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Discovery of Novel Nuclear Factor-κB (NF-κB) Inhibitors using chroman-2-carboxmide derivatives

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Nuclear factor (NF)-κB, an inducible transcription factor, regulates the immune response and plays critical roles in the pathogenesis of chronic inflammatory diseases and a variety of human cancers. It has been suggested that NF-κB function inhibitors may be useful as both anti-inflammatory agents and antitumor agents. During the search for novel compounds that can inhibit NF-κB activation, 6-hydroxy-7-methoxy-chroman-2-carboxylic acid phenyl amide (**KL-1156**) was identified as a good inhibitor of NF-κB activation. NF-κB inhibitory activity of **KL-1156** with an IC_{50} value of 40.4 μM was comparable to that of pyrrolidine dithiocarbamate (PDTC) with an IC_{50} value of 37.2 μM. PDTC acts as an antioxidant and has been found to be a potent inhibitor of NF-κB activation. In the present study, we report the synthesis and inhibitory effect of chroman-2-carboxylic acid *N*-(substituted)phenyl amide. Hydroxy and methoxy substituents of compound **KL-1156** were removed in the target compounds. Substituents on *N*-phenyl ring of the target compounds were selected considering their electronic and hydrophobic character. Their NF-κB inhibitory activities were evaluated on lipopolysaccharide (LPS)-stimulated macrophage RAW 264.7. The NF-κB inhibitory activities of the compounds were compared with that of **KL-1156**.

The target compounds contained various substituents (H, Cl, OMe, CH_3, CF_3, and NO_2) on phenyl ring. The positional effects of the substituents were also explored by examining the compounds with substituents at various position (2-; 3-; 4-; 2,5-; 3,4-; 3,5-). Compounds with H, CF_3 and NO_2 substituents on phenyl ring were inactive (IC_{50}: > 100μM). In compounds bearing substituent at 4-position, the activity decreases in the order of Cl (IC_{50}: 18.2μM), OH (IC_{50}: 44.5μM), and Me (IC_{50}: 95.8μM). In compounds bearing substituent at 3-position, compound with Cl (IC_{50}: 74.7μM) and OMe (IC_{50}: 76.8μM) were equipotent. In compounds bearing substituent at 2-position, only compound with 2-OH substituent showed good activity (IC_{50}: 22.1μM). The positional effects of substituents on inhibitory activities are contradictory. Compound with 2-OH (IC_{50}: 22.1μM) showed more potent activity than compound with 4-OH (IC_{50}: 44.5μM) while compound with 4-Cl substituent were 4 times more potent than compound with 3-Cl (IC_{50}: 74.7μM) substituent. Direct correlation was not observed based on the electronic and hydrophobic character of the substituents.