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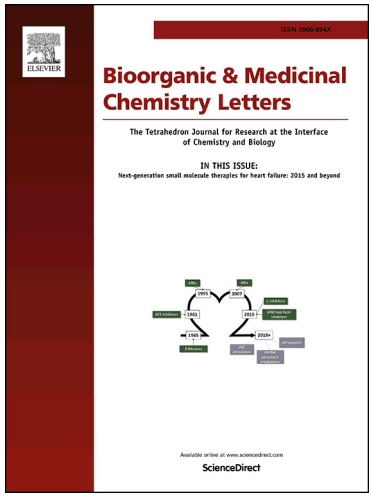

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PII: S0960-894X(19)30315-4
DOI: https://doi.org/10.1016/j.bmcl.2019.05.018
Reference: BMCL 26438

To appear in: *Bioorganic & Medicinal Chemistry Letters*

Received Date: 15 February 2019
Revised Date: 7 May 2019
Accepted Date: 11 May 2019

Please cite this article as: Carullo, G., Perri, M., Manetti, F., Aiello, F., Cristina Caroleo, M., Cione, E., Quercetin-3-Oleoyl Derivatives as New GPR40 Agonists: Molecular Docking Studies and Functional Evaluation, *Bioorganic & Medicinal Chemistry Letters* (2019), doi: https://doi.org/10.1016/j.bmcl.2019.05.018

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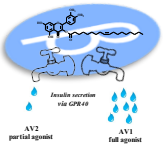

Bioorganic & Medicinal Chemistry Letters
journal homepage: www.elsevier.com

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ARTICLE INFO

Article history:
Received
Revised
Accepted
Available online

Keywords:
GPR40 allosteric site
Insulin secretion
Oleic acid
Quercetin
Type 2 diabetes

ABSTRACT

The G-protein-coupled receptor 40 (GPR40) is an attractive molecular target for the treatment of type 2 diabetes mellitus. Previously, based on the natural oleic acid substrate, an exogenous ligand for this receptor, named **AV1**, was synthesized. In this context, here we validated the activity of **AV1** as a full agonist, while the corresponding catechol analogue, named **AV2**, was investigated for the first time. The ligand-protein interaction between this new molecule and the receptor was highlighted in the lower portion of the GPR40 groove that generally accommodates **DC260126**. The functional assays performed have demonstrated that **AV2** is a suitable GPR40 partial agonist, showing a therapeutic potential and representing a useful tool in the management of type 2 diabetes.

Targets to treat type 2 diabetes mellitus (T2DM), as well as obesity and other comorbidities, are still an unmet medical need.[1] The deorphanization of several G-protein coupled receptors (GPCRs) led to the discovery of new and exciting drugs in the field of diabetes and particular interest is on the GPR40.[2] Its signal transduction is complex and involves the activation of Gq and Gs proteins in a tissue-dependent manner. Moreover, GPR40 is also functionally linked to biased agonism (ligand-specific responses) by the β-arrestin 2-mediated insulinotropic signaling axis.[3] GPR40 deletion decreases glucose-stimulated insulin secretion (GSIS) *in vivo* without affecting islets' metabolism. Islets from GPR40 knockout mice, display lower insulin release in response to fatty acids, suggesting a central role of the receptor in the regulation of insulin secretion.[4] The endogenous ligands of GPR40, such as palmitic, oleic, linoleic, and linolenic acids prefer the orthosteric binding site of it.[5] In this view, several academic groups and pharmaceutical companies designed new and interesting hydrophobic compounds bearing a typical structural triad constituted by a heteroaryl chain, a spacer (bearing a heteroatom such as -O- or –NH) and an acid head.[2] In addition, AMG 837 was also validated as a selective GPR40 agonist.[6] Under this scheme, several structure-activity relationships were established to develop additional agonists, such as GW9508. In 2010, the discovery of TAK-875 by Takeda highlighted high activity and selectivity for GPR40 receptor (human EC_{50}=0.014 μM – human K_i=0.038 μM).

