International Joint Seminar between
School of Pharmaceutical Sciences, Peking University, &
School of Pharmacy/Pharmaceutical Sciences, Kanazawa University
in Kanazawa

大学部局間国際交流協定に基づく
北京大学薬学院・金沢大学薬学系 学術交流セミナー
（金沢大学薬学シンポジウム）

March 8 [FRI], 2013. 14:00-17:00

- Lecture Room 101, Natural Science Building, Kanazawa University, Japan
- Organizer; Kanazawa University, School of Pharmacy/Pharmaceutical Sciences

- Program -

14:00-14:10
Opening Speech / 開会の挨拶
Professor Kazuichi HAYAKAWA (Kanazawa University) / 早川和一 教授（金沢大学薬学系長）

14:10-14:50
"Design, synthesis and antitumor and antiviral activities of allosteric MEK1 inhibitors"
Chao WANG (Peking University) / 王超（北京大学，博士課程）

14:50-15:30
"Total Syntheses of Indole Alkaloids"
Masaya MIZUTANI (Kanazawa University) / 水谷仁弥（金沢大学，博士後期課程）

15:30-16:10
"Study on in vivo metabolism of Paeoniae Radix Rubra"
Jing LIANG (Peking University) / 梁静（北京大学，博士課程）

16:10-16:50
"Pathophysiological role of microRNAs regulating transcriptional factors in human liver"
Yuki ODA (Kanazawa University) / 小田祐輝（金沢大学，博士後期課程）

16:50-17:00
Closing Speech / 閉会の挨拶
Professor Ping XU (Peking University) / 徐萍 教授（北京大学药学院副院长）

18:00- Welcome Party at Yakugaku Presentation Room

１８時より，薬学プレゼンテーション室にて歓迎懇親会が開催されます．教員，学生の皆様の積極的なご参加をお待ちしております．
参加費：500 円

Design, synthesis and antitumor and antiviral activities of allosteric MEK1 inhibitors

Chao WANG (Peking University)

ABSTRACT: To discover novel antitumor and antiviral agents, a series of novel non-biarylamine structures were designed and synthesized as allosteric MEK1 inhibitors. Some of them showed obvious inhibition to ERK pathway and displayed excellent MEK1 binding and inhibitory potency. Cell-based assays suggested that they can significantly inhibit tumor proliferationandvirus replication. These compounds will be potential antitumor and antiviral candidates used for the treatment of cancer and viral disease.

