Ortho-Trifluoromethyl Substituted Aryl Sulfonamides as Potential Cholesteryl Ester Transfer Protein Inhibitors

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Abstract

Many diseases, including dyslipidemia, atherosclerosis, and cardiovascular disease (CVD), have been linked to elevated lipid profiles as a major risk factor. The main focus of recent studies has been on determining the protein called cholesteryl ester transfer protein, or CETP, contributes to the mechanism of reverse cholesterol transport. Cholesteryl esters are carried by high-density lipoprotein (HDL) to low-density lipoprotein (LDL) and very-low-density lipoprotein (VLDL) in this pathway. It is feasible to raise HDL and lower LDL levels by pharmacologically blocking CETP, which can improve lipid profiles.

The main objective of this work is the synthesis of *ortho*-trifluoromethyl substituted aryl sulfonamides as potential CETP inhibitors. Because of the close association between heart disease and cholesterol levels, CETP inhibition will increase HDL and decrease LDL cholesterol levels, which will diminish CVD.

To delve deeper into the investigation, a series of ten sulfonamide derivatives with an *ortho*-trifluoromethyl substitution **6a-6j** were synthesized by reacting 4-((*o*-

trifluoromethylphenyl) thio) aniline **4** with various substituted benzene sulfonyl chlorides **5a**-**5j**. These synthesized compounds were then purified using column chromatography and characterized using spectroscopic techniques such as IR, ^{1}H-NMR, ^{13}C-NMR, and high-resolution mass spectroscopy. *In vitro* biological evaluation was conducted to assess the inhibitory efficacy of these compounds on CETP activity. The results revealed that compound **6f** demonstrated the highest inhibitory efficacy, achieving a remarkable 100% inhibition at a concentration of 10μM.

The study found that having electron-withdrawing groups, like chlorine and nitro at the *meta* position, was the most effective in inhibiting CETP activity. Developing new compounds with CETP inhibitory properties, especially those with 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.