Abstract

Natural products have for generations been used in traditional medicinal systems around the world, and is still a unique and productive source for discovery of new drugs. According to statistics of drugs in clinical use, approximately 40% of all small-molecule drugs approved over the past 30 years are derived from natural products. However, for the past 20 years, the pharmaceutical industry has spent limited resources on natural products research, which is partly due to issues arising when working with complex mixtures: the bioactive compounds isolated from plants or other natural sources are normally obtained in a low yield, and it is time-consuming to isolate the bioactive compounds from the crude extracts. In addition, dereplication of known compounds from natural products is still a challenging task. Thus, in the field of natural products research, there still exists an unfulfilled demand for systematic and efficient approaches to drug discovery.

Recently, the combination of using high-resolution inhibition profiling and HPLC-PDA-HRMS-SPE-NMR has been successfully applied for investigation of bioactive components directly from crude extracts of food, plants and microbial cultures. In this thesis, three plants (Machilus litseifolia, Gerbera piloselloides and Dendrobium officinale) collected in China, were selected for investigation of their antidiabetic constituents using high-resolution inhibition profiling. Three targets (α-glucosidase, α-amylase and PTP1B) associated with type 2 diabetes and antioxidant capacity were used during this work. In the first project, high-resolution α-glucosidase inhibition profiling coupled with HPLC-PDA-HRMS-SPE-NMR was used for identification of α-glucosidase inhibitors from M. litseifolia. This led to the identification of 13 di-coumaroylated flavonol rhamnosides, of which seven were new, and two lignans, of which one is reported for the first time. In addition, a compound with a novel butanolide dimeric skeleton was isolated and structurally characterized. However, due to fast degradation it was not possible to obtain data (e.g. ECD, X-ray data, or optical rotation) to establish the absolute configuration of this compound. In the second project, dual high-resolution PTP1B/α-glucosidase inhibition profiling was performed to pinpoint PTP1B and/or α-glucosidase inhibitors from the crude extract of G. piloselloides. After separation and purification by preparative- and analytical-scale HPLC, 25 new compounds including 10 pairs of enantiomers, of which 2 compounds represent 2 novel terpene-coumarin skeletons, were identified. In the third project, 16 metabolites (two new) were identified from a famous Chinese herb D. officinale by triple high-resolution α-glucosidase/ α-amylase/radical scavenging profiling combined with HPLC-PDA-HRMS-SPE-NMR.
In conclusion, the presented studies have shown that high-resolution inhibition profiling coupled with HPLC-PDA-HRMS-SPE-NMR provides an effective bioanalytical platform for the structural and pharmacological identification of bioactive constituents in complex plant extracts.