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Synthesis of Dihydroorotate Dehydrogenase Inhibitors for Treatment of Rheumatoid Arthritis

Yi-Ju Wang (王以如), Wen-Hsin Huang (黃文鑫) and An-Rong Lee (李安榮)

National Defense Medical Center, Taipei, Taiwan

Dihydroorotate dehydrogenase (DHODH) catalyzes the *de novo* biosynthesis of pyrimidine, which is a precursor to form the base elements in DNA and RNA. Over-activity of DHODH is related to cancer and rheumatoid diseases. Inhibitors of DHODH, such as brequinar and leflunomide, are benefits of immunosuppressive and antiproliferative effects in RA; however, cumulative toxicities have been reported. Researches investigated that brequinar and leflunomide differentially and distinctly act on active site of DHODH. In search of beneficial disease-modifying antirheumatic drugs (DMARDs), a series of hybrid of brequinar-leflunomide compounds have been synthesized in moderate yields in our laboratories.

Those target compounds are under pharmacological evaluations, using brequinar and leflunomide as controls, by both the *in vitro* suppressing the production of nitric oxide (NO) in LPS-elicited macrophage Raw 264.7 cells and the *in-vivo* carrageenan-induced paw edema assay for further a SAR study.