



**Trip Report:
5th International Symposium for Chinese
Medicinal Chemists
Nanjing, P.R., China
November 2- 7, 2006**

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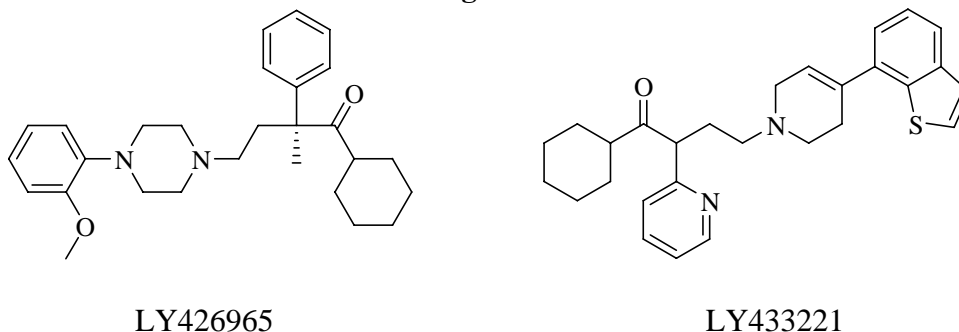
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***Abstract:** The 5th International Symposium for Chinese Medicinal Chemists (ISCMC, 2006) was held in Nanjing, China from Nov. 2-7, 2006. ISCMC, 2006 was organized by China Pharmaceutical University and co-sponsored by the Division of Medicinal Chemistry, China Pharmaceutical Association and Simcere Pharmaceutical Group. More than 400 attendees from different countries around the world attended this conference. Seven plenary lectures, twenty eight invited lectures and nearly one hundred poster presentations covered the areas of medicinal chemistry, organic synthesis, process chemistry and computational chemistry for drug discovery. This report highlights selected material presented at this conference.*

“A Mechanism Based Approach for New Treatment of Depression by Combining 5-HT_{1a} Receptor Antagonist and Serotonin Reuptake Inhibitor,”

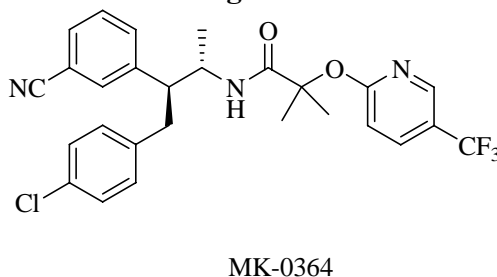
Yao-Chang Xu (Novartis Institutes for BioMedical Research Inc.), Cambridge, MA.

Dr. Xu presented his work carried out at Lilly Research Laboratories. Selective serotonin reuptake inhibitors (SSRIs) have great success in the treatment of depression. However, there are some disadvantages associated with SSRIs including the slow onset of action, unwanted side effects, and the existence of a significant subset of the population that is not responsive to SSRI therapy. It has been hypothesized that the combination of SSRI and selective 5-HT_{1a} receptor antagonist could offer a better treatment of depression with the potential of improving both efficacy and rate of onset over SSRIs alone. Based on this hypothesis, Dr. Xu and his coworkers developed a selective 5-HT_{1a} receptor antagonist, LY426965 (Figure 1) first, and then combined the selective agent with SSRIs to test in the clinic of the mechanism. Further, they pursued to build a single molecule possessing both SSRI activity and 5-HT_{1a} receptor antagonist activity, which led to the development of clinical candidate LY433221 (Figure 1).

Figure 1**“Discovery of a Novel Cannabinoid Inverse Agonist for the Treatment of Obesity,”**

Linus S. Lin (Merck Research Laboratories), Rahway, NY.

It is known that the cannabinoid receptor system is involved in regulating feeding behavior. Cannabinoid-1 receptor (CB₁R) antagonist or inverse agonist has the potential to suppress food intake and reduce body weight. Dr. Lin presented the discovery effort in Merck that led to the identification of MK-0364 (Figure 2), a phase II drug candidate. His talk covered the strategies to optimize potency / in vivo efficacy and approaches to minimize bioactivation /formation of reactive metabolites.