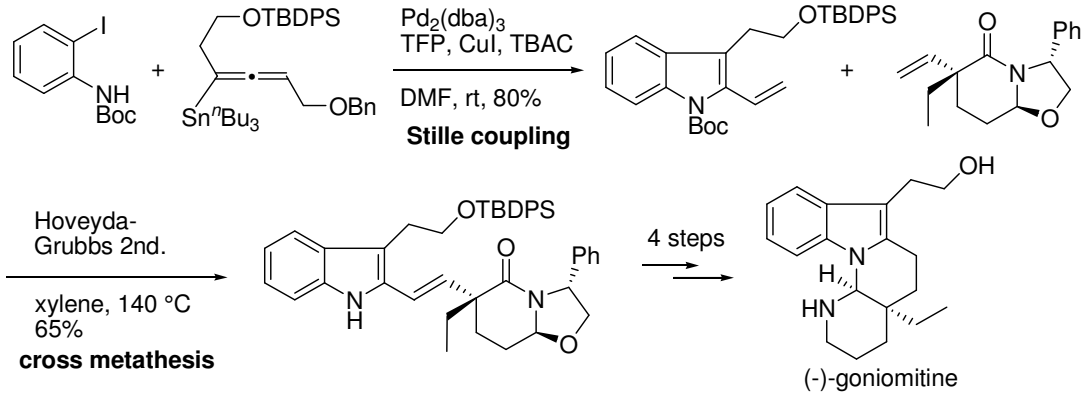
Total Syntheses of Indole Alkaloids

○Masaya Mizutani, Fuyuhiko Inagaki and Chisato Mukai

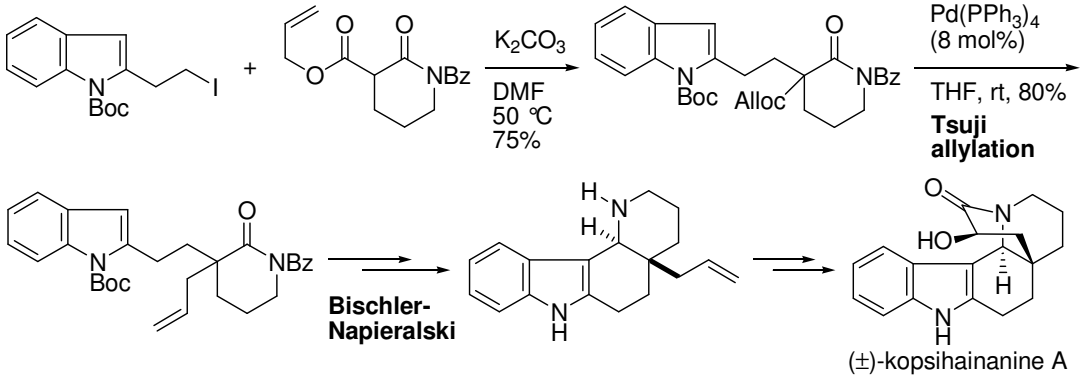
Division of Pharmaceutical Sciences, Graduate School of Natural Science and Technology, Kanazawa University

Indole alkaloids are one of the most attractive natural products with a wide range of biological and pharmacological activities. For better understanding of their bioactivity, development of efficient synthetic procedure and plentiful supply of them are of great significance in pharmaceutical research field. The presentation contains our recent achievement, focusing on total syntheses of goniomitine and kopsihainanine A.

The Stille coupling reaction of 3-(benzyloxymethyl)-1-(*tert*-butyldiphenylsiloxy)-ethyl-1-(tributylstannyl)allene with *N*-(*tert*-butoxycarbonyl)-2-iodoaniline directly produced the corresponding 2-vinylindole derivative, which was independently transformed into natural (-)-goniomitine and unnatural (+)-goniomitine via the cross-metathesis with chiral oxazolopiperidone lactams. Their preliminary bioactive assay revealed that natural (-)-goniomitine has stronger antiproliferative activity than (+)-goniomitine.[1]



Furthermore, the total synthesis of (±)-kopsihainanine A has been achieved via Tsuji allylation, Bischler-Napieralski reaction and biomimetic lactamization. Asymmetric Tsuji allylation was also examined for the enantioselective synthesis of the natural product.



1) Mizutani, M.; Inagaki, F.; Nakanishi, T.; Yanagihara, C.; Tamai, I.; Mukai, C. *Org. Lett.* **2011**, *13*, 1796-1799.

Jing LIANG
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Abstract

(Title: Study on the metabolism of Paeoniae Radix Rubra decoction)

Paeoniae Radix Rubra (PRR, the dried roots of *Paeonia lactiflora*) is a commonly used traditional Chinese medicine (TCM). A clear understanding of the absorption and metabolism of TCMs is very important to their rationally clinical use and pharmacological research. To find more absorbed constituents and metabolites of TCMs, a novel strategy was proposed, which was characterized by the establishment and utilization of the databases of parent compounds, known metabolites and characteristic neutral losses, the comparison of base peak chromatograms and CLogPs, and the use of HPLC-DAD-ESI-IT-TOF-MS^n technique. Then this strategy was firstly applied to screen and identify the absorbed constituents and metabolites of PRR decoction in rats. Totally, 13 new absorbed constituents and 90 new metabolites of PRR decoction were detected. Among these metabolites, the structures of 70 metabolites were identified and the conjugation types and structure skeletons of the other 20 metabolites were preliminarily determined. Moreover, 35 new metabolites of some constituents of PRR, i.e., 22 new metabolites of paeoniflorin, 10 new metabolites of gallic acid-related compounds, 1 new metabolites of (epi)catechin-related compounds, and 2 new metabolites of other compounds were reported for the first time. The results also indicated that (epi)catechin-related compounds, gallic acid-related compounds and paeoniflorin were the main precursors of these metabolites. Phase I reactions (dehydroxylation, decarboxylation, dehydrogenation) and phase II reactions (sulfation, glucuronidation and methylation) were observed as the main metabolic pathways of PRR.

