FLUORINATED BENZAMIDES: DESIGHN, SYNTHESIS AND BIOLOGICAL EVALUATION AS POTENTIAL CETP INHIBITORS

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ABSTRACT

Hyperlipidaemia is one of the most common chronic diseases worldwide. Cholesteryl ester transfer protein (CETP) is a hydrophobic glycoprotein that facilitates the transfer of cholesteryl ester from the atheroprotective HDL to the proatherogenic LDL and VLDL.

In this work, synthesis and characterization of five fluorinated 3-benzylamino benzamides **8a-8c**, **13a** and **13b** that target CETP activity was carried out. Benzamides **8b** and **8a** showed the highest CETP inhibitory activities with IC_{50} of 0.75 μM and 4.1 μM respectively. The *in vitro* biological data shows that the presence of *p*-OCF_3 group (as in **8a**, **8b** and **8c**) enhances CETP inhibitory activity more than *p*-OCF_2CHF_2 (as in **13a** and **13b**) which could be attributed to the bulkiness of the tetrafluoroethoxy group hindering their proper orientation in the binding domain.

Additionally *m*-F derivatives have higher activity against CETP than *p*-F ones leaving the *o*-F analogues with the weakest anti-CETP bioactivity.

The ligand-and structure-based drug design strategies confirm that hydrophobic interaction mediates ligand/protein complex formation and explain the activity of our verified molecules. Further optimization of this core nucleus is required to improve CETP inhibitory activity and to better understand the structure-activity relationship.