Solution-Phase Strategies for the Design, Synthesis, and Screening of Libraries Based on Natural Products

Sang Hee Kim

College of Pharmacy, Seoul National University

The syntheses of different types of stilbenoid libraries have been studied recently. In these courses, the screening of the generated natural product-mimic focused libraries led to the identification of the novel lead compounds for human cytochrome P450 (CYP) 1As, melanin production, and sortase A.

A library of trans-stilbene derivatives was prepared through a new efficient solution phase synthetic pathway and their inhibitory activities were evaluated on human cytochrome P450s (CYP) 1A1, 1A2, and 1B1 to find a potent and selective CYP1 inhibitor. We found that a substituent at the 2-position of the stilbene skeleton plays a very important role in discriminating between CYP1As and CYP1B1. Among the compounds tested, the most selective and potent CYP1B1 inhibitor was 2,3',4,5'-tetramethoxystilbene 7a. Compound 7j, 2-[2-(3,5-dimethoxy-phenyl)-vinyl]-thiophene, showed greater inhibitory activities, but had a lower selectivity towards all the CYP1s tested. We also investigated the mechanism of CYP1B1 inhibition by 7a. Compound 7a is a competitive inhibitor of CYP1B1 with K_i of 3 nM. 4-Hydroxylation of E2 by CYP1B1-expressing membranes or purified CYP1B1 were strongly blocked by compound 7a. However, 7a does not cause a time-dependent inactivation of CYP1B1. It was also found that 7a is relatively stable in the presence of CYP1B1.

As part of our depigmenting agent discovery efforts, we have screened our compound collections, based on measuring the ability of test compounds to inhibit melanin production by using melanoma cells. This led to the identification of compound 1, containing an amide linkage between two aromatic groups, with a modest potency and cytotoxicity. An efficient process for the solution-phase synthesis of biaryl amides has been developed. Girard's reagent T, an inexpensive scavenger, was found to be very efficient in trapping excess aromatic acid chlorides, resulting in water soluble by-products, which were easily removed from the products by liquid-liquid extraction. The ease of use, and the excellent purity of the amide libraries obtained, are important features of this protocol. This biaryl amide template was attractive for the new class of depigmenting agents because of its simple structure, synthetic easiness and stability. We report herein the preparation and evaluation of this class of compounds, as well as the results of preliminary structure-activity relationship studies.

In addition, based on a hit from random screening, a novel class of small-molecule sortase A inhibitors was generated by using an efficient solution phase synthetic pathway. The primary structure-activity relationship and the minimal structural requirements for potency were established through structural modifications and molecular modeling studies.