Pathophysiological role of microRNAs regulating transcriptional factors in human liver

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MicroRNAs (miRNAs) are newly found regulators of gene expression by inhibiting the translation or promoting the degradation of target mRNAs. Recently, we found that miRNAs were involved in the regulation of some human transcriptional factors such as pregnane X receptor, vitamin D receptor, hepatocyte nuclear factor 4α and peroxisome proliferator-activated receptor α [1-4] regulating various genes encoding drug-metabolizing enzymes and drug transporters. To expand our knowledge, this study was conducted to disclose the pathophysiological role of miRNAs regulating human aryl hydrocarbon receptor nuclear translocator (ARNT) and retinoid X receptor α (RXRα).

ARNT forms a heterodimer with aryl hydrocarbon receptor or hypoxia inducible factor 1α to mediate biological responses to xenobiotic exposure and hypoxia. The overexpression of miR-24 into HuH-7 cells significantly decreased the ARNT protein level, but not mRNA level, indicating translational repression. The miR-24-dependent down-regulation of ARNT decreased the expression of its downstream genes such as CYP1A1 and carbonic anhydrase IX. The miR-24 levels in a panel of 26 human livers were inversely correlated with the protein levels or the translational efficiency of ARNT. Thus, we found that miR-24 negatively regulated ARNT expression in human liver, and thereby may modulate response to xenobiotic exposure.

RXRα forms a heterodimer with numerous nuclear receptors to regulate the expression of drug- or lipid-metabolizing enzymes. We found by luciferase assays using HEK293 cells that miR-34a recognizes the element in the coding region but not that in 3'-UTR. The overexpression of miR-34a significantly decreased the RXRα protein and mRNA level in HepG2 cells. The miR-34a facilitated the degradation of the RXRα mRNA. We found that the miR-34a-dependent down-regulation of RXRα decreased the induction of CYP26 and transactivity of CYP3A4. The miR-34a has been reported to be up-regulated by p53 which has an ability to promote liver fibrosis. We found that the increase of miR-34a expression caused by the p53 activation led to down-regulation of RXRα. Interestingly, the miR-34a levels in 8 fibrotic livers were higher than those of 6 normal livers. In contrast, the RXRα protein levels in fibrotic livers were lower than those of normal livers. Taken together, we found that miR-34a negatively regulated the expression of human RXRα, affecting the expression of its downstream gene and playing a role in the promotion of fibrosis.

In conclusion, it was clearly demonstrated that human ARNT and RXRα are negatively regulated by miRNAs. These regulatory mechanisms would affect the metabolism and pathology in the liver.

References:

(1) Takagi S, Nakajima M, Mohri T and Yokoi T. J. Biol. Chem., 283: 9674-9680 (2008).
(2) Mohri T, Nakajima M, Takagi S, Komagata S and Yokoi T. Int. J. Cancer, 125: 1328-1333 (2009).
(3) Takagi S, Nakajima M, Kida K, Yamaura Y, Fukami T and Yokoi T. J. Biol. Chem., 285: 4415-4422 (2010).
(4) Kida K, Nakajima M, Mohri T, Oda Y, Takagi S, Fukami T and Yokoi T. Pharm. Res., 28: 2467-2476 (2011).