Science Bridges China Research Profile

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SUMMARY OF MY RELEVANT RESEARCH AREAS:

Medicinal Chemistry and Chemical Biology of Bioactive Natural Products

药物化学和具生物活性的天然产品的化学生物学

Primary Research interests:

The research in my group focuses on bioactive natural products, through a combination of natural products chemistry, medicinal chemistry and chemical biology techniques, and in collaboration with researchers in biochemistry, molecular biology, cell biology, pharmacology, computational chemistry/biology, structural biology, to achieve the ultimate goal, discovery and development of natural products based new chemical entities, as well as exploration of their mechanism of action.

Currently, our major concerns lie in the field of discovery of natural products with antitumor and anti-Alzheimer's disease effects, structural optimization and structure-activity relationship (SAR) studies of these natural products and related drug development. Molecular interactions of small molecule ligands, especially bioactive natural products, with biomacromolecules, with the emphasis on microtubules (MTs)/tubulin, P-glycoprotein and beta-secretase, are also extensively explored in my group, through collaborations with experts in relevant fields.

Discovery of bioactive natural products effective against tumors, neurodegenerative diseases, and infectious diseases
(1) *Beta-secretase (BACE-1) inhibitory natural products*. BACE-1 inhibitors are well known for their potentials in the therapy of Alzheimer's disease. Guided by bioassays, we have isolated and identified many BACE-1 inhibitors, including first reported natural products (NPs) based BACE-1 inhibitors, chromone glycosides from *Aloe spp*. and phenolic acids bearing long alkyl chains from *Homalomena occulta*., and other known chemotypes, e.g. flavonoids and stilbene oligomers. Currently we are seeking for more natural products with BACE-1 inhibitory activities, and modifying the structures of bioactive natural products isolated by this group.

(2) *Microtubule/tubulin targeting natural products*. Small molecules targeting microtubule/tubulin can be utilized as anticancer agents, and also found to have potential in the treatment of tauopathies including Alzheimer's disease, infectious diseases such as tuberculosis and malaria. Except known microtubule/tubulin targeting taxane diterpenoids and triterpenoids, we are also trying to discover more chemotypes of natural products.

Structural Activity Relationship Studies of Bioactive Natural Products and Their interactions with Biomacromolecules
(1) *New generation of taxol analogues effective against drug resistant tumors*. The drug resistance to paclitaxel (Taxol), as well as the poor water solubility of taxol and relevant formulation problems hampered the utilization of this famous anticancer drug. Through extensive structural modifications, we have found some taxol analogues effective against P-glycoprotein? (P-gp) overexpression, beta-III isotype tubulin high expression and beta-tubulin mutations mediated drug resistant tumors, among which Aziditaxel (Lx2-32C) has entered preclinical development stage. In addition, we also plan to seek for orally active taxanes through modulation of their interactions with P-gp

(2) *Interactions of taxanes with microtubules and subsequent biological outcomes.* Determination of thermodynamic parameters of taxanes binding to MTs allows us to find that the free energy change during the binding process for the

whole molecule can be dissected by the contributions of substituents at different sites. We also proposed that enhancing binding affinity to MT could overcome P-gp mediated drug resistance, which was confirmed by subsequent experiments.Currently, we are modifying multiple sites in taxanes to modulate their interactions with MTs in binding affinity and polymerization promotion ability, hence to improve their efficacy in antitumor effects.

(3) *SAR and mechanism of action (MOA) studies of anticancer triterpenoids*. Starting from previously found anticancer/antiangiogenic triterpenoids, we tried to design and synthesize designed multiple ligands through preparation of the conjugates of various triterpenoids with other cytotoxic segments, as well as systematic modifications of multiple sites in triterpenoids. In addition, forward chemical genetic tools will be applied to probe the MOA of these triterpenoids and related conjugates.

(4) *Interactions of BACE-1 inhibitors and BACE-1*. Exploring the interaction of BACE-1 and the non-competitive NP based BACE-1 inhibitors discovered in this group, by using NMR and? photoaffinity labeling techniques, to reveal the binding sites and assist in rational design of those NP based BACE-1 inhibitors. In addition, X-ray crystallography was also applied to this study.

Topics in which you would like to develop collaborative research:

(1)General drug discovery:
especially with structural biologists (NMR experts and crystallographers), computational chemists/biologists;
(2)General drug delivery:
especially with experts working on new formulations for hydrophobic therapeutic agents;
(3)Anti-tumor agents:
especially with experts working on stem cells and niches research and interested in drugs R&D;
(4)Anti-Alzheimer's disease agents:
especially pharmacologists and/or genetists and/or other biologists with gene-engineering mice (beta-secretase and/or tau protein related) and interested in drugs R&D;