Synthesis of Small Molecules based on Natural Products Targeting Signaling Pathways

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Natural products give us important information for construction of bioactive small molecules. We are interested in the natural products-framework small molecules with complexity and diversity for increasing the number of protein-binding elements. We developed the one-pot synthesis by Michael-aldol reaction of chromone and flavonoid derivatives bearing pyridine units. The endo 2,3-disubstituted chromones were obtained in one step. Furthermore, use of substituted benzaldehydes and subsequent addition of heterocyclic aldehyde gave 3-pyridyl-substituted flavones. Synthesized compounds showed the inhibitory activities of GLI-mediated transcription, which is the final step in the hedgehog (Hh) signaling pathway. Aberrant Hh/GLI signaling has recently been implicated in cancer formation and development. We constructed a cell-based assay of GLI1-mediated transcription and found the potent inhibitor from naturally occurring compounds. We also synthesized natural products *trans*-dihydroarcyriarubin C and melleumin A, B, which were isolated by us from myxomycetes. We found several small molecule inhibitor of Wnt signal transcription, which is abnormally activated in colon cancers.

We also constructed protein-based screening assay systems; (1) high-throughput system for analyzing TCF-β-catenin interaction using fluorophore labeling protein and a microplate reader, and (2) small molecule screening system by using protein immobilized magnetic beads. A vitamin-D Receptor (VDR) immobilized magnetic beads bind to its ligand (1α,25(OH)-vitamin D_3) selectively, even though mixture condition with plant extracts.