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Synthesis, biological evaluation, and molecular docking investigation of benzhydrol- and indole-based dual PPAR-γ/FFAR1 agonists

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ABSTRACT

Type-2 diabetes mellitus is a progressive cluster of metabolic disorders, representing a global public health burden affecting more than 366 million people worldwide. We recently reported the discovery of three series of novel agents showing balanced activity on two metabolic receptors, peroxisome proliferator activated receptor-γ (PPAR-γ) and free fatty acid receptor 1 (FFAR1), also known as GPCR40. Our designing strategy relied on linking the thiazolidinedione head with known GPCR privilege structures. To further investigate this concept, two new scaffolds, the benzhydrol- and indole-based chemotypes, were introduced here in. Our optimization campaign resulted in three compounds; **15a**, **15c**, and **15d**, with affinities in the low micromolar range on both targets. *In vivo* study of selected test compounds, revealed that **15c** possesses a significant anti-hyperglycemic and anti-hyperlipidemic activities superior to rosiglitazone in fat-fed animal models. Molecular docking analysis was conducted to explain the binding modes of both series. These compounds could lead to the development of the unique antidiabetic agent acting as insulin sensitizer as well as insulin secretagogue.

Although type-2 diabetes mellitus (T2DM) is not a recent disease, with a history dated back to the middle of the sixth century, its prevalence is rising every day. The disease is a progressive cluster of metabolic disturbances characterized by chronic hyperglycemia arising from insufficient pancreatic insulin secretion and resistance to insulin action or a combination of both. As for complications, T2DM is one of the primary causes of renal injury, eye problems, amputations and hospitalizations and is associated with high rates of morbidity and mortality.[1] Currently, T2DM is a global public health burden affecting more than 367 million people worldwide. According to the World Health Organization (WHO), the number is expected to reach 557 million by the year 2030.[2]

An efficient management of T2DM comprises of several stages.[3] Typically, the first step could be achieved through lifestyle modifications including healthy diet and exercise. However, when changing lifestyle is not sufficient, pharmacotherapy is required. A variety of oral hypoglycemic medications were developed either to increase insulin secretion (secretagogues), enhance insulin action (insulin sensitizers), or slow glucose absorption.[4] Examples of insulin sensitizers include metformin and thiazolidinediones (TZDs), while oral sulfonylureas and meglitinides are prescribed as insulin secretagogues. Since introduced in the late 90s, TZDs are considered as potent agonists of peroxisome proliferator-activated receptors (PPARs). The latter represent a group of nuclear hormone receptors responsible for the expression of a number of genes concerning with glucose and fat metabolism.[5] The PPARs are abundant in the key target tissues for insulin action including skeletal muscles, adipose tissues, and liver. Out of the three distinct PPAR isoforms, PPAR-α, -β and -γ, the activation of PPAR-γ has the major role in regulating glucose homeostasis, inflammatory responses, cellular differentiation, and apoptosis.[6]

Till date, the first line treatment of T2DM is oral metformin followed by oral sulfonylureas, dipeptidyl peptidase-IV-inhibitors, and TZDs. As the disease progresses, injectable glucagon-like peptide-I analogues or ultimately insulin become necessary to maintain glycaemic control.[3] Despite the established guidelines, there is still no cure for T2DM. Additionally, many of the traditional current therapies are associated with gastro-intestinal discomforts (metformin), hypoglycaemia, and weight gain (sulfonylurea and to lesser extent meglitinides), or edema and increased risk of bone fractures (TZDs).[7]

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In this regard, there has been an influx of novel antidiabetic agents influencing a variety of cellular targets. Recently, free fatty acid receptor-I (FFAR1) has emerged as a promising target, belonging to the class A family of G-protein-coupled receptors (GPCRs). FFAR1 is mainly expressed in the pancreatic β-cells, and to a lesser extent in gastrointestinal enteroendocrine cells, immune cells, and parts of the brain.[8–10] This lipid-binding receptor enhances glucose-stimulated insulin secretion (GSIS) by direct action on β-cells and possibly indirectly through the incretin system. Since FFAR1-induced GSIS is glucose-dependent, FFAR1's mechanism potentially mitigates the risk of hypoglycemia seen with standard insulin secretagogues.[11,12]

In our recent publication, we described the discovery of novel hybrid molecules possessing a balanced dual agonism on PPAR-γ and FFAR1 receptors.[13] These hybrids would act as insulin sensitizers and secretagogues through their action on PPAR-γ and FFAR1, respectively. Unlike marketed secretagogues/sensitizers combination; Amaryl M™ (metformin/glimepiride) and glucovance™ (metformin/glibenclamide), these hybrids could provide less complex pharmacokinetic/pharmacodynamic relationships. Such profiles would lead to more predictable variability between patients and less extensive clinical studies.[14] Additionally, the afforded moderate activity of these hybrids, down to one digit μM, could be beneficial to limit the potential adverse effects raised with potent PPAR-γ agonists. Nevertheless, such hybrids could keep an acceptable overall anti-diabetic efficacy as a result of their collective synergism on both receptors.

