New Product Highlights

GW7647 and GW1929: New peroxisome proliferator-activated receptor (PPAR) agonists

Peroxisome proliferator-activated receptors (PPARs) are members of the nuclear hormone receptor superfamily of ligand activated transcription factors. These receptors play an important role in many cellular functions including lipid metabolism, cell proliferation, differentiation, adipogenesis and inflammatory signaling [1]. Three PPAR subtypes have been identified and are referred to as PPARα, PPARδ (also known as PPARβ) and PPARγ. PPARα is expressed in tissues that exhibit high rates of fatty acid oxidation (FAO), such as heart, liver and muscle [2,3]. PPARγ is the most studied of the three subtypes, particularly because of its role in adipocyte differentiation as well as its involvement in glucose and lipid metabolism [1]. Both receptors have become exciting therapeutic drug targets for various disease states including diabetes, atherosclerosis and hypertension [1]. Sigma-RBI is pleased to offer new research tools for the study of these two subtypes, specifically **GW7647** (Prod. No. G 6793), a PPARα agonist and **GW1929** (Prod. No. G 5668), a PPARγ agonist.

The fibrates, including **gemfibrozil** (Prod. No. G 9518), **ciprofibrate** (Prod. No. C 0330), clofibrate, fenofibrate, and bezafibrate are a class of tryglyceride lowering drugs that mediate their clinical effect through activation of PPARα [1]. GW7647 is from a class of ureidothioisobutyric acids that have improved lipid-lowering activity compared to fenofibrate [4]. Using primary human skeletal muscle cells, Muoio et al. observed up to a three-fold dose-dependent increase in [^{14}C]oleate metabolism, following (an indication of increased fatty acid oxidation) 48-hour treatment of 0.01-1 µM of GW7647. They also observed a 45% decrease in oleate esterification into myotube triacylglycerol (TAG) [5]. This finding suggests a clinical use for PPARα-selective compounds in adult-onset diabetes, since increased muscle lipid content has been shown to be associated with the development of insulin resistance [6].

A range of synthetic and naturally occurring substances activate PPARγ, including the antidiabetic drugs (troglitazone and **ciglitizone**, Prod. No. C 3974), polyunsaturated fatty acids such as **linoleic acid** (Prod. No. L 1268), **linolenic acid** (Prod. No. L 2376) and **arachidonic acid** (Prod. No. A 9673) and 15-deoxy-D-prostaglandin J_2. Other activators include components of oxidized low-density lipoprotein, such as **13-hydroxyoctadecadienoic acid** (13-HODE, Prod. No. H 9146) and **15-hydroxyeicosatetraenoic acid** (15-HETE, Prod. No. H 1142), as well as **tetradecylthioacetic acid** (TTA, Prod. No. T 1698). GW1929 is a novel N-aryl tyrosine activator identified through a high-throughput biochemical assay [7]. When GW1929 was administered orally for 14 days at 5 mg/kg to obese Zucker diabetic fatty (ZDF) rats, a dose-dependent decrease was observed in daily glucose, free fatty acid and triglyceride levels as compared to controls [7]. In a separate study that supports these findings, both male ob/ob mice and ZDF rats treated with GW1929 as compared with other PPARγ agonists exhibited an increase in the expression of the PPARγ target genes, fatty acid transporter protein (FATP) and phosphoenolpyruvate carboxykinase (PEPCK), in white adipose tissue [8]. In addition, a two-fold increase in the fat cell secreting hormone resistin in both ob/ob mice and ZDF rats was observed, a surprising finding, since elevated levels of resistin have been associated with insulin resistance and is proposed as a link between obesity and diabetes [8].

In summary, GW7647 and GW1929 will serve as important research tools in the continued elucidation of the role of PPARα and PPARγ in lipid homeostasis.

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References

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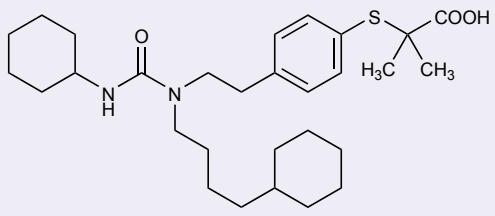
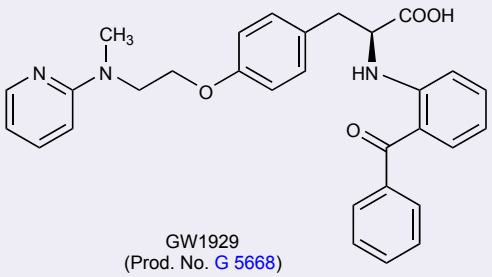


GW7647
(Prod. No. G 6793)



GW1929
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