Figure 2

“A Novel Strategy for the Preparation of Chiral α and /or α' -Substituted Pyrrolidines and Piperidines,”

Yuefei Hu (*Tsinghua University-Simcere Pharmaceutical Group Joint Laboratory for Drug Discovery and Department of Chemistry, Tsinghua University, Beijing, China.*)

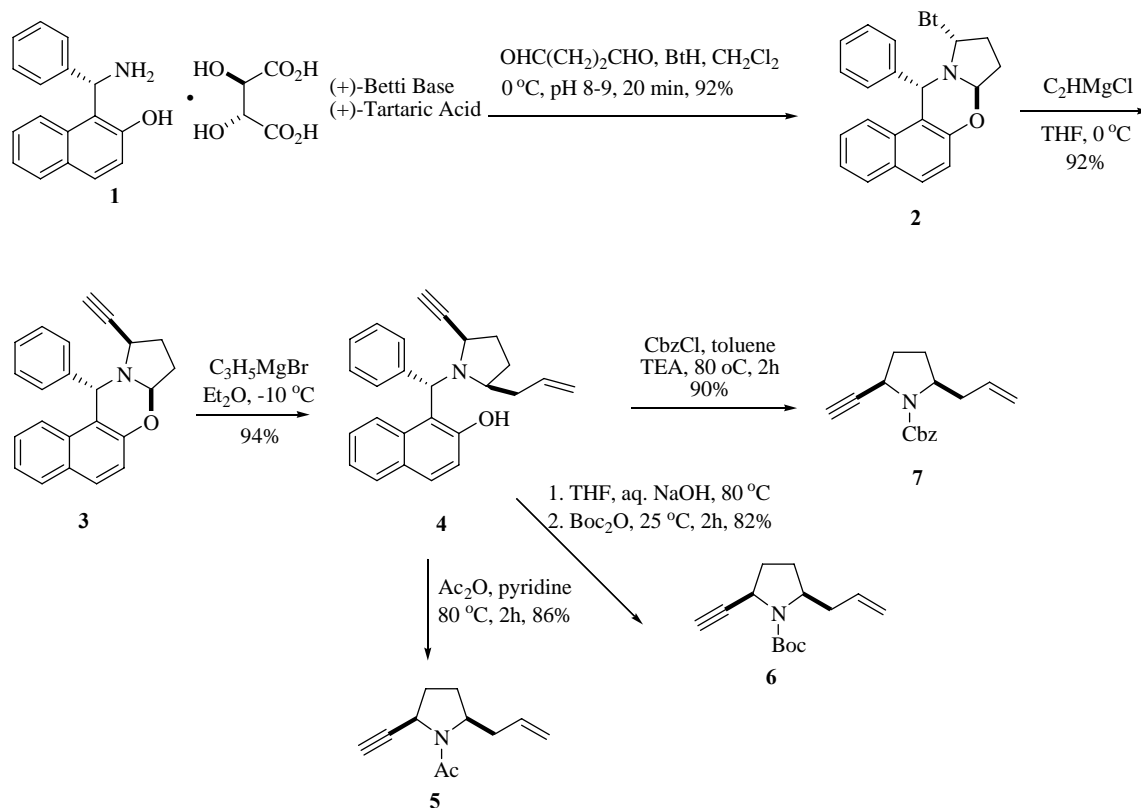
The structure units of substituted pyrrolidines and piperidines (Figure 3) are important moieties occurring in many biologically active compounds. The syntheses of chiral substituted pyrrolidines and piperidines are difficult due to the lack of general and practical methods. In the conference, Dr. Hu presented their new method to build the chiral substituted pyrrolidines and piperidines.

Figure 3



In Scheme 1, the syntheses of chiral substituted pyrrolidines were illustrated. Previously, an efficient kinetic resolution of Betti base (**1**) was developed in Dr. Hu's lab. Starting with one enantiomer of Betti base (**1**), the cyclization with dialdehyde and benzotriazole gave compound **2** in high yield. The first substitute could be installed stereoselectively by the reaction of compound **2** with ethynylmagnesium bromide, which gave compound **3**. The second substitute, if necessary, could be installed stereoselectively by nucleophilic substitution with another Grignard reagent. Using allylmagnesium bromide, compound **4** was obtained. The useful substituted pyrrolidines intermediates **5**, **6** and **7** could be obtained by removing the Betti base template under different reaction conditions.