The design of our lead compounds depends on combining the 5-benzyl-thiazolidinedione scaffold, as TZDs common pharmacophore, with diverse GPCRs' privileged structures, as hydrophobic tails, through a simple alkyl linker (Fig. 1). In another previous study, we illustrated through homology modelling and molecular dynamics simulations that the TZD acidic head is capable of binding to the critical polar residues within both PPAR-γ and FFAR1 binding domains.[15] The biphenyl, phenoxybenzyl, and benzimidazole-based derivatives represent excellent choices as versatile hydrophobic tails (series **MK-1**, **-2** and **-5**; Fig. 2). Such choice was based on preliminary molecular docking studies conducted in our late publication.[13] These three scaffolds showed preferential binding, with both receptors, out of a total 17 docked GPCRs' privileged structures. Notably, our rationalized design came in great consistency with a recently published mini-review article by Yasmin et al.[16], summarizing the chemical modifications around TZDs in past two decades. Through extensive mining, the authors depicted that the 5-[4-alkyloxybenzyl]-thiazolidinedione scaffold, being adopted herein, is considered an optimal motif for furnishing favourable PPAR-γ transactivation.

Regarding our preliminary *in silico* study, eight compounds showed balanced agonistic activity on both PPAR-γ and FFAR1 receptors. Both the benzimidazole series **MK-5** and biphenyl series **MK-1**, ranked second in activity, were proved to be the most suitable scaffolds for this purpose. Assessment of activity was done using luciferase bioluminescence and calcium flux/fluorometric imaging plate reader (FLIPR) assays for PPAR-γ and FFAR1 transactivation, respectively. High intrinsic activities were noticed, with significantly larger maximum fold-induction compared to that of the PPAR-γ full agonist reference, rosiglitazone.

Thrilled by these promising results, our quest for discovering new PPAR-γ/FFAR1 co-agonists was directed towards exploring the other two new scaffolds. So, in this proposed manuscript, we will describe our efforts regarding the synthesis, biological evaluation and molecular docking studies of the benzhydrol- and indole-based hybrids (series **MK-3** and **-4**, respectively, Fig. 2). Moreover, the effect on blood glucose and plasma triglyceride levels were studied *in vivo* using the appropriate animal models.

Despite the novelty of the previously introduced series **MK-2**, a branched biaryl chemotype with a stereogenic centre, it furnished mediocre potencies regarding the PPAR-γ receptor. It was expected that the Y-shaped structures of this series could help the compounds to fit into the two hydrophobic arms of PPAR-γ, while maintaining a suitable size that is not too bulky.[17–19] Nevertheless, promising FFAR1 receptor activity at low micromolar range persuaded us for further investigations. Thus, the benzhydrol-based series, **MK-3**, was introduced herein as a forked biphenyl chemotype. The phenyl shift in series **MK-3** was designed to allow the terminal oxygen to be widely open for optimized H-bonding interaction within the PPAR-γ binding pocket. This was based on predicted polar interaction between

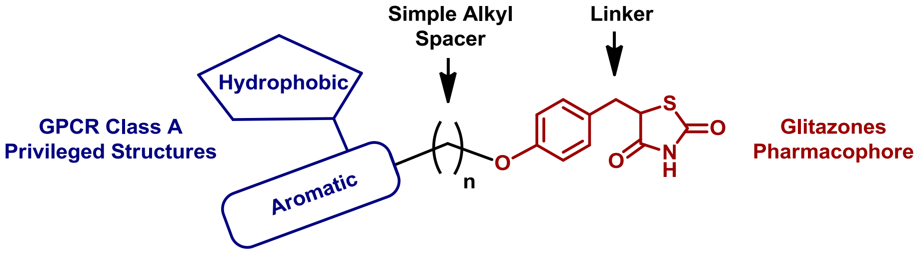

Fig. 1. General topology proposed for dual PPAR-γ/FFAR1 agonists.

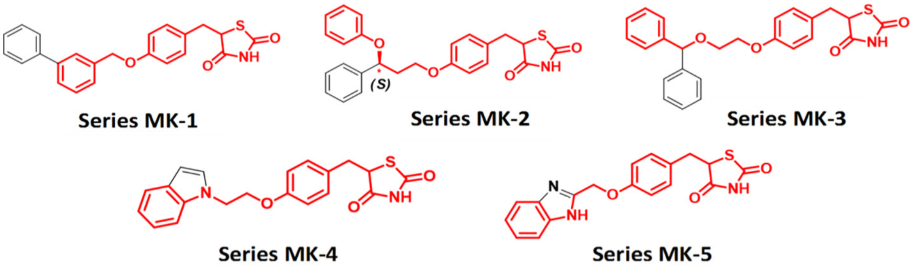

Fig. 2. Leads with the best docking score in both FFAR1 and PPAR-γ receptors, expressing the common phrarmacophore in red.