This compound was indicated as an ago-allosteric modulator of GPR40 by exerting its effect cooperatively with endogenous plasma free fatty acids (FFAs) in human patients, as well as in diabetic animals.[7-9] In our previous study, quercetin/oleic acid hybrid molecule **AV1** was able to evocate insulin release by both pancreatic islets and *in vitro* β-cells system.[10] Herein we further studied **AV1** in the INS-1 832/13 β-cells *in vitro* model validating it as a full agonist of GPR40. This was achieved by using the inhibitor **DC260126** which not only negatively modulated oleic acid-induced GPR40 mRNA expression,[11,12] but it was also predicted to bind the same groove on GPR40, where **AV1** accommodates.[10] Additionally, the corresponding catechol analogue **AV2** was also evaluated and demonstrated to be a GPR40 partial agonist.

Several studies present in literature confirmed the multiple biological activities of quercetin.[13] In this field, the hybrid molecule, obtained through condensation with oleic acid, was able to improve insulin secretion *via* GPR40. In the case of **AV1**, the protection of catechol moiety with a diphenyl methyl ketal group abrogated the antioxidant activity but favored the interaction with a new allosteric site on GPR40. In alternative, the synthesis of **AV2** was performed by a bio-catalytic process. In only one step, involving the C-3 position of quercetin and using pancreatic porcine lipase (PPL), quercetin-3-oleate (**AV2**) was obtained in high yield and allowed to recycle the enzyme for five times.[14] (Figure 1).

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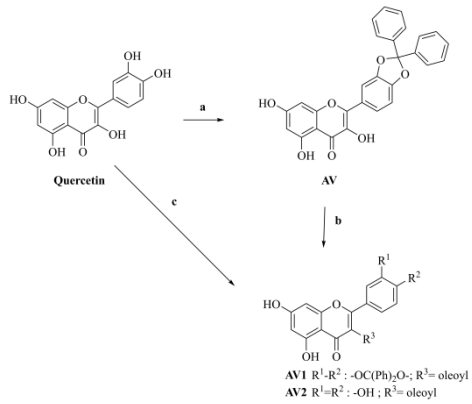

Figure 1. Synthesis of the GPR40 ligands. a) quercetin (1 eq), α,α-dichlorodiphenylmethane (1 eq), 170–180◦C, 10 min. b) procedure to obtain **AV1**: oleic acid (1 eq), *N,N'*-dicyclohexylcarbodiimide (1.2 eq), dimethylaminopyridine (catalytic amount) in dry dichloromethane at 0° C for 30 min, then **AV** solution in dry dichloromethane was added dropwise, at 25 °C, overnight under nitrogen atmosphere. c) procedure to obtain **AV2**: quercetin (1 eq), oleic acid (1 eq), pancreatic porcine lipase (130 mg *per* 100 mg of quercetin), acetone, 48 h.

We previously demonstrated that the exposure of INS-1 832/13 β cells to **AV1** affected GSIS in a dose-dependent manner with peak response at 10 μM, while treatment with the analog **AV2**, in the same range of **AV1** doses, did not show, under similar experimental conditions, any appreciable release of insulin from this cell population.

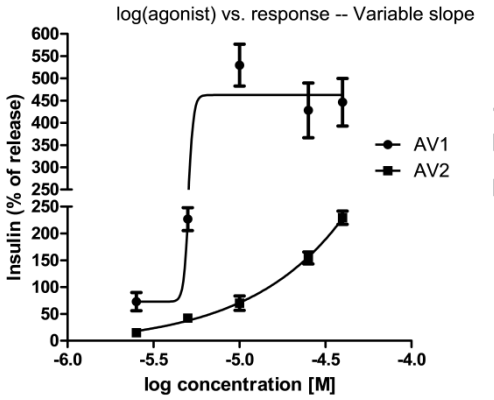

Figure 2. Dose-response curves insulin secretion under GSIS condition with **A**) **AV1** and **B**) **AV2** treatment

To better characterize the impact of these compounds on GSIS, we performed a separate series of experiments exposing INS-1 832/13 β-cells to **AV1** or **AV2** at the doses ranging from 20 to 40 μM for 5 min. Both compounds were able to increase insulin output from this cell population under GSIS condition. However, while **AV1** generated a maximal response, **AV2** showed a partial efficacy (Figure 2). To define the pharmacodynamics profile of AV1, INS-1 832/13 β-cells were exposed to a fixed dose (8 μM) of DC260126, a known antagonist of GPR40, 30 min before treatment with 10 μM AV1 upon GSIS condition. As shown in Figure 3A the exposure of cell cultures to DC260126 influenced the enabler effect of AV1 on GSIS leading to a dramatic decrease of the hormone secretion compared to cell cultures treated with 10 μM AV1 alone.

