1-(4-Ethoxycarbonylphenyl)-2-(4-fluorobenzylthio)-5-(2-ethoxy-5-pyrimidinylmethyl)-4-pyrimidinone (GW1100)

- An inhibitor of the phospholipase A2 enzyme Lp-PLA2 for the treatment of atherosclerosis
- A selective GPR40 antagonist

Chemical Formula: C_{27}H_{25}FN_{11}O_{4}S
Molecular Weight: 520.58

OTAVA Catalogue Number: 7070707009
CAS Registry Number: 306974-70-9
Purity: 97%+


1. Long chain fatty acids have recently been identified as agonists for the G protein-coupled receptors GPR40 and GPR120. Here, we present the first description of GW9508, a small-molecule agonist of the fatty acid receptors GPR40 and GPR120. In addition, we also describe the pharmacology of GW1100, a selective GPR40 antagonist. These molecules were used to further investigate the role of GPR40 in glucose-stimulated insulin secretion in the MIN6 mouse pancreatic beta-cell line.

2. GW9508 and linoleic acid both stimulated intracellular Ca^{2+} mobilization in human embryonic kidney (HEK)293 cells expressing GPR40 (pEC_{50} values of 7.32+/−0.03 and 5.65+/−0.06, respectively) or GPR120 (pEC_{50} values of 5.46+/−0.09 and 5.89+/−0.04, respectively), but not in the parent HEK-293 cell line.

3. GW1100 dose dependently inhibited GPR40-mediated Ca^{2+} elevations stimulated by GW9508 and linoleic acid (pIC_{50} values of 5.99+/−0.03 and 5.99+/−0.06, respectively). GW1100 had no effect on the GPR120-mediated stimulation of intracellular Ca^{2+} release produced by either GW9508 or linoleic acid.

4. GW9508 dose dependently potentiated glucose-stimulated insulin secretion in MIN6 cells, but not in primary rat or mouse islets. Furthermore, GW9508 was able to potentiate the KCl-mediated increase in insulin secretion in MIN6 cells. The effects of GW9508 on insulin secretion were reversed by GW1100, while linoleic acid-stimulated insulin secretion was partially attenuated by GW1100.

5. These results add further evidence to a link between GPR40 and the ability of fatty acids to acutely potentiate insulin secretion and demonstrate that small-molecule GPR40 agonists are glucose-sensitive insulin secretagogues.