling Weng, Nan Zhao, and Jun Zhuang
Sichuan University, Chengdu 610041, China

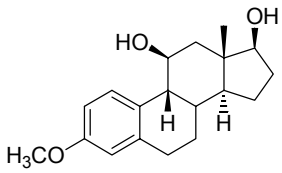
Configuration plays an important role in the agonist/antagonist activity. 14β Unnatural configurational estrogenic compound (IB) and 14α natural isomer (IA) were synthesized. The enantiomers (IA and IB) were catalytically hydrogenated respectively, resulting in the two isomeric compounds with 9β,14β configuration (IIB) and 9β,14α configuration (IIA). Then, the carbonyl groups at 11-position were reduced respectively to give 11α-hydroxy compound (IIIB) and 11β-hydroxy compound (IIIA).



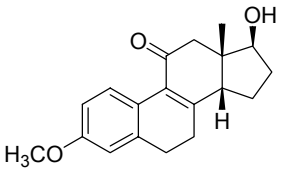
IA



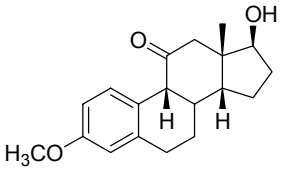
IIA



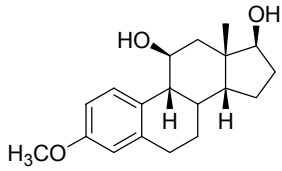
IIIA



IB

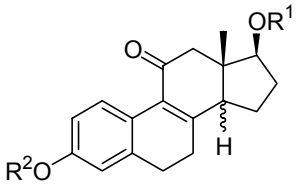


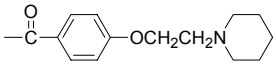
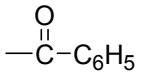
IIB



IIIB

Then, IA and IB were substituded at 17β-position, respectively, and some derivatives were prepared as follow.



Compounds	Configuration	R^1	R^2
IVA	14-α		—OCH_3
IVB	14-β		
VA	14-α		—OCH_3
VB	14-β		
VIA	14-α	—H	—OH
VIB	14-β		

The synthesized compounds were tested for their uterotrophic and antiuterotrophic activities. Preliminary pharmacological tests revealed that new compounds decreased their uterotrophic activity in immature mouse with estrone raloxifene as control and indicated that some of them had antiuterotrophic activity.

References:
1. Gabbard, R. B.; Hamer, L. F.; Sagaloff, A. *Steroid*, **1981**, *37*, 243-255.
2. U.S. Patent, 3,491,189.
3. Qian. X.; Abul-Hajj, Y. J. *J. Steriod Biochem.* **1988**, *29*, 657-664.

PP-51. Synthesis of Carbapenem Sidechains: (2*S*,4*S*)-2-Substituted 4-Mercaptopyrrolidine Derivative

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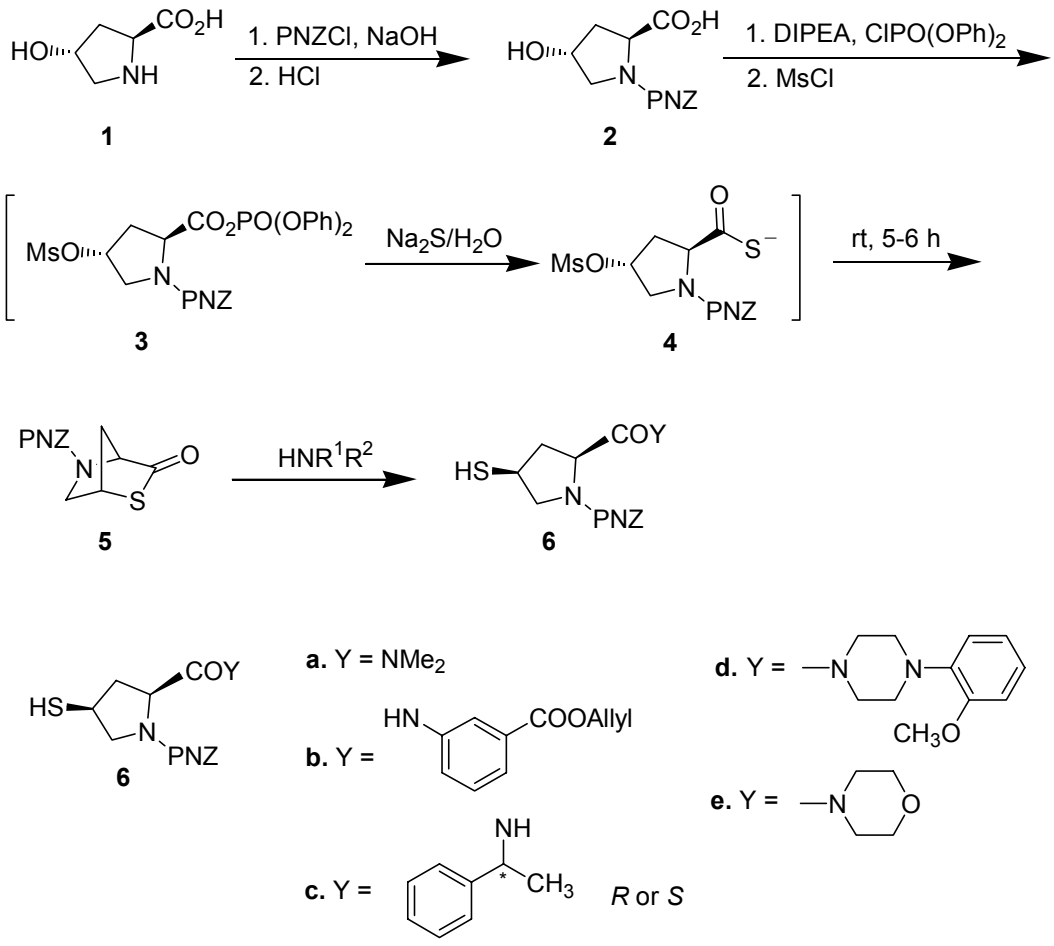
The synthesis of a new series of (2*S*,4*S*)-2-substituted 4-mercaptopyrrolidine derivatives **6** is studied. Intramolecular cyclization of derivative **4** from *trans*-4-hydroxy-*L*-proline (**1**) afforded (1*S*,4*S*)-5-*p*-nitrobenzyloxycarbonyl-2-thia-5-azabicyclo[2.2.1]heptan-3-one (**5**).[1] Reaction of **5** with a series of amines afforded derivatives **6**.



Scheme 1. Synthesis of (2*S*,4*S*)-2-substituted 4-mercaptopyrrolidine derivatives

Reference:
1. Matsumura, H.; Bando, T.; Sunagawa, M. *Heterocycles* **1995**, *41*, 147-159.

PP-52. Synthesis and Antiosteoporosis Activities of Osthole Derivatives

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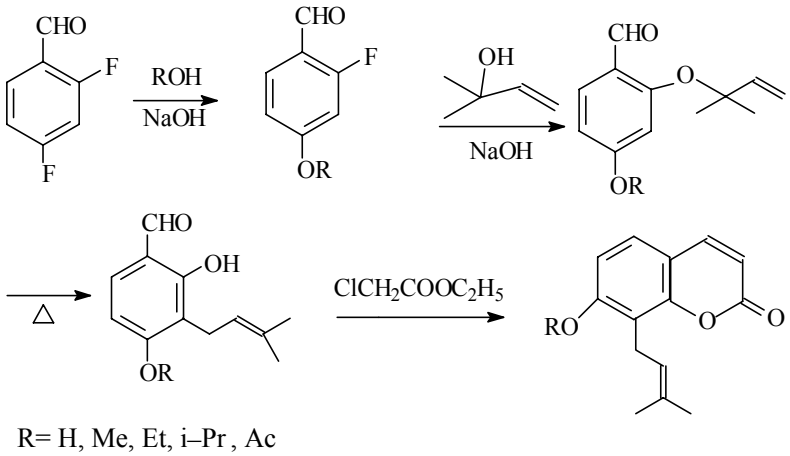
[2]*The Second Military Medical University, Shanghai 200433, China*

As reported, the total coumarins of Fructus Cnidii can slow down the bone turnover and restored the bony substance in Ovearіectomy-induced bone loss rat model. The effective component was Osthole (Osthole methyl ether). We used Osthole as a lead compound, and synthesized some alkyl ether and acyl ester derivatives (synthesis route see Scheme 1) and investigated the effects on serum calcium and bone mineral density (BMD) in Ovariectomized (OVX) rats (see Table 1).

It showed that all compounds increased the serum calcium concentration. The Osthole isopropyl ether showed higher activity than others and increased the BMD as effective as Ipriflavone in OVX rats model. The further pharmacological studies are in progress.



R= H, Me, Et, i–Pr , Ac

Scheme 1. Synthesis route of Osthole alkyl ethers and acyl esters

Table 1. Effects of Osthole derivatives on serum calcium and BMD in OVX rats

Compounds [R]	Serum calcium concentration (μg/mL)	BMD (g/cm/cm)
OVX model	7.20±0.89	0.1603±0.022
Ipriflavone	16.23±1.11*	0.2535±0.013*
L1: H	9.35±1.03	
L2: Me	11.65±1.20*	
L3: Et	10.88±1.15*	
L4: *i*-Pr	15.78±1.08*	0.2409±0.029*
L5: Ac	9.66±0.94	

*P < 0.01

PP-53. The Antitumor Activity of 2-(2,5-Dihydroxyphenyl)-5,10,15,20-tetra(*p*-hydroxyphenyl)porphyrinato Metals and Their Synthesis

Zhang-Ping Chen ( ),[a] Qi-Mao Huang ( ),[a] Xiang Zhou ( ),[a] Xiaolian Jiang ( ),[b] Lu Lu ( ),[a] and Han-Sheng Xu ( )[a]

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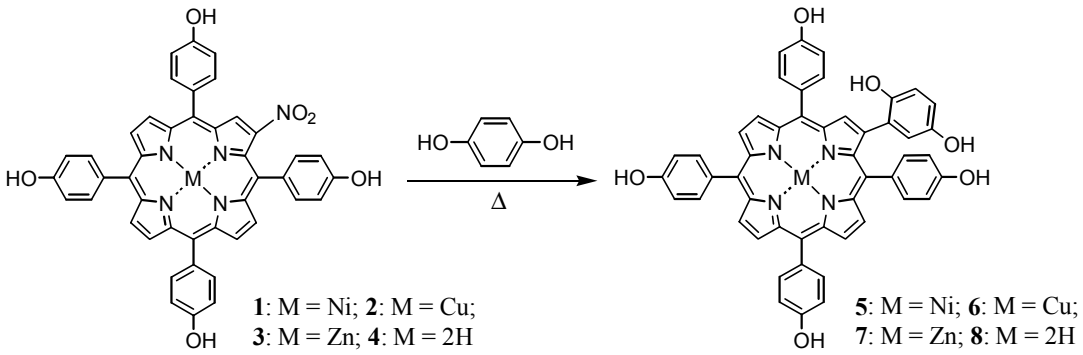
[b]*College of Medicne, Wuhan University, Hubei 430072, China*

2-(2,5-Dihydroxyphenyl)-5,10,15,20-tetra-(*p*-hydroxyphenyl)porphyrinato nickel(II) **5** was synthesized by the direct reaction of 2-nitro-5,10,15,20-tetra-(*p*-hydroxyphenyl)porphyrinato nickel(II)[1] with hydroquinone in 92% yield according to the following scheme. It's antitumor activity in different concentration were tested with K562 cell. It showed that compound **5** had high antitumor activity as shown in Figure 1. When the concentration of **5** is 320 nM, most of the cancer cells were destroyed, and 400 nM, all of the cancer cells were destroyed. The cancer cells could be destroyed also in dark, but it is not so effective as with light. The other metal porphyrins were also synthesized and their antitumor activity tested.



Scheme 1. Synthesis of the target complex

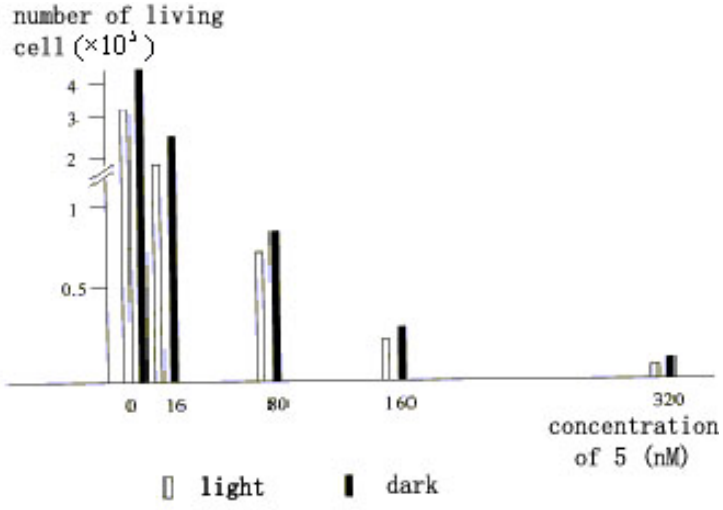


Figure 1. The relationship between cell mortality and porphyrin concentrations

Reference:
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PP-54. De Novo Design and Virtual Library Screening of HIV Entry Inhibitor

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This study focuses on the possible strategy to interfere with HIV viral attachment, the very first step of viral entry. Crystallographic study on gp120 in complex with CD4 and the Fab portion of a neutralizing monoclonal antibody reveals the details of the interactions.[1] Previous mutational study and the structural data show that Phe43 and Arg59 are crucial for the high affinity of gp120-CD4 interactions. LigBuilder is chosen after comparing available methods.[2] The CD4 pharmacophore model and de novo compound models were proposed after gp120-CD4 binding site analysis and GA controlled iterative building processes (Figure 1). Also, we carried out virtual screening to facilitate lead discovery, the flexible docking program FlexX was tested and a parallel computation is under way to suggest possible hits for further analysis (Scheme 1).[3]

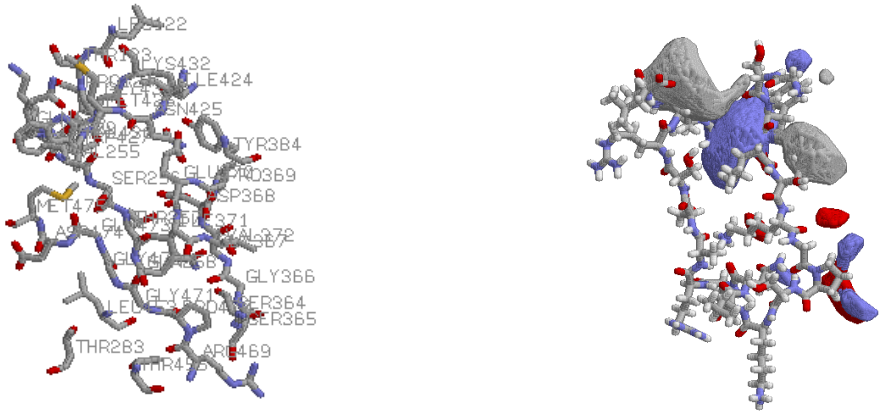
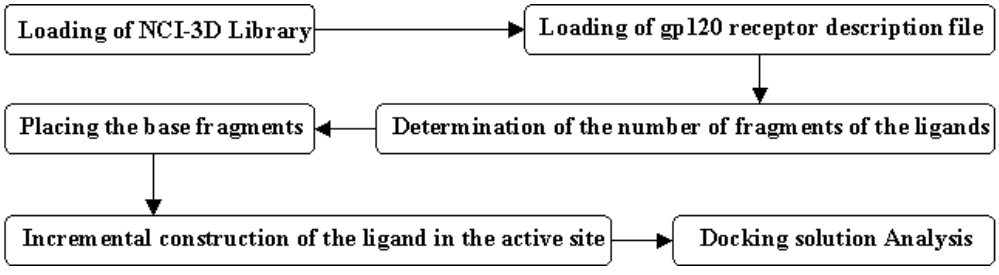


