Synthesis, Characterization, and Biological Study of New Meta-Methylated Sulfonamide Derivatives as Inhibitors of Cholesteryl Ester Transfer Protein

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Abstract

This study focuses on the significance of high lipid profile levels as a notable risk factor for various diseases, including atherosclerosis, dyslipidemia, and cardiovascular disease. Consequently, the identification of effective pharmacological interventions to reduce lipid profiles is crucial. Recent investigations have primarily concentrated on the role of cholesteryl ester transfer protein (CETP) in facilitating the reverse cholesterol transport mechanism, involving the transfer of cholesteryl esters (CE) from high-density lipoprotein (HDL) to low-density lipoprotein (LDL) and very-low-density lipoprotein (VLDL). The inhibition of CETP through pharmacological agents has shown the potential to decrease LDL levels and elevate HDL levels.

To explore this further, ten meta-methylated sulfonamide derivatives **6a**-**6j** were synthesized by reacting 4-(*m*-tolylthiomethyl) aniline **4** with different substituted benzene sulfonyl chlorides **5a**-**5j**. The produced **6a**-**6j** were purified using column chromatography and then utilized using diverse spectroscopic techniques such as fourier-transform infrared spectroscopy, proton nuclear magnetic resonance, carbon-13 nuclear magnetic resonance, and high-resolution mass spectroscopy to characterize their structures. *In vitro* biological evaluation was performed to examine the inhibitory efficacy of these synthesized compounds on CETP activity. Our findings

unveiled that compound **6j** exhibited the highest inhibitory efficacy, achieving 31.5% at a concentration of 10μM.

Notably, it was observed that the presence of hydrophilic electron-withdrawing groups, specifically NO_2 at the para position, proved to be the most potent in hindering CETP activity. This study underscores the importance of CETP as a therapeutic target for lipid-lowering therapy in the context of cardiovascular disease and atherosclerosis. The development of novel compounds with CETP inhibitory properties, particularly those with hydrophilic electron-withdrawing substituents, holds promise for future interventions aimed at modulating lipid profiles.

Keywords: Atherosclerosis, Cardiovascular disease, Cholesteryl ester transfer protein, Lipid-lowering therapy, Methylation, Sulfonamide.