Synthesis and Structure-Activity Relationships of Tetrahydroindazolone Derivatives as Anticancer Agents

Rong-Yu Chen,[a] Chien-Yu Chen,[a] Tzung-Han Tang,[b] Jau-Yang Chen,[a] Chien-Fu Huang,[c] Chun-Tang Chiou,[d] Shin-Hun Juang,[a] Chih-Shiang Chang[a,]*

[a]Graduate Institute of Pharmaceutical Chemistry, College of Pharmacy, China Medical University, Taiwan.

[b]School of Pharmacy, College of Pharmacy, China Medical University, Taiwan.

[c]Department of Biological Science and Technology, I-Shou University, Taiwan.

[d] Division of Herbal Drugs and Natural Products, National Research Institute of Chinese Medicine, Taiwan.

Tetrahydroindazolone (THI) was recently recognized as an important pharmacophore because of its excellent biological activity as a potent inhibitor of heat-shock protein 90. SNX-2112, a novel THI core inhibitor of Hsp90, is currently in phase III clinical trials. In here, tetrahydroindazolone derivatives were synthesized and evaluated for biological activity against colon cancer cell (H226), Human T cell lymphoblast-like cell line (Jurkat), and nasopharyngeal cancer (NPC-TW01). The structure-activity relationship of THI derivatives results were shown that the *N*-1 substituted tetrahydroindazolone possessed more potential activity against cancer cell line than those of corresponding *N*-2 substituted THI derivatives. The 4-methylphenyl THI (**10k**), 2-methylphenyl THI (**10m**), and 3,5-dichlorophenyl THI (**10p**) were demonstrated potent activity against H226, Jurkat, and NPC-TW01 *in vitro*, respectively. The 4-chlorophenyl THI (**10e**) was also shown good activity antitumor efficacy *in vivo*.