DOCTORAL THESIS

Studies on Framework Modification and Bioactivity Evaluation on Transition Metal-catalyzed Benzoheterocyclic Compound

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Date of Award:
2022

Abstract

Benzoheterocyclic compounds are a large group of compounds in nature and small organic molecules, possessing a wide range of pharmacological activities and practical applications. To obtain derivatives from the benzoheterocyclic skeleton has always been the challenge and pursuit for chemists. Transition metal has been reported to be one of the most important catalyst groups in catalyzing different types of reactions. This thesis aims at designing and developing of transition metal-catalyzed functionalization reactions of benzopyran skeleton and quinoline skeleton, to synthesize different groups of benzopyran derivatives and quinoline derivatives efficiently and rapidly. In addition, to evaluate the application prospects of each kind of substrates, the biological activity and potential mechanism of different series of substrates are studied and discussed.

Start with the quinoline skeleton, the method of applying transition metal copper to catalyze the selective trifluromethylthiolation of 8-animoquinolines with -SCF_3 reagent has been developed. Under mild conditions, the protocol exhibits high regioselectivity on C-5 position of 8-aminoquinoline and broad substrates scope in good to moderate yield. Furthermore, the synthesized -SCF_3 derivative SCF-1 is predicted to combine with the Aβ according to the molecular docking study in Discovery Studio. The experiments *in vitro* demonstrate that SCF-1 could attenuated the cell cytotoxicity both in H_2O_2-induced and Aβ-induced SH-SY5Y cells which give guidance for the further investigation in Alzheimer's disease (AD).

As for benzo-2*H*-pyran skeleton, a highly efficient kinetic resolution of chromenes for the first time *via* a Cu-catalyzed asymmetric hydroboration has been reported. This novel approach features simple one-pot synthesis of chiral *flavan-3-ols* containing two vicinal stereogenic centers *via* a highly efficient kinetic resolution pathway (*s* factor up to 1060, >99% ee for most substrates and products, exclusively *trans* products). In addition, the anti-inflammation effects of these diversified *flavan-3-ols* have been further studied by the *in vitro* experiments and RNA-sequencing (RNA-seq) analysis. The modified *flavan-3-ol* natural product derivatives showed inhibitory effects on the expression and secretion of pro-inflammation cytokines including IL-1β, IL-6 and TNF-α, as well as inhibiting the inflammation responses through downregulating the gene transcriptions closely related to IL-17 signaling pathway, PI3K-Akt signaling pathway and TNF signaling pathway, which suggest these newly synthesized compounds are potent lead compounds for treating inflammation diseases.

Next with flavonoid skeleton, a novel (+)-catechin derivative with cinnamenyl substituted (WM-21) is synthesized and proved to inhibit the production of melanin by

regulating tyrosinase (TYR) activity in α-MSH-induced murine melanoma cells (B16F10) and human epidermal melanocytes (HEMs). We also found that WM-21 suppresses the UVA radiation-induced secretion of α-MSH in HaCaT cells while the melanogenesis attenuating process is confirmed by HaCaT cells and HEMs co-culture system. Moreover, WM-21 could suppress UVA-induced oxidative stress via reducing ROS production in HaCaT cells. We further found WM-21 promotes the nuclear translocation and transcriptional activity of Nrf2, which upregulate downstream HO-1 and NQO-1 expression. In conclusion, WM-21 attenuates melanogenesis by suppressing oxidative stress via activating Nrf2/HO-1 signaling, which might be used as a cosmetics ingredient or the candidate for therapy of hyperpigmentation skin disorders.

Key words: Benzoheterocyclic compounds, transition metal, trifluromethylthiolation, 8-aminoquinoline, asymmetric synthesis, anti-inflammatory, melanogenesis