Figure 1. gp120 binding site analysis and the proposed pharmacophore model for ligand design



Scheme 1. Flowchart of FlexX flexible docking/virtual screening procedure

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PP-55. Solid Phase Synthesis of 4-Aminophenyl Aryl Thioureas

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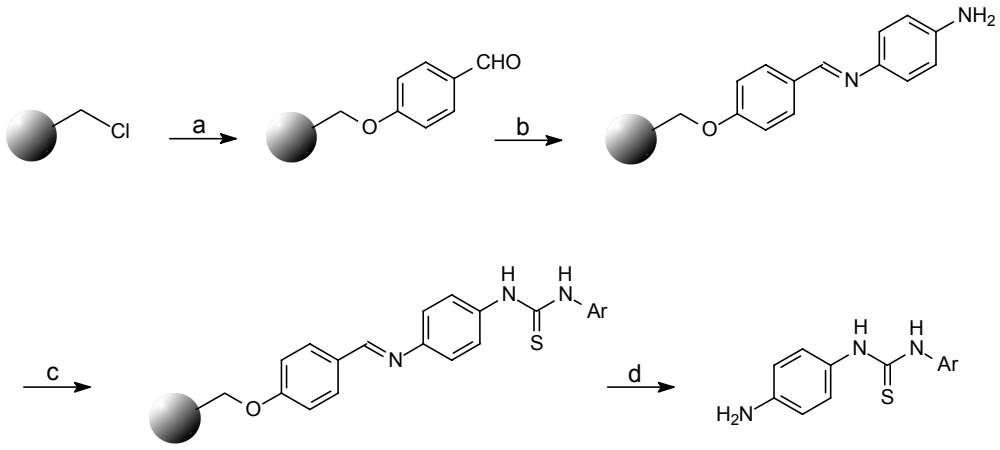
One of the advantages of solid phase synthesis is the ability to prepare unsymmetrical compounds.[1] Thiourea compounds are known to exhibit high potential of biological activities.[2] We have developed a new solid phase protocol for the synthesis of 4-aminophenyl aryl thioureas, which are difficult to obtain by liquid phase route and could act as useful intermediates for the construction of various scaffolds. By using the imine linker, the title compounds were prepared with satisfactory purity (HPLC).



a. *p*-hydroxybenzaldehyde / NaOH / DMA; b. *p*-phenylenediamine / CH_2Cl_2;
c. ArNCS / CH_2Cl_2; d. TFA / CH_2Cl_2

Scheme 1. Solid phase synthesis of 4-aminophenyl aryl thioureas

Table 1. Experimental results

Entry	Ar	Time (h)	Yield (%)	Purity (%)
1	phenyl	48	38	93
2	2-naphthyl	48	50	92
3	4-chlorophenyl	48	24	88
4	4-bromophenyl	48	33	86
5	4-methylphenyl	48	22	85
6	4-methoxyphenyl	48	21	88

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2. Galabov, A. S.; Galabov, B. S.; Neykova, N. A. *J. Med. Chem*. **1980**, *23*, 1048.

PP-56. Traceless Biomimetic Synthesis of Tyrocidines

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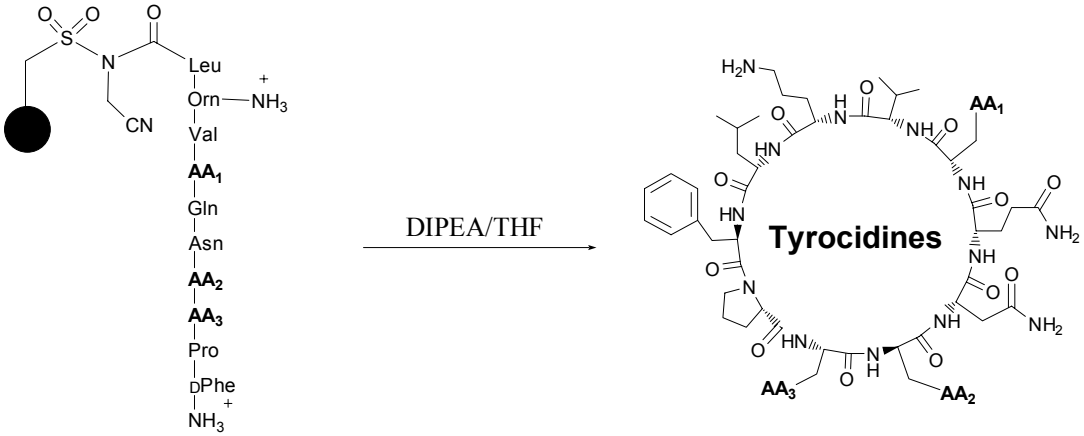
Tyrocidines A–E are cyclic decapeptide antibiotics produced by *Bacillus brevis*. They have been targeted as a scaffold for new drug development to treat microbial resistance because of their unique mode of action on cell membranes and the resulting low risk of provoking resistance. Efficient synthetic method is highly desirable for combinatorial generation of their analogues to find drug candidates maintaining the natural products' high antibiotic activities while lowering or eliminating their unwanted high hemolytic activities. Here we report a novel traceless method for biomimetic synthesis of these natural products. Their linear biosynthetic precursors were assembled on 4-sulfamylbutyryl AM resin using conventional method of Fmoc solid-phase peptide synthesis. After linker activation, the linear precursors were fully deprotected and cyclized under basic conditions. Interestingly, the cyclization reaction was found to be strictly head-to-tail and quantitative, and highly pure cyclic products were obtained with minimal purification. This novel method is likely suitable for high throughput synthesis of the analogues of the natural products for functional screening because of its simplicity and high specificity in head-to-tail cyclic product formation.



Tyrocidine	AA_1	AA_2	AA_3
A	Tyr	Phe	Phe
B	Tyr	Phe	Trp
C	Tyr	Trp	Trp
D	Trp	Trp	Trp
E	Phe	Phe	Phe

Acknowledgement. This work is supported by the Innovation and Technology Fund (ITS/119/00) from the Innovation and Technology Commission of HKSAR.

PP-57. Parallel Solid-phase Synthesis of Streptocidins A–D through Spontaneous Self-cyclization of Their Linear Precursors

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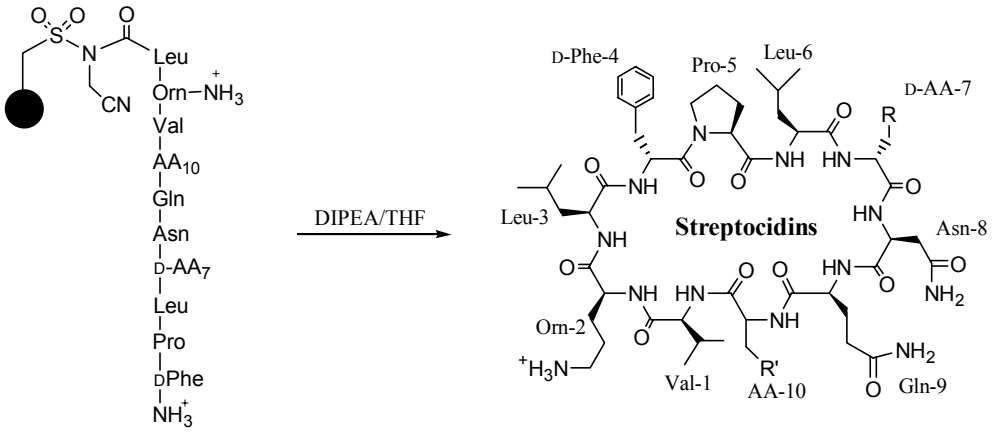
Department of Chemistry and The Biotechnology Research Institute, The Hong Kong University of Science and Technology, Clear Water Bay, Kowloon, Hong Kong SAR, China

Streptocidins are decapeptide antibiotics that were isolated from the culture broth of *Streptomyces sp.* Tu 6071.[1] Recently reported structure characterization and conformation analysis of streptocidins A–D[2] showed that they can be structurally classified to a family of antibiotically active cyclic decapeptides composed of tyrocidines (A–E), loloatins (A–D), and gramicidin S. Since both tyrocidines and gramicidin S precursors adopt a conformation favorable for ring closure under basic conditions, the streptocidins are expected to have the same conformational preference because of their structural similarities to other members in the family. Here, we design a method for parallel solid-phase synthesis of streptocidins A–D through spontaneous self-cyclization of their activated linear precursors on a safety-catch resin.



Streptocidin	AA_7	AA_{10}
A	Tyr	Trp
B	Trp	Trp
C	*D*-Trp	Trp
D	Trp	Phe

Acknowledgement. This work is supported by the Innovation and Technology Fund (ITS/119/00) from the Innovation and Technology Commission of HKSAR.

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2. Holtzel, A.; Jack, R. W.; Nicholson, G. J.; et al. *J. Antibiotics* **2001**, *54*, 434-440.

PP-58. Utilization of Thioesterase from Non-ribosomal Peptide Synthase in Biomimetic Synthesis of Gramicidin S

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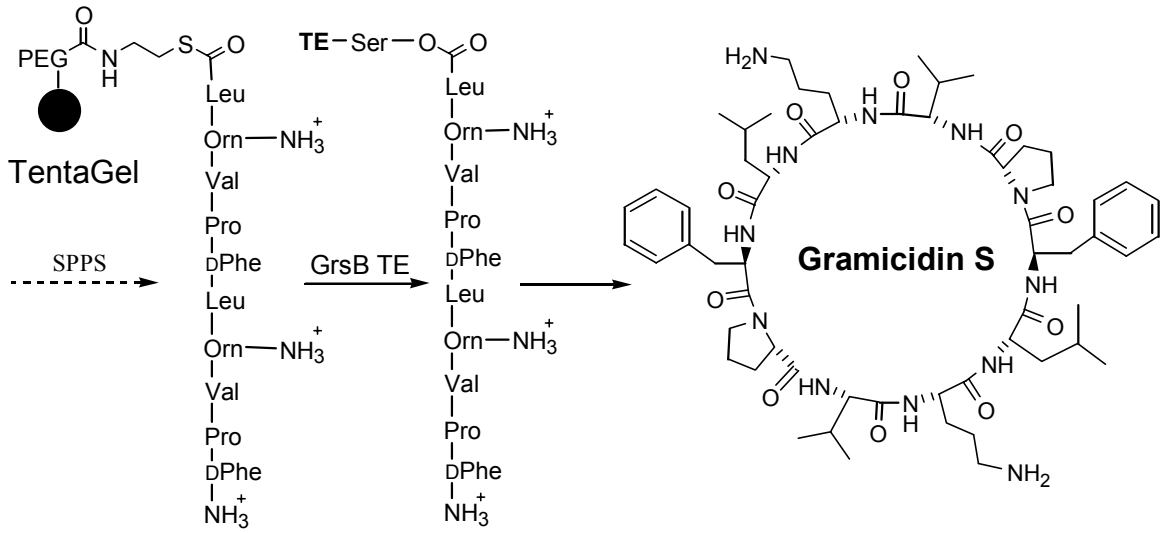
Department of Chemistry and The Biotechnology Research Institute, The Hong Kong University of Science and Technology, Clear Water Bay, Kowloon, Hong Kong SAR, China

Gramicidin S is a cyclic decapeptide antibiotic with two repetitive units of pentapeptide Val-Orn-Leu-*D*Phe-Pro. It has been a focal point of interest of both physicians and medicinal chemists because of its potent broad-spectrum activity against bacterial as well as fungi and unlikeness of provoking microbial resistance. However, synthesis of its analogues for SAR studies and functional optimisation has been a challenge due to lack of an efficient and facile synthetic method. Here we demonstrate that the putative gramicidin thioesterase is active towards a heterogeneous linear decapeptide biosynthetic precursor of gramicidin S and correctly cyclizes it into the natural product. This result indicates that the enzyme is suitable for chemoenzymatic combinatorial synthesis of analogues from linear precursors synthesized on a solid support.



Acknowledgement. This work is supported by the Innovation and Technology Fund (ITS/119/00) from the Innovation and Technology Commission of HKSAR.

PP-59. Synthesis of Gramicidin S by Conformation-dependent Cyclization of Its Linear Biosynthetic Precursor

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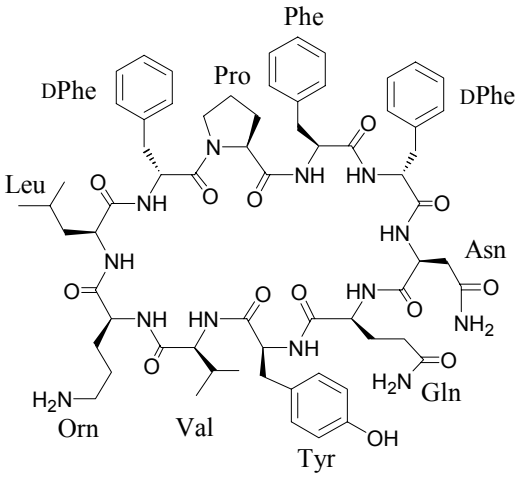
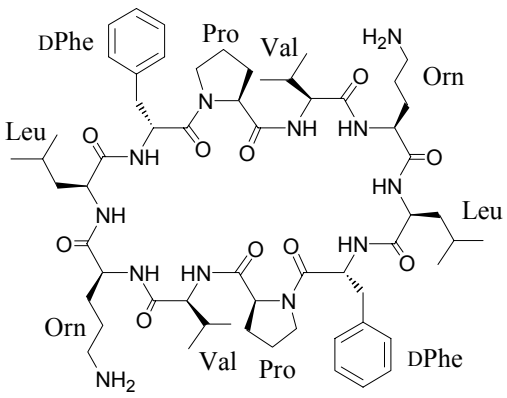
Department of Chemistry and The Biotechnology Research Institute, The Hong Kong University of Science and Technology, Clear Water Bay, Kowloon, Hong Kong SAR, China

Gramicidin S is an amphiphilic decapeptide antibiotic which forms a rigid antiparallel β-pleated sheet structure and uniquely targets cell membranes. Over the last three decades, more than 200 analogues have been synthesized using the traditional methods for structure-activity relationships studies. To optimize its therapeutic index for containment of microbial resistance, however, more analogues are needed and novel facile synthetic method is highly desirable. Based on our recent discovery that the linear biosynthetic precursor of tyrocidine A, a closely related decapeptide antibiotic, adopts a backbone conformation highly favorable for ring closure, we reasoned that the precursor for gramicidin S most likely has a similar conformational preference because of the structural similarities. Here we report the attempt to take advantage of this favorable conformation for biomimetic synthesis of this natural product. The cyclic decapeptide antibiotic was successfully synthesized by spontaneous head-to-tail cyclization under basic conditions from its fully deprotected linear biosynthetic precursor assembled with an optimized direct Fmoc method for solid-phase peptide thioester synthesis. The cyclization reaction is quantitative, indicating that the linear biosynthetic precursor indeed adopts a conformation favorable for ring closure. This conformational preference of this cyclic peptide scaffold will be useful in synthesis of gramicidin S analogues for functional screening.



Tyrocidine A



Gramicidin S

Acknowledgement. This work is supported by the Innovation and Technology Fund (ITS/119/00) from the Innovation and Technology Commission of HKSAR.