Scheme 1

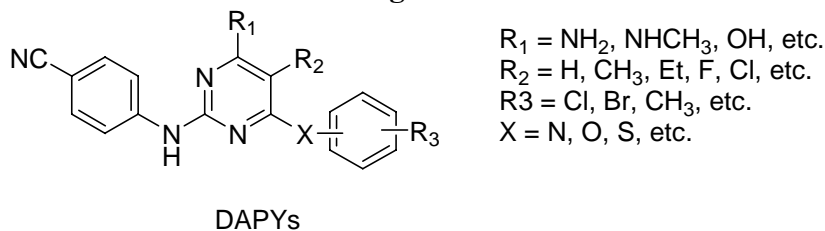


“Non-nucleoside HIV-1 Reverse Transcriptase Inhibitors: Design, Synthesis and Bioactivity of Diarylpyrimiding Analogs (DAPYs),”

Xiaoqing Feng and Fener Chen (Department of Chemistry, Fudan University), Shanghai, China.

Non-nucleoside HIV-1 reverse transcriptase inhibitors (NNRTIs), comparing to nucleoside reverse transcriptase inhibitors (NRTIs), exhibit low toxicity and high potency in the multiple chemotherapeutic treatment. The authors designed and synthesized diarylpyrimidines (DAPYs, Figure 4) and the inhibitory potency against HIV-1 was evaluated (Figure 5). The synthetic route is shown in Scheme 2:

Figure 4



Scheme 2

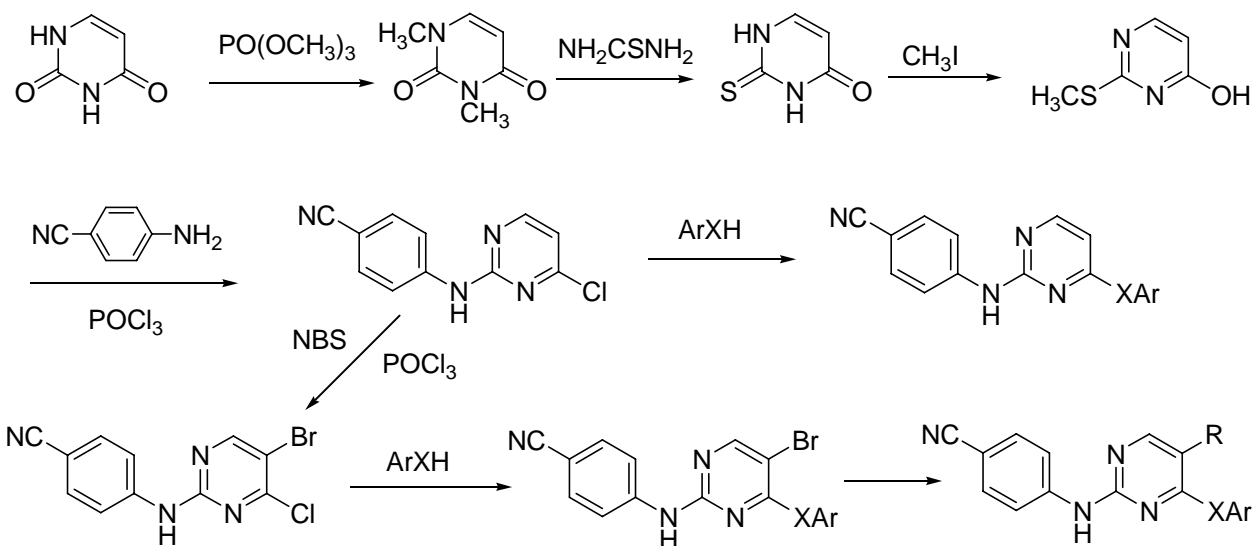
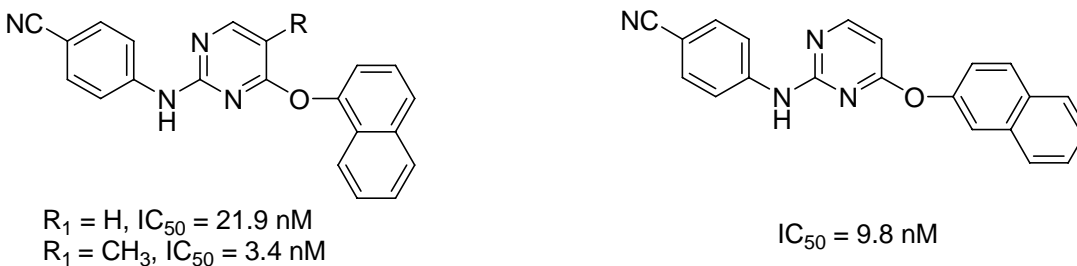
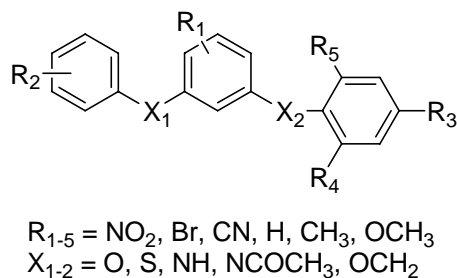


