S40-3 Natural product-based bioactive molecules

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Natural products are rich source of interesting bioactive molecules. But they do not always show sufficient potency, selectivity, and cell permeability. We are working on design and synthesis of molecules having unique bioactivities based on natural products. Selective inhibitors of protein phosphatases are expected to be useful tools for clarifying the biological functions of the phosphatases themselves, and also candidates for novel therapeutics. Inspired by a natural product cantharidin, which is known as a inhibitor of Ser/Thr phosphatases PP1 and PP2A, we succeeded to develop a highly selective inhibitor of PP2B (calucineurin). To develop a Tyr or dual specificity phosphatase (PTP/DSP) inhibitor, we focused on RK-682 as a starting compound. RK-682 was found to inhibit both protein phosphatases and heparanase, which is known to play important role for invasion of cancer cells, and to be poorly cell-permeable. Thus we modified its structure and succeeded to develop RE derivatives, which are cell-permeable inhibitors of a DSP but not heparanase. Furthermore, we have also succeeded to develop a potent heparanase inhibitor without protein phosphatase inhibitory activity.