PP-60. Biomimetic Synthesis of Loloatins through Spontaneous Self-cyclization of Their Linear Precursors

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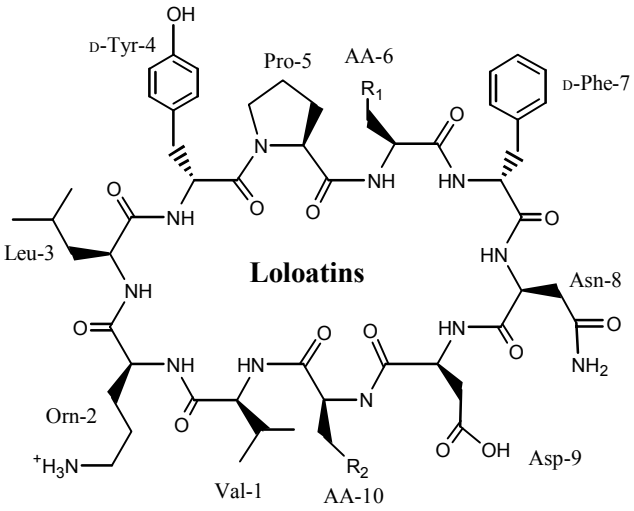
Department of Chemistry and The Biotechnology Research Institute, The Hong Kong University of Science and Technology, Clear Water Bay, Kowloon, Hong Kong SAR, China

Loloatins are novel cyclic decapeptide antibiotics newly isolated from laboratory cultures of a tropical marine bacterium recovered from the Great Barrier Reef in Papua New Guinea. They exhibit distinctive potent antibiotic activities among the family of cyclic peptide antibiotics that include gramicidin S and tyrocidines. To facilitate the structure-activity relationships study, novel and facile synthetic methods are highly desirable although these natural products have been synthesized by traditional methods. Based on their structural similarities to other members in the family, loloatin A–C have been synthesized using a biomimetic method proved successful in total synthesis of gramicidin S and tyrocidines. Development of this novel synthetic method not only will expedite the elucidation of the structure-activity relationships, but also will significantly facilitate the optimization of their therapeutic index for containment of microbial resistance.



Loloatin	R_1	R_2
A	Tyr	Phe
B	Trp	Phe
C	Trp	Trp

Acknowledgement. This work is supported by the Innovation and Technology Fund (ITS/119/00) from the Innovation and Technology Commission of HKSAR.

PP-61. Regioselective Incorporation of Deuterium into the Nucleus of Artemisinin: Development of a Generalized Route to Radiolabelled Artemisinin Derivatives

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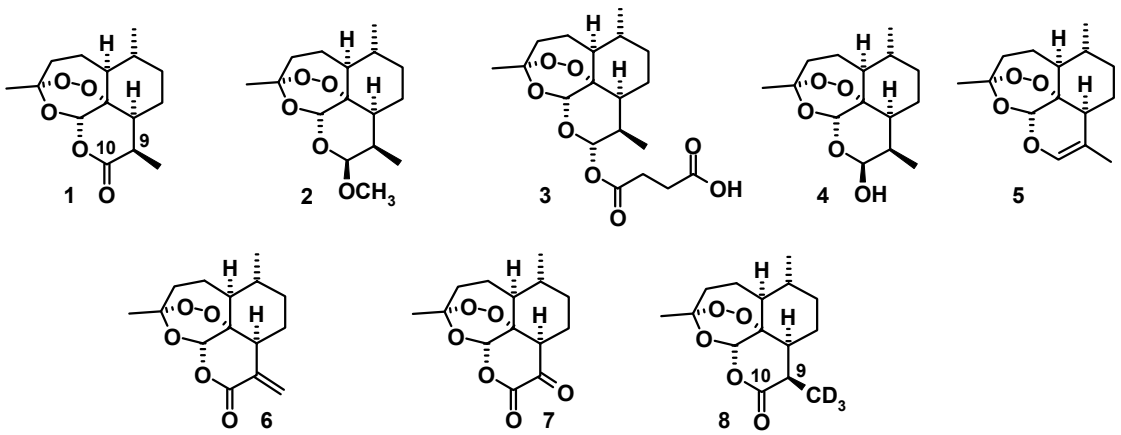
The use of artemisinin **1**, and its derivatives such as artemether **2** and artesunate **3** for treatment of malaria is thoroughly established, although aspects of pharmacokinetics, pharmacodynamics and toxicology have not been resolved because of the inaccessibility of radiolabelled derivatives. Generally these have been prepared with the label in metabolically labile positions such as in the methyl group of **2** or the succinyl residue of **3**. The methyl group of artemether is lost by oxidative dealkylation through the action of CYP enzyme *in vivo*, and the succinyl residue is very easily lost, probably by non-enzymatic hydrolysis. Whilst radiolabelled artemether bearing a C-14 labelled methyl group at C-9 has been prepared by elegant total synthesis,[1] this does not represent a practical approach to such compounds.

As part of a program associated with the development of a new artemisinin antimalarial drug by Bayer AG, we required the radiolabelled drug bearing a ^{14}C-label in the methyl group at C-9. To this end, we converted dihydroartemisinin **4** into the glycal **5**, and thence into artemisitene **6**. The last compound was converted into the dicarbonyl compound **7** according to a literature procedure.[2] In a model study, this was converted into the artemisinin **8** bearing a $-CD_3$ group at C-9. Details of this transformation incorporating what appear to be new chemical transformations, and how these transformations may be adapted to preparing a C-14 labelled methyl group at C-9, will be given.



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PP-62. Against Vancomycin-Resistance Enterococci (VRE) by a Divalent Vancomycin with a Rigid Metal Complex Linker

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[a]*Department of Chemistry, The Hong Kong University of Science and Technology, Clear Water Bay, Kowloon, Hong Kong SAR, China*
[b]*Department of Microbiology, School of Medicine, The University of Hong Kong, Pokfulam Road, Hong Kong SAR, China*

Vancomycin-resistance enterococci strains (VRE) have emerged as a threat to public health. It is important and urgent to develop an effective and rapid approach to counter the VRE bacteria. One promising approach is multi/polyvalency–multiple simultaneous bindings between two biological entities. Here we used a platinum compound as a rigid linker to construct divalent vancomycins (Vans) and evaluated their activities against VRE. Our results showed that the dimers of Van formed by the rigid linker ([Pt(en)]) exhibit potent activity (MIC: 0.8 μg/mL) against VRE, which is ~10^3 times more potent than Van and >20 times more potent than that of dimers or oligomers of Vans linked only by flexible organic bridges. We suggest that the combination of metal coordination and receptor/ligand interactions can offer a promising method to explore the multi/polyvalency for making potent inhibitors.

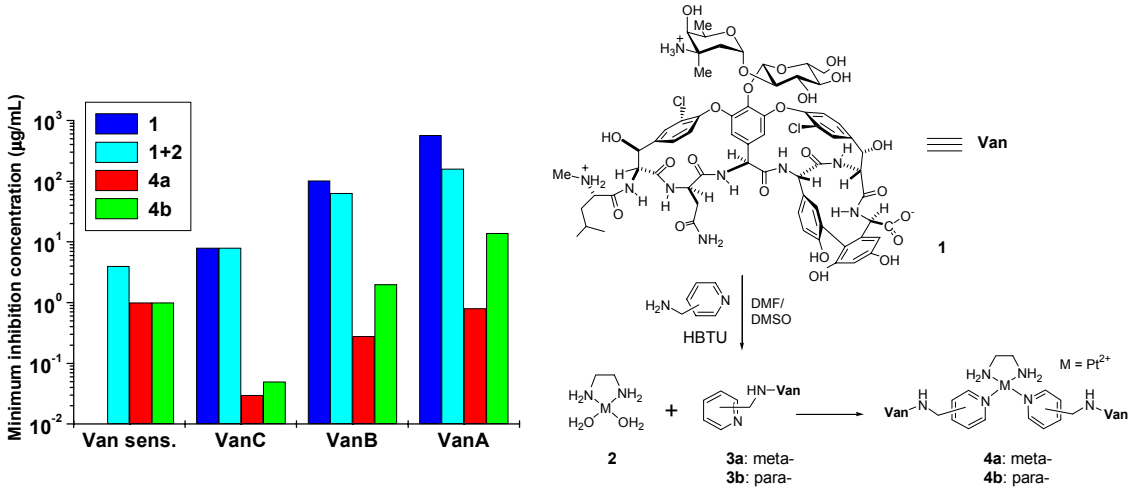

Figure 1. Average minimum concentration of Van (**1**), $[Pt(en)(H_2O)_2](NO_3)_2$+Van (**1+2**), and dimers of Van (**4**) required to inhibit growth of bacterial cells.

PP-63. Hydrophobic Interaction and Hydrogen Bonding Cooperatively Confer A Vancomycin Hydrogel: A Potential Candidate for Biomedical Application

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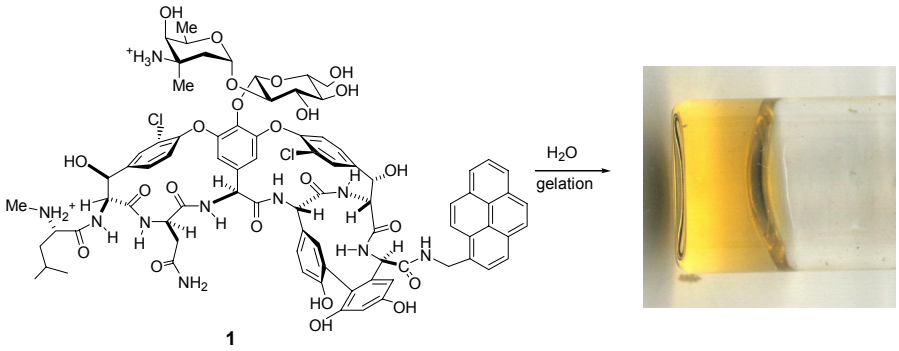
[b]*Department of Microbiology, School of Medicine, The University of Hong Kong, Pokfulam Road, Hong Kong SAR, China*

Here we report an effective antibiotic gelator—vancomycin pyrene (Scheme 1), which forms hydrogels via self-assembly in water using hydrophobic interaction and hydrogen bonding, cooperatively. The fluorescence measurement (Figure 1) of this novel hydrogel confirmed that pyrenes of **1** dimerize exclusively via π–π stacking in the gel. The circular dichroism (CD) and electron microscopy spectra of the gel also indicate that the polymer network in this van-pyrene hydrogel adopts a helical arrangement. Since the van-pyrene itself was found to exhibit potent activity against vancomycin resistance enterococci (VRE) in vitro. We suggest that such antibiotic hydrogel will be applicable in biomaterials and drug-delivery systems.



Scheme 1. The structure of vancomycin–pyrene and the optical image of the gel (0.36%)

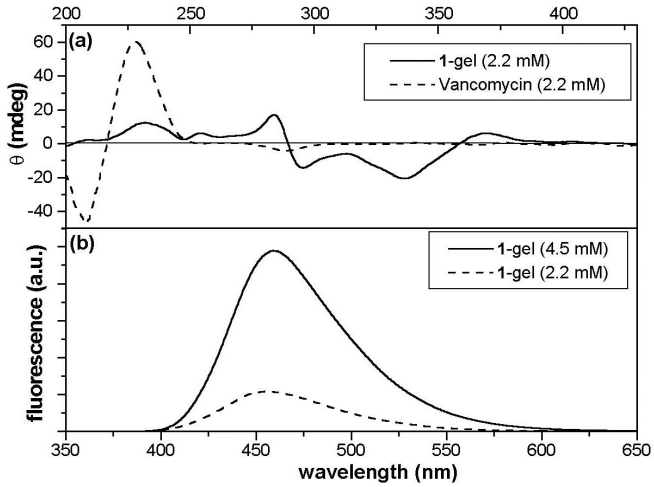


Figure 1. (a). Circular dichroism spectra of the gel. (b). Emission spectra of vancomycin–pyrene hydrogels at different concentrations. (λ_{ex} = 330 nm).

PP-64. The Application of $G\alpha_{16/z}$ Chimeras in High-Throughput Drug Screening

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[a]*Department of Biochemistry and The Biotechnology Research Institute, The Hong Kong University of Science and Technology, Clear Water Bay, Kowloon, Hong Kong SAR, China*
[b]*Department of Chemistry, The Hong Kong University of Science & Technology, Clear Water Bay, Kowloon, Hong Kong SAR, China*

G protein-coupled receptors (GPCRs) are major targets of drug-screening programs. Pharmacologically active compounds that act via GPCRs constitute the largest category of clinical drugs in current use. The GPCR have proven to be valuable targets as they control an enormous array of diverse biochemical and physiological processes. GPCRs are generally distinguished by the type of intracellular G protein α-subunit that they activate. These are termed $G\alpha_{q/11}$, $G\alpha_{i/o}$ and $G\alpha_s$. GPCR activation of these different G protein subtypes results in the activation of different intracellular second messenger systems. Traditionally, this has meant that measuring the ability of a series of ligands to activate different GPCRs requires the establishment of three different assay platforms. The discovery that the $G_{q/11}$ family $G\alpha_{16}$ subunit is promiscuous in its ability to couple to different types of receptor has suggested that it may be possible to develop a single assay platform suitable for all GPCRs.

Based on amino acid sequence alignment and molecular modeling, we have developed a series of $G\alpha_{16/z}$ chimeric proteins and tested them for their GPCR-coupling promiscuity. Chimera 16z44 is able to couple to the majority of $G\alpha_{q/11}$-, $G\alpha_{i/o}$- and $G\alpha_s$-coupled receptors tested to date.[1] The use of this chimera has indeed allowed GPCRs with different G protein-coupling specificities to be screened using a single assay format. Furthermore, we have incorporated these chimeras into a high-throughput drug-screening program that uses a Fluorometric Light Imaging Plate Reader (FLIPR) for the detection of drug-induced intracellular Ca^{2+} mobilization.

As a validation of the potential applications of 16z44 chimera in drug discovery, here we report the identification of two synthetic compounds that act as ligands at melatonin receptors. The screening process took advantage of the 16z44 chimeric system in the FLIPR screening platform. Initially, forty-nine compounds were rapidly screened against thirty-three different GPCRs. Compounds BRI-201 and BRI-204 activated melatonin receptor subtypes MT_1 and MT_2 with high efficacy. They have subsequently been characterized using traditional biochemical assays and the 16z44/FLIPR technology. This has confirmed their efficacy at these two receptor subtypes as well as allowing measurements of their potencies and a comparison with current melatonin agonists. In conclusion, we present the development of a powerful tool that simplifies and increases the speed of screening for GPCR ligands. As a proof of principle we have used this tool to identify and characterize two new melatonin receptor agonists.

Acknowledgements. This work was supported in part by the Hong Kong Jockey Club and grants from the University Grants Committee of Hong Kong (AoE/B-15/01), Research Grants Council of Hong Kong (N_HKUST 602/00), and the Innovation and Technology Commission of Hong Kong (AF166/99 and ITS/119/00).

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PP-65. Development of Bioassays to Screen for Neurotrophin-like Activity Using Fibroblast Cell Lines Stably Expressing Trk Receptors

Fanny C. F. Ip, Karan K.Y. Wong, Hilda H. L. Wong, and Nancy Y. Ip*
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Alzheimer's disease (AD) is the most common type of dementia in the elderly, affecting millions of people worldwide. It is believed that accumulations of abnormal proteins affect neuronal function and lead to neuronal death, particularly in the basal forebrain. Nerve growth factor (NGF), the prototype of the neurotrophin family, has been shown to be important for the development and maintenance of these neurons. Furthermore, transgenic mice expressing the neutralizing antibody against NGF develop an Alzheimer's-like pathology, including amyloid plaques and neurofibrillary tangles. While clinical trial using NGF has been initiated for AD, the inability of NGF to cross the blood-brain barrier and protein instability pose potential problems. It is therefore important to screen for compounds that can mimic the effect of NGF in supporting neuronal survival.

