Novel Ortho-Methylated Diaryl Sulfonamides: Synthesis and Subsequent Biological Evaluation as Promising CETP Inhibitors

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Abstract

Elevated lipid profiles have been identified as a risk factor for conditions, such as atherosclerosis, dyslipidemia, and cardiovascular disease. The role of cholesteryl ester transfer protein (CETP) in facilitating the reverse cholesterol transport mechanism from HDL to VLDL and LDL was investigated.

A series of seven sulfonamide derivatives with an *ortho*-methyl substitution **6a-6g** were synthesized by reacting 4-(*o*-tolylthiomethyl) aniline **4** with various substituted benzene sulfonyl chlorides **5a-5g**. The compounds were purified and characterized using IR, ^{1}H-NMR, ^{13}C-NMR, and HRMS. The CETP inhibitory activity was evaluated *in vitro*, revealing that compound **6f** exhibited the highest inhibitory efficacy, with a 53.1% inhibition at a concentration of 10μM.

Hydrophobic electron-withdrawing groups, like chlorine at the *meta* position, was the most effective in inhibiting CETP activity. Developing new CETP inhibitors, especially those with hydrophobic and electron-withdrawing substituents, shows promise for future interventions to regulate lipid profiles.

Keywords: Antihyperlipidemic, Cardiovascular disease, Cholesteryl ester transfer protein inhibitors, Dyslipidemia, Low density lipoprotein.