Novel Ortho-Chlorinated Benzenesulfonamides: Synthesis, Characterization and Biological Validation as Promising CETP Inhibitors

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Abstract

Atherosclerosis-related disorders are the major cause of death worldwide. Atherosclerosis leads to arterial obstruction or constriction resulting in acute cardiovascular illness. Cholesteryl ester transfer protein (CETP) controls lipids of the plasma by promoting reverse cholesterol transport. It supports transfer of cholesteryl ester from HDL to LDL and VLDL. Drugs that Inhibit CETP limit cardiovascular disease, by decreasing LDL and increasing HDL.

In this study, ten chloro-substituted benzene sulfonamides **6a-6j** were prepared, and their structures were fully determined using ^{1}H-NMR, ^{13}C-NMR, HR-MS, and IR. *In vitro* biological evaluation showed that compounds **6g**, **6f**, **6i** and **6j** had the highest inhibitory activity which ranged from 46.2-53.8% inhibition at 10µM concentration. Compounds **6a**, **6c**, **6e** and **6h** had activities ranged from 42.3-45% inhibition, while compounds **6b** and **6d** had lower activities with a % inhibition of 33.3% and 23.0% respectively. Substituting the sulfonamides with electron withdrawing functionalities such as –Cl or $–NO_2$ enhances the CETP inhibitory activity. Moreover, it was seen that the presence of e-withdrawing group at *meta* and *para* gives the optimum activity.

Furthermore, it was found that the presence of $–NO_2$ group enhances the inhibitory activity more than –Cl moiety, which could be attributed to the hydrophilic character of the $–NO_2$ group that can be involved with H- bonding with CETP binding site.

Keywords: Atherosclerosis, Benzenesulfonamides, Cardiovascular disease, Cholestery lester transfer protein, Ortho-chlorinated.