In order to screen for potential NGF-mimetic activity in traditional Chinese medicine (TCM) that have been prescribed for the enhancement of memory, a specific and efficient bioassay has been established. The specific receptor for NGF, TrkA, is stably expressed in a fibroblast cell line. After the serum deprivation, these cells undergo cell death and will survive only with the addition of NGF. Cell viability can be evaluated using MTT assay. To determine the specificity of the survival effect of TCM activity, fibroblast cell lines expressing receptors for other neurotrophins, TrkB or TrkC, are also established. A number of TCM crude extracts and fractions have been screened using these survival assays, leading to the identification of novel activities in the TCM specific for TrkA or TrkB receptors. Taken together, our bioassays provide an efficient approach to screen for potential neurotrophin-like compounds in TCM.

Acknowledgement. This work is supported by the Areas of Excellence Scheme under the University Grants Committee of the Hong Kong SAR, China (AoE/B-15/01) and the Innovation and Technology Fund under the Innovation and Technology Commission of the Hong Kong SAR, China (AF/166/99).

PP-66. Axial Ligation as an Efficient Tool for Enhancing Selectivity in Catalytic Epoxidation by Manganese Porphyrins

Tat-Shing Lai and Chris C. K. Chang*
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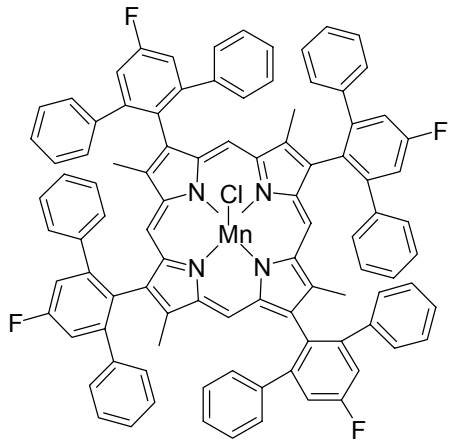
The use of metalloporphyrins as catalysts to carry out selective oxygenation of organic substrates has been proposed to be a simple method for drug synthesis and /or discovery. This idea relies on how selective the catalytic oxidation is. In fact, the last decade has witnessed the success of biomimetic chemistry of metalloporphyrins. The diversity of the porphyrin architectures renders the catalytic reactions regio-, enantio- and stereoselective. For regio- and enantio-controls in epoxidation, the importance of axial ligand for sixth coordination to the oxo-metal oxidizing intermediate will be presented.

The regioselectivity of catalyst **1** for epoxidation of dienes and the enantioselectivity of catalyst **2** for epoxidation of *cis*-β-methylstyrene can be enhanced by the use of pyridine-type base as axial ligand.



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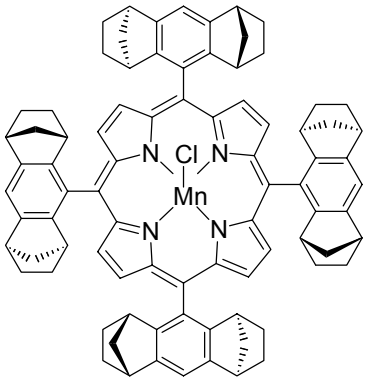

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PP-67. Palladium-Based Kinetic Resolution of Racemic Tosylaziridines

Wing-Leung Mak,[a] Eddie Y. Y. Chan,[a] Tony C. H. Lam,[a] Kevin Y. K. Sau,[a] Hoi-Lun Kwong,[b] Lam-Lung Yeung,*[a] and Wa-Hung Leung*[a]
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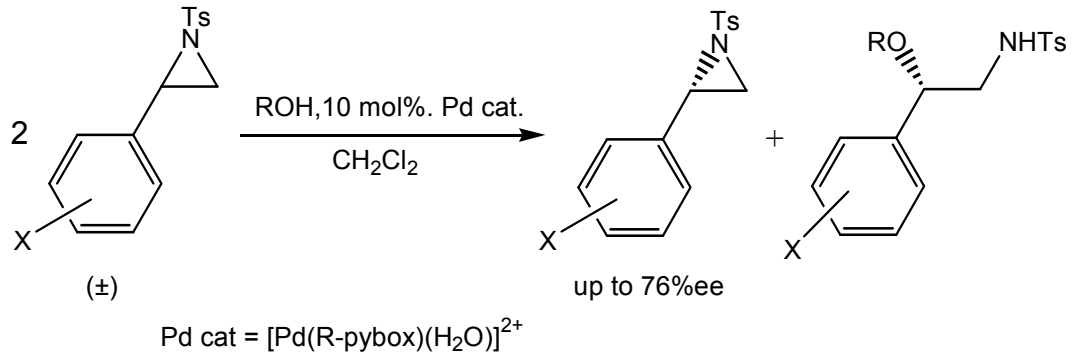
Aziridines become versatile precursors to complex organic molecules with the advent of new catalytic methods for the synthesis of optically pure aziridines.[1] Of special interest is the nucleophilic ring opening of aziridines by *O*-nucleophiles to give β-hydroxy or β-alkoxy amides. Recently, Jacobsen and coworkers demonstrated that chiral Co(salen) complexes are efficient catalysts for hydrolytic kinetic resolution of racemic terminal epoxides.[2] This prompted to investigate the kinetic resolution of racemic aziridines by their asymmetric alcoholysis. In this presentation, we report on the first kinetic resolution of tosylaziridines based on Pd catalysts containing chiral bis(oxazolin-2-yl)pyridine (pybox) ligands. A proposed mechanism for the Pd-mediated alcoholysis of aziridines will be described.



Acknowledgement. This work is supported by the Hong Kong Research Grants Council (project no.: HKUST6125/01P) and the Areas of Excellence Scheme established under the University Grants Committee of the HKSAR, China (project no.: AoE/P-10/01-1).

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PP-68. Ruthenium Complexes with Quadrientate Iminosulfoxide Ligands

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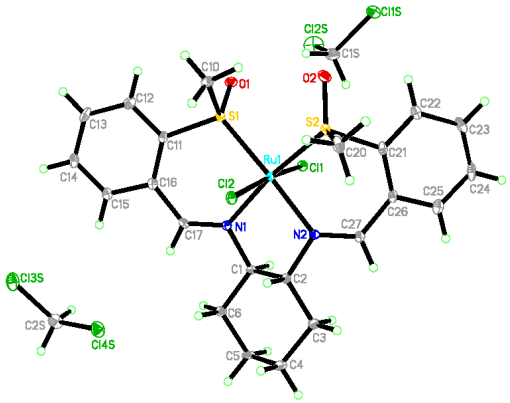
Although optically pure sulfoxides are widely used as chiral auxiliaries in asymmeric synthesis,[1] there are relatively few studies on applications of non-racemic sulfoxide ligands in asymmetric catalysis. Sulfoxides are ambidentate ligands that usually bind to late transition metals, e.g. Ru and Pd, via the soft sulfur site.[2] The use of chiral *S*-bound sulfoxide ligands in asymmetric catalysis is of interest because the sulfinyl group is generally configurationally stable. To this end, we set out to synthesize chelating Schiff base ligands containing chiral sulfoxide functionality. We here report on the synthesis, crystal structures and reactivity of the first Ru complexes with chiral quadridentate iminosulfoxide ligands.



Acknowledgement. This work is supported by the Hong Kong Research Grants Council (project no.: HKUST6125/01P) and the Areas of Excellence Scheme established under the University Grants Committee of the HKSAR, China (project no.: AoE /P-10/01-1).

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PP-69. Development of a New Chiral Oxygen Tripod Ligand for Asymmetric Catalysis

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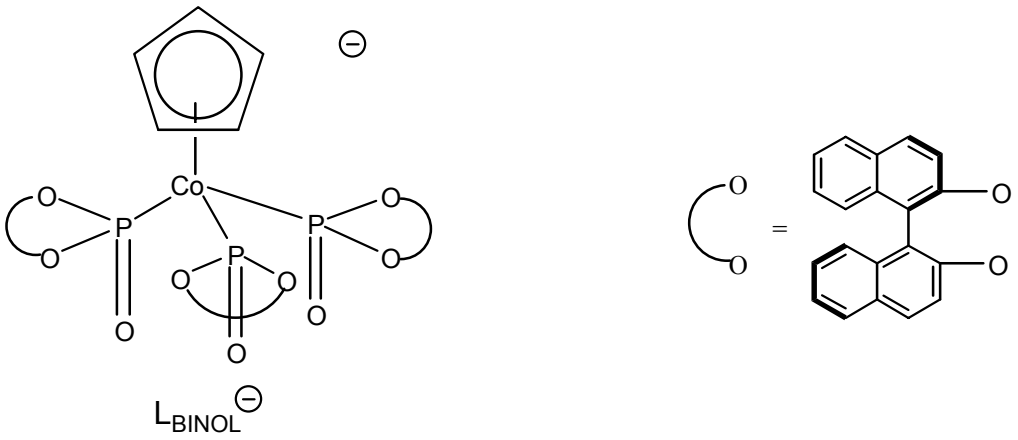
While C_2-symmetric ligands play central roles in asymmetric catalysis, the analogous C_3-symmetric systems have received relatively less attention. To this end, we set out to synthesize new C_3-symmetric 6e ligands that are isolable with cyclopentadienyl. The anionic oxygen tripod ligands $[CpCo\{P(O)(OR)_2\}_3]^-$ or L_{OR}^- have been recognized oxygen analogs of cyclopentadienyl and hydridotrispyrazolylborate. L_{OR}^- are strong π-donor ligands and have high affinity for hard metal ions.[1] In this presentation, we report on the preparation of a chiral oxygen tripod ligand L_{BINOL}^- derived from the chiral phosphite P(O)(BINOL)H ($BINOLH_2$ = 1,1'-binaphthol). The use of M-L_{BINOL} in asymmetric aziridination of olefins has been explored.



Acknowledgement. This work is supported by the Hong Kong Research Grants Council (project no.: HKUST6189/00P & HKUST6125/01P) and the Areas of Excellence Scheme established under the University Grants Committee of the HKSAR, China (project no.: AoE/P-10/01-1).

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PP-70. Synthesis, Chiroptical, and Liquid Crystalline Properties of Cholesterol-Containing Polyphenlyacetylene

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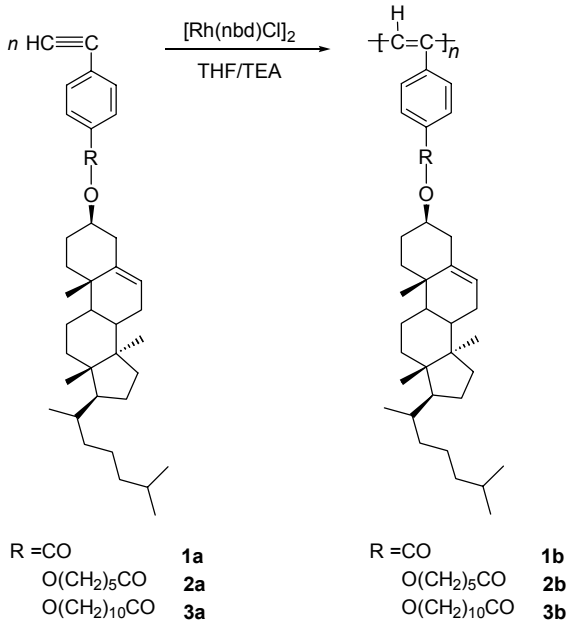
Cholesterol has the ability to change the permeability and fluidity of cell membrane. It is also related to signal transduction, cell adhesion and migration.[1] Synthesis of cholesterol containing polymer has aroused attention owing to its biological characteristic. We prepared three cholesterol-containing monomers by esterification of acetylene acids with cholesterol using 1,3-dicyclohexylcarbodiimine as a dehydrated agent.[2] The synthesis of poly(phenylacetylenes) with cholesterol moiety was described in Scheme 1. Polymerization of the monomers is achieved by $[Rh(nbd)Cl]_2$ catalyst in THF/TEA, giving polymers with high molecular weights (up to 10^5) in high yields (over 80%). The polymers are stable up to 300 ^oC. As the methylene spacer is easier to degrade, it is reasonable that the thermal stability of the polymers decrease as the spacer length is lengthened. The specific rotation of **1b** is much higher than that of **1a**, suggesting that the contribution of the polyphenylacetylene backbone to the overall chirality of the polymer. Whereas **1b** shows strong CD bands owing to the backbone absorption, the main chain CD absorptions of **2b** and **3b** are weak. Although the chiroptical properties of **2b** and **3b** are weak, they are found to exhibit liquid crystalline properties.

Scheme 1



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PP-71. Amphiphilic Nucleoside-Containing Poly(phenylacetylenes)

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Extremely polar phenylacetylene monomers containing 2',3'-*O*-isopropylidenenucleosides pendents {HC≡CC$_6$H$_4$COONuc, Nuc = 2',3'-*O*-isopropylideneuridine (**5a**), 2',3'-*O*-isopropylideneadenosine (**5b**), 2',3'-*O*-isopropylideneinosine (**5c**), 2',3'-*O*-isopropylidenecytidine (**5d**)} were prepared. The structures of **5a**–**5c** are proved to be 5'-ester connection between 4-carboxyphenylacetylene and 2',3'-*O*-isopropylidenenucleosides while **5d** is obtained by 4-NH_2 of 2',3'-*O*-isopropylidenecytidine and 4-carboxyphenylacetylene via an amide bond (Chart 1). Monomers **5a** and **5d** are polymerized by $[Rh(nbd)Cl]_2$, $[Rh(cod)Cl]_2$, and $Rh(cod)(NH_3)Cl$ catalysts, giving polymers **1a** and **1d** with M_w of several thousands. Monomers **5b** and **5c** are hard to polymerize by the above organorhodium complexes, **1b** obtained in trace amount is insoluble in common organic solvent, while the M_w of **1c** is only around that of its monomer **5c**. More nitrogen atoms in **5b** and **5c** than those in **5a** and **5d** may be the crucial factor for their poor polymerizability, due to the poisonous effect of the polar atoms on the organorhodium catalysts.

