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Natural products based FXR antagonists: From plant constituents to *in vivo* active molecules

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Farnesoid X Receptor (FXR), belonging to the nuclear receptor superfamily, has emerged as a key player in the control of multiple metabolic pathways. In May 2016, a steroidal FXR agonist obeticholic acid was approved by FDA for the treatment of Primary Biliary Cholangitis (PBC) in combination with Urso Deoxy Cholic Acid (UDCA) in adults with an inadequate response to UDCA, or as a single therapy in adults unable to tolerate UDCA, validating the utility of FXR interacting agents in human. Extensive studies on the discovery of FXR ligands in the past 1-2 decades has resulted in the report of some steroidal (natural ligand like) and non-steroidal FXR ligands. However, serious side effects were encountered during the application of FXR full agonists to animals and patients with diabetes and liver steatosis, so FXR partial agonists and antagonists have been actively pursued as alternatives to full agonists, although their number and structural diversity are still limited. Most of reported FXR antagonists to date are still steroidal molecules, including the first known antagonist guggulsterone, in addition to a few synthetic non-steroidal ones. In the pursuit of new chemo type of FXR interacting agents from natural products, we found some chalcones and pentacyclic triterpenes as FXR antagonists or co-activators. Further chemical manipulations were applied to optimize their Pharmacodynamics (PD) and Pharmacokinetics (PK) properties. Some benzopyrenes (Ia), benzoxepines (Ib), and substituted triterpenoids (II) were found as potent FXR antagonists, demonstrating hypolipidemic activity and hepatic protection ability in diabetic KKAy mice. These studies demonstrated natural products derived FXR antagonists could exert pharmacological activity in mice safely, which are of potential for the metabolic disease treatment.

Biography

Weishuo Fang has graduated from Peking Union Medical College and was awarded PhD degree in 1997. After two years' of Post-doctoral study in Florida State University, USA, he started his independent career in Institute of Materia Medica, Chinese Academy of Medical Sciences as a Professor. The major theme of his research lab is medicinal chemistry and chemical biology of bioactive natural products. Two research directions have been actively pursued by him in the past decade: Drug discovery against three distinct targets, including microtubule (protein-protein interaction), beta-secretase (enzyme) and farnesoid X receptor (nuclear receptor), to pursue therapeutic agents with new chemo types and/or with superior activity; and construction of a natural product-inspired library based on the privileged structure concept and its application to drug discovery to improve the efficiency of hit/lead discovery.

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