This result suggested that the effect of **AV1** on insulin release was due to an agonist activity on GPR40. Similar results were observed upon pre-treatment with **DC260126** of cell cultures exposed to 40 μM **AV2** (Figure 3B).

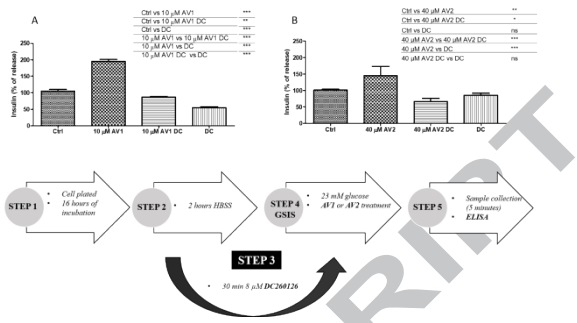

Figure 3. Functional assays of quercetin-oleate hybrid compounds, A) **AV1** and B) **AV2**, with antagonist **DC260126**.

The different pharmacodynamics profile of **AV2** prompted us to evaluate it as partial agonist of the GPR40 receptor. INS-1 832/13 β cells were then exposed to a fixed amount of **AV2** (40 μM) immediately before co-application of increasing concentrations of **AV1** (2.5, 5, 10 and 20 μM) and then the insulin secretion was evaluated upon GSIS condition. At the lowest dose (2.5 μM) of **AV1**, we observed that the concomitant exposure of this cell population to both compounds led to an increase of the insulin secretion upon GSIS conditions which was significantly greater than that for **AV1** alone, suggesting an additive effect of **AV2**. On the other hand, at higher response dose (20 μM) of **AV1**, **AV2** showed antagonist activity, producing a net decrease of the **AV1**-mediated insulin secretion upon GSIS condition (Figure 4A). Similar results were also observed exposing INS-1 832/13 β cells to low fixed concentration of **AV2** equal to its EC_{50} value (21 μM) immediately before co-administration of increasing concentrations of **AV1** (from 2.5 up to 20 μM), further confirming the dual functional profile of **AV2**. However, a shift of the additive effect was detected when cell cultures were concomitantly challenged with 10 μM **AV1**, suggesting that **AV2** exerted its partial agonistic activity in a dose-dependent fashion.

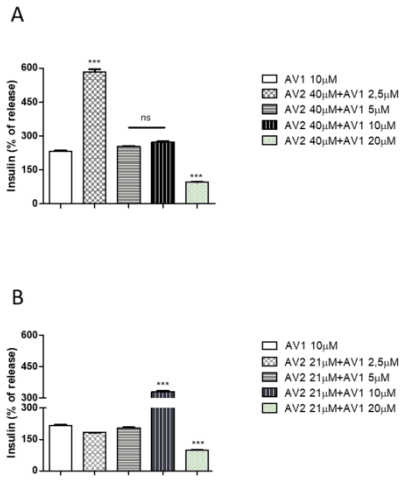

Figure 4. AV2 as a suitable GPR40 partial agonist either at A) 40 μM and at B) 21 μM in presence of a dose curve of **AV1**.