Figure 5



It is interesting that Dr. Xie, from Beijing Institute of Pharmacology & Toxicology, showed a similar scaffold (Figure 6) against NNRITs in another invited lecture in this conference.

Figure 6



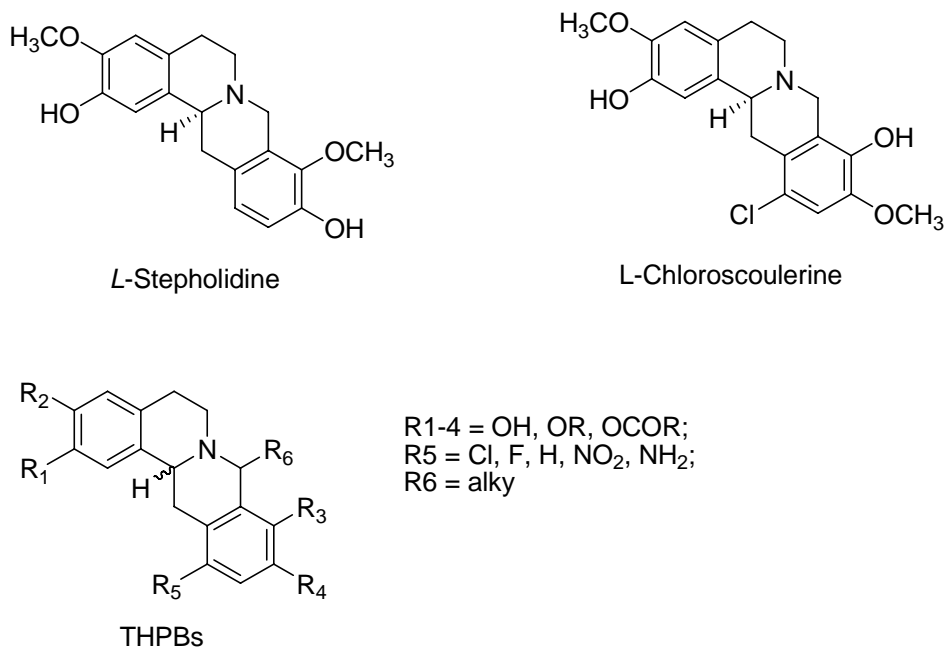
“Synthesis and Pharmacological Profile of Tetrahydroprotoberberine Derivatives as Novel Dopamine Receptor Ligands,”

Jian-Feng Li, Zheng Liu, Ai-Xiang Liu, Jing-Kang Shen, Guo-Zhang Jin, Ru-Yun Ji, Jing-Shan Shen* (Shanghai Institute of Materia Medica, Shanghai Institutes for Biological Sciences, Chinese Academy of Sciences), Shanghai, China.

Schizophrenia is a devastating mental disorder. Current available antipsychotics (typical and atypical) are not effective against all symptoms, such as cognitive impairment.

A new hypothesis is that dopamine D₁ receptors dysfunction is involved in the negative symptoms of schizophrenia whereas the D₂ receptors hyperactivity results in the positive symptoms of this disorder. Therefore an effective antipsychotic drug should be both D₁ agonist and D₂ antagonist.

Figure 7



L-Stepholidine (*L*-SPD, Figure 7), a compound of tetrahydroprotoberberines (THPBs, Figure 7), is a natural product, isolated the Chinese herb *Stephania*. *L*-SPD and its analog, *L*-chloroscoulerine (*L*-CSL, Figure 7) are D₁ agonist and D₂ antagonist. The dual action of these two compounds is consistent with the new theory of the pathogenesis of schizophrenia.

The preliminary clinical trial showed that they are effective in the treatment of schizophrenia. Current studies are focused on improving the low bioavailability of *L*-CSL. Modifications were made on THPBs, which is shown in Figure 7. SAR of these compounds against D₁ and D₂ was evaluated. Some potent compounds will be selected for in vivo studies.