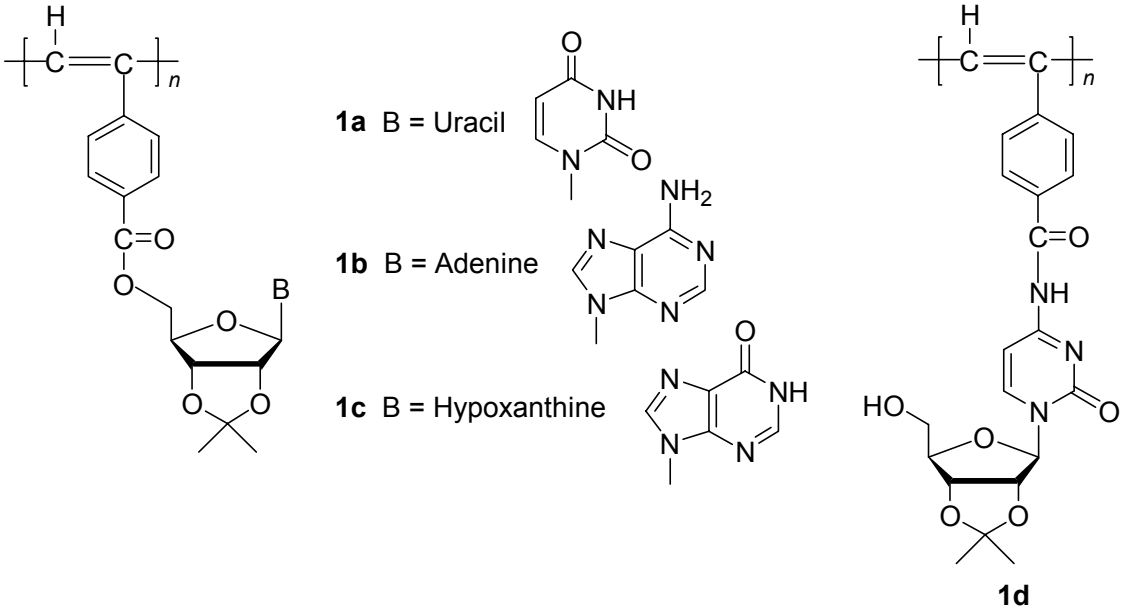

Chart 1

PP-72. Biological Activity of Amino Acid- and Monosaccharide-Containing Polyphenylacetylenes

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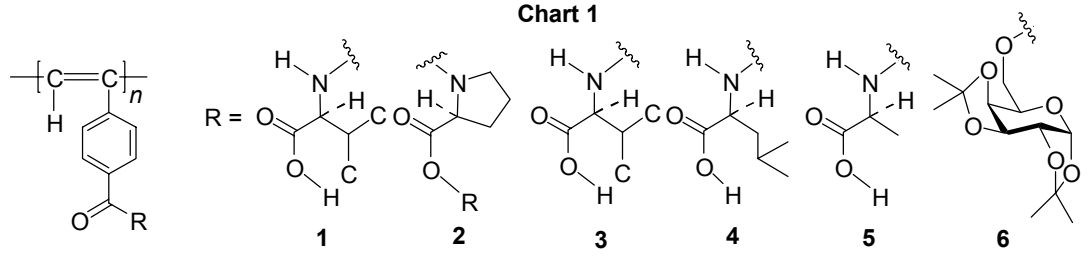
Biological effect on living cells of a new class of acetylenic polymers bearing natural building blocks such as monosaccharide and amino acids (Chart 1) was investigated. Those experiments were conducted *in vitro* in the cultural media containing HeLa cell and the effect of each polymer was evaluated by the cell adhesion (cell morphology and coverage) and cell growth (no. of cells). Statistical data showed that the polymers bearing different pendants could effect on the cell adhesion differently and the cell growth as well. In summary, **1** and **5** seemed to have no significant influences on the cell adhesion in the dosages up to 10.53 and 22.24 μg/cm^2, respectively, while **2**, **3** and **4** did the negative effects. In the dosages of ~10.53, ~5.26 and ~10.53 μg/mL, respectively, **2**, **3** and **4** significantly retarded the growth of the HeLa cells as their cell populations increased much slower than the control. However, in low dosages of **2** and **4** (up to 5.26 μg/cm^2), as shown in the left of Figure 1, the cells grew as normal without suffering the stress from the polymers. Interestingly, in the case of replacing each of the amino acid appendages with 1,2:3,4-di-*O*-isopropylidene-D-galactopyranose units, the resultant polymer not only possessed a better compatibility with HeLa cell but also exhibited a stimulation effect on the cell growth. As illustrated in the right of Figure 1, with small amount of **6** (~0.12 μg/mL), HeLa cell could grow in the population twice of the control. Further increase in the polymer concentration up to 0.96 μg/mL, there was no much negative effect on its growth.

Chart 1



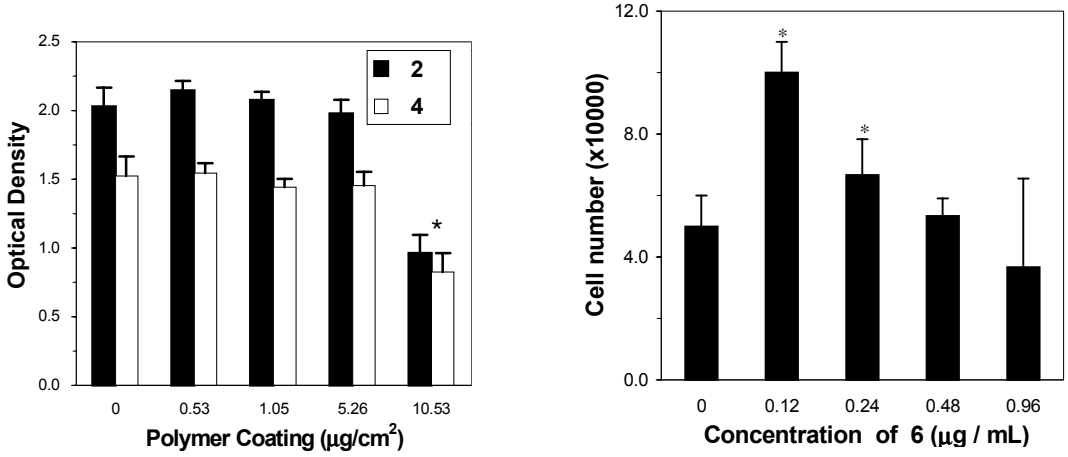


Figure 1. Growth of HeLa cells (left) on the microtiter plates precoated with **2** and **4**, (right) at different concentrations of **6**, after three days of incubation; the data marked with * is of outstanding significance statistically.

PP-73. Air Stable *P*-Chiral Secondary Phosphine Oxides as Ligands for Pd-catalyzed Asymmetric Allylic Alkylation

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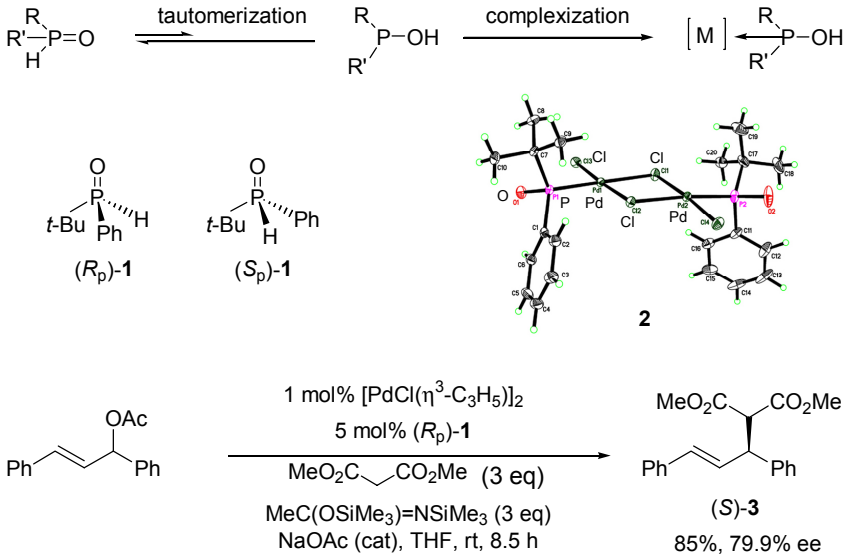
Trivalent phosphorus compounds in low oxidation states are more and less sensitive to air. In particular, di- and tri-alkylphosphines suffer oxidation readily in the presence of trace amount of oxygen or other oxidizing agents. Moreover, chiral phosphine compounds bearing stereogenic phosphorus atom are prone to racemization and therefore require additional stabilization. To overcome this problem, air-stable secondary phosphine oxides [RR'P(O)H] were introduced for using as precursors for some transition metal catalyzed cross-coupling reactions.[1] These air-stable phosphine oxides [RR'P(O)H] in the presence of transition metals undergo tautomerization to the less stable phosphinous acids (RR'POH), which subsequently and expectedly coordinate to the metal centers through phosphorus atom to form metal phosphinous acid complexes. A 1:1 complex **2** of (S_p)-**1** with Pd was determined by X-ray crystollographic analysis. The chirality on phosphorus is maintained.

According to this rationale, we applied, for the first time, the *P*-chiral secondary phosphine oxides in the Pd-catalyzed asymmetric allylic alkylation (AAA). Using 2 mol % Pd and 5 mol % of (R_p)-**1** in the presence of *N*,*O*-bistrimethylsilylacetamide (BSA) and NaOAc in THF, reaction of racemic 1,3-diphenylprop-2-enyl acetate with dimethyl manolate gave 85% yield of (*S*)-**3** in 79.9% ee. Effects of solvent, metal counter ion have been examined and the results will be discussed in detail.



Acknowledgment. This work is supported by the Department of Chemistry, HKUST, the Research Grants Council (through a Direct Allocation Grant, DAG00/01.SC13), and the University Grants Committee (through an Areas of Excellence Scheme, AoE/P-10/01) of the Hong Kong Special Administrative Region, China.

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PP-74. Novel Chiral Arsines as Efficient Ligands for Transition Metal-catalyzed Asymmetric Reactions

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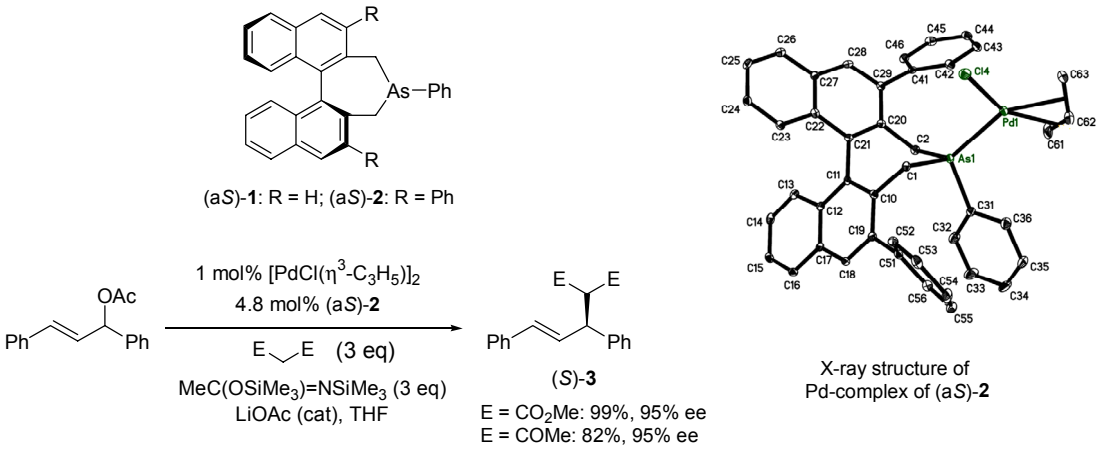
Transition metal-catalyzed asymmetric allylic alkylation (AAA) has attracted much attention during the past decades. A number of successful phosphorus-based bidentate ligands have been developed for the AAA reactions. These chiral ligands include the P,P-ligands, the P,N-ligands, and, to a less extent, the P,O-ligands.[1] However, no example has been reported on monodentate chiral arsine ligands with good result in asymmetric catalysis for carbon–carbon bond formation. Recently, we have designed and synthesized a novel C_2-symmetric chiral arsine (a*S*)-**1** possessing the 1,1'-binaphthyl-2,2'-bis(methylene) backbone and applied in the enantioselective Wittig olefination of 4-substituted cyclohexanones.[2] Here, we report on the synthesis of (a*S*)-**2** and its transition metal-catalyzed AAA reactions.

Using 2 mol% Pd, 4.8 mol% of (a*S*)-**2**, 3 equiv. of *N*,*O*-bistrimethylsilylacetamide (BSA), and catalytic LiOAc in THF, reaction of 1,3-diphenylprop-2-enyl acetate with dimethyl manolate (rt, 4 h) gave 99% yield of (*S*)-**3** (E = CO_2Me) in 95% ee. Under similar conditions (75 °C, 5 h), (*S*)-**3** (E = COMe) was obtained in 82% yield and in 95% ee. Effects of solvent, metal counter ion, and the ligand–Pd ratio on the AAA reactions have been examined and the results will be discussed in detail. The X-ray structure of the 1:1 Pd–(a*S*)-**2** complex was determined. It provides the basis for understanding the catalytic mechanism. Moreover, the chiral arsine ligands are also effective in the Rh-catalyzed asymmetric hydrogenation and the Pd-catalyzed asymmetric Heck reaction. These results will be discussed as well.



Acknowledgment. This work is supported by the Department of Chemistry, HKUST, the University Grants Committee (through an Areas of Excellence Scheme, AoE/P-10/01), and the Research Grants Council (through a Competitive Earmarked Research Grant, HKUST6068/98P) of the Hong Kong Special Administrative Region, China.

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PP-75. Synthesis of Functionalized Atropisomeric Amides

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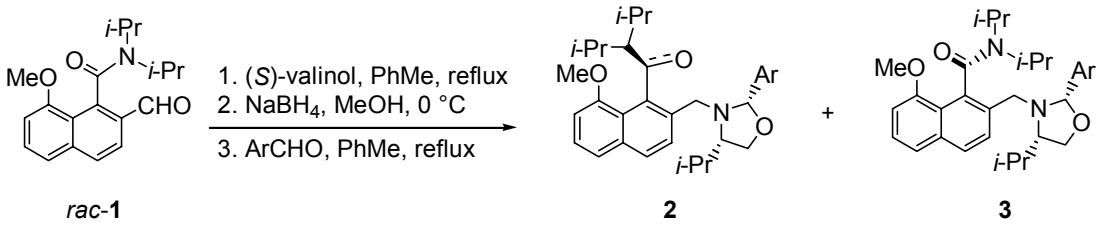
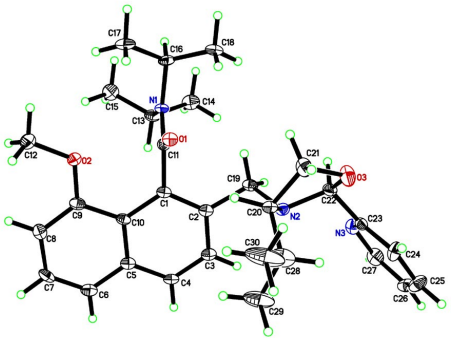
Atropisomeric amides are of increasing interest in asymmetric reaction and catalysis. Recent work from our laboratory demonstrated that high levels of enantioselectivity can be achieved in the desymmetrization of cyclic *meso*-anhydrides[1] and the palladium-catalyzed asymmetric allylic alkylation.[2] In order to explore the full potential of this class of axially chiral molecules in asymmetric catalysis, we aimed to synthesize structurally diverse and functionalized atropisomeric amides.

For example, the racemic aldehyde *rac*-**1** was condensed with (*S*)-(+)-2-amino-3-methyl-1-butabol (*L*-valinol) followed by reduction to give a mixture of the diastereomeric amino alcohols. The latter were further condensed, without separation, with aromatic aldehydes, ArCHO, to give the diastereomers **2** and **3**. After column chromatographic separation over silica gel, pure diastereomers **2** and **3** were obtained. Their structures were determined by spectroscopic analysis. Compound **3** with Ar = 2-pyridinyl was confirmed by X-ray crystallographic analysis. Examples of other reactions will be presented as well.



rac-**1** **2** **3**



X-ray crystal structure of **3** (Ar = 2-Py)

Acknowledgment. This work is supported by the Department of Chemistry, HKUST and the University Grants Committee (through an Areas of Excellence Scheme, AoE/P-10/01) of the Hong Kong Special Administrative Region, China.

