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Synthesis and evaluation of antidiabetic tmpa derivatives via Ir(iii)-catalyzed C−H alkylation

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Antidiabetic medication has revolutionized the treatment of metabolic disorders derived from high blood sugar level. In particular, the use of antidiabetics such as glucagon-like peptide (GLP) agonists, KATP channel inhibitors, AMP-activated protein kinase (AMPK) signaling activators, α-glucosidase inhibitors, and PPAR-γ inhibitors, has received considerable attention as potential medical agents because of their interesting pharmacological effects. Recently, natural antidiabetic octaketide metabolites, cytosporones A and B, have been isolated by Clardy in 2000. Notably, cytosporone B has been demonstrated to bind to the ligand-biding domain of nuclear orphan receptor 77 (Nur77) and stimulate the control of LKB1-mediated AMPK activation. Additionally, unnatural TMPA (ethyl 2-[2,3,4-trimethoxy-6-(1-octanoyl) phenyl]acetate) was also found to enhance AMPKα phosphorylation through reducing the NUR77–LKB1 interaction. Despite of the potent antidiabetic activity and relatively simple structure of TMPA, the single synthetic strategy has been reported for the preparation of TMPA derivatives. However, this strategy presents intrinsic drawbacks, namely, the multi-step synthesis (longest linear 7 steps) and harsh reaction conditions including Friedel–Craft intramolecular acylation, OsO4-mediated dihydroxylation and Pinick oxidation. We herein disclose the ketone-directed Ir(III)- and Rh(III)-catalyzed ortho-C–H alkylation of acetophenones with Meldrum's diazo esters. As results, this protocol may be beneficial to guide the design a variety of antidiabetic TMPA derivatives, and represents a catalytic alternative to transcend the barriers imposed by previous multi-step synthetic approach.

Biography

Saegun Kim is currently pursuing PhD from Sungkyunkwan University, Suwon, Republic of Korea.

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