New *Meta*-Fluorinated Diaryl Sulfonamides: Synthesis and *in Vitro* Study as Promising Cholesteryl Ester Transfer Protein Inhibitors

By

Yasmin Mahmoud Selim Ibrahim

Supervisor

Prof. Dr. Reema Abu Khalaf

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Abstract

Cardiovascular disease (CVD) has been proved to be the leading cause of death in all ethnic groups and societies. Hyperlipidemia is the cornerstone of CVD development and progression. Cholesteryl ester transfer protein (CETP) is a hydrophobic glycoprotein that facilitates the transfer of cholesteryl ester from the atheroprotective high-density lipoprotein (HDL) to the proatherogenic low-density lipoprotein (LDL) and very low-density lipoprotein (VLDL). Inhibiting CETP activity raises HDL concentration which is a negative risk factor for CVD.

In this study, ten *meta*-fluorinated diaryl sulfonamides **6a-6j** were synthesized as CETP inhibitors, and their structure was fully determined using ^{1}H-NMR, ^{13}C-NMR, HR-MS, and IR. *In vitro* biological evaluation showed that compounds with the highest inhibitory efficacy were **6h** (99.5% CETP inhibition) and **6j** (91.3% CETP inhibition) at 10μM concentration. While compounds **6a-6g** and **6i** inhibitory activities ranged from 35.4%-71.2% at 10μM concentration. The nitro substituted compounds **6h-6j** have higher CETP inhibitory activity when compared to compounds **6a-6g**, which could be due to the

bulk size of the nitro group that extends the structure in addition to its electron-withdrawing and hydrophilic properties.

Keywords: Cardiovascular disease, CETP inhibitors, Cholesteryl ester transfer protein, Diaryl sulfonamides, High-density lipoprotein.