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PP-76. General Synthesis of Aza- and Nitro-indoles via a Coupling–Cyclization Approach

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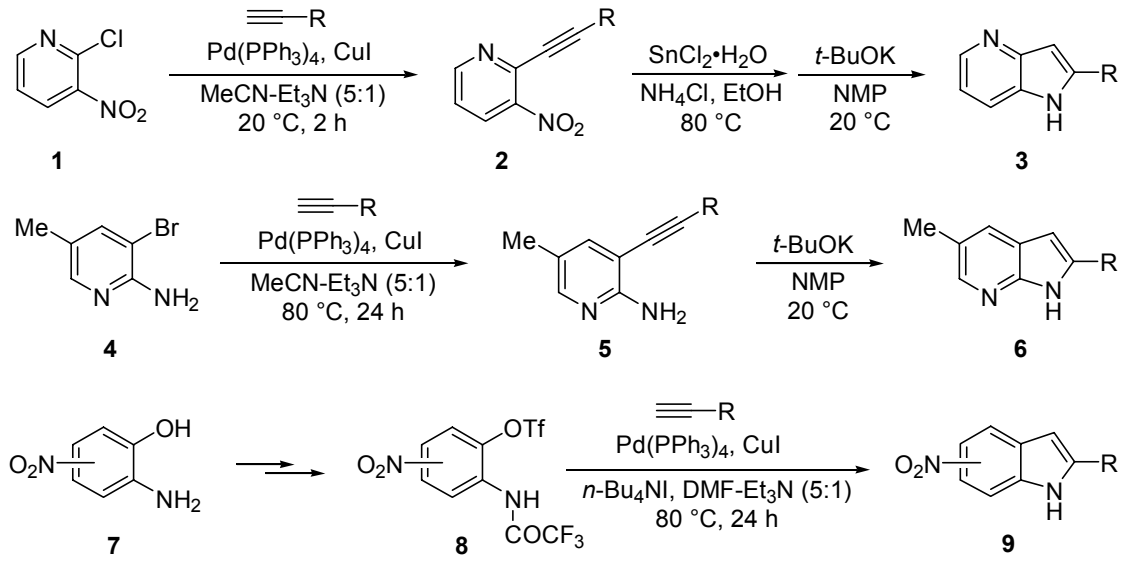
The transition metal-catalyzed heteroannulation has been reported for the synthesis of C5-, C6-, and C7-azaindoles using ortho-aminoiodopyridines as the starting materials. The latter were synthesized from pivaloylaminopyridines via ortho-lithiation as the key step.[1] However, the C4-azaindoles could not be prepared by this methodology. As the continuation of our indoles synthesis,[2,3] we report here: (i) a general synthesis of C4- and C7-azaindoles and (ii) a one-pot synthesis of nitroindoles using commercially available amino- or nitro-halopyridines and aminonitrophenols as the starting materials, respectively.

For example, the C4-azaindoles **3** were synthesized from 2-chloro-3-nitropyridine **1** via the cross-coupling–reduction–cyclization sequence in >80% yield for each step. The Pd-catalyzed cross-coupling of **4** with 1-alkynes took place at 80 °C to give **5** which cyclized to afford the C5-substituted C7-azaindoles **6**. In contrast to the above stepwise synthesis, a one-pot heteroannulation was developed for the synthesis of nitroindoles **9** from the nitroaryl triflates **8** which were easily prepared from 2-aminonitrophenols **7**. Other related results including functionalization at the C3 position of **9** will be presented.



Acknowledgment. This work is supported by the Innovation and Technology Fund of the Hong Kong Special Administrative Region, China (ITS/119/00) to L.-P. Sun, the HKUST Post Doctoral Fellowship Matching Fund to D.-S. Guo, and the Department of Chemistry, HKUST to X. Huang.

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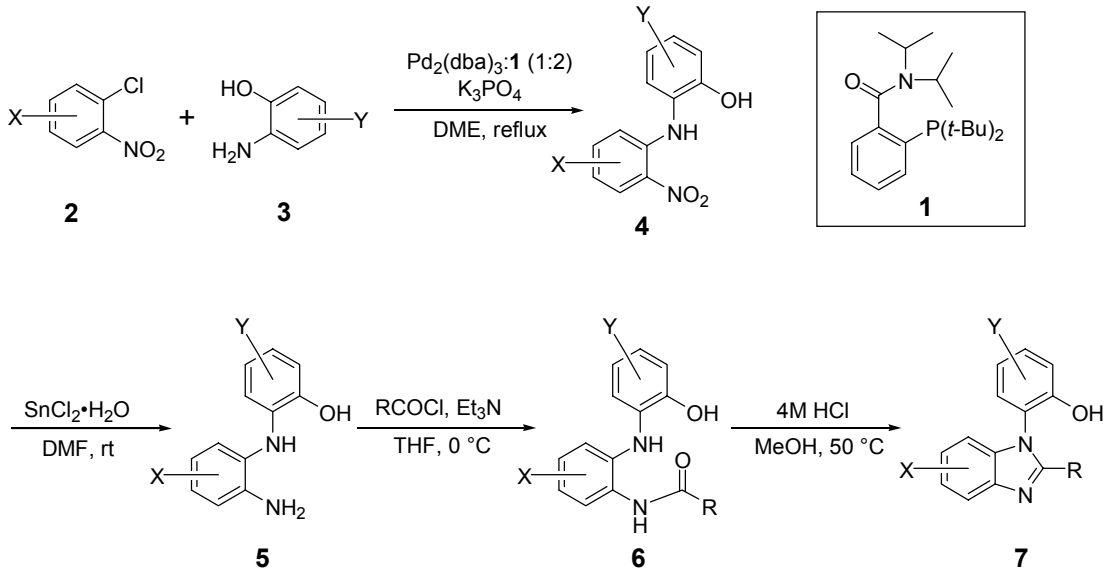
PP-77. Pd-catalyzed Chemoselective Amination of 2-Chloronitroarenes with Aminophenols Using Simple Amide-based P,O-Ligands

Wei-Min Dai* and Xuan Wang
Combinatorial Chemistry Laboratory, The Biotechnology Research Institute and Department of Chemistry, The Hong Kong University of Science and Technology, Clear Water Bay, Kowloon, Hong Kong SAR, China

In connection with our study on diversity-oriented synthesis of heterocycles of biomedical interest,[1] we have developed a general synthesis of benzimidazoles possessing a free OH group starting from 2-chloronitroarenes and 2-, 3-, 4-aminophenols, respectively. The key step is the Pd-catalyzed selective amination of aryl chlorides with aminophenols, which is a hot topic in current organic synthesis.[2] We found that a simple class of amide-based bidentate P,O-ligands such as **1** efficiently promoted the selective amination of **2** with the substituted aminophenols **3** in the presence of 1-5 mol% Pd to afford **4** in good to excellent yields. Reduction of the nitro group in **4** was achieved using $SnCl_2 \cdot 2H_2O$ to give the unsymmetrically substituted 1,2-diaminoarenes **5**. Treatment of **5** with acyl chloride at 0 °C in the presence of Et_3N furnished the substituted 1-acyl-2-aminoarenes **6**. The cyclization procedure was carried out at 50 °C by treating with HCl in MeOH[3] to give the benzimidazoles **7**. Detail results on the Pd-catalyzed amination using **1** as the ligand will be provided.



2 **3** **4** **1** **5** **6** **7**

Acknowledgment. This work is supported by the Innovation and Technology Fund (ITS/119/00) from the Innovation and Technology Commission of the Hong Kong Special Administration Region, China.

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PP-78. A Novel Class of Amide-based P,O-Ligands for Pd-catalyzed Amination of Nitroaryl Chlorides

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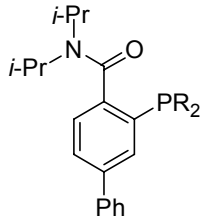
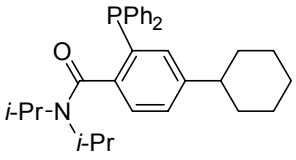
The palladium-catalyzed C–N bond formation has attracted considerable attention in recent years. In general, the electron-rich and bulky phosphine ligands are advantageous for high-yielding amination reactions of aryl chlorides.[1] Recently, we found that the amide-based axially chiral P,O-ligands induced high enantioselectivity in the Pd-catalyzed asymmetric allyl alkylation.[2] We envisaged that this class of novel P,O-ligands has potential applications in the transition metal-catalyzed reactions because they are (i) sterically bulky; (ii) bidentate with a weakly coordinating carbonyl oxygen (in contrast to P,P-ligands); and (iii) easily prepared. We report here the synthesis of the P,O-ligands **1**–**5** and their applications in the Pd-catalyzed amination of nitroaryl chlorides.[3]

The P,O-ligands **1**–**5** were prepared in step from the corresponding amides via *ortho*-lithiation followed by reacting with R_2PCl. The Pd-catalyzed amination of **6** with substituted anilines (R^1, R^2 = H, Ar) or amines was carried out using 5 mol% Pd and 5 mol% ligand in refluxing DME in the presence of 1.4 equiv of K_3PO_4. High yields of **8** were obtained for the reactions of *ortho*- or *para*-chloronitrobenzenes **6** with anilines when ligand **1** was used. The effects of the ligands and structures of the reactants on the amination reactions will be discussed.



1: R = Ph; **2**: R = Cy



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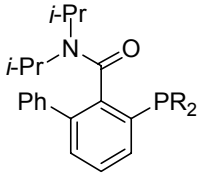
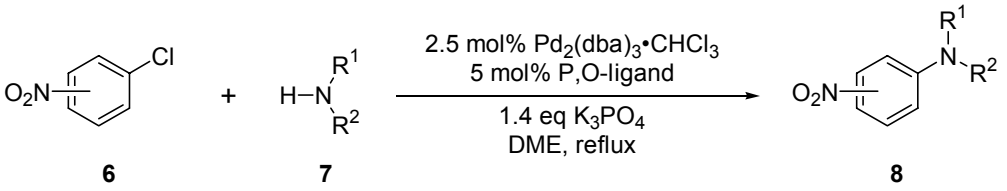


4: R = Ph; **5**: R = Cy



6 **7** **8**

Acknowledgment. This work is supported by the Area of Excellence Scheme (AoE/B-15/01) established under the University Grants Committee of Hong Kong SAR, China.

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1. For a leading reference, see: Wolfe, J. P.; Tomori, H.; Sadighi, J. P.; Yin, J.; Buchwald, S. L. *J. Org. Chem.* **2000**, *65*, 1158.
2. Dai, W.-M.; Yeung, K. K. Y; Liu, J.-T.; Zhang, Y.; Willaims, I. D. *Org. Lett.* **2002**, *4*, 1615.
3. Dai, W.-M.; Wang, X. the preceding paper.

PP-79. An Extremely Efficient Catalyst System for Suzuki Cross-coupling of Unactivated Aryl Chlorides

Wei-Min Dai* and Ye Zhang
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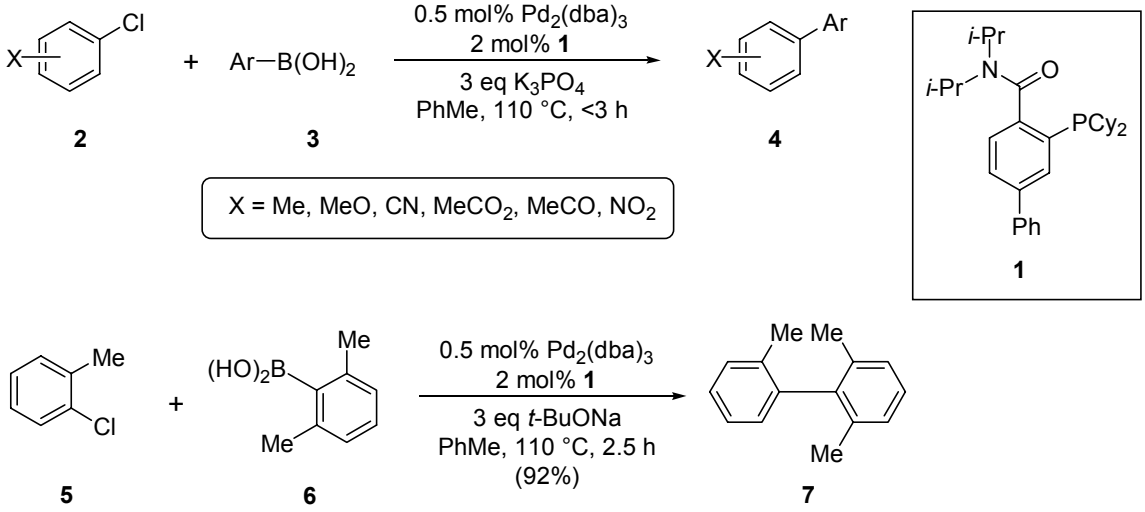
The palladium-catalyzed cross-coupling of aryl/vinyl halides or triflates with arylboronic acids is one of the most important C–C bond-forming reactions. It has found numerous applications in drug discovery and development. Recent efforts have been focused on the Suzuki cross-coupling of unactivated aryl chlorides or sterically hindered substrates.[1] In the preceding presentation, we described a novel class of amide-based P,O-ligands for Pd-catalyzed amination of nitroaryl chlorides.[2] We report here an extremely efficient catalyst system for the Suzuki cross-coupling of unactivated aryl chlorides and sterically hindered substrates using our P,O-ligands such as **1**.

A catalyst consisting of 1 mol% Pd and 2 mol% of **1** was discovered to catalyze the Suzuki cross-coupling reactions of various aryl chlorides **2** with arylboronic acids **3** in the presence of 3 equiv of K_3PO_4 in toluene at 110 °C for less than 3 h to give the biaryls **4** in excellent yields. The substrates **2** possessing either electron-donating or electron-withdrawing group exhibited the same reactivity. The cross-coupling could be carried out in THF at 65 °C to furnish the biaryls **4** in similar high yields. Moreover, the sterically hindered substrates **5** and **6** underwent the cross-coupling to afford **7** in 92% yield when *t*-BuONa was used (versus 59% using K_3PO_4, 7 h). We have systematically investigated the effects of base and Pd-ligand ratio on the Suzuki cross-coupling reactions. The details will be discussed.



2 3 4 1 5 6 7

Acknowledgment. This work is supported by the Department of Chemistry, HKUST and the University Grants Committee (through an Areas of Excellence Scheme, AoE/P-10/01) of the Hong Kong Special Administrative Region, China.

References:

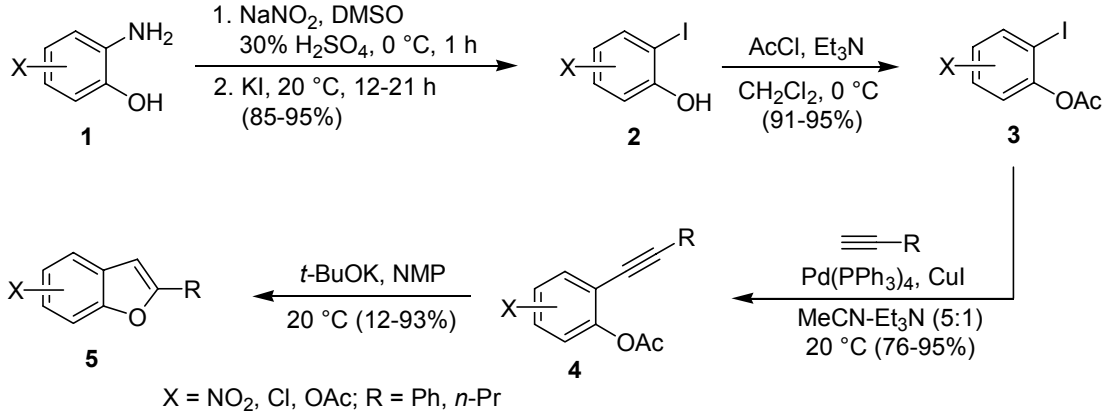
1. For a leading reference, see: Yin, J.; Rainka, M. P.; Zhang, X.-X.; Buchwald, S. L. *J. Am. Chem. Soc*. **2001**, *124*, 1162.
2. Dai, W.-M.; Zhang, Y. the preceding paper.