During the last years, new classes of medications have been developed for patients suffering of T2DM. Among them, just to name a few: sodium-glucose co-transporter-2 (SGLT2) inhibitors (of this latter ADRs were recently recognized),[15] DPP-IV inhibitors, and incretin mimetics.[16] In this frame, the GPR40 receptor is an attractive molecular target in T2DM pharmacotherapy as it is involved in both insulin and GPL-1 release from β-pancreatic and enteroendocrine cells, respectively. Both preclinical and clinical studies have shown that activation of GPR40 improves glycemic control. However, the recent termination of phase III clinical trials using the GPR40 agonist TAK-875 (fasiglifam) has raised important questions concerning the long-term safety and feasibility of targeting GPR40.[17] Oleic acid was known to be a natural GPR40 ligand and our previous findings suggested that this molecule represented a good driver forward GPR40 when it is conjugated with quercetin.[10] Of note, oleic acid and its derivatives (oleoylethanolamide and 2-oleoylglycerol) improve postprandial triglyceride levels and GLP-1 response in insulin-resistant subjects and upregulate GLUT2 expression.[18]

In the attempt to formulate a hypothesis about the binding mode of **AV2** and **DC260126** on GPR40, docking simulations have been performed with the same computational protocol already applied to **AV1**. Previous calculations[10] led us to hypothesize that **AV1** could be accommodated within the long transmembrane crevice constituted by TM4 and TM5 as the lateral walls, and by TM3 as the back wall, and occupied by the oleoyl-glycerol moiety of the X-ray complex between GPR40 and TAK-875 (4phu within the protein data bank).[19,20] These data suggested for the first time[11] that this binding site could recognize exogenous ligands, in agreement with experimental results on other GPR40 agonists appeared at the same time. Subsequent studies supported this hypothesis by providing X-ray complexes where a GPR40 full agonist (namely, the dihydro chromene AP8[12] or the benzofuran "compound 1")[17] was embedded within the same binding groove (5tzy or 5kw2, respectively, within the protein data bank).

Results of docking calculations showed that also the GPR40 antagonist DC260126 could occupy the portion of the GPR40 groove just above the intracellular loop 2 (ICL2). In particular, one oxygen atom of the sulfonyl moiety of **DC260126** made a bifurcated hydrogen bond with the basic side chain of Arg37 (Figure 5A), as already found for the 5-OH group of the quercetin core of **AV1** and **AV2**. Moreover, the second sulfonyl oxygen atom interacted with the backbone NH of Ala116. The fluorophenyl group pointed behind TM3 towards a region of space delimited by Arg104, Arg218, and Arg221. It is very important to note that the Arg side chains created a small pocket characterized by a high fluorophilic character that generated favorable polar interactions between the aromatic F-C aromatic substituent and the guanidinium side chains of Arg residues[21,22] thus providing high stabilization to the **DC260126**-GPR40 complex. The central phenyl ring of **DC260126** was superimposable to the O=C4-C3-(OC=O) ester of **AV2** (Figure 5B), while its butyl chain occupied part of the groove where the long hydrophobic appendage of **AV2** was found. Overall, results from docking calculations showed that the portion of the GPR40 binding pocket that was occupied by **AV2** roughly accommodated both **DC260126** in the lower portion (close to the ICL2) and the oleoyl derivative in the upper part (Figure 5C).