PP-80. General Synthesis of Functionalized Benzo[*b*]furans via a Coupling–Cyclization Approach

Wei-Min Dai* and Kwong Wah Lai
Department of Chemistry, The Hong Kong University of Science and Technology, Clear Water Bay, Kowloon, Hong Kong SAR, China

The palladium-catalyzed cross-coupling–cyclization of iodoanilines or iodoanilides with alkynes has been successfully used in the synthesis of heterocyclic compounds such as indoles and benzo[*b*]furans. In our previous work, we have developed general syntheses of functionalized indoles via the coupling–cyclization approach using the commercially available and inexpensive 2-aminophenols as the starting materials.[1] For example, C4-, C5-, C6-, and C7-nitroindoles and their derivatives were synthesized.[1b] It is of interest for us to expand the chemistry into other heterocycle synthesis. Reported here is the synthesis of functionalized benzo[*b*]furans from same 2-aminophenols **1**.[2]

We activated the aminophenols **1** by converting them into the iodophenols **2** through a one-pot diazotization-iodination procedure in high yields. Compounds **2** were then protected as the acetates **3** which underwent the Sonogashira cross-coupling with 1-alkynes to give **4** in high yields. Finally, the benzo[*b*]furans **5** were obtained through a 5-*endo-dig* cyclization mediated by *t*-BuOK. The chemical yields were high for non-nitro substituted benzo[*b*]furans. Low yield was observed for 4-nitrobenzo[*b*]furan **5** (X = 4-NO_2, R = *n*-Pr, 12%). Nevertheless, the current work represents the first synthesis of nitrobenzo[*b*]furans **5** (X = NO_2) via the coupling–cyclization approach. Results of the one-pot synthesis of benzo[*b*]furans **5** directly from 2-iodophenols **2** will be discussed as well.



Acknowledgment. This work is supported by the Department of Chemistry, HKUST and the University Grants Committee (through an Areas of Excellence Scheme, AoE/P-10/01) of the Hong Kong Special Administrative Region, China.

References:
1. (a) Dai, W.-M.; Guo, D.-S.; Sun, L.-P. *Tetrahedron Lett*. **2001**, *42*, 5275. (b) Dai, W.-M.; Sun, L.-P.; Guo, D.-S. *Tetrahedron Lett*. **2002**, *43*, 7699.
2. Dai, W.-M.; Lai, K. W. *Tetrahedron Lett*. **2002**, *43*, 9377.

PP-81. Characterization of Intermediates in the Action of Enediyne Prodrugs Equipped with a Base Activation Trigger

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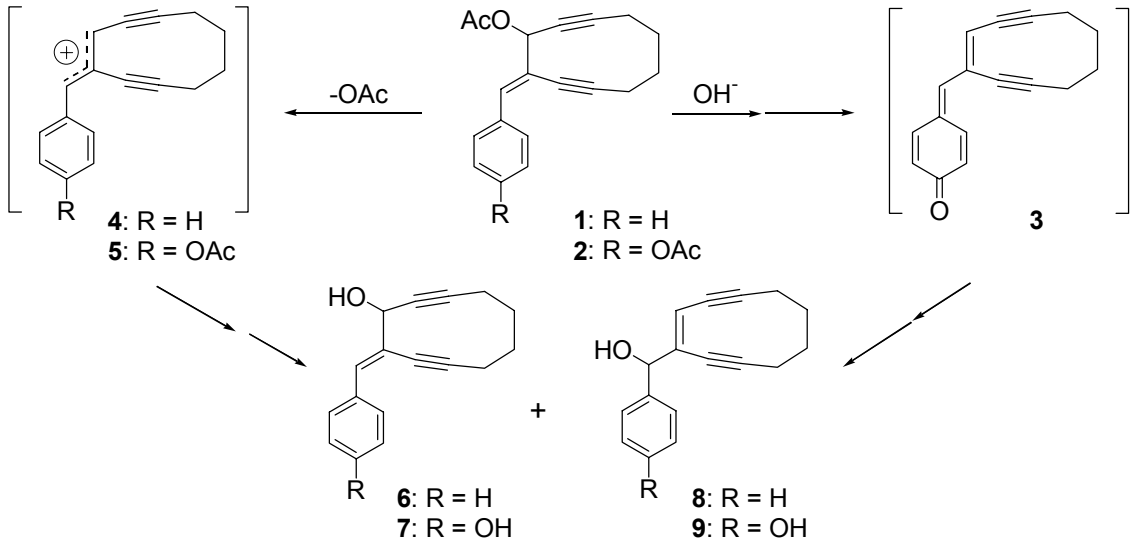
Department of Chemistry, The Hong Kong University of Science and Technology, Clear Water Bay, Kowloon, Hong Kong SAR, China

In the continuation of our research on the formation of enediynes through rearrangement of an allylic double bond,[1-3] we have recently established a novel strategy for design and synthesis of enediyne prodrugs such as **1**.[4] The LC-MS analyses of an incubation mixture of 1 in buffer (pH 8.5, 37 °C) confirmed the formation of the bioactive 10-membered ring enediyne **8**, presumably formed from trapping the allylic carbocation **4** by water.[4]

We report here the chemical synthesis, DNA cleaving potency, and cytotoxicity of the *para*-substituted enediyne prodrugs such as **2** equipped with a base-sensitive triggering group. We expect that the allylic rearrangement via the carbocation **5** should be hampered by the relative instability of **5** compared to **4** while the phenolic acetate moiety in **2** readily undergoes saponification followed by rearrangement into the quinone methide **3**. The latter reacts with a nucleophile such as H_2O to form **7** and **9**, respectively. The LC-MS data have confirmed the formation of **7** and **9** together with their phenolic acetates. Effects of pH and incubation time on the relative abundance of the products will be discussed in detail.



Acknowledgment. This work is supported by the Department of Chemistry, HKUST.

References:
1. Dai, W.-M.; Fong, K. C.; Danjo, H.; Nishimoto, S. *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 779.
2. Dai, W.-M.; Fong, K. C.; Lau, C. W.; Zhou, L.; Hamaguchi, W.; Nishimoto, S. *J. Org. Chem.* **1999**, *64*, 682.
3. Dai, W.-M.; Wu, J.; Fong, K. C.; Lee, Y. H.; Lau, C. W. *J. Org. Chem*. **1999**, *64*, 5062.
4. Dai, W.-M.; Lai, K. W.; Wu, A.; Hamaguchi, W.; Lee, M. Y. H.; Zhou, L.; Ishii, A.; Nishimoto, S. *J. Med. Chem*. **2002**, *45*, 758.

PP-82. Enediyne Prodrugs Equipped with a Hydroxy Group that Can Facilitate an Allylic Rearrangement

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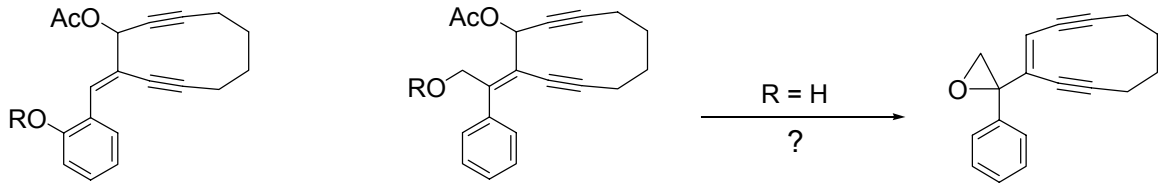
[a]*Department of Chemistry, The Hong Kong University of Science and Technology, Clear Water Bay, Kowloon, Hong Kong SAR, China*
[b]*Department of Energy and Hydrocarbon Chemistry, Graduate School of Engineering, Kyoto University, Sakyo-ku, Kyoto 606-8501, Japan*

As described in the preceding paper,[1] we have established the rearrangement of an allylic double bond in the formation of enediynes.[2-5] We have successfully applied this strategy in design and synthesis of enediyne prodrugs.[5] We report here the synthesis of enediyne prodrugs **1** and **2** possessing an ortho oxygen functionality. Compound **1** is expected to undergo the rearrangement of the exo double bond into the 10-membered ring enediyne in a similar manner as that established for the para analog.[1]

Progress in the synthesis of compounds **3** and **4** will be discussed. With the hydroxymethyl group attached at the exocyclic double bond in **3**, it is assumed that an intramolecular S_N2'-type of rearrangement could be possible to form both the 10-membered ring enediyne and the epoxy units in **5**. Compound **5** is interesting in its possible modes of action on DNA originating from the enediyne (sp^2 carbon-centered radical) and the epoxy (base alkylating agent) moieties. Progress in these aspects will be discussed.



1: R = H
2: R = $SiMe_2t$-Bu

3: R = H
4: R = $SiMe_2t$-Bu

5

Acknowledgment. This work is supported by the Department of Chemistry, HKUST.

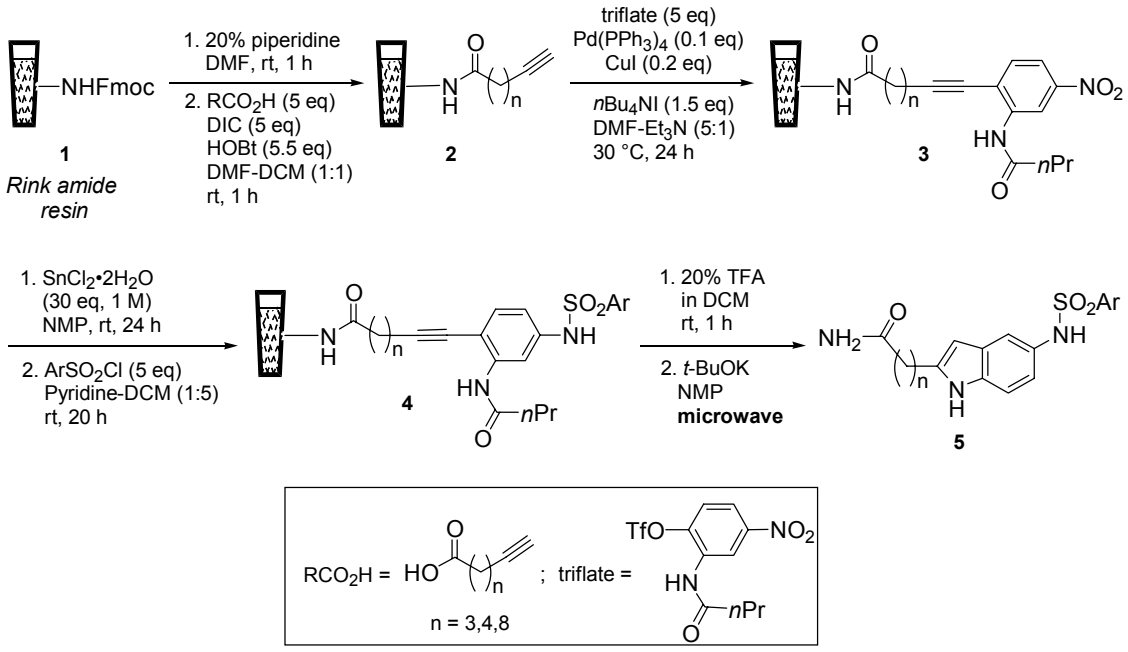
References:

1. Dai, W.-M.; Lai, K. W. the preceding paper.
2. Dai, W.-M.; Fong, K. C.; Danjo, H.; Nishimoto, S. *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 779.
3. Dai, W.-M.; Fong, K. C.; Lau, C. W.; Zhou, L.; Hamaguchi, W.; Nishimoto, S. *J. Org. Chem.* **1999**, *64*, 682.
4. Dai, W.-M.; Wu, J.; Fong, K. C.; Lee, Y. H.; Lau, C. W. *J. Org. Chem*. **1999**, *64*, 5062.
5. Dai, W.-M.; Lai, K. W.; Wu, A.; Hamaguchi, W.; Lee, M. Y. H.; Zhou, L.; Ishii, A.; Nishimoto, S. *J. Med. Chem*. **2002**, *45*, 758.

PP-83. Generation of Indole Libraries Using a Combination of Microreactors and Microwave-Assisted Organic Synthesis

Wei-Min Dai,* Dian-Shun Guo, Li-Ping Sun, and Xianghong Huang
Combinatorial Chemistry Laboratory, The Biotechnology Research Institute and Department of Chemistry, The Hong Kong University of Science and Technology, Clear Water Bay, Kowloon, Hong Kong SAR, China

In connection with our program toward generation of indole libraries, we have developed a novel synthesis of functionalized indoles starting from the commercially available and inexpensive 2-aminophenoles via a cross-coupling and cyclization approach.[1,2] We have attempted the generation of indole libraries according to our indole synthesis. One example is illustrated below. Using the microreactors encoded with a radiofrequency (Rf) tag, the alkynes were loaded onto the Rink amide resin to give **2**. The Pd-catalyzed cross-coupling of **2** with the triflate in the presence of CuI and *n*-Bu_4NI (as the additive)[1,2] afforded **3**, which was transformed into the sulfonamides **4** in excellent yields and purities as checked, after cleavge from the resin, by LC-MS and NMR. However, cyclization of **4** on the solid support met difficulties under the basic conditions (*t*-BuOK, NMP) used for the solution reactions.[1,2] Therefore, compounds **4** were cleaved from the resin and were subjected to the base-mediated cyclization under microwave irradiation. Microwave-assisted organic synthesis has been known to dramatically enhance the reaction rate at high temperature. This advantage provides a solution to overcome the difficult steps in combinatorial chemistry. The details will be discussed along with other examples of indole library syntheses.



Acknowledgment. This work is supported by the Innovation and Technology Fund of the Hong Kong Special Administrative Region, China (ITS/119/00) to L.-P. Sun, the HKUST Post Doctoral Fellowship Matching Fund to D.-S. Guo, and the Department of Chemistry, HKUST to X. Huang.

References:
1. Dai, W.-M.; Guo, D.-S.; Sun, L.-P. *Tetrahedron Lett*. **2001**, *42*, 5275.
2. Dai, W.-M.; Sun, L.-P.; Guo, D.-S. *Tetrahedron Lett*. **2002**, *43*, 7699.

PP-84. Solvent Effect of DMSO on the Chemical Shifts of Phenyl Vinyl Ketones

Jin-Cherng Lien,* Sheng-Chih Chen, Li-Jiau Huang, and Sheng-Chu Kuo
Graduate Institute of Pharmaceutical Chemistry, China Medical College, Taichung 404, Taiwan

In our study on the 1D and 2D NMR spectra of synthetic chalcones in DMSO-d_6, we found that, contrary to our expectation, the signals of α-carbon correlated to the olefinic protons resonating at lower field whereas the signals of β-carbon correlated to the olefinic protons resonating at higher field in the spectra of chalcones. To further investigate such solvent effect, four α,β-unsaturated ketones were prepared and studied separately in $CDCl_3$ and DMSO-d_6. The result indicated that the α,β-unsaturated ketones that possess benzoyl moiety experienced solvent effect in DMSO-d_6 to result in an anomalous chemical shift. The shift arose from the complexation of solute molecule with DMSO that fixed the steric conformation of solute molecule so that H_β was kept apart from its benzene ring whereas its H_α (Figure 1) became more accessible by its benzene ring. Thus, these two olefinic protons would experience different extent of anisotropic effect exerted by the neighboring benzene ring.