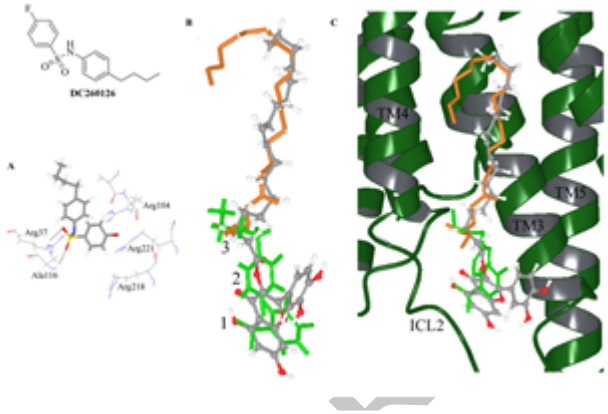

Figure 5. Docking analyses. A) Graphical representation of the best-ranked docked pose of the GPCR40 antagonist DC260126 (atom type ball and stick notation) within the allosteric binding site able to accommodate **AV2**. Hydrogen bonds (black dotted lines) are found between the sulfonyl group and Arg37 and Ala116. Favorable polar interactions are also found between the fluoride substituent and a fluorophilic cage constituted by Arg side chains. B) Comparison between the best docked pose of **AV2** (atom type ball and stick notation) with that of the oleoyl derivative (orange) found in the X-ray complex between GPR40 and TAK-875 (4phu in the protein data bank), as well as the GPR40 antagonist **DC260126** (green). The 5-OH of the **AV2** quercetin core is superposed to one of the sulfonyl oxygens of **DC260126** (1); the O=C4-(C-O-C=O) ester moiety of **AV2** matched the central phenyl ring of DC260126 (2); the butyl chain of **DC260126** is superposed to the lower part of the oleoyl derivative and to the proximal portion of the AV2 alkyl chain (3). Overall, the region of space occupied by AV2 is similar to that where both **DC260126** (below) and the oleoyl derivative are accommodated. C) Graphical representation of **AV2**, **DC260126**, and the oleoyl derivative (see Fig. 2 for colors) within the GPR40 groove delimited by TM4, TM3, and TM5 (from left to right in the picture), and by ICL2.

In the present study, we evaluated the pharmacology of quercetin esters **AV1** and **AV2**. For both compounds, we demonstrated an agonist profile versus GPR40 (Figure 2). However, an analysis of dose-response curves revealed that while **AV1** generated a maximal response, **AV2** demonstrated a partial efficacy on insulin secretion under GSIS condition, thus profiling them as a full and a partial agonist, respectively. The fact that the exposure of INS-1 832/13 β-cells to **DC260126** blocked the facilitatory effect of **AV1** on GSIS, is indicative that both compounds shared the same binding and confirmed that the insulin secretagogue action of **AV1** is due to an agonist activity on GPR40 (Figure 4A and B). Moreover, the evidence of the dual pharmacodynamic profile displayed by **AV2** is worthy of note. Indeed, the effect of this compound on GSIS was additive at low doses of **AV1** and antagonistic over higher **AV1** dose (Figure 4A and B). Although there is considerable evidence from rodent models of T2DM and early phase clinical trials in patients with T2DM to support the use of GPR40 full agonists to potentiate insulin secretion and improve glucose tolerance, concerns exist as to whether chronic activation of GPR40 mediates deleterious effects of FFAs.[20] On the other hand, abnormalities of fatty-acid metabolism are also increasingly recognized as key components of the pathogenesis of the metabolic syndrome and T2DM. Fat-feeding and raised levels of circulating FFAs are clearly sufficient to induce peripheral and hepatic insulin resistance. Accumulation of lipids inside muscle cells and specific increases in muscle long-chain fatty acyl-CoA content have been implicated in causing insulin resistance.[23] In this scenario the dual pharmacodynamic profile of **AV2** might be a useful tool in the therapy management of T2DM since it can be used to both activate GPR40 giving a desired submaximal response and reduce the overstimulation of the receptor when excess amounts

of endogenous ligands are present. GPR40 is a clinically validated target in T2DM treatment and from medicinal chemist viewpoint, more derivatives were synthesized and assayed, but failed the clinical trials especially for their hepatotoxicity. In this context, hybrid molecules bearing oleic acid, which is an endogenous GPR40 ligand, can represent an alternative strategy to develop GPR40 agonists. Hence, the synthesized quercetin-3-oleoyl hybrids bind a new pocket of GPR40 receptor highlighting a possible pharmacological strategy for the management of T2DM. Molecular docking simulations suggested that both quercetin derivatives **AV1** and **AV2** could occupy the same allosteric binding site hypothesized for the GPR40 antagonist **DC260126** and recently demonstrated to accommodate new GPR40 allosteric agonists. The finding that **AV2** acts as partial agonist of GPR40 elects this molecule a promising approach in the therapy of T2DM because of its potential beneficial effect beyond improvement of insulin secretion.

Acknowledgments

The authors are grateful to Ministero dell'Istruzione, dell'Università e della Ricerca (MIUR) (Rome) for "Dipartimento di Eccellenza grant 2018-2022" at both Departments. Santa Chiara Lab is also acknowledged for the use of the Schrodinger suite.

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Supplementary Material

Chemical syntheses, molecular docking calculations and biological assays