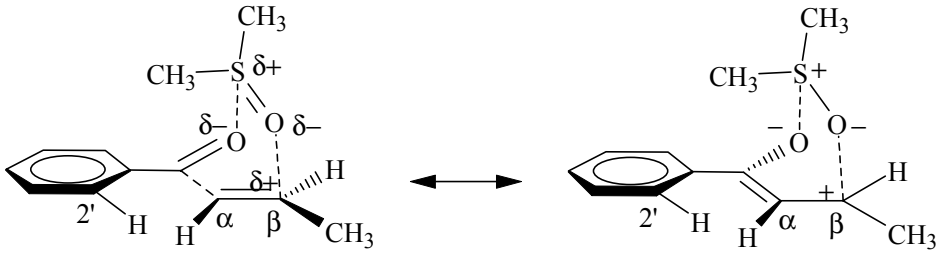


Figure 1. The complex of DMSO-d_6 and (*E*)-1-phenyl-2-buten-1-one

References:
1. Ritchie, C. D.; Lewis, E. S. *J. Am. Chem. Soc.* **1962**, *84*, 591-594.
2. Ritchie, C. D.; Bierl, B. A.; Honour, R. J. *J. Am. Chem. Soc.* **1962**, *84*, 4687-4692.
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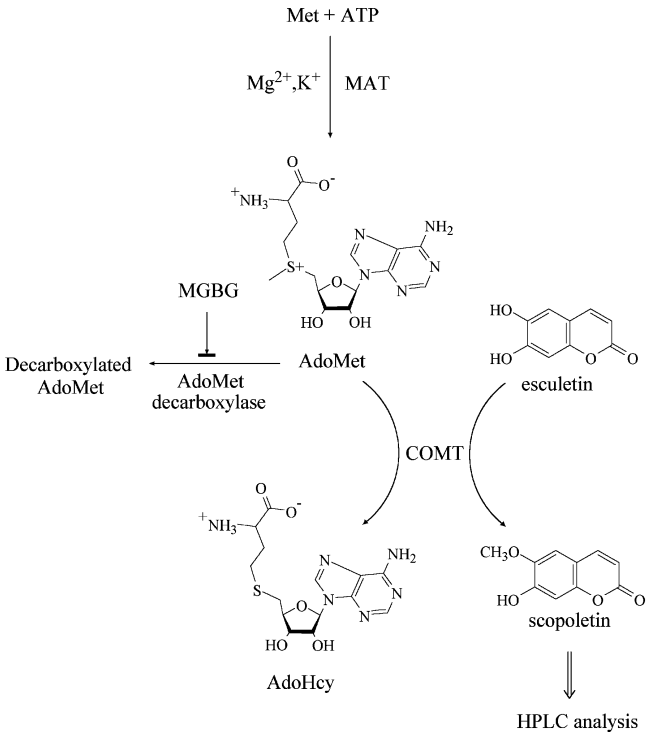
4. Ritchie, C. D.; Pratt, A. *J. Am. Chem. Soc.* **1964**, *86*, 1571-1576.

PP-85. HPLC Determination of Methionine Adenosyltransferase Activity Using COMT-Coupled Fluorometric Detection

Sheng-Horng Wang, Sheng-Chu Kuo, and Sheng-Chih Chen
Graduate Institute of Pharmaceutical Chemistry, China Medical College, Taichung 404, Taiwan

A non-radioactive, sensitive, rapid and specific method for the determination of methionine adenosyltransferase activity has been established. The methyl group of *S*-adenosyl-L-methionine was enzymatically transferred to esculetin with the aid of catechol-*O*-methyltransferase (Scheme 1) and then the resulting scopoletin was extracted with *n*-hexane:ethyl acetate (7:3, v/v) and measured by high-performance liquid chromatography with Si 60 column and fluorometric detection with excitation and emission wavelengths at 347 and 415 nm, respectively. The detection limit for scopoletin was about 100 fmol per injection volume of 40 μL. Using this method to determine MAT activity in HL-60 cells required as little as 2.5 μg of protein and the incubation time for enzymatic reaction could be less than 30 min. The HPLC analysis time was only 5 min per sample. The kinetic study showed that MAT in HL-60 cells exhibited negative cooperativity with a Hill coefficient of 0.5. The values of K_m and V_{max} were 4.1 ± 0.2 μM and 122.0 ± 1.2 nmol AdoMet formed/mg protein/h, respectively.



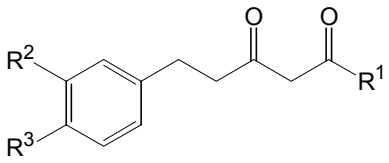
Scheme 1. COMT-coupled fluorometric assay of MAT activity

References:
1. Kotb, M.; Mudd, S. H.; Mato, J. M.; Geller, A. M.; Kredich, N. M.; Chou, J. Y.; Cantoni, G. L. *Trends. Genet.* **1997,** *13*, 51-2.
2. Thomas, H.; Veser, J.; Muller-Enoch, D. *Hoppe. Seylers. Z. Physiol. Chem.* **1976**, *357*, 1347-1351.

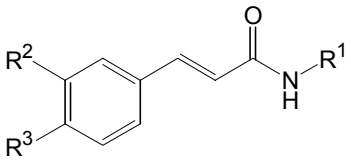
PP-86. Anticancer Activities of Gingerdione and Ferulamide Derivatives

Mei-Hua Hsu, Li-Jiau Huang, Ya-Yun Lai, Chun-Jen Chen, and Sheng-Chu Kuo*
Graduate Institute of Pharmaceutical Chemistry, China Medical College, Taichung 400, Taiwan

Gingerdione and ferulamide derivatives were synthesized to evaluate antiproliferation activity against cancer cells. Among gingerdione derivatives, 1-(3,4-dimethoxyphenyl)-3,5-dodecenedione (**8**) and 1-(3,4-dimethoxyphenyl)-3,5-tetradecenedione (**11**) showed the most potent inhibition against HL-60 cells, and 1-(4-hydroxy-3-methoxyphenyl)-3,5-dodecanedione (**2**) and 1-(4-hydroxy-3-methoxyphenyl)-3,5-tridecanedione (**3**) and 1-(4-hydroxy-3-methoxyphenyl)-3,5-tetradecanedione (**4**) had moderate inhibition against U937 cells. Among the synthesized ferulamide derivatives, *N*, *N*-dimethylferulamide (**22**) was the most potent compound on the inhibition of cell proliferation on both HL-60 and U937 cells. These finding demonstrated that these novel synthesized compounds could be useful for the treatment of leukemia.



Gingerdione derivatives



Ferulamide derivatives

PP-87. Studies on Useful Substance Production by Callus Culture for *Flemingia macrophylla*

Wen-Ju Hu,[a*] Hui-Ya Ho,[b] and Jin-Bin Wu[b]
[a]*Graduate Institute of Chinese Pharmaceutical Sciences, China Medical College, Taichung 404, Taiwan*
[b]*Graduate Institute of Pharmaceutical Chemistry, China Medical College, Taichung 404, Taiwan [E-mail: jbwu@mail.cmc.edu.tw]*

Chien-Chin-Pa (*Flemingia macrophylla*; Leguminosae) was firstly recorded in Chu-Wu-Ming-Shih-Tu-Kao of Chin Dynasty. It is a perennial shrub, which is distributed mainly in Taiwan and in southeast Asia. As a folklore medicine, this plant is used for treating rheumatism and arthritis. Genistin is the major component of its methanolic extracts. In the study, the callus was subculturing on different medium and the different ratio of isoflavones were produced. The metabolites were determinated by HPLC.

The best medium was Modified B5 medium for the content of genistin in callus. On the constract, the best medium for genistein produced was Modified white medium. The dried callii contain 15 times of genistein than the plants which grew 5 years. This experiment about involving isoflavones is still kept on working and the biological activities of the methanolic extracts for two different callii are currently under investigation.

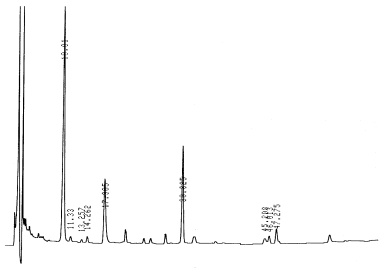


Figure 1. The HPLC spectrum for the methanolic extracts of the plants

References:
1. Wu, J.-B.; Cheng, Y.-D.; Su, L.-L.; Kuo, C.-W.; Kuo, S.-C. *Phytochemistry* **1997**, 1727-1728.
2. Hu, W.-J.; Ho, H.-Y.; Wen, C.-C.; Liao, J.-C.; Wu, J.-B. *17TH Symposium on Natural Products and Biotechnology of Chinese Herbs*, **2002**, pp 173-174.

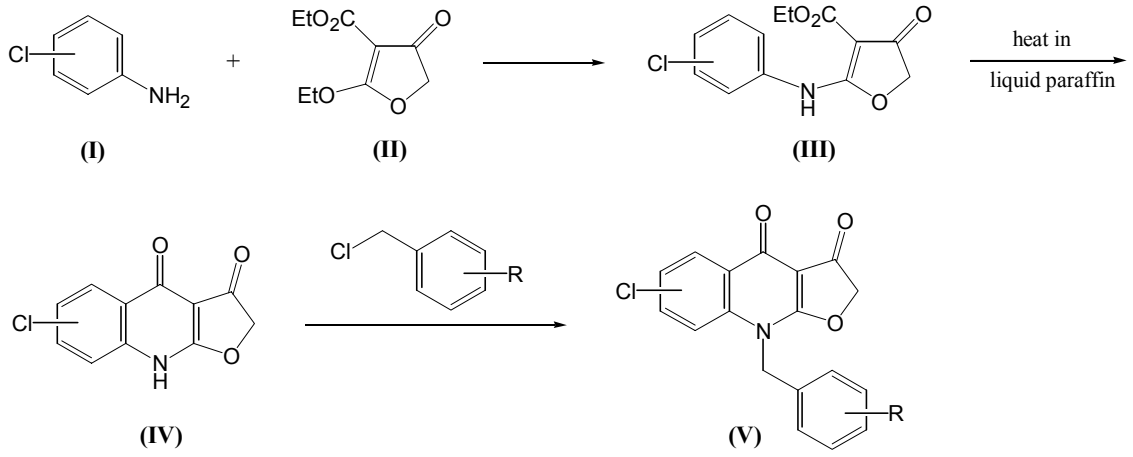
PP-88. Synthesis, Anti-allergic and Anti-inflammatory Activities of *N*-Substituted Benzyl-6(or 7)-chloro-2,3,4,9-tetrahydrofuro[2,3-*b*]quinolin-3,4-diones

Ruoh-Tyng Tseng ( ),[a] Tsung-Ping Lin ( ),[a] Chien-PingChang ( ),[a] and Jih-Pyng Wang ( )[b]

[a]*Graduate Institute of Pharmaceutical Chemistry, China Medical College, Taichung 400, Taiwan*

[b]*Department of Medical Reaserch, Taichung Verterans General Hospital, Taichung, Taiwan*

A series of *N*-substituted benzyl-6 (or 7)-chloro-2,3,4,9-tetrahydro[2,3-*b*]quinolin-3,4-diones were synthesized, and evaluated for anti-allergic and anti-inflammatory activities by inhibition of mast cell degranulation, neutrophil degranulation, and superoxide formation in neutrophils. In general, 7-chloro-substituted derivatives showed more inhibitory activity at 30 μM; on the other hand, 6-chloro-substituted derivatives showed stronger inhibition during fMLP-induced superoxide formation in neutrophils and *N*-*p*-methoxybenzyl-6-chloro-2,3,4,9-tetrahydrofuro[2,3-*b*]quinolin-3,4-dione displayed the greatest effect at 30 μM. The synthetic pathway is shown in Scheme 1.



Scheme 1. Synthetic pathway of tetrahydrofuro[2,3-*b*]quinolin-3,4-diones

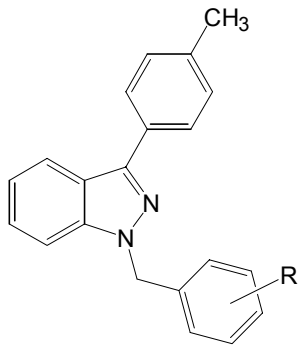
Reference:

1. Lin, T. P.; Chang, C. P.; Tseng, R. T, ; Wang, J. P. *Chin. Pharm. J.,* **2002,** *54(2),*115-126.

PP-89. Anticancer Activities of 3-(4-Methylphenyl)-1*H*-indazole Derivatives

Yi-Chian Lin, Wei-Ling Shih, Hwu-Sin Chen, Sheng-Chu Kuo, and Li-Jiau Huang*
Graduate Institute of Pharmaceutical Chemistry, China Medical College, Taichung 400, Taiwan

3-(4-Methylphenyl)-1*H*-indazole **(1)** was used as the key intermediate and its derivatives 1-substituted benzyl-3-(4-methylphenyl)-1*H*-indazoles **(2–8)** were synthesized to evaluate antiproliferation activity against cancer cells. Compound **5** and compound **8** were found to be the most effective on the cell proliferating inhibition, and the IC_{50} cytotoxicity values were between 2.0-4.3 μM on human leukemia cells (HL-60, U937). These results indicated that the impressive ability of 3-(4-methylphenyl)-1*H*-indazole derivatives to inhibit the growth of human leukemia cells might make them good candidates as novel anticancer agents.



1-Substituted benzyl- 3-(4-methylphenyl)-1*H*-indazole derivatives

TP-1. Highly Efficient and Automated Microwave-Assisted Organic Synthesis through Coherent Synthesis™

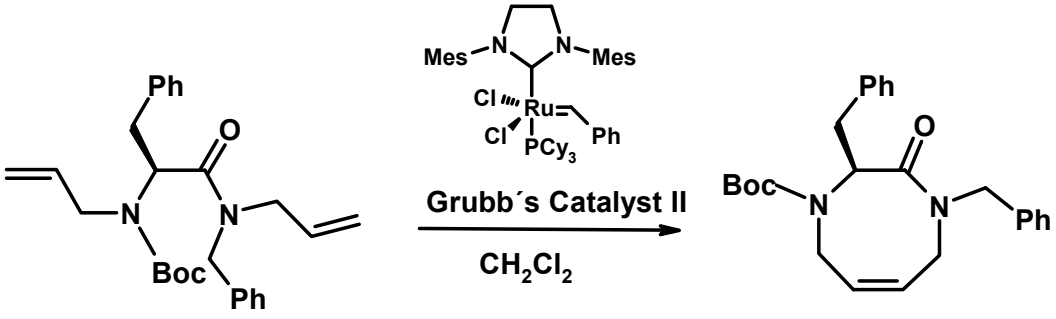
Vijay Gupta
Personal Chemistry AB, Kungsgatan 76, SE-753 18, Uppsala, Sweden
[E-mail: vijay.gupta@personalchemistry.com]

Microwave-assisted organic synthesis has been used for over 10 years, resulting in over 1000 publications. However, concerns for reaction reproducibility and safety hampered the adoption of this powerful technique. Introduction of Coherent Synthesis technology later enabled precise temperature and pressure controls in closed systems as well as reaction reproducibility and safety. In closed systems the organic solvents can be heated to temperatures and pressures, much higher than their boiling points, which allows for significant (a hundred fold) shorter reaction times than those obtained in open microwave systems.

Coherent Synthesis knowledge management system, in addition, allows for reaction warehousing, search tools, reaction browsers, conversion of search results to executable experiments and post-synthesis data capture, thereby, helping to increase the overall efficiency of chemistry development.

Coherent Synthesis allows for highly automated liquid handling and fast synthesis of novel building blocks, reaction optimization, and production of focused libraries. It has been successfully used for both solution-phase and solid-phase syntheses with substantially reduced reaction times and typically increased yields.

A number of interesting and useful organic syntheses have been reported with Coherent Synthesis and will be discussed in the presentation e.g., following 8-membered ring-closing metathesis reaction was carried out in only 6.6 minutes using Emrys™ Synthesizer.



Coherent Synthesis™: 6.6 min, 125 °C, 70%

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The Third International Symposium for Chinese Medicinal Chemists

第三屆世界華人藥物化學研討會

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COVER LOGO:
The logo was designed on the basis of the molecular skeleton of the antimalarial drug, Qinghaosu (artemisinin) isolated from *Artemisia annua*. The logo features a cartoon boy wearing a pair of 2002 glasses (the peroxy moiety) and a red-colored ISCMC jacket.

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